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114th National Congress
of the Italian Society of Internal Medicine

Rome, 26–28 October 2013
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Internal and Emergency Medicine

Official Journal of the Italian Society of Internal Medicine

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Aims and Scope
Internal and Emergency Medicine (IEM) is an independent, international, English-language, peer-reviewed journal designed for internists and emergency physicians. IEM publishes a variety of manuscript types including Original investigations, Review articles, Letters to the Editor, Medical Illustrations and Invited Editorials, Points of view and Commentaries. Occasionally IEM accepts unsolicited Reviews or Editorials. The journal is divided into three sections, i.e., Internal Medicine, Emergency Medicine and Clinical Evidence and Health Technology Assessment, with three separate editorial boards. In the Internal Medicine section, invited Case records and, occasionally, Physical examinations, devoted to underlining the role of a clinical approach in selected clinical cases, are also published. Occasionally, the Emergency Medicine section includes a Morbidity and Mortality Report and an Airway Forum concerning the management of difficult airway problems. Finally, in the Clinical Evidence and Health Technology Assessment section brief discussions of topics of evidence-based medicine (Cochrane’s corner) and Research updates are published. IEM encourages letters of rebuttal and criticism of published articles whereas submission of case reports is not of interest for the journal. Topics of interest include all subjects that relate to the science and practice of Internal and Emergency Medicine. IEM is the official journal of the Italian Society of Internal Medicine and is published eight times per year starting with 2013.

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Oral Communications

Saturday 26 October 2013

Absolute neutrophil count accurately predicts short-term mortality rate in hospitalized patients with acute pulmonary embolism: a retrospective cohort study

Riva N, Turato S, Grazioli S, Squizzato A, Steidl L, Guasti L, Grandi AM, Ageno W, Dentali F

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Background: Leukocytosis has been reported to be an independent risk factor for morbidity and mortality in patients with ischemic cardio-cerebrovascular diseases. However, the influence of specific subtypes of white blood cells on the outcome of patients with venous thromboembolic events has not been explored yet.

The aim of this study was to assess the role of neutrophil granulocytes in predicting short-term mortality rate in hospitalized patients with acute pulmonary embolism (PE).

Methods: Consecutive patients admitted to the tertiary care hospital of Varese (Italy) with an objectively diagnosed PE between January 2005 and December 2009 were included in a retrospective cohort study. Information on clinical presentation, risk factors, blood test results and mortality rate at 1-month and 3-month follow-up was collected.

Results: 473 patients diagnosed with acute PE had leukocyte formula available. However, 66 of them were excluded because of concomitant infection at admission, which could have influenced the leukocyte count. Median age was 72 years (interquartile range 63-81); 46.4% were male. Cancer was present in 31.9%, chronic pulmonary disease in 14.5% and heart failure in 5.4%. Concomitant deep vein thrombosis was diagnosed in 57.7%. Leukocytosis, defined as white blood cells greater than 11,000/mm³, was present in 83 patients (20.4%); relative neutrophilia, defined as neutrophil percentage greater than 80%, in 77 patients (18.9%) and absolute neutrophilia, defined as neutrophil count greater than 5,500/mm³, in 191 patients (46.9%). One-month mortality rate was 13.3% (95% CI 10.2-17.1%). Leukocytosis, relative and absolute neutrophilia were significantly associated with poor outcome (p<0.001 for all three variables). Stratification of patients according to neutrophil quartiles significantly correlated with mortality rate (4.9%, 5.9%, 9.8% and 32.4%, respectively, X² for trend p<0.001). The area under the ROC curve (AUC) for neutrophil quartiles was 0.73 (95% CI 0.66-0.81). When absolute neutrophilia was included in a multivariate Cox regression analysis, together with the clinical predictors from the Pulmonary Embolism Severity Index (PESI) score, it was demonstrated to be an independent predictor of mortality (hazard ratio 3.311, 95% CI 1.709-6.414, p<0.001). Moreover, the addition of absolute neutrophilia to the PESI score significantly improved the prognostic accuracy of the model (AUC for PESI 0.79, 95% CI 0.73-0.85, vs AUC for PESI plus neutrophilia 0.83, 95% CI 0.76-0.89, p for comparison=0.016). Three-month mortality rate was 21.1% (95% CI 17.3-25.5%). The results were similar to those at one-month follow-up. Mortality rate according to neutrophil quartiles was 10.8%, 10.9%, 18.6% and 44.1% (X² for trend p<0.001) and the AUC was 0.70 (95% CI 0.64-0.77). The absolute neutrophilia was confirmed to be an independent predictor of mortality (hazard ratio 2.724, 95% CI 1.669-4.445, p<0.001). At 3-month follow-up the AUC for PESI was 0.81, 95% CI 0.76-0.86, while the AUC for PESI plus neutrophilia was 0.83, 95% CI 0.78-0.88 (p for comparison=0.132).

Conclusions: The results of our study revealed that neutrophil count is significantly associated with short-term adverse prognosis in hospitalized patients with acute PE. The addition of absolute neutrophilia to the clinical predictors of the PESI score significantly improved the prognostic accuracy of the model. Laboratory parameters should be merged together with clinical variables in the creation of future prediction rules.

Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant acinetobacter baumannii. a multicentre, randomised, clinical trial


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Background: Extensively-drug resistant (XDR) Acinetobacter baumannii (Acb) is increasingly recognised as an etiological agent of nosocomial infections associated with high mortality in critically ill patients. Epidemic XDR isolates of Acb may show resistance to almost all classes of antimicrobials, including carbapenems. In these infections, the only viable therapeutic option may be represented by colistin, despite its relatively low intrinsic efficacy, a suboptimal lung penetration and the risk for significant renal toxicity. However, even with colistin treatment, mortality remains high.

Synergy against XDR Acb was shown in both in vitro and experimental studies when colistin was combined with rifampicin, prompting their combined clinical use in XDR Acb infections. Three uncontrolled clinical studies have assessed the safety and clinical efficacy of the colistin-rifampicin combination, showing very high overall response rates, without major adverse events. By altering membrane permeability, colistin may facilitate rifampicin entry within the bacterial cell and therefore enhance its killing activity. However, no proof of superiority of the colistin-rifampicin combination over colistin monotherapy was provided. Therefore, we performed a randomized controlled trial to assess whether the addition of rifampicin to colistin reduced the mortality of patients with life-threatening infections due to XDR Acb compared to colistin alone.

Methods: This multicentre, parallel, randomised, open-label clinical trial enrolled 210 patients with life-threatening infections due to XDR Acb from intensive care units of five tertiary care hospitals. Patients were randomly allocated (1:1) to either colistin alone, 2 MU every 8 hours intravenously or colistin (as above), plus rifampicin 600 mg every 12 hours intravenously.
Primary end point was overall 30 day mortality. Secondary end points were infection-related death, microbiological eradication and hospitalization length.

**Results:** Death within 30 days from randomization occurred in 90 (43%) subjects, without difference between treatment arms (p=0.95). This was confirmed by multivariable analysis (OR 0.88, 95% CI 0.46 to 1.69, p=0.71). A significant increase of microbiological eradication rate was observed in the colistin plus rifampicin arm (p=0.034). No difference was observed for infection-related death and length of hospitalization. No strains of colistin resistance emerged in any of two groups. Adverse events (AE) were observed in 70 (34.6%) patients, without differences between experimental and control arm (35.7% and 33.7%, respectively). The most common AE was renal impairment, that occurred in 53 patients (26.2%) and led to colistin dose reduction or discontinuation in 17% of patients overall. In 1 subject (0.4%), a worsening of renal function leading to renal replacement therapy was recorded. The degree of renal toxicity was assessed according to the RIFLE. Despite receiving the same initial dose of colistin, underweight patients (BMI<18) did not show an increased rate of renal toxicity (3 of 15, 20%). Liver dysfunction associated with hyperbilirubinemia was more frequent, though not significantly, in the experimental arm, leading to rifampicin dose reduction (9%) or discontinuation (48%). No death was related to the study drug administration.

**Conclusions:** In serious XDR Acb infections, 30-day mortality is not reduced by addition of rifampicin to colistin. These results indicate that, at present, rifampicin should not be routinely combined with colistin in clinical practice. However, the increased rate of Aeb eradication with combination treatment could still imply a clinical benefit that should be taken into account.

**The role of human neutrophil elastase and its inhibitor elafin in ulcerative colitis**

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**Background & Aims:** Mucosal inflammation in ulcerative colitis (UC) is characterized by an influx of neutrophils which release large amounts of human neutrophil elastase (HNE), causing extracellular matrix degradation and tissue disruption, ultimately resulting in ulcer formation. Neutrophils also produce the HNE inhibitor elafin. Here we have evaluated the mucosal levels of HNE and elafin in active UC, and we have investigated the modulatory effects of elafin on mucosal proteolytic activity in UC.

**Methods:** Colonic biopsies from inflamed mucosa of 18 patients with active UC and from normal mucosa of 12 control subjects were homogenized to extract mucosal proteins. Proteolytic activity, using elastin as a substrate, and elafin concentration were determined in mucosal homogenates of the *in vitro* effect of the protease inhibitors elafin, marimastat (a broad-spectrum matrix metalloproteinase inhibitor) and of the synthetic elastase inhibitor, AAPV [N-(Methoxysuccinyl)-Ala-Ala-Pro-Val Chloromethyl Ketone] on mucosal proteolytic activity in UC homogenates was determined. Proteolytic activity was also evaluated in organ culture supernatants of biopsies from inflamed UC mucosa cultured *ex vivo* in the presence or absence of elafin.

**Results:** Mucosal homogenates from patients with active UC displayed significantly (p<0.005) higher proteolytic activity in comparison to those from control subjects. Unexpectedly, elafin levels were significantly (p<0.01) increased in mucosal homogenates from active UC compared to control subjects. The *in vitro* addition of elafin, marimastat and AAPV significantly (p<0.05) diminished the proteolytic activity of inflamed UC homogenates. Elafin significantly (p<0.05) reduced the proteolytic activity of supernatants from inflamed UC biopsies cultured *ex vivo*.

**Conclusions:** Colonic mucosa from UC patients displays higher proteolytic activity in comparison to control subjects. Elafin reduces the proteolytic activity of UC mucosal homogenates, with the most notable effect in the samples with the highest activity. These data show a beneficial modulatory effect of elafin on human gut tissue, suggesting a possible role for elafin in the treatment of UC.

**Gene expression and microRNA signature in peripheral blood mononuclear cells of patients with metabolic syndrome**


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**Background:** Metabolic Syndrome (MS) is defined as a combination of metabolic risk factors for cardiovascular disease (visceral adiposity, hypertriglyceridemia, hypertension, glucose intolerance or type 2 diabetes, and low high-density lipoprotein levels), and is complicated by a pro-inflammatory state. Microarray analysis of peripheral blood mononuclear cells (PBMCs) has been proposed as an effective tool for investigating changes in gene expression profiles in a wide range of pathological conditions ranging from inflammatory disease to cancer. In order to characterize the genetic signature of MS and to identify putative novel biomarkers of onset and progression of disease, we studied whole-genome gene and microRNA profiles of PBMCs in patients with MS.

**Materials and Methods:** We enrolled 20 controls (10F:10M) and 20 naive patients (10F:10M; ≥3 criteria for MS upon ATP III). We collected clinical and biochemical data, and blood samples for PBMCs isolation and for the study of gene and microRNA expression profiles (Illumina iScan System). Data were processed using the Illumina Genome Studio Software, the SAS Package (Release 9.1), and the R Package (Version 2.12.2). All the data obtained were analyzed to evaluate differences among groups (Mann-Whitney U test), correlations between clinical and prognostic variables, and levels of expression of specific genes and miRNAs (Pearson’s correlation). The raw p-values were adjusted by the Benjamini-Hochberg procedure, which controls the False Discovery Rate (FDR). Quantitative real-time PCR (RTqPCR) validation of differentially expressed mRNA was performed on an expanded validation cohort (33 controls and 33 subjects with MS); gene selection for RTqPCR validation was based on biological significance and/or strong differential expression of the array.

**Results:** MS patients were characterized by increased abdominal circumference, blood pressure, insulin-resistance, glycemia, and cardiovascular risk, while HDLc levels were decreased (p<0.05). Up to 8000 genes were expressed in the PBMC transcriptome, with 354 significantly up-regulated and 278 down-regulated genes in MS group; of the 622 miRNAs expressed in the PBMCs, 50 were significantly up-regulated and 27 were down-regulated in the MS group (cut-off 1.3 folds; p-value<0.01). With the Ingenuity Pathway Analysis, we dissected the biological networks differentially expressed in MS, and we found a strong up-regulation of genes involved in the modulation inflammatory response, as well as in the promotion of cellular growth and proliferation. On the other hand, we found a down-regulation of genes involved in the maintenance of lipid homeostasis. Using RTqPCR, we confirmed the most important hits found to be differentially modulated, including the mRNA expression levels of IL32, mitogen-acti-
vated protein kinase 1 (MAP4K1), intercellular adhesion molecule 2 (ICAM2) and integrin alpha L (ITGAL), up-regulated in our results and known to be involved in the modulation of cellular interactions and inflammatory response, and of phosphatase and tensin homolog (PTEN), a modulator of cell growth and metabolism), interferon gamma receptor 1 (IFNGR1), ADAM metallopeptidase domain 9 (ADAM9, a gene involved in cancer), and ATP-binding cassette transporter A1 (ABCA1, a key player of reverse cholesterol transport), which were all down-regulated in MS subjects. Furthermore, we found correlations between genes and clinical variables; the most intriguing were ABCA1, which was positively correlated to HDLc and negatively correlated to cardiovascular risk score; PTEN, which was negatively correlated to insulin levels, insulin-resistance (HOMA-IR) and erythrocyte sedimentation rate; IL32, ICAM2 and ITGAL, which were positively correlated to ESR, CRP, fibrinogen and cardiovascular risk score.

Conclusions: PBMCs are active players in MS pathophysiology and their transcriptome is a source of putative biomarkers of MS diagnosis and progression, as well as of candidate targets for the management of lipid disorders and atherosclerosis. Overall, our results point to a strong activation of PBMCs in MS, thus being crucial in sustaining the systemic inflammatory responses and the metabolic imbalance.

This contribution has been awarded as Best Communication.

Neuroserpin gene expression correlates with vascular damage independently of the etiopathogenesis of dementia

Dumanti S.1,2, Casati M.1, Gussago C.1,2, Magni L.1,2, Vasso M.3,4, Fania C.5, Tedone E.1,2, Ferri E.1, Guandalini F.2, Nani C.1,2, Gatto M.L.1,2, Rossi P.D.1, Spagnoli D.2, Gelfi C.3,4, Arroio B.1,2, Mari D.1,2

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Introduction: The research on dementia focuses on population of 65-75 years old subjects in which Alzheimer’s disease (AD) might be recognized as a purely degenerative disease with a major pathogenetic role of beta amyloid. In elderly (over 75 years old) the probability of finding other abnormalities, including cerebrovascular lesion, increases, making the line between AD and vascular dementia (VD) blurred. Indeed in many elderly patients, markers of vascular injury coexist with traditional AD hallmarks. To pinpoint the molecular players of dementia, a promising candidate is neuroserpin (NS), a member of the serine proteinase inhibitor (serpin) secreted by axons but also expressed in peripheral blood. NS is a potent inhibitor of tissue plasminogen activator and plasmin, modulating many processes as neurite outgrowth and synaptic plasticity. NS is also involved in permeability between vascular and nervous system. Mutations in NS gene produce an autosomal‐dominant neurodegenerative disease (FENIB) that shows dementia as clinical feature. The aim of this project is to compare NS levels in biological fluids from patients with AD, VD and patients with idiopathic normal pressure hydrocephalus (iNPH) subjected to spinal tap procedures and atherosclerosis. Overall, our results point to a strong activation of PBMCs in MS, thus being crucial in sustaining the systemic inflammatory responses and the metabolic imbalance.

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This contribution has been awarded as Best Communication.
Clinical, serological and endoscopic indexes of disease activity despite an ad-
tients were on remission. All patients underwent lower endoscopy with mul-
CD, and 1 IC) were considered refractory because of the persistence of
role of current therapies in the development of viral colitis, the patients
multiple biopsies. The viral load was assessed by quantitative PCR on both mu-

44±15 years): 21 with ulcerative colitis (UC), 13 with Crohn’s disease (CD)

Patients and methods: We enrolled 37 IBD patients (23 males, mean age
44±15 years): 21 with ulcerative colitis (UC), 13 with Crohn’s disease (CD)
and 3 with indeterminate colitis (IC). Among them, 17 patients (13 UC, 3
CD, and 1 IC) were considered refractory because of the persistence of
clinical, serological and endoscopic indexes of disease activity despite an ade-
quate treatment (defined as at least a proper dose of either systemic steroids
or biologicals lasting more than 4 weeks), while the remaining 20 pa-
tients were on remission. All patients underwent lower endoscopy with mul-
tiple biopsies. The viral load was assessed by quantitative PCR on both mu-
cosal specimens and peripheral blood. In order to investigate the possible role
of current therapies in the development of viral colitis, the patients were di-
vided into three groups according to the mucosal viral load (≥10³ copies/10⁵
cells, between 10³-10⁵ copies/10⁵ cells, below 10⁵ copies/10⁵
cells) for both EBV and HCMV. The ongoing medications were grouped on
the basis of the class of the drugs as follows: systemic steroids (metilpred-
nisolone, prednisone), topical steroids (beclometasone, budesonide), im-
munosuppressants (azathioprine), and biological agents (infliximab, adali-
mumab), while the treatment duration was expressed in months. Comparison
among data were performed by means of the following tests: Kruskal-Wallis,
Mann-Whitney, Fisher’s exact test, and Wilcoxon matched pairs signed-
ranks as appropriate. The Spearman rank correlation test was also applied.

Therapy-dependent risk of opportunistic viral reactivations
in patients with inflammatory bowel disease

Background and aim: Nowadays, immunosuppressants and biologicals are
considered the mainstay of therapy for inflammatory bowel disease
(IBD) thanks to the possibility of inducing remission and preventing dis-
 ease progression. However, the growing and earlier use of these medica-
tions predisposes the patients to an increased risk of opportunistic infec-
tions, in turn, seems to contribute to the development of refractoriness.
This observation is in keeping with those found in transplanted patients
where systemic steroids emerged as the main trigger of vi-
rnal disease that, usually, is systemic and only occasionally results in an
end-organ disease. By consequence, a warning in the use of systemic
steroids and the need of screening for both HCMV and EBV loads at mu-
cosal level is pointed out by our results. Finally, steroids ad biological
agents should be avoided in patients with a viral load ≥10⁶, and used with
cautions in those with viral load <10⁵.

Results: All refractory patients showed a mucosal viral load greater than
10⁶ copies/10⁵ cells in at least one colonic segment (median values: 6867
and 25043 copies/10⁵ cells for EBV and HCMV, respectively), with 2/17
patients (12%) positive for HCMV, 9/17 patients (53%) for EBV, and 6/17
patients (35%) carrying both viruses. By contrary, a viral load invariably
lower than 10³ copies/10⁵ cells was found in 13 out of 20 (65%) non-re-
fractory IBD patients (4 cases – 30.7% - had HCMV, and 9 cases – 69.3%
carried EBV; median values: 10⁵ and 77 for HCMV and EBV, respec-
tively). Systemic steroids emerged as the main risk factor for both HCMV
and EBV colitis (p=0.018 and 0.0020, respectively), while biological
agents and topical steroids resulted positively related to EBV (p=0.021 and
0.008, respectively) but not to HCMV infection, whilst no statistically
significant association was found between the use of immunosuppressors
and viral colitis. Interestingly, the highest EBV mucosal load values were
found in those patients under combo therapy (biological agents plus sys-
temic or topical steroids). At variance, we did not find any correlation be-
tween the duration of both therapy and underlying disease, age, and gen-
der with an increased risk for the development of viral colitis.

Conclusions: Our data show that steroids, both systemic and topical, and
biological agents put IBD patients at high risk of viral reactivation, inde-
dependently from the duration of the therapy. The reactivation of these op-
portunistic infections, in turn, seems to contribute to the development of
refractoriness. This observation is in keeping with those found in trans-
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cautions in those with viral load <10⁵.

This contribution has been awarded as Best Communication.

Combined anti-viral therapy for chronic c hepatitis is safe
and effective in thalassemia major patients

Mazzoleni M³, Poggiali E², D’Ambrosio R³, Cassinerio E¹, Forti S⁴, Cianciulli P⁵, Lai ME⁶, Bonetti F⁷, Colombo M⁸, Cappellini MD⁹,²

Table 1. Characteristics of 7 patients with GD1

<table>
<thead>
<tr>
<th>Pt</th>
<th>Genotype</th>
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Pt, patient; A, Ashkenazi Jewish; C, Caucasian. M, male; dg, diagnosis; N, no; Y, yes; LVDi, left ventricular diastolic volume index; LVSvi, left ventricular sистolic volume index; LVEF, left ventricular ejection fraction; LA, left atrium; RA, right atrium; LGE, late gadolinium enhancement.
Relationship between uric acid and insulin like growth factor 1 in essential hypertension

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Introduction: High levels of uric acid (UA) are associated with hypertension, diabetes mellitus, metabolic syndrome, vascular and kidney disease. Moreover, the coexistence of both hyperuricemia and endothelial dysfunction increases the risk to develop new diabetes in hypertensive patients. Similarly, insulin-like growth factor-1 (IGF-1) is associated with metabolic and vascular alterations; in fact, low plasma IGF-1 concentrations are associated with insulin resistance and reduced endothelium-dependent vasodilation.

Aim: To evaluate the possible association between UA and IGF-1 levels in uncomplicated hypertensive patients.

Methods: We enrolled 1100 patients with essential hypertension (577 women, 523 men), age 47.8±12. Serum UA levels were measured by an automated technique based on the measurement of Jaffe chromogen and by the URICASE/POD method implemented in an autoanalyzer. Circulating IGF-1 levels were detected by a sensitive immunoradiometric assay. Insulin sensitivity was assessed by HOMA index.

Results: A linear regression analysis showed an inverse and significant relationship between IGF-1 and UA in whole population (r=-0.463, P<0.0001), and in male (r=-0.477; P<0.0001) and female (r=-0.419; P<0.0001) subjects. In the multiple regression analysis UA resulted the most important predictor of IGF-1 in the whole population and in males, explaining, respectively, 21.4% and 22.7% of its variation. By contrast, HOMA index resulted the most important predictor of IGF-1 in female, explaining the 30.6% of its variation.

Conclusion: Hyperuricemia is associated with low IGF-1 levels. This finding has clinical relevance because high levels of UA and low levels of IGF-1 may be considered indicators of cardio-metabolic risk in hypertensive patients and, probably, a potential future therapeutic target to reduce the risk of adverse cardiovascular events.

Anemia in hospitalized elderly patients: the REPOSI study


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Background: Several clinical studies have demonstrated a high prevalence of anemia in elderly community-dwelling individuals, but few previous studies have focused on hospitalized patients. Anemia, even mild, is associated with negative outcomes, including prolonged hospital stay and in-hospital mortality.

Purposes: To evaluate (i) the prevalence of anemia in elderly patients admitted to internal medicine and geriatric wards; (ii) the association between anemia and comorbidity, polypharmacy at admission and some diseases (chronic obstructive pulmonary disease, cardio-cerebral vascular diseases, neoplasms, chronic renal failure, gastrointestinal disorders, diabetes) and their correlation with severity of anemia; (iii) the role of anemia in predicting the length of hospital stay and in-hospital mortality.

Methods: We analyzed the data collected in patients aged 65 years or older admitted from January to December 2010 in 66 Italian internal medicine and geriatric wards participating in the frame of “Registro Politerapie SIMI” (REPOSI), a collaborative and independent registry, organized by the Italian Society of Internal Medicine (SIMI) and the IRCCS-Istituto di Ricerche Farmacologiche “Mario Negri”. Anemia was defined according to the WHO criteria and classified in mild (hemoglobin concentration: 10-11.9 g/dl in women and 10-12.9 g/dl in men) and moderate-severe grade (less than 10 g/dl). Results are expressed as number (%), mean±standard deviation, odds ratio (95% confidence interval).

Results: Of the 1,380 elderly patients enrolled in the REPOSI 2010, 8 subjects were excluded due to missing data leaving 1,372 patients eligible for the analyses. Seventy-five and fifty-three patients (54.9%) were anemic and 47.4% were women. Anemic subjects were one year older than non anemic (mean age 79.5±7.4 versus 78.5±7.2, p=0.01), had a lower body mass index (25.4±4.8 versus 26.6±5.4, p<0.0001), a higher comorbidity (mean number of diagnosis at admission 5.9±2.9 versus 5.4±2.6, p=0.0005), polypharmacy (mean number of drugs 5.7±2.8 versus 4.9±2.6, p<0.0001) and mean comorbidity index score (Cumulative Illness Rating Scale-CIRS, 3.1±1.8 versus 2.7±1.6, p<0.0001). The number of patients with 5 or more diagnoses and 5 or more drugs was higher in anemic compared with non-anemic subjects and increased with severity of anemia (p trend 0.0114 for diagnoeses and <0.0001 for drugs). Anemic compared with non-anemic individuals had a higher rate of neoplasms (22.8% versus 14.2%, p<0.0001), digestive system disorders (39.7% versus 31.2%, p=0.0010) and chronic renal failure (22.4% versus 11.5%, p<0.0001) and a statistically significant trend was seen between the severity of anemia and the prevalence of these diseases (p trend respectively <0.0001, <0.0003, <0.0001). No association between anemia and chronic obstructive pulmonary disease, cardio-cerebral vascular disorders or diabetes was observed (p=0.26, p=0.56, and p=0.68, respectively). The duration of hospital stay was significantly longer in anemic than non-anemic patients (11.9±9.3 versus 9.5±6.4 days, p<0.0001), even after adjusting for age and sex or age, sex, and CIRS score. Anemia was not associated with a higher risk of in-hospital death (OR 1.53 [0.81-2.92], p=0.193).

Conclusions: Our study confirms the high prevalence of anemia in a large population of hospitalized elderly subjects. The severity of anemia is associated with the rate of comorbidity and the number of drugs at admission and seems to be a predictor of length of hospital stay, after controlling for potential confounders. These findings might help clinicians in developing more appropriate diagnostic and therapeutic strategies and preventive interventions to improve the in-hospital management of anemic elderly patients, particularly in a period with increasingly limited economic resources.

Low peripheral T-cell reactivity to heat shock protein 70 and its cofactor GrpE from Trepheryma whipplei in patients affected by Whipple’s disease

Evaluation of traditional cardiovascular risk factors (CRFs) was performed on peripheral arteries in SLE patients. Obtained results from TW induced larger proportions of CD40L + IFN-γ, hsp70, GST-GrpE or the total lysate of TW were low in healthy controls defined TW proteins was comparable to the effect of a total TW lysate. For than of patients affected by WD. This reduced capacity to respond to both peripheral cytotoxic CD8+ T cells, the relative numbers of CD40L + or in vitro culture, CD40L, CD69 and IFN-γ were analyzed by flow cytometry in CD4+ and CD8+ T cells. Results: While activation of CD4+ and CD8+ T cells by SEB was comparable in WD patients and healthy controls, GST hsp70 and GST-GrpE from TW induced larger proportions of CD40L+ IFN-γ+ and CD69+ IFN-γ+ cells among the CD4+ T cell population in the PBMC of healthy controls than of patients affected by WD. This reduced capacity to respond to both defined TW proteins was comparable to the effect of a total TW lysate. For peripheral cytotoxic CD8+ T cells, the relative numbers of CD40L+ or CD69+ activated T cells that also produced IFN-γ in response to GST-hsp70, GST-GrpE or the total lysate of TW were low in healthy controls and even lower in the WD patients.

Impairment of peripheral vascular function in SLE patients. Differences from the vascular pattern of patients at high cardiovascular risk

Gabriele Cioni, Caterina Cenci, Giulia Degl’innocenti, Giacomo Emini, Elena Silvestri, Rossella Marcucci, Mario Milco D’elios, Lorenzo Emini, Domenico Prisco, Rosanna Abbate, Maria Boddi

Department of experimental and clinical medicine, University of Florence

Background: Growing evidence was collected that autoimmune diseases are associated to an enhanced atherosclerotic progression, and to a high incidence of cardiovascular events. Aim of our work was to investigate vascular wall function of peripheral arteries in SLE patients. Obtained results were then compared to those collected in patients with acute coronary syndromes (less 1-year previous event) and in healthy control subjects (no cardiovascular events or autoimmune disease).

Material and methods: 170 patients (controls: 76, ACS: 74, SLE: 20), enrolled at Careggi Hospital, underwent to physical examination, fasting blood sampling and vascular function assessment of peripheral arteries: in particular, peripheral arterial tonometry (PAT) and augmentation index (Aix) by EndoPAT (Itamar, Caesarea, Israel), intima media thickness and pulse wave velocity at common carotid (c-IMT, c-PWv) and femoral arteries (f-IMT, f-PWv) by ultrasound technology (Esaote MyLab70), were assessed. The pattern of traditional cardiovascular risk factors (CRFs) was evaluated according to current guidelines (ADA, ATP III, ESC, ESH, EAS guidelines).

Results: Study population resulted to be homogenous for age (SLE: 51.6±11.3; ACS: 54.3±8.1; controls: 49.7±14.6, p=0.4), but not for sex: 18/20(90%) of SLE patients were women. Among SLE group, 8 (40%) had a previous vascular event (Venous thromboembolism: 3, ischaemic stroke: 4, acute coronary syndrome: 1). ACS patients presented the worst cardiovascular profile, in comparison to others, because of a higher number of CRFs: ACS patients 3±1.2, SLE patients 1.5±1.6, controls 1.4±1.3.

Therapies were performed according guidelines for secondary prevention. ACS patients showed a marked atherosclerotic damage, because of higher c- and f-IMT values in comparison to others (ACS patients: c-IMT=1.9±0.6 mm, f-IMT=1.7±0.8 mm; SLE patients: c-IMT=1.6±0.8 mm, f-IMT=1.5±0.7 mm; controls: c-IMT=1.3±0.9 mm, f-IMT=1.2±0.4); SLE and ACS patients data did not significantly differ, but both resulted to be significantly higher than data found in controls (p=0.02 and p=0.03, respectively). Vascular compliance was significantly impaired in SLE patients (c-PWv=10.5±2.6 m/s, f-PWv=10.2±1.3 m/s), in comparison to ACS patients (c-PWv=9.2±2.3 m/s, f-PWv=9.4±2.1 m/s; p<0.05) and controls (c-PWv=7.1±2.1 m/s, f-PWv=7.2±1.4 m/s; p=0.001). Aix was higher in SLE (17.2±6.3%), in comparison to ACS patients (15.3±1.4%, p=0.2) and controls (8.1±4.2%; p=0.002). SLE patients showed a significantly lower endothelial function, expressed as natural logarithm of reactive hyperaemia index (LnRHI), (0.56±1.2), compared to controls (0.79±1.7; p=0.03) and these values minimally differed between SLEs and ACS groups (0.50±2.3, p=0.3). LnRHI and PWV values were significantly correlated with number of CRFs. At univariate and multivariate analyses, presence of SLE and a previous vascular event were significantly associated to endothelial dysfunction (p=0.02 and 0.03, respectively) and compliance impairment (p=0.02 and 0.03, respectively).

Conclusions: Our data suggested that SLE patients showed a marked atherosclerotic peripheral vascular involvement, similar to patients at very high CV as ACS, because of impairment of local compliance at common carotid and femoral arteries and a marked endothelial dysfunction. Despite the low cardiovascular risk profile, and the absence of a previous CV event in the 60% of subjects, SLE group showed a pattern of anatomical and functional damage of peripheral vessel as that found in patients at very high CV risk profile. These findings could contribute to the improve the early detection of the systemic and local vascular wall arterial damage in SLE patients and we hope they could contribute to the optimization of primary CV prevention in this high risk subgroup of patients.

Prevalence of antiphospholipid antibodies in women undergoing in vitro fertilization


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Introduction: antiphospholipid antibodies syndrome (APS), which may be primary or secondary to other systemic autoimmune diseases, is defined as vascular thrombosis (arterial, venous or small vessels), pregnancy morbidity and persistently positive anti-phospholipid (aPL) tests. Anti-cardiolipin antibodies (aCL), anti-β2-glycoprotein-I antibodies (anti-β2GP1) and lupus anticoagulant (LA) are all included among aPLs. Obstetrical APS is defined by positive aPLs and a history of one or more unexplained deaths of morphologically normal fetus at or beyond the 10th week of gestation (WG) or one or more consecutive spontaneous abortions before the 10th WG. Also one or more premature birth before 34 WG because of
eclampsia, severe pre-eclampsia, or recognized features of placental insufficiency represent one of the diagnostic criteria. Pregnancy in women with a diagnosis of obstetric APS is at increased risk for HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelet count) and thrombosis that may be part of a catastrophic antiphospholipid syndrome (CAPS). To our knowledge an association between infertility and aPLs has not been described. The aim of our study was to evaluate the prevalence of aPLs in a population of women with no known history of systemic autoimmune diseases undergoing in vitro fertilization.

**Patients and Methods:** We retrospectively evaluated clinical records of 240 patients undergoing in vitro fertilization during a period ranging from May 2012 to May 2013. Among them we selected 18 women with no known systemic autoimmune diseases, with a history of infertility and positive aPL antibodies at diagnostic titers. Each of them was evaluated for genetic, anatomic, hormonal and infective causes of infertility. Moreover antinuclear antibodies (ANA), aCL, anti-β2GP1, LA and extractable nuclear antigens (ENA) profile were assessed.

**Results:** The prevalence of aPLs in our population was 7.5%. All women showed at least twice positive aPLs and reported at least once a preceding miscarriage. aCL IgM and LA were the main antibody populations observed, with a prevalence of 46% and 40% respectively. Anti-β2GP1 IgG were positive in 12.5% of the women. ANA were positive in 4/18 patients (22.2%). All these women were diagnosed as having another associated systemic syndrome: 1 had a polyendocrine autoimmune syndrome (thyro-ophathy, hypoparathyroidism, vitiligo, hypogonadism), 1 fulfilled diagnostic criteria for systemic lupus erythematosus (SLE), 1 also showed positive AMA and was diagnosed as having a primary biliary cirrhosis (PBC) and 1 had an autoimmune thyroiditis. Of the remaining 14 patients, 1 had a polycystic ovary syndrome and 2 showed heterozygous methyltetrahydropholate reductase C677T gene mutation with a slight increase of homocysteine levels (12 mmol/L). No patients had other congenital thrombophilic conditions. All patients were treated with subcutaneous low weight heparin plus daily oral acetylsalicylic acid (ASA 100 mg) during the hormonal stimulation and thereafter up to pregnancy test. In those women who showed positive test treatment with ASA was continued up to 26-32 WG, whereas low weight heparin was continued up to 6 weeks after delivery.

**Conclusions:** Prevalence of aPLs in the general population is 1-5%, whereas persistently high titers of aPLs are reported in about 2% of the cases. We observed positive aPLs in 7.5% of the patients undergoing in vitro fertilization, suggesting that the prevalence of aPLs may be increased in infertile patients. We would further underline that aCL IgM and LA were the main antibody populations found. We therefore recommend the measurement of aPLs antibodies in all women undergoing in vitro fertilization with the aim to recognize patients at high risk of miscarriage.

**Dysphagia in inflammatory myopathy: a review of our experience**

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Polymyositis (PM) and dermatomyositis (DM) represent a heterogeneous group of autoimmune diseases, that mainly affect the skeletal muscle. Although pulmonary and cardiac involvements are the major causes of death, gastroesophageal involvement is common: the involvement of the skeletal muscles in the upper esophagus lead to dysphagia to solids and liquids, cough during the meal, reflux into the pharynx and/or mouth, nasal speech or hoarseness and aspiration pneumonia. We retrospectively reviewed the medical course of our patient affected by myositis with gastroesophageal complications, evaluated by clinical and radiographic investigations: 50 of our 95 patients (37 female and 13 male) presented dysphagia at the diagnosis, with no differences between PM and DM (25 PM and 25 DM). Three of them also had dysphonia and 21 dyspnea. Seventeen patients developed interstitial lung disease (ILD), complicated by ventilatory insufficiency in 12. All patients received steroids, often associated with immunosuppressant (methotrexate, MTX; cyclosporine A, CsA; mycophenolate mofetil, MMF; cyclophosphamide, CTX; and azathioprine, AZA). Finally, 23 patients received high dose of intravenous immunoglobulins (IVlg, 2 g/kg monthly), then shifted to the subcutaneous route in 11 of them, with benefit. We documented an increased mortality in patients with dysphagia compared to other patients with myositis (13 death in dysphagia group of 22 total deaths). In conclusion, in our experience, dysphagia is a common manifestation of myositis. Questions about swallowing should routinely be included in inflammatory myopathy patient examinations in order to appropriately refer patients for further investigation of their swallowing function and avoid the complications associated with dysphagia. Combined therapy of high-dose IVIG and steroids should be considered in severe esophageal manifestations.

**Can a single dose of fluticasone propionate discriminates asthma from COPD? A study on airway responsiveness to adenosine**


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Regular treatment with inhaled corticosteroids (ICS) is known to reduce airway hyperresponsiveness (AHR) to adenosine 5’-monophosphate (AMP) in asthma even after a single dose of fluticasone propionate (FP). We propose a a randomized, double-blind, placebo-controlled, crossover study with 23 mild asthmatic and 24 COPD subjects with documented AHR to both AMP and methacholine to measure AHR to inhaled AMP and methacholine 2 h after either 1000 µg FP or matched placebo. In subjects with asthma, 1000 µg FP in a single dose significantly attenuated the constrictor response to AMP, geometric mean (range) PC20AMP values increasing from a 19.2 (1.3-116.3) to 81.5 (9.6-1600.0) (p < 0.001; post-placebo vs post-FP) mg/ml. Change in the airways response to inhaled AMP after FP was well within test variability in patients with COPD, with PC20AMP values 59.6 (11.3-183.9) and 76.3 (21.0-445.3) (p = 0.022; post-placebo vs post-FP) mg/ml. Additionally, FP failed to significantly attenuate the bronchial response to methacholine in both asthma and COPD subjects. A change in doubling dilution, between placebo and following a single dose of FP, in AMP had a better sensitivity and specificity of 95.8% and 65.2%, compared to methacholine of 79.2% and 43.5% respectively in delineating between COPD and asthma. So we can affirm that a single dose of 1000 µg FP rapidly improves AHR to AMP in asthmatics but not in COPD subjects. This may provide a convenient way by which provocation challenge with inhaled AMP may help in discriminating asthma from COPD.

**Basic bedside ultrasound (BBS-US) at admission in Internal Medicine (IM): effect on patient allocation, diagnostic accuracy and in-hospital outcome**

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Aim: To evaluate the effectiveness of BBS-US on acute patients admitted to an IM Unit according with allocation to areas at different level of care, diagnostic accuracy and in-hospital outcome.

Methods: In May 2013 we started a prospective, case-control randomized study on patients admitted from Emergency Department (ED) to Internal Medicine A (MIA) of Maggiore Hospital in Bologna. At arrival in the MIA Unit, all patients were randomly allocated to the intervention group A (nurse and physician evaluation with a modified early warning score-MEWS- to determine the appropriate level of care plus BBS-US exam performed with a hand-held ultrasound system, Sonosite-FujiFilm M-Turbo) or to the standard evaluation group B (nurse and physician evaluation with MEWS). Variable frequency convex and linear probes were used to rapidly (max 10 mins) scan thorax, abdomen and veins of the lower limbs. The US exam was addressed to identify presence/absence of specific pathological features (pleural effusion, pulmonary edema or consolidation; ascites, intestinal occlusion, gall-bladder hydrops, hydrenephrosis; leg thrombosis according with venous US compression). Data were entered in a dedicated software with an algorithm to determine a BBS-US score along with the MEWS score. The software was linked with the Admission-Dimension-Transfer database of the Maggiore Hospital and BBS-US as well MEWS data were correlated with in-hospital different outcome measures (discharge diagnosis, patient transfer to surgical or intensive care units, length of stay) in the two groups of subjects studied. Student T, Fisher exact or non-parametric tests were used when appropriate for statistical analysis.

Results: We report here the results out of the first 49 cases (group A: n. 25, group B: n. 24) evaluated to date. A concordance with discharge diagnosis was obtained in 19/25 patients in group A vs 11/24 in group B (p<0.04), transfer of patients to surgical or intensive care units within 24 hours of admission was found in 8/25 patients in group A and 2/22 in group (p<0.07, ns) and median length of stay in IM unit was 7.48 days vs 8.39 (two tailed p<0.02).

Conclusions: these preliminary data suggest that BBS-US may add diagnostic power to clinical and MEWS evaluation and can improve the outcome of acute patients admitted from ED to IM Units.

Cardiac autonomic regulation and exercise assessment in breast cancer survivors

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Introduction: In breast cancer survivors cardiometabolic risk may be elevated, owing to unwanted effects of adjuvant therapies or of unhealthy lifestyle following the stress of cancer event or of the mechanisms of cancer genesis itself. Since increased cardiometabolic risk may also be associated to an impairment of the autonomic nervous system, we decided to investigate autonomic regulation in a group of breast cancer survivors. On the other hand, according to recent guidelines, an improvement of the aerobic capacity is particularly useful in breast and colon cancer survivors; therefore we decided to analyse also this characteristic of our patients.

Objective: We sought to assess whether the performance of the autonomic nervous system and exercise capacity in a group of selected women might be altered in comparison with a group of healthy woman.

Methods: We examined 56 patients (age 53±0.96) and 36 controls (age 45.7±1.37); the average time from the surgery was 40 months, without relapses. We evaluated autonomic cardiac regulation with non-invasive method based on autoregressive spectral analysis of RR interval and SAP (systolic arterial pressure) variability. We assessed spontaneous baroreflex gain (α index) and low frequency oscillation in systolic arterial pressure. We also estimated exercise capacity with VO2max (Maximal Oxygen Uptake) deduced from cardiopulmonary bycicle exercise test.

Results: In the control group the average value of α index was 21.1±2.1 ms/mmHg, while in the patients group it was 16.2±1.3 ms/mmHg (p <0.04). Also the VO2max value showed a significant difference between the two groups (p<0.001): 25.2±1.6 ml/min/kg in the control group versus 19.4±0.8 in the patients group.

Conclusions: Our results could suggest an impairment of baroreflex gain and VO2max in breast cancer survivors. Based on the observation that aerobic exercise can improve both of these parameters we are currently testing with a longitudinal protocol whether regular physical activity has a beneficial effect on cardiometabolic risk of breast cancer survivors.

This contribution has been awarded as Best Communication.

Effects of a 12-month supervised exercise program on cardiorespiratory fitness, metabolic profile and oxidative status in type 2 diabetic patients

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Aim: Programs aimed at improving cardiorespiratory fitness are an irreplaceable tool for the prevention and treatment of type 2 diabetes mellitus (T2DM). It has been demonstrated that oxidative stress is involved in the pathogenesis of this disease with a decrease of oxidative stress after training and exercise. The aim of our study was to evaluate the efficacy of physical exercise on functional parameters in patients with T2DM and on oxidative stress markers, and to prove the role of cardiopulmonary exercise testing (CPX) in the management of the diabetic patient.

Methods: We selected 20 male patients with T2DM and metabolic syndrome phenotype, overweight (BMI ≥ 25 kg/m^2), aged 40-70 years, with at least 2 years of disease, without diabetes-specific complications. They were randomly divided into an intervention group, which followed a supervised physical activity in a hospital-based setting, and into a sedentary control group. The exercise protocol included both aerobic and resistance training, performed for 12 months. Patients underwent medical examination, biochemical and oxidative investigation and maximal CPX on cycle ergometer. These investigations were carried out at time zero and after 12 months. Oxidative products of phospholipid 1-palmitoyl-2-arachidonyl-sn-glycero-3-phosphorylcholine (1-palmitoyl-2-[5-oxovaleroyl]-sn-glycero-3-phosphorylcholine, POVPC, and 1-palmitoyl-2-glutaroyl-sn-glycero-3-phosphorylcholine, PGPC) were measured in plasma and in Peripheral Blood Mononuclear Cells (PBMC).

Results: In the investigation group we observed a significant increase (p<0.05) in the following parameters: maximum oxygen consumption (from 20.8 to 23.8 ml/kg/min, +14.4%), anaerobic threshold (+23.4%) and maximum workload (+13.3%). Other cardiovascular parameters such as oxygen pulse, maximum heart rate and heart rate at the anaerobic thresholds did not change significantly. No statistically significant variations were observed in the control group, that after 12 months showed a maximum oxygen consumption, a maximum workload and an anaerobic threshold significantly lower (p<0.05) than the intervention group. Furthermore, in the intervention group we observed a significant improvement (p<0.05) in several metabolic parameters: waist circumference (-1.4%), total cholesterol (-14.6%), LDL-cholesterol (-20.2%), fasting insulinemia (-48.5%), HOMA-IR (-52.5%). The intervention group obtained a significant decrease of plasma levels of
POVPC and PGPC at T12 (-28% p= and –29% respectively) respect to controls who obtained a decrease of only -10%, without achieving the statistical significance in PBMC.

Conclusions: This study confirms the theory that subjects with T2DM and overweight have a low physical conditioning compared to healthy subjects. The CPX allowed to customize the exercise prescription, that was effective in improving cardiorespiratory fitness (with mainly benefits in the muscular system), the metabolic asset and the oxidative status of the subjects.

Current bleeding risk scores have a poor predictive value for patients with venous thromboembolism: a retrospective cohort study

Riva N1, Bellesini M1, Di Minno D2, Fantoni C3, Pomero F3, Mamoli N4, Franchini M5, Lupoli R2, Borretta V3, Brondi B, Focchiatti V5, Fenoglio L1, Bonfanti C5, Agno W6, Dentali F1.

1University of Insubria, Varese. 2Federico II University, Naples. 3Ospedale S. Croce e Carle, Cuneo. 4Ospedale Civile, Livorno. 5Azienda Ospedaliera C. Poma, Mantova

Background: Bleeding is a common and feared complication of oral anticoagulant therapy. Several clinical prediction rules have been proposed in the last two decades. Some of them have been tested only in patients with venous thromboembolism (VTE) only for the first three months after the acute event. The aim of this study was to validate the current bleeding risk scores in patients with VTE.

Methods: We retrospectively included all adult patients with acute VTE referred to the Anticoagulation Clinics of five different Italian hospitals (Varese, Napoli, Cuneo, Livorno and Mantova), between January 2010 and June 2012. Patients have been included from the beginning of the treatment with vitamin K antagonists (VKAs) and followed up until one year from the diagnosis or until the end of the anticoagulant treatment, whichever comes first. All bleeding events have been reviewed centrally and classified as major bleeding (MB), according to the International Society on Thrombosis and Haemostasis criteria, and clinically-relevant non-major bleeding (CRNMB), defined as any overt bleeding requiring a medical intervention and/or treatment discontinuation and not meeting any of the criteria for major bleeding. The predictive validity of the classification schemes was explored using the c-statistics.

Results: 559 patients have been included. Mean age was 60.3 (±17.3) years (range 19-97); 47.2% were male. Pulmonary embolism was present in 267 patients, deep vein thrombosis in 429 patients (405 lower limbs, 24 upper limbs) and superficial vein thrombosis in 10 patients. VTE was unprovoked in 57.7%, while active or previous cancer was present in 17.9%. At baseline, 8.3% of patients had thrombocytopenia and 29.7% had anaemia. During a mean follow-up of 9.2 (±3.5) months, 38 bleeding events occurred (13 MB and 25 CRNMB), for a cumulative incidence of 6.8%. The predictive validity of the risk stratification models was low, especially for HAS-BLED, HEMORR2HAGES, ATRIA and RIETE scores. The most accurate models in predicting overall bleeding were mOBRI and ACCP 2012 (c-statistics 0.60, 95%CI 0.51-0.68, and 0.61, 95%CI 0.53-0.69, respectively). The ACCP score had also a modest predictive value for CRNMB alone (c-statistics 0.61, 95%CI 0.51-0.70). Of the 38 bleeding events, 21 occurred during the first three months of treatment (incidence 3.8%) and 17 during the remaining follow-up. At 3-month follow-up, only mOBRI showed a discrete predictive value (c-statistics 0.64, 95%CI 0.54-0.75). However, only the ACCP score showed a discrete predictive value for bleeding events occurring after the first three months of treatment (c-statistics 0.62, 95%CI 0.51-0.73).

Conclusions: The results of our study suggest that the mOBRI score should be preferred for predicting bleeding events during the acute phase of treatment, while the ACCP score might have better accuracy for long-term anticoagulant treatment. Nonetheless, current bleeding risk scores appeared to be inaccurate for patients with venous thromboembolism. Future studies should aim at the creation of a new clinical prediction rule, in order to better define the risk of bleeding of VTE patients.

Antithrombotic treatment of splanchnic vein thrombosis in the ISTH international registry: results of 6-month follow-up

Riva N1, Ageno W4, Schulman S2, Bang Sm3, Sartori Mr4, Grandone E5, Beyer J6, Barillari G7, Di Minno D2, Ducu R, Malato A10, Santoro R11, Poli D12, Verghaer P13, Martinelli L14, Kamphuisen P15, Alatri A16, Becattini C17, Bucherini E18, Dentali F1, IRSTV Investigators

1Insubria University, Varese. 2Hamilton, Canada. 3Seoul, Korea. 4Padova, 5Groningen, Netherlands, 6Cremona, 7Perugia, 8Faenza

Background: Treatment of splanchnic vein thrombosis (SVT) is a clinical challenge due to heterogeneity of clinical presentations, increased bleeding risk and lack of evidences from clinical trials.

Aims: We carried out an international registry aimed to describe current treatment strategies and factors associated with therapeutic decisions in a large prospective cohort of SVT patients.

Methods: Between May 2008 and January 2012, consecutive SVT patients were enrolled in the registry and information on clinical presentation, risk factors, and therapeutic strategies was collected in an electronic database. Clinical outcomes during the first 6 months of treatment were documented. A two-year follow up is ongoing.

Results: 613 patients from 12 countries were enrolled in the registry, Mean age was 53.1 (SD±14.8) years (range 16-85); 62.6% were males, 74.4% Caucasians. SVT occurred in the portal vein in 470 patients, in the mesenteric vein in 266, in the splenic vein in 139, and in the supra-hepatic veins in 56; 38.8% of patients had multiple vein segments involved. In 29.8% of patients SVT diagnosis was incidental. Most common risk factors included cirrhosis (27.8%), solid cancer (22.3%), intra-abdominal inflammation/infection (11.5%), surgery (8.9%), and megaloproliferative neoplasm (MPN;8.2%); in 27.6% of patients SVT was idiopathic. During the acute phase, 471 (76.8%) patients were treated with anticoagulant drugs: unfractionated heparin (10.4%), low molecular weight heparin or fondaparinux (66.4%), vitamin K antagonists (VKA) (48.5%). Four patients received aspirin, 9 received thrombolysis. A total of 135 patients (22.0%) remained untreated. Of patients with incidentally diagnosed SVT, 61.1% received anticoagulant treatment. Currently, information on treatment and clinical events occurred during the first six months of follow-up is available for 570 patients (96.1% of the population available for follow-up, since 3 centres participated in the baseline phase only). Baseline characteristics of patients with available follow-up were similar to those of patients with unavailable follow-up at the time of this analysis. At 6 months, 79.2% of treated patients were still receiving anticoagulant treatment, while the remaining had stopped treatment earlier. Venous thromboembolic events, including recurrent SVT and other site venous thromboembolism occurred in 26 patients (4.56%, 95% CI 3.06-6.70), 19 in treated patients (4.3%) and 7 in non-treated patients (5.5%). Major bleeding occurred in 18 patients (3.16%, 95% CI 1.94-5.04), 12 while on anticoagulant treatment (2.7%) and 6 in non-treated patients (4.7%). Death occurred in 55 patients (9.65%, 95% CI 7.41-12.45), 40 in treated patients (9.0%) and 15 in non-treated patients (11.8%).

Conclusions: The large majority of patients observed in our prospective cohort received anticoagulant treatment for their SVT, and 79.2% of them continued for at least 6 months. The incidence of both recurrent thrombosis and major bleeding events during this 6-month period is non-negligible.
suggested the need for a careful individual evaluation of the risks and benefits of anticoagulant treatment in SVT patients.

This contribution has been awarded as Best Communication.

**Bleeding symptoms at disease presentation and prediction of ensuing bleeding in inherited FVII deficiency**

Matteo Nicola Dario Di Minno, 1 Alberto Dolce, 2 Giovanni Di Minno1 and Guglielmo Mariani

1Department of Clinical and Experimental Medicine, Federico II University, Naples; 2Istituto Nazionale di Statistica, Palermo; 3Medical School, University of Ferrara, Ferrara, Italy

**Background:** Individuals with inherited factor VII (FVII) deficiency display bleeding phenotypes ranging from mild to severe, with 30% of patients having always been asymptomatic (Non-bleeding).

**Methods:** In 626 FVII-deficient individuals, by analyzing data from the International Factor VII (IF7) Registry and the Seven Treatment Evaluation Registry (STER), we determined whether bleeding type at disease presentation and factor VII coagulant activity (FVIIc) predict ensuing bleeds.

**Results:** At disease presentation/diagnosis, 272 (43.5%) individuals were Non-bleeding, 277 (44.2%) had minor bleeds, and 77 (12.3%) had major bleeds. During a median 9-year Index Period (IP) observation, 87.9% of Non-bleeding individuals at presentation remained asymptomatic, 75.1% of minor-bleeders had new minor bleeds, and 83.1% of major-bleeders experienced new major bleeds. Both at presentation and during the IP, FVIIc levels (%) were significantly higher in Non-bleeding individuals compared to those with minor or major bleeds, and were also significantly higher in individuals with minor compared to major bleeds. After adjusting for clinical and demographic variables (see methods section), the RR for any bleeding (major or minor) during the median 9-year IP was 6.02 (95% CI, 1.45-8.38; P = .005) for individuals with major bleeds and minor bleeds at presentation, respectively. The RRs for major bleeding during the IP were 3.49 (95% CI, 1.45-8.38; P = .005) for those in the lowest FVIIc tertile, and 1.99 (95% CI, 0.79-4.96; P = .140) for those in the intermediate tertile of FVIIc (P = .211 and P = .472, respectively). The RR for major bleeding during the IP was not significant for those with the lowest (< 3%) or the intermediate (3-26%) tertile of FVIIc (P = .211 and P = .472, respectively).

**Conclusions:** In FVII deficiency, the first bleeding symptom is an independent predictor of the risk of subsequent major bleeds.

**Peculiarities of myeloproliferative neoplasms in patients with splanchnic vein thrombosis: a sub-analysis from an international registry**

Riva N1, Colaizzo D2, Rodriguez K1, Rancan E1, Pasca S1, Passamonti S1, Betti S1, Poggio R1, Piana A2, Vidili G2, Vaccarino A1, Nardo B12, Di Niso M11, Elli E11, De Stefano V10, Guardascione M10, Senzolo M10, Schulman S14, Dentali F1, Ageno W1, for IRSVT investigators

1University of Insubria, Varese, 2S. Giovanni Rotondo, 3University of Padova, 4Udine, 5Milano, 6Università Cattolica, Roma, 7Galleria Hospital, Genova, 8Università di Genova, 9Sassari, 10Torino, 11Busto Arsizio, 12Chieti, 13Monza, 14Hamilton, Canada

**Background:** Myeloproliferative neoplasms (MPNs) are the leading systemic cause of splanchic vein thrombosis (SVT). Several studies investigated the relationship between SVT and MPNs, but whether SVT patients with MPNs have different features from other SVT patients is unknown. The aim of this study was to explore the characteristics associated with MPNs in an unselected population of SVT patients.

**Methods:** Between May 2008 and January 2012, consecutive patients with objectively diagnosed SVT were enrolled in a prospective registry, involving 33 centers worldwide. Information on clinical presentation, risk factors, and therapeutic strategies was collected and analysed separately for patients with MPN.

**Results:** Of the 613 patients included in this registry, 51 had a known MPN (8.3%). The prevalence of MPNs was lower in Asian compared with Caucasian patients (1.5% vs 10.6%, p=0.001). Essential thrombocythemia was present in 37.3% of these patients, polycythemia vera in 27.5%, myelofibrosis in 17.6% and the remaining were unclassifiable MPNs. JAK2V617F mutation was found in 73.8% of MPN patients tested (64.7% of patients with essential thrombocythemia, 75% with polycythemia vera, 87.5% with myelofibrosis and 80% with unclassifiable MPNs). There was a trend for higher prevalence of MPNs and JAK2 mutation in patients with Budd-Chiari syndrome compared with patients with porto-spleno-mesenteric veins thrombosis (14.0% vs 7.8%, p=0.173, and 35.7% vs 19.6%, p=0.172, respectively). Patients with MPNs were significantly younger than patients with solid cancer, hepatic cirrhosis or intra-abdominal inflammation/infection (median age was 47.5 years vs 60, 58, and 56, respectively, p <0.05 for each comparisons against MPNs). Female gender was predomin-

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**Table 1. Results of full blood count in SVT patients with MPN, compared with other SVT categories**

<table>
<thead>
<tr>
<th>MPN (n=40)</th>
<th>Solid cancer (n=58)</th>
<th>Cirrhosis (n=98)</th>
<th>Surgery (n=15)</th>
<th>Abdominal diseases (n=46)</th>
<th>Unprovoked (n=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Leukocytes</strong> (<em>10^3/mm^3</em>)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 (5.3-14)</td>
<td>7 (5.5-11.2)</td>
<td>4* (3.6-4.7)</td>
<td>4* (3.7-4.3)</td>
<td>4* (3.7-4.3)</td>
<td>4.5 (4.4-4.9)</td>
</tr>
<tr>
<td><strong>Erythrocytes</strong> (<em>10^3/mm^3</em>)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 (4-5.1)</td>
<td>4* (3.6-4.7)</td>
<td>4* (3.4-4.3)</td>
<td>4* (3.7-4.3)</td>
<td>4* (3.7-4.3)</td>
<td>4.5 (4.4-4.9)</td>
</tr>
<tr>
<td><strong>Haemoglobin</strong> (g/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 (10.2-14.4)</td>
<td>11.9 (10.9-13)</td>
<td>11.9 (10.1-13.3)</td>
<td>11.4 (10.6-13.3)</td>
<td>12.1 (9-14)</td>
<td>13.3 (11-14.6)</td>
</tr>
<tr>
<td><strong>Haematocrit</strong> (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>38.5 (34.3-49.9)</td>
<td>38 (34.3-40.5)</td>
<td>35.5* (30.5-40.3)</td>
<td>36.4 (33.8-40.3)</td>
<td>37.1 (34.2-42)</td>
<td>39.1 (34.5-43)</td>
</tr>
<tr>
<td><strong>Platelets</strong> (<em>10^3/mm^3</em>)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>341 (256-562)</td>
<td>213* (147-289.5)</td>
<td>71* (50-104.5)</td>
<td>260 (202-584)</td>
<td>232* (165-323)</td>
<td>199* (127.5-290.3)</td>
</tr>
</tbody>
</table>

*Data shown as median (interquartile range). * p<0.01. Each comparison is against MPNs.*
Thromboembolic risk and anticoagulant therapy in patients with atrial fibrillation: baseline analysis of Italian data from the European PREFER in AF registry

Inberti D*, Zahzam D*, Prisco D**, Silvestri E**, Di Lecce L***, Romeo F****, De Caterina R*****


Background: The recent guidelines of the European Society of Cardiology (ESC) for the treatment and management of Atrial Fibrillation (AF) recommended the use of antithrombotic therapy for the prevention of thromboembolic events in all patients with AF except those at very low risk. CHA2DS2VASc is the recommended score for the evaluation of thromboembolic risk. However, there are few information regarding the risk assessment with this new score in Italy and the general impact of these recommendations in our country.

Methods: The PREFER in AF Registry (PREvention oF thromboembolic events – European Registry in Atrial Fibrillation) enrolled, from January 2012 to January 2013, unselected patients with AF in the following European countries: Austria, France, Germany, Italy (ITA), Spain, Switzerland and the United Kingdom. The study baseline visit, refers to the evaluation of thromboembolic risk, as assessed by the new CHA2DS2VASc risk score, and the use of oral anticoagulant therapy in Italy.

Results: PREFER in AF Registry enrolled 7243 patients in Europe, including 1888 (26%) in Italy, where 98 sites were involved. In Italy, 71.6% of patients were treated, in the last 12 months prior enrollment, with Vitamin K antagonists (VKA). The use of activated factor X inhibitors (0.1%) and thrombin inhibitors (0.2%) was very little due to the still limited access of these drugs in Italy at the time of data collection. 29.6% of patients were treated with antiplatelet drugs (ASA 24.4%, clopidogrel 4.6%, prasugrel 0.5%, ticagrelor 0.1%). CHADS2 score=0 was observed in 11, 4% of Italian patients, 30% of patients reported a CHADS2 score=1 and 58.5% ≥ 2. CHA2DS2VASc score = 0 was detected in 4.7% of patients; 11.3% of patients had a CHA2DS2VASc score = 1, while 84% of patients had a score ≥ 2. CHA2DS2VASc score = 0 was detected in 4.7% of patients; 11.3% of patients had a CHA2DS2VASc score = 1, while 84% of patients had a score ≥ 2.

Conclusions: The results of our analysis suggest that SVT patients with MPN have peculiar epidemiological features, compared with other SVT patients. The diagnostic approach to patients with SVT should not overlook the evaluation of a possible MPN, particularly in the presence of young age, female gender and high level of blood cells.

Clinical validation of a sub-staging proposal of patients with intermediate HCC (BCLC-B)


Policlinico Sant'Oroso-Malpighi Bologna

Background and aims: The intermediate stage of BCLC staging system for hepatocellular carcinoma (HCC) comprises patients with Child-Pugh A and B, with a single unresectable HCC >5 cm or >3 HCC regardless of size, or 2-3 HCC >3 cm, without extrahepatic spread or vascular invasion and with performance status ECOG 0. Prognosis is likely highly variable within the intermediate stage. For this reason and to tailor treatment allocation, a sub-staging of BCLC-B has been recently proposed by Bolondi et al [1] based on literature and expert opinion as reported in the following table, adding in greater detail tumor burden (IN or OUT of the Up-to-seven criterion) and Child-Pugh score (A5 to B9).

<table>
<thead>
<tr>
<th>BCLC sub-stage</th>
<th>B1</th>
<th>B2</th>
<th>B3</th>
<th>B4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT score</td>
<td>5-6-7</td>
<td>5-6</td>
<td>7</td>
<td>8-9</td>
</tr>
<tr>
<td>Tumor burden UrI</td>
<td>IN</td>
<td>OUT</td>
<td>OUT</td>
<td>ANY</td>
</tr>
<tr>
<td>ECOG-PS</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0-1</td>
</tr>
<tr>
<td>Portal thrombosis</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
</tbody>
</table>

Since no validation of the prognostic capability of this new substaging system exist, this study aims to validate its prognostic capacity in a large italian database (ITALICA).

Methods: 391 patients, included in the already existing ITA.LI.CA. (Italian Liver Cancer) database, update end 2008, affected by HCC in BCLC-B stage, were divided in four subgroups (B1-B4) according to the sub-classification. The survival of each group was assessed and compared using Kaplan-Meyer method and log-rank test, after a follow-up of 60 months. Results: Number of patients in the subgroups was B1=162, B2=136, B3=28, B4=65. Each stage was associated with different median overall survival (p<0.0001 among groups), namely B1=34m, B2=24m, B3=15m, B4=12months. The 5y survival were: B1=39,5%; B2=32,4%; B3=10,7%; B4=13,8% (p < 0.001)

Conclusions: The new substaging proposal of intermediate patients according to up-to-seven criteria and specific Child-Pugh numeric score is able to refine prognostic prediction capacity in the intermediate HCC stage.

Reference:

This contribution has been awarded as Best Communication.

The role of interleukin 17 in Crohn’s disease intestinal fibrosis

Background and Aims: While interleukin (IL)-17A is pro-inflammatory, IL-17E (also known as IL-25) has been shown to exert an anti-inflammatory action in Crohn’s disease (CD). Cytokine-driven excessive extracellular matrix deposition and the imbalance between matrix metalloproteinases (MMPs) and their inhibitors play an important role in the process of fibrogenesis and stricture development in CD. It is known that IL-17A increases MMP-3 production by intestinal myofibroblasts, a cell population centrally involved in CD fibrosis. Conversely, there are no studies investigating the effects of IL-17E on extracellular matrix remodelling in the gut. Here we have studied the role of both IL-17A and IL-17E in CD fibrogenesis.

Methods: Colonic surgical specimens were collected from uninflamed strictured and non-strictured areas of 11 patients with fibrostenosing CD and from normal areas of 12 subjects undergoing colectomy for colon cancer. Muscle layer explants were cultured ex vivo and IL-17A, IL-17E, collagen and transforming growth factor (TGF)-β production was measured. Intestinal mucosa was partly homogenised and partly used for myofibroblast isolation. Expression of IL-17A and IL-17E was determined on mucosal homogenates. Myofibroblasts were cultured in vitro with recombinant human IL-17A or IL-17E, then supernatants were used for detection of soluble collagen and tissue inhibitor of MMPs (TIMPs)-1. Migration of myofibroblasts cultured with recombinant human IL-17A or IL-17E was assessed using the wound-healing scratch assay.

Results: IL-17A was significantly increased in strictured CD areas compared to non-strictured CD and control mucosa. IL-17E was expressed by mucosal homogenates from strictured CD, non-strictured CD and control gut, with no significant differences between all the groups. IL-17A, collagen and TGF-β production was higher in strictured CD, whereas IL-17E did not differ between strictured CD, non-strictured CD and control explants. IL-17A but not IL-17E significantly increased collagen production and TIMP-1 expression, mainly in the supernatants of CD strictured myofibroblasts. Migration of strictured CD, non-strictured CD and control myofibroblasts was significantly inhibited by IL-17A but not IL-17E.

Conclusions: Our results suggest that IL-17A but not IL-17E is profibrotic in CD. Further studies are needed to clarify whether blocking IL-17A may counteract the fibrogenic process in CD.

Immunosuppressant effects of mesenchymal stromal cells on an ex vivo model of coeliac disease


Background: Coeliac disease (CD) is an autoimmune enteropathy caused by the loss of immune tolerance towards dietary gluten which develops in genetically susceptible individuals. A complex inflammatory cascade involving both cellular and molecular components ultimately leads to tissue injury, with T lymphocytes and interferon (IFN)-γ playing a leading role. Mesenchymal stromal cells (MSCs) are multipotent non-haematopoietic stem cells endowed with the ability to affect the action of almost all cells involved in immune response, with the ultimate effect of dampen inflammation and favoring a tolerogenic response. Specifically, MSCs are able to suppress T cell activation and proliferation in a non-Human Leukocyte Antigen (HLA)-restricted manner, mainly through the production of several soluble factors, such as HLA-G molecule, and the activity of the enzyme indoleamine 2,3-dioxygenase (IDO). Considering this functional properties, together with the lack of ethical concerns and the low immunogenicity which allows their transplantation without a preconditioning immune-ablative regimen even in an allogenic setting, MSCs seem to be the best candidate for cellular therapy in immune-mediated conditions.

Aim: We aimed at investigating whether MSCs affect the immunological response to gliadin by using an ex vivo model of CD, in terms of cytokine profile, HLA-G production and IDO activity.

Patients and Methods: An almost pure population of MSCs was obtained...
following standard procedure by using mononuclear cells isolated from bone marrow blood samples harvested from an adult donor, which were plated and expanded ex vivo until passage 3, when the adherent population underwent morphological and immunophenotypical characterization. The mucosal samples were collected perendoscopically by using biopsy forceps, whereas chest CT scan reveals multiple, bilateral basal infiltrates. The heart appears structurally and functionally normal and abdominal ultrasonography

<table>
<thead>
<tr>
<th>Child-Pugh score</th>
<th>B1</th>
<th>B2</th>
<th>B3</th>
<th>B4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up-to-7 criterion</td>
<td>IN</td>
<td>OUT</td>
<td>OUT</td>
<td>ANY</td>
</tr>
<tr>
<td>Performance status</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0-1</td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>1st option</td>
<td>TACE</td>
<td>TACE or TARE</td>
<td>TACE or TARE</td>
<td>Best supportive care</td>
</tr>
<tr>
<td>Alternative</td>
<td>OLT, TACE +ablation</td>
<td>Sorafenib</td>
<td>Research trials, TACE, sorafenib</td>
<td>OLT**</td>
</tr>
</tbody>
</table>

*with severe/refractory ascites and/or jaundice; ** only if Up-to-7 IN and PS 0; OLT, orthotopic liver transplantation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization


Results: Overall survival of whole population was 31.5 months (95% C.I. 25.9-37.0). Number of patients in BCLC subgroups was B1 = 27, B2 = 69, B3 = 15, B4 = 17. Each stage appeared associated with different overall survival (p < 0.05 between groups), namely B1 = 32.0 months (95% C.I. 22.3-41.7), B2 = 21.0 months (95% C.I. 15.5-26.5), B3 = 15.0 months (95% C.I. 10.5-19.5), B4 = 22.0 months (95% C.I. 13.9-30.0). The 3-years survival were: B1 = 44.2%; B2 = 22.9%; B3 = 15.2%; B4 = 35.3% (p<0.05).

Conclusions: The new substaging proposal is able to refine prognosis of intermediate patients with HCC treated with conventional TACE. The prognosis of patients in B3 seems to depend mainly on the tumor while that of patients in B4 on the underlying cirrhosis, so further studies are needed to confirm the actual prognostic gradient of these two substages.

Atrial wall abscess and myocarditis diagnosed at post-mortem examination in a patient with fever of unknown origin

Giuse Cavezza, Francesco Capuano, Francesco Paolo D’Armentio*, Federica Agrusta, Bernardo Mancino, Riccardo Uitti, Emanuele Durante-Mangoni

Medicina Interna, Seconda Università di Napoli, Ospedale Monaldi; *Anatomia Patologica, AOU Federico II, Napoli

A 53 year-old woman was admitted to our hospital because of fever of unknown origin. She had had hypertension for 20 years and had progressed to K/DQII stage V kidney disease on chronic haemodialysis since 4 years. Several forearm arteriovenous fistulas had been prepared over the following two years due to recurrent thrombosis. One year after starting haemodialysis, the patient was diagnosed with chronic hepatitis C and started interferon therapy. This treatment course was completed four months before the current admission and apparently resulted in serum HCV-RNA clearance. Two months before admission, the patient presented with lower limb skin ulcers. Cryoglobulins, p-ANCA, c-ANCA, anti-DNA, ASMA, APA, anti-LKM were all negative. Perilesional skin biopsy showed chronic ischemic dermatitis, although vascular doppler imaging did not reveal arterial stenos is nor venous insufficiency. Microbiological swab culture resulted positive for methicillin-sensitive Staphylococcus aureus (MSSA). Amoxicillin/clavulanic acid was started, but skin lesions didn’t show any clinical improvement. Six weeks later, the patient is admitted to our hospital with shivering fever. Physical examination is still significant for lower limb ulcers. Transthoracic echocardiography fails to show endocardial vegetations, whereas chest CT scan reveals multiple, bilateral basal infiltrates. The heart appears structurally and functionally normal and abdominal ultrasonography

Validation of sub-staging classification of patients with intermediate hepatocellular carcinoma (BCLC-B) treated with conventional transarterial chemoembolization


Hepatology Unit, Catholic University of Sacred Heart, “Gemelli” Hospital, Rome

Background and Aims: The intermediate stage of Barcellona Clinic Liver Cancer (BCLC) staging system for hepatocellular carcinoma (HCC) en closes a prognostically heterogeneous population. A sub-staging of BCLC-B has been recently proposed by Bolondi et al. (table), in order to refine prognosis and to tailor treatment allocation. Aim of this study is to validate prognostic capacity of sub-staging proposal on italian single-center database of HCC patients treated with conventional chemoembolization (TACE).

Methods: 128 patients affected by HCC on BCLC-B stage and treated with conventional TACE in the period 1997-2008 at our institution were divided in four subgroups (B1-B4) according to the proposal sub-classification. Follow up was updated to September 2012 (86% died). The survival of each group was assessed and compared using Kaplan–Meier method and log-rank test.
is negative for fluid collections or parenchymal abscesses. Three blood cultures grew MSSA. On these grounds, a diagnosis of *Staphylococcus aureus* bacteremia associated with multiple septic pulmonary foci is done and high-dose antibiotic therapy with teicoplanin and rifampicin is started. After a transient partial improvement, patient clinical conditions worsen, with recurrence of fever despite the addition of amikacin to therapy, and persistent positivity of subsequent blood cultures for MSSA. Diagnostic studies are repeated, but no changes emerge, except for a new-onset, mild mitral regurgitation upon transthoracic echocardiography. Throughout the in-hospital stay, the patient receives intensive haemodialysis and transfusion of blood and fresh frozen plasma due to the concomitant development of coagulopathy (platelet count 75000/mL, prothrombin time 16 sec., partial thromboplastin time 39 sec., fibrinogen 322 mg/dl, D-dimers 4562 ng/ml). Over the following days, patient conditions further worsen, with signs of sepsis and initial respiratory failure (arterial blood gas: pH 7.52, pCO2 25 mmHg, pO2 64 mmHg, HCO3 20.4 mmol/L, SO2 94%, Lac 1.5) complicated by atrial fibrillation. On the twelfth day of admission, the patient dies due to onset of ventricular tachycardia evolving into asystole and irreversible cardiac arrest.

To explain the persistence of sepsis despite targeted antibiotic therapy, post-mortem examination is performed. The heart appears markedly enlarged, with diffuse epicardial petechiae, clustered on the left atrium; the atrial wall is stretched and edematous and pus mixed with fluid, dark blood leaks off upon incision. Valves appear thickened and fibrocalcific, without perforation or vegetation, and the arteriovenous fistula appears patent, without signs of perivascular tissue infection. Septic foci are found in the brain and lungs. On histological examination of multiple cardiac samples, intraparenchymal leukocyte infiltration associated with loose fibrosis (acute myocarditis) is found. Myocardial abscess/bacterial myocarditis is a rare condition, often diagnosed at autopsy, where it shows a prevalence of 0.2-1.5%. It may complicate infective endocarditis or be associated with other septic foci, especially to the lung, during bacteremia. The most frequent etiologic agent is *Staphylococcus aureus*. This case is unique as the source of bacteremia was a peripheral skin ulcer and myocarditis was not associated with valvular or mural endocarditis. This case raises clinically relevant issues: 1) although microbiologically well documented, infections may not respond even to a theoretically adequate antibiotic therapy; 2) in the presence of persistent staphylococcal bacteriaemia, a cardiac origin should always be suspected; 3) trans-thoracic echocardiography hasn’t got enough diagnostic sensitivity to exclude a cardiac infection.

*This contribution has been awarded as Best Abstract for the Gymnasium Session*

**Monday 28 October 2013**

**Critical role of mTOR pathway in multiple myeloma angiogenesis**

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The Mammalian Target of Rapamycin (mTOR) is a serine/threonine kinase which regulates cell growth, proliferation and metabolism. mTOR assembles with either raptor or rictor to form two distinct complexes: mTORC1 and mTORC2. mTORC1 regulates protein synthesis through ribosomal S6 kinase while mTORC2 regulates cell proliferation and cytoskeleton reorganization through protein kinase B (AKT). Deregulation of mTOR pathway is common in many haematologic malignancies, including multiple myeloma (MM). mTOR and its multi-protein complexes of mTORC1 and mTORC2 are constitutively active in MM cells suggesting a key role in neoplastic transformation and progression. Here, we investigated the angiogenic potential of mTOR signaling in MM development. Our data show upregulation of mTOR mRNA and protein in bone marrow endothelial cells (ECs) from MM patients (MMECs) compared with ECs of monoclonal gammopathies of undetermined significance (MGECs). Interestingly, we demonstrated that mTOR in mTORC2 is constitutively activated in MMECs using phosphoserine 473 AKT as readout for activation of mTORC2. While mTOR activation did not show any correlation with ribosomal S6 kinase, suggesting a marginal role of mTORC1 in MM angiogenesis. In order to understand the role of mTOR in MM angiogenesis, we employed the impact of RNA interference of Rictor, the specific subunit of mTORC2, on MMECs functions. We found that downregulation of Rictor decreased MMECs proliferation and moreover altered cytoskeleton organization. These results identify mTOR within the mTORC2 as an important pathway for MM angiogenesis. Modulation of this pathway may serve as a valid antiangiogenic therapeutic intervention in MM.

**The novel estrogen receptor GPR30, enhances cholesterol cholelithogenesis by inhibiting cholesterol 7 alpha-hydroxylase (CYP7A1) and the classic pathway of bile acid synthesis**

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A novel estrogen receptor, the G protein-coupled receptor 30 (GPR30), is mapped on mouse chromosome 5 and co-localized with *Lih18*, a new gallstone gene. Our molecular and genetic data support the candidacy of GPR30 for *Lih18*. Moreover, the lithogenic effect of GPR30 is independent from that of the classic estrogen receptor α (ERα). However, identifying the lithogenic mechanism of GPR30 remains a significant challenge because it is unclear how estrogen, through GPR30, increases susceptibility to gallstone formation.

**Methods:** We studied the lithogenic actions of GPR30 on the formation of cholesterol gallstones, in gonadectomized GPR30 (+/+) mice treated with the GPR30-selective agonist G-1 (200 ng/day) or the GPR30-specific antagonist G15 (900 ng/day), and fed a lithogenic diet for 8 weeks. To elucidate the metabolic abnormalities underlying the major source of the excess cholesterol molecules leading to cholesterol-supersaturated bile as induced by GPR30, we examined whether GPR30 regulates CYP7A1 and the classic pathway of bile acid synthesis through the epidural growth factor receptor (EGFR) pathway.

**Results:** Inhibition of GPR30 by G15 induced cholesterol-supersaturated bile by relative excess cholesterol in relation to low amounts of bile acids, and promoted gallstone formation. In contrast, activation of GPR30 by G-1 reduced gallstone prevalence. The effect was mediated by GPR30-dependent increases in biliary bile acid concentrations, which restored cholesterol solubility in bile. After GPR30 activation by G-1, there was a significant dose-dependent increase in mRNA and protein levels of EGFR and liver receptor homolog-1 (LRH-1), coupled with elevated CYP7A1 mRNA and protein levels in mice. In contrast, suppressing GPR30 by G15 led to a significant decrease in mRNA and protein levels of EGFR and LRH-1, coupled with reduced mRNA and protein levels of CYP7A1 in a dose-dependent manner. *In vitro* studies in hepatocytes found that after inhibiting EGFR by AG1478, a highly potent EGFR kinase inhibitor, mRNA and protein levels of CYP7A1 were unchanged even though GPR30 was activated by its agonist G-1 or repressed by its antagonist G15. Thus, GPR30 could regulate *Cyp7a1* expression through the EGFR cascade.
**Conclusions:** In the lithogenic state, reduced hepatic synthesis of bile acids from the classic pathway, because of GPR30 repression of CYP7A1, significantly inhibits the conversion of cholesterol to bile acids. Thus, the balance of biliary lipids for keeping cholesterol solubilized becomes perturbed by a significant increase in the ratio of cholesterol to bile acids in bile, contributing to the formation of cholesterol-supersaturated bile. Thus, stimulating the GPR30 activity with a liver-specific, GPR30-selective agonist, may provide an efficacious novel strategy for prevention of gallstones.

**Circulating Dickkopf-1 in diabetes mellitus: association with platelet activation. Effects of improved metabolic control and low-dose aspirin**


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**Background:** Dickkopf-1 (DKK-1) is a major regulator of the Wnt signaling pathway, involved in inflammation, atherogenesis, and more recently, in the regulation of glucose metabolism. Since platelets are major contributors to circulating levels of DKK-1 in a few clinical settings, our aims were to characterize the platelet contribution to DKK-1 in T2DM and evaluate associations of DKK-1 with glucose metabolism, platelet activation and endothelial dysfunction.

**Methods and Results:** A cross-sectional comparison of DKK-1, soluble CD40L (sCD40L) reflecting platelet-mediated inflammation, asymmetric dimethylarginine (ADMA), as a marker of endothelial dysfunction, urinary 11-dehydro-TxB2, in vivo marker of platelet activation, was performed among 180 diabetic patients (90 of them on aspirin 100 mg/day) and 30 healthy controls. Plasma DKK-1 levels were markedly higher in patients with T2DM than in age- and gender-matched healthy patients (p<0.0001). DKK-1 levels were significantly lower in diabetic patients on ASA treatment when compared with diabetic patients not on ASA (p=0.01) (figure); in the latter, DKK-1 was significantly correlated with 11-dehydro-TxB2 and ADMA (Rho=0.26; p=0.01, and Rho=0.33; p=0.006, respectively), but not with glycemic control or diabetes duration. In a subgroup of patients treated with acarbose for 20 weeks, improvement of metabolic control was associated with significant reductions in DKK-1 (p=0.005).

**Conclusions:** Circulating DKK-1 is increased in T2DM and is associated with endothelial dysfunction and platelet activation. Plasma DKK-1 levels are reduced by ameliorating glycemic control/insulin sensitivity and low-dose aspirin treatment.

This contribution has been awarded as Best Communication.

**Epicardial fat thickness (EAT) in non alcoholic fatty liver disease: a candidate marker of steatosis and vascular damage**

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**Background:** During aging there is a progressive reduction in vitamin D levels and an increase in inflammatory markers (1). A causal relationship has been hypothesized but never tested in a population study. Vitamin D could control inflammation through regulation of the nuclear proinflammatory transcription factor kappa B (NF-Kb). 25-OH D-deficient subjects have an increased expression of NF-kB and of the inflammatory cytokine Interleukin-6 (IL-6) (2). Therefore, we hypothesize an inverse and independent relationship between vitamin D levels and inflammatory markers.

**Methods:** The study population consisted of 1002 male and female (382 men and 497 women) 65 yrs or older residents in the area of Chianti, Tuscany, Italy. 223 participants with C-reactive protein (CRP) higher than 1 mg/dl, on chronic treatment on corticosteroids and nonsteroidal anti-inflammatory drugs were excluded, leaving the final sample of 879 subjects with complete data on serum concentrations of vitamin D, CRP, IL-6, and soluble interleukin-6 receptor (sIL6r). Serum 25(OH)D was measured by RIA (RIA kit; DiaSorin, Stillwater, MN). Intra- and interassay coefficients
of variation were 8.1 and 10.2%, respectively. Serum IL-6, sIL-6r, were measured in duplicate by high-sensitivity ELISAs (BioSource International, Camarillo, CA). The lower detectable limit was 0.1 pg/ml for IL-6, 8.00 pg/ml for sIL-6r. The interassay coefficient of variation was 7% for all cytokines. CRP was measured with a high-sensitivity ELISA, a competitive immunoassay that uses purified protein and polyclonal anti-CRP antibodies. The interassay coefficient of variation was 5%. The minimum detectable concentration was 0.03 mg/liter. Statistical analyses were performed using general linear models adjusted for age, sex, BMI, physical activity, chronic diseases, and parathyroid hormone (PTH). Vitamin D and inflammatory cytokines were log transformed because of skewed distribution.

**Results:** The mean age at baseline was 75.1±17.16 years. In the analysis adjusted for age, sex and PTH, vitamin D levels were significantly and inversely associated with IL-6 (β±SE -0.10±0.02, P=0.0001) and CRP (β±SE -0.04±0.02, P=0.041) and positively associated with sIL6r (β±SE 0.10±0.03, P=0.006). In the multivariate analysis adjusted for age, sex, BMI, caloric and alcohol intake, smoking, physical activity, cognitive function, depressive status, Parkinson disease, peripheral artery disease, COPD, chronic heart failure, cancer, log (Vit D) was negatively associated with log (IL-6) (β±SE -0.09±0.03, p<0.0001) and positively associated with log (sIL6r) (β±SE -0.10±0.03, p<0.0001).

**Conclusion:** Vitamin D levels were independently and inversely associated with IL-6 and positively associated with sIL6r in older population suggesting a potential anti-inflammatory role for Vit D. Longitudinal studies are needed to better delineate the direction of this association.

**Reference:**

Cardiac autonomic modulation in patients with an ST-Elevation Myocardial Infarction after revascularization therapy

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**Background:** Alterations of autonomic nervous system (ANS) have been widely described in the early hours after an acute myocardial infarction (AMI) and it has been shown that the site of infarction is associated with different autonomic deregulation. Indeed, it is well known that the hyperacute phase of AMI is characterized by sympathetic excitation, mainly observed in anterior myocardial infarction. However, even in inferior myocardial infarction, which is supposed to be associated with a vagal overactivity, an evident parasympathetic predominance has not been demonstrated. Conflicting data are available on the early cardiac autonomic modifications after primary percutaneous coronary intervention (pPCI).

**Aim:** To evaluate ANS modification in patients with ST-elevation myocardial infarction (STEMI) treated with pPCI, either within 24 hours after revascularization (T0) and at clinical stability (T1, 6±2 days), taking into account the site of infarction.

**Methods:** We enrolled 33 consecutive patients (8 females, 25 males, mean age 61±12.1 yrs) admitted to L. Sacco Hospital Emergency Department with a diagnosis of STEMI and treated with pPCI, out of them, 15 had an anterior wall infarction and 18 had an inferior wall infarction. Exclusion criteria were: 1) atrial fibrillation or sick sinus syndrome; 2) frequent atrial or ventricular premature complexes; 3) presence of pacemaker. All these conditions were considered as exclusion criteria because incompatible with the analysis of heart rate variability (HRV). Ethical Committee of our hospital has approved the study and written informed consent was obtained from each patient. ECG and respiration were recorded in supine position for 10 minutes at T0 and at T1 in the two groups of patients (inferior and anterior infarction patients) using a Bluetooth system with ECG monitor and a thoracic piezoelectric belt. ANS was evaluated by symbolic analysis of HRV, a non linear tool able to detect nonreciprocal changes of sympathetic and parasympathetic modulations. Symbolic analysis can identify different patterns: 0V% (markers of sympathetic modulation), 1V% (whose biologic meaning remains unclear), 2LV% and 2ULV% (markers of vagal modulation). From each ECG trace, samples of 200-300 beats were selected for symbolic analyses.

**Results:** Symbolic analysis showed a different pattern of autonomic modulation in the two groups within 24 hours from revascularization. Indeed, 0V pattern, index of sympathetic modulation, was significantly higher at T0 in patients with an inferior STEMI compared to patients with an anterior STEMI (32.7±15.6, 95% IC 24.9-40.5, vs 19.8±12.6, 95% IC 13.5-26.1, p=0.018). Moreover, at T0, anterior STEMI patients had a higher 2LV pattern, index of vagal modulation, compared to inferior STEMI patients (9.6±5.6, 95% IC 2.6-16.6, vs 4.9±3.0, 95% IC 3.4-6.4, p=0.006). This difference was not evident anymore at T1 for 0V (24.5±10.0 in anterior STEMI vs 24.8±12.6 in inferior STEMI, p=NS) and for 2LV (6.9±6.2 in anterior STEMI vs 6.4±4.2 in inferior STEMI, p=NS).

**Conclusion:** In conclusion, unexpectedly we found that patients with an inferior STEMI seemed to be characterized by a sympathetic overactivity within 24 hours after revascularization, while in anterior STEMI patients a vagal modulation seemed to be predominant. In the light of these preliminary results, we could hypothesize that inferior STEMI might be associated with an increased risk of cardiac events immediately after pPCI. Ad hoc clinical studies to verify this hypothesis should be performed.

This contribution has been awarded as Best Communication.

Digoxin or not digoxin? That is the question

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**Objective:** Digoxin is an antiarrhythmic still widely used to control heart rate in patient with atrial fibrillation alone or associated to other antiarrhythmic drugs. Some studies reported an increased rate of all-cause and cardiovascular mortality in patients taking digoxin.

**Methods:** We prospectively analyzed 896 consecutive anticoagulated patients with non valvular atrial fibrillation (NVAF). Patients with prosthetic valves, active cancer and chronic inflammatory diseases were excluded from the study. All-cause and cardiovascular mortality were considered as main outcomes according to the use of digoxin.

**Results:** Patients were followed-up for a median time of 29 months (2267 patients/year). Mean age was 73.5 years and 55.2% were male. At baseline patients on digoxin were more frequently female (p=0.025), had an history of heart failure (p<0.001), and a lower assumption of verapamil (p=0.001) and amiodarone (p<0.001) compared to those not receiving digoxin. Moreover digoxin-treated patients had a significantly higher CHA2DS2VASc score (3.7 vs 3.0 p<0.001), age (75.3 vs 72.9 p<0.001) and lower ejection fraction (51.7 vs 53.5 p=0.023). Ninety (10.6%) deaths...
for all cause occurred during the observation: 62 were cardiovascular deaths including 11 myocardial infarctions, 9 strokes and 42 cardiovascular deaths. Kaplan-Meier curves showed that digoxin was significantly associated to all-cause mortality (log-rank test: p=0.006) and to cardiovascular death (log-rank test: p=0.008). In a Cox proportional hazard model, history of myocardial infarction/cardiac revascularization (HR 2.15 CI 95% 1.28-3.61 p=0.004) and use of digoxin (HR 1.84 CI 95% 1.09-3.11 p=0.022) independently predicted cardiovascular deaths after adjusting for hypertension, diabetes, heart failure, history of myocardial infarction, history of stroke/TIA, gender, use of beta blockers, ACE inhibitors/sartans, verapamil, amiodarone and calcium channel antagonists.

Figure. Kaplan-Meier estimates of time to cardiovascular death (black line=patients without digoxin; grey line=patients on digoxin)

Conclusion: In NVAF anticoagulated patients, use of digoxin was associated to an increased all-cause and cardiovascular mortality. The role of digoxin in AF patients should be reviewed on the basis of the growing evidences of its potential harmful action.

Echocardiographic features and relationships with transcranial Doppler in patients with patent foramen ovale and previous cerebral ischemic events

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Purpose: Patients with patent foramen ovale (PFO) present possible volume overload of cardiac chambers, this finding being possibly relevant in those developing cerebral ischemic events. However, the cardiac features have never been assessed in this clinical setting. Aim of the present study was to investigate echocardiographic characteristics and their relations with transcranial Doppler in PFO patients with previous cerebral ischemic events.

Methods: After the exclusion of patients with previous myocardial infarction, overt heart failure, valve heart disease and atrial fibrillation, the final study population included 68 consecutive outpatients with a recent cryptogenic, juvenile cerebral ischemic event referring for PFO search from January 2011 to May 2013 at our Department. All the patients underwent a complete echo Doppler examination including the quantitative analysis of cardiac chambers and the assessment of systolic and diastolic function of both the ventricles. In addition, bubble test of saline solution injected into a vein of an arm (in order to visualize movement of bubbles from right to left atrium) and transcranial Doppler of middle cerebral artery (first segment M1, trans-temporal view) with additional bubble injection (in order to detect right to left shunting) were performed. Both transthoracic and transcranial bubble tests were performed at rest and during/after Valsalva manoeuvre. Presence and number of high intensity transient signals (HITS) per cardiac cycle were determined. Patients were divided in 2 groups: 33 without PFO and 35 with PFO.

Results: The two groups were comparable for sex, age, body mass index, systolic and diastolic blood pressure and heart rate. Patients with positive “bubble” transthoracic echocardiography had greater left ventricular ejection fraction (LVEF), aortic root diameter and left atrial volume index (all p<0.01) as well as larger right atrial diameter (3.8±0.6 cm versus 3.3±0.5 cm, p<0.01), right atrial diameter index (p<0.02) and pulmonary arterial pressure (p<0.01) than patients without PFO. In patients diagnosed for PFO the number of HITS per cardiac cycle at transcranial Doppler of middle cerebral artery was positively related with right atrial diameter (r=0.34, p<0.01), right atrial diameter index (r=0.55, p<0.001) and LVEF (r=0.35, p<0.01).

Conclusions: Our findings demonstrate that in a group of patients with previous cryptogenic juvenile cerebral ischemic events PFO detection is combined with echocardiographic changes of both left and right cardiac chambers. These changes include increase of left atrial volume, aortic root and right atrial size as well as an increase of LVEF and higher pulmonary arterial pressure. In addition, the number of high intensity transient signals per cardiac cycle in middle cerebral artery at transcranial Doppler appears to be positively related with possible right atrial overload and also with the degree of left ventricular systolic performance. These findings can contribute to explain possible discrepancies of bubble test between transthoracic and transcranial echo Doppler examinations in this clinical setting.

Myocardial function and HRV in obese children/adolescents: the role played by insulin resistance


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Background: It has been estimated that the prevalence of obesity is growing among children/adolescents in western and developing countries. A number of evidences reported subtle cardiovascular abnormalities in obese children, responsible for a higher mortality later in life. Moreover, a disturbed autonomic control of heart rate has previously been described in such subjects.

Aims: The present study aimed to evaluate in obese children/adolescents myocardial function and morphology, cardiac autonomic control, and any relationship between some of these parameters and the degree of insulin resistance.

Methods: Thirty obese and 30 matched normal-weight children/adolescents underwent a complete clinical examination, blood sampling for laboratory analyses, standard and tissue Doppler imaging (TDI) echocardiographic evaluation, and R-R interval variability (HRV) analysis at rest and during a standardized (70°) head-up tilt. Homeostasis model assessment of insulin resistance (HOMA-IR) was used in order to separate insulin resistant (IR+) from non insulin resistant (IR-) obese children.

Results: Obese children showed: a) significant (P < 0.05, at least) increase in left ventricular diameters and mass, and a decrease in the E'/A' ratio; b) an enlargement of right ventricle, together with a reduced S' and E'/A' ratio;
c) high values at rest of LFRR, an index of cardiac sympathetic modulation, and low resting values of HFRR, an index of parasympathetic modulation; and, d) a decreased HFRR response to the tilt stimulus. By comparing the two subgroups of obese children/adolescents, it resulted that IR+ individuals showed greater values of the right ventricular E'/A' ratio and of resting LFRR, lower values of HFRR at rest, and a scantly tilt-induced change in both LFRR and HFRR. In IR+ subjects, HOMA-IR values were significantly related to resting values of both LFRR and HFRR, right ventricle diameter, and the E'/A' ratio of the right ventricle. Moreover, the E'/A' ratio of the right ventricle correlated with resting values of LFRR in such subgroup of subjects.

**Discussion/Conclusions:** Obesity likely affects myocardial function and autonomic control of heart rate by means of metabolic pathways not clearly defined to date, especially in the setting of poorly insulin sensitive children/adolescents. We suggest that subclinical diastolic dysfunction of the right ventricle and cardiac autonomic imbalance are closely related in insulin resistant obese children/adolescents, and are related to the degree of insulin resistance in such individuals.

**Gh deficiency and Chronic Heart Failure**


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**Introduction:** Several studies have reported abnormalities of the GH/IGF-1 axis in Chronic Heart Failure (CHF). No study have so far systematically investigated the pituitary function in large population of CHF patients, nor have addressed their impact on clinical status, exercise performance, LV architecture.

**Populations and methods:** We studied 130 consecutive patients with CHF, NYHA class I to III, who underwent a basal hormonal evaluation of IGF-1 and IGF binding protein-3 (IGFBP-3) and a GH stimulation test. All patients underwent extensive cardiovascular study with complete echocardiography, cardiopulmonary exercise testing, NT-proBNP levels measurement. GH deficiency (GHD) and severity classes of GH deficit were diagnosed according to GH peak after specific stimulus with normative value for GHD set at 9 μg/L. In this study GHRH plus arginine stimulation was employed and peak GH cut-off values for increasing severity of GHD were 3, 9, and 16.5 μg/L.

**Results:** 51% of patients had some degree of GH secretion impairment (very severe=13%, severe=19%, partial=18%, no GHD=49%). GHD population showed worse peak VO2 (p=0.001) and worse ventilator efficiency (p=0.002 for VE/VCO2) associated to higher LV volumes (p=0.008; p=0.015 for end-diastolic LV and end-systolic LV, respectively). LV end-diastolic volume, LV end-systolic volume and peak VO2 uptake were also consistently related to GHD severity.

**Conclusion:** Impairment in GH secretion is highly prevalent in CHF. Higher severity of GHD in CHF is associated with worse clinical status, cardiopulmonary performance, and LV remodeling.

**Obstructive sleep apnea affects atrial remodelling in never treated hypertensives**

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**Introduction:** Obstructive sleep apnea (OSA) is a common but underdiagnosed disease that increases cardiovascular morbidity and mortality. Potential cardiovascular complications of OSA include systemic and pulmonary hypertension, cardiac arrhythmias, coronary artery disease and other clinical conditions. At this time, however, there are no data about the possible association between OSA and left atrium dimensions.

**Aim:** To evaluate in hypertensive patients the effect of OSA on left atrial enlargement.

**Methods:** We enrolled 112 never treated hypertensives. All patients underwent to clinical examination, measurement of lipid profile, fasting glucose and insulin, HOMA index and creatinine. Estimated glomerular filtration rate (eGFR) was determined by CKD-EPI equation. M and B-mode echocardiogram was performed to calculate interventricular septum (IVS) and posterior wall (PW) thickness, left ventricular end diastolic diameter (EDLVD), stroke volume (SV), left atrial volume indexed for height3 (ILAV) and left ventricular mass (LVM) indexed for height3 (LVMI). Pulsed Doppler was used to evaluate ventricular emptying velocity (E and A, m/sec) and diastolic function expressed as E/A ratio. In addition, overnight polysomnography was performed to evaluate apnea–hypopnea index (AHI), defined as the average number of apneas and hypopneas per sleep hour. According to AHI, the patients were divided into three groups: group I(AHI<15), group II (15≤AHI<30), group III (AHI≥30). All data were processed with ANOVA and χ2 when appropriated. The independent effect of AHI on ILAV was evaluated by multiple regression analysis. Significant difference were assumed to be at P<0.05.

**Results:** Among three groups, significant differences (P<0.05) were observed for BMI, HOMA, eGFR, SV, ILAV, E/A and E. In particular, we observed a difference in ILAV (20.3 gr/h2 in group I, 19.9 gr/h2 in group II and 26.3 gr/h2 in group III, respectively; P<0.0001), E (0.76, 0.64 and 0.69 m/sec in I, II, and III group, respectively; P<0.0001) E/A ratio (1.0, 0.82 and 0.72 in I, II and III group, respectively; P<0.0001). In the multivariate analysis the strongest predictor of ILAV was AHI, that explained the 20.1% of its variation (P<0.0001).

**Conclusions:** Our data showed that in never treated hypertensive patients affected by OSA, AHI is an independent and strong predictor of atrial volume enlargement.

**Prevalence of carotid artery stenosis in patients admitted to cardiac intensive care unit. Who needs carotid ultrasound screening?**

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**Introduction:** Several studies investigated the relationship between carotid and coronary artery disease (CAD). Moreover carotid disease is proved to predict stroke occurrence during coronary artery bypass grafting (CABG) together to age >70 years old, smoking habit, peripheral artery disease (PAD), previous transient ischemic attack (TIA) or stroke and neck bruit. The aim of our study was to evaluate the prevalence of carotid artery disease (CVD) in patients admitted to the Cardiovascular Intensive Care Unity (CICU) of the University of Florence. The relationship between carotid artery stenosis and admission diagnosis or cardiovascular (CV) risk factor occurrence or the severity of coronary lesions was investigated in order to establish a predictive model for the selection of patients to submit to carotid ultrasound screening.

**Methods:** We prospectively studied patients admitted to our CICU from January to December 2012 with diagnosis of stable angina, acute coronary syndrome, myocardial infarction or heart failure. Eco Color Doppler of carotid arteries was performed by using a Philips Sonos 5005 equipped by a 7.5 MHz linear probe. A >70% carotid stenosis was diagnosed when systolic peak velocity >1.5 m/s, end-diastolic velocity >0.5 m/s and peak systolic internal carotid/common carotid ratio ≥2.2 were measured. A systolic peak velocity >2.5 m/s, end-diastolic velocity >1 m/s and peak systolic
ternal carotid/common carotid ratio >3 identified a >70% carotid stenosis. All patients benefited from a standardized protocol including data collection on cardiovascular risk factors, complete blood count and blood chemistry and past history. Moreover some patients were submitted to coronarography.

Results: We screened 367 patients consecutively admitted to CICU. Twenty-nine patients were excluded from the study because of a positive history for neurological disorders (stroke or TIA). Among the remaining 338 patients, 91 had no carotid lesions and 262 (77.5%) presented at least a carotid plaque. Fifteen (4.4%) had >70% stenosis lesion. The prevalence of CV risk factors were compared between patients with and without carotid lesions; age (p<0.001), hypertension (p<0.001), diabetes (p<0.001), PAD (p=0.006), chronic obstructive pulmonary disease (p=0.008) and serum creatinine at admission (p=0.02) significantly predicted a >70% carotid stenosis occurrence. Among patients with >70% stenosis, 10 were submitted to coronarography: 6 (60%) had a three vessels disease, 2 (20%) a two vessels disease, 2 (20%) a single vessel disease, no patients had no lesions. The extent of coronary involvement is related to the presence of >70% carotid stenosis (OR: 2.04; CI 95%: 0.91-4.68; p=0.084). There is no relation between the presence of >70% stenosis lesion and admission diagnosis. Univariate analysis showed that the presence of >70% stenosis lesion was related to hypertension (p=0.058), chronic kidney disease (CKD) (p=0.020) and PAD (p<0.001). Multivariate analysis further identified PAD as a significant predictor for >70% stenosis (OR:10.2; CI 95%: 3.16-33.0; P>0.001) when corrected for hypertension (OR: 2.62; CI 95%: 0.55-12.5; p=0.226) and CKD (OR: 1.80; CI 95%: 0.48-0.74; p=0.383).

Conclusion: The severity of carotid lesions was related to the extent of coronary involvement, but not to diagnosis at admission. CKD, hypertension and PAD select a subgroup of patients at high risk for >70% stenosis carotid lesion.

Silent myocardial infarction complicates the acute phase of pneumonia: relationship with platelet thromboxane B2 production


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Background: Myocardial infarction may complicate the clinical course of pneumonia. The role of platelets is still unclear.

Methods: Two-hundred-fifty consecutive patients hospitalized for community-acquired pneumonia were included and followed-up until discharge. Upon admission serum thromboxane (TX) B2, a stable metabolite of platelet TxA2, was measured; serum high-sensitivity Troponin T and ECG were measured every 12 and 24 hours, respectively. Myocardial infarction during the hospitalization phase was the primary end-point of the study.

Results: Thirty-five patients (14%) experienced myocardial infarction, which occurred within 48 hours from pneumonia presentation. Myocardial infarction was not associated with chest pain in all patients except one. Logistic regression analysis showed pneumonia severity index (p<0.001), history of coronary heart disease (p=0.006) and serum TxB2 (p=0.002) as independent predictors of myocardial infarction. Patients in the highest quartile of TxB2 (≥200ng/ml) had a higher relative risk of myocardial infarction compared to patients in the other quartiles (OR 4.595; 95% CI: 1.958-10.785; p<0.001). Among 110 patients (44%) taking aspirin (100 mg/day), myocardial infarction rate was not significantly different compared to aspirin-untreated ones (18 vs. 11%; p=0.132). Aspirin-treated patients with myocardial infarction had higher serum TxB2 compared to those without myocardial infarction (p<0.001).

Conclusions: Silent myocardial infarction is a frequent and early complication of pneumonia; daily monitoring of serum troponins and ECG is, therefore, essential to detect it. Platelet TxB2 over-production increases the risk of myocardial infarction; 100 mg/day aspirin seems to be insufficient to blunt it.

NT-proBNP linking renal function decline and cardiovascular mortality: the population-based Casale Monferrato study


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Background: Diabetes is a leading cause of chronic kidney disease (CKD) in the Western countries and patients with CKD are exposed to increased morbidity and mortality as a result of cardiovascular (CV) events. Nevertheless the underlying pathophysiology remains poorly understood. Endothelial dysfunction, cardiac remodelling, and atherosclerosis occurs in early CKD stages and are believed to contribute to the enhanced CV risk of patients with CKD. At the same time, NT-proBNP, released from cardiomyocytes in response to ventricular wall stretch/tension, is a sensitive marker of both left ventricular hypertrophy and volume expansion. We have recently reported that NT-proBNP is also a strong independent predictor of short-term CV mortality risk in type 2 diabetic patients, including those without preexisting CVD. Although NT-proBNP values are enhanced in subjects with CKD, prospective data on the relationship between eGFR, albuminuria, and NT-proBNP on CV mortality over the whole range of renal function are limited and no data are available in type 2 diabetic patients. In the present study, we have prospectively assessed the role of NT-proBNP, eGFR, and albuminuria on 5-years both overall and CV mortality in a population-based cohort of people with type 2 diabetes.

Materials and methods: The study-base were 3,249 type 2 diabetic patients, residents in the year 2000 in the town of Casale Monferrato, They were identified by using independent sources (diabetes clinics; administrative data sources), using the capture-recapture method, with a high degree of estimated ascertainment (95%). All measurements were centralized. Six years after the baseline examinations, mortality data up to December 31st, 2006 were obtained from the demographical files of towns of residence and both hospital and autopsy records. Cox proportional hazards modelling was used to estimate the hazard ratios (HR) and 95% confidence intervals (95% CI) of cardiovascular and all-cause mortality by eGFR values, independently of conventional and new risk factors.

Results: 1,730 (54.2%) patients showed no clinical evidence of heart failure and had samples available for NT-proBNP and eGFR measurement/calculation. Overall CKD (eGFR <60 ml/min/1.73 m2) prevalence was 13.7%. During the 5-years follow-up period (median 5.5 years, range 0.1-7.3), 368 people died out of 86714 person-years. With respect to people with normal renal function, those with CKD had a 1.86-fold greater CV mortality risk, independently of age, sex, and diabetes duration (model 1). Further adjustment for AER only slightly modified HRs (model 2). A statistically significant increased risk of CV mortality was also observed in people with eGFR between 60-89 ml/min/1.73m2 compared to those with eGFR levels ≥ 90 ml/min/1.73m2. After inclusion of logNT-proBNB into the model (model 3), HRs of eGFR were no longer significant, whereas the significant association between micro-macroalbuminuria and CV mortality was still observed.

Conclusions: our prospective population-based study indicates that NT-proBNP is a significant predictor of CV mortality independently of eGFR. NT-proBNP also mediates the predictive effect of eGFR on CV mortality. This implies that an increased NT-pro-BNP in a subject with a lower eGFR should be taken seriously as a prognostic marker for a worse CV outcome.
and not be discarded as merely the result of decreased renal clearance. The underlying pathophysiology remains unclear; however, NT-pro-BNP is likely to directly reflect the subclinical cardiac damage from silent myocardial ischemia, left ventricular hypertrophy, or increased apoptosis that impacts on CV mortality and is often associated with CKD.

**Osteoporosis metabolic syndrome and inflammaging**

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Immunosenescence is characterized by a remarkable decline of adaptive immunity which is accomplished by a simultaneous increase of the activation of innate immunity. This phenomenon tends to increase with age, configuring that particular inflammation state of the elderly, defined inflammaging. The underlying immunological dysfunction is essentially characterized by increase of senescent lymphocytes and macrophage activation, resulting in overproduction of proinflammatory cytokines such as TNF, IL1, IL6 and IL17. This rearrangement of the immune system clinically is manifested by appearance of autoimmune phenomena and increasing indices of inflammation such as ESR and CRP, constituting the substrate for the development of age-related chronic inflammatory diseases, such as osteoporosis and metabolic syndrome. Osteoporosis is a pathological condition typical of the elderly subject, characterized by a reduction in bone mass and an altered bone quality leading to enhanced bone fragility which results in an increased risk of fractures. Recent discoveries in the field of osteoimmunology have finally determined that, in addition to endocrinological, metabolic and mechanical factors, inflammaging plays a central role in the induction and progression of bone resorption. Activated macrophages and senescent T lymphocytes favor osteoclast activation either directly by the complex RANKL-RANK, either indirectly through the production of proinflammatory cytokines. Metabolic syndrome is a condition characterized by the concomitant presence of various clinical manifestations such as insulin resistance, impaired glucose tolerance, systemic arterial hypertension, dyslipidemia, and visceral obesity. Even metabolic syndrome is accompanied by a systemic inflammatory condition, maintained by the overproduction of proinflammatory cytokines that favor the evolution to complications such as diabetes and cardiovascular disease. In the light of these considerations, to assess the relationship between osteoporosis and metabolic syndrome in the elderly we considered 1250 patients consecutively affered to the Center for Osteoporosis in the last one year. Accurate clinical examination, assessment of anthropometric parameters and laboratory tests were performed. Subjects with important comorbidities or treated with drugs inducing bone resorption were excluded. We defined the presence of metabolic syndrome on the basis of diagnostic criteria proposed in 2005 by International Diabetes Federation: presence of abdominal obesity (waist circumference>94 cm in male and >80 cm in female) plus the presence of at least two of the following criteria: triglycerides >150 mg/dl, HDL cholesterol <40 in male and >50 mg/dl in female or lipid-lowering therapy, blood pressure >130/85 mmHg or antihypertensive therapy, and fasting blood glucose >100 mg/dl or previous diagnosis of type 2 diabetes mellitus. We then extrapolated a sample of 180 patients aged more than 65 years with a diagnosis of metabolic syndrome, and a control group of 137 patients without metabolic syndrome. Bone mineral density was evaluated by ultrasonography of the heel and confirmed, if necessary, by DXA. Our results showed values of T score significantly lower in patients with metabolic syndrome compared to the control (-3±1.51 vs -1.7±1.70 p<0.05). Osteoporotic fractures were present in 19% of patients with metabolic syndrome compared with 6% of controls. As expected, comparison of the mean values of inflammatory markers (ESR and CRP) in the two groups evidenced higher values in patients with metabolic syndrome. Low serum levels of autoantibodies (ANA, RF, TPOAb), although in the absence of overt autoimmune diseases, were more frequent in patients with metabolic syndrome (18%) compared to controls (16%). In conclusion, our study showed that subjects with metabolic syndrome have a lower bone mineral density compared to healthy subjects of the same age and they are at higher risk of osteoporotic fractures. Metabolic syndrome is therefore an additional risk factor for osteoporosis. Moreover, inflammaging would seem to be an important pathogenetic factor in this close correlation between osteoporosis and metabolic syndrome. Indeed during ageing, both life style and the inflammatory background (inflamaging) plays a role in the onset and progression of osteoporosis and metabolic syndrome.

**Epicardial adipose tissue transcriptomics in coronary atherosclerosis**


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**Background and Aims:** Epicardial adipose tissue (EAT) is the energetic buffer of the heart with a putative role in the development of atherosclerosis. We profiled EAT gene and microRNA expression charts in patients with or without coronary artery disease (CAD) with the aim of identifying novel CAD-related cascades and biomarkers in EAT. PATIENTS AND METHODS. We enrolled 44 patients undergoing cardiac valve-replacement (controls; no evidence of CAD) or coronary artery bypass graft surgery (CAD group). We collected subcutaneous (SAT) and epicardial adipose tissue specimens, and serum. Genes and microRNAs expression patterns were studied by microarrays, and confirmed by RT-qPCR. RESULTS. Compared to controls, in EAT of CAD patients 88 genes were down-regulated while 57 were up-regulated. In CAD, we found a down-regulation of genes encoding proteins involved in lipid metabolism, mitochondrial function, and nuclear receptor transcriptional activity, and an up-regulation of those involved in antigen presentation, inflammation, and cytokine production. These results were confirmed by qPCR and immunofluorescence. In EAT of CAD patients, 15 microRNAs were up-regulated, while 16 were down-regulated, including known players in inflammation and adipocyte physiology. We pointed to EAT-correlated genes in SAT, and to EAT-derived circulating pro-inflammatory chemokines as candidate biomarkers of CAD. CONCLUSIONS. We present here EAT-specific gene and miRNA signatures that could serve as a source of candidate biomarkers and targets for CAD, and could provide insights for understanding the role EAT in the pathophysiology of CAD. This contribution has been awarded as Best Communication.

**Low grade systemic inflammation and insulin resistance, instead of metabolic syndrome, as predictors of mortality in older population**

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**Objective:** Metabolic Syndrome (MS) is a typical condition of middle-aged and older people and its prevalence progressively increases with aging.
Association between MS and total and cardiovascular (CV) mortality has been strongly confirmed in longitudinal studies among middle-aged population. Conversely data on older population are inconsistent, thus we evaluated whether insulin resistance (IR) and low grade systemic inflammation (LGSI), two conditions consistently associated with MS pathogenesis, play a role on the risk for 9-years CVD/mortality in older individuals with and without MS.

**Methods:** 1011 community dwelling older individuals from the InChianti study were included in the study. MS was diagnosed by the 2005 updated NCEP-ATP III criteria. IR was calculated by HOMA model; high sensitivity C reactive protein (hs.CRP) was measured by ELISA. Subjects were divided into two groups based on presence/absence of IR (HOMA ≥ 2.27, median value) and LGSI (hs.CRP ≥ 3 g/L): Group 1: no IR nor LGSI (reference); Group 2: LGSI, no IR; Group 3: IR, no LGSI; Group 4: both IR and LGSI. Hazard Ratios (HR) for 9 years all-cause and cardiovascular (CVD) mortality according to IR/LGSI groups, were separately estimated in subjects with (n.311) and without MS (n.700) by Cox proportional hazard multivariate regression analysis.

**Results:** The prevalence of MS was 17% in subjects without IR and LGSI (group 1), 24% in subjects with isolated LGSI, 35% in those with isolated IR, and 49% in those with IR and LGSI (p for trend <0.001).

We found no association between MS with overall nor CV mortality (respectively HR:1.07, 95%CI:0.86-1.34; and HR:1.29, 95%CI:0.92-1.81). Conversely the combination of IR and LGSI was associated with overall and CV mortality, regardless of the presence of MS. Indeed, among subjects both with MS and without MS, the simultaneous presence of IR and LGSI (group 4) was associated with an increase in the risk for 9 years overall mortality (no MS: HR 1.72, 95%CI:1.001-3.17; MS: HR 1.51, 95%CI:1.02-2.28) and CV mortality (no MS: HR 2.07, 95%CI:1.12-3.72; MS: HR 9.88, 95%CI:2.18-4.16). Furthermore the presence of IR (HR: 6.90, 95%CI:1.45-32) or LGSI (HR 7.56, 95%CI:1.63-35) alone was associated exclusively with CV mortality only among individuals with MS.

**Conclusions:** Our findings do not question the usefulness of MS in identifying a cluster of vascular risk factors, but debunk its value in identifying elderly subjects with high mortality risk. Conversely HOMA and CRP hs, two relatively simple laboratory parameters related with MS pathogenesis, are good clinical predictors of mortality risk in advanced age.

**MicroRNA profiling unravel a new potential mechanism of insulin resistance in diabetes: effects of glycemic control**


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**Background:** Type 2 Diabetes (T2DM) is a chronic disease characterized by an inadequate beta-cell response to the progressive insulin resistance. MicroRNAs are short (20-22 nucleotides), endogenous, non-coding, RNAs representing a powerful class of regulators of gene expression. Previous population study found a modulation of circulating in patients with diabetes, however there are no data about microRNA modulation in newly diagnoised diabetic patients and the effect of glycemic control on microRNA expression.

**Materials and Methods:** blood samples were collected from 12 newly diagnoised, naïve diabetic patients with poor-metabolic control and 12 balanced control patients. Diabetic patients were evaluated at the time of the diagnosis before starting any therapy and after 12 months of treatment. Wide microRNA expression profiling was performed on both samples, and the expression of some of the miRNAs found to be dysregulated was validated by RealTime-PCR. Algorithm-identified putative microRNA targets were evaluated by RT-PCR and ELISA.

**Results:** microarray analysis showed that 4 miRNAs were up- and 21 miRNAs were down-regulated in diabetic patients. RT-PCR validation confirmed a significant down-regulation for let-7a (p=0.01) and let-7f (p=0.015) and up-regulation of miR-326 (p=0.017). Notably, an inverse negative correlation was found between circulating miR-326 and its target adiponectin (rs -0.509, p=0.011). Finally, after 12-months of anti-diabetic treatment, let-7a and let-7f levels significantly increased; whereas no significant differences were found for miR-326 levels.

**Conclusion:** Naïve poorly controlled diabetic patients show a dysregulation of some microRNAs involved in the pathophysiology of insulin resistance, a phenomenon that may be reversed, at least in part, by glycemic control. These findings may contribute to improve our knowledge on diabetes pathophysiology and point out new molecular targets for future therapeutic strategies.

**Non-alcoholic fatty liver disease, metabolic syndrome and cardiometabolic risk: two different patterns in relation to PNPLA3 M148M gene variant**


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**Background and Aims:** Many studies reported a strong relationship between non-alcoholic fatty liver disease (NAFLD) and metabolic syndrome. Moreover, nonsynonymus variant I148M located in Patatin-like phospholipase domain-containing protein 3 gene (PNPLA3), also known as Adiponutrin, has been reported to be associated with NAFLD and with a more severe liver damage.

Our purpose was to assess the influence of PNPLA3 variant on cardiometabolic phenotype in a large series of patients with NAFLD.

**Methods:** NAFLD was diagnosed by ultrasonographic Hamaguchi’s criteria, in 211 subject with no history of alcohol abuse. Subjects were enrolled and genotyped for PNPLA3 I148M variant determined by TaqMan assays. Metabolic syndrome was defined according to the ATPIII modified criteria.

**Results:** PNPLA3 genotype frequencies were II= 45.3%, IM=40.5%, MM=14.2% and the overall prevalence of MS was 68%. MS was more frequently observed in PNPLA3 wild type allele carriers (II=71.6% vs IM=72.1% vs MM=50% [p=0.024]). Odds ratio for MS was 3.3 times lower in MM carriers as compared to IM and II alleles carriers Median waist circumference (cm) and serum triglycerides (mg/dl) were higher in I allele carriers [110 (103.5/118) vs 105 (101/113.5) vs 106 (96.7/118.5), p=0.065 and 157 (112/193) vs 141 (107.7/185) vs 115 (90.7/148.7), p=0.006, respectively], while mean ALT (UI) was higher in M carriers (26 (19/35) vs 30.5 (22/45) vs 30 (22.7/40.5) [p=0.014]).

MM carriers had lower median HOMA-IR and higher median HDL-C (mg/dl) compared to wild-type, although not at statistically significant level (2.8 vs 3.6 and 50.5 vs 45, respectively). Framingham cardiovascular risk score was significantly higher in II vs MM carriers (9% vs 4% p=0.024 respectively). Body mass index, blood pressure and other biochemical parameters did not differ across genotypes.

**Conclusions:** Subjects whit NAFLD carrying PNPLA3 M variant are at risk to develop more severe liver disease but they show a lower prevalence of metabolic syndrome and reduced cardiometabolic risk. Moreover, we suggest that PNPLA3 may help to differentiate clinical phenotypes of NAFLD and be an important candidate gene to discriminate NAFLD with possible metabolic and cardiovascular consequences from fatty liver at risk for liver related complications.
Reduced nocturnal hypoglycaemia with insulin degludec as compared to insulin glargine: results of a 2-year randomised trial in type 2 diabetes


Università degli Studi Catanzaro IT

Introduction: As a result of the progressive nature of type 2 diabetes (T2D), more than 50% of patients eventually require insulin therapy in addition to oral antidiabetic drugs (OADs) in order to achieve the glycaemic goal of HbA1c <7%. American Diabetes Association (ADA) and Euroasian Diabetes Association (EASD) recommend initiating basal insulin in patients with T2D not reaching glycaemic goals either directly after metformin or after a combination of OADs.2,3

Long-acting insulin analogues are designed to provide a stable and predictable basal insulin supply when injected once-daily (OD). Insulin degludec (IDeg) is a novel basal insulin analogue which is ultra-long-acting due to formation of soluble multi-hexamers at the site of injection. In clinical pharmacology studies, IDeg showed a flat and stable insulin-action profile with a duration of action more than 42 hours at clinically relevant doses. The aim of this treat-to-target trial was to compare the long-term safety, tolerability, and efficacy of IDeg with insulin glargine (IGlar) administered OD in a basal regimen in combination with metformin with or without a dipeptidyl peptidase-4 (DPP-4) inhibitor, in insulin-naive patients with T2D.

Methods: Patients were previously treated with metformin in any combination with the following OADs: DPP-4 inhibitors, sulfonylureas (SUs) or glinides, or acarbose. Patients on metformin or DPP-4 inhibitors were to maintain their pre-trial dose and dosing frequency; other OADs were discontinued. IGlar was administered OD at the same time every day (per approved labelling) and IDeg was administered OD with the main evening meal. Basal insulin titration:

- Starting dose for both insulins was 10U OD.
- Basal insulin was titrated once-weekly to a target of 3.9-4.9 mmol/L, using a treat-to-target approach based on the average of 3 consecutive pre-breakfast self-measured plasma glucose (SMPG) values.

Definitions of hypoglycaemia: Confirmed hypoglycaemia was defined as episodes with PG <3.1 mmol/L (56 mg/dL), or severe episodes requiring assistance. Nocturnal hypoglycaemia was defined as confirmed hypoglycaemia occurring between 00:01 and 05:59 (both inclusive).

Results: A similar proportion of patients in IDeg (65%) and IGlar (60%) completed the trial and no difference was observed between groups in the withdrawal pattern. Both treatment groups had comparable demographic and baseline characteristics.

Hypoglycaemia Rates of overall confirmed hypoglycaemia were 16% lower with IDeg compared to IGlar (1.72 vs. 2.05 episodes/patient-year, respectively); estimated rate ratio (ERR) IDeg/IGlar: 0.84 [95% CI: 0.68; 1.04], p=0.12, ns. Rates of nocturnal confirmed hypoglycaemia were statistically significantly lower by 43% with IDeg compared to IGlar, with rates of 0.27 vs 0.46 episodes/patient-year; ERR: 0.57 [95% CI: 0.40; 0.81], p=0.002. Rates of severe hypoglycaemia were low in both treatment groups but were 69% lower with IDeg compared to IGlar (0.006 vs. 0.021 episodes/patient-year); ERR: 0.31 [95% CI: 0.11; 0.85], which was statistically significant, p=0.023.

The observed mean HbA1c decreased from 8.2% at baseline to 7.2% with IDeg and 7.1% with IGlar after 104 weeks of treatment. There was no statistical difference in mean HbA1c reduction between treatments (estimated treatment difference (ETD): 0.12 [95% CI: -0.01; 0.25], p=0.078, ns. The observed mean FPG reduction after 104 weeks of treatment was 3.6 mmol/L with IDeg and 3.2 mmol/L with IGlar; the reduction in FPG observed was significantly greater with IDeg than IGlar after 104 weeks of treatment (ETD: -0.38 mmol/L [95% CI: -0.70; -0.06], p=0.019).

Conclusions: In this 105 week, treat-to-target trial in 1030 insulin-naive patients with type 2 diabetes, treatment with IDeg improved HbA1c similar to IGlar, resulted in significantly greater FPG reductions compared with IGlar, and statistically significantly lowered the risk of nocturnal confirmed (43% lower) and severe (69% lower) hypoglycaemia compared with IGlar. Long-term treatment with IDeg is safe and well-tolerated with a safety profile similar to IGlar. Daily basal insulin doses were similar between the two treatment groups.

Effect of Pegvisomant on left ventricular mass in refractory acromegalic patients: a two years-follow-up observational study


Objective: Acromegaly is associated with an increased morbidity and mortality, especially due to cardiovascular involvement. Morpho-functional biventricular impairment, i.e. left ventricular hypertrophy (LVH) is described; improvement in myocardial structure and function has been observed after medical or surgical treatment. Pegvisomant (PegV) is a GH receptor antagonist, indicated for acromegalic patients with unsuccessful surgical, radiation, and/or medical treatment, with the goal of obtaining normal IGF-1 serum levels. Aim of this observational study is to evaluate the effect of PegV on left ventricular structure.

Methods: We evaluated 8 consecutive patients (4 male), with active acromegaly, eligible to PegV treatment (mean disease duration before PegV: 8 years±3.9). Starting from 10mg daily, PegV was titrated to reach the expected levels of IGF-1 for sex and age. All patients underwent cardiac assessment and transthoracic echocardiogram (TTE) yearly from acromegaly diagnosis; in our study we considered the following TTE results: 2 years before starting PegV (T -2), at the enrolment for PegV therapy (T0) and after two years of treatment (T2). We compared left ventricular dimensions (LVEDD: left ventricle end diastolic diameter; RWT: relative wall thickness) and mass (LVM and LVM index, expressed as g/h².7, in order to avoid the impact of overweight or body surface area). The statistical analysis was based on “Student’s” t test for paired data.

Results: At six months therapy all patients normalized IGF-1 levels, which remained stable during the whole follow up. At T0 (starting treatment) patients mean age was 50.6 (SD 10.6) years; mean LVDD was 5.6 (SD 0.45) cm; mean relative wall thickness (RWT) was 0.31 (SD 0.04) cm; mean LVM was 219.3 (SD 65.6) g; mean LVMi was 51.53 (SD 9.67) g/h².7. Mass and LVMi were significantly higher at T-2 than at T0 (p<0.05 for both) whereas significantly lower at T+2 vs T0 (p<0.05 for both). All parameters are reported in Table 1.

Table 1. Left Ventricle Parameters

<table>
<thead>
<tr>
<th></th>
<th>T -2</th>
<th>T 0</th>
<th>T +2</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDD (cm)</td>
<td>5.60±0.41</td>
<td>5.63±0.45</td>
<td>5.50±0.49</td>
</tr>
<tr>
<td>RWT</td>
<td>0.30±0.04</td>
<td>0.31±0.04</td>
<td>0.28±0.03</td>
</tr>
<tr>
<td>LVM (g)</td>
<td>209.3±60.3 *</td>
<td>219.3±65.6</td>
<td>189.5±51.9 *</td>
</tr>
<tr>
<td>LVMi (g/h².7)</td>
<td>49.3±8.4 *</td>
<td>51.53±9.67</td>
<td>44.9±5.6 *</td>
</tr>
</tbody>
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*Values: mean±SD; * : p<0.05 vs T0
1. The observed LVM reduction after PegV treatment could play a role in improving the cardiovascular prognosis of hypertrophic acromegalic patients.

2. Global DNA hypomethylation in peripheral blood mononuclear cells: a possible novel, reliable biomarker of cancer risk

3. Conclusion: In our preliminary study, successful PegV treatment (IGF-1 serum level reduction) seems to be effective in inducing a significant LV mass reduction, whereas previous treatments had no effect of this kind (Fig. 1). The observed LVM reduction after PegV treatment could play a role in improving the cardiovascular prognosis of hypertrophic acromegalic patients.

4. Introduction: global DNA methylation is an epigenetic phenomenon that affects the regulation of gene expression and genome integrity. Aberrant DNA methylation is an early molecular event in cancerogenesis and a global DNA hypomethylation is an almost universal finding in many human cancer tissues and cancer precursor cells. Differently from mutations and loss of heterozygosity DNA methylation is a reversible phenomenon and it can be modified by nutrients such as folate as well as influenced by the common 677 C>T polymorphism in methylenetetrahydrofolate reductase (MTHFR) gene. An interaction between folate status and MTHFR variant can affect global DNA methylation and thereby potentially modify the risk of cancer. Peripheral blood mononuclear cells (PBMCs) are easily accessible in humans and our aim was to test PBMCs DNA methylation according to the folate-MTHFR677C>T polymorphism interaction, as a potential biomarker for cancer risk.

5. Materials and methods: from an original sample-set of 753 male and female adults we selected 68 subjects who were diagnosed of cancer at the time of enrolment to the study and 62 subjects who developed cancer during an eight-year follow-up period, along with 68 age- and sex-matched controls at enrolment and 58 age- and sex-matched controls, at follow-up. Global DNA methylation, expressed as percent (%) 5-methylcytosine (mCyt/(mCyt+Cyt) was determined using a liquid chromatography/mass spectrometry (LC/MS). Plasma folate concentrations were measured by an automated chemiluminescence method. The MTHFR677 C>T polymorphism analysis was performed by PCR followed by HinfI digestion.

6. Results: cancer subjects had lower plasma folate concentrations (P=0.003) and higher frequency of homozygous mutants for the MTHFR677 C>T polymorphism than controls (P=0.013). Moreover, cancer subjects who already had cancer at enrolment showed reduced PBMCs-global DNA methylation compared to controls (P<0.0001). A DNA methylation threshold of 4.74% clearly categorized cancer patients from controls: subjects with DNA methylation < 4.74% showed a much increased prevalence of cancer than those with higher levels (P<0.001). Subjects with cancer at follow-up had, already at enrolment, reduced DNA methylation compared to controls (P<0.0001). Moreover, MTHFR677 C>T genotype and folate interact for determining DNA methylation, so that MTHFR677TT carriers with low folate had the lowest DNA methylation (P=0.019) (Fig. 1). Consistently, only the subgroup of MTHFR677TT homozygous carrier associated with low plasma folate concentrations showed a higher risk of cancer (P=0.013) while no significant association was observed for MTHFR677TT subjects with high folate (Fig. 2).

7. Discussion and conclusion: in this study we enlightened the value of DNA methylation as a clinical index to screen patient affected by cancer or at risk to develop cancer disease. In effect global DNA methylation of cancer subjects was invariably decreased compared to controls and, moreover, we also observed that global DNA methylation in PBMCs at the enrollment was lower in subjects who developed cancer during the eight year follow-up period compared to those who did not develop cancer during the same period.
Radioembolization with Yttrium90 versus sorafenib in cirrhotic patients with hepatocellular carcinoma: a cohort study with a propensity score analysis


Background and aims: Sorafenib and transarterial Y90-radioembolization (TARE) are possible treatments for advanced (BCLC stage C) hepatocellular carcinoma (HCC) or tumors not amenable or resistant to curative options and transarterial chemoembolization (TACE). No study directly comparing the effectiveness of Sorafenib and TARE is currently available. This study compares patient survival achieved with these two therapies.

Methods: Retrospective study. Between September 2005 and October 2012, 112 patients were treated with Sorafenib and 75 patients with TARE in our Department. Selection criteria: Child-Pugh class A/B, performance status (PS) ≤2. HCC not amenable to curative therapies or TACE, neoplastic liver involvement <50%, no metastases and no previous systemic chemotherapy. Comparisons were made with Mann-Whitney U, Pearson χ² or Fisher exact tests. Survivals were calculated with Kaplan-Meier method and compared with log rank test. Propensity analysis provided one-to-one match between Sorafenib and TARE patients for independent prognostic factors at multivariate analysis.

Results: Inclusion criteria selected 74 Sorafenib patients (71±10 years, male 87%, BCLC B/C 53%/47%) and 63 TARE patients (66±9 years, male 79%, BCLC B/C 41%/59%). The two groups did not significantly differ for gender, aetiology, previous HCC treatments, portal vein thrombosis, Child-Pugh class, MELD score, BCLC stage, alpha-fetoprotein levels, creatinine, platelet count. Instead, TARE patients were younger, had less comorbidities and more solitary HCC. Median overall survival did not differ between Sorafenib (14.4 months; 95% CI: 4.3-24.5) and TARE (13.2; 6.1-20.2; P=0.959) patients, and mortality rate at 1, 2 and 3 years was 48%, 71% and 85% in Sorafenib cases, and 48%, 72%, and 78% in TARE individuals. Propensity model matched 32 patients for independent non co-axial prognostic factors: age, PS, MELD, portal thrombosis (no, main trunk, peripheral branches) and tumour gross pathology. In this matched subgroup, median survival was 13.1 months (1.2-25.9) for Sorafenib patients and 11.2 months (6.7-15.7) for TARE patients (P=0.392).

Conclusions: In cirrhotic patients with advanced or not otherwise treatable HCC, Sorafenib and TARE provided similar overall survival.

The impact of allergic diseases on the emergency room of the general hospital-university of Padova from 2008 to 2012


Background and aims: Allergic diseases are common in Western countries and the prevalence of atopy is around 15% in general population. Nevertheless, at our knowledge only one manuscript has been published till now in Italy (Dantonio C et al, Eur Ann.Allergy Clin.Immunol. 2008; 40:122-129 ) about the epidemiology and the management of allergy in adults at the Emergency Department (ED), and few others elsewhere (Gaete TJ et al, Ann.Allergy Asthma Immunol 2007; 98:360-365. Lin RY et al, id, 2008; 101: 185-92. Lin RY et al, id, 2008;101: 387-93), mainly focused on angioedema.

Aim of the study: to assess the global impact of allergic diseases at the Emergency Department of Padua University Hospital from 2008 to 2012 through the analysis of many parameters, including the following ones: prevalence of admissions for allergy; distribution of allergic symptoms among the different forms of allergy: suspected etiology; anaphylaxis; anamnestic; mode of arrival; triage code; duration of stay and outcome; biochemical analyses; therapy; specialists’ consultations performed at the ED in real time and/or within 72 hrs after discharge; inter-annual variability.

Materials and methods: we identified 63 nosological codes, among the 2.742 ones used by the ED, suggestive of an allergic etiology; thereafter, by Q-liik, e-health and SSI programs we recovered and read the 6497 discharge reports with the aforementioned codes and were able to identify 4040 cases of admissions clearly related to an allergic disease. To evaluate the parameters described above and compare data obtained for allergies with those from the total numbers of ED entries in the period 2008-2012 we carried out the test of hypothesis χ² and Fisher’s exact test using the SAS 9.2 program for Windows (SAS Institute Inc, Cary, NC)

Results: 1. Allergy represented 0.9% of all the causes of admission at the ED of Padua in the five years examined. Symptoms were distributed as follows: 56.86% urticaria/angioedema, 18.27% asthma, 2.87% anaphylaxis, 0.77% anaphylactic shock, 0.37% rhinitis and/or conjunctivitis. The prevalence of female gender was quite different between allergy and total admissions (56.36% vs 47.00%), as well as age distribution showing a higher percentage of young adults in the allergic group (p < 0.001). Although only 10% of the allergic patients asked for assistance to the emergency care phone number (118), in front of the 24% of requests coming for total admissions (p< 0.001), the prevalence of both yellow and red codes showed to be higher in the first ones (37.55% vs 27.32%, and 5.35% vs 3.55%, respectively; p < 0.001). A presumed etiology was established for 52.46% of allergic admissions, mainly drugs (21.49%) and foods (14.65%). Isolated angioedema including the hereditary subset, 6.96% dermatitis, 2.87% anaphylaxis, 0.77% anaphylactic shock, 0.37% rhinitis and/or conjunctivitis. The prevalence of female gender was quite different between allergy and total admissions (56.36% vs 47.00%), as well as age distribution showing a higher percentage of young adults in the allergic group (p< 0.001). Although only 10% of the allergic patients asked for assistance to the emergency care phone number (118), in front of the 24% of requests coming for total admissions (p< 0.001), the prevalence of both yellow and red codes showed to be higher in the first ones (37.55% vs 27.32%, and 5.35% vs 3.55%, respectively; p < 0.001). A presumed etiology was established for 52.46% of allergic admissions, mainly drugs (21.49%) and foods (14.65%). Isolated angioedema was associated to ACE-inhibitors intake in 17.62% of cases, whilst only 5.73% of patients with urticaria were taking nonsteroidal anti-inflammatory drugs that are usually considered to be a triggering factor for hives. On admission, 20.28% of patients were on multi-drug therapy with more than 3 drugs. Allergic symptoms were treated with corticosteroids and antihistamines in 77.82% and 66.1% of cases respectively, whilst epinephrine was administered predominantly in anaphylactic shock (87.1%), anaphylaxis (31.03%) and more sporadically in asthma and angioedema. Short-term Intensive Observation protocol was applied to 9.31% of allergies and 3.5%, of global accesses (p<0.001), with a lower percentage of hospitalizations due to allergies (3.2% vs 18.18%; p≤0.001). Only 7 patients - 5 of those intubated on site by the rescue personnel of 118 or on their arrival at the ED - were admitted to the intensive care unit, were two died (one for angioedema and one for asthma). 63.49% of the patients were evaluated by a specialist (pulmonologist, oto-laryngologist, allergist or dermatologist) in the emergency room or within 72 hours from discharge.

Conclusions: Our results demonstrate a significant impact of allergic dis-
cases on the emergency department, both in terms of epidemiology and clinical resources’ consumption, as confirmed by the amounts of yellow and red codes that are increasing over the years and were assigned to 50% of the admissions for allergy in 2012. Cutaneous complains represented the main cause of admission, with the highest incidence observed for urticaria and angioedema (70.87%) and with a prevalence of the female gender in childbearing age as typical of immune diseases. In about 50% of cases a possible etiology was suggested, almost due to drug intake. Multi-drug therapy confirmed to be a risk factor for the development of allergic reactions, as well as ACE-inhibitors were for angioedema. The few deaths observed and the low percentage of hospitalizations show as a well-organized ED may successfully approach all the allergic diseases seeking for emergency care. Specialist evaluation should be performed in the emergency room when available, or planned after discharge if possible also to avoid recurrences for the same cause.

A multicenter observational study for early diagnosis of Gaucher disease in patients with splenomegaly and/or thrombocytopenia

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Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milano

Background: Gaucher disease (GD) is an autosomal recessive lysosomal storage disorder resulting from deficiency of beta-glucosidase and the accumulation of glucocerebroside in the reticuloendothelial cells. Prevalence of GD is elevated in Ashkenazi Jewish population (1/4500-1/10000), and rare in the non-Ashkenazi (1/40000-1/60000). GD is a multisystemic disease; cytopenias and splenomegaly are frequently the presenting symptoms leading to hematological evaluation. Data from the Gaucher Registry 2008 show that splenomegaly and thrombocytopenia are present at diagnosis in more than 5000 patients (respectively 86% and 60%). Because of the non-specific presenting symptoms, diagnostic delays are frequent, leading to severe complications including hematological malignancies. Enzyme replacement therapy is available and effective in reversing or preventing many manifestations, including hepatosplenomegaly, marrow infiltration, cytopenias and osteopenia (Weinreb 2002). A global survey among 406 Hematology-Oncology specialists demonstrated that only 20% consider GD in the differential diagnosis of cytopenia, hepatosplenomegaly, and bone pain (Mistry 2007). It is clear that a different approach based on a specific diagnostic algorithm is necessary to avoid under-diagnosis (Mistry PK 2010).

Aims: The aim of this multicenter observational study is to evaluate the prevalence of GD in a selected population presenting to hematological clinic with at least one of the two including criteria: 1) splenomegaly, 2) thrombocytopenia associated to at least one of the following symptoms: anemia (Hb<11 g/dl for women, and Hb<12 g/dl for men), MGUS, polyclonal gammapathy in patient younger than 30 yo, splenectomy or history of bone pain. Exclusion criteria include: a) splenomegaly due to portal hypertension in cirrhosis, b) hematological malignancy, c) hemoglobinopathies or other hemolitic anemias.

Methods: Thirty five Italian Hematologic Centers participate in this study. According to a preliminary survey, 18% of all hematologic first evaluations are positive for splenomegaly and/or thrombocytopenia, among them 11% did not received an appropriate diagnosis. According to these data 762 patients are expected to be tested every year (mean of 1100 first evaluations/year for each center). Patients fulfilling including criteria who have given their informed consent are recruited into the study and tested for beta-glucosidase enzyme activity on Dried Blood Spot (DBS). All the analysis is centralized and performed by the Laboratory of diagnosis of Metabolic Diseases Ospedale Gaslini, Genova. Results can show normal, decrease or borderline beta-glucosidase activity. In the last case, DBS must be repeated to confirm the result. Beta-glucosidase deficiency and GD diagnosis must be subsequently confirmed dosing the enzyme activity in the leukocytes from fresh blood and by DNA analysis.

The expected duration of the study was 24 months, starting from September 2010, subsequently extended up to the enrollment of 500 patients (recruitment still active at present).

Results: Starting from September 2010 170 patients (51 female, 119 male; median age 50 years, range 18-84) have been enrolled. All the patients are non-Ashkenazi, among them 61% had splenomegaly, 4% thrombocytopenia and 35% both of them. Seven patients have been diagnosed with GD.

<table>
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<tr>
<th>PARAMETERS</th>
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<tr>
<td>Hb (g/dl) mean±SD</td>
<td>13.4±2.3</td>
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<tr>
<td>PLATELETS (num/mm³)</td>
<td>mean±SD</td>
<td>128±72</td>
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<tr>
<td></td>
<td>median (range)</td>
<td>108 (356-8)</td>
</tr>
<tr>
<td>SPLEEN (cm) mean±SD</td>
<td>16.1±2.7</td>
<td></td>
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<tr>
<td>FERRITIN (ng/dl) mean±SD</td>
<td>237±287</td>
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<td></td>
<td>median (range)</td>
<td>120 (1500-5)</td>
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Conclusion: Our results are clinically relevant, showing that the use of a simple diagnostic algorithm helps to identify GD patients at an early stage presenting to hematologists with splenomegaly, leading to an appropriate and prompt therapy to prevent the development of complications.

Proangiogenic effect of bone marrow fibroblasts in patients with multiple myeloma


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Bone marrow (BM) stromal cells favor progression of multiple myeloma (MM) but cancer-associated fibroblasts (CAFs) have not been studied yet. CAFs were increased in patients with active MM (at diagnosis, at relapse) compared to those in remission, those with monoclonal gammapathy of undetermined significance (MGUS), and those with deficiency anemia. They displayed an activated phenotype, and produced high levels of TGFβ, IL-6, SDF1α, and IGF1. They showed a heterogeneous phenotype which entailed their origin from resident fibroblasts, and from endothelial cells (ECs) and hematopoietic stem and progenitor cells via endothelial-mesenchymal transition, and from mesenchymal stem cells via mesenchymal transition, all induced by CAFs themselves and MM cells. Active MM CAFs induce proliferation and apoptosis-resistance of MM cells through cytokines and cell-to-cell contact. Studies in syngeneic 5T33MM and xenografted mouse models showed that MM cells induced the CAFs expansion which, in turn, favored MM initiation and progression as well as angiogenesis. In vivo Matrigel plug assays and in vitro chemotaxis showed the ability of active MM CAFs (as cells and CM) to attract mouse and human CD31+ ECs, and have a direct angiogenic effect. They support MM tumor growth by promoting its neovascularization and contribute to the angiogenic switch and the subsequent angiogenic phase which parallel transition of MGUS into MM. Moreover in patients’ and mice BM biopsies nests of CAFs were found in close contact with MM cells suggesting a vascular protective niche. Targeting CAFs in MM patients may be envisaged as a therapeutic strategy.

This contribution has been awarded as Best Communication.
Does the longevity of parents influence telomere length and the health status?

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Introduction: Chromosome ends or telomeres are specialized structures consisting of highly conserved TTAGGG repeats that become shorter with every cell division. Telomere shortening occurring with aging is thought to induce a progressive decrease of cellular replication rate, ultimately leading to senescence of cells. As a consequence, telomere length (TL) is considered a marker of biological age and is reported to be associated with age-related diseases. Centenarians and their offspring are an useful model to study healthy aging and longevity. Nevertheless, the mechanisms underlying their longevity are still partly unclear.

Aim: The aim of this project is to compare TL in peripheral leucocytes from centenarians, centenarians’ offspring, offspring of both non-long-lived parents (NLO) and randomly recruited healthy elderly (CT) and to characterize these populations for the prevalence of various diseases.

Methods: A total of 196 individuals were enrolled in the study: 64 centenarians (mean age 101.1±1.9 years); 70 centenarians’ offspring (mean age 70.4±6.3 years); 33 NLO (mean age 73±7.2 years) and 29 CT (mean age 72.8±4 years). A standard structured questionnaire was administered to all the subjects in order to collect information regarding the health status, currently used drugs, clinical history, and lifestyle. In addiction, the history of past and current diseases was accurately collected checking the participants medical documentation and the current drug therapy. To date, TL was assessed by quantitative PCR in peripheral leucocytes from 30 centenarians, 31 centenarians’ offspring, 21 NLO and 29 CT. Statistical analysis was performed by SPSS version 20.

Results: As expected, we found in centenarians an higher prevalence of various diseases, including dementia (p<0.001), ictus (p<0.001), heart failure (p<0.001) and angina (p=0.009) compared to both centenarians’ offspring and NLO. Interestingly, centenarians’ offspring showed a lower prevalence of arrhythmia (p=0.002), hypertension (p<0.001) and chronic obstructive pulmonary disease (p<0.001) not only compared to centenarians but also to NLO.

TL (expressed as mean±standard error) for centenarians, centenarians’ offspring, NLO and CT was 0.97±0.02, 1.15±0.05, 1.00±0.03 and 0.93±0.04 respectively. Interestingly, centenarians’ offspring had longer telomeres compared to both centenarians (p=0.004) and CT (p<0.001). Moreover, a very close to significance difference in TL was found between centenarians’ offspring and NLO (p=0.065). We subsequently evaluated TL only in women. Female centenarians’ offspring had longer telomeres not only compared to female centenarians (p<0.001) and female CT (p<0.001) but also to female NLO (p=0.001), while NLO and CT showed no difference.

Conclusions: Collectively, centenarians’ offspring appeared healthier than age-matched NLO and furthermore exhibited a statistically significant difference in TL respect to the other groups, indicating a possible slower rate of aging in these subjects. The same study model was also employed in our previous research project showing specific DNA methylation profiles in female centenarians’ offspring. In particular, they had a characteristic hypermethylation in genes involved in nucleotide biosynthesis, metabolism and control of signal transmission. Further analysis may clarify the possible linkage among these epigenetic modifications, telomere length and longevity.

Vitamin D levels and endothelium vasodilatation in older subjects

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1Dpt of Clin and Experim Med, Section of Geriatrics, Univ of Parma; 2Geriatr Unit, Univ-Hospital of Parma; 3Diagnostics Ematoclin, Univ-Hospital of Parma; 4Dpt of Pub Health and Caring Scienc, Uppsala Univ, Sweden; 5Dpt of Med, Uppsala Univ, Sweden

Background: Vitamin D has been shown as important determinant of physical and muscle function in older individuals. One the potential mechanisms underlying the relationship between vitamin D and physical function is the modulation of endothelial function, given the presence of vitamin D receptor at this level. However, the relationship between vitamin D levels and endothelial function has never been addressed in a study population of older individuals.

Methods: We studied 497 women and 505 men 70 years or older of Prospective Study of the Vasculature in Uppsala Seniors Study (PIVUS), with complete data on endothelial function, endothelium-independent vasodilation (EIDV), vitamin D and SHBG. Endothelium-dependent vasodilation (EDV) was assessed by invasive forearm technique with acetyl-choline, flow-mediated vasodilation (FMD) and the pulse wave analysis (reflecton index, RI). Vitamin D was measured by chemiluminescent immunoassay technology. The coefficient of variation for interassay analyses is 18.4% at a 25-OH D level of 39.5 nmol/L and 11.7% at 121.25 nmol/L. Multivariate regression analysis adjusted for multiple confounders was used to assess the relationship between vitamin D and endothelial function.

Results: In men, but not in women, we found a positive relationship between vitamin D and EIDV after adjustment for BMI (β±SE= 1.41±0.54, p<0.001), and further adjustment for insulin, smoking, CRP, HDL cholesterol, diabetes, hypertension, medications and sex hormones (β±SE= 1.94.5±0.61, p=0.0017) (Table 2). No relationship was found between vitamin D and EDV, FMD, RI and EIDV in both genders.

Conclusions: In older men, but not in women, vitamin D is positively and independently associated with endothelium-independent vasodilation. Further studies are needed to evaluate the role of vitamin D in endothelial derived diseases in older population.

Predictive power of circulating progenitor cell number on longevity in elderly population

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Cardiovascular diseases (CVD) and related complications are the main causes of morbidity and mortality in the elderly. Circulating progenitor cells (CPCs), including CD34+ cells, are to date considered a regenerative/repair potential for CV system, since they are a population of cells in different states of maturation with the ability to differentiate into different cell types, including cardiomyocytes, smooth muscle cells (SMCs), endothelial progenitor cells (EPCs) and endothelial cells (ECs), thus participating in the turnover of healthy and damaged tissues of cardiovascular system, delaying the development of atherosclerosis and CVD.

In the present study we observed 100 octogenarians for seven years, in order to address the question of whether CD34+ cell number is a predictor of longevity in selected survivors. We also checked for associations of cell ex-
pression of manganese superoxide dismutase (Mn-SOD), catalase (CAT), and glutathione peroxidase type-1 (GPx-1) antioxidative enzymes, and reactive oxygen species (ROS), with no correlation of CD34+ progenitor cells and mortality. We found that in very old subjects the number of CD34+ cells at baseline were higher in subjects who reached older age at death or were still living at the end of observation period (52 subjects, mean plasma concentration 4.09±0.71 cells/µL), with respect to subjects who died from all causes (48 subjects, mean plasma concentration 1.93±1.02 cells/µL, p<0.0001), including CV deaths.

We also noted that when MnSOD, CAT and GPx-1 are consistently expressed in the upper tertile, this condition allows reduced production/accumulation of intracellular ROS (on the average 51.2±14.1 FU); on the other hand, when MnSOD, CAT and GPx-1 were expressed in the lower tertile, ROS levels were increased (61.2±16.2, p<0.001).

Higher ROS levels were correlated with lower CD34+ cell number; and with lower survival or age reached at the end of observation period. Dependence analysis (Cox regression model) confirmed the central role of CD34+ cell number at the baseline in predicting survival time.

Furthermore, HDL-C plasma levels and the classic CV risk factors (hypertension, smoking, hypercholesterolemia), with the exception of diabetes, showed a loss of their predictive power. A significant association between the redox system of CD34+ cells and mortality was also observed. These data suggest that, even in the elderly, CD34+ cells maintain regenerative/repair potential and consequently their role in predicting mortality, whereas traditional CV risk factors appear to loss their predictive potential, except for diabetes mellitus, that however was associated with lower CD34+ cell number. This study suggest that CD34+ cells could be considered as a biomarker of longevity even in very old subjects.

**Moderate dietary sodium restriction in outpatients with cirrhosis and ascites in the real life: adherence and more**

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**Department of Medicine DIMED, University of Padova, Italy**

**Background:** Regardless the controversial results of clinical trials, it is current opinion that in patients with cirrhosis and ascites, a moderate dietary sodium restriction (<90 mmol Na/day) should be indicated. Nevertheless, there is a lack of specific investigations on the correct adherence to a moderately dietary sodium restriction. In addition, some findings suggests that a dietary sodium restriction may impair the total calories intake, favouring the occurrence of complications with a negative effect on survival.

**Aims:** to evaluate the adherence of patients with cirrhosis and ascites to a moderately low salt diet and the impact of this on total intake of calories and on serum sodium concentration.

**Methods:** 120 patients with cirrhosis and ascites followed as outpatients were interviewed by the same operator on the basis of a pre-established questionnaire including 14 questions related to the low-salt diet. A quantitative assessment of nutrient and salt intake was performed via computerized software program (Winfood software package-MediMatica, Italy).

**Results:** Among the 120 included patients, only 37 were found to follow a moderate dietary sodium restriction (Group A). Of the remaining 83 patients (group B), 54 (65.1%) were convinced to follow a low-salt diet whilst 29 (34.9%) stated that they did not follow it intentionally. The mean daily sodium intake in patients of Group A and Group B was 79.5±5.5 mmol/day and 205.9±14.1 mmol/day respectively (p<0.0001). The adherence to a moderate dietary sodium restriction was related to the severity of cirrhosis as expressed by the MELD score (18.4±1.1 vs 16.4±0.5, p<0.05), serum level of urea (9.9±0.8 vs 7.6±0.5 µmol/l, p< 0.05), and presence of refractory ascites (67.6 vs 48.2, p<0.05). Adherence was higher among candidates to liver transplantation and among those who were followed as outpatients in a more strict way, by a new model of integrated specialized caregiving, the Care Management Program. Patients of Group A had a 18% reduction of the mean daily total intake of calories compared with Groups B patients (1582.5±43.6 vs 1658.7±45.5 kcal, p<0.0005) while there was no differences on the occurrence of hyponatremia (134.4±0.7 vs 133.7±0.5, p=NS).

**Conclusions:** Our data show a poor adherence of patients with cirrhosis and ascites to a moderate dietary sodium restriction. Adherence to diet seems to increase with the worsening of liver disease, probably due to the reduction of alternative therapeutic options. In addition, a deficiency in educational process to a moderate dietary sodium restriction can lead the patient to follow it through dangerous tools such as the reduction of the daily intake of food.

**Effect of mesenchymal stem cell treatment in colitis-associated colon cancer**

L.R. Lopetuso1, F. Scaldaferri1, V. Petito1, A. Puglisi1, S. Vettrano2, E. Sala1, M.E. Caristo4, V. Arena2, V. Cufian2, A. Sgambato2, A. Gasbarrini

1Internal Medicine, Gastroenterology Division, Catholic University of Rome, Rome, Italy 2Pathology, Catholic University of Rome, Rome, Italy 3Division of Gastroenterology, Humanitas Clinical and Research Center, Rozzano, Milan, Italy 4Experimental Center, Catholic University of Rome, Rome, Italy

**Background:** Mesenchymal stem cells (MSC) are potent immune regulators, proposed for local and systemic use in human and experimental IBD. Recent studies have reported that stem cells can promote cancer induction and progression, warning the use of stem cell in clinical condition associated to increased cancer risk, such as ulcerative colitis. Despite this, very few information exist on whether and how the use of mesenchymal stem cells influences cancer induction in chronic colitis.

**Aim&Methods:** Aim of this study was to evaluate the potential cancer risk associated to the therapeutic effect of MSC in murine model of colon cancer associated to chronic colitis. MSCs were isolated from adipose tissue of C57BL/6 mice, and afterwards analyzed for mesenchymal stem cell markers, proposed for local and systemic use in human and experimental IBD. Recent studies have reported that stem cells can promote cancer induction and progression, warning the use of stem cell in clinical condition associated to increased cancer risk, such as ulcerative colitis. Despite this, very few information exist on whether and how the use of mesenchymal stem cells influences cancer induction in chronic colitis.

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injection significantly reduced DAI in treated mice compared to controls, especially during the first 6 weeks of treatment. MSC treated mice showed also a lower body weight loss and a better survival rate compared to controls (100% vs 65%). At macroscopic analysis, MSC treated mice showed a reduced rate of colon cancer development compared to controls (33% vs 67%). However, the number of tumors per mouse did not differ significantly among mice which actually developed cancer (1.7 vs 1.5 tumors/mouse). In nude mice, there was no significant difference in tumor size between groups, while no lesions were found in mice injected with MSC alone. 

**Conclusion:** In conclusion, MSC did not increase cancer risk in this colitis model and did not affect the progression of pre-existing tumor lesions. MSC exerted an immune-modulatory effect in vivo, by decreasing the severity of colitis in mouse, suggesting that their anti-inflammatory effects may counterbalance their pro-carcinogenetic potential, even in pre-cancer condition such as chronic colitis. Further analyses are required to better define mechanisms of action underlying these findings.

**Protective effect of a specific mutant p53 during the early stage of hepatic steatosis: is it really a good news?**


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**Background and aims:** Nonalcoholic fatty liver disease (NAFLD) is the most common form of chronic liver disease worldwide. It is considered a multifactorial disorder, encompassing a broad spectrum of histopathology, ranging from simple steatosis to steatohepatitis which may progress to cirrhosis, leading ultimately to hepatocarcinoma development. Nevertheless, the molecular mechanisms underlying NAFLD development have not yet been completely elucidated. The p53 protein, besides its role as tumor suppressor, has recently emerged as an important regulator of cellular metabolism, particularly in response to stressful challenges, but its role in the onset and progression of NAFLD remains poorly understood. Thus, we analyzed how different forms of p53 may affect the metabolic stress response induced by an overload of free fatty acids (FFAs) in an *in vitro* model of NAFLD.

**Methods:** Two cell lines expressing different forms of the p53 protein, namely HepG2 (wild-type p53, wt) and HuH7.5.1 (Y220C mutant p53) were cultured for 14h and 24h in an enriched medium containing oleic and palmitic acid (2:1 ratio, respectively) at a final concentration of 1mM, the most abundant FFAs in western diets and liver triglycerides. Intracellular lipid accumulation was evaluated by AdiporRed assay. Cell viability was assessed using MTS assay, whereas apoptosis was quantified by the Caspase-3 activity assay and FACS analysis. The effect of the FFA overload on intracellular production of reactive oxygen species (ROS) was measured by the use of Dihydrorhodamine 123 (DHR123). mRNA and protein expression profiles of p53 and lipid metabolism-related genes were evaluated by qRT-PCR analysis and Western blotting, respectively. Transfection of the wt form of p53 in HuH7.5.1 was done in order to confirm the specific role of the mutant p53 in the observed modulation of its target genes.

**Results:** In the two cell lines the FFA treatment enhanced intracellular lipid content compared to controls. However, a statistically significant difference in the intracellular lipid accumulation between HepG2 and HuH7.5.1 cells was detected only after 14h, but no longer after 24h. Therefore, we focused our attention on the early stage of steatosis (14h). Following the FFA treatment, gene and protein expression of p53 and its active form were up-regulated in HepG2 and down-regulated in HuH7.5.1 cells. The FFA overload induced a similar down-regulation of the *de novo* lipid synthesis genes in both cell lines. On the contrary, the FFAs differently modulated genes and proteins of the fatty acid b-oxidation (FAO) pathway between the two cell lines as well as their production of ROS. Transfection experiments of the wt p53 in HuH7.5.1 cells, demonstrated that this cell-specific behavior was dependent on p53 status.

**Conclusions:** The FFA-induced stress triggers diverse adaptive p53-mediated responses of hepatic lipid metabolism depending on the status of p53. Strikingly, during the early stage of steatosis (14h), our results show that the Y220C mutant form of p53, compared to the wt form, fosters the FAO pathway leading to reduced intra-hepatic lipid accumulation and ROS production. These data prompt us to consider the Y220C mutation paradoxically protective against steatosis, although it is known to be one of the more prevalent oncogenic mutations. Thus, the mutant form of p53, inducing FAO, prevents cells from undergoing apoptosis, increasing their susceptibility to transformation. These findings may in part explain the occurrence of neoplastic nodules in steatotic patients who showed low liver inflammation, and who never developed fibrosis or cirrhosis. Altogether, our data provide further insights into the mechanisms underlying p53 regulation of hepatic lipid metabolism, paving the way for new therapeutic applications, and suggesting to carefully look at specific single nucleotide polymorphisms (SNPs) of p53 (such as the Y220C) to prevent hepatic transformation in the presence of liver steatosis. This contribution has been awarded as Best Communication.

**Sensorimotor abnormalities of the proximal stomach in functional dyspepsia: postprandial distress vs epigastric pain syndrome**

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**Background and Aims:** The Rome III classification of functional gastrointestinal disorders described two new entities for research purposes: the post-prandial distress syndrome (PDS), characterized by the presence of meal-related early satiation and fullness, and the epigastric pain syndrome (EPS), characterized by the prominent symptom of epigastric pain, which may or may not be meal-related. In a recent paper it was shown that in a large series of functional dyspepsia patients the highest symptom intensity after a meal was scored for postprandial fullness in those who report meal-related symptoms and epigastric pain compared to those reporting meal unrelated symptoms (1). Little information is available on the pathophysiology of these two syndromes as conflicting results are available for gastric emptying time, gastric accommodation and fasting sensitivity thresholds. The postprandial onset of symptoms in PDS patients focusses attention on the postprandial characteristics of sensorimotor activity of the stomach. Therefore, the aim of this study was to evaluate both fasting and postprandial gastric sensitivity thresholds, in addition to gastric accommodation and emptying time, in a group of patients with functional dyspepsia, according to the presence of meal-related or meal-unrelated symptoms.

**Patients and Methods:** Sixty consecutive HP negative, IBS-negative, GERD negative patients (38 F, 22 M, mean age 38±4 yrs) affected by functional dyspepsia according to Rome III criteria, took part in the study. Thirty-eight patients suffered from PDS and 22 had EPS. Fifteen healthy volunteers were also enrolled. At entry, symptom evaluation by a validated dyspepsia questionnaire was performed. Fasting and postprandial gastric sensorimotor activity was assessed by gastric barostat. A double lumen polyvinyl tube with an adherent, infinitely compliant plastic bag was inserted in the stomach. The tube was connected to a computer-driven programmable volume-displacement barostat device which maintains a constant preselected pressure within the bag, changing the bag volume of air by an electronic feed-
back mechanism. During sequential ramp distensions, the subjects were instructed to score their perception on a 0-6 scale. The perception threshold was defined as a perception score of 1 or more and the discomfort threshold as a perception score of 5 or more. Gastric accommodation was evaluated after a liquid meal administration (200 ml/200 Kcal). Gastric emptying time for solids was measured using the $^{13}$C-octanoic acid breath test.

**Results:** Both fasting and postprandial mean perception thresholds were similar among PDS, EPS and HV; mean fasting discomfort threshold was significantly different between the two groups of dyspeptic patients (12.1±3.8 mmHg in PDS patients, 11.0±2.9 mmHg in EPS patients) and healthy volunteers (16.3±2.2 mmHg; ANOVA p<0.0001). The mean postprandial discomfort threshold was also significantly different between the two groups of dyspeptic patients (9.3±4.2 mmHg in PDS patients, 10.5±3.3 mmHg in EPS patients) and healthy volunteers (15.8±2.5 mmHg; ANOVA p<0.0001). Very interestingly, postprandial discomfort threshold was significantly lower than fasting value (P<0.001) in PDS patients but not in the other groups. Mean postprandial modification of discomfort threshold was -2.8±4.4 mmHg in PDS patients, -0.55±1.7 mmHg in EPS patients (p=0.016). Mean gastric accommodation was similar among the three groups of subjects. Mean gastric emptying time was significantly different between dyspeptic patients (PDS 140±55 min and EPS 130±54) and HV (73±14 min; p=0.001; ANOVA).

**Conclusions:** Postprandial modification of visceral sensitivity may account for occurrence of postprandial symptoms.

**References:**

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**Short term albumin infusion as modulator of oxidative stress and platelet function in liver cirrhosis: a new therapeutic perspective**

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**Background and Aims:** Serum albumin is one of the most important antioxidant of human body that is reduced coincidentally with liver damage. The decrease of serum albumin could partly account for enhanced oxidative stress detected in cirrhotic patients. Recently, we demonstrated that in liver cirrhosis platelets are activated with a mechanism related to NOX2-generating isoprostanes. Thus, the aim of this proof-of-concept study was to test the effect of albumin infusion in modulating oxidative stress and platelet activity in cirrhotic patients.

**Methods:** In cirrhotic patients with serum albumin less than 2.5 g/dl, the effect of five-day albumin infusion (at least 40 g/die) on urinary 8-iso-prostaglandin F2α (8-iso-PGF2α) and soluble NOX2-derived peptide (sNOX2-dp) as oxidative stress markers and in vivo platelet activation indexes (soluble CD40 Ligand and soluble P-selectin) have been evaluated.

**Results:** Oxidative stress and platelet activation indexes decreased after albumin infusion in 3 cirrhotic patients (2 M, 1 F, aged 65±13 yr). In particular, urinary excretion of isoprostanes [from 572±111.40 to 313±134 pg/mg creatinine, p<0.001], soluble NOX2-dp levels [from 30±5 to 18±7.6 pg/ml, p<0.001], soluble CD40 Ligand [from 4.4±1.09 to 2.66±0.3 ng/ml, p<0.001], and soluble P-selectin [from 122±15 to 105±14 ng/ml, p<0.001] significantly decreased after 5 days of albumin infusion.

**Conclusions:** This study suggests a likely role of serum albumin infusion in modulating oxidative stress and platelet activation in cirrhotic patients. Further interventional trials are required to support this intriguing therapeutic perspective.

**Assessment risk of multidrug-resistant pathogens in community-onset pneumonia: the ARUC score**


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Pneumonia caused by multidrug-resistant (MDR) pathogens traditionally has been confined to the hospital setting. The rapid emergence of MDR bacteria that cause pneumonia in the community has created the need to identify risk factors for acquiring resistant pathogens by evaluating the contacts patients have with the healthcare environment as well as the patient’s characteristics. It has been demonstrated that a large group of patients with risk factors for acquiring MDR bacteria may present with differences in terms of epidemiology, clinical presentation and outcome. In the last year were published two important works (Shorr et al; Aliberti et al) that, responding to these questions, have created new scores to discriminate patients with an increased risk of developing community-onset pneumonia due to MDR pathogens. As matter of fact, the previous classification of health-care associated pneumonia (HCAP) seems to be no longer sufficient for early identification of patients with an increased risk of pneumonia due to MDR bacteria. The aim of our study was to validate these scores among our patients, coming from the community, who were hospitalized with pneumonia; a second purpose was to develop a new risk-scoring tool that could be used to identify subjects who come from the community to the hospital with pneumonia caused by resistant organisms. During the study period, from January 2011 to January 2013, were enrolled 1035 patients with community-onset pneumonia hospitalized, first, in the Emergency Department and, then, in the medical or infectious diseases wards of Policlinico Umberto I of Rome. Out of these, 612 patients were classified as community-acquired pneumonia (CAP), while 423 patients as HCAP, and were collected 133 variables for each patient. Among pathogens isolated, MDR represented the 27% of cases in CAP-group and 60% of patients in the HCAP-group. The scores proposed by Shorr and Aliberti were applied on our population, to evaluate sensitivity and specificity. The study population was further divided in 119 patients with MDR isolation and compared with 916 patients without MDR isolation. On the basis of multivariate analysis, was created a new score reported in Table 1. The new score, named ARUC (Assessment Risk of mUltidrug-resistant pathogens in Community-onset pneumonia) score, was compared with the score of Shorr and the score of Aliberti by the ROC curves: the sensitivity and specificity of ARUC score,
applied on our study population, were, respectively, 98% and 82%. In conclusion, the AUC score is an important evolution of the previous two scores, presented by Shorr and Aliberti, and of the HCAP definition for the early identification of patients with pneumonia due to MDR bacteria.

References

Determinants of vegetation size and embolic risk in infective endocarditis


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Background: Embolic events (EE) are a major complication of infective endocarditis (IE), adversely influencing the disease outcome. A larger vegetation size was consistently shown to increase the risk of EE. On hospital admission, weighting the embolic risk may improve patient management. Aim of this study was to identify determinants of vegetation size and embolic risk in patients with IE.

Patients and Methods: Four hundred and sixty-three consecutive patients, admitted to our center from Dec. 1999 to Dec. 2012, and discharged with a diagnosis of definite IE according to the modified Duke criteria, were enrolled in a prospective cohort study. Age, gender, comorbidities, type of structure involved, biochemical and microbiological data were analyzed in relation to vegetation size and location, evaluated on transthoracic or transesophageal echocardiography, and to the occurrence of EE.

Results: Most patients were male (71.9%), median age 59y [IQR 43-70]. Three hundred and three patients (65.5%) had a single valve endocarditis with native valve involved in 72.8% of cases. IE was mostly on left heart side (48.8% aortic, 35.3% mitral vs 12.2% tricuspid and 1.3% pulmonary). Fifty-two (11.2%) patients presented with multiple valve IE, and 17.9% of patients had PMK/AICD endocarditis (65 on PMK 18 on AICD), while 12 patients (2.6%) had valve and device involvement. The most common pathogens were streptococci (31.1%), coagulase-negative staphylococci (18.1%), Staphylococcus aureus (14.5%), and enterococci (10.4%). In the 213 pts whose vegetation size was prospectively recorded, median length was 1.4 cm [IQR 0.9-2 cm] (min 0.1-max 7.2 cm). A consistent increase in vegetation size was observed with advancing age (1.3 cm at <45 yrs vs 1.6 cm at >70 yrs). Left sided and particularly aortic IE cases had smaller vegetations than right sided (1.05 and 1.35 cm on aortic and mitral valve vs 1.7 and 1.8 cm on tricuspid and PMK/AICD, respectively; p<0.01). Smaller vegetations were observed in patients with prosthetic IE, all on anti-thrombotic agents at IE onset (0.9 [IQR 0.6-1.37] vs 1.5 cm [IQR 1.0-2.0] in native valve IE; p<0.01). A history of myocardial infarction was more common (15% vs 7%; p=0.098) among patients with larger vegetations (i.e. >1.4 cm). Malignancies were also more prevalent in patients with larger vegetations (27% vs 15%; p=0.047). White blood cells and D-dimer levels were higher in patients with larger vegetations (9.745 vs 8.930/uL and 673 vs 596.5 ng/mL). Moreover a progressive elevation of C-reactive protein (CRP) values with increasing vegetation size was noted. Two hundred and twenty-seven patients (49%) experienced an EE, in 150 cases (66.1%) as one of the presentation symptoms. However, most of these patients (84.7%) experienced a second EE during the index hospitalization in our unit. EE were more common in males than in females (47% vs 37%) and were more common in younger patients (32.6% in pts <45 yrs vs 18.5% >72 yrs). The rate of EE increased progressively with enlarging vegetation size, with an incidence of embolism reaching 62.7% with a vegetation size ≥2 cm. The occurrence of EE was 58.1% in right sided and 44.8% in left sided IE cases (p=0.016). Increasing CRP levels on admission correlated with a higher rate of EE. Moreover, D-dimer levels were also significantly higher in patients with an EE at IE onset than in those who did not experience any embolism (1.030 vs 503 ng/ml; p=0.0018). Finally, mortality was significantly higher in patients with EE (13.6% vs 7.2% in those without any embolic complication; p=0.035).

Conclusion: EE represent a common complication of IE, occurring in almost half of cases. Embolism is correlated with vegetation size, right heart involvement and a younger patient age, and is associated with a higher mortality rate. Patients with aortic valve involvement and/or prosthetic valve infection showed smaller vegetations and a lower rate of EE. Our data, derived from a large, prospective cohort study, may provide useful information for embolic risk stratification and aid in the clinical decision making in patients with active IE.

This contribution has been awarded as Best Communication.

Changes in ventricular kinetic in iron overload thalassemia major-related cardiomyopathy

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Background and aims: Cardiac iron overload due to chronic blood transfusion is traditionally considered to be the main cause of thalassemia cardiomyopathy. Detection of subclinical cardiac involvement is crucial to reverse iron overload cardiomyopathy through prompt changes in therapy. Unfortunately, echocardiographic standard parameters are not good predictors for neither cardiac dysfunction nor significant iron deposition in β-thalassemia major (β-TM). Strain imaging is a novel echocardiographic method that can detect early stages of myocardial dysfunction before conventional echo parameters become abnormal. The aim of the study was to determine myocardial strain in β-TM patients and assess its relationship with myocardial iron deposition as detected by T2*-cardiac MRI (CMR), the up-to-date standard for quantifying cardiac iron overload.

Methods: 55 β-TM patients were prospectively enrolled. One of the inclusion criteria was the availability of a T2*-CMR imaging, with a relatively short echo-CMR interval. Clinical and laboratory data were collected. All cases underwent standard echocardiography and subsequent off-line strain imaging through 2D-speckle tracking analysis to assess segmental peak systolic strains (longitudinal, circumferential, radial) and end-systolic rotation of the myocardium at the level of papillary muscles. The results were compared with those of 20 previously analyzed normal controls. Echocardiographic strain imaging data were subsequently compared with cardiac T2*-CMR values. Two groups were studied: patients with significant cardiac iron overload and cardiac T2* value ≤20 ms (low T2*, n=21), and patients with T2* >20 ms (normal T2*, n=34). Student’s t-test and Pearson correlation analyses were used; a P value <0.05 was considered significant.

Results: No significant differences were observed in echocardiographic indexed volumes and ejection fraction between cases and controls. However, compared to controls, β-TM patients showed significant, uniform lower circumferential and radial strain, both global (P<0.01) and for all segments.
Moreover, remarkable quantitative and qualitative differences were observed in the end-systolic rotation, with a considerable reduction in all segmental rotation values (all P values <0.001) and a change in the direction of rotation in 4 out of 6 segments. On the contrary, no statistically significant difference in regional strains and rotation was detected between the low- and the normal T2* group, despite a general and uniform trend for lower values in the low T2* group, especially for rotation values. Noteworthy, no significant differences were observed in standard echocardiographic and CMR parameters. Finally, there was no significant correlation between myocardial strains and rotation, cardiac T2* values (severity of iron overload), and other markers of iron overload such as serum ferritin levels, hepatic T2* and iron intake. Neither standard echocardiographic and CMR parameter, nor traditional markers predicted significant myocardial iron deposition.

**Discussion:** The myocardial subclinical dysfunction observed in β-TM patients well correlated with the characteristic distribution of iron deposition into the myocardium described in literature, with the subepicardial layer, which mainly determines rotation, being the preeminent site. However, in contrast to a few previously published reports, we were unable to observe any correlation between strains, torsion and the severity of cardiac iron overload (i.e., T2*). These preliminary findings support recent acquisitions in literature showing that myocardial iron overload, although still considered to hold a central role as a triggering factor, is not the only mechanism involved in the development of β-thalassemia major cardiomyopathy. In fact, the pathophysiology seems to be multifactorial, and is not simply the direct consequence of myocardial iron infiltration, but the combined outcome of several factors most of which still to be clarified, including immune-inflammatory and genetic ones, together with a role of systemic effects of iron load, which may affect the heart indirectly, as well as mal-adaptive myocardial hypertrophy due to volume overload.

**Conclusions:** Although echocardiographic strain imaging cannot substitute T2*-CMR imaging to assess significant cardiac iron overload, it can predict subclinical myocardial dysfunction irrespective of T2*-CMR values. Therefore it may be able to detect early markers of subclinical cardiomyopathy and could be useful for the correct timing of cardioactive therapy.
**Poster Session**

**Saturday, October 26th 2013**

**Allergology and Clinical Immunology**

An uncommon cause of refractory pleural effusion in an elderly patient

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A 79-year-old patient with progressively worsening dyspnoea and weight loss was referred to our Clinic from a Pneumology Unit. On examination, he presented with swelling of the legs, genitalia and neck and chronic bilateral pleural effusion. He had no clinical, laboratory or radiological evidence of pulmonary tuberculosis or malignancy. The haemogram was normal and ESR was 25mm/hr. He hadn’t had renal insufficiency, liver function and thyroid profile were normal. ANA was positive at 1:320. Urine examination showed slight proteinuria. Pleural drainage showed 1.5 liters of clear effusion and was negative for neoplasia or infection. A treatment with diuretics was successfully started. He was diagnosed with Undifferentiated Connective Tissue Disease and started therapy with hydroxychloroquine and low-dose steroids.

One year later, he presented with asthenia, dehydration and constipation. He had mild renal insufficiency with blood urea of 50 mg/dl, creatinine 1.36 mg/dl and proteinuria (1.5 g/24h). Serum levels of pro-BNP were increased (4157 pg/ml), and liver function tests were altered with increased transaminases and elevated GGT, ALP and bilirubine. Serum proteins electrophoresis and immunofixation were negative, urine immunofixation showed the presence of a monoclonal kappa chain protein (1500 mg/dl). The echocardiography showed bi-atrial enlargement and chest CT demonstrated mild pleural effusion with bilateral pachipleuritis. Abdominal CT scan was normal. Abdominal fat aspiration stained positive with Congo red and amyloid deposition was confirmed by immunohistochemistry. This patient didn’t had a detectable monoclonal K protein, but he had proteinuria and urine monoclonal protein. Transthoracic echocardiography didn’t show a typical appearance (ventricular hypertrophy or inter-atrial septum hypertrophy with restrictive pattern), but serum levels of NT-pro-BNP were strongly increased. He developed a significant involvement of the kidney, liver and the heart induced by amyloid deposition.

The prognosis of patients with AL amyloidosis is poor, even if in recent years has improved. Median survival is 13 months without treatment and can be extended with courses of oral melphalan and prednisone. However, such treatment not infrequently results in incomplete remission of disease or failure of organ dysfunction reversal due to amyloid deposition.

Here we discuss the differential diagnosis and treatment options for AL amyloidosis, also considering the patient’s age and his comorbidities.

**Latex immunotherapy effectiveness**

Arianna Aruanno, Eleonora Nucera, Alessandro Buonomo, Valentina Pecora, Amira Colagiovanni, Angela Rizzi, Lucilla Pascolini, Anna Giulia Ricci, Simona Mezzacappa, Alessia Di Rienzo, Michele Centrone, Domenico Schiavino

Servizio di Allergologia - Policlinico A. Gemelli, Roma

**Background:** Since 1970 allergic reactions to natural rubber latex (NRL) have been reported and during the last decades they have become an emerging clinical problem of public health. Symptoms of NRL allergy ranged from contact urticaria and asthma to systemic anaphylaxis and they are elicited by direct contact with NRL items (i.e. medical devices) or by inhalation of latex airborne proteins. Proper diagnosis of latex allergy (skin prick test, specific IgE value, provocation challenge test) is important for appropriate preventive measures and treatment. The only etiological and decisive therapy, able to influence the natural history of latex allergy, is represented by the specific desensitization. This treatment is characterized by a very small incidence of adverse reactions, good patient compliance and especially by a high success rate. At the end of therapy, in fact, almost all patients are able to wear latex gloves, to undergo medical or surgical intervention, to stay in environments where there is latex.

Our protocol of rush latex desensitization treatment is performed in 4 days, during which increasing doses of latex extract (Alk-Abellò, Milan) are administered under patient’s tongue until the highest dose of 500 μg of latex. A maintenance therapy (10 drops of undiluted solution three times a week) is followed at home. Every patient is equipped with an emergency kit that includes autoinjectable epinephrine, betamethasone and chlorphenamine and suggested to undergo future specialist visits in latex-safe environment until the latex tolerance is not been acquired.

**Research design and methods:** We studied 39 and 35 NRL allergic patients, who are still performing a sublingual desensitization treatment, respectively, for more than 4 years (group 1) and for less than 4 years (group 2), according to our protocol described in Figure 1. Adverse reactions were monitored. The primary endpoint was the results of latex challenge tests, while the secondary endpoints were the latex skin prick test and the serum specific IgE.

**Results:** No sublingual immunotherapy-related side effects were observed. A significant reduction of the positive cutaneous challenge test was observed both in the first and in the second group (p < 0.0001 and p < 0.05). Also the mucous challenge presented the same statistical significance (p < 0.04), while the positive conjunctival and nasal provocation test showed significant reduction only after 4 years of immunotherapy (respectively p < 0.01 and p < 0.02).

Concerning the immunological changes, although we found out a reduction of skin prick test wheal areas and specific IgE values, these data didn’t seem to be statistically significant in both groups.

**Conclusions:** Four years of latex sublingual desensitization treatment seem to be safe and can be used as an effective treatment for the NRL allergic patients who have difficulties in applying adequate avoidance measures.
Figure 1. Rush sublingual desensitization treatment to latex

<table>
<thead>
<tr>
<th>Day</th>
<th>Concentration</th>
<th>Administered dose</th>
<th>Total dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1°</td>
<td>From $10^{-18}$ to $10^{-10}$</td>
<td>1 drop every administration</td>
<td>28 per $10^{-10}$ μg of NRL</td>
</tr>
<tr>
<td>2°</td>
<td>From $10^{-9}$ to $10^{-1}$</td>
<td>1 drop every administration</td>
<td>2.8 μg of NRL</td>
</tr>
<tr>
<td>3°</td>
<td>Undiluted solution (500 μg/ml)</td>
<td>1,2,3,4,5,10 drops</td>
<td>500 μg of NRL</td>
</tr>
</tbody>
</table>

Maintenance treatment
10 drops 3 times a week

Integrated gastro-rheumatologic evaluation in patients affected by inflammatory bowel disease: our experience

Balloni A, Cepeci W, Rossini M, Luchetti MM, Gabrielli A

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Introduction: Extraintestinal manifestations are common in Inflammatory Bowel Disease (IBD) affecting up to 35% of patients. Peripheral arthritis, enthesitis and axial arthropathy are typical extraintestinal manifestation in Crohn’s Disease (CD) and Ulcerative Colitis (UC) (1). Those manifestations are closely related to IBD activity and the treatment must consider both intestinal and extraintestinal symptoms. Diagnosis of Enteropathic Spondyloarthritides (ES) is generally established on the medical history and physical examination. The management of patients requires an active cooperation between the gastroenterologist and rheumatologist (2).

Objective: We describe our clinical experience of integrated gastroenterological and rheumatological evaluation in the early diagnosis, treatment and follow-up of patients affected by Enteropathic Spondyloarthrititis.

Material and Methods: We evaluated the presence of signs and symptoms of Spondyloarthrititis, in patients affected by IBD admitted to our integrated gastroenterological and rheumatological ambulatory, for two years (2011-2012). During the medical examination the Gastroenterologist is helped by a Internal Physician expert in rheumatologic disease who investigated patients about the presence or the absence of inflammatory pain of joints and enthesis (inflammatory low-back pain, morning stiffness, enthesitis, dactylitis, peripheral arthritis, good response to NSAIDs). Diagnosis was made in accord to to the European Spondyloarthropathy Study Group (ESSG) criteria. Patients selected during this first qualitative screening underwent to a second depth medical evaluation including clinimetric assessment for Spondyloarthrititis (BASMI, BASFI, BASDAI, MASES and evaluation of peripheral swollen e painful joints) and general quality of life scores (SF-36, HAQ and VAS), search of HLA-B27 and radiological exams (MRI/Rx of sacroiliac joint or spine, Rx of peripheral joints, Echography of enthesis). Results: We evaluated 290 consecutive patients affected by IBD. We diagnosed a Enteropathic Spondyloarthrititis (ES) in 32 patients (9,1%): 9 patients present an axial arthropathy with spondylitis or sacroileitis, 13 patients present a peripheral involvement, 10 patients present both axial and peripheral involvement. In our data, the prevalence of ES is similar to other European studies (average 10-20%). We report a prevalence of female sex with an average age of 48 years, and a clinical presentation of the disease before of 45 years old. In 75% of patients clinical rheumatological symptoms were concomitant with bowel symptoms (within a year). Only in 25% of patients the presentation was later (more than 2 years). The integrated evaluation permitted us to modify therapy in 22 patients, achieving a clinical improvement of intestinal and extraintestinal manifestations.

Conclusions: An integrated gastroenterological and rheumatological evaluation is able to identify early a cohort of patients affected by IBD an Enteropathic Spondyloarthrititis. Early diagnosis of ES is useful for the clinician to modify therapy and clinical approach to the patients, with the aim of stop the progression of flogosis and the damage progression to functional inability.

References:

Silicone-induced hypercalcemia in a patient who underwent sex reassignment surgery


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A 48-years-old Hispanic woman presented to our observation dehydrated, with nausea, vomiting, abdominal pain and fever. She had a history of sex reassignment surgery along with mastoplastic and several silicone injections, chronic renal failure, arterial hypertension and dyslipidemia. Clinical examination was unremarkable except for the presence of extensive, non-tender, subcutaneous calcifications on the lower abdomen and glutes, likely related to previous silicone injections. Moreover she had surgical wounds on both buttocks, of which the left one was likely infected. Laboratory tests showed leukocytosis, increased inflammatory markers, increment of baseline serum creatinine to 6.4 mg/dl, hypercalcemia (14.7 mg/dl) and hypercalciuria (397 mg/24h), low serum intact parathyroid hormone levels (5.3 pg/ml) and in range 1,25 dihydroxyvitamin D levels. The HIV test resulted negative. A MRI of the abdomen depicted the subcutaneous lumps as siliconomas. The patient was treated with prednisone 25 mg/die, massive intravenous hydration and furosemide, with progressive renal function recovery and hypercalcaemia resolution. A gluteus wounds swab showed the presence of E.Coli, so a prompt antibiotic therapy with Ertapenem was started. Siliconosis, an immune mediated condition induced by silicone implants, is one of the four entities included in ASIA syndrome (Autoimmune/autoinflammatory syndrome induced by adjuvants). A granulomatous reaction to silicone injections may cause hypercalcemia, which can be either mediated by 1,25-dihydroxyvitamin D produced by macrophages or by increased PTHrP levels (stimulated by TNF-α and IL-6). This hypothesis is moreover supported by the excellent response of hypercalcemia to glucocorticoid therapy, which decreases PTHrP levels and inhibit the macrophage-derived 1-α-hydroxilase, hence leading to 1,25(OH)2D reduction. The pathomechanism of silicone-induced hypercalcemia is not entirely understood and seems to be different from the vitamin D dependent mechanism of granulomatous disease, but it may be related to some altered unspecified prostaglandin metabolism. Although the rarity of silicone-induced hypercalcemia makes further study of underlying mechanisms difficult. when removal of disseminated silicone seems to be impossible, cortisone treatment is a suitable therapy.

HAART therapy and nephrotoxic agents. An issue not to be neglected!


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We describe the interesting case of a 58 years-old man who presented with dyspnoea. His clinical history was remarkable for a HIV infection under HAART therapy with Ritonavir 100 mg plus Azatanivir 300 mg plus Tenofovir and Emtricitabine. Moreover his clinical history was characterized by a HCV infection and a larynx neoplasm which was treated with chemotherapy and radiotherapy. Few days before being admitted to the hospital he underwent a total body CT scan that showed multiple hypo-dense nodules of the brain, suspected for being secondary lesions, but a MRI of the brain classified these lesions as abscesses. At the time of admission in our department his physical examination was remarkable for diffuse bronchospasm, with no other signs or symptoms. An empirical antibiotic therapy was therefore started for the brain abscesses consisting of Vancomycin and Meropenem. Because of the respiratory discomfort metlyprednisolone was started, which caused progressive increase of the blood glucose levels. Hence we decided to prescribe metformin. But a month after the admission the patient suddenly got an acute renal failure, with prolonged period of anuria and creatinine rising from 1 mg/dl to 4 mg/dl. Moreover the arterial blood gas revealed a marked lactic acidosis. Promptly tenofovir, metformin and vancomycin were stopped, and a dialysis treatment was started, but unfortunately the patient died from acute gastrointestinal bleeding. Tenofovir is proved to be a very effective therapy in HIV patient, but health professionals must be aware of the possible side effects of the association with other nephrotoxic agents as vancomycin and metformin. Therefore a close monitoring of serum creatinine is strongly warranted.

Management of hyperglycaemia in a clinic of internal medicine: a tailored approach

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Context: The growing prevalence of diabetes mellitus (DM) and the effect of “acute stressors” on the carbohydrate metabolism are gradually increasing the rate of hospitalization for hyperglycaemia; this condition, even when it is not the main reason for hospital admission and the patient is not known as diabetic, is often observed at the emergency room or during the first days in the ward. In addition the problem can occur following other triggers, such as surgery or particular drug treatments, and hyperglycaemia has clearly an important impact on the outcome of these patients.

Objective: Aim of our study was to define a protocol, shared by physicians and nurses, in order to improve the management of cases of hyperglycaemia and eventually hypo-glycaemia. The protocol was prepared in agreement with international guidelines of DM management but with some adjustments related to our assistance needs. Another aim of the study was to verify whether the determination of glycated haemoglobin (HbA1c) in acutely ill patients could reduce cases of misdiagnosed DM.

Patients: We studied 41 patients transferred from the emergency department to our unit of internal medicine and showing, in the first 24-48 hours, at least two fasting glycaemic values above 140 mg/dl or one postprandial value above 180 mg/dl. In these patients a determination of HbA1c was requested. Therefore a differential stress-induced hyperglycaemia and overt DM. Exclusion criteria were the treatment with parenteral or enteral nutrition and the inability to eat. Patients were divided in two groups by temporal criteria: the first 21 patients (Group A) were treated by a “sliding-scale” insulin regimen whereas the subsequent 20 patients (Group B) by a “basal-bolus” regimen with corrections of the insulin units decided by the nurses on the bases of glycaemic values in agreement with a precise medical prescription. The 2 groups resulted adequately sex and age-matched (Group A 13 male and 8 female, mean age 72±11.8 years, Group B 10 male and 10 female, mean age 74±9.1 years) and with a similar value of HbA1c (8.15%±1.3 vs 8.02%±1.28, respectively).

Intervention: All patients were subjected to three pre-prandial glycaemic controls daily and one 2-hours post-prandial glycaemic control at 9 p.m. Group A patients were treated with currently used “sliding-scale” regimen of our unit, in which regular insulin was administered only for glycaemia >200 mg/dl (for glycaemia ≤200 no insulin was injected, for glycaemia between 201 and 250 mg/dl 4 units, for glycaemia between 251 and 300 mg/dl 6 units, and for glycaemia above 301 mg/dl 8 units), whereas group B patients were treated by a tailored “basal-bolus” regimen. We determined the daily insulin requirements: for patients with age over 70 years or with a glomerular filtration rate under 60 ml/min we calculated 0.2 insulin units/kg/day; for the other patients 0.4 insulin units/kg/day if fasting glucose level were between 140 and 200 mg/dl or 0.5 insulin units/kg/day if fasting levels were over 200 mg/dl. 50% of the total amount was administered as glargine insulin, injected at 10 p.m., and the other 50% as regular human insulin, subdivided in breakfast (10% of the total amount), lunch (20%) and dinner (20%) administration. An adjustment to this prescription could be done based on pre-prandial glycaemic values: to decide these adjustments group B patients were defined as “highly sensitive” (HS) or “normally sensitive” (NS). HS patients included those never treated by insulin, with a poor prognosis quoad vitam, or with severely impaired renal function. This differentiation was made to tailor insulin treatment: the additional doses to the prescribed insulin were, in the HS-group, of 1 Unit for glycaemia between 141 and 180 mg/dl, of 2 Units for glycaemia between 181 and 220 mg/dl, of 3 Units for glycaemia between 221 and 260 mg/dl, of 4 Units for glycaemia between 261 and 300 mg/dl, of 5 Units for glycaemia between 301 and 350 mg/dl, of 6 Units for glycaemia above 351 mg/dl. The NS-group had a similar regimen but with twofold units. In fact the additional doses to the prescribed insulin in HS patients were less than in NS patients.

Results: Group B patients showed better results than Group A patients in terms of glycaemic levels and variability. Both pre-prandial (Group B 142.8±17.5 mg/dl, Group A 188±52.8 mg/dl, P<0.05) and post-prandial (Group B 183.4±15.5 mg/dl, Group A 223±56.9 mg/dl, P<0.05) glycaemic values were significantly lower. In addition cases of hypoglycaemia were dramatically reduced (Group A 33.3%, Group B 5%, P=0.045). Finally a higher attention to the hyperglycaemic state together with sampling of HbA1c allowed to make a new diagnosis of DM in 17% of the 41 patients, in agreement with the scientific literature.

Conclusion: The protocol was successfully managed by physicians and nurses. The experimental “basal-bolus” regimen demonstrated a better glycaemic control versus “sliding-scale” insulin regimen, with lower glycaemic variability: consequently a lower number of cases of hypoglycaemia occurred. Lastly our tailored “basal bolus” protocol seems to be useful also in terms of health costs, with a significant decrease of days in hospital. This aspect needs, of course, to be confirmed with a larger number of patients.

ABO blood group and venous thromboembolism

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Background: Research on ABO have reported an association between ABO and different diseases processes. Genome-wide association studies have conclusively linked the ABO locus to pancreatic and gastric cancer, myocardial infarction and coronary heart diseases and ischemic stroke. Some studies have investigated the relation between blood groups and venous thromboembolism (VTE), suggesting an increased risk for VTE among individuals with non-O blood types (1-2).
The following chart describes the frequency and the risk of VTE:

<table>
<thead>
<tr>
<th>ICD-9</th>
<th>Gruppo</th>
<th>n°</th>
<th>%</th>
<th>Chi square</th>
<th>p</th>
<th>OR</th>
<th>C.I.95%</th>
<th>Sup</th>
</tr>
</thead>
<tbody>
<tr>
<td>415.1</td>
<td>PE</td>
<td>A-AB</td>
<td>645</td>
<td>50.8</td>
<td>10,494</td>
<td>0.001</td>
<td>1,201</td>
<td>1,075</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>495</td>
<td>39.0</td>
<td>8,889</td>
<td>0.003</td>
<td>0,841</td>
<td>0,751</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A</td>
<td>385</td>
<td>46.5</td>
<td>6,175</td>
<td>0.013</td>
<td>1,190</td>
<td>1,037</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AB</td>
<td>48</td>
<td>5,8</td>
<td>6,538</td>
<td>0.011</td>
<td>1,464</td>
<td>1,091</td>
</tr>
<tr>
<td>451</td>
<td>PVT</td>
<td>A-AB</td>
<td>433</td>
<td>52,3</td>
<td>12,151</td>
<td>0.001</td>
<td>1,276</td>
<td>1,112</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B-AB</td>
<td>143</td>
<td>17,3</td>
<td>4,573</td>
<td>0.032</td>
<td>1,219</td>
<td>1,016</td>
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<tr>
<td></td>
<td></td>
<td>0</td>
<td>300</td>
<td>36,2</td>
<td>16,05</td>
<td>0.0001</td>
<td>0,748</td>
<td>0,649</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A</td>
<td>453</td>
<td>49,1</td>
<td>17,832</td>
<td>0.001</td>
<td>1,322</td>
<td>1,161</td>
</tr>
<tr>
<td>453</td>
<td>OVET</td>
<td>A-AB</td>
<td>501</td>
<td>54,3</td>
<td>24,001</td>
<td>0.001</td>
<td>1,384</td>
<td>1,214</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>339</td>
<td>36,7</td>
<td>15,402</td>
<td>0.0001</td>
<td>0,764</td>
<td>0,668</td>
</tr>
</tbody>
</table>

The aim of this study was to verify which type of ABO blood group genotypes prevail in a population admitted to Ferrara Hospital for VTE.

**Study Design and Methods:** In this study we analyzed the discharge hospital sheets (DSO) of the 345,607 patients admitted to Ferrara Hospitals from 1 January 2000 to 31 December 2011. We considered all patients with VTE diagnosis (both primary or secondary): Pulmonary Embolism And Infarction (PE - ICD 9 code 415.1), Phebitis And Thrombophlebitis (PVT – ICD9 code 451) and Other Venous Embolism And Thrombosis (OVET – ICD 9 code 453). All the patients’ blood group has been determined by the Provincial Immunohematological and Transfusional Service for medical reasons (transfusion, pregnancy, blood donation...). For each patient, we considered the first medical event.

**Results:** We analyzed 345,607 DSO, relative to 164,438 patients. For 65,402 of them we determined the blood group (39.8 % of all the admitted patients). 1,270 of them was affected by PE, 923 had a PVT and 923 OVET. In a multivariate analysis (including sex, age, diabetes, obesity, hypertension, dyslipidemia, hyperuricemia, hyperhomocysteinaemia, neoplasm), patients with VTE events, the A- allele was associated with an increased risk of disease.

**Conclusion:** The results of the present analysis confirm previous studies findings indicating an increased risk of thrombosis associated with the non-O blood group.

VTE is a major health problem that results in a significant burden on hospitals and patients, so it will be very important to find risk factors and create surveillance or prevention program. Non-O blood group is a candidate to be one of the most important genetic risk factors for venous thrombosis.

**References:**

**A clinical atypical syndrome**

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A 70-year-old man was admitted to our Internal Medicine Division because of acrocyanosis, bilateral hand pain, diffuse myalgias, low-grade fever and mild dyspnea at rest.

The patient was a previous strong smoker, had a history of diabetes mellitus, hypertension and coronary heart disease in optimal treatment and was asymptomatic up to 15 days before admission.

We observed at physical examination acrocyanosis of the hands, digital clubbing, diffuse ronchi and rales in the chest, small palpable superficial lymph nodes. The temperature was 37.7°C, the respiratory rate 26/minute, the blood pressure was normal and the oxygen saturation was 88% while the patient was breathing ambient air.

Considering a prevalent lung disease, we carried out complete routine blood panel, N-terminal pro-B-type natriuretic peptide, procalcitonin, blood cultures, autoimmunity tests as well as chest X-ray (with diffuse pulmonary opacities) and following CT of the chest and abdomen in injection of contrast material.

The blood tests were normal except for hemoglobin 10.9 g/dl, ESR 76, CRP 9 mg/dl, LDH 1084 U/l, CPK 3377 U/l, ANA positive at 1:640, ENA 10.9 (n.v < 0.2) with strong positivity of anti-Jo1 (7.3 with normal value <1.1), CIC 24.5 (n.v < 4.4); trace of proteinuria in the urinalysis. The CT revealed bilateral diffuse lung ground-glass opacities, especially in subpleural position and some mediastinal lymphadenopathy; nothing in the CT of the abdomen.

A bronchoscopic lung biopsy was performed with negative direct bacteriologic and cultures. Hystological examination showed no inflammation and a pattern of diffuse interstitial fibrosis.

The patient was treated with immunosuppressive therapy (azathioprine and prednisone) with slow and progressive resolution of the symptoms and normalization of the blood tests.

After six months from his admission the patient is asymptomatic and the acrocyanosis has disappeared.

The role of inducible nitric oxide synthase in the pathogenesis of chronic idiopathic urticaria

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**Background:** Urticaria is a common complaint, affecting about 10% of the general population and characterized by extremely itchy, raised, erythema-
tous plaques often associated to angioedema. More frequently, especially in
the pediatric age, symptoms are acute and elicited by allergic triggers able
to induce mast cell degranulation and histamine release. However, hives
may be long lasting and when present for at least 6 weeks, almost daily ba-
sis, chronic urticaria (CU) occurs. CU has a profound impact on the quali-
ty of life and it is often refractory to antihistamine therapy, requiring high
doses of steroids or use of immunosuppressant drugs to control symptoms.
Although considered to be in most of cases idiopathic, the finding of skin
reactivity to autologous serum, as well as the detection of functional IgG
targeted to IgE or to the high affinity IgE-receptor (FceR), suggested an au-
toimmune pathogenesis of the disease in a subgroup of patients. Further da-
ta, on the other hand, pointed to the involvement of different factors able to
induce mast cell degranulation or directly act on the cutaneous microvas-
culature. The capacity of nitric oxide (NO) to elicit vasodilatation and to in-
crease vascular permeability suggests that NO might be included among
these putative mediators.

Objectives of the study: To investigate the role of the inducible isofrom of
NO-synthase (iNOS), mainly expressed by circulating monocytes in in-
flammatory conditions, in the pathogenesis of chronic idiopathic urticaria
(CIU).

Methods: On blood mononuclear cells from 30 symptomatic patients with
CIU and 10 healthy control subjects (CONT), we assessed:
A. iNOS transcriptional expression, by retrotranscription of messenger
RNAs and subsequent Polymerase Chain Reaction with specific primer
for iNOS.
B. iNOS protein expression, by Western Blot with specific, polyclonal an-
ti-iNOS immunoglobulins.
C. NOS enzymatic activity, by a colorimetric assay for nitrates.

Data were analyzed with Wilcoxon test (independent samples).

Results: No significant difference in the transcriptional expression of iNOS
was found between CIU patients and healthy subjects (0.63±0.31 vs.
0.52±0.23; means±SD; p=0.301; Fig 1) On the other hand, iNOS protein ex-
pression was higher in CIU patients than control population (1.79±0.86 vs.
1.11±0.31; p=0.005; Fig 2), and paralleled by a significant increase in NOS
enzymatic activity (nmol NO/µg protein lysate: 49.76±29.31 vs.
27.25±14.70; p=0.043).

Conclusions: The increased expression of both iNOS protein and NOS en-
zymatic activity in CIU patients, with no differences in transcriptional ex-
pression between patients and controls, suggests an activation of nitric ox-
ide synthesis by posttranscriptional regulation. Although this findings might
represent an aspecific epyphenomenon, due to an inflammatory response
elicited in CIU by autoimmune processes, it is remarkable that most of CIU
patients don’t show neither skin reactivity to autologous serum nor the
presence of functional anti-IgE or anti-FceR IgG, leaving the pathogenesis
unaccounted for. Therefore, based on our results we can speculate the in-
volvement of nitric oxide in the pathogenesis of CIU and consider the op-
portunity to assess the efficacy of enzymatic inhibitors of iNOS - or of argi-
nine inhibitors - in the treatment of chronic idiopathic urticaria.

African experience of a resident in internal medicine: real life

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The flight from Rome starts in the best way, after I am stopped for board-
ing scissors that I have in my dressing kit, they fortunately let me pass.
Thus began my first flight by plane without major problems. After 12hrs I
land in Mombasa and so begins the adventure of a resident in internal med-
icine. A 2 hours trip takes me from the airport to Malindi and then Takaye,
my final destination. What appears to my eyes immediately are the huts,
huts between the buildings, over ruined and dusty roads. The weather is
heavy, this is the hottest summer in the last 10 years (just my luck), from
one p.m. it becomes difficult to even talk, just imagine in another lan-
guage. Even the movements are tiring, here everything is in the middle of
the savannah. The only means of transport is the tuctuc, an Ape 50 with an
electric start, modified to carry three people and certified by the stamp of
the municipal police in Malindi (I did not understand where the seatbelts
were). Today I saw for the first time the surgery, at the Takaye Primary
School, a government school in which there is a point of first Aid run by
Pole Pole Kenya Onlus, and I met the nurse Esther. The surgery is small,
but there is all the (minimum) essential, it is clean but with an unwanted
tenant ... ants. Here everything is very slow, and I’m getting used to this
very willingly, even medicine is slower: every medical visit is a magical
rite of which liturgy are courtesy and upbringing. In this surgery we pro-
vide support for small wounds, minor trauma, insect bites, burns or rash-
es etc... And so I come to meet my first clinical problem, the tungiasis, a
"flea" of sand that lays its larvae in the subcutaneous tissue, and infests the
feet of anyone in this village. I was invited to look at the feet and the
wounds of these children, who are so afraid even at the thought that I can
touch them. I have experienced impotence and the sense of failure in front
of their demand for health and happiness. I also realized the novelty of the
task assigned: trying to develop a mindset of prevention. This task will be
very difficult to reach because everyone (like us) wants the treatment as
soon as possible... This morning the surgery “limps”: irritated eyes ... eye
drops; cough ... syrup. Here you have to be like this: never send someone
home without some kind of drug, if even the most trivial of analgesics. You
risk a kind of syndrome of abandonment if you send someone home with-
out any treatment. I experienced a second challenge: communication.
There are those who only speak Swahili, and it is almost impossible to
draw up the current medical history, let alone the past medical history.
Here if I say “a week ago” is like saying “a year ago” so it’s very hard to
put things in order... I spent some time with Esther to improve my Swahili,
which will soon become better than my English. The professional rela-
tionship and friendship that she is developing allows her to acquire new
knowledge and skills, and it allows me to get closer to the culture of this
country, an essential step to establish a relationship of trust and respect be-
tween doctor and patient/tribal culture. Here everything is different: there
is an extreme scarcity of resources, and sometimes the only instruments
the doctor has are his hands and his head. I feel stunned every time I real-
ize that what I learned in medical school is often not applicable, and I al-
ways need to reinvent something feasible. The presence of a public health
system, which includes some services with fee, requires a strict control of
the “health care spending”, which is in any way largely covered by the pa-
tient; it is inevitable that the diagnostic and therapeutic choices have to
bend under this sword of Damocles.
In this situation it is even more necessary for the physician to rely on clin-
cal method and not merely instrumental diagnostics, and this provides a
satisfaction, although it is often the hardest thing to apply. Being able to
look at this whole situation with equanimity, to have the consciousness
of its own jurisdiction and see the positive side and possibility, for me is a
great achievement in my training. When I left I was not sure what I was
looking for. Africa is giving me something I did not expect: a greater sense
of myself, a greater ability to look at all that, and a greater confidence that
the world is full of potentiality and above all that I am too. I thank the
whole group, starting from my teachers and including friends and col-
leagues who have been of help and support and with whom I would like to
share this writing. MAISHA MAREFU namely Long Life.

Continuity care network: frail patient among hospital
and home

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According to a Hospital Health Service Administration project our General
Medicine Hospital Unit started trial on frail patients difficult discharge.
The test focused on a sustained continuity of care Program involving our
Unit and Home (Community) Health care provider (professionals) in 4
Districts in ASL RMC area (ASL RMC area being extremely broad, par-
ticularly of two districts neighbouring our hospital) and started on march
the 1rst, 2013 over two months. Complex patient discharge is part of care
responsibility in all respects. Continuity of care begins with thorough
evaluation of patient needs and his/her unofficial care network starting
since hospital admission or soon after. According to the project and to our
Unit actual setup, the patient criteria admission to Continuity of care
Program are identified in stable clinical conditions. A pre-selection sheet
form for eligibility is filled out, aiming to pinpoint social background. In
case of eligibility Home Health Care Team providers (medical doctor,
nurse and physiotherapist) named UVM and relatives are then summoned.
At patient bedside, together with a hospital staff physician involved in the
case, appropriateness of home discharge is evaluated and personalized
care plan (PAI) is drafted.

Results: from 1 march to 30 April 2013, 125 patients have been admitted.
Pre-selection form has been carried-out. 7 case have been considered eli-
gible’s, for whom UVM has been summoned, PAI was drawn up and home

A clinical case of Cogan syndrome

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A young woman of 26 years-old, was admitted to our Emergency
Department (ED) with symptoms arising 3 days before and characterized
by: intense bilateral eye pain, photophobia and transient episodes of de-
clining visus. The patient suffered from about 5 months of subjective vert-
tigo, unsteadiness in walking, nausea, vomiting and tinnitus. She underwent
a neurological examination and cerebral computed tomography in urgency
resulted normal and subsequently a brain MRI resulted normal too.
So she was examined from an otorlaryngologist and she underwent an au-
dio-vestibular examination. A diagnosis of Ménière’s disease was made.
Patient didn’t benefit from the therapy particularly, and she started to ex-
perience a slow but progressive hearing loss. Patient also suffered from
episodes of fever and arthralgia. The exams carried out on arrival showed a
high PCR (100 mg/dL) and an increase in white blood cells (16900 µl).
Tests of liver and renal function were normal. An ophthalmologic exami-
nation revealed the presence of a bilateral interstitial keratitis. The exami-
nation from an otorlaryngologist reconfirmed the diagnosis of Ménière’s dis-
ease. Patient’s clinical diagnosis suggested the need for hospitalization for
further exams.
During hospitalization were reconfirmed high indexes of blood phlogosis
(VES 88 mm L/h) and the presence of rheumatoid factor, cryoglobulinemia,
the presence of Antibodies anti-smooth muscle, Antibodies anti- phospho-
lipids and Lupus Anticoagulant (LAC).
It was therefore done a diagnosis of Cogan syndrome or ouculo-audio-
vestibular syndrome.
Patient was submitted to corticosteroid therapy with ocular symptoms dis-
appear but with little benefit on hearing loss.
Cogan’s syndrome, for unknown etiopathogenesis, mainly affects young
adults and 1/3 of patients shows a systemic Vasculitis-like disease. Infection
and autoimmunity are considered and probably involved but their role re-
mains hypothetical.
Detection of delayed drug sensitization to aminopenicillins by an in vitro flow cytometry method: the lymphocyte activation test (LAT)


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Background: It is possible to differentiate the allergic reactions to drugs in immediate (IR) and delayed type (DR), based on the time between the administration of the drug and the onset of the reaction. IR occurs within 1 hour, while DR occurs from 2 to 36 hours. For the in vitro diagnosis of IR it is available a validated method known as basophil activation test (BAT). For the DR there is a lack of reliable diagnostic methods. Only lymphocyte transformation test (LTT) seems to be able for detection of DR, but it requires 6-7 days of cells stimulation and the employment of radioactive isotopes to detect T cells activation, with obvious limitations in its diffused application.

Method: We performed a Lymphocytes Activation Test (LAT) in blood samples from patients with suspected delayed sensitization to aminopenicillins (AMP), such as amoxicillin and ampicillin. We selected 8 subjects referring DR to AMP, 6 healthy subjects, 12 allergic subjects not sensitized to AMP and 7 subjects referring IR to AMP, to evaluate the specificity and sensitivity of our test. The concept of LAT is very similar to BAT; it requires an incubation of WBC at 37°C for 12-16 hours with suspected drug molecules and a buffer enriched of calcium and brefeldin A. Subsequently cells were fixed, permeabilized and labeled by fluorescent mAbs in order to detect cell surface CD4/CD69 and intracellular IL4 expression. Finally cells were analyzed by flow cytometry to detect activated T cells. Positivity was established calculating the ratio between percentage of CD69-IL4 positive T cells in stimulated samples and CD69-IL4 positive T cells in unstimulated samples; this ratio is defined as Stimulation Index (SI). When SI≥2 we consider the test as positive.

Results: We observed that healthy subjects, allergic subjects (to other antigens) and subjects with immediate reactions to AMP showed no positivity to LAT while all the 8 subjects referring delayed reactions to AMP showed positive signals to LAT, of which 5 only by CD69, 2 only by IL-4 and 1 by CD69/IL-4.

Conclusion: Our method compared to LTT, reduced incubation time from 6-7 days to 12-16 hours, and simplified procedures using flow cytometry instead of radioactive methods, thus making LAT vs. LTT more simple and safe to use. The data seems to evidence that LAT have high specificity and good sensitivity. Despite the small samples, our results are very promising and could be the right way for the development of a reliable in vitro diagnostic protocol for delayed adverse drug reactions as useful support for the prevention of delayed adverse drug reactions, in particular in patient with multiple drug therapy.

Vertebral arteritis causing fever of unknown origin: a case report

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A 82 years old man was admitted to our Department because of worsening dyspnea, cough with sputum, sore throat, mild fatigue and fever. In his history: left knee prosthesis (3 years before), arterial hypertension, cerebral and carotid artery atherosclerosis, COPD; recent pelvis trauma resulting in ischial pubic branch fracture; smoking and alcohol intake in the past.

At admission, a moderate respiratory distress requiring oxygen mask therapy was present. Chest examination showed only bilateral crackles, throat inspection revealed hyperemic diffuse areas. Inflammatory markers were elevated, chest X ray showed an area of patchy infiltrates in the retrocardiac area. Legionella and pneumococcal antigen searches on urine sample resulted negative; anti Mycoplasma pneumoniae and anti Chlamydia pneumoniae serology were consistent with past exposition.

The patient was initially treated with levofloxacin; persisting fever and symptoms, ceftriaxone was added after six days. His respiratory distress gradually improved and a chest CT examination showed the complete resolution of the pneumonia. Nevertheless, fever was still present, sore throat worsened, tongue became painful, palatal edema appeared, resulting in severe dysphagia; inflammatory markers persisted increased.

A CT of the maxillary area and neck showed maxillary cyst and a mild chronic sinusitis pattern, and confirmed a tongue-palatal edema. A biopsy of the tongue mucosal surface was performed, but histological analysis was consistent with unspecific chronic inflammation. After ENT evaluation, patient started a large-spectrum antibiotic, antifungal and antiviral therapy, resulting in gradual oral improvement and subjective benefit, but fever and throat symptoms persisted and elevated inflammatory markers worsened.

Then, according to the FUO diagnostic screening, we performed a consequent series of examinations. An echocardiogram revealed hypertrophic cardiopathy, mild mitral insufficiency, mild aortic stenosis, mild tricuspidal insufficiency, but not valvular vegetations. A complete chest and abdomen CT revealed only a dilated abdominal aorta (maximum diameter 33 mm) with calcified walls. A facial CT examination confirmed the presence of chronic sinus inflammation and a maxillary cyst. A left knee X-ray examination was consistent with normal arthro-prosthetic anatomy, without signs of inflammatory diseases. Hemocultures, Mantoux and Quantiferon tests, search for M. tuberculosis in gastric content samples, Wright test were all negative. Neoplastic markers (CEA, CA 19.9, CA 125, PSA), ANA, ANCA and complementemia resulted normal. Bence-Jones proteinuria search was negative. Peripheral blood immunophenotype, bone marrow smear examination and biopsy were normal. A PET scan showed a clearly enhanced FDG uptake in correspondence of the left portions of some cervical vertebra, suggesting the presence of an inflammatory monolateral disease at C1, C2, C3, C4, C7, worthy of diagnostic evaluation by a MR study; but MR showed only degenerative joint abnormalities. Then, the reevaluation of the PET images raised the possibility that the hypermetabolic pattern ob-

Figure. Stimulation Index of CD69 and IL-4 in patients referring non-immediate reactions
served in the cervical area was of vascular origin, compatible with left ver-
tebral artery. Although this localization was the unique documented (pe-
ripheral pulses were normal), and a biopsy of the homolateral superficial
temporal artery showed no signs of giant cell arteritis, we started a corti-
costeroid treatment with methylprednisolone 40 mg daily; after a month of
such therapy, fever and throat symptoms disappeared, inflammatory mark-
ers normalized. Then, azathioprine 100 mg daily was added as a steroid-
sparing agent, allowing the gradual tapering of the steroid to a mainte-
nance dose of 5 mg daily of prednisone. A PET examination performed af-
ter eight weeks of treatment revealed a normal pattern, without area(s) of
enhanced FDG uptake.

Ventricular tachycardia in a young woman

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In April 2012, Ms. Alessandra, 27 years old, had been suffering from palpi-
tation during her sports activities for almost a month. For this reason she
had turned to a heart specialist. The ECG had revealed wandered ventric-
ular heartbeat, ventricular tachycardia and a 0.52 sec QTc. ECG Holter
revealed isolated polymorphic wandered ventricular heartbeat and a 24-
hour QTc variable from 450 ms to 500 ms. May 2012, Alessandra came to
our hospital for further examinations. Her family history did not reveal
any case of sudden death, any case of a long QT. The only relevant aspects
were a scanty menstruation for almost 1 year and a hypothyroidism for at
least 7 years treated with hormones. Nothing important concerning her physical
examination. BMI 22 Kg/m². ECG with no BEV or BEVS, but a 0.52 sec QTc.
Concerning the results of the serum electrolytes: Na⁺ 138 mg/dl, K⁺
2.5 mg/dl, Mg²⁺ 1.6 mEq/ml. Bloodgases: metabolic alkalosis. So we tried to
correct her potassium levels “per venam”. The day after, her ECG and
bloodgases were normalized. Her long secondary QT was the result of low
levels of potassium. We needed to rule out some causes of hy-
pokalaemia: transfer of potassium in the intracellular compartment due to
thyreoctosis crisis, but the level of the thyroid hormones is normal; insuf-
icient intestinal absorption due to insufficient supply and/or gastrointes-
tinal loss due to the use of laxatives or loss of potassium at kidney level
due to diuretic medicines, but the patient told us of her normal food
routine, denying the use of diuretic medicines or laxatives or recent
episodes of diarrhea... Loss of potassium at cutaneous level due to deep
sweating. In relation to this last point, the patient told us that she had been
attending gym for 4-5 hours per day, practicing KICK BOXING. In the
meanwhile, the results of her urinary electrolytes revealed an amount of
urea during 24 hours of about 6 liters with a urinary pH of 1007. The pa-
tient went on denying the use of diuretic medicines, but told us to drink
about 8-9 liters of water per day, because a year before, after an episode of
renal colic, her doctor had suggested her to drink more! Therefore, the
deep sweating combined with the absorption of so many liters of water per
day without mineral salts could explain her low level of potassium. The
day after, we dismissed Alessandra with the following diagnosis: “Extra-
systolic arhythmias due to low level of potassium and deep sweat-
ing. Hypothyroidism subject to a treatment”, with the recommendation to
drink 1.5 liters of water at most, to practice a moderate play, to swallow vi-
tamin supplements and mineral salts containing potassium and magne-
sium. At the end of July, Ms. Alessandra told us that she had suffered
from palpitations while staying in Milan by her sister. The ECG and blood-
gases revealed a long QT and a metabolic alkalosis with low levels of potas-
sium. We decided to arrange an ordinary recovery with administration of
potassium and magnesium. Alessandra told us that during the weeks before
she had gone on drinking more than 8-9 liters of water per day in a com-
pulsive way. At this point, we started thinking about a condition of “psy-
chogenic polydipsia”, whose diagnosis was undermined by the lack of its
main characteristic element, the hyponatremia. During the following days,
we were able to discover that: 1) The bloodgases registered in the morning re-
vealed a metabolic alkalosis which almost disappeared in the afternoon; 2)
The levels of potassium grew in relation to the slight improvements regis-
tered; 3) The blood levels of chloride were low in the morning and im-
proved in the afternoon. It was clear that Alessandra was not telling us all
the truth. During a sunny afternoon of August her mother told us that her
daughter had been very irascible during the last months, overeating with-
out control, while her sister had seen her vomiting several times while
staying in Milan. At this point, we asked for a psychiatric advice. This con-
firmed our suspects: Alessandra was suffering from a psychogenic poly-
dipsia and compulsive eating. This condition explained the reason why,
even by drinking a lot, Alessandra was not suffering from hyponatremia
which was “neutralized” by the secondary hyponatremia of the vomit.

The day after, we dismissed Alessandra with this diagnosis: “Serious low lev-
els of potassium in a patient suffering from compulsive eating and psy-
chogenic polydipsia. Hypothyroidism subject to a treatment”. We also sug-
gested to get through to a good psychiatrist. We have never seen her
again. What has Alessandra taught us? The most important lesson to learn
is that we must always examine each case in detail, ask the patients the
same questions more than once if necessary, pay attention to details and
ever be satisfied by the appearance of a diagnosis which could seem sim-
ple and evident but wrong.

Anisakis simplex hypersensitivity in central and southern
Italy: clinical features

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Background: The nematode Anisakis simplex (AS) is a worldwide dis-
tributed parasite, belonging to the order Ascaridida, that infects consumers
of raw or undercooked parasitized fish. The ingestion of anisakis infected
fish could cause an acute IgE-mediated generalized reaction (urticaria–an-
gioedema–anaphylaxis).

Methods: A retrospective study was conducted on 112 patients with sus-
pected food allergy enrolled from January 2007 to January 2012. Inclusion
criteria were positive skin prick test and/or positive specific IgE for
Anisakis simplex. We evaluated the clinical characteristics of patients, the
benefit of fish-free diet and of the treatment with mebendazole in sympto-
matic patients.

Results: 97 of 112 patients included in the study showed evident symptoms
after fish intake. 26 of them reported the occurrence of gastrointestinal
symptoms (6 nausea and vomiting, 9 diarrhea, 11 colic pains and meta-
prosism); 73 had cutaneous symptoms (31 urticaria, 20 pruritus and 22 an-
gioedema); 42 of 112 patients followed a free-fish and seafood products di-
et; in those who had gastrointestinal symptoms, 70% had benefit from diet
with resolution of symptoms. The diet was effective in the 65% of patients
with acute SOA (urticarial-angioedema syndrome) and in the 38% of the
patients with chronic urticaria. 10 patients did not respond to diet and were
replaced with mebendazole, 40% of them have benefits. 32 patients corre-
lated the onset of symptoms to the ingestion of a particular fish species, in
particular marinated anchovies were among the species most involved. 49
patients also performed skin prick test for dermatophagoides and 15/49
(31%) showed a positive test.

Conclusion: Anisakis simplex has a pathogenetic role in hypersensitivity
reactions and gastrointestinal disorders. It could play an equally important
role in chronic urticaria although the pathogenetic mechanism is not fully known. In symptomatic patients a free-fish and seafood products diet show clinical improvement while the efficacy in vivo of an antihistaminic needs further study. The fish species, like anchovies, associated with sensitization in Italy reflect the spread of the Anisakis simplex larvae in seafood of the Mediterranean Sea. The results confirm the evidence of cross-reactivity between Anisakis simplex and Dermatophagoides. Prevention methods by freezing fish products at -20 °C for at least 24 h and adequate cooking are able to kill the parasite but not to cancel entirely the allergenicity (some allergens found to be resistant to temperatures of 100 °C).

Vitamin D levels in atopy

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Over the last few years we are witnessing a renewed interest in vitamin D. This is due to two different reasons: the high prevalence of hypovitaminosis D in most industrialized countries and the insight of new vitamin D activities. For a long time vitamin D was exclusively related to homeostasis of bone tissue and its dosage has been requested only in patients with problems related to alterations in calcium-phosphorus metabolism and bone and joint diseases such as osteoporosis. The discovery of vitamin D receptors (VDR) and enzymes activating vitamin D in types of cells different from those involved in bone mineral homeostasis, led to reconsider the role of vitamin D and to identify new, non-classical effects on human health. In the field of immunology, for example, it has been recently demonstrated that the vitamin D is a pluripotent regulator of the immune system. The metabolically active form of vitamin D, 1, 25-dihydroxyvitamin D (1,25(OH)2D), influences both the innate and adaptive immune responses specifically acting on different cytokines and cell types. In the light of these new knowledge many research groups have focused on a possible correlation between vitamin D levels and immune-mediated diseases. While in autoimmunity the role of vitamin D has been clarified almost completely, about the role of vitamin D in the pathogenesis of allergic diseases there are still conflicting data. According to some research groups, the hypovitaminosis D would represent a risk factor for the onset of atopy; for others there would be no correlation about, and even, some studies suggest that supplementation of vitamin D in allergic subjects with hypovitaminosis would result in a worsening of symptoms. To better understand the relationship between vitamin D and allergy, we examined a cohort of 250 individuals (142 female, of whom 88 with less than 65 and 54 with more than 65 years, and 108 male, of whom 65 under 65 and 43 over 65 years) arrived consecutively at our center for allergic diseases in 2012. All of our patients were subjected to careful medical history, allergy testing in vivo, assay of total IgE and specific IgE, to confirm the presence of atopy, and further blood chemistry tests. The dosage of 25-hydroxyvitamin D (25(OH)D), a biological marker useful for evaluating the systemic levels of Vitamin D, was tested. Twenty six subjects were excluded because of a history of syndromes associated with hypovitaminosis D and/or the use of drugs that increase catabolism of vitamin D. The average of vitamin D levels in our cohort of subjects was 19.9 ng/ml. Comparing serum levels of vitamin D based on gender, we found, as expected, higher levels in men than in women (23.24 ng/ml vs 17.6 ng/ml p<0.05). Looking at different age groups, in agreement with data in literature, we confirmed levels of vitamin D statistically lower in elderly subjects compared to those under 65 (17.15 ng/ml vs 20.9 ng/ml p<0.01). Therefore, we divided our cohort into two groups: atopic and non-atopic. Blood levels of 25 (OH)D in atopic compared with non-atopic subjects were lower and this difference was statistically significant (17.7 ng/ml vs 21.7 ng/ml, p <0.05). We further divided atopic and non-atopic subjects according to age in three group (under 20, over 20 and under 65, and over 65 years) in order to verify the difference in serum levels of vitamin D between allergic and non-allergic in the various age ranges. According to our results, levels of 25(OH)D in atopic were lower than those in non-atopic subjects in all age groups with greater emphasis in elderly. Finally we assessed the levels of total IgE according to the state of vitamin D serum. The values of total IgE, although not statistically significant, were higher (365 kUA/l) in subjects with marked hypovitaminosis D (<10 mg/ml) compared to the group with vitamin D greater than 30 ng/ml (IgE tot 163.7 kUA/l), however, this difference did not reach statistical significance (p>0.05). The preliminary results of this study therefore suggest an association between low levels of vitamin D and atopy. The fact that data in literature are so conflicting could be explained by both the pleiotropic and perhaps still not completely clear role of vitamin D in the regulation of the immune system, and the equally complex pathogenesis of allergic diseases. The vitamin D would therefore seem to be more than a simple vitamin. In fact, vitamin D not only has a role in the regulation of calcium-phosphorus metabolism, but it also acts as a true immunomodulator.

There was a Shinalese woman in coma

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In November 2012 a 56 years old Shinalese woman was brought to the emergency department with a 3-day history of fever, productive cough and altered mental status from baseline. She had a past medical history of hypertension under pharmacological treatment with ACE-I and type 2 diabetes in diet treatment. She was febrile (38,7°C) and had tachycardia (114 bpm), normal blood pressure (120/80 mmHg) and hypoxemia (89% on 2L). She had a Glasgow Coma Scale score of 8 (M-5; E-2; V-1). Physical examination suggested euveloma. The first laboratory test showed serum [Na+] 109 mEq/l; serum potassium 3.8 mEq/l; blood urea nitrogen 40 mg/dl; serum creatinine 0.7 mg/dl; glucose: 194 mg/dl; plasma osmolality 228 mOsm/Kg and urine osmolality 400 mOsm/Kg. Chest radiography showed a right lower lobe infiltrate with prominent air-bronchograms. The cranial CT revealed cerebral edema. The patient was started on intravenous antibiotics and saline solution at 5 % and the natraemia was recovered up to 115 mEq/l in the following 10 hours. Twenty-four hours after, her level of consciousness improved and was admitted to our department of Internal Medicine. On admission, laboratory test showed leukocytosis (13.200/cmm) with neutrophilia (10.800/cmm); her serum [Na+]: 126 mEq/l; CPK: 8012 U/l; glucose: 189 mg/dl. Her vital signs had normalized and she was saturing well on ambient air. She remained euveloma. General examination did not reveal any clue except for sign of pneumonia. She had myalgia and tiredness. Electrocardiogram and CPK-MB and troponin I level were normal. So, she had a rhabdomyolysis. For this reason, she received saline solution at 0.9% and diuretic treatment to avoid renal failure. Her serum sodium and CPK value were 133 mEq/l and 197 U/l on 5rd day respectively. Patient’s general condition improved well and was discharged on 7th day. So, our patient was admitted with pneumonia, hyponatraemia and rhabdomyolysis. Her initial laboratory assessment would suggest SIADH. Additional testing ruled out endocrinopathy ( thyroid-stimulating hormone 2.2 mU/l; a.m. serum cortisol 16 mcg/dl). The association of hyponatraemia with respiratory illness has been recognized for more than 70 years. The prevalence of hyponatraemia (serum [Na+]<135 mEq/l) is up to 29% of patients with pneumonia. The mechanism of hyponatraemia in pneumonia is incompletely understood. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) is most often implicated. Severe hyponatraemia is one of the most uncommon causes of rhabdomyolysis. In our case, other causes of rhabdomyolysis such as trauma,seizures, drugs, inflammatory myopathy and ereditary metabolic myopathies were excluded by detailed history, clinical and biochemical ex-
Prevalence of and risk factors for ultrasound-detected renal artery stenosis in an ambulatory population of hypertensives

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Background: Nefrovascular hypertension is the most common type of secondary hypertension. Specifically, the prevalence of atherosclerotic renal artery stenosis (RAS) is increasing because of progressive population aging. In hypertensive patients screening, the study of renal arterial district by ecocolor Doppler allows to detect RAS and to define the hemodynamic impact on the ipsilateral kidney. This study was aimed at evaluating RAS prevalence and predictors in a population of hypertensives.

Methods: We retrospectively analyzed renal arterial vessels ecocolor Doppler exams performed in patients with recently diagnosed hypertension, essential hypertension complicated by chronic renal failure (CRF). RAS was defined when exceeded the 95% upper confidence limit expected for the age decade and not due to metastatic localization. In our case report, a woman developed a severe and extensive form of dermatitis, initially attributed to a paraneoplastic manifestation of ovarian cancer. However, further investigations, including the surgery and subsequent histological examination, allowed us to formulate the correct diagnosis of adenocarcinoma of the colon in a very advanced stage of disease (lymph nodes metastasis and massive peritoneal carcinomatosis). More than 50 paraneoplastic dermatoses have been described in the literature, some of which are correlated with specific malignancies. Therefore, these manifestations may represent an important aid in the diagnosis of the underlying disease. In some cases, as in our patient, paraneoplastic dermatoses constitute the only clinical manifestation of an occult tumor. A correct interpretation of these conditions is important for the early diagnosis of the underlying cancer, resulting in an improvement of the prognosis and the course of the disease.

Baseline liver enzymes and incident diabetes mellitus and vascular events: first results from a large real-life population study


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Background and aims: Many large population-based studies have shown the association between baseline levels of liver enzymes, mainly ALT and...
GGT, and the medium-term incidence of diabetes mellitus (DM) and vascular events. Nonetheless, the postdictive role of liver enzymes has never been confirmed in a real-life context, where patients are not tested per-protocol and results are obtained from labs with different analyzers. We aimed to verify the association between baseline ALT, GGT and AST/ALT ratio, the latter as a proxy of liver disease evolution, and the incidence of DM, stroke and coronary heart disease (CHD), in a large real-life population.

**Patients and Methods:** Subjects who underwent routine blood tests including AST, ALT and GGT between 2000 and 2005 were extracted from a validated software employed by 120 general practitioners in the area of Naples, in charge of about 170,000 subjects. Incident DM, stroke and CHD were registered after a median follow-up time of 102 months (8.5 years). After exclusion criteria (known liver disease, HBsAg+, HCVAb+, age<20), data from 16,689 subjects were analyzed.

**Results:** Mean age of the study population was 62.3 +/- 17.7, male/female 43.8/56.2%. Cumulative incident DM, stroke and CHD were respectively 5.1%, 1.2% and 4.6%. In multivariate-adjusted analysis, ALT was associated with incident DM (OR 1.17; CI 1.06-1.29; p=0.002), but not with stroke and CHD. GGT was associated with incident DM (OR 1.32; CI 1.19-1.46; p<0.001), and stroke (OR 1.25; CI 1.05-1.49; p=0.009), but not with CHD, while AST/ALT ratio was not associated with any outcome. DM was diagnosed in 3.2%, 5.2% and 6.9% of subjects with baseline GGT in the lower, medium and upper tertile, respectively (p=0.02).

**Conclusion:** Except for GGT and incident stroke, our study, the first carried out in a real-life setting, does not support an association between baseline liver enzymes and the occurrence of vascular events, while confirms an independent predictive role of both ALT and GGT levels for incident DM. These results add to the accumulating evidence that the liver is a strong contributor to insulin resistance rather than a simple target of dysmetabolism.

**Alteration of the salivary secretory proteome profile in adults affected by antibody deficiency diseases**


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The primary immunodeficiencies (PIDs) are a heterogeneous group of inherited disorders that affect the cells and proteins of the immune system. Defects in antibody production are the most common type, comprising about 60% of the primary immunodeficiencies encountered in practice. Primary antibody deficiency (PAD) syndromes constitute a heterogeneous group of disorders, with a large variability in clinical and immunological phenotypes. Adult or late-onset forms of PID have been described. The acidic soluble fraction of the salivary proteome of 6 adult subjects affected by PID by RP-HPLC-ESI-MS and compared with that of 17 sex- and age-matched healthy subjects. The qualitative and quantitative analysis of oral proteins and peptides was performed by a top-down label-free approach. The study evidenced a significant decrease of cystatin S, S1, S2, SN, SA, as well as of cystatin C, in the group of patients compared to controls. Cystatins are secreted extracellularly, where they inhibit proteasomes, thereby limiting proteolysis and tissue damage. Cystatin D is a potent inhibitor of human coronavirus at physiologic salivary concentrations. These results are similar to a previous study in which a down regulation of protease inhibitors, including S-cystatins, was previously observed in saliva of subjects infected by HIV-1. Therefore, the lower levels of cystatins could be a signature of immune diseases including PAD diseases and could explain the multifactorial reduction of immune defences observed in patients. S100A proteins were affected by the immunodeficiency as well, showing mostly a significant decrease of the different S100A9 isoforms in the patients with respect to controls.

Histatins did not significantly change in abundance. Among α-defensins, only a slight down-regulation of antimicrobial α-defensin-1 was observed in our patients. We found that bPRPs fragments, which derive from BASIC PROLINE-RICH PROTEINS (bPRPs) metabolism in oral cavity and play a role in mucosal defence against chemical and infective agents, were significantly reduced in abundance in patients than in controls. Thus, lower levels of many of analysed proteins may lead to increased tissue damage and lower defences against viral infections and deserve further molecular and functional characterization for their potential implications in diagnostic and therapeutic aspects. Research is ongoing to confirm the relationship between the modification of the salivary proteome and immune deficiency diseases.

**Cutaneous manifestations of common variable immunodeficiency**

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Common variable immune deficiency (CVID) is the most common symptomatic primary immune defect in the adulthood. It is characterized by humoral immune deficiency with pulmonary and gastrointestinal infections but it is not infrequent the presence of autoimmune diseases and cutaneous manifestations. We report here on the skin involvement associated with CVID in a series of Italian patients followed by our Centre. The purpose of the study was to evaluate the prevalence of skin diseases in a group of patients with CVID. We evaluated 36 consecutively followed patients with CVID. Skin diseases affected 5 (13.9%) CVID patients. There were 3 females and 2 males and the mean age was 47.4 years. The skin involvement of our patients was characterized by: vitiligo (1 female), cutaneous granuloma (1 male), purigo nodularis (1 female), psoriasis (1 female) and epidermodyplasia verruciformis (1 male, diagnosed by Prof. G. Spadaro, Immunologia Clinica ed Allergologia, Ospedale Federico II, Napoli). In three of these patients the cutaneous manifestation was the first symptom of CVID. In addition to the treatment with intravenous and subcutaneous immunoglobulin as replacement therapy, glucocorticoids and new agents, such as Etanercept (anti-TNF) were used. Skin diseases are relatively common in CVID and sometimes can be a manifestation of the immunodeficiency but usually the manifestation concern granulomatous lesions. Our patients are an example of a possible presentation of CVID. Maintaining a high level of clinical suspicion and an early diagnosis and treatment are crucial for the management of this life-threatening immunodeficiency.

**Unusual secondary pleural involvement by cancer**

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A 78-year-old woman was admitted to the emergency room because of worsening dyspnea and nonproductive cough. Chest X ray disclosed conspicuous pleural effusions bilaterally. She was initially discharged home with domiciliary therapy (steroids, antibiotics, diuretics). The patient was
then admitted to our Institution for further investigations. On admission, she was frankly dyspnoic (respiratory rate 25/min; O2 saturation 88% in ambient air); blood pressure was 120/70 mmHg, heart rate was 92 and regular. Physical examination disclosed bibasilar dullness, with absence of tactile fremitus and inaudible breath sounds. Chest X ray confirmed bilateral pleural effusions up to the seventh rib. Laboratory tests showed increased LDH (626 U/L), ferritin (208 ng/mL), and CRP (2.10 mg/dL). Arterial blood gas test was significant for hypoxemia (pO2 53 mmHg), suggesting type 1 respiratory failure. Echocardiography revealed a circumferential, organizing pericardial effusion (~300 ml). Abdominal US scan was remarkable only for a polar cyst in the left kidney. Total body CT scan only confirmed bilateral pleural effusions. The patient was subjected to thoracentesis in order to ameliorate dyspnea, which yielded a bloody fluid with biochemical features of exudate (pleural fluid LDH 1053 U/L, serum LDH 626 U/L, ratio 1.68; pleural fluid albumin 2.49 g/dL). Cytologic examination revealed clusters of epithelial-like cells with atypical nuclei. On further questioning, the patient reported to have been suffering from metrorrhagia since the previous two months. Eventually, transvaginal US scan disclosed an endometrial lesion within an enlarged uterus, which turned out to be endometrial carcinoma on histologic evaluation of tissue biopsy. In conclusion, here we report a case of endometrial carcinoma with metastasis in an unusual site and no further typical localizations. Therefore, in case of secondary pleural involvement by cancer, gynecologic neoplasms should also be considered while searching for the primary tumor.

Systemic Lupus Erythematosus and primary biliary cirrhosis: a new association?


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Introduction: primary biliary cirrhosis (PBC) is an autoimmune disease predominantly of middle-aged women in which there is a progressive destruction of interlobular bile ducts. The diagnosis of PBC can be established when two of the following three criteria are met: (1) biochemical evidence of cholestasis based mainly on alkaline phosphatase elevation, (2) presence of antimitochondrial antibodies (AMA), (3) histologic evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts. AMA are present in up to 95% of cases. The association between Systemic Lupus Erythematosus (SLE) and PBC is rare and, to our knowledge, only 24 cases have been reported in the literature. The aim of our study was to investigate further the association between SLE and PBC.

Patients and Methods: we retrospectively evaluated clinical records of about 64 SLE patients, diagnosed on the basis of ACR criteria, attending our outpatient Clinica of Internal Medicine with the aim to evaluate the prevalence of hepatic involvement and AMA in this population. AMA, transaminases, γ-glutamyltranspeptidase (γ-GT) and alkaline phosphatase (AF), were assessed for each patient. Moreover in AMA patients cholangioRMN and biopsy were also collected.

Results: in our casistic 4 patients showed persistently increased values of γ-GT and AF. All 4 were AMA positive. Of these 4: 2 patients underwent to liver biopsy that was consistent with the diagnosis of BPC, 1 not accepted liver biopsy and 1 discontinued outpatient visit. All 4 patients fulfilled the PBC diagnostic criteria.

Conclusions: We describe further 4 new cases of association between SLE and PBC suggesting that this association may occur more frequently than previously described. Since lupus hepatitis is a possible feature of SLE, we recommend AMA assessment in all the patients that show increased liver enzymes and cholestasis indexes in order to correctly diagnose this new possible association.

Nontraditional risk factors and ventricular hypertrophy in the early stages of chronic kidney disease

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Background: Chronic kidney disease (CKD) is an important public health problem with high prevalence, increasing incidence, and very high cardiovascular (CV) morbidity and mortality. Traditional risk factors, such as hyperlipidemia and hypertension, fail to fully explain this increased risk, hence the interest in nontraditional risk factors, such as vitamin D deficiency and insulin resistance (IR). Identifying and treating risk factors for early CKD may be the best approach to prevent and delay adverse outcome. Vitamin D influences the cardiac structure and function thanks to vitamin D receptors (VDRs) expressed in the heart. Other nonclassical targets include arteries, immune system, endocrine organs and nervous system. Therefore, the deficiency of active forms of vitamin D in CKD may explain various abnormalities in biological functions and the survival disadvantage in this disease condition. There is evidence that the vitamin D and/or PTH axis is important in the pathogenesis of glucose intolerance and IR in patients with CKD. IR is present in the early stages of CKD and has an inverse association with 25-hydroxyvitamin D levels. IR is closely associated with atherosclerosis and CV mortality in the general population. Although IR is shown in nondiabetic CKD, its association with vitamin D deficiency and vascular disease in this population is unknown and what this study aims to investigate.

Materials and Methods: The study comprised 71 patients with CKD in stage 1 to 3 (eGFR<30 mL/min·1.73 m2), 29 females and 42 males with a median age of 54.6 years, and 15 healthy controls matched for age and sex. The flogosis indexes, vitD levels, IR, carotid intima-media thickness (cIMT), and left ventricular mass index (LVMI) were measured. Data management and analysis were done with the IBM® SPSS® Statistics 18 software for Windows®. The significance level was set at 0.05. Results: In our study, the mean value of LVMI and cIMT were significantly higher in patients with eGFR ≥30mL/min compared with patients with eGFR <30 mL/min.
The purinergic P2X7 receptor in Behçet’s disease monocytes: expression, function and modulation by TNF-alpha


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Background: The purinergic P2X7 receptor (P2X7r) is expressed in innate immunity cells (e.g. monocyte/macrophages), playing a key role in IL-1β release. Since innate immunity activation and IL-1β release seem to be deeply implicated in Behçet’s disease (BD), a systemic immune-inflammatory disorder of unknown origin, we hypothesized the P2X7r involvement in the pathogenesis of the disease.

Methods: Monocytes were isolated from 18 BD patients and 17 healthy controls matched for age and sex. P2X7r expression (flow-cytometry), and function (cytosolic free Ca2+ flux measurements in single-cell fluorescent microscopy, and IL-1β release [ELISA]) were studied. Moreover, the effect of TNFα on P2X7r expression and function was evaluated in monocytes from healthy controls.

Results: In BD monocytes, an increased P2X7r expression and Ca2+ permeability induced by the selective P2X7r agonist 2′,3′-O-(4-benzoylbenzoyl)ATP (BzATP) were observed. Moreover, IL-1β release from lipopolysaccharides-primed monocytes stimulated with BzATP was markedly higher in BD patients than in controls. TNFα-incubated monocytes from healthy subjects almost reproduced the findings observed in BD patients, as demonstrated by the significant increase in P2X7r expression and BzATP-induced Ca2+ intake.

Conclusions: Our results provide evidence that in monocytes from BD patients both the expression and function of the P2X7r are increased with respect to healthy controls as the possible result, at least in part, of a positive modulating effect of TNFα on the receptor. These data indicate P2X7r as a new potential therapeutic target for the control of BD, further supporting the rationale for the use of anti-TNFα drugs in the treatment of the disease.

Allergy to lipid transfer protein: genetic basis


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Lipid transfer proteins (LTPs), profilins and PR-10 are the most important panallergens in South-Centre Italy. LTPs are stable molecules, predominantly present in the fruit peel, which can induce systemic symptoms after ingestion of plant-derived foods.

The aim of our study was to assess the genetic basis related to panallergens sensitization. We wanted to evaluate the possible correlation between HLA-DRB1 haplotypes and food allergy.

We enrolled 47 subjects with the history of adverse reactions after the ingestion of plant-derived foods and allergological evaluation (skin prick tests and quantification of specific IgE) positive for some food and at least one panallergen.

On the basis of the sensitization to LTP the patients were divided into two groups: LTP+ = 36; LTP− = 11.

We extracted the genomic DNA from each patient and detected the HLA-DRB1 haplotypes using the INNO-LIPA HLA-DRB1 kit.

We compared our results with the Literature data about the frequency of HLA-DRB1 haplotypes in South-Centre Italy.

We observed a marked prevalence of HLA-DRB1 homozygosity in all examined patients, both positive and negative for LTP (23%), compared to general population (3%). In addition, the HLA-DRB1 13 was twice as frequent in the LTP+ group as it was in the general population whereas it was completely absent in the LTP− group. On the other hand, alleles 4, 7 and 15 occurred to be twice more often in LTP+ group than in the general population and the LTP+ group.

This study shows a high rate of sensitization to LTP in the South-Centre Italian population according to the Literature about food allergy in this geographical area, therefore panallergens should be considered a clinically relevant food allergens. Although further investigations are necessary we hypothesize that the alleles 4, 7, 15 have a protective role against the allergy to LTP. On the other hand the presence of the haplotype HLA-DR1 13 could be a risk factor for LTP allergy.

A strange case of acute onset systemic inflammatory disease responding to colchicine

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A 38 year old woman was admitted to our hospital on 11 September 2012 because of fever, pulmonary consolidation, bilateral pleural effusion, pericardial effusion and septic shock during a trip in Crete.

In August 2012, during a trip in Crete, she presented headache, fever, bilious vomit, diarrhea and an itchy, confluent, extensive measles-like rash at trunk and at the root of the limbs that vanished spontaneously in 24h. She was admitted to a Cretan Hospital: blood pressure was 100/60, body temperature 38.8 °C. The remaining findings of the physical examination were normal. Later that day she was transferred to ICU for septic shock and supported with noradrenaline. Blood cultures and coprocultures were negative. The leukocyte count was 11.000 cells per microliter (with 85% neutrophils) while the platelet count was 30000. C-reactive protein was 222 mg/dl (normal values <6 mg/L). CT scan showed consolidation and atelectasis at inferior lobes, pleural effusion, pericardial effusion, ascites and mild splenomegaly. Echocardiography was normal. Antibiotic therapy with piperacillin-tazobactam, levofloxacin and vancomycin plus hydrocortisone was started. The autoimmune antibody panel was negative. Her clinical condition progressively improved (CRP 41, WBC 10300, p 359000) and after 12 days the patient was discharged from the ICU and then from the Cretan hospital on cefixime, ciprofloxacin and methylprednisolone 16mg bid.
However, fever recurred the day before she was released from the hospital. The patient returned to Italy and she was admitted to San Raffaele Hospital. She was started on antibiotic therapy with meropenem, vancomycin and doxycycline and a thorax CT scan was performed, improved from the previous one. Pleural effusion and pulmonary consolidation recurred. Echocardiography showed a 8mm pericardial effusion and abdomen CT showed mild amount of free abdominal fluid and a mild splenomegaly. Vancomycin was replaced with linezolid. All the microbiological (including HIV and TB) and autoimmune exams were negative. The only notable findings were a severe IgA deficiency (0.01 gr/l) and mild proteinuria (680 mg/24h). The microbial investigations were confirmed negative and an elevation of the inflammation markers was documented (ESR 58, CRP 123). She had high fever with daily spikes up to 40 °C without any other symptoms related to the site of the infection; then the antibiotic therapy was discontinued. The pericardial effusion was stable, while the pulmonary consolidation and the splenomegaly regressed. So, in consideration of the pericardial involvement, colchicine 1mg die was started. Meanwhile total body Positron Emission Tomography showed moderate increase in the uptake at brachial and femoral vessels bilaterally. Total body Magnetic Resonance showed thin superficial femoral arteries and occlusion of left interosseus artery at its middle third. Vascular echocolor Doppler showed only stenosis of the celiac trunk. Since the colchicine has been started, the patient progressively and rapidly became afebrile, her condition improved and the inflammatory markers decreased (CRP at discharge 20 mg/l). The patient was discharged with the diagnosis of undefined systemic inflammatory disease and colchicine 1mg/die was continued.

While the initial event seemed to be of septic nature, the subsequent course was more difficult to understand. We considered Takayasu’s arteritis and autoinflammatory syndromes. We favored Takayasu because of the young age of the patient, the vascular involvement (PET caption at large vessel, celiac triadop stenosis, interosseus artery occlusion), fever and asthenia. However the diagnostic criteria were not satisfied. Moreover the responsiveness to colchicine is curious.

On the other hand the diagnosis of a periodic fever syndrome, in particular Familial Mediterranean Fever or TRAPS syndrome, is unlikely because of the age of the patient and the unusual clinical presentation. Only high fever, serosal involvement (pericardial, pleural and peritoneal effusions) and colchicine responsiveness suggested this condition, in particular Familial Mediterranean Fever. Moreover there were no other cases in her family.

From Pakistan with...

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On May 19th 2013 a Pakistani 40 year-old woman was admitted to our Hospital with high fever (up to 40 °C), worsening dyspnoea and multiple arthralgia. At the beginning of April 2013 she moved to Italy and, soon after her arrival, she experienced diffuse arthralgia, successfully treated with NSAIDs. At the end of April her blood analysis showed a sideropenic microcytic anaemia (Hb 9.9 g/dL, MCV 74 fL, iron 25 mcg/dL, ferritin 31 mg/mL) and elevation of inflammatory markers: ESR 59 mm/1h and C Reactive Protein 1.62 mg/dL (n.v. 0-0.5 mg/dL). An ultrasonography scan of head, neck and abdomen showed bilateral lateral cerebral and supraclavicular lymphadenopathy with reactive aspect and mild splenomegaly (13.1 cm). On May 18th the patient presented to our ER with back pain extended to the chest, dyspnoea and fever up to 40 °C. She complained of night sweats. She was very asthenic. Physical examination was unremarkable, except for the presence of bibasilar chest stony dullness to percussion, reduced vesicular murmur in the left fields and left supraclavicular and lateral cervical lymphadenopathy (max diameter 2 cm). Arterial oxygen saturation was 90%, she had mild respiratory alkalosis due to hyperventilation. Blood analysis revealed Hb 9.3 g/L, MCV 71.6 fL, WBC 5200 cells/μL, ESR 81 mm/1h (n.v. 1-15 mm/1h), CRP 204 mg/dL (n.v. < 6 mg/dL), PT-INR 1.20, fibrinogen 458 mg/dL (n.v.150-400 mg/dL). ECG showed sinus tachycardia. Urinalysis revealed mild proteinuria (70 mg/dL), haemoglobinuria (0.5 mg/dL) and presence of leukocytes. Acetaminophen was started, blood cultures were obtained and the patient was admitted to our Internal Medicine Department. Chest X-Ray showed increased interstitial thickenings and minimal bibasilar pleural effusion. Because of clinical conditions and chest X-Ray, we performed a chest CT scan that showed pulmonary consolidation in the inferior lobes, bilateral pleural effusion, several axillary, supraclavicular and mediastinal microlymphadenopathy and mild hepatosplenomegaly (spleen largest dimension 15 cm). On May 20th blood analysis showed reduction in leukocytes count (3500 cells/μL). In consideration of that, antibiotic therapy with levofloxacin was started, even if all the microbiological exams (including HIV and Mycobacterium tuberculosis) resulted negative. Autoimmune antibody panel showed: ANA >1:640 with homogeneous pattern, SSA, RNP and pANCA positive (although anti-MPO were negative). Urinary sediment analysis showed isomorph urethrocysts, amorphous debris and granular cylinders. On May 23rd knee arthritis appeared. Steroid therapy was started with a progressive general recovery. Because of the sideropenic anaemia, probably due to abundant menses, martial therapy was given with benefit to the patient, first intravenously then orally. The acute onset of the disease, the elevation of inflammatory markers and the systemic involvement suggested a septic event. For this reason, we started antimicrobial therapy without significant improvement of the clinical conditions. Tuberculosis was also excluded. Multiple district lymphadenopathies, poor general conditions and night sweats were suspicious for lymphoma; however lymph nodes seemed to be reactive rather than proliferative.

A diagnosis of systemic lupus erythematosus was then made. The 1997 updated American College of Rheumatology criteria were satisfied [1]: arthritis, leukopenia, pleuritis, granular cylinders at urinary sediment and the presence of high titer ANA were present. So, on May 30th immunosuppressive treatment was started with hydroxychloroquine 200mg die and prednisone 50mg die. Since renal involvement was not severe, we decided not to perform renal biopsy. Moreover, gastric and bone protection therapy was started. Already on the first day of treatment, clinical conditions improved: the patient felt better, fever disappeared, oxygen could be discontinued. 10 days later, inflammatory markers decreased (CRP 47 mg/dL) and the patient fully recovered.

References:

Procarbazine hypersensitivity and tolerance induction


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Background: Procarbazine is an alkylating agent used for treatment of brain tumors. It is often well tolerated, however, 6-8% of treated patients developed macular-papular rashes or urticaria. Most of reactions caused by
procabazine are non-immune-mediated. In the literature there are no reports about tolerance induction to procabazine. We report a case of tolerance induction in a pediatric patient with a clinical history of hypersensitivity reaction to procabazine.

**Method:** This is a case of 6 years old child affected by glioma. He was in therapy with procabazine (100 mg) and dexamethasone (0.6 mg) daily. During the first cycle of chemotherapy he developed generalized urticaria and so the treatment was stopped. He started the second cycle but he presented generalized urticaria again so patient was hospitalized.

**Result:** Patient referred to our Allergy Department and he underwent to allogerological examination. Procabazine is only available in capsule form so skin prick test (SPT) were performed using undiluted commercial preparation (50 mg/ml) prepared by dissolving the powder in saline. Histamine was used as a positive control. Patch tests were performed using the same drug as for SPT according to European Network on Drug Allergy (ENDA) recommendations. SPT and patch tests resulted negative and we concluded for a nonallergic drug hypersensitivity reaction. Previous parental authority, the patient was underwent to a protocol of oral desensitization to procabazine. Gradually increasing doses of procabazine were administrated in five days. Each dose was administered every 20 minutes. On the first day, the patient received 0.15 mg of procabazine and the final dose of 100 mg was achieved. Before the initiation of the protocol were administrated cetirizine 10 mg/ml (20 drops) every day. Patient received the first desensitization in our department and continued to intake procabazine at home at the dose of 100 mg/day for 12 days without adverse reactions.

**Conclusion:** In our case there is no chemotherapeutic drug as an alternative to procabazine so the desensitization was necessary. Most of rechallenge with procabazine in patients with adverse reactions were positive and the drug be stopped. Desensitization is a high risk treatment and it is mainly indicated in IgE-mediated reactions but it is effective even in non IgE-mediated hypersensitivity reactions.

**Treatment of cancer related pai in patient with impaired coaulation**

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We describe the clinical case of a 62 year old woman came to our observation for the appearance of widespread bruising and intense bone pains. She was affected by rheumatoid arthritis treated with symptomatic therapy. The patient reffered onset of back ache treated with steroids and then dexamethasone, suspended for the appearance of widespread bruising (not reversible after discontinuation of the drug) and then used diclofenac and bepenthemadone without improvement in symptoms.

Lab tests showed: Hb: 10.9 g/dl (10.9-13.4), Plt: 59.000/ul (150000-500000), WBC: 19.450/ul (4000-9320), PT INR: “longer than the detection, calculation can not be performed “Fibrinogen: 19 mg/dl (200-400), D-dimers: 1.98 mg/dl (<0.5), AT 115% (80-130), CRP: 14.5 mg/L (<2.9), bilirubin tot: 1.90 mg/dl (0.20-1), direct bilirubin: 00:41 mg/dl (0-0.2), Indirect bilirubin: 1.49 mg/dl (0-0.75) AST: 94 U/L (15-37), ALT: 36 U/L (27-178), GGT: 55 U/L (8-55), albumin: 4.7 g/dl (3.4-5), CA 19.9 68211 U/ml (0-37), the day after D- dimers, 24.13 mg/l, fibrinogen “undetectable.”

For anemia, we made blood transfusion, as well as transfusion of fresh frozen plasma and platelets. In suspicion of haematological disease, bone marrow biopsy is practiced, that showed “localization of medullary carcinoma NOS (not otherwise specified).” The ultrasound abdomen described, to IV hepatic segment, a space-occupying solid hypoechoic lesion with diameter of approximately 39 mm; after the administration of contrast medi-um, the lesion appears hypoechoic in all phases. We then made liver biopsy; histological examination defined the lesion as “moderately differentiated adenocarcinoma; possible primitive hepatic cholangiocarcinoma type.” The PET-CT scan showed diffuse lymphadenopathy and multiple bone metas-tases. The pain was classified every day with the VAS (visual analogue scale, 0-10), initially reported in intensity 10. The treatment of pain has been limited by the clinical condition (platelet and coagulation deficits).

Analgesic therapy has undergone continuous changes in relation to the increas-ingly intense pain of the patient: Methylprednisolone 20mg/die ev, ev Morphine 10mg divided into 2 daily doses, Fentanyl 100UG sc every 72h and Gabapentin os 600mg/die, but for the occurrence of tolerance and side effects such as chronic constipation, sedation, nausea and vomiting, Fentanyl was administered sc every 48h up to 150ug/die, suspending Morphine (used only as needed). The case in question has been difficult to manage not only to the complexity of the clinical condition but also for the emotional impli-cations. With the association Morphine, Fentanyl, methylprednisolone Gabapentin we got a good control of pain (VAS 4) which allowed the patient to tolerate the pain severely disabling the terminal phase of his malignancy.

**Not always the blue-tailed fish is…healthy!!!!!**

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**Introduction:** Scombroid food poisoning is a foodborne illness due to eating decayed fish. Although it is listed a common kind of seafood poisoning, it is often missed because it resembles an allergic reaction!!! It is most commonly reported with bluefish sardines and anchovies very spread in its use in Sicily, tuna, mackerel, bonito when inadequately refrigerated or preserved after being caught. Its name is derived by the early descriptions of the illness associated with Scombroidea fish, but it can due also to nonscombroid vectors, such as mahi-mahi and amberjack. However the very toxic agent implicated in the intoxication is histamine, although other chemicals with not clear role have been found in decaying fish flesh. Symptoms are represented by skin flushing and diffuse blanching erythema, palpitations and tachy-cardia, throbbing headache, oral burning, wheezing and bronchospams in asthmatic patients, nausea, abdominal cramps with diarrhoea and collapse, hypotension or hypertension, and rarely loss of vision which occur within 10-30 minutes and up two hours of ingesting the fish and generally are self-limited.

**Case report:** A 32 year-old woman without significant medical history, smoker, was admitted to our Dept for severe skin flushing, palpitations and tachycardia, sudden headache, oral burning and tongue swelling, nausea and abdominal cramps with diarrhoea, deep hypotension with collapse. At history only relapsing episodes of asthma since she was a child. Two hours prior to presentation of symptoms, she had ingested fish and in particular sardines and anchovies. She exhibited skin erythema and slight severe wheezing with swelling of her lips and tongue ad appeared very suf-fering and anxious for her clinical conditions. On admission, her temperature was 37.8 °C, heart rate was 110 beats/ min, blood pressure was 115/72 mmHg and respiratory rate was 26 breathing/min. Physical examination revealed fine crackles and marked dullness of the right middle lobe. Laboratory testing was remarkable for leukocytosis (13.400/mmc) and ele-vated C-reactive protein (CRP, 392 mg/dl, normal < 5), increase of LDH (734 U/dl), increase of a2-globulins, ESR (130 mm/hour) and fibrinogen (583 mg/dl). Hepatic, pancreatic and renal parameters as well as urinalysis were normal. Capillary blood gas analysis confirmed moderate hypoxia.
and respiratory alkalosis due to hyperventilation (pO2 66 mmHg, pCO2 26 mmHg, pH 7.51, HCO3 21.1 mmol l−1). Chest radiography resulted normal. On the basis of the anamnestic data we hypothesized a severe case of scombroid syndrome worsened by her asmatic habitus and status and promptly administered oral antihistamines and intravenous rehydration with fluids steroids and supportive care with oxygen obtaining the rapid improvement of our patient’s clinical conditions. We discharged our patient two days after in quite good clinical conditions recommending her to evite bluefish in the future!!!

**Discussion:** The physio-pathogenesis of the scombroid syndrome is related to the presence in many types of fish of histidine which at the temperature above 16 °C on air contact is converted to histamine via histidine decarboxylase enzyme produced by enteric bacteria Morganella morganii. On the other hand, histamine is not destroyed by normal cooking temperatures, and since histamine is a mediator of allergic reactions the symptoms produced are those of a severe allergic responses. Treatment is represented by supportive care such as fluids and oxygen. H1 and H2 receptor blocking medications can also be given with some success. Oral antihistamines are very effective, showing improvement within 10-15 minutes. Normally symptoms of scombroid syndrome are self-limited,… but probably a particular attention and care could need, as in such our case report, the patient afflicted with allergy and asthma.

**Late onset of myasthenia gravis in a patient with Good’s syndrome**

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A 64 years old women was referred to our unit to define a clinical picture characterized by respiratory insufficiency, dysphagia and weakness of the proximal muscles with a muscle biopsy compatible with polymyositis. Her medical history started in May 2003 with the diagnosis of Good’s syndrome (thymoma and hypogammaglobulinemia) secondary to a well-differentiated thymic carcinoma treated with surgery and radiotherapy presenting with severe hypogammaglobulinemia and pancytopenia. Over the years the patient underwent periodic infusions of Ig ev, while the cytopenia remained stationary. In August 2012, the patient was hospitalized in another facility for worsening dyspnea, global respiratory failure requiring non invasive mechanical ventilation (NIV), but for the persistence of respiratory failure despite the NIV was subjected to tracheostomy, treated with prednisone 1 mg/kg/day and sent to our department. At the admission the patient had difficulty to keep her head erect, easy fatigue of the eye and buccal muscles with no other motor deficits; she was bearing tracheostomy connected to the B-PAP ventilator and nasogastric tube for dysphagia. At blood tests: pancytopenia (Hgb: 9.9 g/dl, MCV 88 fL, WBC: 2700/mm^3, PLT: 30000/mm^3), hypogammaglobulinemia: (8.2%, 450 mg/dl), evidence of modest inflammation (PCR: 1.8 mg/dl, ferritin: 238 ng/ml), positivity of anti-acetylcholine receptor antibody (ARAb): 10.5 nmol/l (nv: <0.4 nmol/l), CPK not elevated.

In conclusion, the patient had developed a myasthenia gravis with ARAb positive nine years after the removal of the thymoma. Few cases of MG that develops in patients postthymectomy and with no preoperative history of the disease are reported in literature (1,2). Moreover, are also described pre-thymectomy ARAb positive cases, with no clinical evidence of MG, associated with raise in ARAb after thymectomy and subsequent development of MG. Therefore, thymectomy do not prevent entirely postoperative MG and exacerbated ARAb levels after thymectomy can suggest an extrathymic production of ARAb. That emphasize the importance of immunosuppressive treatment of patients with myasthenia gravis, particularly those with complex immune diseases like our patient.

**Bibliografia:**


**A rare cause of interstitial lung disease**

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A 70 years old woman was admitted to our ward for worsening dyspnoea and mild fever. From three months she also complained hand’s acrocyanosis, swelling and rigidity. She denied arthralgy or Raynaud phenomenon. In her past she underwent surgery for uterin carcinoma. Since three years she had been complaining episodes of dyspnoea and asthma. She performed chest X ray (increased bronchovascular markings exspecially on the right lower lobe), echocardiography and autoimmunity test were negative. One month before admission she referred rash on chest and hands after antibiotics for Helicobacter Pylori (amoxicillin/clavulanate and clarithromicynce). She worked as a teacher and no professional respiratory exposure in her history was found.

Admission physical examination: BP 120/60, HR 100 bpm, SpO2 90 % aa, RR 22/min, BT 36.8°C. Dyspnoea for minimal effort. Heart: mild systolic murmur 2/6 on mitral focus. Chest: bilateral basal dry crackles. Abdomen: epatomegaly. Hands were swallowed, no arthritis signs, there were fingers’ dyschromiae and hypercheratosis. Neurological exam: no strenght or sensitivity deficit. In the Emergency room she performed blood gas analysis: pH 7.41, pCO2 58, pO2 45, HCO3 - 28; chest X-ray: bilateral pleural effusion, flogistic consolidation on right lower lobe. Blood tests: ESR 17, CRP 0.02, procalcitotonin 0.11 and WBC 4.6/mm^3 showed no inflammation. Slight transaminase augmentation and HCV positivity (RNA 682 757). Thyroid test, immunoglobulin dosage, C3, C4, beta2 microglobulin were normal. Microbiological tests: sierology for Mycoplasma pn, Legionella and Chlamidia pn, quantiferon, sputum culture, CMV-EBV-, HSV1-2, VZV-DNA, HIV-RNA, were all negative. EKG was normal. We suspected a lung interstitial disease (ILD) associated with connective tissue disease, So we performed a high resolution CT that showed consolidation in both lower lobes, bronchiecstiasia with thickness wall bronchi, ground glass opacities; subcarinal lymph nodes enlargement. Tracheal rings califications. Mild pericardial effusion. PET: mild 18-FDG captation in bilateral lower lobes consolidations as in active flogistic fibrosis pattern. Capillaroscopy: reduced capillary density, tortuous capillaries.
Echocardiography: normal PAPs. Functional respiratory tests found moderate restrictive syndrome and severe TLCO decrease (44%). Autoantibody analysis was negative except high positivity for antibody Anti-Threonyl-tRNA Synthetase (anti-PL7), confirmed in a second sample and cytoplasmatic fluorescence at ANA analyses. Bronchoscopy showed normal tracheobronchial morphology. BAL: lymphocytosis (20%), CD4/CD8 0.5. All microbiological BAL sample tests (EBV DNA, CMV DNA, HSV DNA, VZV DNA, PJP IFA test, bacterial and fungal culture) were negative, no tumoral cells were found. Transbronchial biopsy showed a non specific idiopathic pneumonia (NSIP). Considering NSIP histology, “mechanic’s hands” and PL-7 positivity, anti-synthetase syndrome (ASS) was diagnosed. We started steroid therapy (prednisone 37.5 mg), in order to eventually start cyclosporin A that may also control HCV viremia. She is sicilian and decided to do the follow up in Palermo’s Hospital so we lose post discharge data. Antisynthetase syndrome was first described in 1990, is recognized by its characteristic clinical manifestations associated with the presence of an anti-tRNA synthetase antibody, a family of intracytoplasmatic enzymes wich play a role in protein synthesis. The main associated clinical features are myositis, ILD, arthritis, fever, Raynaud phenomenon and mechanic’s hands. To our knowledge eight different antisynthetase antibodies have been described, anti-Jo-1 is the most frequent, followed by anti PL 12; while anti PL7 is one of the rarest (5%). Individual autoantibody specificities may be associated with distinctive clinical features. Non-Jo-1 antisynthetase antibodies seem to be markers of hypomyopathic forms with prominent lung involvement as in our patient. In fact she had no myopathic signs: normal CPK and EMG but a severe ILD with skin signs were evident. There are no practical guidelines about ASS therapy but steroid and immunosuppressive drugs are reported in literature as first line treatment. Lymphocytosis on BAL is a steroid good response index.

Hematology

An unusual case of anemia


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A 50 years old-man was admitted to our Division for a three-months history shortness of breath and fatigue. He had a clinical history of alcoholic cirrhosis and ulcerative colitis. His home therapy was: potassium canrenoate 100 mg daily, mesalazine 800 mg thrice daily and allopurinol 300 mg daily. Physical examination showed PA 130/70 mmHg, HR 82 bpm, RF 18 breaths/min and a marked splenomegaly, confirmed by an abdominal ultrasound (bipolar diameter 16 cm). Laboratory tests showed macrocytic anemia (Hb 8.1 g/dl, MCV 107.2 fL), increased levels of reticulocyte count (percentage value 8.1%, absolute value 205 x 10³/mmc), LDH and indirect peribilirubinemia (606 U/L and 1 mg/dl respectively), decreased levels of haptoglobin (< 30 mg/dl), and positive direct and indirect Coombs tests. Furthermore we found a significant hypogammaglobulinemia (IgG 318 mg/dl, IgA 16 mg/dl and IgM 18 mg/dl). The autoimmune panel was negative. Bone marrow biopsy showed a hyperplasia of erythroid series with macrocytic aspects, without other features. We started high-dose IV immunoglobulins and corticosteroids with a quick clinical and laboratory improvement (Hb 10.2 g/dl).

On the basis of clinical and laboratory, we made a diagnosis of autoimmune hemolytic anemia (AIHA) associated with a common variable immunodeficiency (CVID). CVID is the most common clinically significant primary immune defect. The diagnosis of CVID is based on significantly reduced levels of IgG and IgA and/or IgM, accompanied by impaired or absent antibody production. CVID is essentially a diagnosis of exclusion, as other causes of hypogammaglobulinemia, including known gene defects, medications, protein loss, or malignancy, must be excluded. Unlike other genetic immune defects, CVID is generally diagnosed in the third or fourth decade of life; however, a diagnostic delay of 6 to 8 years after the appearance of the first characteristic symptom is common. Although 70% to 80% of patients had recurrent pulmonary infections, auto-immunity and inflammatory complications are also common. Autoimmune diseases affect about 20% of CVID patients and are frequently the first manifestation of immune deficiency. The most common conditions are immune thrombocytopenic purpura, AIHA (which occur singly, consecutively or concurrently with Evans syndrome), primary biliary cirrhosis, systemic erythematous lupus and inflammatory bowel disease. Treatment includes high-dose of immunoglobulins, corticosteroids and selected immunosuppressants.

A singular case of ascites

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Case Report: A 87-year-old man was referred to our Unit because of abdominal distension in the last few months associated with dyspnea. He reported a history of hypertension, chronic renal failure, ear epithelioma treated with surgery and Parkinson’s disease. He denied risk factors for liver damage, such as alcohol consumption or prior viral hepatitis. On the admission, physical examination revealed the presence of reticular superficial veins, everted umbelical scar and sideward dullness. Furthermore, the vesicular murmur was reduced, and the patient was alert and collaborative. The arterial blood pressure was 140/70 mmHg. Physical examination also showed generalized lymphadenopathy with painless and firm consistency: bilateral submandibular, supraclavicular, infraclavicular, cervical, axillary and inguinal lymph nodes were involved. A chest X-ray showed the presence of a bilateral pleural fluid, which was greater on the right side. Laboratory tests documented a severe pancytopenia: 2.77x10⁵ WBC, 8.9 g/dl Hb, 68x10³ PLT, and an increase of creatinine (1.75 mg/dl) and beta 2 microglobuline (10 mcg/ml). A TORCH assay excluded viral infections. An abdominal ultrasound showed ascitic fluid, splenomegaly and a solid mass in the splenorenal cavity. The liver had regular margins and preserved echostucture. Markers of viral hepatitis (A,B,C and D) and autoimmune disease (ASMA, ANA and LKMI) were both negative. A liver chisrosis was therefore excluded, as well as heart failure and hypoproteinemia on the basis of echocardiogram and serum proteins in the normal range, respectively. The patient was treated with an evacuative and diagnostics paracentesis. The abdominal fluid color was brownish-yellow, and serum ascites albumin gradient (SAAG) indicated a transudate fluid. A full body Computer Tomography (CT) was also performed, and confirmed the presence of generalized lymphadenopathy. A supravacularimm lymph node (4.4x2,4x1.6 cm) biopsy was made, and revealed the presence of malignant tissue suggestive of a diagnosis of Nodular Sclerosis Hodgkin Disease (NSHD).

Discussion: Ascitic fluid is an usual complication of liver and heart disease. Rarely can be the first clinical manifestation of Hodgkin Lymphoma. In our case, the presence of lymphadenopathy of the hepatic hilum resulted in a reduction of lymphatic drainage and caused the rapid onset of ascitic fluid.

References:

A rare case of hepatic and splenic involvement by Hodgkin’s disease

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An 80-year-old woman was admitted to the hospital for jaundice and anemia. A recent use of non-steroid anti-inflammatory drugs was reported, due to x-ray examination showing a small lung nodule measuring 15 mm in maximum diameter in the left inferior lobe with low standardized uptake value (SUV max 0.95) and revealed also hypermetabolic activity with SUV of 5.8 in the mandibular body. After an accurate oral exam, the maxillofacial surgeon found a painful ulcerated lesion on the gingival tissue which was biopsed. Histopathologic examination demonstrated an angiodestructive polymorphous lymphoid infiltrate with extensive necrosis. Numerous CD3+, CD4+ and CD8+ T cells were observed with only rare CD56+ and CD57+ NK cells. There were numerous CD20+ B blast cells, which expressed LMP1 and EBV-protein gene 3. Bone marrow biopsy revealed a 5% nodular infiltration by blast CD20+ B cells that were positive for LMP1 and EBV induced protein gene 3, with normal trilineage hematopoesis. A diagnosis of lymphomatoid granulomatosis (LYG) grade 3 was established. Postoperative evaluation by total body CT scan confirmed the lung nodule and demonstrated mild splenomegaly and multiple retroperitoneal lymph nodes. Our therapeutic approach consisted of rituximab, cyclophosphamide, doxorubicin, vincristin and prednisone (R-CHOP). Currently, he is followed by hematologists and, after two cycles of chemoimmunotherapy, he completely resolved the onset symptoms. Discussion: LYG represents a B cell lymphoproliferative disorder that seems to be driven by infection of the lesional cells by Epstein-Barr virus (EBV). Etiologically, the disorder is more commonly diagnosed in patients with immunodeficiency and predisposing conditions including Wiskott-Aldrich syndrome, human immunodeficiency virus infection and allogenic organ transplantation. Histologically, LYG lesions are characterized by an angiocentric and angiodestructive lymphoid infiltrate. LYG can be classified into three grades based on the proportion of large atypical EBV positive B-cells and necrosis. Clinically, pulmonary involvement is often present. However, this disorder can affect other extranodal sites including skin, central nervous system and kidneys. Upper respiratory tract and gastrointestinal tract may be affected, but this is relatively uncommon. This condition should be treated through an individualized decision based on the patient’s characteristics. Low-grade tumors can be managed with immunomodulatory therapy like interferon-alpha; however, grade 3 should be treated as a diffuse large B-cell lymphoma. The contemporary pulmonary and gingival tissue involvement is an atypical presentation, especially when it occurs in an immunocompetent subject. Indeed, although the involvement of the oral cavity and gingival tissue is reported in patients with HIV/AIDS, documented LYG lesions affecting the oral cavity in an immunocompetent individual are extremely rare.

In search of lost erythroblast


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A 68-year-old man with a 9-year history of untreated asymptomatic chronic lymphocytic leukemia (CLL) arrived in our department with generalized weakness, dyspnea, fatigue, and anorexia. The clinical exam revealed pallor and moderate splenomegaly. The lymph nodes were not palpable and the rest of the physical examination was normal. Blood tests demonstrated marked anemia (hemoglobin of 6.1 g/dL, MCV 98 fL, MCHC 34.9 g/dL), platelets 155 x 10^9/mm^3, white cells 7.35 x 10^9/mm^3 (77.8% lymphocytes, 21% neutrophils). There was no evidence of hemolysis by virtue of negative Coombs test result, normal serum LDH level and absence of reticulocyte count. Serum ferritin was elevated, and vitamin B 12 and folate levels were normal.
Moreover, human parvovirus B19 IgG and IgM antibodies were negative, and erythropoietin levels was increased (350 mIU/mL). A bone marrow biopsy showed massive infiltration by CLL cells (80%), with tumor cells positive for CD20, BCL2, CD5, CD23, and almost complete absence of erythroid precursors. A diagnosis of B-CLL Binet C accompanied with pure red cell aplasia (PRCA) was established. Our therapeutic approach was based on a combination of low dose of chlorambucil (6 mg/m²/day) and rituximab (375 mg/m²/week). After a month, we observed a marked increase in reticulocyte count and an improvement in hemoglobin levels (10.1 g/dL). Unfortunately after two months he developed a lung infection. Thus, immunotherapy was interrupted, and estridial treatment was reduced and intravenous empirical antimicrobial therapy was unsuccessfully introduced. The patient died for a severe respiratory acute distress.

Anemia is a frequent complication of CLL, due to bone marrow infiltration by leukemic cells, autoimmune hemolytic anemia, PRCA and chemotherapy-induced anemia. PRCA is characterized by severe normocytic, normochromic anemia, reticulocytopenia and absence of erythroblasts in bone marrow. The estimated incidence of PRCA may be as high as 6% but many cases are undetected; in fact, severe normochromic anemia with reticulocytopenia is a frequent manifestation of advanced-stage CLL and is usually attributed only to the bone marrow infiltration by CLL. Therapeutic approach to PRCA consists of various agents, including corticosteroids, cyclophosphamide, cyclosporine A, intravenous immunoglobulins and, finally, rituximab. In our case rituximab administration was selected on the basis of its efficacy against both PRCA and bone marrow infiltration.

**Tumor burden at diagnosis: a key clinical parameter in Hodgkin’s lymphoma**

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The clinical signs and symptoms of Hodgkin’s lymphoma are the final result of a complex network of active autocrine and paracrine secretion of cytokines which are at first triggered by the scarce neoplastic component and then amplified by the prevalent inflammatory and stromal cells. The intensity of this immunologic crosstalk is responsible for histopathological features, lymph node enlargement, systemic symptoms and laboratory abnormalities of the disease. Under this point of view, the tumor burden (TB) can be considered the final expression of the whole cytological disorder, while other prognostic factors generally depend on the activity of a few, selected, cytokines. This is likely the reason for the confirmed superior predictivity of (TB) – whatever the method of assessment – over every other prognostic factor hitherto tested.

The present report shows the conclusive results of the investigation on the TB of 506 patients from 3 distinct trials (ABVD vs. BEACOPP in advanced stages; ABVD + IF-RT in early-stage unfavorably presenting disease, with two different schedules according to early response; and VBM + IF-RT in early, favorable-stage disease).

TB was measured through the evaluation of the diagnostic whole body CT scan and revealed to be strongly related to the resistance to treatment as it is clinically expressed by failing to achieve complete remission at the end of treatment or to maintain it for at least 12 months. This type of resistance is presently the main obstacle to the cure of the disease. Interestingly, the relationships between TB and resistance are strong and very different according to the type of treatment and the curves illustrating these relationships are distinctly separated. The relative risk of early treatment failure can be predicted on the basis of the TB at diagnosis and the therapy administered. By this way the treatment could be prospectively chosen on the basis of the measured TB and the requested level of acceptable risk. For example, the same 5-fold and 10-fold increases in risk of resistance can be expected in patients presenting with a rTB of 52 and 74 cm³/m² if treated with VBM + IF-RT, in patients with a rTB of 135 and 192 cm³/m² when treated with ABVD + optional IF-RT, and in patients with a rTB of 179 and 256 cm³/m² if treated with BEACOPP + optional IF-RT. Alternatively, it can be thought that a hypothetical patient having a rTB of 100 cm³/m² has a relative risk of resistance of 2.4 if treated with BEACOPP + optional IF-RT, of 3.3 if treated with ABVD + optional IF-RT and of 22.1 if treated with VBM + IF-RT. Moreover, TB can offer a comparable measure of the absolute strength and efficacy of each type of treatment, with a follow-up of only 12 months from the end of treatment. These acquirements could be very useful when designing new clinical trials or evaluating their results.

The relative complexity of the TB assessment has been an obstacle to its application. But, now, a simple and indirect estimate of the TB has been developed maintaining a prognostic advantage over every other determinant, IPI score included. Furthermore, promising results are coming from a semi-automatic PET/CT scan measuring metabolically active volumes, instead of whole visible masses. TB in Hodgkin’s lymphoma is a productive field of investigation still worth exploring.

**Iron overload in oncohematologic patients: is there a need for iron chelation?**


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**Background:** Oncohematologic diseases often require chronic red blood cell (RBC) transfusional support which frequently results in iron overload. In myelodysplastic syndromes (MDS), in particular, many studies show that both transfusion-dependency and the consequent iron overload are independent prognostic factors for overall survival and risk of leukemic evolution. Consensus statements have been developed for several transfusion-dependent conditions to provide clinicians a guidance in the monitoring and treatment of secondary iron overload.

**Aim:** The aim of this study is to evaluate iron load in a group of oncohematologic patients admitted to an Internal Medicine Unit and their clinical characteristics in order to obtain the prevalence of iron overload and a general overview of the current standard of care regarding the diagnosis and the management of iron overload in such patients.

**Materials and methods:** This observational study was conducted from January 2011 to April 2013. Oncohematologic patients admitted to Medicina Interna 1A at Fondazione Ca’ Granda Ospedale Maggiore Policlinico were enrolled. We evaluated ferritin levels and transferrin saturation index at time of oncohematologic disease’s diagnosis, the total number of transfused RBC units from that moment until our hospitalization and ferritin values, transferrin saturation and comorbidities at admission time. Normal values were considered according to the hospital laboratory’s ones.

**Results:** The results are summarized in tables 1 and 2. We collected data from 98 patients with a mean age of 72.9±13.6. From diagnosis until inclusion in the study, 33/98 patients (33.7%) had received more than 10 RBC units (a mean of 35.1±21.7), the remaining 65 (66.3%) had received only few sporadic transfusions (a mean of 1.4±2.2). The most frequent underlying disorder in transfusion-dependent patients was MDS (51.5%). The first group showed a significant increase of both ferritin levels (from...
655.6±830.7 to 3182.2±4242.9 ng/mL) and transferrin saturation index (from 23.7±19.3 to 62.1±29.7%), while in the second group we observed no relevant variation of transferrin saturation index and a mild increase of ferritin (from 456.9±765.3 to 904.6±1246.9 ng/mL), compatible with an inflammatory condition (Table 1). We also considered iron overload comorbidities (diabetes, chronic heart failure, atrial fibrillation, ipothyroidism and hepatopathy) and we found a higher overall prevalence in patients with multiple transfusions than in the other group, although age and sex were similar (Table 2). Besides, among the 33 patients requiring chronic transfusions, only 8 (24.2%) had undergone chelation therapy during their medical history. We found more frequent comorbidities in not-chelated patients than in chelated group, but the number of patients was too small to reach a statistical significance.

**Discussion:** Since many hematologic malignancies require chronic blood transfusions, patients should be strictly screened and monitored for iron overload. All guidelines agree that serum ferritin levels and transferrin saturation should be assessed at diagnosis and then regularly measured every three/six months. In addition the use of a personal RBC transfusion diary should be encouraged, because so far it is not a common practice.

Once iron overload has been identified, it should be treated to reduce the risks of morbidity and mortality, but among our patients only 8/33 (24.2%) had received an attempt of chelation therapy. Increased awareness of the risks of iron overload from chronic transfusion therapy in onc hematologic patients should result in a greater use of interventions, such as iron chelation, to reduce total body iron and the risk of long-term sequelae.

**Important therapeutic response in a non-secreting plasmablastic multiple myeloma complicated by acute renal impairment**


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A 70 years-old man was admitted to our Division because of a two-months history of inappetence, slight weight loss (about 4 kilos), fatigue and worsening non-traumatic lumbar pain exacerbated by movement and coughing. He rated the pain at 7 on a scale of 0 to 10 (representing 10 the worst pain imaginable), resulting in functional impairment and analgesic supine position. In order to treat the pain, he took nimesulide (100 mg twice daily) within two weeks, only reaching its temporary slight improvement. Regarding lifestyle, he smoked about 20 cigarettes daily and had no history of alcohol or other toxic substances abuse. In his medical history arterial hypertension and diabetes mellitus were reported, treated with irbesartan 300 mg daily and metformin 500 mg thrice daily respectively. Moreover, he recently underwent transurethral resection of the prostate for benign prostatic hyperplasia. Physical examination showed pale skin, PA 92/63 mmHg, HR 104 bpm, costovertebral angle tenderness on the right side and mild hepatomegaly. Baseline hematic laboratory results were as follows: RBC 3.08 x 10^6/mmc, Hb 9.8 g/dL, HCT 28.6%, MCV 92.8 fl, MCH 31.9 pg, MCHC 34.4 g/dL, RDW 15.7 g/dL, WBC count 4.3 x 10^9/mmc, PLT count 252 x 10^9/mmc, creatinine 5.46 mg/dL, BUN 174 mg/dL, Na+ 132 mEq/L, K+ 4.9 mEq/L, uric acid 16.0 mg/dL, albumin 3.47 g/dL, free calcium 12.3 mg/dL, phosphate 5.7 mg/dL, VES 15 mm/h. He had normal LDH, iron balance, vitamin B12, folic acid levels, vitamin D and PTH. Spot urinalysis evidenced proteinuria (100 mg/dL), hemo globulinuria (1 mg/dL), leucocituria (500 leu/ul), erythrocytes and leucocytes in the CAST. Basing on laboratory signs of renal impairment, a kidney ultrasonography was performed, showing no noteworthy alterations. Moreover, a skeletal survey was carried out (evidencing diffuse osteoporosis with no discrete focal lytic lesions) completed by MR of the dorsal, lumbar and sacral spine (vertebral bodies diffusely altered and sub sidiency of L3). Suspecting a monoclonal gammopathy, we performed β2-microglobulin (9.5 mg/L), serum protein electrophoresis (showing hypogamma globulinemia, 0.42 g/dL), 24-hours urine free light-chain test (positivity for k light chains, 31.3 mg/L) and serum immunofixation, (confirming the presence of monoclonal k light chains). Bone marrow aspiration and trephine biopsy revealed 80% hypercellularity of plasmablastic myeloma cells CD138+ with immunophenotype IgG-k and expression of CD20 and cicline D1. Taking into account all these findings, we diagnosed a
plasmablastic subtype of non-secreting (NS) multiple myeloma (MM) complicated by a likely multifactorial acute nephropathy (NSAIDs nephrotoxicity, hypercalcemia, hyperuricemia). MM is a B-cell neoplasm of the bone marrow with symptoms including anemia, bone lytic lesions and/or bone demineralization, hypercalcemia, renal impairment, and compromised immune function. NS subtype ranges from 1% to 5% of all MM cases, only distinguished by the absence of serum/urinary M-protein. Both treatment and prognosis are identical to the secreting forms. Nevertheless, plasmablastic subtype of MM has a higher frequency of extramedullary involvement, almost total marrow replacement, renal impairment, hypercalcemia and a reduced overall survival. Renal impairment occurs in 20-40% of newly diagnosed patients with MM, resulting from a multifactorial etiology (paraprotein-associated causes, hypercalcemia, hyperuricemia, infections, dehydration, nephrotoxic drugs, plasma cell infiltration) and implying a poor outcome. The aim of this report is to emphasize the very good response to chemotherapy observed in our patient: it consisted in a 21-day cycle of combined treatment with bortezomib (1.3 mg/m2 daily on days 1, and 8), melphalan (18 mg daily on days 1, 2, 3, and 4), prednisone (50 mg twice daily on days 1, 2, 3, and 4) and acyclovir (400 mg twice daily). An early improvement of symptoms and renal function were reached, so i.v. zolendronic acid (4 mg monthly) associated to oral calcium (500 mg daily) and vitamin D (400 U1 daily) supplements were administered. After four cycles of chemotherapy, an almost complete resolution of both pain and renal impairment was obtained. Most recent blood tests were: RBC 3.90 x 10^12/mm, Hb 12.3 g/dL, HCT 36.8%, MCV 94.4 fL, MCH 31.5 pg, MCHC 33.4 g/dL, RDW 15.4 g/dL, WBC count 3.49 x 10^9/mm, PLT count 181 x 10^9/mm, creatinine 0.78 mg/dL, BUN 42 mg/dL, ClCr >60 mL/min, Na+ 136 mEq/L, K+ 4.0 mEq/L, uric acid 3.3 mg/dL, free calcium 8.94 mg/dL, β2-microglobulin 3.8 mg/L.

**Efficacy of Filgrastim, Lenograstim and Peg-Filgrastim in the mobilization of peripheral blood progenitor cells in patients with lymphoproliferative disorders**

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**Purpose:** Patients with lymphoproliferative disorders, who are candidate to autologous stem cell transplantation (ASCT), require mobilization with chemotherapy and granulocyte-colony stimulating factor (G-CSF). This study looked for differences in hematopoietic peripheral stem cells (HPSCs) mobilization in response to the three available G-CSFs: namely Lenograstim, Filgrastim, and Peg-Filgrastim.

**Patients and methods:** Between 2000 and 2012, 146 patients (66 M and 80 F) who underwent ASCT for multiple myeloma (MM), non-Hodgkin’s Lymphoma (NHL) or Hodgkin’s Lymphoma (HL) were consecutively included in this controlled, non-randomized study. All patients received induction therapy, then a mobilization regimen with cyclophosphamide 3 to 7 g/mq at day 0 plus Lenograstim 10 μg/kg/daily (Arm A) from day 5, or Filgrastim (Arm B) from day 5, or peg-Filgrastim (Arm C) 6 mg at day 6. From days 12 to 14, HPSCs were collected by two to three daily leukaphereses.

**Results:** Lenograstim mobilized more CD34+ cells than the other two G-CSFs. The ability to reach a collection target >3x10^6 CD34/Kg body weight (bw) in two leukaphereses was higher for Lenograstim. No differences between the three regimens were observed regarding toxicity and days to WBC and platelet recovery.

**Conclusion:** High-dose cyclophosphamide plus Lenograstim achieved adequate mobilization and the collection target more quickly and with fewer leukaphereses as compared with Filgrastim and peg-Filgrastim. Thus, Lenograstim may represent the ideal G-CSF for PBSC mobilization in patients with lymphoproliferative diseases. Further studies are needed to confirm these results and better understand the biological bases of these differences.

**Higher liver transplantation rate in Budd-Chiari syndrome due to myeloproliferative neoplasms**

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**Background:** Splanchnic vein thromboses (SVT), which include portal vein thrombosis (PVT) and thrombosis of the hepatic veins causing Budd-Chiari syndrome (BCS), are frequent presenting complications of myeloproliferative neoplasms (MPN) both yet known or undiagnosed. BCS is due to MPN in approximately 50% of cases. Therapeutic options for BCS include medical therapy (anticoagulants, cytoreduction, diuretics) and invasive treatments: transjugular intrahepatic porto-systemic shunting (TIPS) and orthotopic liver transplantation (OLT). TIPS and OLT are effective and rescue therapies in patients with BCS, both soon after diagnosis and later during follow-up, and seem to have similar long-term outcome. OLT can be the first invasive therapy in presence of a worse hepatic disease at presentation or may be delayed when liver fails or hepatic cell carcinoma (HCC) arises.

We report the rate and outcomes of invasive procedures in a cohort of patients with MPN and BCS followed in a single center.

**Patients:** Between 1983 and 2011 we studied 27 MPN patients with BCS. 16 were affected by ET, 10 by PV and 1 by PMF. 22 were females and 5 males. Their median age at diagnosis was 33.7 years and at BCS 34.9 years. At the time of diagnosis average hematological parameters were: platelets 430.5±210.7 x 10^9/L, WBC 11.6±5.6 x 10^9/L and hemoglobin 149±34 g/L. Twenty patients carried JAK2V617F mutation, 2 were JAK2-WT; in the remaining 5, JAK2 was not available. In 18 cases BCS occurred at diagnosis while in 9 during follow up (median 6.2 years). The patients received a step-wise treatment approach comprehending medical therapy (MT: anticoagulants, diuretics, cytoreduction) and invasive procedures as TIPS and OLT.

**Results:** Twelve patients (44.4%) received MT; in 6 patients (22%) TIPS was used and in 2 cases were shifted to OLT (1 HCC and 1 progressive liver failure); 9 other patients underwent OLT as first invasive procedure. Therefore a total of 11 patients (40.7%) underwent OLT (5 cirrhosis, 3 acute liver failure and 3 HCC).

| Table 1. |
| Treatment | MT | TIPS | OLT |
| Number of patients | 12 (2/10) | 6 (1/5) | 11 (2/9) |
| MPN disease (PV/ET/PMF) | 4/8/0 | 3/3/0 | 4/6/1 |
| Follow-up median (y) | 7.4 | 5.5 | 5.2 |
| Secondary BCS associated thrombosis* | 1 (8%) | 3 (50%) | 5 (45.5%) |
| Long lasting thrombosis during treatment§ | 2 | 0 | 0 |
| Bleedings§ | 4 | 0 | 0 |
| Death | 2 | 0 | 1 |

*7 portal district thrombosis, 1 cerebral vein thrombosis, 1 pulmonary embolism #1 myocardial infarction and 1 cerebral vein thrombosis §14.8% of all patients
Discussion: In a large study evaluating 157 BCS of different etiology, OLT was performed in 12.7% of cases and MPN did not result to be related to a higher need of invasive intervention. In contrast, 50% of our BCS-MPN patients underwent OLT and a total of 63% of cases received an invasive therapeutic procedure. Most of our patients undergo invasive procedures after a secondary BCS-associated vein thrombosis. In particular portal-vein associated thromboses contribute in worsening liver failure and this may define the way to OLT. Conservative approach with medical therapy seems to be associated with an increased rate of complication but the low number of our patients did not permit statistical evaluation and our observation need to be confirmed in larger and prospective studies.

Anemia in Internal Medicine: a retrospective observational study of anemia prevalence in elderly multipathological patients

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Background: Anemia negatively impacts the quality of life and it is strongly related to increased mortality and risk of hospitalization in elderly, disabled, seriously ill or hospitalized patients. Anemia is a common condition in elderly, frequently as an outcome of interactions between mechanisms related to aging or due to the presence of chronic underlying pathologies. Despite the increasing prevalence of anemia with aging, no data are available on the distribution of this pathology in internal medicine inpatients.

Aims: The aims of the present study were to determine the prevalence and etiology of anemia in a population of patients admitted to an Internal Medicine department, and, furthermore, to analyze the correlation between anemia and gender, age and comorbidities.

Methods: The present study is a retrospective observational study concerning a population of patients admitted in an Italian department of Internal Medicine during a year. Clinical data and results from extensive blood tests were collected at admission. Anemia was defined according to World Health Organization criteria (hemoglobin below 12 g/dl in women and 13 g/dl in men).

Results: We have collected data from 560 patients mainly elderly (mean age±SD: 73.5 years±14.5). The most common chronic diseases in the study population were: cardiovascular pathologies (arterial hypertension 71%, chronic heart disease 53%), cerebrovascular disease (31%) and cancer (30%). High prevalence of anemia (59%) was found, with a variation by age ranging from 53.5% in patients aged <65 years to 66.1% in patients aged >85 years. Anemia was classified as mild in more than half of the cases. Classifying anemia on the basis of a single cause showed that the most common diagnosis was multifactorial anemia (40%), followed by anemia of chronic disorders (23%), anemia of hematological diseases (13%) and anemia due to iron, vitamin B12 or folate deficiency (8%). Anemia due to chronic renal failure was observed in only 5% of cases, although anemia was globally present in 28% of patients with chronic renal failure. Finally, in 9% of cases it was not possible to identify the main causes of anemia.

Conclusions: The results of this study show a high incidence of anemia in patients admitted to an Internal Medicine department. Anemia is a pathological common condition, that needs a careful clinical management because it can adversely affect the outcome as well as slow down and complicate the diagnostic process.

Fistful of platelets


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A 28 years-old woman was admitted to our Division of Internal Medicine for epistaxis and gingival bleeding. In her clinical history there was a diagnosis of gestational thrombocytopenia (GTP) during the previous pregnancy, treated with corticosteroids and immunoglobulin e.v., with positive outcome. At the physical examination arterial pressure was 115/80, HR 86, T 36.5°C without other complaints. Laboratory test showed a very low platelet count (4,000 migl/mmc). We started the treatment with Prednisolone 1mg/Kg/day for 5 days with an improvement of platelet count (70,000 migl/mmc). Immunological screening and platelet antibodies were negative; an abdomen echo-ultrasound didn’t show signs of splenomegaly. Patient was discharged with 25 mg of prednisone one time a day. After a week there was a new drop of platelet count (12,000 migl/mmc) and we decided to start again Prednisone 1 mg/Kg/day + immunoglobulin 0.4 mg/kg/day e.v. for 5 days, with a quick improvement (150,000 migl/mmc). Platelet count remained stable for all time of pregnancy with 12,5 mg of Prednisolone one time a day. GTP is the most common cause of thrombocytopenia in pregnant women, accounting for approximately 75% all cases. The reason for this fall in the platelet count in unknown, although it has been speculated it may reflect dilution, decreased platelet production, and increased platelet turnover during pregnancy. Most experts consider the diagnosis of GTP to be less likely when the platelet count falls below 70.000 migl/mmc. Immune thrombocytopenia (ITP) is an uncommon cause of thrombocytopenia in pregnancy, occurring in between 1 in 1000 and 1 in 10,000 pregnant women. Although ITP may present at any point in pregnancy, it is one of the few causes of thrombocytopenia that may become manifest in the first trimester. Because ITP may be indistinguishable from GTP, patients with ITP in pregnancy often have a prior history of this or other immune-mediated disorders. Thrombocytopenia occurs also in up to 50% of women with preeclampsia and syndrome HHELP (hemolysis, liver function test and low platelet). The treatment is generally not required in patients with platelet counts greater than 20,000 to 30,000/ml and without signs of bleeding. Corticosteroids are the first-line of therapy for thrombocytopenia in pregnant women, with response rates of 70% to 80%, followed by immunoglobulin e.v. or by combinations of these therapy. If this approach fails, laporoscopic splenectomy may be safely performed during pregnancy. In our case, considering the low platelet count, the early period of pregnancy and the presence of a prior history of this, we concluded for a diagnosis of ITP in pregnancy.

A singular case of weakness

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Case report: A 45-year-old man was referred to our attention for moderate weakness. His previous medical history was unremarkable, except for non–alcoholic fatty-liver disease and hypertension controlled with combined therapy. Physical examination reveals a temperature of 37.0°C, pulse of 83/min, and blood pressure of 172/92 mm Hg. An abdominal examination reveals hepatomegaly. He denies any alcohol consumption. Ultrasound of the abdomen revealed mild hepatomegaly with increased echotexture suggesting grade 2 hepatosteatosis.
Qualitative and satisfaction to anticoagulant therapy of Italian patients with atrial fibrillation enrolled in the European PREFER in AF Registry

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Background: The majority of Italian patients with atrial fibrillation (AF) are treated with long term vitamin K antagonists therapy for the prevention of thromboembolic events. This treatment requires periodical assessment of coagulation parameters by specific laboratory tests (INR - International Normalized Ratio).

Few data is available about the quality of life of patients with AF and the self-perception of chronic anticoagulation therapy and related laboratory procedures.

Methods: The PREFER in AF Registry (PREvention of Thromboembolic events – European Registry in Atrial Fibrillation) enrolled, from January 2012 to January 2013, unsellected patients with AF in the following European countries: Austria, France, Germany, Italy (ITA), Spain, Switzerland and United Kingdom.

Validated self-administered questionnaires assessed patients’ quality of life (EQ-5D) and their perception of anticoagulant therapy (PACT-Q2), in terms of expectations and satisfaction of their treatment. The following data refers to Italian patients and was collected during the study baseline visit.

Results: The PREFER in AF Registry enrolled 7243 patients in Europe, including 1888 (26%) in Italy, where 98 sites were involved. Quality of life assessment (investigated by the EQ-5D questionnaire) revealed that, among Italian patients, a proportion of 55% did not have problems in carrying out normal daily activities; similar data was observed among other European countries. However, only 37.7% of Italian patients did not feel anxiety or depression, compared to a proportion of 53% among European patients. The results of the PACT-Q2 questionnaire (filled by 58.4% of Italian patients, n=1103) have instead highlighted some interesting differences on the self-perception of anticoagulant therapy among Italian patients, compared to European patients. Only 36% of Italian patients (in comparison to a proportion of 70.3% reported in EU) did not consider difficult taking the anticoagulant therapy. Only 30.8% (EU proportion: 57.8%) was not annoyed from taking therapy. A proportion of 28.6% (EU proportion: 57.7%) among Italian patients did not consider complicated the dose adjustment of the anticoagulant therapy and a proportion of 30.2% (EU proportion: 65.7%) did not report difficulties at all to plan their time activities due to anticoagulant therapy. Only 21% of patients was not bothered by regular monitoring tests required with anticoagulant therapy (EU proportion: 52.2%). Finally, only 25.7% of Italian patients (EU proportion: 51.1%) did not consider a problem avoiding some foods that have interactions with their therapy.

Conclusions: The assessment of quality of life and, more important, the self-perception of the treatment, expressed by the patients enrolled in the European Registry PREFER in AF, highlighted among Italian patients a level of dissatisfaction and difficulties in the management of anticoagulant therapy, greater than those observed in other European countries. It is difficult to explain the possible causes of these differences; maybe the results of the Registry after 1 year of follow-up can help to clarify.

Disputes on antithrombotic prophylaxis management in paralyzed young people

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A paraplegic 32 years old man, was hospitalized in our clinic with a diagnosis of “pulmonary embolism”. He complained about the sudden appearance of pain at the right hemithorax that was accentuated when breathing, with productive cough and haemoptysis of discrete entities. He denied to be affected by dysnea and fever. At the Emergency Room he performed an ECG and an echocardiography which were normal. Furthermore a chest x-ray was carried out showing: “a clouding of the middle lobe, probably associated with bronchiectasis” and a CT of the chest: “signs of partial thromboembolism of lower lobar branch of the right pulmonary artery and its segmental branches and of lobar branch superior at the emergency. There was basal and ipsilateral pleural effusion. There were also multiple triangular, sub-pleural thickening of ischemic areas. Bronchiectasis saccular of the posterior basal right segment with signs of inflammation”. A doppler ultrasound has excluded signs of deep venous thrombosis in place. Blood tests showed mild leucocytosis and an increase reactive C protein and D-dimers. Blood gas analysis showed mild hypoxemia. In 2001, following an accident, the patient suffered a spinal cord injury of D12-L1 and fracture of the left femur with a result paraplegia and urinary incontinence. Immediately he had to undergone surgery for internal fixation and positioning of spinal dorsal stabilizer. In that occasion he practiced heparin therapy for a few months. The next year the patient had a deep venous thrombosis of the right femoral artery. In that occasion he induced oral anticoagulant therapy, suspended after two years because of the appearance of purplish petechiae in the lower limbs. In 2006, the patient was subjected to cistoplastica surgery and after a few days he presented a new episode of deep vein thrombosis that extended from the left femoral vein to popliteal vein. In a vena cava I placed filter that will have been removed about a month later and re-start the oral anticoagulant therapy. After a few
years he had been advised to take antipla telet therapy, but the patient ignored the advice and avoided the therapy. The pathology of post-traumatic spinal cord exposes the patient at high risk of venous thromboembolism. The recurrent question is whether these paraplegic patients, even if young, need to take anticoagulant therapy for life. In the literature there are no studies that confirm the need to undertake immediately a long-term prophylaxis. This exposes the patient to additional risks besides being costly. Hence it is undertaken only in patients at very high risk for example, after the first episode of venous thromboembolism. Therefore lot of care should be given to prophylactic physical mobilization, elevation of the legs, massage, compression stockings and intermittent pneumatic compression.

Venous thromboembolism in patients with Crohn disease

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Crohn’s disease is associated with several intestinal and extra-intestinal complications. Among the latter, some are more common (iritis and uveitis, ankylosing spondylitis, primary sclerosing cholangitis, erythema nodosum, pyoderma gangrenosum) whereas others such as cardiovascular disease, are less frequent.

A 76 years old woman, suffering from Crohn’s disease for 20 years and treated with Infl iximab and Mesalazine, was admitted in our hospital with dyspnea. She was subjected to the pulmonary CT angiography that showed pulmonary embolism. Then she was initiated to a therapy with warfarin sodium. In the previous month it was performed a colonscopy that didn’t detected any signs of active inflammation. She then performed rehospitaliza tion in our clinic for Day Hospital after 8 months. Echo color doppler of the lower limbs did not detect signs of deep vein thrombosis, while the pulmonary CT angiography was negative for perfusion defects. Anticoagulant therapy then was suspended. The activation of the coagulation system in patients with Inflammatory Bowel Disease (IBD) would be responsible of thrombotic diathesis, with the possibility of atrial thrombi formation, deep vein thrombosis and pulmonary embolism. The literature shows that the risk of venous thromboembolism in patients with IBD has increased by about three times compared to the general population, and it’s strongly related to Crohn’s disease, less to ulcerative colitis. Although the incidence of thrombotic events increases with age, the relative risk is greater in young people. Each patient at high risk of recurrent events, can be treated with oral anticoagulants in the long term.

The combined use of vitamin K antagonists and antiplatelet agents in atrial fibrillation: Italian analysis of baseline data from the European PREFER in AF Registry

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*Background: The combined long-term use of vitamin K antagonists (VKA) and antiplatele t agents (AP) in patients with Atrial Fibrillation (AF) is generally discouraged because it entails increased risk of bleeding in the face of uncertain efficacy benefits. Therefore we evaluated the frequency of such prescription pattern and patients characteristics.

Methods: The PREFER of thromboembolic events – European Registry in Atrial Fibrillation (PREFER in AF) prospectively enrolled patients with AF in France, Germany, Austria, Switzerland, Italy, Spain and United Kingdom, from Jan 2012 to Jan 2013. Here, we report the patterns of combined therapy with anticoagulants and antiplatelet therapy among Italian patients at baseline visit.

Results: PREFER in AF Registry enrolled 7243 patients in Europe, including 1888 (26%) in Italy, where 98 sites were involved. A proportion of 62.4% among Italian patients were treated, during the last 12 months prior enrollment, with VKA (warfarin and acenocoumarol), whereas a proportion of 18.1% were treated with AP (mainly ASA and clopidogrel); a combined treatment with VKA and AP was observed in 8.8 % of Italian patients. Finally a proportion of 10.4% of patients was not treated with any of the two drug classes. Compared to patients who were prescribed VKA only, patients on combination therapy (VKA + AP) had similar mean age (71.8±9.87 vs. 71.6±9.88, respectively) and BMI (27.8±4.33 vs. 27.2±4.46, respectively); higher proportion of diabetes (29.3% vs. 20.1%), dyslipidemia (59.9% vs. 37.8%), chronic renal insufficiency (18.6% vs.12.1%) and a greater incidence of comorbidity with coronary heart disease (58.7% vs. 16.5%). They also reported a higher mean CHA2DS2-VASc thromboembolic risk score (3.9 vs 3.4) and a higher mean HAS-BLED bleeding risk score (2.9 vs. 2.0). Most of the combination treatments were judged by all means inappropriate according to the ESC guidelines, since not given due to recent acute coronary syndrome. Differences observed among these two groups in Italian patients are similar to those reported for other European countries involved in the registry.

Conclusions: The combined use of VKA and AP seems common in Italian patients with AF, mostly explained by the coexistence of coronary heart disease, and not influenced by considerations on the risks of bleeding or thromboembolism. Such prescription patterns, should be the target of appropriate educational guideline implementation programs, in order to encourage the use of combined VKA + AP treatment in appropriate patients.

The laboratory management of oral anticoagulant therapy in patients with atrial fibrillation in Italy: a comparison among countries participating in the European PREFER in AF Registry


*Background: The majority of Italian patients with Atrial Fibrillation (AF) are treated with long term vitamin K antagonists therapy for the prevention of thromboembolic events. This treatment requires a periodical assessment of coagulation parameters by specific laboratory tests (INR - International Normalized Ratio). The anticoagulation management of these patients is different among European countries; few studies have evaluated the impact of these differences on the quality of INR values.

Methods: The PREFER in AF Registry (PREFER of thromboembolic events – European Registry in Atrial Fibrillation) enrolled, from January 2012 to January 2013, unsel ected patients with AF in the following European countries: Austria, France, Germany, Italy (ITA), Spain, Switzerland and the United Kingdom.

The following data has been collected during the study baseline visit and refers to a sub-analysis, regarding a comparison between Italian patients and other European countries, focused on the assessment and management of INR monitoring.
Results: PREFER in AF Registry enrolled 7243 patients in Europe, including 1888 (26%) in Italy, where 98 sites were involved. A proportion of 64.7% among Italian patients reported at least one INR measurement during the last month prior to enrollment (vs. 67.6% of EU patients). The mean amount of INR assessments in the last month before enrollment was higher in Italy (2.8±1.89) than other European countries (France: 1.8±1.3; Germany: 1.7±1.4; Spain: 1.6±1.3, UK: 2.3±2.2). Also the mean amount of INR measurements in the last year was greater in Italy (16±9.7) than in France (12.8±6.7), Germany (15.7±10.4), Spain (11.4±5.3) and United Kingdom (15.2±9.0). The proportion of INR assessments carried out at anticoagulation centers was higher in Italy than EU (44.4% vs 19.3%). The Time in Therapeutic Range (TTR), evaluated on the last 3 INR measurements, was lower in Italy (72.2%) than in Germany (82.5%), France (77.2%) and UK (73.4%), but higher than Spain (68.6%).

Conclusions: In Italy, compared to other European countries, anticoagulation centers are the main point of reference for INR assessment and management of patients with AF treated with vitamin K antagonists for prevention of thromboembolic events. Italy is also the EU country with the highest mean number of INR laboratory measurements, both in the last month and in the last year. However, the high frequency of INR assessments in Italy is not associated with a better control of INR levels (evaluated by TTR) with respect to other European countries. These data are of great interest in view of the upcoming introduction of the new oral anticoagulants in Italy.

Prognostic significance of hypernatremia and hyponatremia among patients with spontaneous intracerebral hemorrhage

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Background: Spontaneous intracerebral hemorrhage (ICH) is a major public health problem with an increasing hospital admissions in the past years, probably as a result of the increasing age of the population and changes in racial demographics. ICH is associated with a high mortality and disability rate. A few studies have assessed the role of potential prognostic factors in patients with an acute ICH. In hospitalized patients abnormal serum sodium levels (hyponatremia and hypernatremia) were frequently described as predictors of poor prognosis. On the other hand, whether these abnormalities should be useful in predicting the prognosis in patients with spontaneous ICH is yet to be determined.

Methods: Consecutive patients hospitalized between 2006 and 2012 in two hospitals (Varese and Cuneo) with an objective diagnosis of ICH were potentially eligible for inclusion for the purpose of the study. Patients with traumatic ICH were excluded, as well as patients with ICH secondary to aneurysms and arteriogenous malformation and patients treated with anticoagulant or a combined anticoagulant and antiplatelet therapy. Glasgow coma scale (GCS) score at admission and mRS at the time of discharge were evaluated in all the patients, as well as anamnestic data concerning previous stroke events, history of hypertension and diabetes mellitus. The site of origin, the presence of intraventricular hemorrhage, the volume and the necessity for surgical therapy were also registered. ICH volume was measured according to the ABC/2 method. Death rate and clinical outcome at the time of discharge were evaluated. Patients with a mRS 4 at discharge were considered as having a poor outcome. Characteristics of patients with good and poor outcome were compared using Student's t-test (for continuous variables) and the chi-square or Fisher's exact test (for dichotomous variables). Only variables found significant in the univariate analysis were used as covariates in the multivariate analysis. Results of multivariate analysis were presented as odds ratios (ORs) and corresponding 95% confidence intervals (CIs).

Results: 479 (mean age of 71.8±13.0 years, 219 women patients) were included in the study. Mean GCS at presentation was 11.0±4.6 and 151 patients (31.5%) had a GCS ≤8. Fifty two ICHs (10.9%) were intratentorial and 197 (40.5%) had a volume ≥30 mL according to the ABC/2 method. At the end of hospitalization 139 patients (29.0%) had died and 280 patients (58.5%) were judged to have a poor prognosis (mRS ≥4). Sodium levels at the time of hospitalization were similar in patients poor or good outcome (138.8 vs 139.4 mg/dl) and prevalence of hyponatremia (<130 mg/dl) and hypernatremia (>150 mg/dl) were similar in the two groups. At univariate analysis, age (P < 0.001), female sex (P = 0.07), GCS (P < 0.001) antiplatelet therapy (P=0.05), lobar location (P=0.009), thalamus location (P=0.05), basal nuclei location (P = 0.026), intraventricular hemorrhage (P < 0.0001), hemorrhage volume≥ 30 mL (P < 0.001) and surgical hematoma evacuation (P = 0.001) were marginally or significantly different in patients with a good outcome and poor outcome, whereas anamnese of hypertension or diabetes mellitus, infratentorial location or and were not (P > 0.10). In the multivariate analysis, GCS ≤ 8, hemorrhage volume > 30 mL, age, intraventricular hemorrhage, surgical hematoma evacuation remained significantly associated with a worse prognosis at discharge whereas basal nuclei and thalamus location remained significantly associated with a worse prognosis at discharge (p<0.05 for all the variables). Sodium level was re-evaluated in 404 patients (84.3%); in 63 patients (13.2%) was not possible because they died soon after the presentation at the emergency department and the remaining 12 patients (2.5%) did not repeat the evaluation during hospitalization. In these patients, hypo and hyper-natriemia were significantly more frequent in patients with a poor outcome than in patients with a good outcome. When these variable was introduced in the multivariate model, hyponatremia was only marginally significant associated with a worse prognosis at discharge (OR1.80, 95% CI 0.99, 3.29) whereas hypernatremia remained significantly associated with a worse prognosis at discharge (OR 12.1 95% CI 2.76, 53.4). Furthermore, patients with a hypernatremia during hospitalization had a significantly higher mortality at univariate and multivariate analysis (p<0.05).

Discussion: According to the results of our study, sodium level alterations evaluated during hospitalization but not during the hyper acute phase in patients with a spontaneous ICH were significantly associated with a worse outcome at discharge and this parameter should be evaluated along with the other prognostic factors in these patients. Future prospective studies are warranted to confirm our preliminary findings.

The prognostic significance of residual vein obstruction in patients with treated deep vein thrombosis: a patient-level meta-analysis


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Background: Risk stratification for recurrence after unprovoked deep vein thrombosis (DVT) could improve clinical decisions on the optimal duration of anticoagulant therapy. Residual venous obstruction (RVO) may be pivotal in clinicians’ decision-making but results from clinical studies and study-level meta-analyses are conflicting.

Aims: We aimed to determine if RVO is a valid predictor of recurrent venous thromboembolism (VTE) in patients with a first symptomatic unprovoked proximal DVT who had received at least 3 months of anticoagulant therapy.

Methods: Systematic search of electronic databases (Medline, Embase,
Cochrane Library) until September 2012, supplemented by manual reviewing of the reference lists and contacting content experts. Prospective studies that investigated the association between RVO and recurrent VTE in patients with a first unprovoked proximal DVT were selected. Individual patient-level data were obtained from the datasets of selected studies and merged into a single database. A multivariate, shared-frailty Cox model was used to calculate hazard ratios (HRs) for recurrent VTE which included the following covariates: RVO; age; sex; anticoagulation duration before RVO assessment; and anticoagulation continuation after RVO assessment.

**Results:** There were 2,527 patients studied from 10 prospective studies. RVO was found in 1,380 patients (55.1%) after a median of 6 months (inter-quartile range [IQR]: 3-7.6) from a first unprovoked DVT. Recurrent VTE occurred in 399 patients (15.8%) during a median follow-up of 23.3 months (IQR: 12.8-30) from RVO assessment. After multivariate Cox analysis, RVO was independently associated with recurrent VTE (HR = 1.32, 95% CI: 1.06-1.65). RVO was a stronger predictor of recurrent VTE if detected early, i.e. at 3 months (HR = 2.17; 95% CI: 1.11-4.25), but no longer predictive if detected later, i.e. >6 months (HR = 1.19; 95% CI: 0.87-1.61) after DVT is diagnosed.

**Conclusion:** In patients with unprovoked DVT who have received at least 3 months of anticoagulant therapy, RVO is a weak overall predictor of recurrent VTE and has predictive utility if detected at an earlier time (3 months) but not later time (>6 months) after a diagnosis of DVT.

**Are the “classic” statistic methods enough for an accurate stratification of pretest probability in acute pulmonary embolism?**

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**Introduction:** Pulmonary embolism (PE) is a common acute event characterized by high mortality. Its diagnosis is often missed due to a confounding clinical presentation. Moreover, clinical data, laboratoristic values and clinical prediction rulers (CPRs) still show a low discriminant capacity, often with poor diagnostic performances.

**Objective:** To analyze the weight of each objective variable used by the most applied scores to predict acute PE in patients admitted for dyspnea.

**Patients and Methods:** We retrospectively enrolled 987 patients admitted for dyspnea to our Internal and Subintensive Medicine Department and submitted to a complete diagnostic process to confirm or exclude PE. Final diagnosis was put with angio-CT scan. 26 clinical and instrumental variables were analyzed, and dDimer and WBC were logarithmic transformed to make them numerically comparable with the other values. We plotted the distribution of each variable in both the PE+ and PE- populations. Pearson’s bivariate correlation was used to evaluate the relationship among variables in the two groups, PE+ and PE-.

**Results:** The distribution of all the variables was comparable in the PE+ and PE- groups, except for a significant difference in dDimer, WBC, systolic pressure, cardiac frequency, PAPs, pO2, and pCO2, as already reported by literature. The variables resulted highly uncorrelated at bivariate analysis; moreover there was not a strong separation of the two populations using the most commonly used variables and CPRs. For this reason, in our opinion, to apply directly the classical statistical methods, like principal component analysis, could not be effective to select the most predictive features. This results suggested us to use new methods coming from topological data analysis.

**Conclusions:** This study shows that the classical statistic approach has major limitations in the diagnostic process to acute PE. Topological data analysis can be used to enlighten new and hidden correlations among variables and build new and more effective CPRs without increasing the data space.
Contraindications to oral anticoagulant therapy in patients with atrial fibrillation: a descriptive analysis of Italian patients data from the European PREFER in AF Registry

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Background: Relative and absolute contraindications to oral anticoagulant treatment for the prevention of thromboembolic events in patients with Atrial Fibrillation (AF) are well known. However, few data is available regarding the real incidence of these contraindications among Italian patients.

Methods: The PREFER in AF Registry (PREvention oF thromboembolic events – European Registry in Atrial Fibrillation) enrolled, from January 2012 to January 2013, unselected patients with AF in the following European countries: Austria, France, Germany, Italy (ITA), Spain, Switzerland and the United Kingdom. The following data, collected at the study baseline visit, refers to a descriptive analysis of incidence of contraindications to oral anticoagulant therapy in Italian patients, and was collected regardless of any treatment actually prescribed.

Results: PREFER in AF Registry enrolled 7243 patients in Europe, including 1888 (26%) in Italy, where 98 sites were involved. A proportion of 71.6% among Italian patients were treated, during the last 12 months prior enrollment, with vitamin K antagonists (62% with warfarin and 9.6% with acenocoumarol). Among Italian patients, a proportion of 2.2% reported an active phase cancer and the same proportion reported bleedings in the last year prior enrollment. Major gastrointestinal bleedings were reported among 2.0% of patients, cerebrovascular bleedings among 0.5% of patients (proportion of other major bleedings:1.5%).

A poor adherence to treatment in the last 12 months was observed among 6.2% of patients, with respect to a European patients proportion of 2.6%. Regarding other contraindications to therapy, refusal to take anticoagulant therapy was reported in 1.3% of Italian patients (EU proportion: 0.4%). Chronic liver insufficiency was observed among 2.8% of Italian patients, whereas the proportion of patients with chronic renal insufficiency was 14.5%. GFR rates between 90 and 60 were observed among 2.3% of patients at baseline visit, whereas the proportion of patients with GFR values <60 was 9.3%.

Conclusions: Baseline data of the European Registry PREFER in AF confirmed the presence of many possible contraindications to the use of oral anticoagulant therapy in Italian patients with AF, the most frequent of which were represented by chronic renal failure, liver failure, history of previous bleeding, poor treatment adherence. The knowledge of these contraindications has a considerable importance in light of the upcoming market introduction of the new oral anticoagulants (NOAC), since it could help to identify the most appropriate therapy for each patient.

Acquired haemophilia: a case report


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Acute hemorrhagic syndrome with acquired haemophilia (AHA) is a relatively rare bleeding disorder with an incidence approximately of 0.2-1.9 per million population per year, more frequent (15/100000) age greater than 85 years, with a high mortality rate of more than 20%.

A 78 year old man was admitted to our Department the appearance of large hemotoma of the right thigh. Routine laboratory investigations showed anemia (6.4 g/dl), biochemical tests and INR were normal. Coagulation panel showed an increased partial thromboplastin time (aPTT: 3.32), then we measured coagulation factors, with detection of factor VIII equal to 1%. The next mixtest PTT confirmed the presence of anti-FVIII inhibitor high titred (15 Bethesda U/ml). The patient was treated with transfusion therapy, hemostatic with FVIIa, immunosuppression with steroids 1 mg/kg with a gradual reduction of the hematoma itself. In suspected paraneoplastic AHA the patient underwent total body CT and PET CT with subsequent finding of “large area of iperreaccumulo radioframaco in the lingular segment of the left upper lobe pulmonary relationship of contiguity with the adjacent pleura”.

AHA is a rare bleeding disorder caused by the autoantibody directed against factor VIII in patients without previous history of a bleeding disorder. These autoantibodies are IgG class immunoglobulins, most commonly the IgG4 class. The disease is commonly associated with other underlying medical conditions such as pregnancy and postpartum status, autoimmune disorders, malignancies, dermatological conditions, infections or drug interactions. Approximately 50% of the patients remain idiopathic with no known underlying pathological condition.

Rendu-Osler-Weber and pulmonary thromboembolism: internistic therapeutic doubt

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Introduction: Hereditary haemorrhagic telangiectasia (HHT) or Rendu-Osler-Weber disease is a genetic autosomal-dominant disorder characterized by the presence of vascular telangiectases in mucocutaneous tissues, visceral organs and the central nervous system. The most common symptom in HHT patients is epistaxis, which can sometimes be so profuse that it requires multiple transfusion and iron supplementation.

Case report: male, age 80, with arterial hypertension, with frequent epistaxis and telangiectasias on the face, tongue and the auricles, was admitted to the SC of Internal Medicine of the A. O. of Salerno, for dyspnea and anemia. At the entrance, laboratory data showed Hb = 6.5 g/dl, in normal platelet count and coagulation testing, echocardiography described a severe tricuspid regurgitation with PAP of 75 mmHg. The Echo Doppler of the lower limbs showed a thrombosis of the popliteal vein with partial recanalization signs bilaterally. The tac brain showed lacunar ischemic borne by the head of the caudate nucleus. The chest CT angiography showed mural thrombus at the level of the main pulmonary arteries and lobar branches bilaterally with thrombotic occlusion of multiple segmental and sub-segmental vessels, such as thromboembolic chronic disease. It was proceeded also in caustic venules of the nasal vestibule of left side. The evaluation of the intervention radiologist excluded the placement of a vena cava filter although angio CT scan of the inferior vena cava revealed no intraluminal gaps. Endoscopic procedures testified to the existence of angiodysplasia gastro-duodenal, reflux esophagitis, diverticulosis of the colon and sigmoid polyps. Therapy with compatible blood transfusions, proton pump inhibitors, bisoprolol, diuretics and low molecular weight heparin (4.000 U./bid) allowed a rapid clinical improvement with recovery of Hb values =10.5 g/dl. Therapy with compatible blood transfusions, proton pump inhibitors, bisoprolol, diuretics and low molecular weight heparin (4.000 U./bid) allowed a rapid clinical improvement with recovery of Hb values =10.5 g/dl and resolution of dyspnea. The patient was discharged with ambulatory follow-up indication.

Discussion: The therapeutic question between the placing of an vena cava filter and a treatment with low molecular weight heparin was resolved
on behalf the option medical in relation to age and interest of the patient multiplicity of the disease. Among others, the placing of an vena cava filter was not free from complications in a patient such complex and not very cooperative. In addition, the patient’s clinical condition did not place contraindications to anticoagulant therapy, who have not manifested nor failure nor complications. The benefit-risk assessment of treatment necessarily imposed an collegial consulting that took account of the patient clinical data and treatment options. On the other hand, the application of a vena cava filter would have to avoid the thromboembolic event, especially at the pulmonary level, but the said contingency clinic, in the present case, as documented TC pulmonary vessels had already occurred, even in a broad scale, resulting in a considerable increase of pulmonary hypertension, so that procedure no longer had a reasonable preventive application. It is preferred, also, the choice of a therapeutic regimen with low molecular weight heparin, set me up without a treatment with coumarins imbricated with low molecular weight, despite the the adequate protection with in -

The prothrombotic factor PAI-1 is associated to insulin resistance and markers of inflammation in primary hypertensive patients

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Population studies showed an association between the prothrombotic factor “Plasminogen Activator Inhibitor Type-1” (PAI-1) and insulin sensitivity, but this association has never been investigated in hypertension. The aim of this study was to examine the relationship between PAI-1 and variables of glucose metabolism in essential hypertension. In 277 consecutive non-diabetic hypertensive patients without clinically relevant cardiovascular complications, we measured anthropometric and biochemical variables including renal function, plasma lipid profile, fasting glucose, insulin and C-peptide, PAI-1, prothrombin fragment 1+2 (F1+2), and D-dimer as markers of a prothrombotic state, and C-reactive protein (CRP) as a marker of proinflammatory state. The Homeostatic Model Assessment (HOMA) index was calculated as an index of sensitivity to insulin. Duration of hypertension, body mass index, CRP levels and PAI-1 (Figure) increased progressively in quartiles of HOMA. On univariate regression analysis, PAI-1 was directly related with duration (r=0.168, P<0.05) and grade of hypertension (r=0.120, P<0.05), BMI (r=0.200, P<0.001), HOMA index (r=0.326, P<0.0001), CRP (r=0.362, P<0.001), triglycerides (r=0.189, P<0.01) and LDL-cholesterol (r=0.182, P<0.01), and inversely related with HDL-cholesterol (r=-0.181, P<0.01). A multivariate analysis included demographic and anthropometric variables, alcohol intake and smoking habit, grade and duration of hypertension, use of antihypertensive drugs, renal function and plasma lipid levels, HOMA index and CRP indicated that PAI-1 levels are independently related with alcohol intake (β=0.197, P<0.01), grade and duration of hypertension (respectively: β=0.164 and β=0.151, both P<0.05), LDL cholesterol (β=0.153, P<0.05), HOMA index (β=0.247, P<0.001), and CRP (β=0.281, P<0.0001). These results indicate that a prothrombotic state is associated with grade and duration of disease, insulin resistance and a proinflammatory status in hypertension.

Complications of long-term vascular accesses

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Case presentation: A 61 years old woman affected by chronic diarrhea came to our attention for fever, chills, asthenia and severe hypokalaemia (K+: 1.8 mEq/L).

Clinical history: A mediastinal large B-cell non-Hodgkins lymphoma, actually in complete remission, was diagnosed and treated (chemotherapy) approximately 15 years before the present admission. The patient has been complaining of severe diarrhea (up to 20 discharges/day) without abdominal pain for about 10 years; in the previous years she underwent laboratory, endoscop -ic and radiological examinations, in addition to a diagnostic laparotomy, but the cause of the diarrhea was not found. Because of the persistence of severe diarrhea she underwent a frequent e.v. potassium supplementation through a port-a-cath infusion device that had been positioned 8 years earlier.

Clinical course: Admission blood tests showed increased inflammatory indices. Blood cultures were positive for a methicillin-resistant Staphylococcus Epidermidis; an antibiogram guided antibiotic therapy was instituted, with clinical improvement. As a complication of antibiotic therapy the patient developed a Clostridium Difficile infection, with relapse of diarrhoea. Within a few days the patient developed a superior vena cava syndrome with neck and face edema, dyspnea, dysphagia and oxymegoglobin desaturation; a chest TC with angiographic scan showed a 4 cm thrombosis of the superior vena cava, dilatation of the azygos and hemazygos veins and ectasia of numerous venous collaterals in the mediastinum. Anticoagulant therapy was started and the port-a-cath was removed. A microbial vegetation was present on the catheter tip; for the high risk of septicemia, stenting revascularisation of the thrombotic occlusion was postponed. During the hospitalization the patient also developed diffuse lymphoedemagismalgies; an excisional biopsy showed an histological pattern of reactive lymphadenitis; however, in consideration of the patient’s history of lymphoproliferative disease a hematologic follow-up will be instituted.

Conclusions: Our patient developed a catheter-related sepsis which, in turn,
caused a thrombosis of the superior vena cava. Long term central vascular accesses are frequently used in clinical practice for drug infusion or sample taking, particularly in the oncology setting; central catheters, however, expose patients to the risk of severe complications. The reported case highlights the importance of an accurate evaluation of the risk-benefit ratio of catheter placement and the need for an accurate catheter maintenance by patients and/or their care givers in order to prevent life-threatening complications.

Characteristics of patients with atrial fibrillation: a descriptive analysis of differences and similarities between Italy and Europe in the PREFER in AF Registry


Background: The profile of Atrial Fibrillation (AF) patients in Europe (EU) and other European countries is well known but few information is available about common and different characteristics between Italian and European patients, especially regarding the pattern of patients’ treatment and management.

Methods: The PREFER in AF Registry (PREvention oF thromboembolic events – European Registry in Atrial Fibrillation) enrolled, from January 2012 to January 2013, unselected patients with AF in the following European countries: Austria, France, Germany, Italy (ITA), Spain, Switzerland and the United Kingdom. The following data reports a comparison of Italian and European patients characteristics at the time of study baseline visit.

Results: PREFER in AF Registry enrolled 7243 patients in Europe, including 1888 (26%) in Italy, where 98 sites were involved. Mean age of Italian patients was 70.9 (±1.08) years, slightly lower than in Europe (71.5±10.70 years). The incidence of permanent AF in Italy was 35.5%, persistent 31.7% (7.7% higher than EU), paroxysmal 26.9%. A proportion of 73.5% of Italian patients had hypertension, similar to European data, while the proportion of obese patients (BMI>30kg/m²) was lower than EU (21.9% vs. 27.5%, respectively).

A previous ischemic stroke was observed in 6.5% of Italian patients (EU: 8.4%). The mean CHADS2/thromboembolism risk score was 1.9±1.22 (EU 1.8±1.29), while the mean score for CHA2DS2-VASc was 3.3±1.73 (EU 3.4±1.76). Clinical events/hospitalizations in the last 12 months prior enrollment were observed in 31% of Italian patients, with respect to a proportion of 23.4% observed in EU. The most frequent events were symptomatic AF (ITA: 17.4%; EU: 12.3%), heart failure (ITA 6.5%; EU 5.8%) and acute coronary syndrome (ITA 4.1%; EU 2.7%). Italy was the European country with the lowest proportion of patients treated with Vitamin K antagonists (71.6%; EU: 78.3%).

Conclusions: Although the profile of Italian patients with AF was homogeneous in many aspects to the one of EU Countries, differences appeared regarding a higher incidence of clinical events/hospitalizations in Italy and a lower use of vitamin K antagonists treatment compared to EU patients.

Venous thromboprophylaxis in patients with acute ischemic stroke: adherence to the american college of chest physicians guidelines and prognostic role of the Padua Prediction Score


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Background: Hospitalized patients with acute ischemic stroke are at increased risk of venous thromboembolism (VTE), mostly due to prolonged reduced mobility and pulmonary embolism (PE) is one of the leading causes of death after cerebral infarction. Thromboprophylaxis has been shown to be highly effective in medical patients and is currently recommended by international guidelines, but its overall benefit in patients with acute ischemic stroke remains controversial because of the fear for bleeding, mainly hemorrhagic transformation of the ischemic lesion. Aim of the present study is to investigate current prescription of pharmacological thromboprophylaxis in patients with ischemic stroke and to explore the prognostic accuracy of the Padua Prediction Score (PPS).

Methods: We retrospectively collected data on consecutive adult patients admitted to a medical department for acute ischemic stroke from January 2010 till December 2011 at the Ospedale di Circolo, Varese, Italy. The primary outcome of this study was to assess the agreement between prescription of pharmacological thromboprophylaxis and the 8th and 9th edition of the American College of Chest Physicians (ACCP) guidelines on antithrombotic therapies. Secondary outcome was to assess the prognostic accuracy of Padua Prediction Score (PPS) in identifying patients at high risk of adverse events (death, VTE and bleeding) during hospital stay.

Results: A total of 267 patients were included. Mean age was 75.6±12.4 years. Median hospital stay was 12 days (range, 1-60). According to the 8th ACCP guidelines, 189 (70.8%) patients were at high VTE risk due to reduced mobility. Thromboprophylaxis was prescribed in 173 (64.8%) patients. Among them, 146 (84.4%) were considered at high VTE risk. The strength of agreement between the 8th ACCP guidelines and pharmacological thromboprophylaxis prescription was moderate (Cohen’s kappa: 0.402, 95% confidence interval [CI] 0.28 – 0.52).

According to the 9th edition of ACCP guidelines, 200 (74.9%) patients were at high-risk of VTE (PPS ≥ 4). Mean PPS was 5±2.05. Reduced mobility and age were the main VTE risk factors (70.8% and 75.3%, respectively). Among patients receiving thromboprophylaxis, 149 (74.5%) had a PPS ≥ 4 and 23 (34.3%) had PPS<4. The strength of agreement between PPS stratification and thromboprophylaxis prescription was fair (Cohen’s kappa: 0.359, 95% CI 0.24 – 0.48).

Thirty-one (11.6%) patients died during hospital stay, 3 (1.1%) had symptomatic VTE and 34 (12.7%) had a bleeding episode. At the multivariate logistic regression (adjusted for gender and thromboprophylaxis prescription), a PPS ≥ 4 was associated with an increased risk of the combined endpoint of death, VTE and bleeding events (OR 4.23, 95% CI 1.56 - 11.43).

Conclusions: Pharmacological thromboprophylaxis is still underused in patients admitted with ischemic stroke. As our cohort of patients was admitted before the publication of the 9th edition of the ACCP guidelines, implementation of PPS in clinical practice may improve thromboprophylaxis prescription. In addition, the association among PPS ≥ 4 and adverse events during hospital stay suggests the potential use of PPS as general prognostic tool in ischemic stroke patients.

Use of argatroban during hemodialysis in a case of recent hit requiring oral anticoagulation

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A 46-year-old male patient with autosomal dominant polycystic kidney disease (ADPKD) underwent unilateral nephrectomy for chronic pain. Due to low urine output and worsening renal function, peritoneal dialysis was...
started and subcutaneous prophylactic dalteparin was administered (2500 U). On day 5 from heparin prophylaxis, thrombocytopenia developed (from 397 to 54 x 10^9/L). Catheter-related internal jugular vein thrombosis was detected by duplex ultrasound (US). A high pretest clinical scoring system (4Ts) for HIT was calculated.

Heparin-related IgG (H/PF4 Abs) were detected at high titre (3901 OD, n.v.<450 OD) using a commercial PF4/polyanion ELISA (Genetic Testing Inc., GTI, Waukesha, Wisc., USA). The results was confirmed by visual examination of heparin-induced platelet activation assays (HIPA). The patient was started on argatroban and switched to warfarin at complete platelet count recovery (>150 x 10^9/L).

One month later the patient was readmitted with acute abdominal pain and gross hematuria. Left nephrectomy due to cyst rupture was performed. Due to persistence of anti-heparin abs at a lower titre (523 OD) and to US scan finding showing residual thrombosis of the right upper limb and recent DVT of the left upper limb, the patient was started on argatroban maintaining aPTT at 1.5 to 3 times baseline. On day 15 from nephrectomy the patient was switched to warfarin.

Hemodialysis was then started on a three times a week schedule, using synthetic polysulfone membranes. Blood flow rate ranged from 150 to 250 ml/min with a bicarbonate dialysate at a flow rate of 2000 mL/h. Argatroban was administered as a 125 mg/kg bolus followed by 1.5 mg/kg/min.

Three months later the allograft became available and the patient was successfully transplanted with full renal function recovery. As in the pre-operative evaluation anti-heparin antibodies were not found, prophylaxis was carried out with fondaparinux.

Several regimens of argatroban have been studied and found to be equally effective and safe in patients with end-stage renal disease during hemodialysis. No data are available on the use of argatroban in the hemodialytic circuit in patients on OCT.

Our case report is of interest as it describes an unaddressed clinical situation related to the use of argatroban during hemodialysis in a patient receiving warfarin for a recent episode of HIT. The thrombosis is the first issue that may arise from this case deals with the real need to administer anticoagulant in the dialytic circuit in a patient taking OCT. In fact, warfarin use as a sole anticoagulant during hemodialysis could have been considered. Therapeutic or low dose warfarin in renal replacement therapy has been reported to be associated to high rate of hemodialysis catheter failure and this was our major concern in view of the thrombotic episodes experienced by our patient in the recent past. Whether alternative methods of anticoagulation are preferable (including saline flushing, citrate) have not been systematically investigated.

The dose of argatroban to be administered concurrently to warfarin was empirically chosen based on guidelines suggested for HIT [7]. In this setting, INR ≥4 is recommended based on the high risk of thrombosis at a lower INR in patients with HIT. As our goal was to avoid fibrin strands or sludging in the dialyzer circuit while minimizing the bleeding risk, argatroban was administered with the purpose to keep a therapeutic INR below 4 and an aPTT at about 1.5 the basal value. In our patient this protocol was successful either in avoiding bleeding as well as in reaching a successful anticoagulation.

Finally, just a short comment on the choice to administer fondaparinux in the peri-transplant period. According to published guidelines, a short-time heparin course may have been considered in our patient as platelet factor 4/heparin antibodies were absent at the time of transplantation. This reasoning comes from experiences in the different clinical scenario of the cardiopulmonary bypass. In this setting exposure to heparin is restricted to the operative period and it did not elicit HIT antibodies. However, exposure to heparin in our case would have been on a regular basis with the purpose of hemodialysis, therefore jeopardizing the patient’s remission of HIT. The use of argatroban as anticoagulant in hemodialysis can be successfully considered in patients on oral anticoagulants with a recent history of HIT.
**Introduction:** The use of thromboprophylaxis with low weight molecular heparin (LWMH) in hospitalized medical patients was found to be unsatisfactory in many studies performed in various countries, therefore is very important to identify areas and methods for optimizing this practice. Our study aimed at evaluating the current practice as well as at comparing the prescription of pharmacological prophylaxis in Rome and Lazio internal medicine (IM) units and emergency medicine (EM) units.

**Methods:** This cross sectional, observational study involved 23 IM and 10 EM of 21 hospitals. In each hospital the patients data were collected in one predefined day in a form with all the information about risk factors for venous thromboembolism (VTE) and the prescription of pharmacological prophylaxis.

**Results:** We analyzed data pertaining to 742 patients, 222 (30%) in charge to EM and 520 (70%) to IM; patients with at least one risk factor were 74% in IM and 62% in EM. In our study the VTE risk resulted very different between the scores: 12% according to Kucher score, 16% according to the American College Chest Physicians guidelines 2008 (ACCP’08) 1A recommendations and 55% according to Chopard score.

In patients at risk for VTE, LWMH was administered only in 46,6% - 66,7% according the three scores; the prophylaxis was always less frequent in EM than IM. This difference was evident also when the analysis was conducted by taking into consideration the most prevalent risk factors, i.e. immobilization, heart or respiratory failure and active cancer.

**Conclusions:** We did found no close link between scores positivity and LWMH prescription: thromboprophylaxis is often omitted, according the three scores, in IM (33.3 to 45.5 %) and even more in EM (37.5 to 53.4%). On the other hand even patients with no risk factors or with just one factor were treated with LWMH. The less frequent prophylaxis in EM compared to IM is possibly due to a greater attention towards the acute illness in EM and to the more frequent immobilization in IM.

**Endocrinology**

**An unexpected diagnosis**

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We describe a case of a 60-yr-old woman with two synchronous neoplasias, one discovered accidentally. Her history was remarkable for breast cancer in a sister, one discovered exposition to known cancer risk factor. At breast cancer screening a suspicious nodule was detected in right breast and excisional biopsy histological examination described infiltrating lobular carcinoma mixed with ductal carcinoma, G2 stadium (Elston-Ellis (pT1N0Mx)) ER+. Bone scintigraphy was negative while abdominal US with Sonoveue revealed two hepatic hypercohoic nodules at VI e VII segment, the biggest one of 7 cm in diameter with high early vascularization and early wash-out. Nodules were confirmed by abdominal CT and, suspecting breast metastasis, patient underwent 18F-FDG PET-CT which showed an area of pathological disomogeneous caption in corrispon-dence of VI hepatic segment. Hepatobiliary scintigraphy was performed with no capation in that area. Serum AFP, CA15.3, CA 19.9, CEA, CA125 were normal. Since nature of hepatic lesions remained undetermined, percutaneous biopsy was obtained. Hystological examination revealed cellular elements compatible with neuroendocrine morphology and immuno-histochemical profile (positivity to Chromogranin A). In order to identify the primitive tumor Octreoscan® was performed showing high capation only in hepatic lesions. EGDS and colonscopy were negative, while capsule endoscopy described a 2 cm raised area covered by regular mucosa probably with ulceration at the apex at the distal jejunal-ileum, confirmed at enteroRMN.

Patient denied diarrhea or abdominal discomfort, but mild flushing after eating since long time before was referred, suggesting a carcinoid syndrome. Laboratory tests revealed high levels of chromogranin A and 5-hydroxindolacetic acid. An echocardiogram showed with thickened tricuspidal valves with middle-severe regurgitation of tricuspidalic valve, as described in carcinoid syndrome. Somatostatin analogue therapy was started. The patient underwent small intestine resection with lateral entero-enteroanastomosis, right hepatectomy and interaortocaval linfadenectomy. Hystological examination described well-differentiated neuroendocrine carcinoma of small bowel infiltrating perivesical fibrroadipose tissue with hepatic and linfonodal metastasis (pT3N1M1). Chromogranin A and 5-hydroxindolacetic acid two months later. As commonly reported in literature neuroendocrine tumors are diagnosed accidentally. In neuroendocrine tumor patient history and symptoms could have an important role for their suspicion.

**Thyroid alterations in a cohort of peripuberlal patients**


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**Introduction:** Subclinical thyroid disease is quite a common disorder in pediatric patients, and both primary care physicians and pediatric endocrinologists frequently face the decision of what to do regarding these children. In the pediatric population, the reported prevalence is lower than 2%, even if epidemiological studies concerning thyreopathies in childhood and adolescence are limited. It is of paramount importance to know how this condition will evolve and when it should be treated. Large studies regarding the natural history of subclinical thyroid disease and its consequences in childhood are still lacking.

**Aim:** To evaluate the prevalence in peripuberlal pediatric population (13–14 years old) of subclinical thyroid disease.

**Patients and methods:** We prospectively collected patients attending junior high school in the Osimo and Offagna districts. Young patients were evaluated first by an Internist with endocrinologic competences and then by a radiologist. Each patient was asked for antropometric parameters (age, weight, height, age of menarche) and anamnestic risk factors (familiarity for thyroid disease, use of iodized salt, use of multivitaminic complex, assumption of milk, smoke, geographic provenience of parents). Each patient was evaluated with physical examination and ultrasound exam of the thyroid region. At the end of the visit we wrote a report with indication for any diagnostic insight (TSH, ultrasound follow-up).

**Results:** We evaluated 424 young patients (240 male, 184 female) aged between 13 and 14 years. We found ultrasound abnormalities in 49 patients, representing 12% of the sample. In fact, 19 ultrasound exams were suspect for thyroiditis, 17 showed colloid cysts, 8 struma while 5 patients resulted positive for solid nodular lesions. We found a positive history for thyroid pathologies in 24,5% of the sample.
Conclusions: Our data suggest that thyroid alterations are more frequent than predicted in prepuberal age. These results suggest the utility of developing screening policies in this subset of patients in order to enlighten the presence of subclinical alterations of the structure and the functions of the thyroid gland to correct earlier risk factors and prevent the development of an overt endocrinologic disease.

References:

Atypical features of adrenal mass

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A 71-year-old woman was admitted to Department of Surgery for an incidentally discovered large adrenal mass through routine abdominal ultrasound. The lesion was localized between the right hepatic lobe and the right kidney, with dishomogeneous features, 55 x 31 mm size, attributable to the right adrenal gland. Subsequently an MRI was performed confirming the presence of a retrocaval, right adrenal mass, with cystic feature, dimensions of 60x 50x 35 mm, characterized by regular walls, thin septa, with increased contrast enhancement (Fig. 1 a, b).

Her medical history reported impaired fasting glucose and paroxysmal arterial hypertension associated with palpitations, diaphoresis and flushing since the age of 30. Blood tests showed normal values of renin-angiotensin-aldosterone system; urinary cortisol within the limits; while the values of urinary VMA and metanephrines were increased (VMA 15 mg/24h; nv < 13,6) (Metanephrines 1600 µg/24h; nv 20-325). In order to confirm the presence of pheochromocytoma, the patient underwent MIBG...
scintigraphy, but it didn’t reveal any areas of pathological accumulation of radiouclide in the abdomen (Fig. 2). Nevertheless, the patient underwent to surgery because of the large size of the adrenal mass. Right laparotomyic adrenalectomy was performed, after proper preparation with plasma volume expansion and α-blockade therapy (doxazosin). Histological examination showed a pseudocystic proliferation, without necrotic areas or vascular invasion, confirming diagnosis of pheochromocytoma. Follow-up reevaluation 3 months after adrenalectomy showed blood pressure 120/70 mmHg in withdraw antihypertensive therapy, normal values of urinary metanephynes and VMA; the patient reported regression of the previous symptoms.

**Diagnosis on a case of Conn disease**

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Patient 57 years old with severe hypertension, hypertensive encephalopathy, cardiomyopathy hypertensive, dyslipidemia, anxious depressive syndrome, came to our attention for headache, sweating and malaise. In ED blood pressure was 240/155 mmHg, blood sample (K + 3 mmol/L, Na +: 141 mmol/L).

Blood tests was performed and documented: WBC11,930, neutrophils 72.5%, lymphocytes 17.8%, monocytes 4.1%, glucose 112 mg/dl, serum proteins: albumin 40.16, alpha1 2.62, alpha2 5.18, beta1 3.93, 4.90 beta2, gamma 12.21, ACTH 21, Chlorine 109, Calcium 8.7, Total protein 6.1, potassium 3.3, mmol/L cloruria 356.

ECG (signs of left ventricular hypertrophy).

Brain CT scan (no lesions).

CT abdomen with contrast medium: “presence of micronodular lesion on left adrenal gland (7 mm)”.

Then the patient was subjected to phlebography of the renal vein, inferior vena cava, venous sampling (performing selective i.v.catherization and venous sampling of renal and adrenal veins bilaterally and vena cava infraand supra-renal) for aldosterone. The results were the following:

Vena cava below renal function: 82 pg/ml range (N V 8-172)
- Renal vena cava over 109 pg/ml
- Right adrenal vein: 112 pg/ml
- Right renal vein: 115 pg/ml
- Suprarenal vein Left: 318 pg/ml
- Left Renal Vein: 94 pg/ml

Patient was discharged with medical therapy and waiting for adrenalectomy.

**Discussion:** Condition of primary iperaldosteronism should be suspected in all patients with hypertension. Until some time ago Conn’s syndrome was placed only for those patients with low blood levels of potassium and hypertension, not controlled with medical therapy. Recently, however, it has been shown that approximately 40% of patients with Conn’s syndrome have normal blood levels of potassium. The diagnosis requires dosage of aldosterone and renin activity, In Conn’s syndrome are present increased levels of aldosterone and reduced or absent activity of renin. The prognosis is good. After surgery normalization of hypertension in a good percentage of cases. In patients with bilateral hyperplasia treated with spironolactone is usually required the association of calcium antagonists for the control of hypertension.

**Primary aldosteronism with concurrent primary hyperparathyroidism in patient who exhibited arrhythmic disorders**

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A 25-year-old Caucasian woman was admitted to our Emergency Department (ED), with palpitations, abdominal pain and worsening dyspnea. Her medical history reported a recent admission to other hospital for acute flaccid paralysis, severe hypokalemia (K 1.2 mEq/L; standard range 3.4-5.5 mEq/L) complicated with cardiopulmonary arrest due to ventricular fibrillation, successfully treated with resuscitation. Abdominal examination revealed a generalized defensive contraction without any palpable mass. Abdominal revaluation 2 months after adrenalectomy showed blood pressure ≤ 130/80 mmHg, heart rate 76 beats/min and QT interval normal (0.42 sec). Potassium concentration was 4.5 mEq/L, sodium level 138 mEq/L, with normalization of PRA, PAC, PAC/PRA ratio and urinary al-

![Figure 1a](image1a.png)

![Figure 1b](image1b.png)
Negative markers of myocardial necrosis. You start therapy with aspirin ev 1 grx3/die, Amoxicillin – Clavulanic Ac. 2.2 grx3/die. During the stay we are witnessing the emergence of hyperpyrexia (TC max 38 °C), controls blood tests documenting increased inflammatory markers (ESR 94 mm/h, CRP 18.4 mg/dl), increased white blood cell (WBC 18.02 x10 ^3/ul) with neutrophilia (14.72 x10 ^3/ul), decreased hemoglobin (9 g/dl), low cortisol (3.2 mcg/dl), increased ACTH (808.3 pg/ml), hypoglycemia (59 mg/dl) and increased GGT (256 U/L). During an episode of fever, the patient presents with severe hypotension (SBP 50 mmHg) and loss of consciousness, with recovery after therapy with intravenous hydrocortisone. You make urgent echocardiogram was negative for signs of hemodynamic commitment, and chest X-ray, with detection of bilateral pleural effusions, not present in the previous Rx. You change the antibiotic therapy with Piperacillin/Tazobactam 4.5 mgx3/die and Teicoplanin 200 mg 1/day, Colchicine 0.5 mg/day, and increased therapy with cortisone acetate, with benefit. It assists in the disappearance of fever, normalization of inflammatory markers (CRP 0.48 mg/dl, ESR 10 mm/h) and leukocytes (WBC 7,44 x10 ^3/ul), increase in hemoglobin (10.1 g/dl), reduction of GGT (186 U/L), reduction of ACTH (443 pg/ml) and increased cortisol (23 mcg/dl). Negative investigations for research and viral etiology of rheumatology pericardite, and blood cultures performed in the course of fever. The control echocardiographic documentation of the pay - ment reduction, partially organized (maximum thickness of 13 mm and 9 mm before Vdx posterolateral to Vsx). On X-ray chest, the payment bilateral persists. The patient was discharged asymptomatic, afebrile with therapy with Ibuprofen and diuretic. To the clinical, after echocardiography, with detection of mild circumferential payment being organized, and chest X-ray, documenting resolution of pleural effusion, the patient is in good condition, afebrile and asymptomatic.

About a month later, he presented to our observation a man of 50 years, with a history of recurrent pericarditis treated with steroid and anxiety syndrome, for 10 days from oppressive chest pain, increased with the acts of the breath and with the stripes of the cough; refers bowel diarrhea in the previous days and hyperpyrexia (TC max 37.8 °C). This is patient discharged 20 days before by another OU, with a diagnosis of “diarrheal syndrome in a patient recently treated with cortisone for recurrent pericarditis.” At the entrance, the patient has good vestments, PA 125/75 mmHg, 70 bpm FC, afebrile, the ECG shows sinus rhythm with low voltage in the limb leads, and echocardiography documents “… circumferential pericardial effusion, to Vdx of approximately 2 cm and at the level of the posterolateral wall of the Vsx “. Objectivity cardiovascular, parafonici and rhythmic heart sounds, good hemodynamic compensation, no signs of tamponade. In the laboratory tests: leukocytosis (WBC 12.63 x10 ^3/ul), mild anemia (Hb 12.8 mg/dl), increased inflammatory markers (ESR 25 mm/h, CRP 10.2 mg/dl), high cortisol (163.1 mcg/dl), reduced ACTH (3.7 pg/ml), increased GGT (211 U/L). Negative markers of myocardial necrosis. You start therapy with aspirin ev 1 grx3/die, Amoxicillin – Clavulanic Ac. 2.2 grx3/die.

Pericarditis and adrenal insufficiency: a not uncommon association

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A man of 52 years, with a history of M. Addison’s type I autoimmune treatment, come to the shelter for precordialgia and heartburn, and accentuated by the acts of the breath. This is discharged patient 7 days before the OU Emergency Medicine with a diagnosis of “Acute pericarditis”. At the entrance, the patient has good vestments, PA 125/75 mmHg, 70 bpm FC, afebrile, the ECG shows sinus rhythm with low voltage in the limb leads, and echocardiography documents “… circumferential pericardial effusion, to Vdx of approximately 2 cm and at the level of the posterolateral wall of the Vsx “. Objectivity cardiovascular, parafonici and rhythmic heart sounds, good hemodynamic compensation, no signs of tamponade. In the laboratory tests: leukocytosis (WBC 12.63 x10 ^3/ul), mild anemia (Hb 12.8 mg/dl), increased inflammatory markers (ESR 25 mm/h, CRP 10.2 mg/dl), high cortisol (163.1 mcg/dl), reduced ACTH (3.7 pg/ml), increased GGT (211 U/L). Negative markers of myocardial necrosis. You start therapy with aspirin ev 1 grx3/die, Amoxicillin – Clavulanic Ac. 2.2 grx3/die. During the stay we are witnessing the emergence of hyperpyrexia (TC max 38 °C).
mmHg), with laboratory finding of reduced values of ACTH (4.8 pg/ml, the next control 1.6 pg/ml), reduced cortisol levels (<0.20 mcg/dl) and low values of cortisoluria of 24h (45 mcgr/24h), reduced cortisol after stimulation with ACTH (h8 <0.20 mcg/dl, h8.30am 1.2 mcg/dl h9 2.0 mcg/dl). In suspected central origin of cortisol deficiency, making dosage of pituitary hormones, normal, and MRI brain, which do not show alterations of the pituitary. The laboratory data and the clinical diagnosis of adrenal insufficiency pose. The patient is discharged in fair condition, with replacement therapy for adrenal insufficiency with Cortisone Acetate; does not in this case introduced colchicine therapy despite the anamnesi the patient positive for recurrent pericarditis given the presence of the symptom diar-rhea at the time of diagnosis. 

Discussion: Common underlying pathophysiological mechanisms peri-carditis and adrenal insufficiency are not known, it is known, however, the increased susceptibility to infection in patients with adrenal insufficiency as well as the possibility of autoimmune etiology underlying both the Addison’s disease that pericarditis. Despite the low prevalence in the pop-ulation dell’iposurrenalismo, and even more rare possibility that these subjects should be met with pericarditis, acute or subacute, having ob-served in a short period of time so these two cases invites us to think of a possible association between these two diseases.

The DPP-4 inhibitors in the treatment of type 2 diabetes already treated with only metformin and not in metabolic target. experience of integrated management within hospital/territory

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Over the last years, the therapy of the type 2 diabetes mellitus has used the introduction of a new class of oral drugs, like the inhibitors of the enzyme DPP-4. The oral inhibitors of DPP-4 selectively inhibit the enzyme responsible for the degradation of the incretin GLP-1 and GIP, resulting in increased levels of endogenous and biologically active GLP-1 thus of the insulin. Considering these new therapeutic opportunities in type 2 dia-betes, the present research aims the following goals:
1. To know the characteristics of the patient with diabetes mellitus (age, sex, BMI, lipid profile, Hba1c).
2. To assess the metabolic control after the introduction in therapy of the DPP-4 inhibitors.
3. To evaluate possible side effects of the therapy.

Materials and methods: The research investigates the benefits of the use of DPP-4 inhibitors in patients with type 2 diabetes mellitus already treat-ed with metformin not in metabolic target in a sample of approximately 3000 patients in the city of Messina. Looking for an integrated manage-ment between the hospital and the primary care, the patients are sent by the clinic of Internal Medicine of the Hospital Papardo of Messina for the in-troduction in therapy of the DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin). The patients were then monitored by primary care physi-cians and periodically in the clinic of Internal Medicine with evaluation in clinic and in laboratory every 4 months. During the observation period, several characteristics of patients in treatment are evaluated: BMI, lipid profile, Hba1c, side effects.

Conclusions: The study shows that the treated subjects have a decrease in HBA1c of approximately 1% and a decrease in LDL levels by about 20%. The BMI does not change significantly, it mainly decreases in patients who have associated medical therapy, adequate diet and physical activity. No patients have to stop or change the drug due to any specific side effects.

These results allow us to claim that therapy with DDP-4 inhibitors is an important therapeutic opportunity in the treatment of type 2 diabetics already treated with metformin alone and not in metabolic target.

Nondiabetic woman with recurrent episodes of hypoglicemia as a result of Addison’s disease


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A 64-year-old woman with new onset headache, confusion, mental status changes was hospitalized. No history of diabetes and use of oral hypo-glycemic agents reported. At clinical examination the patient was obese (BMI=35.2 kg/m2), hypotensive (BP=90/60 mmHg), and with hyperpig-mented gingiva. Hypoglycaemia (serum glucose level=35 mg/dL) was doc-umented and treated. Laboratory testing revealed her insulin was elevated (serum insulin level=26.5 mU/L; normal <3 mU/L). Instead, her C-peptide (serum C-peptide level=2.8 ng/ml), the thyroid-stimulating horm-one (TSH=0.91 µU/mL), the free triiodothyronine (FT3=2.92 ng/dL) and the free thyroxine (FT4=1.12 ng/dL) levels were in normal range. She later presented with other episodes of long-lasting hypoglycaemia. An electroen-cephalogram and an TC scan showed no neurological cause of the symptoms as well as the oesceoscan not revealed the presence of insulinoma. Measurement of the adrenocorticotropic hormone (ACTH) (1180 pg/mL) and the basal serum cortisol (1.45 µg/dL) levels led to a diagnosis of primary adrenal insufficiency (Addison’s disease) confirmed by ACTH stimulation test (serum cortisol after ACTH administration= 1.58 µg/dL). The symptoms ended after she received corticosteroid therapy. Hypoglycaemia therefore confirms as a manifestation of primary adrenal insufficiency. The prevalence of this disease has underestimated also for the lack of reliable screening tests commonly used in clinical practice. Screening tests (for example, cortisol salivary test) should be more widespread.

Parathyroidectomy eliminates arrhythmic risk in primary hyperparathyroidism, as evaluated by exercise test


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Objective: To investigate if parathyroidectomy reverses risk factors for ar-rhythmias, related to the QT dynamic changes evaluated during bicycle ergometry exercise test (ET) in patients with primary hyperparathyroidism (PHPT).

Methods: Twenty four postmenopausal women affected by PHPT (mean age 60.0±8.4 years) and thirty, sex and age-matched, controls underwent ET, echocardiographic and biochemical evaluation. The following stages were considered during ET: rest, peak exercise, recovery. The patients were random-ized to two groups: 12 underwent parathyroidectomy (Group A) and 12 were followed-up conservatively (Group B). After 6 months the patients underwent the same evaluation as when enrolled.

Results: There was no significant difference between PHPT patients and controls, apart from the expected mean higher levels of total calcium and PTH in PHPT patients (2.70±0.15 vs 2.30±0.14 mmol/L, p<0.01, 83.6±22.6 vs 34.2±10.3 ng/L, p<0.01, respectively). Group A and B,
The aim of our study is to investigate in patients with diabetes type 2 the presence of psycho-affective disorders, alexithymia, and to assess stress levels by calculating the quotient of Stress (QoS).

Materials and methods: The study was conducted on 24 subjects, including 16 females and 8 males, aged between 40 and 70 years, suffering from diabetes mellitus type 2; 4 of these were withdrawn from the study because of objective difficulties for the compilation of tests. The control group, homogeneous by sex and age, is made up of 15 subjects free from diabetes and/or diseases that interfere on the outcome of the parameters studied. Psychometric evaluation was performed with the following tests: the Middlesex Hospital Questionarie (MHQ), the Zung Anxiety and Depression Test, Toronto Alexithymia Scale (TAS-20), the Questionnaire for the Assessment Psychophysics (Stress Quotient).

Results: The MHQ test showed (in brackets the results of the control group) in patients with DM the presence of Anxiety Disorder in 45% (9%), Phobic Tract in 14% (11%), Obsessive Tract in 31% (0%), Somatization in 30% (18%), Depressive Disorder in 20% (9%) and Conversion Disorder in 6% (0%).

The Zung test confirms the presence in the group of patients with DM Anxiety Disorder in 62% (11%) and Depressive Disorder in 25% (9%). The TAS-20 test shows the presence of Alexithymia Tract in 23% of diabetic subjects. It should be emphasized, in this regard, the presence of border-line Tract in 37% and placement of 12% of them in the area of “risk alexithymia.”

The test of Psychophysical evaluation (QoS) in diabetic subjects showed the presence of a high QoS in 56% (28.9) and a QoS to “high limits” in 37%.

Conclusions: Parathyroidectomy reduces the occurrence of VPBs and restored the QTc adaptation during ET in patients affected by PHPT.

Psychological profile, quotient stress and diabetes mellitus: experience in 20 patients


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Background: Many studies have long been important to indicate a relationship between mental and emotional disorders, in particular the Depressive and Anxiety Disorder and Diabetes Mellitus (DM), known as metabolic disease characterized by an altered activity of insulin because of reduced availability of the hormone (DM type 1), or difficulty to perform its task (DM type 2) or the combination of the two factors. In addition, more recently, have been reported particularly suggestive data on the relationship between “stressful life events, stress reaction and hyperglycemic response” that seem to suggest, on the pathophysiological level, interpretations of considerable interest.

Aim of the study: The aim of our study is to investigate in patients with diabetes type 2 the presence of psycho-affective disorders, alexithymia, and to assess stress levels by calculating the quotient of Stress (QoS). Materials and methods: The study was conducted on 24 subjects, including 16 females and 8 males, aged between 40 and 70 years, suffering from diabetes mellitus type 2; 4 of these were withdrawn from the study because of objective difficulties for the compilation of tests. The control group, homogeneous by sex and age, is made up of 15 subjects free from diabetes and/or diseases that interfere on the outcome of the parameters studied. Psychometric evaluation was performed with the following tests: the Middlesex Hospital Questionarie (MHQ), the Zung Anxiety and Depression Test, Toronto Alexithymia Scale (TAS-20), the Questionnaire for the Assessment Psychophysics (Stress Quotient).

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The test of Psychophysical evaluation (QoS) in diabetic subjects showed the presence of a high QoS in 56% (28.9) and a QoS to “high limits” in 37%.

Conclusions: Parathyroidectomy reduces the occurrence of VPBs and restored the QTc adaptation during ET in patients affected by PHPT.
Echocardiographic pattern and diastolic dysfunction evaluation in patients with acromegaly or Cushing’s syndrome

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Introduction: Patients with acromegaly or Cushing’s syndrome have an increased risk of morbidity and mortality due to cardiovascular diseases owing to metabolic and structural modifications induced by hormone hyperperfusion. Both diseases result in diastolic and systolic dysfunction via different pathophysiological cascades.

Aim: The aim of this preliminary study was to characterize the echocardiographic pattern and the presence of diastolic dysfunction in Cushing’s syndrome and acromegalic patients and to evaluate the relationship between echocardiographic indexes and biochemical markers of diseases in these subgroups of patients.

Study design: We considered 15 acromegalic patients, 11 Cushing patients and 7 control patients sex- and age-matched (Median age: 51 years) with normal systolic function. Some hormonal parameters of interest (GH, IGF-1, late night salivary cortisol concentration, free urinary cortisol) have been assayed when the diagnosis was formulated and they were reassessed when echocardiography was performed. Concomitant cardiovascular risk factors, ongoing medical therapy and past surgical treatment were reviewed at this time. In 6 patients the endocrinopathy was well controlled by the means of pharmacological therapy; in 20 patients it was not.

Diastolic dysfunction was assessed by mitral-flow and tissue doppler and pulmonary venous flow indexes (i.e. E/A, E/E', E/Vp and S/D) and scored into four stages of severity (Absent, stage I, II, III).

Results: No difference in gender prevalence, BMI and body surface distribution was shown in the three groups of patients although they were different when the prevalence of dyslipidemia (Dyslipidemia yes/no: Acromegaly vs Cushing, 2/14 vs 8/3, p = 0.003), the need for statin regimen (Statin yes/no: Acromegaly vs Cushing, 1/14 vs 4/6, p = 0.041) and the quantity of anti-hypertensive drugs needed for blood pressure control (Acromegaly vs Cushing, p = 0.048) was taken into consideration.

The distribution of E/E’ was statistically different among Cushing, acromegalic and control patients (Median values; acromegaly: -6.00, Cushing: -7.38, control patients: -3.98; p = 0.009) as it was for the distribution of left atrium diameter (Median values; acromegaly: 44 mm, Cushing: 43 mm, control patients: 39 mm; p = 0.031), posterior wall thickness (PWT) (Median values; acromegaly: 12 mm, Cushing: 11 mm, control patients: 10 mm; p = 0.001), interventricular septum thickness (IVST) (Median values; acromegaly: 12 mm, Cushing: 11 mm, control patients: 9 mm; p = 0.001). Moreover, the distribution of E/E’ was statistically different among patients with active and controlled disease (Median values; active disease: -6.88, controlled disease: -5.31; p = 0.023).

E/Vp and S/D have proven to be related to late night cortisol concentration in saliva (E/Vp: r = 0.696, p = 0.037; S/D: r = 0.824, p = 0.044).

Conclusions: Although low-powered, this study confirms the relationship between diastolic dysfunction, Cushing’s syndrome, acromegaly and the pharmacological control of these diseases even in a small-sized population. The result about wall and septum thickness is of interest as they are the morphological landmarks of hypertension, fibrosis and diastolic dysfunction. Nevertheless, more data and analysis are to be warranted in order to speculate in this field. In order to clarify the relationships highlighted in this preliminary study, a prospective study with control groups is due to be planned and scheduled.

Acanthosis, Vitiligo. Obesity. Micropolycystic ovary syndrome clinically

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Woman, 41 years old.

She was admitted to our ward because of febricula and glycaemic disorders for a few months.

Physical examination: obesity, vitiligo, dark dyschromias of the nape, armpits and groin.

Remote pathological anamnesis: hormone replacement therapy after thyroidecemy; micropolyycistic ovary syndrome with clinical signs of hyperandrogenism(hirsutism) treated with fluamide; severe obesity.

The patient had no febricula during hospitalization. The diarrhoeic episodes occurred, ended after metformin suspension.

Normal laboratory exams, except for hyperinsulinemia (25,90 u/ml;v.n.=7,10-15,60 U/ml).

The ECG, chest X-ray, abdominal and transvaginal ultrasounds were normal. The CT scan of the spinal column showed discopathy at L4-L5 and L5-S1 levels.

The use of a hypocaloric diet resulted in glycemiac normalization.

Furthermore the patient was treated with LMWH during hospitalization.


Differences in metabolic profile in obese patients with and without Binge Eating Disorder


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Introduction: Binge Eating disorder (BED) is a syndrome strongly linked with obesity, although not limited to this disease. BED is characterized by recurrent episodes of binge eating, associated with loss of control as well as significant distress in the absence of regular compensatory weight-reducing behaviors. The prevalence of BED in the normal adult population varies from 2% to 5%. Among obese adults seeking treatment for obesity, however, this proportion rises to 30%.

Both BED and binging behavior are associated with a poorer response to weight loss therapy and poorer glycemic control in patients with diabetes mellitus.

Aim: We evaluated whether obese patients with Binge Eating disorders had different metabolic profile compared obese non-BED patients including glucose tolerance and insulin sensitivity.

Patients and Methods: Fifty patients who sought care for their obesity through a weight loss program at the Internal Medicine Day Hospital of University “Magna Graecia” of Catanzaro were recruited for the present research.

Subjects were included in the study if they met the following criteria: age ranging from 18 to 55 years, BMI ≥ 30 kg/m². The exclusion criteria were represented by known inflammatory disease, history of malignant disease, or pathologies or drugs able to modify glucose metabolism. All patients underwent anthropometrical evaluation including BMI, waist circumfer-
ence, waist-hip ratio. After a 12-h fasting, a 75 g oral glucose tolerant test (OGTT) to 5 hours was performed with sampling for plasma glucose, insulin and C-peptide. The insulin resistance was evaluated by HOMA-IR. All patients answered to the Binge Eating Scale (BES). It is an easily administered scale, with adequate internal consistency and validity, that assesses symptoms of binge eating. Total BES score <17 indicates unlikely BED, 17-27 score possible BED and values >27 probable BED. All obese participants have been subsequently interviewed by a Psychiatrist with adequate training in the field of Eating Disorders in order to confirm the diagnosis of BED and the Binge Eating Disorder and to deepen the eating behaviors (i.e.: night eating, sweet-eating, grazing,…) and exercise habits.

**Results:** Thirty-two percent of the patients were classified as severe binge eaters (BES>27), 4% were in the intermediate rank and 64% were in the normal range. The clinical interview through the SCID-I confirmed the diagnosis of Binge Eating Disorder for all the obese patients with BES scores<17 while no BED diagnosis was confirmed among participant with BES<17. Therefore, the patients was subsequently divided into two groups: obese non-BED patients (n=32) and obese-BED patients (n=18).

Age and sex did not differ between the two groups even if obese-BED patients showed a higher proportion of females. High percentages of hyperphagia were evident in both groups but obese-BED patients exhibited significantly higher rates of bingef, grazing, emotional eating, post-dinner-eating and craving for carbohydrates. Obese-BED patients exhibited lower body weight, waist circumference and BMI when compared with obese non-BED patients. In addition, obese-BED patients showed lower fasting glucose levels, higher basal insulin levels, higher area under the curve (AUC) of insulin during OGTT, and increased insulin resistance, evaluated by HOMA-IR than obese non-BED patients. Furthermore, although obese-BED patients had lower area under the curve (AUC) of glucose during OGTT, showed a higher glycemic variability and higher HbA1c levels when compared with obese control.

**Conclusion:** Although preliminary, our data demonstrated that obese-BED patients have lower fasting glucose levels, higher basal insulin levels, increased insulin resistance and a higher glycemic variability compared with obese non-BED patients. This different metabolic profile could explain higher rates of bingef, grazing, post-dinner-eating and craving for carbohydrates observed in these patients.

**Case report of severe hypocalemia**

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**Case presentation:** A 51 years old Caucasian man was admitted in Emergency Room department complaining increasing muscle pain since one month. He had no remarkable events in his past medical history, he lived with support of social services and worked as gardener; since some months he has referred weight loss, fatigue and increasing muscle pain, not responsive to non-steroidal antinflammatory drugs (NSAID). Physical examination was normal, no neurological or neuro-muscular abnormalities were present; laboratory testing showed a severe hypocalemia (4.09 mg/dl, ionized Ca++ 0.55 mmol/L), with normal levels of albumin (3.8 g/l), were present; laboratory testing showed a severe hypocalcemia (4.09 → 4.85 → 5.67 → 6.8 → 8.25 mg/dl), muscular pain disappeared; patients was then hospitalized, and followed up as outpatient. We have intention to study her sister too.

**Discussion:** in this case, hypocalemia resulted for inadequate PTH secretion. Causes of hypoparathyroidism can be congenital or acquired. The most common acquired causes are damage of parathroid glands after neck surgery or irradiation, immunomediated damage usually as part of autoimmune polyendocrine syndrome, or as consequence of hypomagnesemia. Genetic disorders include a lot of possible different syndromes; unfortunately precise genetic diagnosis is difficult to obtain. In this case, the differential diagnosis is between isolated immunomedated damage, or a congenit defect that include hypoparathyroidism and mental involution.

**Hepatology**

Searching for predictors of response to pegylated interferon alfa 2a therapy in patients with HBV chronic hepatitis: reliable indications from results of clinical practice from most representative italian patients (HBeAG- and genotype D)

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**Background and aims:** Chronic hepatitis due to hepatitis B virus (CHB) is a global health problem. Among different drugs currently approved for CHB treatment, peg-interferon alfa 2a (PEG-IFN), has more adverse effects compared to the other therapies, but has a limited duration and allows to obtain the higher rate of anti-HBs seroconversion and response off-therapy. Aim of this study was to identify predictors of response to PEG-IFN therapy in HBeAg negative patients from results of daily clinical practice.

**Methods:** We studied 47 consecutive HBeAg negative patients with HBV genotype D (mean age was 47±11 years, 9 female); 5 of 47 (11%) had compensated liver cirrhosis. All patients were treated with PEG-IFN alpha 2a, 180 mcg/week for 72 weeks. Granulocyte-stimulating factors were used in case of significant neutropenia. All patients were assessed for clinical status, blood cell parameters, serum ALT and HBV-DNA levels at the start of therapy and for serum HBV DNA every 4 weeks of therapy, at the end (EoT) and 6 months after of the end of therapy (FU). Stopping rule criterion during therapy was serum HBV DNA > 20.000 UI/ml after 24 weeks of therapy. Positive response at EoT or at FU was defined as the
P53 is involved in maintenance of copper homeostasis in experimental model of NAFLD

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**Background and Aims:** Nonalcoholic Fatty Liver Disease (NAFLD) is a pathological condition that from simple steatosis can progress to Non-Alcoholic Steatohepatitis (NASH), which may lead to cirrhosis and hepatocarcinoma (HCC). The molecular mechanisms underlying NAFLD development have not been completely understood. In the last years, p53 protein has been proposed as a new player in NAFLD pathogenesis, because growing evidences highlight its relevance as metabolic modulator. One of its known targets is Synthesis of Cytochrome c Oxidase 2 (SCO2). SCO2 is a copper (Cu) chaperone involved in the assembly of the mitochondrial complex IV and in the maintenance of copper homeostasis, because it’s implicated in the cellular secretory pathway of this metal. Cu is essential for aerobic respiration and its unbalance may affect lipid metabolism and may lead to oxidative stress onset. Some works suggested a role for Cu in NAFLD; thus, our study aims to investigate the potential role of p53 in modulating copper homeostasis in an *in vitro* model of steatosis.

**Methods:** Human hepatocarcinoma cell lines, HepG2, characterized by a wild-type p53 (wt), and Huh7.5.1, with the Y220C mutated form of p53, were cultured for 14 and 24 hours in a medium containing a solution of Free Fatty Acids (FFAs), oleic and palmitic acids in a 2:1 ratio (final concentration 0.5 mM). Cellular lipid content and cytotoxic effects were evaluated by AdipoRed and AlamarBlue assays respectively. Through Atomic Absorption Spectrometry we evaluated intracellular Cu content. mRNA and protein expression of p53, its target genes and some relevant genes involved in copper trafficking were analyzed through qRT-PCR and Western blot, respectively.

**Results:** In both cell lines, FFAs treatment produced a similar enhancement of intracellular lipid content and did not cause cytotoxic effects. FFAs treatment induced an up-regulation of p53 in both HepG2 and Huh7.5.1 after 14 hours, but at 24 hours, we appreciated an up-regulation of the wt p53 and a down-regulation of the mutated form. Western blot analysis of the p53 phosphorylated at Ser15, the activated form, and its target p21 showed a trend similar to p53 in both cell lines. In HepG2 cells FFAs did not alter the intracellular copper content. On the contrary, after 24 hours, treatment produced a copper decrease in Huh 7.5.1. Furthermore, our investigations revealed that FFAs differentially modulated genes involved in copper trafficking. In HepG2 cells treatment induced an up-regulation of Cu secretory pathway at 14 hours that is counterbalanced by the up-regulation of the gene responsible of Cu import in the cells, Ctr1, and a parallel down-modulation of the secretory genes at 24 hours. This cellular response to FFAs did not occur in Huh 7.5.1; in fact, while the expression pattern of genes involved in copper trafficking is similar to that observed in HepG2 after 14 hours of treatment, at 24 hours we have not appreciated any counterbalance.

**Conclusions:** This study suggests a pivotal role of the p53 in the modulation of copper homeostasis, providing new potential insights into the mechanisms underlying p53 involvement in NAFLD pathogenesis.

**Prospective longitudinal study of patients with HCV-related or cryptogenic compensated cirrhosis**

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**Background:** Cirrhosis affects 1% of the world’s population and is strongly associated with liver cancer and death. Cirrhosis represents the advanced stage of liver disease and its etiology includes chronic viral infection (HBV and HCV), autoimmune diseases, side effects of alcohol and non-alcoholic steatohepatitis. Among all etiologies of cirrhosis, viral hepatitis is far the most frequent. Approximately, 1% of the world’s population is suffering from Hepatitis C Virus (HCV) infection. The aim of our study was to propose a prospective observational study to assess the clinical outcome of patients with HCV-related or cryptogenic compensated cirrhosis (C3) treated with Peg-interferon alfa 2a after 12 weeks. Our study was conducted from January 2004 to December 2007. Two hundred and forty patients (174 HCV-related and 85 cryptogenic cirrhosis) with median follow up of 74 months (range 48-112 months) were available for the analysis. Ninety-nine patients showed a stable disease over time, whereas 60 showed clinically relevant progression of the liver disease and/or HCC development and 50 of them died during the fol-
low up. Concerning the “main events” occurred in the study population, no difference was observed between HCV-positive and cryptogenic cirrhosis. Diabetes was significantly associated with cryptogenic cirrhosis (p = 0.004), but neither diabetes nor arterial hypertension were significantly associated with any of the “main events” considered. The presence of hypergammaglobulinemia (defined as values of serum gamma-globulin >1.8 g/dl) was associated with parameters indicative of portal hypertension (as increased portal vein diameter, thrombocytopenia and/or splenomegaly), and with the incidence of hepatic decompensation during the follow up (p=0.0001). Importantly, hypergammaglobulinemia was significantly associated also with HCC development (p=0.002). Finally, the presence/absence of esophageal varices at baseline was significantly associated with liver decompensation (p <0.0001) but not with HCC development.

Conclusions: This prospective study shows that patients with HCV or cryptogenic cirrhosis have a similar outcome in terms of risk of hepatic decompensation, HCC development and death. The presence of esophageal varices at initial stages of cirrhosis associates with progression of the disease and liver decompensation, whereas hypergammaglobulinemia is a strong predictor of both liver decompensation and HCC development.

**Comparison between Tanscatheter Arterial Chemoembolization (TACE) and Tanscatheter Arterial Chemoembolization combined with percutaneous radiofrequency ablation (TACE-RFA) for treatment of intermediate hepatocellular carcinoma**


**Policlinico Gemelli, UCSC, Roma**

**Background**: At the state of the art, patients with multinodular HCC at stage B of BCLC classification, are suitable only to palliative treatments, such as transcatheter arterial chemoembolization (TACE). Recent studies evaluated the application of new strategies of treatment in this subset of patients, such as balloon-occluded RFA combined with TACE, in order to increase the local response and the survival rate.

**Objectives**: Our aim was to compare safety, tolerability and influence on liver function of TACE and single step balloon-occluded RFA followed by TACE (TACE-RFA), in patients affected by unresectable multinodular hepatocellular carcinoma. The second purpose of our study was to evaluate the efficacy and Overall Survival in patients treated with these two therapeutic strategies.

**Methods**: Since January 2010 to March 2012, a group of 14 patients with multinodular unilobar unresectable HCC were submitted to TACE + RFA (GROUP 1: 14 pts). These patients were individually matched according to type of tumor, age, sex and liver disease stage with a group of 15 patients treated only with TACE (GROUP 2: 15 pts) selected by the archive of the Multidisciplinary Group for the Treatment of Hepatocellular Carcinoma of our Centre (HEPATOCATT). We monitored changes in liver laboratory tests, development of major complications after procedures and time of hospitalization. Then, early local efficacy was evaluated on multiphasic CT performed at 1-month and 6-months of follow-up based on m-RECIST criteria. We also analyzed total number of ulterior treatments performed during the year following the procedure. Moreover Kaplan-Meier analysis were performed to evaluate overall survival in these groups.

**Results**: Plasma total bilirubin (TB) increased from pre-procedural 1.02±0.56 mg/dL to 1.48±0.55 mg/dL on post-procedural day three (P = 0.038) in GROUP 1 and from 1.57±1 mg/dL to 2.11±1.6 mg/dL (P = 0.277) in GROUP 2. Alanine aminotransferase (ALT) also increased greatly three days after treatment from 45.3±44.9 IU/L to 154.3±107.2 IU/L (P < 0.003) in GROUP 1, from 55.67±41.23 IU/L to 88.53±68.36 IU/L (P = 0.122) in GROUP 2. These parameters returned to normal range within 3-4 weeks. 5/18 patients in GROUP 1 and 6/19 in GROUP 2 developed fever (TC max 38°C) in the first day after the procedure. No patients developed major complications in our study. Changes in Child-Pugh score one month after treatment were not statistically significant in both groups (GROUP 1 from 6.14±1.77 to 6.93±1.82 p=0.183; GROUP 2 from 6.33±1.11 to 6.87±1.55 p=0.282). Hospitalization time was 8.23±3.35 days in GROUP 1 and 9.60±5.67 in GROUP 2 (P = 0.4395).

Conclusion: Technical success, defined as complete or partial devascularization during the arterial phase of all nodules, was achieved in 85% of patients in GROUP 1 (12/14; 6CR, 6PR) and 80% in GROUP 2 (12/15; 5 CR, 7PR) on 1-month follow up CT (p=0.89). At 6 months follow-up, local recurrence (Progression Disease) developed in 5/14 (35%) patients of GROUP 1 and 5/15 (33.3%) in GROUP 2 (p=0.78). Interestingly during one year follow up we observed that patient in GROUP 2 underwent a greater number of total following treatments (4 procedures in GROUP 1 and 13 in GROUP 2). The Kaplan-Meier analysis didn’t demonstrate statistically significant differences in Overall Survival among the two groups (median survival in GROUP 1: 342 days; in GROUP 2: 487 days; p= 0.822).

**Conclusion**: Liver function parameters and clinical features (plasma total bilirubin, Child-Pugh score, development of fever and complications) were not significantly deteriorated after both procedures; only ALT parameters showed a greater transient increase after TACE-RFA than TACE. Although these therapeutic strategies didn’t show a statistically significant difference in OS and efficacy, patients that underwent TACE needed greater number of following treatments. Therefore TACE-RFA could be more favorable than TACE alone in terms of cost-effectiveness in patients with multinodular unresectable HCC.

**A counter hepatitis**


**University of L’Aquila - Department of Life, Health and Environmental Sciences**

A 73 year-old male, affected by hypertension and valvular heart disease, with previous mechanical heart aortic valve prosthesis implantation, was admitted to our Department for a three days symptomatology characterized by pain at the right hypochondrium, nausea, jaundice and asthenia. His home therapy was ramipril 5 mg 1 cp bid and warfarin 5 mg 1 cp die. The month before benign prostatic hypertrophy (BHP) was diagnosed, treated with Beta-sitosterolo (BS) + Serenoa Repens (SR) 1 cp die. Physical examination showed moderate hepatomegaly, regular heart rate and aortic click sound, blood pressure 150/95 mmHg and heart rate 72 bpm. The patient de- nies alcohol abuse. Laboratory exams revealed hypertransaminasemia (ALT 700 UI/l, AST 882 UI/150), increase of cholesterol indexes (GGT 339 UI/l, ALP 1235 UI/l, total bilirubin 2.42 mg/dl, direct 0.53 IU/L , indirect 1.89UI/L). The ECG showed sinus rhythm with left ventricular hypertrophy signs. Abdominal ultrasound examination exhibited a moderate hepato- megaly, absence of focal lesions without intra- or extrahypertrophic biliary ductal dilation. Home therapy was discontinued except for warfarin. Fasting was recommended and therapy with Inavenous 5% glucose solution and glutathione 1fl bid was started. Acute liver injury was diagnosed and further tests were performed in order to establish its aetiology. Serologic work-up revealed negative drug and toxicology screens, negative testing for acute viral hepatitis including hepatitis A, B, C, Ebstein-Barr virus, cytomegalovirus and herpes simplex virus. Antinuclear antibody, anti-smooth
Treatment of single-nodule hepatocellular carcinoma: comparison between surgical resection and Transcatheter Arterial Chemoembolization combined with percutaneous radiofrequency (TACE-RFA)


Background and aims: Currently surgical resection is the standard treatment option in patients with single nodule HCC, even if loco-regional ablation with percutaneous radiofrequency is emerging as a valuable treatment option especially in patients with a single small HCC < 3 cm. Recent evidence shows that the combination of radiofrequency and transarterial chemoembolization may have a higher rate of complete response because of synergistic effect in the treatment of single HCC, even greater than 3 cm. The aim of this study was to compare the survival rate and the time to progression of disease in patients with single-nodule hepatocellular carcinoma greater than 3 cm who underwent surgical resection or single step balloon-occluded RFA followed by TACE (TACE-RFA). We also evaluated the difference in post-procedural deterioration of liver function between the two treatments.

Methods: Medical records of 37 HCC patients selected by the archive of the Multidisciplinary Group for the Treatment of Hepatocellular Carcinoma of our Centre (HEPATOCATT) with single nodule (maximum diameter > 3cm and Child-Pugh class A-B) treated with surgical resection (n=18) or RFA combined to TACE (n=19) since January 2010 to March 2012, were retrospectively reviewed. The patients survival outcomes were compared. Survival and Time To Progression (TTP) curves were obtained with the Kaplan-Meier method and compared by using the log-rank test. Changes in liver laboratory tests after the procedures were considered to attest deterioration of liver function.

Results: Patients of the two study groups were similar in epidemiological features, liver disease stage and lesion characteristics. Tumor size was comparable in both group (mean tumor size: surgical group 5.67±3.82 cm; TACE-RFA group 4.65±2.12 cm; P=0.3187). During follow-up (mean,15 months; range, 1-26 months), local tumor progression was observed in 11/19 (57.9%) patients of treated lesions in the combined treatment group and in 13/18 (72.2%) in the surgical treatment group; P=0.57. There were not statistically significant differences in TTP rates among the two groups (median TTP in surgical group: 278±167.18 days; in TACE-RFA group: 226±196.54 days; P=0.777). The 1-year local tumor progression rates evaluated by Kaplan Meier analysis, were comparable in the TACE + RFA group and in the surgical group (40%, respectively, P=0.777). Interestingly the recurrence was always multinodular in surgical group. The 1-year overall survival rate was 70% with combined treatment and 88% with surgical resection (P=0.09). Changes in Child-Pugh score one month after treatment were statistically significant only in surgical group (surgical group from 5.22±0.44 to 6.38±0.9 p<0.0001; TACE-RFA group from 6.20±1.75 to 6.64±2.06 p=0.551).

Conclusions: In our retrospective analysis we observed that in patients with single nodule HCC > 3 cm, survival rate and local tumor progression rate after treatment with single step balloon-occluded RFA followed by TACE (TACE-RFA) or surgical resection are similar. However our data showed that surgery can lead to deterioration of liver function more frequently than loco-regional treatment.

Treatment of portal vein tumor thrombosis (PVTT) can impact survival of patients with advanced HCC?


Policlinico Gemelli, UCSC, Roma

Introduction: HCC with PVTT is often associated with poor prognosis. Many efforts have been made to improve prognosis in this setting, but nowadays there is not a treatment of choice for HCC related PVTT.

Aims&methods: We retrospectively assessed epidemiologic data, tumor and underlying liver disease features, overall survival and treatment-related survival of 60 patients affected by advanced HCC complicated by PVTT. Moreover we evaluated variables associated to PVTT development and severity, and the impact of tumor thrombosis treatment on survival of patients with advanced HCC. We included both main portal vein and segmentary branches thrombosis. Diagnosis was made according to typical dynamic contrast pattern on radiological main techniques. We calculated overall survival by the time of both PVTT diagnosis and tumor onset. In addition we evaluated a possible role of performed treatment on conditioning prognosis. A Kaplan-Meier analysis was performed.

Results: From May 2008 to April 2012 60 patients (51 male, 9 female; mean age 66±5.6) were recruited for retrospective evaluation. 33/60 (55%) patients underwent systemic antiangiogenic therapy; 6/60 (10%) were referred to external beam radiation therapy on thrombus; 21/60 (35%) not receive any active therapy. All patients received the best treatment on HCC concomitant nodules. A multivariate analysis showed that time between the onset of thrombosis and the diagnosis of HCC is significantly correlated to the presence of portal hypertension. At the end of observation (47 months), survival for each group was 18%, 50% and 23%, respectively. The overall survival from the diagnosis of HCC was 753±88 days and it is significantly correlated to younger age at diagnosis, BCLC stage and treatment performed on HCC nodule, but not according to PVTT treatment. The overall survival from the diagnosis of PVTT was 397±77 days. According to each group, mean survival was 408±86 days for the first group (antiangiogenic therapy), 855±273 days for the second group (radiation therapy), 140±29 days for patients who had not received any therapy (p<0.001), regardless of age or severity of underlying liver disease.

Conclusion: PVTT treatment seems to improve survival of patients with advanced HCC, regardless of age. In particular radiation therapy seems to be the best treatment option for this kind of patients. Nevertheless PVTT treatment seems not to affect overall survival from time of diagnosis of
HCC. Further studies are necessary to evaluate the impact of patients and tumor characteristics on treatment efficacy.

The serological monitoring of the treatment of hepatocellular carcinoma

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Background: The role of Alpha-fetoprotein (AFP) and of common serological tests (e.g. ALT, AST, platelets, serum albumin and PT-INR) in the monitoring of patients affected by hepatocellular carcinoma (HCC) and underwent to loco-regional or radiological treatment is still controversial.

Objective: We evaluated in a retrospective study the accuracy of the values of alpha-fetoprotein in the first diagnosis of HCC and in the assessment of necrosis and recurrence after specific treatment and the diagnostic accuracy of main hepatic function indices in the monitoring of the treatment.

Patients and methods: 54 subjects were included in the study affected by liver cirrhosis and HCC (27 with single nodule of HCC and 27 with multiple lesions). Routine biochemical tests for the evaluation of hepatic function and Child-Pugh classification as well as instrumental diagnostic tests were performed: Ultrasound contrast enhanced (CEUS), CT or MRI. The patients were subjected to specific treatment of the tumor in relation to the BCLC criteria and the current guidelines (AASLD 2010): thermal ablation (radiofrequency or microwave) in 79 nodules, intra-arterial chemoembolization (TACE) in 38 cases, surgical resection in 1 case; PEI (Percutaneous Ethanol Injection) in 12 cases, more than one procedure in 13 cases. The serological markers were evaluated at basal and three months after the procedures. Statistical analysis involved the evaluation of cases of true positives, true negatives, false positives and false negatives, using as gold standard CT or MRI scan to judge the complete or partial necrosis after treatment or the recurrent disease. Sensitivity, specificity, positive predictive value, negative predictive value were evaluated. The comparison between the mean values of the same biochemical indices were calculated using the Student’s t test for paired data was used for comparison among the basal and the follow up values.

Results: Value of AFP before treatment was 304,07+/-1399,1 (M+/-SD, U/l); sensitività of AFP for the diagnosis of HCC was 60%. The study showed that the loco-regional treatment with radiofrequency is more effective (67% of patients had complete necrosis) compared to TACE, which instead induces complete necrosis in only 50% of cases. Diagnostic accuracy of AFP in the diagnosis of complete or partial necrosis three months after treatment was: sensitivity 44%, specificity 71%, positive predictive value 52%, negative predictive value 64%.

Among the other serological markers, albumin and AST remained stable after treatment, while ALT reduced (from 93,5+/-77,8 to 73,1+/-56,4, p <0.05); PT INR improved ( from 1.18+/-0.15 to 1.12+/-0.19, p<0.01) and platelets reduced (from 141.030+/-63.657 to 122.080+/-57.832, p<0.01).

Conclusions: AFP has a low sensitivity in the diagnosis of HCC; its role in the follow up of patients underwent to treatment seems to be limited to the diagnosis of absence of disease; the reduction of platelets observed after treatment has not been elsewhere described to our knowledge and it is possibly due to a greater splenic sequestration consequent to modification of portal pressure due to more or less extensive necrosis. This data needs to be supported by further observations on larger case series.

Microwave ablation of liver cancer: post ablation syndrome easily managed by a multidisciplinary approach

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Background: Image-guided ablation techniques of liver tumors, either primary or metastatic, are procedures commonly performed by interventional radiologists operating within third level multidisciplinary centers. Locoregional treatments in particular play a key role in the management of hepatocellular carcinoma (HCC). Image-guided tumor ablation is recommended in patients with early-stage HCC when surgical options are precluded and can replace resection in selected patients. Microwave ablation (MWA) is emerging as a valuable alternative to radiofrequency ablation (RFA) for thermal destruction of HCC. New technologies for MWA have been developed, in order to induce larger areas of necrosis in comparison to RFA. The advantage of MWA over RFA is that treatment outcome is less affected by vessels in proximity to the tumor. Post-ablation syndrome (PAS) is defined as a combination of flu-like symptoms, which includes fever, malaise, nausea and vomiting (complete PAS) occurring after the procedure. Pain at the site of ablation is also common.

Aim: To prospectively investigate the frequency and severity of PAS and post-procedure pain in a cohort of patients undergoing hepatic MWA. It is not known indeed to what extent the theoretical advantage of MWA over other ablation techniques can be used in clinical application without a significant increase in the rate of adverse effects or complications.

Materials and methods: From March 2009 to November 2011, we consecutively enrolled 54 patients undergoing microwave ablation for liver tumors and administered them a questionnaire to investigate PAS and pain at 1, 7 and 40 days post-ablation. Four patients did not return all questionnaires and were excluded from the analysis. Laboratory tests known to vary significantly after ablation were performed, and ablation parameters were recorded. We evaluated potential predictors of PAS and pain, both at 1 and 7 days, by means of a logistic regression model.

Results: Fifty patients underwent a single microwave ablation session, 33 for HCC and 17 for liver metastases. Median ablation volume at CT was: 31 cm³ for HCC, 42 cm³ for metastasis. Overall, 60% of patients experienced PAS in the first week (48% partial, 12% complete PAS). AST post-ablation levels were significantly associated with PAS during the week after discharge. Overall, median visual analog scale for pain at puncture site was 1 cm and 0.24 cm at 1 and 7 days, respectively. The risk of having at least moderate pain in the first week was significantly related to ablation volume and ablation time, and post-ablation rise of AST. By 40 days post-ablation, all symptoms of PAS and pain had completely resolved. No major complications occurred.

Conclusion: The incidence and severity of PAS with hepatic MWA is similar to that reported for RFA, the best predictive factor being post-ablation AST elevation. Post-MWA pain was best predicted by volume of ablation and transaminase elevations. PAS is a common phenomenon after MWA, but is self-limiting in the majority of cases within about a week after the procedure. However, it requires prior knowledge of the problem and the provision of effective clinical support for the patient, according to need. Our experience in applying MWA techniques, confirms the importance of a multidisciplinary approach to the management of liver cancer, including, among others core specializations, internal medicine-hepatology.
Low cholesterol diet modulates the balance of Th17 and Treg cells in patients with chronic hepatitis C virus infection

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Hepatitis C virus (HCV) infection is one of the leading causes of liver disease and is characterized by the association with several autoimmune disorders. During chronic HCV infection an increased amount of circulating and intrahepatic T helper 17 (Th17) cells has been reported. Th17 are an IL-17-producing subset of T-helper lymphocytes involved in both liver inflammation and autoimmunity. Liver X Receptors (LXRs) activity influences the production of Th17 cells; LXRs are sensors of cholesterol oxo-derivatives and metabolic checkpoints. Thus, we evaluated whether a low cholesterol diet (LCD) may modulate peripheral T helper lymphocyte subsets in a cohort of 30 chronic HCV-infected patients. After thirty days of LCD, we observed a substantial reduction in the frequency of IL-17--producing subset of T-helper lymphocytes involved in both liver inflammation and autoimmunity. Different vasoactive mediators (active both as vasodilators and as vasoconstrictors) can modulate the vascular liver resistance and disturbances in “Endothelium-dependent” vasodilation. This condition, also known as “endothelial dysfunction”, has been claimed as a possible factor responsible for increased vascular hepatic resistance and PH development in LC. Aims of this study were to assess in 60 consecutive LC patients (mean age 65±10 years, 17 female) without portal thrombosis (40 with compensated and 20 with decompensated disease) underwent a complete clinical, radiological and biochemical evaluation in order to assess the stage of disease (Child-Pugh-Turcotte and MELD score) and drug history; all subjects were assessed for MED [P-selectin, von Willebrand factor (vWF)], endothelin-1 (ET-1), thrombomodulin (TM) and nitric oxide (NO)] serum levels and FMD (measured by ultrasound as the percentage change in brachial artery diameter in response to “shear stress”). MED and FMD were also assessed in 11 healthy subjects (mean age 26±6, female) (controls). Results: After correction for age and other confounding factors, plasma levels of all MED increased with the degree of liver dysfunction (p for trend <.001 in all cases); accordingly, FMD values decreased with worsening of the stage of liver cirrhosis [controls (9.9±1.1%), compensated cirrhosis (13.6±2.3%), decompensated cirrhosis (5±1.3%), p for trend<0.01]. In patients with liver cirrhosis a statistically significant correlation between MEF plasma levels and FMD was observed for ET-1: r=-.4427 (p=.0004) and P-selectin: r=-.477 (p=.0001), vWF (r=-.166, p=.05), but not for TM (r=.245, p=.05951) and NO (p=.961). The table shows the results (univariate and multivariate linear regression analysis) of different factor associated with FMD values in LC patients. The shadow of cholangiocarcinoma behind a case of pulmonary thromboembolism


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Case report: A 65 year old man came to the emergency room of our hospital for shortness of breath, chest pain right hemithorax, cough arose during the night and orthopnea. He was already suffering from chronic bronchitis, chronic ischemic heart disease, he had undergone coronary artery bypass grafting and a month before had a surgical placement of stent type Endologix for abdominal aortic aneurysm. A few months before he was also subjected to removal of fixation devices for a previous fracture of the left leg. The fixation devices were not removed completely and he underwent to os-
teomyelitis, subsequently resolved with drug therapy. The patient was therefore admitted to the operating unit of Internal Medicine. The physical examination revealed blood pressure of 130/80 mmHg, a heart rate of 64 beats per minute, the patient was tachipnoic and suffering, cyanotic. There was an hypoxemia (pO2 65.8) with hypocapnia (pCO2 29.4) and pH of 7.45. The ECG was normal. The chest X-ray showed a widespread emphasis on the design and the pulmonary hilum perileur bases, with obliteration of the sinuses phrenic cost. The echocardiogram showed a diffuse hypokinetic left ventricle with an ejection fraction of 25% and an increase in the right cavities and pulmonary hypertension (PAPs of 60 mmHg). Laboratory tests were almost normal except for an increase in D dimers (1145mg/ml), GGT (210 U/L), alkaline phosphatase (185 U/L) and LDH (1561 U/L).

**Discussion:** evaluated the medical history, the symptoms and clinical signs, as well as laboratory and instrumental tests (increased right cavities and pulmonary hypertension and reduction of the EF to 25%), we thought to an initial diagnosis of pulmonary thromboembolism. The patient began therapy with low molecular weight heparin and being the pulmonary angiography the survey gold standard for the study of pulmonary circulation, the patient was started to the procedure. However, the test gave us a new unexpected element. CT angiography showed a regular opacification of the pulmonary artery and its main lobar and segmental branches, decaying the first diagnosis of pulmonary thromboembolism. Rather lowest scans showed a massive expansive formation of the liver (about 9 x 8 cm) in correspondence of the II-IV segment and two other satellite lesions of about 2 cm with poor impregnation and late arterial internal impregnation with areas of poor vascularization. The finding, to be integrated with MRI, deposed in the first instance for a heteroplasic primitive bile ducts lesion. The patient has not been subjected to resonance because claustrophobic and laying still synthesis means metal at the level of the left leg. Rather, a biopsy was performed under US guidance which confirmed cholangiocarcinoma. In our case, the patient had only a right hemithorax pain and an increase of intrahepatic cholangiocarcinoma in fact proved in this case an unexpected element. CT angiography showed a diffuse hypokinetic left ventricle with an ejection fraction of 25% and an increase in the right cavities and pulmonary hypertension (PAPs of 60 mmHg). Laboratory tests were almost normal except for an increase in D dimers (1145mg/ml), GGT (210 U/L), alkaline phosphatase (185 U/L) and LDH (1561 U/L).

**Conclusions:** The pulmonary thromboembolism may be unrecognized, and even the presence of clinical paradigm features doesn’t provide a firm diagnosis. The intrahepatic cholangiocarcinoma in fact proved in this case even more insidious and difficult diagnosis than pulmonary thromboembolism itself, so much that our patient’s lesion reached a considerable size without symptoms and was diagnosed incidentally during instrumental investigations to exclude other diseases, and the last in part the suspected pulmonary thromboembolism could be a paraneoplastic syndrome in our case.

**Rotigotine-induced liver injury heralding previously undiagnosed cryptogenic cirrhosis**

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A 77-year old woman presented to the Emergency Room because of nausea, vomiting, anorexia and altered mental state. She had a previous diagnosis of Parkinson’s disease and had started a therapy with rotigotine via transdermal route about three months before the admission. She denied alcohol abuse, consumption of mushrooms and exposure to herbal products. Her physical examination revealed marked eye and skin jaundice and a slight hepatomegaly. Laboratory profile was characterized by GGT/GPT 1718/2562 U/l, GGT 386 U/L, AP 275 U/L, total bilirubin 15.4 mg/dl (conjugated fraction 7.21 mg/dl), INR 1.6, PLT 125000/mmc. Serology for HAV, HBV, HCV, HDV, HEV, CMV, EBV, HSV, VDRL, toxoplasmosis, parvovirus B19, HZV, HHV 6; Antinuclear, antimitochondrial, antismooth muscle, anti liver kidney and anti neutrophil cytoplasmic antibodies were all negative, as ceruloplasmin and serie copper levels. CT scan showed an inhomogeneous liver compatible with an acute inflammatory reaction. Liver biopsy findings were consistent with acute cholestatic hepatitis associated with deeply altered liver architecture owing to nodular changes and marked fibrosis (pre-cirrhotic stage). During the recovery, the patient displayed progressive dissociation in the behavior of transaminases and bilirubin with normalization of GOT and GPT in a few days and increase in bilirubin levels up to 43.08 mg/dl (conjugated fraction 26.86 mg/dl). Empiric treatments with ursodeoxylic acid, methylprednisolone, ademetionine, acethylycisteine and plasmafereis failed to affect bilirubin tests significantly. Only rotigotine interruption led to a progressive normalization of total and fractioned bilirubin levels in about 7 months.

Drug-induced liver injury (DILI) is a serious health problem and a significant cause of morbidity and mortality, accounting for at least 13% of acute liver failure cases in the US. Classes of drugs most commonly involved in DILI include antibiotics, analgesics, NSAIDs and medicinal herbs. Rotigotine is a dopamine agonist with high affinity for D3, D2 and D1 receptors: it’s licensed for either monotherapy treatment of early Parkinson’s disease, or as an adjunct to levodopa in advanced disease, and in restless leg syndrome. Its most common adverse effects include local skin reactions, nausea, vomiting, drowsiness, headache and peripheral edema. We have reported on the first case of rotigotine-induced liver injury, cholestatic type, in a patient with previously unrecognized cryptogenic cirrhosis.

**Changes of bilirubin and liver enzymes during ischemic stroke. Mechanisms and possible significance**


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**Background:** According to personal experience and some previous studies, small but significant changes of bilirubin and liver enzymes occur during the acute phase of stroke. Various explanations have been proposed for this fact, including the hypothesis of a beneficial antioxidant action of bilirubin in response to oxidative stress, the need to neutralize the toxic glutamate released from cerebral lesions, or even the contraction of the sphincter of Oddi caused by stroke-induced dysautonomic changes. This prospective study was performed to describe more precisely these changes, and to search for their possible explanations.

**Methods:** One hundred and eighty patients with ischemic stroke, who had been consecutively admitted to our Stroke Unit (SU) from 1/4/2011 to 27/6/2012, were enrolled in the study. The patients with chronic liver disease or jaundice, inflammatory or neoplastic disease of the biliary tree or pancreas, positivity of the markers of hepatitis B or C, or alcohol abuse, were excluded from the study. In the days 0 (Emergency Room, ER), 1 (admission to SU), 3, 7, and 14, the patients underwent serial measurements of bilirubin, GGT, GPT, gamma-GT, alkaline phosphatase, C-reactive protein (CRP) and leukocytes. In the days 1 and 7 two abdominal ultrason sound assessments were performed in order to detect changes in the calibre of the main biliary duct and to search for possible dilatations of the intra-hepatic biliary tree. A brain CT scan performed on the 3rd day was used to calculate the volume in ml of the cerebral lesion. The statistical analysis mainly consisted of the assessment, by Wilcoxon’s test for paired data, of the changes of the median curves of the above parameters, and of a se-
ries of univariate and multivariate correlations (simple and multiple linear regression, after log-transformation of the non-gaussian variables).

**Results:** The analysis of the time course of the above parameters showed that the most rapid increment concerned the markers of inflammation: CRP (highly significant increment between ER and admittance to SU) and leukocytes (maximum value in ER, and decrease between admittance to SU and 7th day). Bilirubin followed the same course, with rapid increment between ER and SU, plateau up to the third day, and subsequent decrease. GOT, GPT and gamma-GT had a more late and progressive increment until the 7th day, with subsequent plateau up to the 14th day. Although the aforementioned changes were highly significant, the maximum values of the median curves were rather modest: CRP 1.42 mg/dl, leukocytes 8810/mmc, bilirubin 0.72 mg/dl, GOT 22 U/l, GPT 20 U/l, gamma-GT 26 U/l. Alkaline phosphatase and calibre of the main biliary duct did not change during the period of study.

The median value of cerebral infarct volume was 4.5 ml (range 0-462.3). The values corresponding to the peak times of the median curves of laboratory parameters were used for correlation analysis. In univariate analysis the infarct volume correlated with leukocytes (r=0.39, P<0.0001), gamma-GT (r=0.33, P=0.0006), GOT (r=0.30, P=0.002), CRP (r=0.21, P=0.03) and direct bilirubin (r=0.18, P=0.04). GOT, GPT and gamma-GT were highly correlated to each other. Gamma-GT was highly correlated with leukocytes (r=0.36, P=0.0001). The calibre of the main biliary duct correlated only with direct bilirubin. Multivariate analysis allowed the identification of the independent associations. In particular, the infarct volume was independently associated only with GOT (r=0.24, P=0.02) and leukocytes (r=0.39, P=0.0004). GOT, in turn, was associated with GPT, while leukocytes were associated with CRP and gamma-GT. Direct bilirubin was associated with gamma-GT.

**Conclusions:** The changes of bilirubin and liver enzymes during ischemic stroke reflect two phenomena, which are both associated with cerebral infarct volume: 1) inflammation, with increment of leukocytes, CRP, gamma-GT (which can be considered an acute phase reactant) and direct bilirubin and 2) an unknown mechanism, independent of inflammation, which causes directly the increment of GOT levels, and indirectly of GPT levels. One possible explanation is the release of glutamate from cerebral lesions, which may induce an increased hepatic synthesis of the enzymes involved in its metabolism.

**Acute supplementation with polyunsaturated fatty acids modulate NOX2 activity in liver cirrhosis**


**Background:** NOX2 up-regulation has been suggested to mediate platelet activation and to perpetuate liver damage via an oxidative stress-mediated mechanism in liver cirrhosis (LC). In previous platelets experiments, we tested the in-vitro effect on NOX2 platelet activity of n6/n3 polyunsaturated fatty acids (PUFA) ratio, reported as typically higher in Child Pugh C class LC patients. We found that in vitro lowering n6/n3 PUFA ratio resulted in an inhibition of NOX2-generated oxidative stress. To evaluate the acute in vivo effect of N3 PUFA supplementation in modulating NOX2-mediated oxidative stress, we planned an intervention study.

**Methods And Results:** A seven days supplementation with n3 PUFA (3 g per day) was assigned to 5 consecutive Child Pugh C class cirrhotic patients admitted to our internal medicine ward. Changes from baseline in serum soluble NOX2-derived peptide (sNOX2-dp), platelet isoprostanes and platelet reactive oxygen species (ROS) were evaluated at 2 and 24 hours after administration. Serum PUFA n3 and n6 were also measured before and during the supplementation period. Comparing to the baseline, we found a progressive reduction of sNOX2-dp starting 2 hours (53±8 vs 43±8 pg/ml) after administration with a further reduction until 24 hours (53±8 vs 41±13 pg/ml). A similar trend after 2 and 24 hours was observed for the platelet isoprostanes production (29±196 vs 196±157 pg/mg creatinine and 294±196 vs 166±160 pg/mg creatinine respectively).

Moreover, we found a statistically significant reduction in platelet ROS levels (p<0.05) at 24 hours after administration (22±6 vs 16±5 SI).

As expected, the n6/n3 PUFA ratio after 24 hours supplementation therapy was significantly reduced.

**Conclusion:** This study suggests that a n6/n3 PUFA ratio reduction, obtained by a n3 PUFA supplementation therapy, is able to down-regulate the NOX2-derived oxidative stress in LC patients. These data required to be confirmed in a randomized controlled clinical trial.

**Urinary ethyl glucuronide improves the detection of alcohol consumption in liver transplant candidates and recipients**

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**Background and Aims:** The detection of alcohol consumption in liver transplant candidates (LTCs) and recipients (LTRs) is needed to allow a proper assessment of transplant eligibility and an early management of alcohol relapse, respectively. In this clinical setting urinary ethyl glucuronide (uEtG) was prospectively evaluated and compared to serum ethanol (sETOH), urinary ethanol (uETOH) carbohydrate-deficient transferrin (CDT), Alcohol Use Disorders Identification Test for alcohol consumption (AUDIT-c), aspartate transaminase (AST)/ alanine transaminase (ALT) ratio, gamma glutamyl transeptidease (GGT), and mean corpuscular volume (MCV).

**Methods:** uEtG, sETOH, uETOH, CTD, AUDITc, AST/ALT ratio, GGT and MCV were assessed in 121 LTCs and LTRs, visiting our Liver Unit as outpatient. When alcohol consumption was detected by any marker of alcohol consumption, patients were scheduled for another visit and confronted with their test results. The gold standard for the identification of alcohol consumption was the admission by the patient.

**Results:** Alcohol consumption was found in 30.57% of patients. uEtG showed the best sensitivity in detecting alcohol consumption when compared to AUDIT-c (88.68 vs 49.05%; p<0.001), CDT (88.68 vs 33.96%; p<0.001), sETOH (p<0.001) and uETOH (p<0.001). uEtG was found to be the strongest predictor of alcohol consumption both at univariate and multivariate analysis (OR= 414.5; p<0.0001). At the multivariate analysis uEtG and AUDIT-c were found to be the only independent predictors of alcohol consumption.

uEtG showed a more accurate prediction rate of alcohol consumption when compared to CDT (AUROC=0.94 vs 0.63; p<0.001) and AUDIT-c (AUROC=0.94 vs 0.73; p<0.001). The combination of uEtG with AUDIT-c and CDT, showed a more accurate prediction rate of alcohol consumption when compared to the combination of CDT and AUDIT-c (AUROC= 0.98 vs 0.80; p<0.001).

**Conclusions:** uEtG represents a sensitive, specific and accurate marker of alcohol consumption in LTCs and LTRs, and improves detection of alcohol consumption when compared with other markers in these patients. Hence, it should be routinely used in the assessment of LTCs and LTRs.
Contrast enhanced ultrasound (CEUS) in the diagnosis and in the follow up of hepatocellular carcinoma

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Background: Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer and it is one of the most common tumors in the world (1). Early diagnosis of HCC is very important and it is based on the follow up every three months with liver ultrasound and alfetoprotein dosage of patients with cirrhosis. The diagnosis of HCC also uses imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), contrast-enhanced ultrasound (CEUS). CEUS in the early arterial phase shows the arterial blood vessels located in the peri- and/or intranodular area (2). For this reason the HCC after 15-30 seconds from the administration of contrast agent, in the arterial phase, becomes hyperechoic than the surrounding liver parenchyma. In the portal phase (50-80 seconds) and late phase (180-240 seconds), linked to the clearance of the contrast agent earlier from HCC compared with liver parenchyma, the nodule of HCC becomes iso-hyperechoic (3,4). The role of CEUS in the diagnosis of HCC is controversial: AASLD (2011) and EASL (2012) exclude a role for the diagnosis of nodule in patients with cirrhosis while AISF (2012) state a specific role for larger HCC (5).

Objective: To evaluate the accuracy of CEUS in the diagnosis of HCC in cirrhosis and of relapse or residual of HCC after treatment.

Patients and methods: The study was carried out by retrospective evaluation of 113 cirrhotic patients with hepatocellular carcinoma (median age 71yrs, 83M/30F, 86 HCV and 15 HBV cirrhosis) followed in the Clinica Medica “A. Murri” in the Policlinico Hospital of Bari. For each patient the diagnosis of HCC was confirmed by the execution of procedures for diagnostic imaging (CT, MRI, CEUS) and by liver biopsy with subsequent histological and cytological examination. 92 subjects underwent to treatment (6 surgery, 62 TACE, 98 RFA; 25 a combination of TACE and RFA, 14 sorafenib). The diagnosis of HCC on CEUS was confirmed on the typical pattern: sustained hyper enhancement in the arterial phase, loss of hyper enhancement in portal and delayed phases.

Results: 73 patients had both CEUS (n=73) and CT (n=71) or MRI (n=2) for the initial diagnosis of HCC, of which 23 with a nodule ≤20mm, 50 with a nodule >20mm; among treated patients, 28 presented a residual or a relapse of HCC and 34 a complete necrosis after treatment. Sensitivity, specificity, PPV, NPV of CEUS and TC/MRI in the initial diagnosis of HCC were: small HCC: 66,6 vs94, 100 vs100, 100 vs100, 33 vs75; larger HCC: 75 vs94, 100 vs100, 100 vs100, 28 vs60. In the diagnosis of residual or relapse of HCC and in that of complete necrosis, the concordance CEUS/TC or MRI was 94% and 89%, false negative CEUS were 3% and 11%, false negative TC/MRI were 3% and 0.

Conclusion: CEUS is a noninvasive examination of great utility in the diagnosis of HCC: in particular, it has a high sensitivity and positive predictive value that allow to make the diagnosis in a high percentage of cases even without using other imaging techniques or liver biopsy (6). Unfortunately CEUS has a low negative predictive value, which means that even if its results is negative, in patients with clinical suspicion of HCC, should be necessary to perform CT or MRI. Moreover, CEUS has a high diagnostic accuracy, low costs and absence of complications, therefore it may have a role in the initial diagnosis of large HCC and in the follow up of treated HCC nodules (7).

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Pro-oncogenic miRNA profile determined by SerpinB3

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miRNAs are small non-coding RNAs which target complementary miRNAs sequences, usually resulting in gene silencing. They can exhibit oncogenic or tumor suppressor properties, modulating cell homeostasis. Several data have documented that miRNAs are typically deregulated in different types of cancers, including hepatocellular carcinoma (HCC). Some of the miRNAs, such as miR-122, miR-221, miR-1 and miR-21 have been found to repress post-transcriptionally the expression of genes involved in cell cycle regulation, cell proliferation, apoptosis, cell migration and invasion. In HCC, serum levels of miR-122, miR-221 and miR-16 have been described deregulated, suggesting that they may be used as diagnostic biomarkers for early cancer detection. The ov-serpin SerpinB3, has been found previously increased in liver tumor cancers and associated with apoptosis resistance and increased cell proliferation and invasiveness, but to date no studies have been reported on its possible effects on miRNAs profile modulation. To address this point, an array study profile has been carried out in SerpinB3-transfected HepG2 cells and in HepG2 control cells. miRNAs were detected using the miFinder RT2 miRNA PCR Arrays (MAM-102ZD SABiosciences, MD) that contains the expression profile of the 88 most abundantly expressed and best characterized miRNA sequences.

Despite the great number of miRNA considered, only 8 miRNAs showed a significantly different expression (p<0.05) in SerpinB3 expressing cells, compared to controls and they included: miR-122, miR-125b, let-7f, miR-126-3p, miR-146b-5p, miR-100-5p, miR-143 and miR-215.

Our findings indicate that SerpinB3 induces a deregulation of several miRNAs involved in liver cancer and that the predominant effect consists in downregulation of tumor suppressor miRNAs. Only miR-143 was found overexpressed, with a fold change of 2.87, while the remaining 7 miRNAs were significantly downregulated. The behaviour of miR-143 has been found non-unique and while a protective effect has been described in non hepatic tumors, in HCC a pro-metastatic activity ultimately prevails. The overall effect determined by SerpinB3 in primary liver cancer is an increased oncopogenic potential derived by miRNAs profile modulation. This biological mechanism, in addition to the anti-apoptotic properties and increased invasive potential induced by this serpin, enhance and strengthen the malignant milieu determined by SerpinB3 through multi-strategic and multi-dimensional ways.

Treatment of hepatocellular carcinoma complicating liver cirrhosis in aged patients

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Background: Increased life expectation due to the overall improvement in clinical management of liver cirrhosis (LC) is significantly increasing the proportion of aged patients (≥ 70 years) with hepatocellular carcinoma (HCC) in western countries. Nevertheless, poor attention is still paid to the clinical man-
agreement of HCC in elderly patients and age is often considered as a limiting factor for main curative approaches for HCC. Aim of our study was to assess the efficacy of different treatment approaches in young and aged patients with HCC complicating liver cirrhosis and to evaluate possible differences in terms of prognostic factors between the two groups of patients.

Materials and Methods: We retrospectively studied 664 (150 female) [n= 235 (80 f) ≥ 70 years old (elderly group) and 429 (70 f) ≤ 69 years old (control group)] patients affected by HCC complicating LC. All patients were enrolled in our centre from Jan 1998 to Dec 2011 and assessed for demographical, etiological, biochemical (liver function and BCLC stage at HCC diagnosis,), clinical (comorbidity, time and kind of treatment for HCC), imaging and survival data.

Results: The table summarizes the main demographic and clinical characteristics of the two groups of patients

<table>
<thead>
<tr>
<th></th>
<th>ELDERLY GROUP (≥ 70y) (n=235)</th>
<th>CONTROL GROUP (≤69y) (n=429)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males, n(%)</td>
<td>155 (65.9%)</td>
<td>359 (83.6%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Etiology:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV/HBV/HCV+HBV/Cryptogenic/Alcohol/Other, n</td>
<td>159/21/12/22/18/3</td>
<td>254/66/46/30/32/1</td>
<td>.007</td>
</tr>
<tr>
<td>Comorbidities (yes/no), n</td>
<td>140/95</td>
<td>95/334</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Performance status** (0-1/2), n</td>
<td>164/71</td>
<td>297/132</td>
<td>0.951</td>
</tr>
<tr>
<td>Child Turcotte-Pugh (CTP) score, mean ± SD</td>
<td>56 (±2.0)</td>
<td>35 (±1.6)</td>
<td>.142</td>
</tr>
<tr>
<td>Diagnosis through screening schedule n (%)</td>
<td>117/79/39</td>
<td>205/149/75</td>
<td>.881*</td>
</tr>
<tr>
<td>Hepatic lesions: Single/ Multiple, n</td>
<td>80/159</td>
<td>159/270</td>
<td>.391</td>
</tr>
<tr>
<td>Stage(BCLC) A/B/C/D, n</td>
<td>30/63/107/35</td>
<td>72/131/169/66</td>
<td>.134</td>
</tr>
<tr>
<td>Extrahepatic metastases, n (%)</td>
<td>10 (4.3%)</td>
<td>28 (6.5%)</td>
<td>.377</td>
</tr>
<tr>
<td>Treated (all treatments), (%)</td>
<td>130 (55.3%)</td>
<td>312 (72.2%)</td>
<td>.000</td>
</tr>
<tr>
<td>Curative approach n (%)</td>
<td>70 (53.8%)</td>
<td>151 (48.4%)</td>
<td>.347</td>
</tr>
<tr>
<td>Not curative approach, n (%)</td>
<td>128/36/22</td>
<td>44/136/32</td>
<td>.021</td>
</tr>
<tr>
<td>TACE/Other, n</td>
<td>60 (46.2%)</td>
<td>161 (51.6%)</td>
<td>.615</td>
</tr>
<tr>
<td>56/4</td>
<td>143/18</td>
<td>.331</td>
<td></td>
</tr>
<tr>
<td>Treatment at Recurrence (all treatment), n(%)</td>
<td>74 (88.1%)</td>
<td>162 (79.8%)</td>
<td>.063</td>
</tr>
<tr>
<td>Resection/OLT/PEI/RFA/TACE+RFA/TACE/Other, n</td>
<td>00/20/21/0/30/03</td>
<td>25/35/36/70/14</td>
<td>.061</td>
</tr>
</tbody>
</table>

No significant differences were found in the overall survival rates between the groups (Chi-square= .774 HR= 0.898 95% CI 0.57-1.34, p= 0.398).

Background and aims: Nonalcoholic Fatty Liver Disease (NAFLD) has becoming the most common form of chronic liver disease worldwide. It is often recognized as a pathological condition that from simple steatosis can progress to Nonalcoholic Steatohepatitis (NASH) associated with inflammation, fibrosis, cirrhosis and eventually may lead to hepatocarcinoma (HCC). Since NAFLD shares key features of the Metabolic Syndrome (MS), such as obesity and insulin resistance, it is considered the hepatic manifestation of the MS, one of the main cardiovascular disease (CVD) risk. This association is proved from several literature evidences. Thus, we focused our attention on the possible relationship between liver and heart in order to understand if a suffering liver could be used as a warning signal of cardiovascular risk.

Methods: Our study was performed both in a mouse model of liver steatosis, obtained feeding the animals with a High Fat Diet (HFD) for 3, 6 and 12 months, and in Peripheral Blood Mononuclear Cells (PBMCs) from NAFLD patients. By qRT-PCR and western blot we analyzed a panel of genes and proteins potentially involved in lipid metabolism and CVD both in mice and patients.

Results: Our results showed a time scale in metabolism between mice livers and hearts. The up-regulation of 66 genes related to lipid metabolism which were found in mice livers immediately after 3 months of diet, was later shown in their hearts (after 12 months of HFD). Moreover, we appreciated that in PBMCs from NAFLD patients we found a similar genes modulation to that we observed in mice livers after 3 months of diet. Our attention was focused on early hepatic up-regulation of two genes: Krüppel-like Factor 15 (KLF15) and Tafazzin (TAZ), known to be related markers of cardiovascular risk during liver steatosis.

Conclusions: We addressed our work in understanding if cardiovascular
damage may be evaluated by the study of liver damage. Our data indicate a possible strict correlation between liver and cardiovascular system. Thus, liver seems to be the “primum movens” of the sequel of pathological events related to MS. Furthermore, we appreciated a similar modulation of gene expression profiles both in mice livers and PBMCs from NAFLD patients. Thus, our study sheds a glimmer of light in clarifying the temporal correlation linking NAFLD and cardiovascular risk and it extends to the possibility to evaluate cardiovascular risk by analyzing liver, which is an organ surely more accessible than heart.

**Cardiovascular Diseases**

**Endothelial progenitor cells, renal function and vascular damage**

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**Introduction:** Chronic kidney disease (CKD) is one of the most important risk factors for the development of cardiovascular disease (CVDs). This association is mainly due to the coexistence of cardiovascular risk factors, such as hypertension, dyslipidemia, diabetes, obesity and smoking. The endothelial progenitor cells (EPCs) are produced by the bone marrow in response to different exogenous and endogenous factors. The presence of a high cardiovascular risk profile is associated with a reduction of number and function of EPCs.

**Aim:** We evaluate the association between subclinical vascular damage, kidney dysfunction and levels of endothelial progenitor cells (EPCs) in a group of uncomplicated and untreated hypertensive patients. In particular, we tested the hypothesis that low levels of EPCs are associated with an early deterioration of renal function, that is the consequence of endothelial dysfunction and systemic vascular organ damage.

**Methods:** We enrolled 60 Caucasian (33 men and 27 women), age 46.3±13.5 years. Glomerular filtration rate (GFR) was calculated by CKD-epi formula. The pool of circulating EPCs was determined by flow cytometry analysis of the following specific surface antigens: CD34, CD133, VEGFR2 (KDR). Insulin-resistance was calculated by HOMA-index. The presence of EPCs, which explained 38.4% of its variation (P <0.0001), TNF-α and IL-6, which in turn respectively explained a further 14.3% (P <0.0001) and 3.9% (P = 0.028) of the variation of RHI.

**Results:** In the present study we demonstrated in a group of newly diagnosed hypertensive patients, at low cardiovascular risk, that there is a close relation between the level of circulating EPCs, vascular damage and renal function. In particular, the subjects with lower values of GFR have low levels of EPCs. The reduction of EPCs, in turn, is associated with endothelial dysfunction and subclinical organ damage. Therefore the levels of EPCs represent a reliable marker of endothelial and kidney dysfunction. Their dosage could represent an early marker of endothelial dysfunction, even if other studies are still necessary to clarify their possible application in the treatment.

**Cardiac AL and ATTR amyloidosis: a superimposable ECG and echocardiographic presentation?**

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**Purpose:** In light chain (AL) and hereditary transthyretin-related (m-ATTR) amyloidosis the prognostic outcome is strongly influenced by cardiac
involvement. However, the natural history is quite different. We have performed a detailed comparison between AL and m-ATTR of all ECG-derived variables at the time of diagnosis.

**Methods:** We enrolled 160 consecutive, never-treated patients affected by cardiac AL and 57 patients with cardiac m-ATTR. All patients underwent standard 12-lead ECG and trans-thoracic echocardiography at the time of first diagnosis. In all patients PQ, QRS, QT and QT corrected intervals were measured. The prevalence of intra-ventricular (defined as left bundle branch block, complete and incomplete right bundle branch block, left anterior hemiblock) conduction delays, fragmented QRS (fQRS) and low QRS voltages was assessed. Conduction delays were considered as a consequence of the intramyocardial amyloid deposition. fQRS and pseudonecrosis were considered expression of reactive fibrosis area.

The presence of strain-like repolarization and fQRS was considered due to direct amyloid fibrils toxicity. QRS score was obtained as the sum of the Q, R and S wave amplitude in all leads. LV mass index was considered as an indirect measure of cardiac amyloid deposition. Serum levels of brain natriuretic peptide (BNP), N-terminal BNP pro-hormon (NT-proBNP) and cardiac troponin I (cTnI) were measured. We also confronted two sub-populations of patients, matching AL and m-ATTR patients by LVMI values.

**Results:** Despite higher LV mass index, m-ATTR is characterized by a lower prevalence of low-voltage pattern, fQRS and strain-like repolarization abnormalities, and by longer PQ and QRS and shorter QTc intervals (Table; mean values±standard deviation or median (range 25%-75%)). These data were confirmed when performing the same analysis on the LVMI-matched sub-populations.

**Conclusions:** Despite a higher amyloid “load”/deposition, m-ATTR is characterised not only by higher QRS voltages, but also by a lower prevalence of repolarization abnormalities and fQRS. Moreover, in m-ATTR there is an higher prevalence of conduction delays. Since AL amyloidosis is also characterised by higher serum levels of biochemical markers of cardiac damage and by a worse prognosis, this ECG presentation may suggest a different physiopathology of fibril-related myocardial damage. The latter appears mainly due to amyloid deposition per se in m-ATTR, and more related to a “toxic” mechanism in AL amyloidosis.

**Effects of essential aminoacid oral supplementation on metabolic parameters during OGTT**

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**Introduction:** Recent findings showed a potential role of the essential amino-acids (EAAs) in improving skeletal and cardiac muscle function, both in animal models and in patients with heart failure, sarcopenia and other chronic diseases. Moreover there are some evidences demonstrating that EAAs have a positive effect on metabolic profile in patients with type 2 diabetes (T2D). In particular, EAAs oral supplementation is able to improve the glycemic control in patients with uncontrolled Hb1Ac on the top of therapy. Recently, many evidences suggest that 1-h post-load plasma glucose ≥155 mg/dl is able to identify normoglucose tolerant (NGT) subjects at high risk for T2D development and subclinical organ damage.

**Aim:** To test the effects of EAA oral supplementation on glucose and insulin profile in NGT subjects.

**Methods:** We enrolled 15 NGT patients identified by OGTT and repeated after 8 weeks of oral supplementation with 4 grams/day of EAsAs compound obtained by a mixture of preconceived essential AA (Aminotrofic). During the OGTT, blood samples were collected for the evaluation of insulin and plasma glucose. Insulin sensitivity was assessed by the Matsuda index [insulin sensitivity index (ISI)]. Metabolic effects of EAAs were evaluated measuring the Area Under Curve (AUC) of plasma glucose and insulin.

We estimate statistical significance by paired t-test; values P <0.05 were considered significant.

**Results:** Of 15 enrolled patients, aged 40-70 years (55.7±10.4), 9 were NGT≥155 and 6 were NGT<155. EAAs supplementation was able to significantly reduce both glucose profile and insulin response during OGTT, as demonstrated by the comparison of AUCs (AUC-gluc 1113.2 vs 146.5 P=0.006; AUC-ins 73.9 vs 113.7 P=0.005). These effects resulted in an increase of insulin sensitivity (Matsuda index 10.8 vs 5.9 P=0.04).

**Conclusions:** These results demonstrate a positive effect of EAAs oral supplementation in improving the metabolic profile of NGT≥155 subjects that are at high risk for T2D development and subclinical organ damage. Finally, it is possible to hypothesize that EAAs may be a possible therapeutic strategy to reduce the cardio-metabolic risk profile.

**Traditional and emerging risk factors for asymptomatic ventricular arrhythmias: prospective observational study in an unselected cohort**


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**Aim:** To evaluate relationships between asymptomatic ventricular arrhythmias, cardiac remodelling and heart rate variability (HRV).

**Materials and Methods:** Among 664 consecutive patients undergoing 24-hr ECG recordings in a period of 24 months, 326 patients (154 M; 172 F), aged 76±11 (14-96) years, participated in the study because showed hyper- and/or hyperkinetic arrhythmias. In all patients a M-2D echocardiography for evaluation of ejection fraction (EF), relative wall thickness (RWT), left ventricular volume (LVV), left ventricular mass indiciied for body mass index (LVMI) and a fasting blood sampling were carried out. Serum total, LDL e HDL Cholesterol, Triglycerides, B-tipe Natriuretic Peptide (BNP), calcium, sodium, potassium, FT3, FT4, TSH, Hb. Estimated glomerular filtration rate (eGFR) was calculated by CKD-EPI formula. Ventricular arrhythmias were classified according to Lown. HRV was derived from standard deviation of normal RR intervals.

**Results:** 66% of patients was on anti-hypertensive and 37% on anti-arrhythmic therapy. Major findings are as follows: 1) an inverse association (P=0.0001) between Lown class and concentric remodelling; 2) a direct association (P=0.001) between Lown class and eccentric hypertrophy. Independent predictors of Lown class were LVMI (P=0.002), total cholesterol (P=0.005), LDL cholesterol (P=0.002), smoking (P=0.041), age and EF (P=0.045). Independent traditional predictors of HRV were diabetes and age (P=0.01), while emerging predictors were RWT (P=0.02) and EF (P=0.03).

**Conclusions:** 1) concentric remodelling is an early predictor of asymptomatic ventricular arrhythmias and HRV; 2) LVMI is more powerful than EF to predict asymptomatic ventricular arrhythmias; 3) EF is a direct predictor of HRV; 4) diabetes is the most powerful inverse predictor of HRV.
Splenic artery aneurysm in a patient repeatedly treated, surgically and percutaneously, for renal artery stenosis due to fibromuscular dysplasia. The importance of long-term follow-up


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Introduction: Ifibromuscular dysplasia (FMD) is a non-inflammatory, non-atherosclerotic condition affecting medium size arteries and that may result in stenosis, occlusion, aneurysm, dissection. Renal, carotid and vertebral arteries are most commonly involved. Arterial hypertension occur in most of the patients with renal artery stenosis caused by FMD and resistant hypertension in 16% of them, mainly for activation of the renin-angiotensin-aldosterone system. However, the natural history of FMD remains poorly defined. Here we report the 28-year follow-up of a female patient initially presenting with isolate unilateral renal FMD and severe hypertension.

Case report: In 1985 a 26 years old woman was diagnosed with severe arterial hypertension due to right renal artery stenosis, that was successfully treated with aorto-renal by-pass with autologous saphenous graft. The post-operative histological examination revealed FMD with subadventitial fibrosis. In 1993 she underwent percutaneous angioplasty (PTA) at the origin of the right renal artery, while it showed a stenosis at the insertion of the venous graft on the renal artery. The abdominal CT did not confirm with certainty the intrastent stenosis of the left renal artery. Subsequently, the serum marker of myocardial necrosis resulted persistently negative. During the hospital stay, hypertensive retinopathy grade 3 and significant concentric left ventricular hypertrophy with severe diastolic dysfunction was evidenced. In 2000 she presented again with elevation of blood pressure levels not withstanding the progressive increase in doses and numbers of antihypertensive drugs (combination of nifedipine slow release 60 mg o.d., captopril 50 mg t.i.d., amiloride/hydrochlorothiazide 5/50 mg o.d.). In this occasion critical stenosis of the left renal artery was diagnosed, that was successfully managed with PTA and stenting.

In October 2012, a Doppler ultrasound performed during the follow-up suggested an intrastent stenosis of the left renal artery. Subsequently, the CT-angiography did not confirm with certainty the intrastent stenosis of the left renal artery, while it showed a stenosis at the insertion of the venous graft on the right renal artery, with pre- and post-stenotic aneurismatic dilation. Incidentally, also an aneurism of a branch of the splenic artery was found. At the conventional catheter angiography, the intrastent stenosis of the left renal artery was not confirmed, and, moreover, due to the angiographic characteristics of the right renal artery stenosis, with a moderate systolic pressure gradient, a conservative management was chosen (without further local percutaneous intervention). Instead, the aneurysm of the branch of the splenic artery was treated with endovascular coils embolization.

5 months after this procedure, the patient was well and blood pressure was in good control with nifedipine slow release 30 mg o.d. and atenolol 100 mg o.d.

Conclusions: The case presented confirms that FMD can have various manifestations (either stenosis or aneurysm) and that lesions at different vascular sites can develop in the same patient over time, underscoring the importance of careful long-term follow-up. Moreover, this case witnesses the progress of the techniques to manage the vascular manifestations of FMD.

Adrenal hyperplasia in an obese patient with resistant hypertension and obstructive sleep apnea: cause, consequence or coincidence?


Adrenal hyperplasia in obese patients with obstructive sleep apnea is currently under investigation, and they might represent a confounding element for the diagnosis of Cushing’s disease, especially in its subclinical form. Moreover, these patients may present with elevated catecholamine levels in the absence of a pheochromocytoma or paraganglioma, as described by very few case reports in literature.

In our case, we might speculate a causal-effect relationship between obstructive sleep apnea and neuroendocrinal alterations as well as between obstructive sleep apnea and bilateral renal hyperplasia. Further studies are needed to explore these possible associations.

Introduction: The diagnostic work-up for resistant arterial hypertension can sometimes be difficult. Obstructive sleep apnea is increasingly being recognized an important cause of resistant arterial hypertension. Notwithstanding the pathogenesis of arterial hypertension in patients with obstructive sleep apnea is being progressively clarified, the precise neuroendocrinal alterations of obstructive sleep apnea are still under investigation.

Here we describe the case of resistant hypertension and obstructive sleep apnea syndrome, presenting with subtle endocrinological alterations and adrenal hyperplasia.

Case report: A 70-years-old obese woman came to the Emergency Room for hypertensive acute pulmonary edema (at presentation arterial pressure 260/120 mmHg, heart rate 93 beats per minute, respiratory rate 36/minute, peripheral oxygen saturation 90% while breathing room air). Her past medical history included arterial hypertension of long duration, dyslipidemia and type 2 diabetes mellitus. Her usual drug therapy consisted of lansoprazole 15 mg o.d., doxazosin 2 mg o.d., hydrochlorothiazide 25 mg o.d., lercanidipine 20 mg o.d., transdermal clonidine 5 mg weekly, atorvastatin 20 mg o.d., metformine 850 mg o.d., insulin aspart 10+15+15 UI, insulin glargine 30 UI o.d.

After initial stabilization with pharmacological therapy (intravenous morphine, nitrate and furosemide, oral captopril) and oxygen, the patient was admitted to the Department of Internal Medicine. The serum markers of myocardial necrosis resulted persistently negative.

During the hospital stay, hypertensive retinopathy grade 3 and significant concentric left ventricular hypertrophy with severe diastolic dysfunction were found. A diagnostic work-up to investigate possible causes of secondary arterial hypertension was then performed.

At the laboratory examinations serum cortisol (7.00 A.M.) resulted 22.0 and 29.2 µg/dL (n.v. 6.2-19.4) in two subsequent determinations; correspondingly, ACTH was 16 and 11 pg/mL (n.v. 9-52). Urinary cortisol resulted within normal limits. The serum cortisol after the Nugent’s test was 3.6 µg/dL (being the normal values with greater sensitivity 1.8 µg/dL and those with greater specificity < 5 µg/dL).

Serum renin and aldosterone resulted depressed, being renin 0.8 and 1.2 µU/mL (n.v. 2.8-39.9) and aldosterone 1.6 and 3.3 ng/dL (n.v. 2-15) in two occasions.

Urinary epinephrine, norepinephrine and metanephrine resulted within normal limits, but normetanephrine resulted 545 µg/24h (n.v. 105-354). The abdominal CT demonstrated bilateral adrenal hyperplasia, especially of the left gland.

A cardiorespiratory sleep study performed after satisfactory cardiorespiratory stabilization revealed obstructive sleep apnea of moderate degree (AHl 19.8/hour, ODI 22.8/hour, mean oxygen saturation 90%, nadir oxygen saturation 58%).

Conclusions: The case presented underlines the difficulties to interpret the results of the examinations aiming to determine secondary causes of resistant arterial hypertension. The possible alterations of the adrenal axis in obese patients with obstructive sleep apnea are currently under investigation, and they might represent a confounding element for the diagnosis of Cushing’s disease, especially in its subclinical form. Moreover, these patients may present with elevated catecholamine levels in the absence of a pheochromocytoma or paraganglioma, as described by very few case reports in literature.

In our case, we might speculate a causal-effect relationship between obstructive sleep apnea and neuroendocrinal alterations as well as between obstructive sleep apnea and bilateral renal hyperplasia. Further studies are needed to explore these possible associations.
Cardiovascular risk factors in young patients with ischaemic stroke: a prevalence study

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Background and purpose: Stroke occurs in about 10% of patients <50 years of age and is an important cause of disability in young subjects. [1] This retrospective study aimed to describe the prevalence of traditional cardiovascular risk factors in a sample of young patients with ischaemic stroke, in a hospital-based population.

Materials and methods: The medical records of 124 consecutive patients aged 19-54, admitted to the Neurology Unit of the University Hospital of Ferrara between 2009-2012, and discharged with diagnosis of documented acute ischaemic stroke were analyzed. Cardiac imaging (ECG, transthoracic echocardiography), carotid ultrasound, laboratory tests (lipidic profile, glucose, coagulative tests, homocysteine, autoimmune sierology) and transcranial duplex ultrasound were performed in all patients. A positive history of migraine, contraceptive treatment, and drugs abuse was investigated.

Hypertension was defined as a blood pressure >140/90 mmHg; hypercholesterolemia was defined as total cholesterol levels >200 mg/dl. We classified stroke subtypes according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST). [2]

Results: The mean age of the study population was 44 years, and 54% were males. The most frequent etiology was cardioembolic (28%), followed by large artery atherosclerosis (17%) and small vessels disease (17%). Stroke of undetermined etiology accounted for 36% of cases. The commonest cardiovascular risk factor were hypercholesterolemia (57%), smoking (54%), and hypertension (38%); 52% of patients presented at least two of these risk factors, while only 17% had no one of these. As expected, hypertension was associated with small vessels disease stroke subtype; indeed, 82% of patients with this condition presented hypertension (p<0.001). No significant associations between other cardiovascular risk factors and stroke subtypes were found.

Conclusions: Our data are on line with most of international results about the prevalence of ischaemic stroke subtypes [3] and cardiovascular risk factors [4]. We conclude that hypercholesterolemia, hypertension and smoking are the most important risk factors among young patients with ischaemic stroke, but only hypertension is significantly associated with a peculiar stroke subtype.

References:

Correlation BNP-Miller score, “BRILLS” study: comparative analysis with student tests for continuous variables in 30 patients with venous thrombosis.

Three year experience (2010 - 2012)


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Introduction: The “BRILLS” study, acronym resulting from “Brain natriuretic peptide – Miller Score”, enrolled 30 patients with venous thromboembolism (central pulmonary embolism) between the ages of 48 and 82, which were hospitalised in the “Short-stay Observation” and “Sub-Intensive C” Simple Structure of the “Internal Medicine for Urgency” Complex Structure during a three year period from January 2010 to December 2012. In all patients, the pre and post-lysis of the Miller Score was measured and the pre-lysis BNP was dosed (VN=0-100 pg/ml). A comparative analysis based on continuous variables with Student’s “t” parametric test was carried out to verify if there was a significant relation between the pre-lysis BNP and Miller Score.

Purpose of the study: The “BRILLS” study has the following objectives: check for any relations existing between the pre-lysis BNP values and the pre-lysis Miller Score in the 30 patients enrolled in the “BRILLS” study during the three year period between January 2010 and December 2012; check for the statistical significance observed by applying Student’s “t” parametric test as the comparative analysis test to establish if the relationship of the variables in question are due to chance.

Materials and procedure: The pre-lysis BNP values and the pre-lysis Miller Score values in the 30 enrolled patients were compared. Thus, the test calculates the relative value (VR) of the t index to be associated to the difference detected according to the following formula: t = (M1-M2) / \sqrt{DS_1^2/N_1 + DS_2^2/N_2}.

Analysis of the results: Student’s “t” test applied to the 30 patients shows a highly significant correlation (p<0.001) of the two variables examined (pre-lysis BNP values and Miller Score) and, thus, not attributable to chance. In fact, the “t” value obtained is 7.86 and the VC (critical value) of “t” for p<0.001 is 3.659 with GL=29.

Discussion: The heart secretes natriuretic peptides as a homeostatic signal in order to maintain pressure stability and volume, and prevent excessive retention of salt and water. The Atrial natriuretic peptide (ANP) was the first to be identified at the atrial myocardium level in rats. Subsequently, the BNP (Brain Natriuretic Peptide) was identified at the brain level in pigs. The natriuretic peptides carry out different actions: 1) they modulate the sympathetic nervous system and the renin-angiotensin-aldosterone downwards; 2) they facilitate natriuresis and diuresis through afferent and efferent hemodynamic mechanisms in the kidney and distal tubules; 3) they reduce the peripheral vascular resistance; 4) they facilitate smooth muscle relaxation. Moreover, the natriuretic peptides can inhibit cardiac hypertrophy, contrasting mitogenesis responsible for ventricular remodelling. The BNP is secreted predominantly by the cardiac ventricles, in response to an increase in the stretching or the wall tension of the left ventricle. The peptide may constitute a kind of “spare” hormone that is activated only after a prolonged period of overload. The cardiac myocytes secrete pro-BNP, a precursor of BNP composed of 108 amino acids. After having been secreted into the ventricles, the pro-BNP is transformed into a biologically active C-terminal portion and a biologically inactive N-terminal portion (NT-proBNP). The data obtained suggest that the co-variation of the pre-lysis BNP values and pre-lysis RV diameter in the 30 patients enrolled in the “PRIME” study expresses a highly significant difference of which the clinical significance resides in the marked dilatation of the right cardiac sections, in the presence high pressure attributable to the pulmonary embolism, resulting in the release, by stretched myocytes, of high amounts of BNP.

Conclusions: The “BRILLS” study showed how, in the group of 30 patients with venous thromboembolism (central pulmonary embolism), there is a highly significant correlation between the two variables in question: pre-lysis BNP and pre-lysis Miller Score. This correlation shows an absolute positive concordance according to Student’s comparative analysis.


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Introduction: The “BRINDEX” study, acronym resulting from “Brain natriuretic peptide – pulmonoNary embolism inDEX”, enrolled 30 patients with venous thromboembolism (central pulmonary embolism) between the ages of 48 and 82, which were hospitalised in the “Short-stay Observation” and “Sub-Intensive C” Simple Structure of the “Internal Medicine for Urgency” Complex Structure during a three year period from January 2010 to December 2012. In all patients, the pre-lysis Pulmonary Embolism Index (PEI) tomographic index was measured and the pre-lysis BNP was dosed (VN=0-100 pg/ml). A comparative analysis based on continuous variables with Student’s “t” parametric test was carried out to verify if there is a significant relation between the pre-lysis BNP values and the pre-lysis PEI values.

Purpose of the study: The “BRINDEX” study has the following objectives: check for any relations existing between the pre-lysis BNP values and the pre-lysis PEI in the 30 patients enrolled in the “BRINDEX” study during the period going from January 2010 to December 2012; check the statistical significance by applying Student’s “t” parametric test as the benchmarking test for continuous variables to determine whether the relationships of the variables considered are due to chance.

Materials and procedure: The pre-lysis BNP values were compared with the pre-lysis PEI values in the 30 enrolled patients. Therefore, the test calculates the relative value (VR) of the “t” index to be associated to the differences detected according to the following formula: t = (M1-M2)/√DS1²/N1 + DS2²/N2.

Analysis of the results: Student’s “t” test applied to the 30 patients shows a highly significant correlation (p<0.001) of the two variables in question (pre-lysis BNP and PEI values) and, thus, is not attributable to chance. In fact, the “t” value obtained is 8.04 and the VC (critical value) of “t” for p=0.001 is 3.659 with GL=29.

Discussion: The heart secretes natriuretic peptides as a homeostatic signal in order to maintain pressure stability and volume, and prevent excessive retention of salt and water. The Atrial natriuretic peptide (ANP) was the first to be identified at the atrial myocardium level in rats. Subsequently, the BNP (Brain Natriuretic Peptide) is identified at the brain level in pigs. The natriuretic peptides carry out different actions: 1) they modulate the sympathetic nervous system and the renin-angiotensin-aldosterone downswards; 2) they facilitate natriuresis and diuresis through afferent and efferent hemodynamic mechanisms in the kidney and distal tubules; 3) they reduce the peripheral vascular resistance; 4) they facilitate smooth muscle relaxation. Moreover, the natriuretic peptides can inhibit cardiac hypertrophy, contrasting mitogenesis responsible for ventricular remodelling. The BNP is secreted predominantly by the cardiac ventricles, in response to an increase in the stretching or the wall tension of the left ventricle. The peptide may constitute a kind of “spare” hormone that is activated only after a prolonged period of overload. The cardiac myocytes secrete pro-BNP, a precursor of BNP composed of 108 amino acids. After having been secreted into the ventricles, the pro-BNP is transformed into a biologically active C-terminal portion and a biologically inactive N-terminal portion (NT-proBNP). The data obtained suggest that the co-variation of the pre-lysis BNP values and the pre-lysis PEI in the 30 patients enrolled in the “BRINDEX” study expresses a highly significant difference of which the clinical significance resides in the marked dilatation of the right cardiac sections, in the presence of high pressure regimes attributable to pulmonary embolism, calculated using the PEI Index, and resulting in the release, by stretched myocytes, of high amounts of BNP.

Conclusions: The “BRINDEX” study showed how, in the group of 30 patients with venous thromboembolism (central pulmonary embolism), there is a highly significant correlation between the two variables in question: pre-lysis BNP and pre-lysis PEI. This correlation shows an absolute positive concordance according to Student’s comparative analysis “t” test and is an expression, not of casual association, of a strong correlation between the pre-lysis BNP values and pre-lysis PEI values in the 30 patients with central pulmonary embolism.


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Introduction: The “BINDEX” study, acronym resulting from “Brain natriuretic peptide – pulmoNary embolism severity inDEX”, enrolled 30 patients with venous thromboembolism (central pulmonary embolism) between the ages of 48 and 82, which were hospitalised in the “Short-stay Observation” and “Sub-Intensive C” Simple Structure of the “Internal Medicine for Urgency” Complex Structure during a three year period from January 2010 to December 2012. In all patients, the pre-lysis Pulmonary Embolism Severity Index (PESI) was measured and the pre-lysis BNP was dosed (VN=0-100 pg/ml). A comparative analysis based on continuous variables with Student’s “t” parametric test was carried out to verify if there is a significant relation between the pre-lysis BNP values and the pre-lysis PEI values.

Purpose of the study: The “BINDEX” study has the following objectives: check for any relations existing between the pre-lysis BNP values and the pre-lysis PESI values in the 30 enrolled patients. Therefore, the test calculates the relative value (VR) of the “t” index to be associated to the differences detected according to the following formula: t = (M1-M2)/√DS1²/N1 + DS2²/N2.

Analysis of the results: Student’s “t” test applied to the 30 patients shows a highly significant correlation (p<0.001) of the two variables in question (pre-lysis BNP and PEI values) and, thus, is not attributable to chance. In fact, the “t” value obtained is 5.58 and the VC (critical value) of “t” for p=0.001 is 3.659 with GL=29.

Discussion: The heart secretes natriuretic peptides as a homeostatic signal in order to maintain pressure stability and volume, and prevent excessive retention of salt and water. The Atrial natriuretic peptide (ANP) was the first
to be identified at the atrial myocardium level in rats. Subsequently, the BNP (Brain Natriuretic Peptide) was identified at the brain level in pigs. The natriuretic peptides carry out different actions: 1) they modulate the sympathetic nervous system and the renin-angiotensin-aldosterone downwards; 2) they facilitate natriuresis and diuresis through afferent and efferent hemodynamic mechanisms in the kidney and distal tubules; 3) they reduce the peripheral vascular resistance; 4) they facilitate smooth muscle relaxation. Moreover, the natriuretic peptides can inhibit cardiac hypertrophy, contrasting mitogenesis responsible for ventricular remodelling. The BNP is secreted predominantly by the cardiac ventricles, in response to an increase in the stretching or the wall tension of the left ventricle. The peptide may constitute a kind of “spare” hormone that is activated only after a prolonged period of overload. The cardiac myocytes secrete pro-BNP, a precursor of BNP composed of 108 amino acids. After having been secreted into the ventricles, the pro-BNP is transformed into a biologically active C-terminal portion and a biologically inactive N-terminal portion (NT-proBNP). The data obtained suggest that the co-variation of the pre-lysis BNP values and the pre-lysis PESI in the 30 patients enrolled in the “BINDEX” study expresses a highly significant difference of which the clinical significance resides in the marked dilatation of the right cardiac sections, in the presence of high pressure regimes attributable to pulmonary embolism, calculated using the PEI Index, and resulting in the release, by stretched myocytes, of high amounts of BNP.

Conclusions: The “BINDEX” study shows how, in the group of 30 patients with venous thromboembolism (central pulmonary embolism), there is a highly significant correlation between the two variables in question: pre-lysis BNP and pre-lysis PESI. This correlation shows an absolute positive concordance according to Student’s comparative analysis “t” test and is an expression, not of casual association, of a strong correlation between the pre-lysis BNP values and the pre-lysis PESI values in the 30 patients with central pulmonary embolism.

Subclavian steal syndrome: case report


Introduction: We describe the case of a 67-year-old man who was referred to us for a presyncopal episode after effort with the left upper limb (lifting a weight) and paresthesia that configured a clinical picture of subclavian steal syndrome.

Case report: On physical examination, a coarse murmure was detected at the base of the neck. The skin temperature of the upper left limb was maintained. The patient was afebrile. The right PAO was 140/90 mmHg, the left PAO was 110/50 mmHg, the heart rate was 80 bpm and rhythmic. The following was carried out during hospitalisation: repeated ECG showing sinus rhythm; blood tests that were within the limits; markers for primary and secondary thrombophilia: within limits; chest x-ray: absence of ongoing pleural parenchymal alterations; TT echocardiogram: normal kinesis, (FE 60%), right sections within limits, absence of pericardial effusion; venous doppler ultrasound on upper and lower limbs: patency of the superficial and deep venous axes; arterial doppler ultrasound of the lower limbs: flussimetric control was within the limits; Doppler ultrasound of the supra-aortic vessels: inversion of the flow of the left vertebral with occlusion of the prevertebral left subclavian artery; cranian ct scan: absence of tomodensitometric alternations in the acute phase; angio MRI of the left upper limb: arteries correctly viewed; angio MRI of the aortic trunk and supra-aortic vessels: evidence of subclavian steal. The patient is treated with PTA and stent implantation on the left subclavian artery as demonstrated by the angiographic check of the supra-aortic vessels performed after the procedure. The patient was treated with LMWH and clopidogrel for 1 month, salicylates and clopidogrel for 1 year, and salicylates for life. A check with arterial Doppler ultrasound of the supra-aortic vessels was carried out under protected discharge after approximately 20 days, which showed correct positioning of the stent and flussimetric control on the subclavian artery in the limits without inversion onto the left vertebral artery. After discharge, the patient no longer had paresthesias of the upper limb and no longer had pre-syncopes after effort of the upper left limb.

Discussion: The subclavian steal syndrome is a particular hemodynamic situation in which there is a, not uncommon, epiaortic circulation of a pre vertebral subclavian artery. The cause is usually atherosclerosis. The connecting circulation between the large supra-aortic vessels (subclavian, vertebral, external and internal carotid arteries) is abundantly represented; for example, cases of occlusion of the common carotid artery with circulation of the internal and external in an inverted direction are frequently found: this is partly due to the communication between two communicating anterior and partly due to the interpolation anastomosis between the carotid arteries. However, the most important thing is that the afferent anterior cerebral circulation (carotid arteries) communicates with the posterior circulation through the circle of Willis. In this condition, the presence of subclavian stenosis, placed between its origin and the origin of the vertebral, involves not only the drop in pressure in the same subclavian, but also in the vertebral from which it originated. Since the blood stream flows by pressure gradients, at the circle, in particular at the basilar, the flow inverts and moves back towards the vertebral at low pressure, and, from here, to the next section beyond the stenosis. This creates a circuit for which the subclavian “steals” the blood from the ipsilateral vertebral and the circle of Willis. The debit of the robbed subclavian is paid by the anterior circulation and the contralateral vertebral. It seems pretty obvious that the symptoms relating to this theft can be triggered by a muscular effort of the limb affected by the stenosis (this results in a greater volume of theft to overcome the hyperaemic efforts of the subclavian that must supply the arm muscles) and that this will be characteristic of the area predominantly robbed (anterior in the case of carotid-vertebral compensation and posterior in the case of vertebral-vertebral compensation). Therefore, TIA, vertigo, lipotimia and visual disturbances may be presented at each prolonged effort of the robbed limb, as is the case of our patient.

Conclusions: The authors presented a case report of subclavian steal syndrome in a 67-year-old man, which became evident with presyncope after effort of the upper left limb.


Introduction: The “PRIME” study, acronym resulting from “brain natriuretic Peptide – RIght ventricular diaMEter”, enrolled 30 patients with venous thromboembolism (central pulmonary embolism) between the ages of 48 and 82, which were hospitalised in the “Short-stay Observation” and “Sub-Intensive C” Simple Structure of the “Internal Medicine for Urgency” Complex Structure during a three year period from January 2010 to December 2012. As a pre-lysis, the right ventricular diameter (RV diameter)
Association between plasma levels of levothyroxine and prevalence of atrial fibrillation in patients with essential hypertension and normal thyroid function

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Dietary modification and common carotid intima-media thickness in patients with essential hypertension: results of a prospective study

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Although prevalence of atrial fibrillation (AF) is high in patients with hypertension or dysthyroidisms, it is not clear whether thyroid hormones can play a role in the pathogenesis of AF in hypertensive patients with normal thyroid function. The aim of the present study was to retrospectively compare thyroid function and echocardiographic and biohumoral variables of 25 hypertensive patients with AF (age 72±6 years, M/F=12/13) and 50 control hypertensive patients without AF (age 72±5 years, M/F=24/26). Clinical presentation of AF was of both paroxysmal and persistent type (11 and 14 patients, respectively). Study design was case-control with a 1:2 ratio and patients were matched for age, gender, body mass index (BMI), blood pressure, duration of hypertension, and renal function. Patients with AF presented, respect to control, higher prevalence of carotid vascular disease (92% Vs. 68%, P=0.045), past cerebrovascular events (28% Vs. 8%, P=0.008), and usage of digitalis (16% Vs. 2%, P=0.022) and oral anticoagulants (56% Vs. 2%, P=0.001), higher right and left atrial diameter (58±9 Vs. 53±7 mm, P=0.020 and 58±11 Vs. 51±7, P=0.009, respectively), and lower total and LDL cholesterol (170±34 Vs 209±48 mg/dL, P=0.001 and 94±31 Vs. 130±44 mg/dL, respectively) and left ventricular ejection fraction (60±12 Vs. 68±8%, P=0.002). No differences were seen for other lipids, glucose, insulin, fibrinogen, C-reactive protein and homocysteine. Analysis of thyroid function showed a higher plasma level of free levothyroxine (fT4) in hypertensive patients with FA respect to controls (Figure), whereas triiodothyronine (fT3) and thyrotropin (TSH) did not differ between groups. Multivariate logistic regression analysis that included age, male gender, BMI, blood pressure, LDL cholesterol, glycemia, renal function and left atrial diameter showed an independent relationship between fT4, divided in quartiles, and prevalence of AF (Odd Ratio 6.8, CI 95% 1.7-26.6, P=0.006). In conclusion, prevalence of AF is associated with higher plasma levels of fT4 in hypertensive patients, even with normal thyroid function, respect to matched controls.
The carotid intima-media thickness (cIMT) is an early marker of atherosclerosis that is related to the cardiovascular risk. Since polyunsaturated fatty acids of the omega-3 family have proved to be protective in patients with high cardiovascular risk, we hypothesized that these fatty acids may affect cIMT also in hypertensive patients. We assessed the effect of increasing polyunsaturated to saturated fatty acid (PUFA/SFA) ratio by nutritional counseling with 3 weekly fish meals on cIMT of 36 well controlled mild to moderate hypertensive patients (age 63±7 yr.; M/F 16/20; BMI 28.1±4.1 Kg/m²). Ambulatory blood pressure, plasma lipid profile, variables of glucose metabolism, markers of systemic inflammation and renal function, were evaluated together with cIMT measured by ultrasonography. Fatty acid profile and the PUFA/SFA ratio of the red blood cell membranes was determined by gas chromatography at baseline and after 1 year of treatment. At baseline, lower cIMT was related to higher PUFA/SFA ratio (Figure A), but the relationship was lost in the multivariate analysis that included age, gender, body mass index, HOMA index, blood pressure, total and HDL cholesterol, fibrinogen, and estimated glomerular filtration rate. After one year, the PUFA/SFA ratio in red blood cell membranes increased (Δ>0) in 53% of patients, and this variation was associated to significant reduction of cIMT (mean reduction -0.23 mm, 95% CI: from -0.45 to -0.02 mm, **P=0.016; Figure B). In conclusion, increasing PUFA/SFA ratio in red blood cell membranes of hypertensive patients by nutritional counseling with frequent fish meals decreases cIMT.

Turn off the cell phone. Phone calls acutely increase BP levels in hypertensive patients

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The cellular phone has burst into our everyday life, and is often and indispensable communication tool even for medical purposes (e.g. telemedicine). However, the noise generated by the phone ringing and its ‘intrusion’ into the doctor’s office during blood pressure (BP) measurement could affect BP readings, leading to unreliable diagnostic and therapeutic considerations.

The aim of this study was to test whether mobile phone calls received during blood pressure (BP) measurement may alter systolic and diastolic BP and heart rate (HR) in hypertensive patients.

Ninety-four mild-to-moderate hypertensive subjects (49 females, mean age 53±15 years) on pharmacological treatment, underwent 2 consecutive series of 6 BP measurements by using an automated oscillometric device (BpTRU, VMS MedTech Ltd, Coquitlam Canada), set to take readings at 1-minute intervals.

Before the test patients were asked about their habitual use of cellular phone (mean number of daily in- or out-calls, attitude to turn off the telephone, and whether their mobile phone was switched-on during the visit). Their telephone numbers were also recorded in the questionnaire.

During one of the two consecutive series, each of 6 measurements, patient’s mobile phone number was dialled three times by one of the investigators; the calling number on the phone display was unknown to the patients. The provocation test was considered as complete when the subjects answered and spoke on at least one of the three phone calls made by the physician.

Patients were randomly assigned to receive the phone calls during the first or the second series of automated measurements. In each series, after the first BP reading, the patients remained alone, seated in a comfortable armchair, in the consulting room. Mean systolic and diastolic BP and HR obtained during measurements with and without phone calls were compared (Student’s t test for paired, two-sided, alpha-level P < 0.05).

Results:
Main results are depicted in the table.

Systolic BP significantly increased (+ 7.1 mm Hg) during exposure to phone calls while Diastolic BP rise (+ 4.7 mm Hg) did not result statistically significant. Heart Rate was not substantially affected by phone rings. Systolic BP rise was less evident in patients who were accustomed to use more frequently the mobile phone (more than 30 calls per day) and in patients treated with beta-adrenergic-blockers.

In conclusion, telephone calls received during BP measurement may significantly increase systolic BP in hypertensive subjects, leading to overestima-

Table 1.

<table>
<thead>
<tr>
<th></th>
<th>No phone calls</th>
<th>During phone calls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg ± SD)</td>
<td>121.4±9.0</td>
<td>128.5±10.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diastolic BP (mmHg ± SD)</td>
<td>77.4±9.0</td>
<td>82.1±10.6</td>
<td>NS</td>
</tr>
<tr>
<td>Heart Rate (bpm’ ± SD)</td>
<td>70.7±9.5</td>
<td>71.9±9.9</td>
<td>NS</td>
</tr>
</tbody>
</table>
tion of BP levels. Therefore, at least during BP measurement, patients should be advised to turn off their mobile phone.

**Myopericarditis and perimyocarditis are benign myopericardial inflammatory syndromes. Results from a multicenter prospective cohort study**


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**Background:** Myopericardial inflammatory syndromes include acute pericarditis (AP) (normal troponin and normal left ventricular function-LVF), myopericarditis (MP) (elevated troponin but normal LVF) and perimyocardi-
ditis (PM) (acute pericarditis with elevated troponin and abnormal LVF). The natural history of MP/PM is poorly known and recently published data have presented contrasting data on their outcomes.

**Aim of the study:** to evaluate the clinical presentation, and outcome of MP/PM confirmed by cardiac magnetic resonance and compare these features with those of simple AP in a multicenter prospective cohort study

**Patients and methods:** 486 consecutive patients (median age 39 ys, range 18-83 ys, 300/186 M/F) with AP (346 pts) or MP (114 pts) or PM (26 pts) were prospectively evaluated from Jan 2007 to Dec 2011. The diagnosis of AP was based on the presence of 2 of 4 clinical criteria (chest pain, pericardial rubs, widespread ST-segment elevation or PR depression, and new or worsening pericardial effusion). MP/PM was suspected with cardiac troponin elevation and/or new or worsening ventricular dysfunction on echocardiography, and confirmed by cardiac magnetic resonance. Coronary artery disease was excluded in cases with coronary risk factors or dubious presentation with need for a differential diagnosis with acute coronary syndromes by means of coronary angiography at initial presentation. Aspirin or a non-steroidal anti-inflammatory drug (NSAID), generally ibuprofen, was considered the mainstay of treatment. Corticosteroids were considered as the second choice for patients with contraindications or intolerance to aspirin and NSAIDs. Colchicine use was optional for patients with pure AP and was limited in patients with MP/PM. During follow-up (median follow-up 36 months-range 6-66), clinical evaluation, ECG and routine blood chemistry was performed at 1 month, 6 months, and 12 months, and then every year, if the course was uncomplicated.

**Results:** The etiology was similar in different myopericardial subgroups (idiopathic in 84-85%, infectious in 4-5%, and connective tissue disease or inflammatory bowel disease in 10-12% of cases). Patients with MP/PM were younger and more frequently male than those with AP (p<0.001). Pericardial rubs on physical examination and pericardial effusion on echocardiography were more commonly associated with AP (p<0.01). On the contrary heart failure signs and symptoms and cardiac arrhythmias were recorded with increasing frequency in patients with MP/PM. Signs of inflammation (white blood cells elevations and C-reactive protein elevation) were more common in AP than in MP/PM (p<0.001), while markers of myocardial lesions (cTnI and CK-MB) had higher levels in patients with increasing degrees of myocardial involvement (PM) than in MP (p<0.001). The initial presentation mimicked a ST-segment elevation myocardial infarction in 87 of 114 (76.3%) cases of MP and 20 of 26 (76.9%) cases of PM and only 8 of 346 cases of AP (2.3%; p<0.001). Left ventricular ejection fraction (LV) was preserved in AP as well as in MP (59±4%), and was mildly reduced in those with PM (44±9%; p<0.001). After a median follow-up of 36 months normalization of LV function was achieved in 90% of patients with MP/PM. No deaths were recorded, as well as evolution to heart failure or symptomatic LV dysfunction. No cases of cardiac tamponade and con-strictive pericarditis were recorded in patients with MP/PM. Recurrences were more common in AP (31.8%) than MP (10.5%) or PM (11.5%; p<0.001) and generally occurred as recurrent pericarditis. Recurrence-free survival was similar in patients with MP/PM. Pericardial effusion at presentation (HR 2.2) and corticosteroid therapy (HR 6.7) were risk factors for recurrences. Troponin elevation was not associated with an increase of complications.

**Conclusion and clinical applications:** Myopericardial inflammatory syndromes (MP/PM) are benign clinical syndromes that can be frequently encountered in patients with an initial suspicion of pericarditis. Myopericardial inflammatory involvement should be suspected in any young patient with heart failure signs and symptoms, ST-segment elevation at presentation, cardiac arrhythmia. On the contrary pericardial rubs and pericardial effusion is usually associated with less myocardial involvement. Recurrences are the most common complication during follow-up and are more frequently recorded in patients with AP than MP/PM. Pericardial effusion at presentation and corticosteroid therapy are risk factor for recurrences. Unlike acute coronary syndromes, troponin elevation is not a negative prognostic marker in this setting.

**Early myocardial dysfunction by three-dimensional speckle tracking echocardiography in asymptomatic patients with myotonic dystrophy**

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**Purpose:** Myotonic dystrophy (MD), also recognized as myotonia atrophica, is an inherited disorder of muscle weakness and wasting characterized by sustained involuntary muscle contraction. Despite some controversial results, it is known that patients with MD may develop a specific late cardiomyopathy, while only subclinical left ventricular (LV) diastolic dysfunction is detectable in the early stages of disease by using standard imaging techniques. Our study aimed to identify early LV involvement in asymptomatic patients with MD by real-time 3D Speckle Tracking Echocardiography (STE).

**Methods:** After excluding patients with arterial hypertension, overt heart failure, coronary artery disease and atrial fibrillation, the final study population comprised 21 MD asymptomatic patients (mean age: 34 years) and 21 normal controls (N), matched for sex and age. The participants underwent a standard echo Doppler assessment (including cardiac chamber quantification and assessment of both systolic and diastolic function) and a real-time 3D echo examination with both volumetric and STE post-processing. Real-time 3D echo was performed according to standardized procedures (frame rate of recording ≥40% of the individual heart rate). 3D derived LV end-diastolic volume and end-systolic volumes, ejection fraction and LV mass index as well as global longitudinal strain (GLS), global circumferential strain (GCS), global area strain (GAS) and global radial strain (GRS) were compared between the 2 groups.

**Results:** The 2 groups were comparable for body mass index, blood pressure and heart rate. Standard echo Doppler did not show significant difference of LV mass index, relative wall thickness, ejection fraction, transmitral E/A ratio, E velocity deceleration time and E/E’ ratio but LV end-diastolic volume was marginally smaller in MD than in N (p<0.05). 3D volumetric assessment confirmed smaller end-diastolic volume (95.7±23.2 ml vs 123±34.9 ml, p<0.01) and lower sphericity index (0.31±0.11 versus 0.39±0.11, p<0.02), without significant difference of ejection fraction and LV mass index. 3D STE showed lower values of GCS (-14.0±1.77% vs. -16.4±2.4%, p<0.005), GAS (-25.5±4.2% vs. 28.6±3.5%, p<0.02) and GRS (37.2±8.4% vs 42.3±8.7%, p<0.01) in MD than in N, without significant difference of GLS. In the pooled population GAS was positively related with sphericity index (r
Non-alcoholic fatty liver disease and arterial stiffness in morbid obesity
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Background: Non-alcoholic fatty liver disease (NAFLD) is a common comorbidity of obesity. NAFLD has been found to be related to an increased arterial stiffness in patients with essential hypertension and to an increased risk of cardiovascular morbidity. Increased gamma-glutamyltransferase (γ-GT) level is frequently observed in NAFLD and has been associated with arterial stiffness and cardiovascular disease in unselected population.

Aim of the study: The aim of this study was to investigate the relationship between NAFLD, arterial stiffness and metabolic parameters in a cohort of subject with morbid obesity candidates for bariatric surgery.

Patients and methods: We included 97 morbid obese patients (mean body mass index – BMI – 44 kg/m², aged between 18 and 62 years old. All patients underwent measurement of anthropometric and metabolic parameters, ultrasonographic assessment of abdominal visceral fat area and liver steatosis (absent, mild, moderate or severe). Carotid-radial pulse wave velocity (PWV), a noninvasive measure of arterial stiffness, was measured by tonometric method. The population was divided into three groups according to liver steatosis severity and serum γ-GT levels: group A included subjects with absent/mild steatosis and γ-GT levels < 50 UL/l (n. 30), group B included subjects with moderate/severe steatosis and γ-GT levels < 50 UL/l (n. 52) and group C included subjects with moderate/severe steatosis and γ-GT levels ≥ 50 UL/l (n. 15).

Results: Group A showed lower levels of systolic (PAS) and diastolic (PAD) blood pressure, lower BMI, waist circumference and visceral fat area compared to the other two groups. With worsening liver steatosis we observed increased triglycerides, lower HDL-cholesterol, increased fasting glucose and glycated hemoglobin levels. PWV was significant higher in the group C compared to the group A (p=0.035). In a linear regression analysis PAS (b 0.24; p=0.02), triglycerides (b 0.42; p≤0.001) and γ-GT (b 0.24; p≤0.02) were independently associated with increased PWV. Age, HDL, LDL, fasting glucose and degree of steatosis were also included in the model, but failed to enter the final equation.

Discussion: Obese subjects with moderate/severe steatosis and elevated γ-GT levels have a worse metabolic profile and a significant increased arterial stiffness compared to subjects with absent/mild steatosis and normal γ-GT. Our findings are of interest because arterial stiffness is increasingly recognized as a cardiovascular risk factor and we suggest that combined evaluation of liver ultrasound and serum γ-GT levels may provide useful information for the identification of obese patients at greater risk of cardiovascular disease. γ-GT levels are independently associated with increased level of arterial stiffness. This evidence is biologically plausible because of relationship between γ-GT and oxidative stress but further studies are needed to fully elucidate the mechanisms linking γ-GT and arteriosclerosis.

Serum uric acid levels and endothelial function

University of L’Aquila – Department of Life, Health and Environmental Sciences

Objective: Several studies supported the hypothesis that asymptomatic hyperuricemia could be associated not only to hypertension, type 2 diabetes and renal failure but also could represent an independent risk factor for cardiovascular disease. Endothelium plays a crucial role in atherogenesis and related adverse outcomes. It has been described that hyperuricemia can stimulate endothelial dysfunction by reducing nitric oxide bioavailability. However, the biological mechanisms linking hyperuricemia to cardiovascular disease have not been completely elucidated. According to this, aim of our study was to research the relationship between serum uric acid (SUA) levels and vascular function.

Design and methods: 15 hyperuricemic subjects (mean age 48.0±17.4) and 15 healthy normouricemic controls (mean age 51.4±12.4) without comorbidities and cardiovascular risk factors, were recruited. Patients of both groups did not take any treatment interfering with SUA. Anthropometric parameters, blood pressure, fasting serum lipid, glucose, insulin, high-sensitive C-reactive protein (hs-CRP), SUA levels and HOMA index were evaluated in all participants. Flow mediated dilation (FMD) of the brachial artery, carotid-femoral pulse wave velocity (PWV), and aortic augmentation index (AIx), were measured.

Results: Age, gender, renal function, anthropometric parameters, blood pressure, hs-CRP and glucose profile were similar in both groups. HDL-cholesterol was higher in normouricemic compared with hyperuricemic group (p<0.001). FMD was significantly impaired in hyperuricemic subjects (4.60±1%) compared with controls (7.88±1.8%) (p<0.001) and inversely correlated with SUA (r = -0.78, p<0.0001). No significant difference was observed for PWV and AIx between the two groups.

Conclusion: Our results indicated a relationship between hyperuricemia and FMD, suggesting a potential pathophysiological role of hyperuricemia in the development of vascular endothelial dysfunction, i.e. the primum movens of atherosclerotic process. Therefore, further benefits in preventing atherosclerosis and cardiovascular events could be hypothesized with the optimal control of SUA.

Relation of left ventricular mass to VEGF and MCP-1 in essential hypertension
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Hypertensive left ventricular hypertrophy (LVH) is an established cardiovascular risk factor. The underlying mechanisms for the unfavourable prognosis in patients with LVH are, however, not fully understood. Several studies indicate that inflammation plays a pivotal role in the pathophysiology of essential hypertension. Vascular endothelial growth factor (VEGF) is currently discussed as a possible mediator of inflammation. VEGF is one of the most potent angiogenic factors known and is thought to function as an endogenous regulator of endothelial integrity. Animal
studies have revealed that VEGF promotes endothelial regeneration and induces migration and activation of monocyte through induction of chemokines such as monocyte chemoattractant protein (MCP)-1. However, there is still a debate over the vasculoprotective vs pro-inflammatory effect of VEGF.

Hypertension is a well established risk factor for atherosclerotic disease. However, the precise mechanisms by which hypertension promotes cardiovascular complications are unclear.

We performed this study to investigate the hypothesis that VEGF and MCP-1 play a role as inflammatory mediators in essential hypertension and to examine possible relationships between serum levels of VEGF, MCP-1, and left ventricular mass in patients with essential hypertension. Therefore in this study we examined 120 never treated mild essential hypertensive (n=60 with LVH and n=60 without LVH) and 60 healthy normotensive subjects.

In all subjects LVMI (echocardiography) and serum levels of VEGF and MCP-1 were determined (ELISA, R&D System). Hypertensive patients showed increased plasma levels of VEGF (p < 0.05) and MCP-1 (p < 0.05) than in normotensives.

Multivariate analysis demonstrated VEGF to be an independent predictors of MCP-1 levels.

VEGF and MCP-1 levels were higher in hypertensives with LVH than in hypertensives without LVH and normotensives (p<0.01); furthermore VEGF and MCP-1 are correlated positively to LVMI (r=0.50, p<0.01 and 0.46, p<0.05, respectively).

This study suggests that in mild hypertension, inflammatory pathway has already been activated.

We observed increased plasma levels of VEGF and MCP-1; stepwise multivariate analysis suggests that elevated VEGF levels contribute to the elevated MCP-1 levels. Furthermore, VEGF and MCP-1 are positively associated with left ventricular mass.

In conclusion, the present study seems to suggest new insights into the pathophysiologic mechanisms in essential hypertension linking inflammation, abnormal angiogenesis and early cardiac structural changes.

**Stroke outcomes and blood pressure variability indices in a cohort of patients with internal carotid occlusion**

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**Objective:** Arterial Blood Pressure (BP) variability has increasingly been recognized as a poor functional outcome predictor in patients with stroke. Our aim was to evaluate the relationship between BP variability during the acute phase and the 3-month clinical outcome in ischemic stroke patients with internal carotid artery (ICA) occlusion.

**Methods:** This study was conducted at the University Hospital of Ancona, Italy during a 5-year period. Acute ischemic stroke patients with ultrasound evidence of ICA occlusion were considered for enrolment. At least 10 BP measurements during the first 48 hours after stroke onset were obtained, and BP profile of each patient was described using various summary parameters: average of recordings (mean), maximum (max), minimum (min), difference between max and min (max-min), standard deviation (SD) and coefficient of variation (CV) for both systolic and diastolic BP. Clinical outcome at 3 months was defined using the modified Rankin Scale (mRS) score corrected for baseline severity.

**Results:** Eighty-nine consecutive stroke patients with ICA occlusion were included. At the 3-month follow-up, 55 had a good outcome (Group 1) and 34 a poor outcome (Group 2). Max values, max-min, SD and CV of both systolic and diastolic BP resulted significantly higher in Group 2 compared to Group 1 patients (p < 0.05, multivariate adjusted model).

**Discussion:** These findings suggest that BP variability can negatively influence clinical outcome of patients with acute ischemic stroke ipsilateral to an ICA occlusion. Repeating BP measurements might provide reliable prognostic indicators in this subgroup of stroke patients.

**Arterial systemic thrombo-embolism and cardiometabolic risk factors**

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**Case report:** A 83-years-old white woman presented to our clinic with a 3-days history of pain localized in the left side abdomen, in both arms, in the right leg; togheter with sensitive and motorial alterations. In Hospital Emergency Department we found out an unknown atrial fibrillation with an hypothetical ecocardiografic thoracic aortic vessel dissection. The angioTC scan showed an aortic thoracic vessel ectasia with a spread aortic vessel atheromasia with regular diameter and course and a little infarct left kidney area. The patient, admited to our Internal Medicine Department, appeared active, overweight, with elevated blood pressure, irregular heart rate, systolic murmur, absent carotid vessel murmur. The breath was free by lung dump sounds, abdominal pain spread in the left side; visceral movement was slow. Negative Blumberg and Murphy signs, positive left Giordano sign, absent both peripheral artery arm pulses, present peripheral left leg pulse, weak peripherical artery right leg; negative the neurological test.The patient dind’t report alcoholic either smoking dependence. She told us about remote bilateral saphenectomy, pneumoiaec, hypertensive cardiopathy with PM implantation. The blood examination was normal except elevated gliated haemoglobin, and some liver functional indices. Color-duplex ultrasound examination about all the four limbs found out multiple embolies in...
both the peripheral arterial arms vessels and peripheral arterial right leg vessels. Thus, absent venous deep thrombosis. Trans-thoracic echocardiography point out an hypertensive hypokinetic cardiopathy, with aortic valvular steno-insufficiency, a mitral and tricuspid valvular insufficiency, a medium lung hypertension, a left and right atrial dilatation. Later on, we madea transesophageal echocardiography. We showed absence of valvular vegetation and atrial thrombi, but a patent foramen ovale with minimal left to righ shunt. Negative was the research about gastric, colon, breast cancer, gynecological,dermatological, and abdominal neoplasms. We performed a therapy with intravenous heparin sodium, then low molecular weight heparin and finally warfarin. Hospitalization was complicated by two episodes of transient ischaemic attacks. During the hospital stay, low sugar and caloric diet allowed a good glicemic control and a significant weight loss. Before discharge a vascular surgical evaluation documented a partial re- canalization of arterial thrombotic occlusion of the arms with the persistence of the right leg arterial occlusion but with collateral circulation. Discharge diagnosis was: Systemic arterial embolism with kidney infarction and transient ischemic attacks in old woman, affected by diabetes mellitus, overweight, hypertension, atrial fibrillation. The patient was followed regularly in the outpatient internal medicine with the complete resolution of the clinical picture.

Discussion and conclusion: In this case, during the arterial systemic massive thrombosis screening, we excluded the neoplastic factor, but we couldn’t study the slope thrombophic due to the presence of anticolagulant therapy in progress. In the scientific studies we didn’t find out a causal relationship between homocysteine, phospholipid antibodies, antithrombin III, C and S proteins (1,2). Similarly we excluded various peripheral arterial not atherosclerotic disease among which obliterans thromboangiitis, large vessels vasculitis, entrapment of popliteal artery (1). In agreement with recent scientific literature (3,4,5) the patient presented the association of different cardiometabolic risk factors about the arterial massive thrombo-embolism especially the old age, female sex, atrial fibrillation, hypertension, diabetes mellitus, heart failure, transitory ischemic attacks.

Reference:

Prevalence and features of cardio-renal syndrome in a cohort of consecutive patients admitted to an internal medicine department


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Introduction: Cardio-Renal Syndrome (SCR) describes a cardiac and renal acute or chronic failure, in which the dysfunction of one of the organs causes acute or chronic insufficiency of the other organ. The prevalence of this syndrome is unknown. The aim of this study was to evaluate the SCR frequency and the risk factors in a cohort of patients hospitalized in Internal Medicine.

Materials and methods: We retrospectively enrolled 1087 consecutive patients admitted from December 2009 to December 2012. Diagnosis of SCR was made in 190 patients according to the recommendations of Acute Dialysis Quality Initiative.

Results: 190 (17.5%) of 1087 patients were selected and classified in the 5 types of SCR. Type 1 SCR was observed in 61 cases (32.1%), type 2 in 30 (15.8%), type 3 in 15 (7.9%), type 4 in 11 (5.8%) and type 5 in 73 (38.4%). SCR occurs in male more than in female (68.9%). The age distribution was significantly different in the 5 classes of patients (p <0.001) and the older age was recorded in the SCR type 1 (average of 79.9 years). Average length of hospitalization was 16.5 days and the highest was observed in SCR type 5. The death was significantly different among the classes (p= 0.006) and in particular SCR type 1 showed higher rate of death (p <0.001, odds ratio 4.23). Acute renal failure had a different distribution among the classes, especially in SCR types 1, 3 and 5 (p <0.0001). Risk factors as chronic renal failure presented a significant difference in the groups (p <0.001) with greater frequency in type 3 and 4. Comparing type 1 and type 5 (group A) with type 2, 3 and 4 (group B), arterial hypertension was mostly represented in group A than in group B (p = 0.003). Among trigger factors, infections showed a statistically significant distribution in the classes (p < 0.05). Comparing SCR type 1, 3 and 5 with SCR type 2 and 4, infections were more frequent in the first group (86 vs 17 patients, p< 0.05). Pneumonia showed a greater frequency in classes 1 and 5, compared to other classes (p <0.01) and community-acquired pneumonia was more represented than nosocomial pneumonia (p <0.05).

Conclusions: SCR type 5 was the most frequent class, followed by type 1. SCR type 1 has shown high rate of morbidity and mortality. Probably SCR type 5 is the most frequent because of the numerous potential conditions that may induce it. Community-acquired pneumonia is an important trigger factor for SCR. The management of the SCR is multidisciplinary and randomized studies are still needed to reduce the mortality and morbidity associated with the disease. For early diagnosis and to optimize the therapy, it is very important to identify both the risk factors, such as chronic renal failure or hypertension, and the trigger factors, such as infections, associated with the SCR.

Cocoa consumption dose-dependently improves flow-mediated dilation and decreases arterial stiffness in healthy subjects

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Background: Flavonoids from cocoa might exert some beneficial vascular effects and reduce the risk of cardiovascular morbidity and mortality. Although data from literature suggest flavonoids may present with all the biological potential to positively affect vascular function, not all the involved mechanisms have been exhaustively clarified. Further, no study specifically focused on dose-response effects. Our study aimed to investigate the effects of different doses of cocoa on endothelial function and arterial stiffness.

Methods: According to a randomized, double-blind, controlled, cross-over design, 20 healthy volunteers were assigned to receive either five treatments with daily intake of 10 g cocoa (0, 80, 200, 500 and 800 mg cocoa flavonoids/day) in five periods lasting 1 week each.

Results: cocoa dose-dependently increased flow-mediated dilation (FMD) from 6.2% (control) to 7.3, 7.6, 8.1 and 8.2% after the different flavonoid doses, respectively (p < 0.0001). Compared with control, even 80 mg cocoa flavonoids per day increased FMD (p < 0.0001). Further, the change in FMD after consumption of 800 mg per day was not only significant when compared with control (p < 0.0001) but also with 80 mg/day (p = 0.0003) and 200 mg/day (p = 0.05). Compared with control, carotid-femoral artery PWV significantly (from 8.14 m/s after control to 7.39 m/s after 800 mg/die; p < 0.0001) and dose-dependently decreased (0 mg vs 200 mg: p = 0.0008; 0 mg vs 500 mg: p < 0.0001; 0 mg vs 800 mg: p < 0.0001)

Conclusions: Our study showed for the first time that cocoa dose-dependently improved FMD and decreased PWV. Our findings are clinically relevant, suggesting cocoa, with very low calorie intake, might be reasonably incorporated into a dietary approach representing a consistent tool in cardiovascular prevention.

Blood pressure and vascular effects of black tea consumption in hypertensive subjects

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Hypertension is the leading risk factor for cardiovascular morbidity and mortality. Black tea consumption improved flow-mediated vasodilation (FMD) in previous studies and we hypothesised this may positively affect blood pressure (BP) and digital volume pulse (DVP), also protecting from fat-challenged vascular alterations.

We assessed black tea effects with and without a fat load on office BP, FMD and DVP in never treated grade 1 hypertensives without additional cardiovascular risk factors.

According to a randomized, double-blind, controlled, cross-over design, 19 patients were assigned to consume black tea (150 mg polyphenols) or placebo drink matched for caffeine, color and taste, twice a day for eight days (13 day wash-out period). On day 7 measurements were in a fasted state, while on day 8 subjects consumed whipping cream (1 gram fat per kg) 30 minutes after consuming test products. FMD, DVP and BP were measured at baseline and 1, 2, 3 and 4 hours after consumption of the test products. Compared to placebo, baseline systolic (-3.3 mmHg) and diastolic (-2.6 mmHg) BP decreased and FMD improved after tea consumption (+1.3%; p < 0.0001). An additional cup of tea further increased FMD at 1, 2, 3 and 4 hours after consumption (p < 0.0001). Fat challenge significantly increased BP (p < 0.0001) and decreased FMD (p < 0.0001). This was counteracted by tea consumption. Tea improved reflection index (small vessel tone; p < 0.0001) and stiffness index (large arterial stiffness; p < 0.0001) with additional effects after acute tea consumption with and without fat load.

This study confirms positive effects of tea on endothelial function, also suggesting black tea protects against fat load-induced arterial dysfunctions in hypertensive subjects. The vascular benefits of tea are also reflected in BP lowering and peripheral arterial protection under fasted and postprandial conditions. Our findings are of clinical relevance and interest from a population-based point of view, because of the consumer-relevant black tea used in this study, and tea being globally the most consumed beverage after water.

Circulating progenitor cells in hypertensive subjects: a treatment with olmesartan and atorvastatin is effective in improving cell number and profile besides expected pharmacological effects


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Circulating progenitor cells (CPCs), identified by the expression of surface CD34 antigen, are a population of cells in different states of maturation with the ability to differentiate into different cell types, including cardiomyocytes, smooth muscle cells (SMCs), endothelial progenitor cells (EPCs) and endothelial cells (ECs). CPCs then may participate in the turnover of healthy and damaged tissues of cardiovascular system, delaying the development of atherosclerosis and cardiovascular disease (CVD) and representing a regenerative/ reparative potential for CV system.

Oxidative stress, and the consequent increased production/accumulation of reactive oxygen species (ROS), is a common feature of CV risk factors including hypertension. ROS, indeed, have a dual role: in high concentrations they are toxic for cells, whereas low ROS levels can participate in intracellular signaling, stimulating mechanisms that prevent tissue injury and promote angiogenesis.

MicroRNAs (miRs) 221 and 222 have been identified in circulating progenitor cells (CPCs), where they participate in the cell differentiation and proliferation, inhibiting cell migration and homing, also by inhibiting the synthesis of the receptor for the Stem Cell Factor c-Kit. Moreover, miR221/222 modulate different genes regulating the angiogenesis and inflammation. In an “in vitro” study the lowering of miRs in ECs reduced the ROS production and angiogenesis, suggesting a role of miRs in regulating the redox signaling.

Previously we found that in CPCs from hypertensive patients without additional risk for CAD, miR221/222 are increased and associated with cell number and production of reactive oxygen species (ROS). The aim of the present study was to evaluate whether in hypertensives a treatment with olmesartan may have effects on the number of CPCs and on levels of miR221/222 and ROS. We also evaluated whether additional effects may be obtained with an add-on treatment with atorvastatin.

We included 41 hypertensives (27 M/14 F; mean age 38.1±5.1 years) with no additional risk factor for CAD and 22 matched controls; we evaluated circulating CD34+ cell number, intracellular miR221/222 and ROS levels at baseline (T0) and after a six months treatment with 20 mg/die of olmesartan (T1); blood pressure, fibrinogen, CRP, glucose and lipid profile were also evaluated. Then, hypertensives were randomized to receive an add-on treatment with atorvastatin (T2a), or to continue with olmesartan alone (T2p) for further 3 months. All parameters were evaluated at the end of the study period.

At T1, systolic and diastolic blood pressure (Δ: -13.5 and -19.5, respectively, both p < 0.001), ROS (Δ: -17.5, p < 0.001) and miR221/222 (Δ: -21%, respectively, p = 0.002 and p < 0.001, respectively) were significantly decreased with respect to T0, while the number of cells was increased (Δ: +22.4%, p < 0.001). CRP and fibrinogen levels were also reduced (Δ: -25.4% and -11.5%, respectively, p < 0.001 and p < 0.005, respectively). After the treatment with atorvastatin (T2a) ROS, miRs, CRP and fibrinogen levels...
were further decreased (Δ: -23.6%; -31.1%; -46.3%; -26.8%, and -14.1%; p <0.005 for ROS, miRs, CRP; p<0.01 for fibrinogen), and CPCs significantly higher (Δ: +25.0%, p=0.004); blood pressure values also were further reduced, while lipid profile amelioration didn’t reached the statistical significance. At T2p no further changes were detected as compared to T1. Olmesartan is effective in reducing miRs and ROS levels in CPCs from hypertensives, as well as in increasing CPC number. An add-on treatment with atorvastatin may improve these effects.

Predictive role of IGF-1 in mild to moderate chronic heart failure


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Introduction: Several studies have reported abnormalities of the GH/IGF-1 axis in Chronic Heart Failure (CHF). Specifically, some investigators found normal IGF-1 values, some decreased, and some even increased. Few studies have so far systematically evaluated circulating levels of IGF-1 and IGFBP-3 in a large population of CHF patients, and addressed their impact on clinical status, exercise performance, LV architecture and function and mortality.

Populations and methods: We studied 158 consecutive patients with CHF, NYHA class I to III, who underwent a blood work including basal hormonal evaluation of IGF-1 and IGFBP-3. Moreover, all patients underwent baseline extensive cardiovascular study with complete echocardiography, NT-proBNP measurement and cardiopulmonary exercise testing. We also studied basal hormonal pattern in 135 age- sex- and BMI-matched controls.

The IGF-1 peripheral activity was estimated as the molar ratio of serum IGF-1 to IGFBP-3 and was calculate by the formula IGF-1/IGFBP-3 * 3.7. CHF patients were followed-up for a mean duration of 36 months (range 4-84 months) and all-cause mortality data were collected.

Results: Total serum IGF-1 values in controls and CHF were similar (137.7±5.2 vs. 135.4±4.6, p=.78) and IGF-1/IGFBP-3 molar ratio was significantly higher in CHF than in controls (138.1±3.8 vs. 154.8±3.9, p=.003).

Considering IGF-1 median value (130 mg/L), patients with lower IGF-1 had reduced peak VO2 uptake (p=.031) and workload (p=.023) and similar LV architecture and function (see Table) compared with patients with median IGF-1 higher than 130 mg/L.

Low IGF-1 levels resulted predictors of all-cause mortality (log rank <.0001, see Figure), whereas levels of IGF-1/IGFBP-3 below the median value did not.

Conclusion: Mean IGF-1 levels in mild-to-moderate CHF and control subjects were similar. IGF-1 values below the median identify a subgroup of patients with impaired cardiopulmonary performance and higher all-cause mortality.

The assessment of psychic and affective traits in a cohort of patients with arterial hypertension


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Background: Arterial hypertension (AH) is a chronic disease in which high blood pressure occurs (diastolic pressure ≥90 mm Hg and/or systolic values ≥140 mm Hg). AH is an important public health problem worldwide with high economic costs and a severe impairment of quality of life. Growing evidence suggests high levels of comorbidity between AH and mental illness.

Aim: The aim of the present study was to identify the presence of several psychoneurosis and affective status as well as non physiological stress levels in patients with AH.

Materials and methods: We enrolled 45 subjects with AH (F:M=27:18, age range: 22-75yrs old) and 45 controls. The subjects were scored with the following tests: Middlesex Hospital Questionnaire (MHQ), the Zung Self-Rating Depression Scale, the Zung Self-Rating Anxiety Scale, Toronto Alexithymia Scale (TAS-20), questionnaire for stress levels.

Results: Free-floating anxiety, phobic anxiety, obsessive-compulsive traits and symptoms, somatic symptoms, depressive symptoms, and hysterical traits and symptoms were significantly greater in HA patients than controls (38% vs 9%, 29% vs 14%, 40% vs 0%, 35.5% vs 18%, 33% vs 9%, 20% vs 6%, respectively) (p<0.001), by using MHQ. Anxiety and depression were significantly higher in AH patients than controls (65% vs 11%, 35.5% vs 9%, respectively), by using the Zung Self-Rating Scales. Alexithymia was higher in AH patients than controls (20% vs 3.8%). Higher levels of pathological stress were present in AH patients than in controls (71.1% vs 28.9%).

Conclusions: A high prevalence of psychic and affective disorders were found in our population as well as a high rate of pathological stress levels. AH patients may be noncompliant to treatment for many reasons, including their psychological distress and lifestyle variables. A complete analysis on psychosomatic traits associated with hypertension is critically important and must be included in the patient evaluation as a scientific basis for developing strategies for appropriate hypertension management in the community.

Obstructive sleep apnea affects inappropriate left ventricular mass in never treated hypertensives

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Introduction: Obstructive sleep apnea (OSA) is a common but under-diagnosed disease that influences development of hypertension, affects left ventricular hypertrophy (LVH) and increases cardiovascular morbidity and mortality. In hypertensive setting, some patients present levels of inappropriate left ventricular mass (iLVM), exceeding the amount needed to sustain cardiac workload for sex and body size. The calculation of iLVM represents an independent factor of cardiovascular events and it remains a significant predictor of cardiovascular risk either in the presence or in the absence of traditionally defined LVH. At this time there are not data about the possible association between OSA and iLVM.

Aim: To evaluate in hypertensive patients the effect of OSA on variation of iLVM.

Methods: We enrolled 112 never treated hypertensives. All patients were underwent to clinical examination, measurement of lipid profile, fasting glucose and insulin, HOMA index and creatinine. Estimated glomerular filtration rate (eGFR) was measured by CKD-EPI equation. Echocardiogram was performed for the calculation of stroke volume (SV) and LVM indexed for height (LVMI). Stroke work (SW) was estimated as systolic blood pressure for SV and converted into gram/meters by multiplying for 0.0144. The theoretical value of the LVM (iLVM) was estimated using an equation previously developed by de Simone et al. The iLVM was defined as difference between ILVMI and LVMI, expressed in grams. In addition, overnight polysomnography was performed to evaluate apnea–hypopnea index (AHI), defined as the average number of apneas and hypopneas per sleep hour. According to AHI, the patients were divided in three groups: group I (AHI<15), group II (15≤AHI<30), group III (AHI≥30). All data were processed with ANOVA and χ²-square when appropriated. The independent effect of AHI on iLVM was evaluated by multiple regression analysis. Significantly difference were assumed to be at P<0.05.

Results: Among three groups, significant difference (P<0.05) were observed for BMI, HOMA, eGFR, SV and LVMI. Moreover, we observed a significant difference in SW (16.1, 15.8 and 20.1 in I, II, and III group, respectively; P=0.001) and in iLVM (∆-2.9, -0.9 and -11.1 gr, in I, II and III group, respectively; P<0.0001). In a multivariate model the strongest determinant of iLVM was AHI, explaining 19% of its variation (P<0.0001), followed by BMI that explained another 4%.

Conclusions: Our data showed that AHI represents a strong predictor of iLVM in never treated hypertensive patients affected by OSA. The iLVM increases parallel to worsening of AHI.

Brugada electrocardiographic findings in an 80-year-old man with fever

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An 80-year-old man was admitted to our inpatient-unit because of pneumonia. An electrocardiogram (ECG) performed during fever (39°C) showed a regular rhythm, normal PR interval, RSR’ with ST-elevation in V1-V3 leads with normal QRS duration. In particular, V2 lead showed a coved-type ST-segment, consistent with type-1 Brugada alteration (figure 1). Patient’s clinical and family history were unremarkable for symptomatic arrhythmias, syncope or sudden death. An electrocardiogram performed with normal body temperature (36.5 °C) showed ST-elevation in V1-V3 leads, with a saddleback-type ST-segment in V2, consistent with type-2 Brugada alteration (figure 2). Brugada syndrome, first described in 1992 (1), is a clinical entity characterized by typical ECG alterations associated to a high risk of sudden cardiac death. These ECG patterns can be seen spontaneously, induced by sodium channel blocking agents or by hyperthermia. One of the proposed pathological mechanisms is an alteration in the sodium channels, with temperature-induced accelerated inactivation or impaired conductance (2).

It has been reported that fever can induce a Brugada-type ECG pattern in asymptomatic patients disclosing Brugada syndrome, even outperforming flecainide test (3). Since febrile illness, unmasking Brugada electrical disturbances, could precipitate ventricular arrhythmias, it is important to aggressively reduce body temperature in order to minimize the risk of sudden cardiac death.

V1-V2-V3-V4 t-wave inversion: left or right heart?

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An 84-year-old woman, affected by Alzheimer’s disease, was brought to the emergency department (ED) in November 2012 by her caregiver, who referred that the patient had been suffering from intense dyspnea for the past 2 days. The patient was dependent in the activities of daily living and had history of total gastrectomy for gastric neoplasm in 2003. At admission, blood pressure was 130/80 mmHg, pulse rate was 107 beats per minute, oxygen saturation (SatO2) was 88%.
The result of a 12-lead electrocardiogram (ECG) is shown in Figure 1. What are these ECG alterations suggestive of? Do they suggest an electric disturbance of the left or of the right ventricle?

This ECG shows T-wave inversion in leads DIII, V1, V2, V3, V4. Differential diagnosis for these findings includes myocardial ischemia/infarction of the anterior left ventricle region, or a right ventricle overload. This ECG may be due to ischemia, especially when associated to dyspnea caused by pulmonary edema. However, in the absence of pulmonary edema, the association of dyspnea with the above ECG abnormalities may recognize a different etiology and thus deserves careful evaluation.

In the ED, High Sensitivity T Troponin was elevated (0.212 ng/ml; n.v. <0.014ng/ml). This finding, in association with clinical symptoms (acute dyspnea in a subject with Alzheimer’s disease) and ECG abnormalities, led to a diagnosis of an anterior NSTEMI and to the admittance of the patient to our Division.

In our unit the patient was confirmed to have low oxygen saturation (SatO2 85-88%), with hypoxia and hypocapnia at blood gas analysis, in the absence of clinical or radiological evidence at chest X-ray of pulmonary edema (figure 2). Further clinical history collected from the caregiver, showed a previous deep venous thrombosis. This drew our attention to the hypothesis of a pulmonary embolism (PE) in a bedridden subject not receiving anticoagulant prophylaxis. Cardiac ultrasound showed a left ventricle with normal global and regional kinetic, a dilated and hypokinetic right ventricle, a tricuspidal insufficiency, and pulmonary hypertension. Based on these findings, a contrast enhanced chest CT-scan, which confirmed the diagnosis of PE, was performed (figure 3-4).

**Comment:** A variety of ECG changes have been described in patients with suspected PE. The typical pattern of acute cor pulmonale, firstly described by McGinn and White in 1935, is the S1Q3T3 pattern, but this is classical only found only in individuals with massive PE (1). Additional ECG changes which may be associated with PE include atrial arrhythmias, right bundle branch block, inferior Q-waves, precordial T-wave inversion, and ST-segment changes (2,3). These findings are also associated with poor prognosis (2,3). Our patient presented with T wave inversions in DIII, V1, V2, V3, V4 leads. According to Ferrari and co-workers, this finding may correlate with severe right ventricular dysfunction (2). The ECG represents the first instrumental examination in patients admitted to the ED with dyspnea. In this cases, T wave inversions, along with increased levels of HS-T Troponin, may suggest a diagnosis of myocardial ischemia. However, such ECG findings may be misleading, since, even when associated with increased HS-T Troponin, are not specific of left ventricle ischemia and may be found also in subjects with PE and right ventricle overload.

**Is a restrictive LV filling pattern invariably present in restrictive cardiomyopathy? The case of cardiac AL amyloidosis**

**Background and aim:** Cardiac AL amyloidosis (CA) represents an arthropetal form of restrictive heart disease, very often associated with preserved ejection fraction (EF) heart failure. Aim of the present study was to assess echo-derived indices of diastolic dysfunction in CA.

**Methods:** Between 2008 and 2010, we enrolled 374 never treated patients with AL amyloidosis, 238 of whom (68%) presenting cardiac involvement according to the International Society of Amyloidosis criteria. In 219 CA patients with EF > 50% (85%), diastolic dysfunction was staged in 3 categories according to the European and American Society of Echocardiography guidelines.

**Results:** Rather unexpectedly, severe diastolic dysfunction (stage III) was evident in only 82 patients (37.4%), while 84 (38.4%) and 53 patients (24.2%) were classified as stage II and stage I diastolic dysfunction, respectively. Overall, the extent of diastolic dysfunction was related with NT-proBNP values. As shown in Table I, indexed LV mass, an indirect measure of amyloid deposition, was similarly higher in stage II and III when compared with stage I patients. Stage III patients were younger, with a significantly worse systolic function, as assessed by mitral annulus longitudinal excursion (MAPSE) and midwall fractional shortening.

**Conclusion:** Severe diastolic dysfunction with a clear-cut restrictive LV filling pattern is evident in only one third of the patient population with cardiac amyloidosis. Despite preserved ejection fraction, patients with stage III diastolic dysfunction are younger and with markedly depressed systolic function, indicating a more aggressive disease.
Impact of pulse pressure on non invasively estimated left ventricular filling pressure in newly diagnosed uncomplicated hypertensive patients


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Purpose: The pulsatile component (pulse pressure, PP) is the consequence of intermittent left ventricular ejection. Although elevated PP, an indirect marker of arterial stiffness, has been shown to be associated to cardiac organ damage and increased risk of cardiovascular events, its relations with LV diastolic function have been poorly investigated. The present study aimed to assess the impact of PP on non invasively estimated LV filling pressure (LVFP) in newly diagnosed, uncomplicated arterial hypertension.

Methods: After excluding patients with type 2 diabetes mellitus, coronary artery disease, overt heart failure, valve heart disease, primary cardiomypathies, atrial fibrillation and those undergoing anti-hypertensive therapy, the study population included 70 newly diagnosed, never treated hypertensive patients and 56 normotensive, healthy controls. All the participants underwent a complete echo Doppler examination including determination of LV mass index (LVMi), relative diastolic wall thickness (RDWT), left atrial volume index (LAVi), Doppler diastolic transmitral inflow, pulsed tissue Doppler of mitral annulus and E/e’ ratio (e’ average = septal e’ + lateral e’/2) as a non invasive estimate of LVFP. The study population was divided into 2 groups independent on blood pressure values according to brachial PP (systolic blood pressure – diastolic blood pressure): 91 with PP ≤ 50 mmHg (Group 1) and 35 with PP > 50 mmHg (Group 2).

Results: The 2 groups were comparable for sex, age, body mass index (BMI), heart rate and diastolic blood pressure (BP) while systolic BP was higher in Group 2 (p<0.0001). PP was 42.3±7.2 mmHg in Group 1 and 65.2±8.1 mm Hg in Group 2 (p<0.0001). Echo Doppler analysis showed higher values of LVMi, LAVi and of E/e’ ratio (7.2±2.1 versus 6.5±1.6) (all p<0.01) as well as lower transmitral E/A ratio and E velocity longer deceleration time (both p<0.02) in Group 2 than in Group 1, without significant difference of RDWT. After adjusting for several confounders including age, heart rate, BMI and LVMi by multiple linear regression analysis, PP and E/e’ ratio were independently associated in the pooled population (standardized β coefficient = 0.39, p<0.0001) (cumulative R² = 0.22, p<0.0001).

Conclusions: Pulse pressure is positively associated with the degree of non invasively estimated LVFP in patients with newly diagnosed, uncomplicated arterial hypertension. These findings confirm the association between arterial stiffness and LV diastolic function explored by other techniques and open a track on the assessment of a possible impact of pharmacological treatment on the arterial-ventricular coupling.

Role of combination therapy with olmesartan and amlodipine to reach target blood pressure in uncomplicated hypertensive patients


Department of Medical and Surgical Sciences, University Magna Graecia of Catanzaro, Italy

Introduction: Hypertension is one of the most important risk factors for the development of cardiovascular diseases. For a better risk stratification, it is necessary to consider the presence of subclinical organ damage. In the choice of the anti-hypertensive drugs it is required, beyond the reduction of blood pressure values, the prevention of the development of organ damage. Recently, the association therapy has emerged as the first choice to reach the target pressure values. The advantages are related to greater effectiveness for the synergism of the actions and a lower incidence of adverse effects.

Aim: To evaluate, in hypertensive patients that received two or more antihypertensive drugs and not to target, the efficacy of combination therapy with ARBs (olmesartan) and CCB (amlodipine) in achieving target blood pressure.

Methods: We enrolled 92 hypertensive patients in treatment with two or more antihypertensive drugs that did not obtain the target pressure (SBP 24h>130 mmHg; DBP 24h>80 mmHg) at the ambulatory blood pressure monitoring 24-h (ABPM). All patients underwent to treatment with olmesartan 20 mg/die and amlodipine 5 mg/die, in substitution to previous medication and they were re-evaluated after four weeks by rerunning ABPM.

Results: The SPB/DBP recorded at baseline were 145.8±9.1/84.7±5.1, 149.6±8.7±88.1±5.7, 141.5±9.7±81.1±4.6 mmHg, during 24 hours, diurnal and nocturnal periods. After one month of treatment the 24h SBP were 126.5±3.6 mmHg (13.2% reduction) and 24h DBP 76.3±3.7 mmHg (10%).

The diurnal systolic values were 130.0±4.7 mmHg (13%), the diastolic ones 80.5±5.4 (8.7%) while during the night were 122.5±4.9 mmHg and 71.7±7.0 (6-11%). In all subjects the therapeutic goals were reached and there were no new episodes of peripheral edema or other side effects.

Conclusions: Present data confirm the efficacy and safety of the combination therapy that may be considered an important therapeutic choice in hypertensive patients.

A case of headache and fluent aphasia: when alternative diagnoses are present at the same time

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Dipartimento di Medicina Sperimentale e Clinica, Università di Firenze. AOU Careggi

We present a case of a 48-year-old man with a sudden onset migraine at rest with visual aura combined to, minutes later, an episode of 10-minutes fluent aphasia and blurred vision of the left eye. Thirty minutes later, another event of fluent aphasia and blurred vision of the left eye occurred and resolved after 10 minutes. In the past two weeks, several episodes of nuchal headache of moderate intensity occurred, without fever, nausea, vomiting or history of trauma; he took non-steroidal anti-inflammatory drugs (NSAID), with parental history of nuchal headache, aphasia or blurred vision. He was referred to Emergency Room 90 minutes after the onset of symptoms. He appeared alert and oriented, asymptomatic for migraine, nuchal headache, aphasia or blurred vision. He was non-smoker. The patient got to Emergency Room 90 minutes after the onset of symptoms. He appeared alert and oriented, asymptomatic for migraine, nuchal headache, aphasia or blurred vision. The temperature was normal, the blood pressure 160/105 mmHg, the pulse 90 beats per minute, the oxygen saturation 98% on room air. The neurological examination was normal and the National Institutes of Health Stroke Scale (NIHSS) score was 0/42. On physical examination, there was only a slight left carotid bruit. An electrocardiogram (ECG) showed a normal sinus rhythm. A computed tomography (CT) of the head was normal. Laboratory blood tests at admission showed only mild increase of alanine aminotransferase (ALT) (81 U/L). A duplex ultrasonography of the neck showed normal carotid and vertebral arteries flow. A transthoracic echocardiography revealed normal left ventricular systolic function and an atrial septal aneurysm. Aspirin 300 mg and statin was begun and the patient was transferred to our department for further investigations.

Treatment with nebivolol 5 mg daily and telmisartan 80 mg daily was added, with satisfactory blood pressure control. An electroencephalogram excluded epileptiform paroxysmal abnormalities. A transesophageal cardiac ultrasoundography confirmed the atrial septal aneurysm associated to patent fora-
The metabolic syndrome and left ventricular function evaluated by using the index of myocardial performance

Seconda Università degli Studi di Napoli - V Divisione di Medicina Interna - Napoli

Introduction: The metabolic syndrome represents a clustering of cardiovascular risk factors affecting about 22% of the adult population in industrialized countries and over 40% of those aged 50 and older.

Purpose: To evaluate the impact of metabolic syndrome (MS) on global left ventricular function by using the index of myocardial performance IMP: Isovolumetric Relaxation Time (IVRT)+ Isovolumetric Contraction Time (IVCT)/Left Ventricular Ejection Time (ET).

Material and methods: Study population included 54 patients (33 male and 21 female); age= 54±11 years with metabolic syndrome and 50 control subjects (30 male and 20 female) age= 53±10 years (tab. 1).

Exclusion criteria: History of myocardial infection, significant coronary artery disease, cardiomyopathy, valvular heart disease, atrial fibrillation, atrioventricular block, diabetes mellitus.

Results: Left ventricular ejection fraction, left ventricular end-systolic diameter and left ventricular end-diastolic diameter were detected to be within normal ranges in both groups regarding this echocardiographic parameter.

Conclusions: In the present study, we have shown the presence of impaired global left ventricular function in patients with MS vs control subjects without MS. This finding emphasizes the importance of early diagnosis and management of metabolic syndrome to prevent the progression of ventricular dysfunction to structural and symptomatic cardiac disease.

Table 1. Clinical characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Metabolic syndrome</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>53±10</td>
<td>54±11</td>
<td>0.79</td>
</tr>
<tr>
<td>Gender F/M</td>
<td>26/10</td>
<td>23/13</td>
<td>0.18</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12</td>
<td>27</td>
<td>0.001</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>95±11</td>
<td>101±14</td>
<td>0.07</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>200±43</td>
<td>209±41</td>
<td>&lt;0.20</td>
</tr>
<tr>
<td>LDL-Cholesterol (mg/dl)</td>
<td>129±37</td>
<td>126±35</td>
<td>&lt;0.65</td>
</tr>
<tr>
<td>HDL-Cholesterol (mg/dl)</td>
<td>44±11</td>
<td>39±9</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>140±77</td>
<td>244±49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>93±10</td>
<td>101±9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 2. Echocardiographic parameters

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Metabolic syndrome</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic diam.</td>
<td>45±0.26</td>
<td>46±0.29</td>
<td>0.45</td>
</tr>
<tr>
<td>LV end-systolic diam.</td>
<td>33±0.18</td>
<td>34±0.20</td>
<td>0.79</td>
</tr>
<tr>
<td>Fractional Shortening (%)</td>
<td>35±3</td>
<td>36±3</td>
<td>0.58</td>
</tr>
<tr>
<td>Ejection Fraction (%)</td>
<td>66±4</td>
<td>66±5</td>
<td>0.64</td>
</tr>
<tr>
<td>IVS (mm)</td>
<td>9.7±1.2</td>
<td>10.5±1.7</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>PW (mm)</td>
<td>9.3±0.7</td>
<td>9.9±1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.94±0.30</td>
<td>0.76±0.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Deceleration time (ms)</td>
<td>174±25</td>
<td>201±34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVRT (ms)</td>
<td>84±10</td>
<td>103±14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVCT (ms)</td>
<td>36±5</td>
<td>50±7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejection time (ms)</td>
<td>311±22</td>
<td>277±17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IMP</td>
<td>0.38±0.04</td>
<td>0.55±0.06</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Metabolic syndrome is an independent predictor of cardiovascular events in patients with nonvalvular atrial fibrillation receiving oral anticoagulants: results of a prospective study

Centro di Aterotrombosi - I Clinica Medica - Dipartimento di Medicina Interna e Specialità Mediche Policlinico Umberto I di Roma

Objective: Metabolic syndrome (MetS) is a multifactorial condition associated with an increased risk of cardiac and cerebral ischemic events. An increased risk to develop atrial fibrillation (AF) has been well recognized in patients with MetS. Studies reporting on the prevalence of MetS in AF population are still lacking. Furthermore the impact of MetS on the incidence of cardiovascular events in patients with non valvular AF (NVAF) taking oral anticoagulants (OAT) has never been investigated.

Methods: We prospectively analyzed 810 consecutive patients with NVAF under OAT. Exclusion criteria were: prosthetic valves, active cancer, chronic inflammatory diseases. Metabolic syndrome was defined according to modified ATP-III criteria.

Results: Patients were followed-up for a median time of 25.4 months (IQR: 15.1-46.2; 2033 patients/year). Mean age was 73.1 years and 55.3% were male. 25.4% patients were obese (BMI ≥30), and 58.6% met the criteria for MetS. At baseline patients with and without MetS were significantly different for BMI, waist circumference, CHA2 DS2-VASc score, HDL choles-

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terol, triglycerides, glycemia, hypertension, diabetes, heart failure, history of myocardial infarction. Use of ACE inhibitors/sartans, beta blockers, oral hypoglycemic agents, insulin and statins was significantly more frequent in patients with MetS. No differences were found in age, TTR and history of stroke/TIA between the two groups. Eighty nine patients (10.98%) experienced a primary outcome during follow-up: 31 AMI/Revascularization, 22 stroke/TIA and 36 cardiovascular deaths. Kaplan Meier curves showed that NVAF patients with MetS had more probability of experiencing MACEs (log-rank test: p=0.003) compared to NVAF ones without MetS; a sub-analysis demonstrated that NVAF patients with MetS had more probability of experiencing AMI/Revascularization compared to those without (log-rank test: p=0.005). In a Cox proportional hazard model age (≥75 years), history of stroke/TIA, history of myocardial infarction/cardiac revascularization and MetS independently predicted cardiovascular events.

Conclusion: In NVAF receiving OAT MetS is an independent predictor of cardiovascular events and particularly of AMI/Revascularization events.

Management of the hypertension in diabetic patient
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Introduction: Affecting one fourth of the adult global population (it is estimated 1 billion people worldwide) hypertension is the leading cause of death and the most common one for an ambulatory visit. Moreover the non-adherence, for several reasons, to the therapy most times based on several classes of drugs, is elevated and the control of pressure is low and especially it has been calculated that only 30% of the diabetic patients reaches the blood pressure (BP) target. Diabetes Mellitus (DM) however affects worldwide about 350 million people, and WHO predicts that deaths due to diabetes will double by 2030. Nowadays this is the sixth leading cause of death. Furthermore it is the main cause of end-stage renal disease (ESRD) and non traumatic amputations. The premature mortality in type 2 diabetic patients is also due mainly to cardiovascular disease (CVD) and the coexistent hypertension (HTN) contributes significantly to the development of CVD and renal disease. HTN is moreover more common in subjects with the type 2 of DM than the non-diabetic population and on the other hand hypertensive patients develop DM 2.5 times more than normotensive people. The insulin resistance and hyperinsulinemia predispose to the development of HTN, in addiction to potential genetic predisposition, vascular and endothelial dysfunction, sodium retention, increased sympathetic nervous system activity and tissue system renin angiotensin (RAS) that play an important role in the pathogenesis of HTN in diabetic patients. The high amount of intracellular calcium in vascular smooth muscle (VSM) cells cause vasoconstriction, proliferation and hypertrophy of VSM cells, and at the same times inflammation and oxidative stress. Thus the treatment of this comorbidities is very important and may really prevent cardiovascular events. The goal of the treatment should be below 140/90 mm Hg, probably down to 130-135/mm Hg (although the evidence for this is scarce). On the other hand we think that the best results could be obtained with a more ambitious goal (PA<130/80 but not below this value, except perhaps for particular cases of <125/75 mm Hg) and by starting the therapy at the pressure value of pre-hypertension.

Objective: Our goal is, on the base of our clinical experience, to determine the possible best therapy in the treatment of this frequent comorbidity.

Patients and methods: We have followed in the last decades, in our Center of HTN, 2500 hypertensive adult patients aged 18-75 years of both sexes, never treated before or with HTN apparently resistant to the therapy established from the family physician, with periodic semestral ambulatory control. Every patient was evaluated with a complete laboratory screening, including the blood and urine analysis, electrocardiography, echocardiography, funduscopic exam, echocardiography of the great arterial vessels. Approximately 60-70% of these patients have DM mainly of Type 2, or impaired glucose tolerance, cardiometabolic syndrome and/or familiarity towards diabetes. Nonpharmacological treatment regimens, such as low salt diet, weight loss, exercise and alcohol restriction have been efficacious to reduce BP. Of course the glycemic control is fundamental, but when it is necessary to start antihypertensive drugs on the basis of guidelines from ESH/ESC, thiazide diuretics, β-blockers, calcium channel blockers (CCBs), ACE inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs) are recommended for initiation and maintenance of antihypertensive treatment both as monotherapy and in suitable combinations (β-blockers in the British recommendations have been downgraded and JNC on Prevention, Detection, Evaluation and Treatment of High BP reports have given thiazide diuretics a prominent role based mainly on the results from ALLHAT). In our clinical practice we prefer to start therapy in the management of HTN of diabetic patients with ACE inhibitors or ARBs, considering their protective effects, especially in proteimuric diabetic nephropathy. If it is not achieved the target BP it is useful, as a second line of therapy, to add a thiazide diuretic at low dose in order to prevent possible negative metabolic effects, considering that, at high doses, diuretics may worsen the insulin resistance and determine new onset of diabetes. Since at least 65% of hypertensive patients require two or more drugs to achieve BP target, CCBs, and especially dihydropyridine CCBs, are effective antihypertensive agents and should be reserved for patients with diabetes who cannot tolerate preferred antihypertensive agents or as adjuncts to ACE-Is or ARBs to achieve BP target. β-blockers as a rule should not be used as first line treatment in patients with DM due to unfavourable effect on endocrine metabolism, but can be used in patients with history of myocardial infarction, heart failure, coronary artery disease, or stable angina (in this case we prefer using carvedilol for its α-blocking activity and primarily for a direct vasodilatory action, or nebivolol that is a highly selective β1- blocker that work by generating NO and has antioxidant effects: both don’t worsen insulin sensitivity, α-blockers, although they improve the lipid profile and insulin sensitivity, are not recommended as first-line therapy and are not commonly used because of side effects such as postural hypotension. However this has been found to provide an excellent relief from the symptomatic prostatism in older men, and it may be a useful add-on therapy. Clonidine, a centrally acting α2 agonist, can also be useful in patients with supine hHTN associated with orthostatic hypotension, but adverse effects limit its use. The antagonists of aldosterone, such as spironolactone and eplerenone (and in Italy canrenone) are nowadays known to affect insulin resistance and pancreatic beta-cell function and are gaining more favour in diabetic patients. This can be effective in selected patients such as those with hypokalemia; but hyperkalemia, a possible side effect, represents an important risk for diabetics especially those with impaired renal function, in combination with a RAS blocker.

Conclusions: Diabetic hypertensive patients have a high risk of CVD and BP goal must be achieved: intensive lifestyle intervention and combinations of different antihypertensive drugs have to be initiated; a combination of RAS blocker and CCBs should probably be the first choice.

Potential target for novel therapies in atherosclerotic disease: effect of dark chocolate on peripheral arterial disease

I Clinica Medica, Dipartimento di Medicina Interna e Specialità Mediche, Sapienza University, Rome

Background: Peripheral arterial disease (PAD) is a clinical setting characterized by an exceptionally high risk for cardiovascular events. Oxidative stress
seems to play a role in impairing flow-mediated dilation (FMD) and contributing to atherosclerosis in patients with PAD. Cocoa seems to exert artery dilatation via oxidative stress inhibition.

**Objectives:** To investigate whether in PAD patients, dark chocolate elicits artery dilatation via down-regulation of NOX2, the catalytic core of NADPH oxidase.

**Methods:** Flow-mediated dilatation (FMD), oxidative stress (as assessed by urinary isoprostanes excretion), nitric oxide generation (as assessed by serum levels of nitrate/nitrite (NOx)), NOX2 activity (as assessed by blood levels of soluble NOX2 derived peptide (sNOX2-dp)) and serum epicatechin were studied in 18 PAD patients in a crossover, single-blind study. Patients were randomly allocated to 40 g dark chocolate (>85% cocoa) or 40 g of milk chocolate (<35% cocoa). FMD, urinary isoprostanes, NOx and sNOX2-dp, platelet oxidative stress and NOX2 activation were assessed at baseline and 2 h after chocolate ingestion.

**Results:** After dark chocolate intake, urinary isoprostanes and sNOX2-dp significantly decreased and FMD and NOx significantly increased in PAD patients. No changes of the above variables were observed after milk chocolate intake. Serum epicatechin significantly increased only after dark chocolate ingestion. Ex-vivo study showed, in platelets of PAD patients, that after dark chocolate, 8-iso-PGF2α and NOX2 activation significantly decreased; no effect of milk chocolate was detected.

**Conclusion:** This study suggests that in PAD patients, cocoa enhances artery dilatation by lowering of NOX2 activation. These results could open new therapeutic strategies to counteract oxidative stress and atherosclerotic progression in PAD.

**Echocardiographic and renal echodoppler characterization of a mice model of cardiorenal syndrome and evaluation of heme oxygenase-1 induction therapeutic effect**


*Department of Internal Medicine (DIMED), University of Padova, Padova, Italy; **Department of Drug Sciences, Biochemistry Section, University of Catania, Catania, Italy

Cardiorenal syndrome (CRS) is the acute (type1) or chronic (type2) worsening of renal function due to heart failure (HF) and to the activation of renin angiotensin system and the consequent renal vasoconstriction. Heme oxygenase 1 (HO-1) is the enzyme responsible for heme degradation to bilirubin, carbon monoxide and iron. Previous studies have shown that upregulation of HO-1 exerts a cardio protective effect in animal models of HF by reducing infarct size and post ischemic ventricular pathological remodeling. HO-1 exerts also a renoprotective effect against angiotensin II induced renal damage. Thus HO-1 induction could be a therapy for HF and CRS. High resolution EcoDoppler technique can be used to evaluate cardiac function and renal perfusion in small animals. There are no animal models that reproduce the physiopathology of CRS type 1 and 2. Aims of this study were: 1) the echocardiographic and renal echoDoppler characterization of a mice model of post ischemic HF and CRS with a high resolution echo machine 2) to evaluate the effect of HO-1 induction on renal vasoconstriction due to CRS. CD1 mice underwent left anterior descending coronary ligation (LAD). Mice were divided in 4 groups: 1) control group; 2) 5 mice with myocardial infarction without treatment (MI); 3) 5 mice with myocardial infarction treated daily with the HO-1 inducer Sodium Nitroprusside (SNP, 30μg/Kg); 4) 5 mice with myocardial infarction treated daily with SNP and three times a week with a new imidazolic HO-1 inhibitor named inhibitor-1 (10 mg/kg). Mice were treated from day 15 after LAD, until sacrifice (30 days after LAD). Mice underwent high resolution echocardiography and renal EcoDoppler performed with VEVO2100 high resolution echomachine 15 and 30 days after LAD. Renal vasoconstriction was quantified by renal pulsatility index (kPI) evaluation. Mice with LAD developed left ventricle dilatation (end diastolic area: p<0.01 vs controls) with reduction of ejection fraction (EF: p<0.05 vs controls) and diastolic dysfunction (myocardial performance index: p< 0.01 vs controls). Renal vasoconstriction was also significantly increased (kPI p<0.01 vs controls). HF and renal vasoconstriction were evident 15 days after LAD. In mice treated with SNP there was a significant improvement of cardiac contractile function (ejection fraction and fractional shortening: p <0.05 vs MI) and of renal vasoconstriction (k PI p<0.01 vs MI). HO-1 inhibitor administration reversed inductor effects. Conclusions: 15 days after LAD mice have significant cardiac and renal alterations detectable by high resolution echocardiography and renal echoDoppler. Thus LAD can be used as model of HF and CRS. HO-1 induction improves cardiac function and renal vasoconstriction in mice with echographically detectable HF and CRS.

**Essential role of immunosuppressive T-regulatory cells and heme oxygenase-1 up-regulation in improving heart function in post ischemic myocardium**

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Post ischemic heart failure is one of the most prevalent diseases worldwide. It is the consequence of pathological remodeling after myocardial ischemic damage. T lymphocytes mediated immune response is known to play an important role in post-ischemic cardiac remodeling. T regulatory lymphocytes (Treg) are a subpopulation of T helper lymphocytes with a regulatory and immunosuppressive role. Heme oxygenase-1 (HO-1) induction improves heart function after ischemic damage by its anti inflammatory, anti oxidative and antiapoptotic effect. Aim of this study was to assess the role of T-lymphocyte on HO-1 effect on post ischemic cardiac remodeling. We compared the effect of HO-1 induction on post-ischemic heart failure in T-lymphocytes immunodeficient mice (SCID) and in immunocompetent mice (C57). Post ischemic heart failure was induced by left anterior coronary artery ligation. Mice were divided into 4 groups: sham, myocardial infarction (MI), MI treated with HO-1 inducer Cobalt Protoporphyrin with and without HO-1 inhibitor, Stannous Mesoporphyrin. All mice underwent echocardiography 30 days after surgery and, in C57 mice, T lymphocytes subpopulations were measured by Fluorescence Activated Cell Sorting (FACS). Mice with MI had increased levels of inflammatory cytokines as compared to the controls (p<0.05), significant myocardial fibrosis (p<0.05 vs controls) and lower capillary density (p<0.01 vs controls). Echocardiography showed that left ventricle end diastolic area (EDA), was significantly reduced in CoPP treated groups compared to MI groups (C57, EDA: MI: 0.216±0.02 cm; MI+CoPP: 0.172±0.03 cm; (-13%) p<0.01) and the beneficial effect of HO-1 induction was more evident in SCID mice (SCID, EDA: MI: 0.190±0.02 cm; MI+CoPP: 0.100±0.01 cm, (-25%) p<0.01). In CoPP treated C57 mice Treg subpopulation was significantly increased (20±3% vs 5±3%; p< 0.01). All these beneficial effects were reversed by SnMP. Conclusions: HO-1 via its effect on T-cells mediated immunity, reverses dysfunctional remodeling and enhances peri infarct survival in the post ischemic miocardium. Targeted enhancement of T reg cells via HO-1 in-
duction could thus provide adjuvant avenues for reducing morbidity and mortality in patients with post MI heart failure.

**Oxidative stress in patients affected by primary aldosteronism**

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**Introduction:** Primary aldosteronism (PA), one of the most common form of secondary hypertension, is associated with a significant increase of global cardiovascular risk (CVD) (ischemic heart, cerebrovascular events, arhythmias) (RR 4.6). The specific treatment of the PA (surgical in adrenal adenoma - APA- or pharmacological in idiopathic forms -IHA) significantly reduces CVD risk. Recently, in addition to high blood pressure values and direct action of aldosterone, newly mechanisms are involved in the development of increased CVD risk and organ damage in PA subjects, such as metabolic, endothelial and coagulation alterations.

**Aim of the study:** Evaluate parameters of oxidative stress in 38 patients (21 M, 17 F, mean age 53.3±4.7 years) with PA [11 APA (4M, 7F, mean age 50.2±4.5 years ) and 27 IHA (17M, 10F, mean age 54.5±5.3 years)] at diagnosis and after specific treatment (surgical or pharmacological), respect with control group of 41 patients with low renin essential hypertension (IEBR) (21M, 20F, mean age 49±7.4 years).

**Results:** PA subjects (both APA or IHA) showed significantly increase of plasma levels of NADPH oxidase (NOX2) and urinary isoprostanes (34.9±4.3 g/dl and 216.3±15.7 ng/mg, respectively; p<0.05) than IEBR subjects (27.1±3.7 g/dl and 144.8±9.4 ng/mg, respectively; p<0.05). In APA patients undergoing to adrenalectomy, after 6 months follow-up, we observed reduction of both circulating levels of NOX2 (29±2.1 µg/dl vs 22.4±1.7 µg/dl; p<0.05) and urinary levels of isoprostanes (221.1±10.5 µg/dl vs 144.8±9.4 ng/mg, respectively; p<0.05). In APA patients undergoing to adrenalectomy, after 6 months follow-up, we observed reduction of both circulating levels of NOX2 (29±2.1 µg/dl vs 22.4±1.7 µg/dl; p<0.05) and urinary levels of isoprostanes (221.1±10.5 µg/dl vs 144.8±9.4 ng/mg, respectively; p<0.05).

**Conclusions:** our study firstly show an increased oxidative stress in PA subjects, characterized by an increase in serum levels of NOX2 and urinary excretion of isoprostanes. After adrenalectomy in APA patients, we found reduction of serum NOX2 and urinary isoprostanes and normalization of blood pressure values.

**Relationship between echocardiographic measurement of left ventricular mass and finger nail fold capillaroscopy in patients with isolated systolic hypertension (ISH)**


**S.O.C. Internal Medicine - Az. Osp. “Pugliese-Ciaccio” Catanzaro**

Hypertension is associated with alterations in vessel structure usually leading to an increase in wall to lumen ratio. Hypertension is a serious health problem in most developed countries and is the major risk factor for cerebral and cardiovascular disease, and lowering blood pressure levels is the most cost-effective way of reducing cardiovascular morbidity and mortality.

**The Aim:** Was to evaluate finger nail-fold capillaroscopy in a consecutive and non selected series of hypertensive patients with ISH, and to compare the micro vascular findings to these observed by echocardiography for detection of left ventricular mass, left ventricular hypertrophy and increased cardiovascular risk.

**Methods:** Eighty hospitalized patients mean age 61.36±11.40, (range 55-71), with isolated systolic hypertension, 52 M and 28 F were studied. The time period of disease between 4 and 30 years (mean 11.7±6.06 years). Admission criteria included systolic blood pressure > 140 mmHg and diastolic blood pressure < 85 mmHg. All the patients underwent an Echocardiography according to standard laboratory procedures. All echocardiograms were read by the same operator. End-diastolic left ventricular internal diameters (LVIDd), posterior wall (PWT), interventricular septal thickness (ST) were measured according to the recommendations of the American Society of Echocardiography. Were also measured left ventricular mass and left ventricular mass index. Left ventricular hypertrophy was defined as concentric when LVID was > 44. Nail fold capillaroscopy was performed using a Videocap 3.0 (DS Medica) with magnification 200x.Comparison of the capillaroscopic parameters was made with 50 age and sex matched healthy controls.

**Results:** Nail fold capillaroscopic analysis revealed that the decrease in number of capillary loops was more marked in the patients with Isolated Systolic Hypertension vs control group (8, 5 loops/mm. Vs 11, 5/mm).

Lengthened capillaries in 77% of pts with ISH vs. 10% control group. Thinner capillaries 56% in pts with ISH vs. 20% in control group. Microhemorrhages in 38% of pts with ISH vs. 10% in control group. Dilated and tortuous capillaries, arteriolarousenous, and fleabite iuxta-capillary microhemorrhages, were found more frequently in the patients with ISH. Echocardiography findings indicated (Tab. V): interventricular septum thickness (IVST mean value: 10.2±1.3 mm. vs. 8.4±1.4 mm. Control group), left ventricular internal diameter in diastole (LVIDd mean value: 50.4±4.4 mm. vs. 46.4±4.3 mm.), relative wall thickness (RWT mean value: 40.1±6.3% vs. 36.1±7.8%), posterior wall thickness (PWT mean value: 10.3±1.3 mm. vs. 8.6±1.7 mm.), left ventricular mass (LVM mean value: 192.5±38.9 g. vs. 135.5±34.3 g.), left ventricular mass index (LVMi mean value: 55.8±0.8 g/m² vs. 34.9±8.5 g/m²). This procedure is a valuable procedure for LV mass estimation and it allows detection of LV hypertrophy and increased cardiovascular risk.

**Conclusion:** Patients with higher value of left ventricular mass index revealed many micro vascular anomalies in finger nail-fold capillaroscopy. Those micro vascular abnormalities characterize the morphological picture of endothelial injury or dysfunction that is considered the primum movens of the cascade of events leading to an atherosclerotic plaque. Those results revealed a relationship between finger nail-fold capillaroscopic findings and left ventricular mass. Similarly to echocardiography, capillaroscopy is clinically useful to identify subjects at increased cardiovascular risk who need a more aggressive management.

**Evaluation of carotid intima-media thickness as a marker of macrovascular involvement in patients with systemic sclerosis**


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Systemic Sclerosis is an autoimmune rheumatic disease that has vascular injury as one of its main clinical markers. The vascular involvement of SSc has been considered to be mainly micro vascular; however increased prevalence of macro vascular disease has been reported in recent literature. The common carotid artery intima media thickness (CCA-IMT) is widely used as an early indicator of atherosclerotic process. The systemic inflammatory status can induce matrix metalloproteinases and can both stimulate smooth muscle cell migration through the internal elastic lamina into the
The aim: To evaluate CCA-IMT in patients with SSc to verify a possible association with disease severity and to assess the relationship of Carotid intima-media thickness with known cardiovascular risk factor.

Methods: 114 female pts, all postmenopausal, with SSc (ACR SSc criteria fulfilled), mean age 56.42±4.76 years, mean disease duration 9.69±5.9 years, mean BMI 25.4±3.4 kg/m2 were studied. According to the criteria defined by LeRoy (1989), 72 pts had Diffuse SSc subtype (63.1%) and 42 pts Limited SSc subtype (36.9%). We explored associations of disease subset, antibody profile, organ involvement, number of DU, occurrence of new DU, overall DU clinical status: improved, stabilized, and worsened.

Results: We revealed: systolic blood pressure 144.8±20.1 mmHg (SSc) vs 143.3±20.4 (Control) pNS; Body mass index 25.4±3.4 (SSc) vs 24.4±2.6 (U) pNS; age 56.42±4.76 (SSc) vs 55.82±4.92 years (Control) pNS; total cholesterol 213±28 mg/dl (SSc) vs 190±30 (Control) pNS; LDL cholesterol 130±30 (SSc) vs 129±31 (Control) pNS; HDL cholesterol 39±14 (SSc) vs 43±15 (Control) pNS; The mean common carotid artery intima media thickness (mm) were: 0.92±0.36 D-SSc vs 0.74±0.32 L-SSc vs 0.63±0.32 control group, p<0.01. In five D-SSc pts (4.3%) we found a localized irregular intima media thickening of 1.5mm and were defined as carotid artery plaque and were related lower MRSS.

Conclusion: In our study modified Rodnan skin thickness score (MRSS) is relative to common carotid artery-intima media thickness (CCA-IMT) in SSc patients, which means this macrovascular disease is associated with disease activity. We revealed highest value of total cholesterol and significantly lower HDL cholesterol. These results are of clinical relevance for counseling patients and for considering prophylactic strategies with statins.

A higher (1000 ng/ml) D-dimer cut-off value safely rule-out pulmonary embolism in elderly emergency department patients


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Background: The diagnosis of acute Pulmonary Embolism (PE) is based on the assessment of clinical probability using scores or clinical judgment in combination with D-dimer and pulmonary computed tomography angiography (CTA). D-dimer concentration increases with age, therefore its specificity for PE decreases. Therefore, some authors have proposed higher cut-off values to increase the proportion of patients in whom PE could be safely excluded, in order to reduce the number of CTA avoiding contrast agent and radiation risks and shortening hospital stay. Few studies have explored the potential of higher D-dimer cut-off values in patients aged 80 years or more.

Purpose: To evaluate whether increasing the standard threshold of serum D-dimer to a higher cut-off value could increase the specificity of D-dimer assay for the exclusion of PE without reducing the sensitivity in the setting of elderly patients referring to the Emergency Department (ED) with clinically suspected PE.

Material and Methods: All patients with a CTA performed in the ED of Vimercate’s Hospital, a 500-bed general hospital, from 2010 through 2012 for clinical suspicion of PE were included in a retrospective cohort study. Helical CT scans were performed on Philips CT and General Electric CT which included 64- detector capability. D-Dimer was measured with particle enhanced immunoturbidimetric assay Innova D DIMER on the Behring Coagulation System (BCS) analyzer (Siemens Medical Solutions Diagnostics, Deerfield, IL, USA) normal value: less than 490 ng/mL. A Receiver Operating Characteristic (ROC) curve was constructed. Sensitivity (S), Specificity (SP), Positive (PPV) and Negative Predictive Value (NPV) were calculated for different D-dimer cut-off values established according to the ROC curve analysis and clinical criteria.

Results: Of the 481 patients included (305 women, 63.4%, mean age±SD 73.0±16.1). Overall prevalence of confirmed PE was 22.5% (108 cases). According to anatomical site of the highest order branch affected, 37 PE were of the main trunk (34.3%), 40 lobar (37.0%), 27 segmental (25.0%) and 4 subsegmental (3.7%). ROC curve of D-dimer showed an area under the curve of 0.749 (95% confidence interval 0.698-0.800), Figure 1. One hundred ninety one patients were aged 80 years or more (143 women, 74.9%) PE: 37 cases (19.4%). In subjects aged >= 80 years D-dimer cut-off of 490 ng/mL yields S, SP, PPV and NPV values of 100%, 1%, 19% and 100%. For D-dimer cut-offs of 1000 and 1500 ng/mL values of S, SP, PPV and NPV were 100%, 8%, 21%, 100% and 92%, 25%, 23%, 93%, respectively.

Conclusion: In elderly ED patients with clinically suspected PE, a higher (1000 ng/dL) D-dimer threshold value increases the specificity of D-dimer assay for the exclusion of PE without reducing sensitivity and maintaining a NPV of 100%. The application of that threshold would lead to a safely reduction of the number of pulmonary CTA necessary to exclude PE in this population.
Psoriasis, obesity and neurovegetative cardiovascular assessment


Background: Psoriasis is a chronic, inflammatory, immune-mediated skin disease that is often associated with metabolic syndrome and other disorders, including obesity and dyslipidemia. In a previous study we observed that the Heart Rate Variability (HRV), analyzed through linear and nonlinear methods, is altered in young patients with moderate psoriasis with a prevalence of the indexes of the sympathetic modulation.

Objectives: The aim of this study was to evaluate whether in young patients with obesity and/or moderate psoriasis, in absence of other comorbidities, the autonomic function is affected.

Material and Methods: We enrolled 57 subjects, aged between 18 and 35 years, of both sexes matched for age, divided in 4 groups: 17 Normal control subjects, 17 affected by moderate psoriasis, both groups with BMI < 24, 11 affected by moderate psoriasis and 12 normal subjects, both groups with BMI > 28.

A record of digital ECG (XAI-MEDICA) for 10-minute in rest condition was obtained from all the subjects included in the study and then analyzed with XAI-MEDICA software for HRV linear analysis and with KUBIOS-HRV software for the HRV non linear analysis. Linear methods included traditional statistical analysis (SDNN, RMSSD) and the analysis of the HRV through the frequency domain calculating the LF, HF and LF/HF Ratio components. Nonlinear methods included the Poincarè plot (SD1 and SD2 indexes) and the detrended fluctuation analysis (DFA - $a_1$, $a_2$ indexes).

One Way ANOVA for repeated measures was used to compare the 4 groups; p value was set at 0.05.

Results: In all patients with psoriasis (with BMI<24 and >=28) and in obese subjects without psoriasis, sympathetic indexes (LF, LF/HF ratio and al-phan indexes) were significantly increased together with the decrease of the parasympathetic indexes (SDNN, RMSSD and SD1) respect to the normal controls. We didn’t find any significant differences between the patients with only psoriasis and only obesity or with both conditions.

Conclusions: Our data indicate that in the moderate psoriasis and in obesity there is a reduction of the parasympathetic with the concomitant increase of the sympathetic indexes using linear and non linear methods of HRV. Since the increase in sympathetic activity may be associated with a higher cardiovascular risk (ventricular arrhythmias, sudden cardiac death, etc.), moderate psoriasis, such as obesity, could be considered as an independent risk factor. Therefore, patients with psoriasis should be screened for cardiovascular risk factors.

Gender and age at diagnosis in cardiac AL amyloidosis

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Purpose: Light chain (AL) amyloidosis is a rare disease with severe prognosis, that is mainly determined by the presence of cardiac involvement. So far, the effects of gender and age on ECG and echocardiographic presentation at the time of diagnosis have not been investigated.

Methods: We enrolled 160 consecutive never treated patients, in whom diagnosis of cardiac AL amyloidosis was concluded between 2008 and 2010, according to the International Society of Amyloidosis criteria. The prevalence of female and male patients was 45% (n=72) and 55% (n=88), respectively. Twelve-lead electrocardiogram, echocardiogram and serum NT-proBNP, Troponin I and free light chains were obtained at diagnosis. Age at presentation ranged from 35 to 88 years, and patients were divided in age quartiles. Prognosis was assessed after a median follow-up of 326 days.

Results: No difference between genders was observed in serum NT-proBNP, TnI and free light chain levels. When compared with women, male patients had prolonged PQ (190 vs 170 ms, p<0.001) and QRS (91 vs 84 ms, p=0.013) intervals, whereas corrected QT interval and heart rate were superimposable. There was no gender-related difference either in the prevalence of low-voltage ECG pattern or in peripheral QRS score (i.e. the sum of ECG voltages in peripheral leads). Focusing on the echocardiographic parameters, indexed mean ventricular wall thickness were higher (p<0.009), and indexed chamber volumes smaller (p<0.02) in female patients, indicating a more concentric geometry despite superimposable values of indexed LV mass (an indirect measure of amyloid deposition). Moreover, higher lateral and septal E/E’ (an estimate of left ventricular filling pressure, p<0.02) was observed in women, suggesting a worse diastolic function. Biomarker levels, ECG and echocardiographic parameters were not influenced by patients’ age. Survival was not affected by gender and age at the time of diagnosis, and a trend towards a better prognosis in women and younger patients fell short of statistical significance.

Conclusions: In cardiac AL amyloidosis, women show a higher extent of
diastolic dysfunction and of a more concentric geometry, despite comparably indexed LV mass, i.e., an indirect measure of amyloid deposition. ECG, echo-derived, and biochemical parameters were not influenced by patient’s age at the time of diagnosis.

**Aspirin reload before percutaneous coronary intervention: impact on reperfusion indexes**


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**Background:** Incomplete aspirin (ASA) platelet inhibition and intervention- 

tional microvascular obstruction (MVO) have been suggested as putative mechanisms of adverse clinical outcome in patients undergoing elective percutaneous coronary intervention (PCI) despite optimal dual antiplatelet therapy. Thromboxane (TX) A2 might be involved as a key mediator of platelet activation and as a potent coronary vasoconstrictor.

**Aim and Methods:** Pre-procedural Aspirin reload for Native coronary dis-

ease Treated by Angioplasty: Reperfusion indexes Evaluation and Improvement of clinical outcome (PANTAREI) study is an interventional, multicenter, randomized study planned to evaluate the effect of ASA reload (325 mg orally at least 1 hour before elective PCI) on: (i) serum TxB2 level-

s (stable metabolite of TxA2) changes after 60 and 120 min; (ii) changes of reperfusion indexes, evaluated by corrected TIMI Frame Count (cTFC) and myocardial blush grade (MBG); (iii) modifications of myocardial injury indexes expressed by serum cardiac Troponin I (TnI) tested at 6, 12 and 24 hours after PCI.

**Results:** We enrolled 91 patients (74 M and 17 F, 66±10 yrs.), already on chronic low-dose ASA therapy, scheduled for elective PCI and randomly assigned to receive ASA reload (N=46) or no-reload (N=45) before the procedure. Compared to no-reload group, TxB2 significantly decreased after 120' from PCI in ASA reload group. After procedure, both groups showed a statistically significant reduction in cTFC and in percentage of pa-

\[\text{tients with MBG≥2} \text{(Reload= 39% ; No-Reload=69%)}. \text{Moreover, at the end of procedure, both reperfusion indexes were lower in the ASA reload group compared with the no-reload group (p=0.01). Patients who achieved a normal microvascular perfusion showed a significantly lower TxB2 serum values (p=0.05).} \]

**Conclusions:** The present study shows that 325-mg ASA loading dose, before elective PCI, would provide a significant clinical benefit. These findings suggest a possible physiopathological role of serum thromboxane complete inhibition in the prevention of "interventional MVO".

**Very prolonged asystole during tilt test: a case report**

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The vasovagal syncope is a frequent clinical problem, representing 21% of all type of syncope, although this percentage is probably underestimated since 36.6% of vasovagal syncope is of unknown origin. The cardioinhibitory syncope is classified as type 2 vasovagal syncope (VASIS classification) and can be triggered by the tilt-test. It can be asystolic (Type 2B, 4-33% of tilt test-induced syncope) when asystole occurs for more than 3 sec-

**Congenital adrenal hyperplasia and the heart**


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**Introduction:** Patients with Congenital Adrenal Hyperplasia (CAH) are treated with lifelong high doses of glucocorticoids. This kind of therapy may be associated with cardiovascular risk because of its negative impact

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*Figure 1. Asystole. The first sinusal heart beat appears after approximately 40 seconds. Artefacts from the cardiac massage are visible.*
on metabolic profile and blood pressure controls. Aim of the current study was to investigate exercise performance and left ventricular architecture and function, in a group of young adults affected by CAH.

**Patients and Methods:** We evaluated 20 CAH patients (10 female and 10 male: age 13±2.4 years) and compared them with 20 age- sex-matched controls (10 female and 10 male: age 13±3 years). All patients underwent echocardiographic assessment and symptom-limited exercise testing. Hormonal and biochemical parameters were also measured.

**Results:** Patients with CAH displayed mild diastolic dysfunction [IVRT (ms): 112±20 vs 100±14; p:0.03; Deceleration Time (ms): 136±22 vs 113±15, p: 0.00003]. Systolic Blood Pressure (SBP) at peak exercise was higher in CAH patients [SBP (mmHg): 150±17 vs 135±15; p: 0.0005] as well as the difference between SBP at baseline and at peak workload [ASBP (mmHg): 39±14 vs 30±14, p: 0.05]. Both parameters were related with HOMA Index (respectively SBP: r: 0.65 p: 0.001; ASBP: r: 0.55 p:0.05). Moreover patients with CAH exhibited impaired exercise Performance [Peak Workload (W): 98±27 vs 121±27; p:0.01]. In Male CAH, the degree of diastolic dysfunction was negatively related to serum Testosterone values [IVRT (ms): r: -0.864 p: 0.02; Deceleration Time (ms) r: -0.764 p: 0.001].

**Conclusion:** Congenital Adrenal Hyperplasia is associated with mild diastolic dysfunction and high blood pressure in response to exercise. Moreover CAH patients have an impaired exercise performance.

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**Head to head comparison of standard echo doppler and 3D speckle tracking echocardiography in detection of subclinical anthracycline cardiotoxicity in breast cancer**

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**Purpose:** The subclinical diagnosis of chemotherapy-induced cardiotoxicity is a critical issue in the setting of oncologic patients in order to prevent overt heart failure and to avoid early treatment withdrawal. The present study aimed to assess the diagnostic power of real-time 3D Speckle Tracking Echocardiography (STE) in comparison with standard echo Doppler in detection of subclinical anthracycline (ANT) derived cardiotoxicity in breast cancer patients.

**Methods:** Fifty-five consecutive patients (F/M = 54/1, mean age = 48 years) with breast cancer were treated by multiple protocols including ANT (epirubicin, cumulative dose = 505±68 mg/m2, range = 360-720 mg/m2) and cyclophosphamide and/or 5-fluorouracil for 3-4 cycles. Exclusion criteria included coronary artery disease, valve heart failure, primary cardiomyopathies and atrial fibrillation. Before starting and after treatment (3 months follow-up) all the patients underwent complete standard echo Doppler exam and real time 3D echo evaluation. Standard echo Doppler included determination of 2D ejection fraction (EF) and pulsed Tissue Doppler of the mitral annulus, with the calculation of the ratio between early diastolic velocity of mitral inflow and early diastolic velocity of mitral annulus (E/e’ ratio). Real-time 3D echo was performed according to standardized methods (frame rate ≥ 40% of individual heart rate) and included determination of left ventricular volumes and EF as well as 3D STE-derived global longitudinal strain (GLS), global circumferential strain (GCS), global area strain (GAS) and global radial strain (GRS) were also measured whenever feasible.

**Results:** All the patients completed the cycles of chemotherapy. None complained about symptoms and/or signs of heart failure such to interrupt the chemotherapy before the end of the cycles. Among standard echo Doppler parameters, 2D EF (62.9±6.4% after and 61.8±7.9% before), transmural E/A ratio and E velocity deceleration time were not significantly changed by treatment whereas E/e’ ratio was higher after (7.25±1.8) than before treatment (6.7±1.7) (p<0.01). Among 3D echo parameters left ventricular end-systolic volume was increased (p<0.01) and EF reduced (58.8±8 vs 61.7±7.1%, p<0.02) after treatment. Among 3D STE parameters, GLS (p<0.01), GRS (p<0.001), GCS (p<0.0001) and GAS (-28.4±5.9 vs. -31.6±3.6, p<0.0001) were all significantly reduced after ANT. Worthy of note, 3D volumetric assessment was feasible in 35/55 patients (63.8%) and 3D STE in 33/55 patients (60%). The main causes of this low feasibility were left breast cancer location, previous radiotherapy and breast prosthesis implantation.

**Conclusions:** Our study demonstrates the potential superiority of real time 3D echocardiography in diagnosing subclinical cardiotoxicity of anthracyclines in breast cancer patients but also the suboptimal feasibility of this novel imaging technique in this clinical setting. Among standard echo Doppler parameters E/e’ ratio appears to offer significant advantages over other standard echo Doppler parameters in revealing early signs of cardiotoxicity. These findings can have clinical implications in the imaging follow-up of breast cancer patients during treatment.

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**Sympatho-vagal imbalance during oral glucose tolerance test in newly diagnosed hypertensives**


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**Introduction:** The autonomic nervous system (ANS) is characterized by two components: the sympathetic and parasympathetic. ANS influences the Heart Rate Variability (HRV) that reflects the sympatho-vagal balance. Several techniques have been developed to evaluate HRV, even if the most common are the time and frequency domain analysis. Besides, many data demonstrated that in patients with cardiovascular risk factors, such as diabetes and hypertension, the reduction of HRV, due to an increase of sympathetic activity, is an independent predictor for clinical events. Recently, many evidences suggest that 1h post-load plasma glucose ≥ 155 mg/dl is able to identify normoglucone tolerant (NGT) subjects at high risk for type 2 diabetes (T2D) and development of subclinical organ damage.

**Aim:** To evaluate variability of sympatho-vagal balance, by using HRV analysis, in a group of never-treated hypertensives during oral glucose tolerance test (OGTT).

**Methods:** We enrolled 92 never-treated hypertensive subjects (56 women, 36 men), aged 55±9.8 years. During OGTT, the patients underwent to short-term recordings to evaluate the HRV in the time domain, particularly the standard deviation of NN intervals (SDNN) at 0, 30, 60, 90 and 120 minutes. Insulin sensitivity was assessed by Matsuda index.

**Results:** According to OGTT values we divided the population in four groups: 1) NGT with 1-hour post-load plasma glucose <155 mg/dl (n=38), 2) NGT with 1-hour post-load plasma glucose ≥ 155 mg/dl (n=18), 3) impaired glucose tolerance (IGT, n=20) and 4) T2D (n=16). There were no significant differences among groups for gender distribution, age, systolic and diastolic blood pressure, total cholesterol and triglyceride. From the first to the fourth group of glucose tolerance status, there was a progressive increase of fasting and post-load glucose and insulin (P<0.0001), accounting for the reduction of Matsuda index. The values of SDNN were significantly (P<0.001) reduced during OGTT in all groups. Moreover, HRV was significantly different between groups from 60 minutes to the end of the test. In particular, in group 2 (64±17), 3 (56±15) and 4 (49±11), SDNN was significantly (P<0.0001) lower than group 1 (66±17). Similarly result were observed at 90 and 120 minutes.
A strange “bronchitis”

Schiavo A*, Renis M**


Introduction: In evaluating chest pain, we must never neglect the most likely diagnosis.

Case report: I.E., male, 41 y.o, smoker (over 45 p/y), former addict. In the last two months has uselessly practiced antibiotics and steroids for chest pain, diagnosed as “bronchitis” by his doctor. Since he complains of chest tightness with recurrent pain in the arms, we suspect angina pectoris, and we deepen anamnesis that reveals family history of myocardial infarction (a brother at 45).

CXR, ECG and echocardiography: normal. Total cholesterol 221 (LDL 161, HDL 37); stress test: “Test can not be assessed for failure to achieve sub-maximal heart rate, but positive for symptoms”.

Following our clinical suspicion, the patient undergoes coronaryography: “critical stenosis (90%) to the right coronary artery (dominant)”.

Discussion: Chest pain should never be underestimated. We must always consider the overall cardiovascular risk (CVR), and therefore blood cholesterol, smoking and cardiovascular events in family, all represented in our patient.

Conclusions: Clinical history is the main time of clinical evaluation to formulate diagnostic hypothesis. The shrewd assessment of symptoms must define the circumstances in which they arise, in order to reconstruct the true clinical picture. Our patient is more likely to suffer from heart than from lung disease. In fact, smoking, the primary cause of COPD, is an independent risk factor for CV disease, too. Chest pain occurring in a recurrent way and with typical radiation, should make us think of heart disease, which is the first pathological condition to be excluded; even the high cardiovascular risk should suggest heart disease.

The clinical case underlines the importance of detailed anamnesis, first of all.

Effect of both liraglutide and sitagliptin on left ventricular ejection fraction and functional status in diabetic patients with chronic heart failure


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Introduction: Increasing evidence suggests that there is a strong association between type 2 diabetes (T2DM) and heart failure. The improvement of the glycemic control of patients with T2DM and heart failure is challenging due to side-effects profile of current therapies including hypoglycemia, weight gain, and fluid retention. The recently introduced therapies with GLP-1 receptor (GLP-1R) agonists have shown to produce beneficial effects on several cardiovascular risk factors in addition to their potential glycemic benefits. However, it is unknown whether treatment with GLP-1R agonists is able to have beneficial effects on cardiac function beyond their effect on glucose control.

Aim: The aim of the study was to compare the efficacy of Liraglutide, Sitagliptin and insulin Glargine as adjunct treatments to standard therapy on ventricular function in post-ischemic T2DM patients with class II/III heart failure, defined according to the New York Heart Association (NYHA) guidelines and/or a left ventricular ejection fraction (LVEF) ≤45%.

Methods: This was an open-label, randomized, 52-week active-comparator, parallel-group study. The study group consisted of 31 T2DM Caucasians, aged between 45-75 years, with history of acute myocardial infarction (AMI), and NYHA class II/III and/or LVEF of ≤45%. The participants were treated with standard therapy for chronic heart failure. All subjects were treated with metformin and/or sulfonylurea for at least three months with suboptimal glucose control (HbA1c ≥7.0 and <10%). Subjects were excluded if they had heart failure due to or associated with uncorrected thyroid disease, clinically significant active cardiovascular disease, history of chronic pancreatitis, history of any malignant disease, history of alcohol or drug abuse, liver or kidney failure and use of any drug which could interfere with glucose metabolism, including systemic corticosteroids. The participants were randomized to receive 1.8 mg Liraglutide, 100 mg Sitagliptin or insulin Glargine in addition to metformin and/or sulfonylurea. Starting dose of liraglutide was 0.6 mg, increased every week to 1.2 mg and then to 1.8 mg. Insulin Glargine was titred according to treat to target protocol. The participants underwent a complete anthropometric evaluation, laboratory determinations, electrocardiogram, echocardiogram, Minnesota Living with Heart Failure questionnaire, 6 min Walk Test for evaluation of the functional capacity at baseline, and then, at 6, 12, 26 and 52 weeks after randomization. The present analysis was restricted only at the participants that completed the study.

Results: 17 out 31 subjects enrolled completed the study. The participants were well matched for age and sex. Mean BMI was >30 kg/m² with no differences among the three groups. At baseline, subjects treated with Liraglutide exhibited higher fasting glucose and HbA1c levels as compared with subjects treated with Sitagliptin or insulin Glargine. All the treatments were able to induce a reduction in fasting glucose and HbA1c levels.

Treatment with Liraglutide was associated with an improvement in LVEF compared with baseline (46±2% vs. 40±0.9%, respectively). This significant improvement was already observed after 12 weeks of treatment. On the contrary, treatment with Sitagliptin or insulin Glargine was associated with no changes in the LVEF. Both end-diastolic and end-systolic left ventricular volumes were reduced in Liraglutide-treated patients but not in the patients treated with Sitagliptin or insulin Glargine. Liraglutide treatment was also associated with an improvement of functional capacity, an improvement of quality of life, and a reduction of pro-BNP levels. By contrast, no changes were observed in patients treated with Sitagliptin or insulin Glargine.

Treatment with either Liraglutide or Sitagliptin was associated with a reduction in left ventricular mass.

Conclusions: These data provide for the first time evidence that treatment with Liraglutide is associated with improvement of cardiac function and functional capacity in post-ischemic T2DM patients with heart failure.

Effects of oral supplementation with essential amino acids on hemodynamic parameters and vascular stiffness in essential hypertension


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Introduction: Recent findings suggest that essential amino acids (EAAs), are able to improve the cardio-metabolic profile both in animals and in subjects with chronic disease, such as heart failure, chronic obstruction pneumonopathy disease and type 2 diabetes. These effects are almost partially related to the increase of the insulin-mediated nitric-oxide production in endothelium, with a subsequent improvement of insulin sensitivity and endothelial function, as suggested by in vitro studies. On the other hand, the endothelial dysfunction, that represents the first step in atherosclerotic process, is closely related to arterial stiffness (AS). The AS that occurs in hypertension, represents a strong indicator of subclinical organ damage and it is associated with an increase of cardiovascular mortality and morbidity.

Aim: We designed the study to evaluate the effects of oral supplementation with EAAs on hemodynamic parameters and AS in hypertensive patients.

Methods: We enrolled 15 newly diagnosed hypertensive patients (10 males and 5 females, mean age of 56.3±10.2 years). All patients underwent evaluations of anthropometric and biochemical parameters, blood pressure, hemodynamic and AS parameters at baseline, after 3 months of conventional anti-hypertensive therapy, and after 2 months of oral supplementation with a preconstituted mix of EAAs (4gr/die - Aminotrofic©) in addition to conventional therapy.

Pulse wave velocity (PWV) and its central hemodynamic correlates, as central systolic and diastolic blood pressure (cSBP and cDBP), augmentation pressure (AP) and augmentation index (AI), were obtained by a validated system (Sphygmocor™; AtCor Medical, Sydney, Australia) that employs high-fidelity applanation tonometry (Millar) and appropriate computer software for the analysis of pressure wave (Sphygmocor™).

Data were processed by repeated measures ANOVA, paired t-test and chi-square test when appropriated; P values <0.05 were considered significant.

Results: 3 months of anti-hypertensive therapy was able to reduce the cSBP and cDBP (126.5 vs 141.9 mmHg, P<0.001; 79.1 vs 89.4 mmHg, P=0.006, respectively). 2 months of EAAs oral supplementation lead to a significant improvement of AS in addition to that obtained with the conventional therapy (n=7) were characterized by lower Lfnu [9.1 (4.1-29.8) vs 45.2 (17.7-45.9); p=0.03] on admission. Patients with CURB-65 score ≥ 3 were characterized by lower LFnu compared to patients with CURB-65 score < 3 [19.5 (5.3-37.7) vs 49.7 (16.1-71.1); p= 0.016]. No significant results were observed evaluating PSI score. Patients with a PaO2/FiO2 ratio < 200 showed a higher 2UV% in comparison to those with a PaO2/FiO2 ratio ≥ 200 [35.1 (24.1-45.2) vs 21.7 (12.6-38.3); p=0.08].

Patients with a TCS > 3 days (n=38) showed a decreased VLF component on admission compared to patients with a TCS ≤ 3 days [32.8 (0-91.7) vs 85.6 (25.9-299.2); p=0.03]. Patients with an adverse outcome during hospitalization (n=7) were characterized by lower LFnu [9.1 (4.1-29.8) vs 45.2 (17.7-45.9); p=0.02] and higher 2UV% [42.3 (37.3-44.9) vs 19.9 (12.2-32.3); p=0.002] on admission in comparison to patients without an adverse outcome. No other HRV indices were correlated with both outcomes.

Conclusion: CAP patients with a severe disease on admission showed a preserved vagal modulation associated with an altered sympathetic modulation, possibly due to the loss of rhythmical properties of sympathetic outflow. A predominant parasympathetic modulation and a reduced sympathetic oscillation on admission are predictors of adverse outcomes in CAP patients.

Arterial stiffness and ischemic stroke in subjects with and without metabolic syndrome

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Metabolic syndrome (MetS) is a highly prevalent constellation of vascular risk factors, including elevated blood pressure, elevated blood glucose, obesity, and dyslipidemia. Metabolic syndrome and arterial stiffness are recognized risk factors for ischemic stroke. The association between MetS and arterial stiffness has been demonstrated in healthy subjects hypertensives and a combined group of patients with various arterial diseases. No study has evaluated the relationship between arterial stiffness and ischemic stroke in patients with metabolic syndrome. We conducted a study to evaluate arterial stiffness markers in subjects with acute ischemic stroke and metabolic syndrome and in relation to TOAST sub-
type of stroke. We enrolled 130 patients with acute ischemic stroke and metabolic syndrome, 127 patients with acute ischemic stroke without metabolic syndrome and 120 control subjects without acute stroke. Applanation tonometry was used to record the augmentation index (Aix) and pulse wave velocity (PWV). Stroke patients with metabolic syndrome, compared to subjects without metabolic syndrome and with stroke and control subjects without stroke showed higher mean Augmentation Index (Aix) and PWV. Both these arterial stiffness indexes subjects in subjects with each TOAST subtype of stroke and metabolic syndrome were significantly higher compared to values observed in subjects without metabolic syndrome. In subjects with ischemic stroke and metabolic syndrome, compared to those with ischemic stroke and without metabolic syndrome, pulse wave velocity (PWV) was more significantly and positively correlated with body mass index (BMI), systolic blood pressure (SBP), hypertension, diabetes, glucose blood levels, LDL cholesterol levels, total cholesterol levels, CAD, micro-albuminuria, carotid plaque, previous brain infarct at neuro-imaging. Our findings also show the highest values of arterial stiffness indexes in subjects with lacunar TOAST subtype of small vessel disease and atherosclerosis on arterial stiffness pathogenesis in the clinical setting of metabolic syndrome. In conclusion, the results of our study support the view that patients with metabolic syndrome and acute ischemic stroke have higher values of arterial stiffness indexes compared to stroke controls without metabolic syndrome. Our findings also show the highest values of arterial stiffness indexes in subjects with lacunar TOAST subtype of stroke and metabolic syndrome as an expression of an important role of both small vessel disease and atherosclerosis on arterial stiffness pathogenesis in the clinical setting of metabolic syndrome.

**Cronobiology of acute aortic rupture or dissection: a systematic review and a meta-analysis of the literature**

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**Background:** Many studies and meta-analysis showed that the occurrence of some cardio and cerebrovascular diseases (including myocardial infarction, stroke and pulmonary embolism) exhibit a cronobiological variability. On the other hand, evidences of the periodicity in the incidence of acute rupture or dissection of aortic aneurysm are more conflicting. Acute aortic disease (AAD) has usually a dramatic presentation with a mortality rate of 50-70%. Aortic aneurysm (AAD) has a mortality rate of 50-70%, in December (chi-square 358.25, p <0.001) with an RR of 1.118 (99% CI 1.117, 1.118), on Monday (chi-square 75.87, p <0.001), with an RR of 1.124 (99% CI [1.122, 1.126]) and in the hours between 6-12 a.m (chi-square 4.58, p <0.001) with an RR of 1.580 (99% CI 1.564, 1.597). Subgroup analyses including only ruptures or dissections confirmed the results of principal analyses.

**Conclusion:** Our data strongly support the presence of an infradian and circadian pattern in the incidence of acute aortic events, with a significantly higher risk in Winter, in December, on Monday and between 6-12 a.m. Future studies are needed to better clarify the mechanisms behind this pattern and its clinical implications.

**Elastic aortic properties assessed by tissue and strain doppler imaging in patients with X syndrome**

Enrico Vizzardi, Eleftheria Trichaki, Ivanon Bonadei, Edoardo Sciatti, Valentina Regazzoni, Mara Gavazzoni, Najat Ashoafair, Riccardo Raddino, Marco Metra

**Introduction:** Elastic properties of the aorta represent an important determinant of left ventricular function and coronary blood flow but there are few data about aortic stiffness in patients with X syndrome. Aim: To investigate the elastic aortic properties (aortic stiffness and distensibility) and arterial wall motion velocities as measured by tissue Doppler Imaging (TDI) in patients with cardiac X syndrome.

**Materials and Methods:** 15 patients with X syndrome (typical chest pain and angiographically normal coronary arteries associated with a positive exercise test) were enrolled in the study. The control group consisted of 15 healthy patients. The aortic elastic indexes, namely distensibility (cm² dyne⁻¹) and stiffness index (β index) were calculated from M-mode echocardiographically-derived thoracic aortic diameters using accepted formulae, and TDI parameters were measured on the wall of the ascending aorta 3 cm above the aortic valve. Anterior wall aortic expansion velocity (S), early (E) and late (A) diastolic retraction velocity and peak systolic strain were determined.

**Results:** Aortic elastic properties were more impaired in the syndrome X group than in the control group. Aortic distensibility was significantly lower in the syndrome X group (3.2±1.3 vs. 7.95±4 cm² dyne⁻¹, p<0.001), while stiffness index was higher (7.3±2.1 vs 4.1±1.6, p<0.001) than in the control group. Peak systolic (S) and diastolic waves (E and A waves) of the aortic wall TDI were similar in patients and controls (S wave: 5.7±1.6 cm/sec vs. 5.8±1.6 cm/sec, E wave: -4.8±2.0 vs. -4.1±2.0 cm/sec; A wave: -4.3±2.1 vs. -4.7±2.1 cm/sec) while tissue strain of the aortic wall was lower in patients with X syndrome than controls (-12.8±7.7 vs. -22.3±5.9, p<0.0001).

**Conclusion:** Deterioration in aortic elasticity properties in patients with cardiac syndrome X suggests that this disease may be a more generalized disturbance of the vasculature.

**Evaluation of ascending aorta wall stiffness in rheumatoid arthritis patients by tissue doppler imaging and strain doppler echocardiography during anti-tumor necrosis factor-α therapy**

Materials and Methods: 57 patients with hypertensive cardiopathy (38 men and 19 women) were enrolled in the study. Hypertension and hypertensive cardiopathy defined by the ESC/ESH recommendations. The control group consisted of 40 healthy people (24 men and 16 women). The aortic elastic indexes, namely distensibility (cm² dyne⁻¹) and stiffness index (β index) were calculated from M-mode echocardiographically-derived thoracic aortic diameters using accepted formulae, and TDI parameters were measured on the wall of the ascending aorta 3 cm above the aortic valve. Anterior wall aorta expansion velocity (S), early (E) and late (A) diastolic retraction velocity and peak systolic strain were determined.

Results: Aortic elastic properties were more impaired in the diabetic group than in the control group. Aortic distensibility was significantly lower in the hypertensive group (2.09±1.17 vs. 4.86±2.93 cm² dyne⁻¹; p<0.0001), while stiffness index was higher (12.72±6.30 vs. 6.30±4.27, p<0.0001) than in the control group. Peak systolic (S) and diastolic waves (E and A waves) of the aortic wall TDI were similar in patients and controls (S wave: 6.70±2.56 cm/sec vs. 6.41±2.16 cm/sec, p=0.557; E wave: -5.43±2.69 vs. -5.39±2.24 cm/sec, p=0.940; A wave: -6.64±2.71 vs. -5.72±2.11 cm/sec, p=0.075), while tissue strain of the aortic wall was lower in patients with hypertensive cardiopathy than controls (-17.94±7.46% vs. -26.45±8.23%, p<0.0001) as well as M-mode calculated strain (0.06±0.03 vs. 0.12±0.07, p<0.0001).

Conclusion: Deterioration in aortic elasticity properties in patients with hypertension supports the demonstrated role of this cardiovascular risk factor. In fact, ascending aorta dilation and stiffness strongly correlate with hypertension-induced organ damage. Thus, this finding suggests that ascending aorta evaluation should be routinely performed during a standard echocardiographic examination in the hypertensive patient, in order to assess his cardiovascular risk profile.

Acute ischemic stroke: relationship between clinical impairment and autonomic cardiovascular modulation


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Background: It is well known that acute ischemic stroke (IS) is associated with alterations of autonomic cardiovascular control. However, while a sympathetic-vagal deregulation may contribute to the underlying risk factors (for instance the progression of atherosclerosis), evidence on the role of the autonomic nervous system (ANS) in the acute phase of IS is still lacking. Heart rate variability (HRV) is a non invasive and reliable tool able to investigate the ANS control of cardiovascular function, identifying the sympathetic and parasympathetic rhythmic components on cardiovascular time series. Many stroke scales have been developed in the attempt to help the clinician in the evaluation of patients with acute stroke. The NIHSS (National Institutes of Health Stroke Scale) is a validated scale used to quantify the impairment caused by a stroke; nowadays it is applied both to identify candidates for intravenous thrombolysis and as a valuable predictor of long–term outcome after IS.

Aim: To investigate the possible correlation between the autonomic cardiac changes and clinical modifications of neurological impairment 72 hours after the presentation to the Emergency Department, using the difference in NIHSS score (Delta NIHSS).

Methods: We enrolled 13 consecutive subjects suffering from acute IS (7 males, 6 females; mean age 69 years). ECG and respiration were recorded within 36 hours from admission to the Emergency Department (T0), using an ECG monitor and a piezoelectric belt (the BT16 acquisition sys-
tem). For those patients who were eligible for thrombolysis, recordings were performed before the treatment. In 12 subjects the recordings were repeated at the time of clinical stability (T1). In order to evaluate the autonomic cardiovascular control, linear spectral and non-linear symbolic analysis of HRV were performed. Autoregressive spectral analysis was applied to identify the main oscillatory patterns embedded in the signal: low-frequency (LF, ranging from 0.04 to 0.15 Hz) oscillations, markers of sympathetic activity and high-frequency (HF, ranging from 0.15 to 0.4 Hz) components, marker of parasympathetic modulation. Symbolic analysis allows to assess different patterns: 0V% (markers of sympathetic modulation), 1V% (whose biological meaning remains unclear), 2LV% and 2ULV% (markers of vagal modulation). From each ECG trace, samples of 200-300 beats were selected for spectral and symbolic analyses.

Results: The results showed that LFnu (normalized units) component decreased significantly from T0 to T1 (52.6±32.8 vs 36.1±33.9; 95% CI for difference of means 0.7 to 32.4; p < 0.05). A simple linear regression revealed a significant relationship between Delta NIHSS and sympathetic indices of spectral and symbolic analysis. In fact, an increase of LFnu as well as of 0V% pattern, indices of sympathetic modulation, were positively associated with an increase in Delta NIHSS (correlation coefficient R = 0.58 and 0.71 respectively ; p < 0.05). On the other hand, increasing Delta NIHSS was associated with decreasing HFnu component (R=0.56; p < 0.05).

Conclusions: These data were consistent with the hypothesis that acute IS is characterized by a sympathetic hyperactivity, which is decreased at the time of clinical stability.

We can speculate that, in the acute phase of IS, preserved oscillatory sympathetic modulation might be a good predictor of a better outcome in the short term; viceversa, a loss of the sympathetic rhythmicity is a sign of autonomic imbalance known to be connected with disease and poor outcome.

Future studies are needed to explore the possible influence of treatments such as thrombolysis on cardiovascular autonomic modulation and to correlate HRV parameters in acute phase with short and long term outcome.

Sunday 27 October 2013

Clinical Cases for the Gymnasium Session

An unusual case of nausea and dysphagia


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A 51-year-old woman complained an episode of vomiting after several months of dysphagia and nausea. The patient reported that the episode was characterized by discharge of a soft appendage like a pink sausage that retracted disappearing into the mouth in a few minutes. Lab exams showed only a hypochromic microcytic anemia. A barium esophagogram was scheduled. In that occasion, the patient showed a digital photo taken, a few day before, during another episode of nausea and consequent vomit. The barium esophagogram pointed out a minus image in particular at the medium and superior third of the esophagus. Esophagoscopy demonstrated a double soft appendage occupying all esophagus lumen that started from the superior third of the esophagus, splitting into two parts right after the side of the glos-tis and ended into the stomach. The Internist, that first assessed the patient, endoscopist, and thoracic surgeon planned an endoscopic resection under thoracic surgeon supervision in the operating room. The resection was successful, and pathologist pointed out a giant fibrovascular polyp of the esophagus. This case is extraordinarily rare, and literature does not report impressive findings like these. Finally, endoscopic resection seems an appropriate treatment for other cases like ours.

Refractory dyspnea. Case report of platypnea-orthodeoxia


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A 77 year old caucasian man came to our observation in outpatient care unit because of dyspnea with minimal exertion, considering that the same activity was well tolerated in the past, unproductive cough and asthenia. Former electrician and former smoker. SpO2 84%, Blood Pressure (BP) 136/88; paraphonic heart sounds, pauses apparently free of sounds. Chest auscultation showed a decreased vesicular breath sounds on lungs bases and subcruptent blastes. The patient is hypertensive and he had an Acute Myocardial Infarction (AMI) in 1992 that was treated with fibrinolitics, normal complete blood count (CBC) and routine blood chemistry with no relevant alterations. ECG showed Q wave in lead III, on beta-blocker, statin and Cardioaspirin therapy. According to the medical history, smoking habits and the clinical features, lung function was investigated by spirometry and EGA. EGA showed hypoxemic respiratory failure. Spirometry confirmed an obstructive impairment, but with a concomitant restrictive impairment. All these data corroborate the diagnosis of COPD. However the medical history of IMA, hypertension and the auscoltatory findings were highly predictive for cardiogenic dyspnea. Therefore, on the basis of physical examination and electrocardiographic findings of ischemic heart disease, it was hypothesized a probable heart failure. Since the health care setting (outpatient) and the good general condition of the patient, it was decided to treat the patient immediately as COPD with associated heart failure. Therefore, we started therapy with long-acting b2 agonist and antimuscarinic drugs. We also added furosemide therapy. A month later, the patient came back after the treatment failed. Intolerant to antimuscarinic drugs since the first dose, he reported persistence of symptoms. During the medical visit persistence of the auscultatory findings was evidenced and unexpected saturation values (93% vs 84%), obtained after the patient layed down on the infusion chair for a prolonged period, the saturation values collapsed shortly after the patient passed into the orthostatic position, therefore a platypnea orthodeoxia was detected. We decided to measure dynamically the oxygen saturation, we recorded 15 minutes of saturation of the patient in the orthostatic position and 15 minutes of saturation in the supine position. The trace has documented the actual saturation difference between the supine and standing positions. This pattern is called “platypnea-orthodeoxia”. This picture is referred to some conditions like right-left shunt, pulmonary hypertension or external compression on the left atrium. Echocardiographic test showed no signs referable to intracardiac communications or pulmonary hypertension, also the preserved ejection fraction and the normal size of the inferior vena cava allowed us to exclude cardiac aetiology of the symptoms reported by the patient. In order to exclude the presence of mediastinal or lung masses compressing cardiac structures a chest CT scan was carried out, and it led to the diagnosis of idiopathic pulmonary fibrosis. The patient was treated with acetylcysteine and corticosteroids which is the only treatments that can improve the life quality of these patients, but that have not proved to be effective in reducing the mortality of the disease that still has a poor prognosis.
Unusual chest X-ray findings in a young male with suspect spondylitis

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We observed a 25 years old male complaining asymmetric arthropy of wrist and hands, inflammatory low back pain and low-grade fever for one month. He further reported two episodes of abdominal pain, lasted few hours. The tests performed during one of these episodes showed mild neutrophil leukocytosis and CRP positive in 2/3 samples. Basing upon the clinical suspicion of enteropathic spondyloarthritides, we prescribed further immunological tests as well as a chest X-ray (as a part of a pre-treatment screening).

Surprisingly, an high titer of Rheumatoid Factor was found and the chest X-Ray revealed a bilateral, patchy, interstitial pneumonia. Even in the absence of any respiratory symptom, the patient was therefore admitted in hospital for further investigation. At the admission, the first examinations showed a normocapnic mild hypoxemia (PaO2 80 mmHg, SO2 97%), normal pulmonary volumes and DLCO, a mild normochromic normocytic anemia and elevated CRP and ESR. A CT-scan of lung revealed a diffuse perivascular interstitial involvement, with ground-glass and tree-in-bud patterns, prevalent in decline pulmonary segments. Blood tests showed a low-titer positivity for IgM and IgA antibodies against Mycoplasma Pneumoniae, together with an high titer positivity for IgG. Levofloxacin 1000 mg/d, was started. In the fourth day severe painful paresthesias involving the left median nerve region and the right tumb appeared. The EMG/ENG confirmed an acute, proximal neuropathy of the left median nerve.

The hypotesis of a systemic vasculitis rose and, accordingly a blood test for ANCA was performed. A sero-hematic liquid was retrieved by bronchoalveolar lavage (endobronchial hemorrhage), the histological findings were consistent to the diagnosis of necrotizing vasculitis and an high titer of c-ANCA was found. These results led to the diagnosis of Wegener Granulomatosis. We treated the patient with high dose of steroids and Rituximab (375 mg/mq/w for 4 times) with a prompt clinical and radiological improvement.

References:

An uncommon “complication” of Gaucher’s disease - A case report

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We report on a 47 year old woman affected by type 1 Gaucher’s disease, who was found to have a large aneurysm of the splenic artery at a diagnostic screening for splenomegaly.

At age 26 in 1989, she was admitted to the local Hospital in southern Italy for anaemia, thrombocytopenia and splenomegaly. She was also affected by arterial hypertension. At that time she underwent her first adenom echography that showed a small liver and spleen enlargement. Due to the haematological abnormalities, she underwent a bone marrow aspiration and biopsy. The diagnosis was suspected by the examination of the bone marrow, in which Gaucher’s cells were identified. Between 1989 and 1999, due to the lack of an appropriate treatment, the patient was repeatedly followed in the local Hospital and supported with symptomatic treatment based on vitamins and iron supplement to prevent anemia. In 1999, after confirmation of the diagnosis by measurement of acid beta-glucoisidase activity in peripheral blood leukocytes, the patient started the enzyme replacement therapy with Ceredase, later switching to Cerezyme (1800 UI every 2 weeks).

In 2006, at regular follow-up, a TC scan showed a large aneurysm of the splenic artery of approximately 6 x 4 cm and thin walls, almost entirely calcified at the splenic hilum.

Albeit being informed of a 2-10% risk of rupture, the patient decided to refuse surgery, worrying about the risk of splenectomy and the possible worsening of Gaucher’s disease.

When hypertransaminasemia and abdominal pain appear together

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C.V. is a 51 years old woman with history of gastrointestinal diseases as irritable bowel, gastroesophageal reflux with associated esophagitis, helicobacter pylori gastritis treated with antibiotics. She had endometriosis in 2006 treated with surgery. She presented to our Structure complaining with diffuse abdominal pain, localized especially in the right upper quadrant and progressive fatigue. At admission, we performed the laboratory tests showed in table 1: the patient had an important hepatocyte damage, associated with cholestasis. We ruled out possible primary causes, such as infectious diseases (negative research for HBV, HCV, HIV and minor hepatothropic viruses) defining it as a primary autoimmune process. To distinguish between possible hypotheses, we performed abdomen echography. The liver showed no macroscopic abnormalities so the patient underwent liver biopsy. Histology demonstrated the presence of chronic hepatitis with moderate activity, with perihepatocytic fibrosis forming of septa and bridges, also with images of micronodular. These findings might be compatible with autoimmune hepatitis, although we could not exclude the possibility of an overlap with a disease of the biliary system such as primary biliary cirrhosis (PBC).

We used the revised IAHG score (International Autoimmune Hepatitis Group) to calculate the probability of Autoimmune Hepatitis (AIH). The score is calculated by evaluating 15 items, including ANA, AMA, IgG level, hepatitis viral markers, drug history, alcohol intake and gender (specifically, female age), total bilirubin, albumin, PT and existence of peripheral edema. The identification of definite AIH is based on an aggregate score of >15 points. For our patient, the calculated score is 10. The revised IAHG score highlights the importance of the ALP/AST ratio and histological findings. Score between 10 and 15 denotes the presence of probable overlap between AIH and bilar system diseases.

We could start drug therapy: the patient was treated with ursodeoxycholic acid (UDCA) in doses of 15 mg/kg per day, together was treated with a course of prednisolone 1 mg/kg once daily. 3 months later, the patient showed normalization of laboratory parameters, no pain or other symptoms. During follow-up, she was evaluated with laboratory study every three months, abdominal ultrasonography (USG) six months later and esophagogastroduodenoscopy (EGD) 1 year. In our case gastric biopsy to gastroscopy yielded mild chronic gastritis, in absence of helicobacter pylori infection.
A peculiar case of hepatic multifocal “nodule in nodule”


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Introduction: In the contest of a cirrhotic liver, the appearance of a high-grade dysplastic nodule represents a pre-cancerous lesion, with a very high odd ratio (16.8) to developing a hepatocellular carcinoma. Thus, high-grade dysplastic nodule may represent either a direct precursor of carcinoma (“nodule in nodule”) either a marker of an increased risk of transformation of the cirrhotic liver.

Case presentation: 53 years-old woman, with a history of non-alcoholic steatohepatitis, underwent a follow-up abdominal ultrasound. The scan revealed on segment IV, a hypochoic nodule of 3.8 cm. She denied any symptoms. Her Body Mass Index was 28 Kg/m2, and she had no history of alcohol consumption. Medical history included type 2 diabetes mellitus, hypercholesterolemia, asymptomatic cholelithiasis, and right cataract surgery on 2010. Current medications included glulisine insulin, glargine insulin, simvastatin and ursodeoxycholic acid. Laboratory tests revealed normal values for liver enzymes.

On April 2013, she underwent a bisegmentectomy S2-S4 and cholecystectomy. On gross observation, the margin of resection in a micro-macronodular cirrhosis. In the context of the nodule of 4 cm, brown, were identified three distinct smaller yellowish nodules progressively lighter in color. Pathological examination revealed a grade dysplastic nodule of 4 cm placed at 0.4 cm from the margin of resection in a micro-macronodular cirrhosis. In the context of the nodule of 4 cm, brown, identified three distinct smaller yellowish nodules progressively lighter in color. Pathological examination revealed a grade dysplastic nodule of 4 cm placed at 0.4 cm from the margin of resection in a micro-macronodular cirrhosis. In the context of the nodule of 4 cm, brown, identified three distinct smaller yellowish nodules progressively lighter in color. Pathological examination revealed a high grade dysplastic nodule of 4 cm placed at 0.4 cm from the margin of resection in a micro-macronodular cirrhosis.

Conclusion: This peculiar case shows how the development of a hepatocellular carcinoma on a high-grade dysplastic nodule (“nodule in nodule”) may occur in a setting of multifocal mode.

Going back in the nineteenth century

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A 61-year-old man presented because of gradually worsening chest pain and fever. His medical history included bipolar disorder, for which the patient had been taking valproic acid and sertraline since ten years. Physical examination was notable for scrotal effusion, reportedly progressing over the last months. X-ray investigation showed slight bilateral pleural effusion and cardiomegaly. Laboratory data included leukocytosis and marked increase in CRP and erythrocyte sedimentation rate.

Cardiac echocardiogram revealed a large pericardial fibrinous effusion, as scrotal ultrasound did. A chest and abdominal CT scan confirmed the presence of pleural, pericardial and abdominal effusions.

Differential diagnosis of serous membranes’ effusion includes bacterial, viral and tuberculous diseases, autoimmune and autoinflammatory disorders, drug-related polyserositis, malignancies, endocrine disorders and transudate-forming conditions (cardiac failure, chronic kidney diseases, nephrotic syndrome, hypoalbuminemia, etc.).

Pericardiocentesis and bilateral thoracentesis were required owing to the onset of cardiac tamponade and respiratory failure; morphologic and biochemical analysis revealed an exudate (albumin 2.1 g/dL, LDH 309 U/L) with few leukocytes (110/mm^3 - lymphocytic prevalence).

Further laboratory tests revealed slight increase in AST, ALT, amilase and lipase levels, mild proteinuria (0.7 g/die) with normal morphologic urinary analysis, while C3 and C4 levels were within normal range. Antibodies against HIV, EBV, CMV, HHV8, coxsackie virus, ECHO virus, B. burgdorferi, M. pneumoniae, Brucella, C. pneumoniae and trachomatis.

Autoimmunity tests were also negative (ANA, ENA, RF, CCP, ANCA, ASMA, AMA, LAC, β2 glycoprotein, cardiolipin). Essudate cultures, in-

The revised IAHG score takes into account significantly important prognostic factors of AIH and PBC. In terms of prognostic indicators, the level of serum bilirubin concentration is the best indicator for prognostic purposes. Pretreatment levels of serum bilirubin, bilirubin levels during follow up, and the occurrence of normal levels of serum bilirubin were significantly associated with prognosis.

21 Previous studies reported the duration of increased initial serum bilirubin, as well as the level of bilirubin, to be important prognostic factors. When serum bilirubin is 10 mg/dL or greater, the average survival period is reported to be 1.4 years.

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In the two previous years the patient traveled to several foreign countries (Portugal, Turkey, Mexico, Namibia).

Physical examination showed abdominal tenderness, pain was elicited only by deep palpation of the epigastric region. The remainder of the exam was normal. ECG and x-ray investigation showed no abnormalities. Laboratory exams revealed mild anemia, leucocytosis with neutrophilic prevalence and marked increase in inflammation markers (C-reactive protein, erythrocyte sedimentation rate, ferritin), which went parallel with the trend of fever.

A diagnostic work-up for fever of unknown origin was started. Weil-Felix, Widal and Wright reactions were negative, as well as autoimmunity screening, IGRA test and serological test for infectious chronic diseases (amebiasis, strongyloidiasis, EBV, HIV, toxoplasmosis, schistosomiasis and Lyme’s disease). Blood cultures didn’t show any bacterial growth. Echocardiography ruled out infective endocarditis.

Abdominal ultrasound revealed four hypo-echoic hepatic focal lesions: the biggest one was situated in liver’s hilar region next to gallbladder (4.8 x 4 cm); the exam also showed complete thrombosis of left portal branch. Contrast-enhanced ultrasound suggested neoplastic origin of the thrombosis. A contrast-enhanced CT scan confirmed the lesions and portal thrombosis, while a CT-PET scan ruled out extraepathic localizations.

Differential diagnosis includes both primary liver tumors and hepatic metastasis, infections of neoplastic lesions, liver abscesses, granulomatous diseases (eg tuberculosis, sarcoidosis), duodenal and pancreatic neoplasms. Repeated multiple hepatic fine needle biopsies revealed only slight neutrophilic infiltrate associated with portal fibrosis, necrotic-inflammatory material and fibrous tissue. Esophagogastroduodenoscopy showed a large duodenal diverticulum, situated in the same region of the previous peptic ulcer, while the esophageal varices were not confirmed. Negativity of biopsies, good response to azithromycin and histology (presence of fibroblast/fibrous tissue) oriented us to an inflammatory/infectious nature of the lesions (eg IPT - Inflammatory Pseudotumor of the liver), although possibility of malignancy couldn’t be excluded at all. Empiric antibiotic therapy for liver abscesses was administered with quick resolution of fever. Video-assisted laparoscopy failed to obtain larger biopsy specimens from the lesions because of the presence of easily bleeding inflammatory adhesions among the inferior face of the liver, stomach, omentum and duodenum. During surgery, ultrasound revealed complete resolution of the V segment lesion.

These results confirmed us the diagnosis of IPT of the liver, caused by inflammatory/bacterial trigger from perforated peptic ulcer with localized peritonitis that occurred subclinically one year before, and that was masked by the intermittent administration of antibiotics for UTI. The patient was discharged from hospital with a 6-week oral course of levofloxacin and metronidazole with complete resolution of symptoms. Abdominal ultrasound and contrast-enhanced CT scan obtained respectively four and eight weeks from discharge showed complete resolution of the lesions and re-vascularization of the left portal branch.

A ticking time bomb

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A 61-year-old man was admitted to our department because of remittent fever that had aroused three months before. Fever, up to 40°C, was preceded by chills, resolved spontaneously after few hours with intense diaphoresis and was associated with abdominal pain, referred as epigastric-sided and continuous or sometimes as diffuse and transient; it was associated with marked weight loss (8-10 kg in the previous year). A ten-day course with azithromycin resulted in temporary resolution of fever, that relapsed few days after discontinuation of the antibiotic.

Patient’s medical history included an endoscopic diagnosis of duodenal peptic ulcer and small esophageal varices followed by PPI therapy with resolution of dispeptic symptoms. He had been taking short and low-dose courses of antibiotics from nine to five months before for recurrent urinary tract infections (UTI). In the two previous years the patient traveled to several foreign countries (Portugal, Turkey, Mexico, Namibia).

Physical examination showed abdominal tenderness, pain was elicited only by deep palpation of the epigastric region. The remainder of the exam was normal. ECG and x-ray investigation showed no abnormalities. Laboratory exams revealed mild anemia, leucocytosis with neutrophilic prevalence and marked increase in inflammation markers (C-reactive protein, erythrocyte sedimentation rate, ferritin), which went parallel with the trend of fever.

A diagnostic work-up for fever of unknown origin was started. Weil-Felix, Widal and Wright reactions were negative, as well as autoimmunity screening, IGRA test and serological test for infectious chronic diseases (amebiasis, strongyloidiasis, EBV, HIV, toxoplasmosis, schistosomiasis and Lyme’s disease). Blood cultures didn’t show any bacterial growth. Echocardiography ruled out infective endocarditis.

Abdominal ultrasound revealed four hypo-echoic hepatic focal lesions: the biggest one was situated in liver’s hilar region next to gallbladder (4.8 x 4 cm); the exam also showed complete thrombosis of left portal branch. Contrast-enhanced ultrasound suggested neoplastic origin of the thrombosis. A contrast-enhanced TC scan confirmed the lesions and portal thrombosis, while a CT-PET scan ruled out extraepathic localizations.

Differential diagnosis includes both primary liver tumors and hepatic metastasis, infections of neoplastic lesions, liver abscesses, granulomatous diseases (eg tuberculosis, sarcoidosis), duodenal and pancreatic neoplasms. Repeated multiple hepatic fine needle biopsies revealed only slight neutrophilic infiltrate associated with portal fibrosis, necrotic-inflammatory material and fibrous tissue. Esophagogastroduodenoscopy showed a large duodenal diverticulum, situated in the same region of the previous peptic ulcer, while the esophageal varices were not confirmed. Negativity of biopsies, good response to azithromycin and histology (presence of fibroblast/fibrous tissue) oriented us to an inflammatory/infectious nature of the lesions (eg IPT - Inflammatory Pseudotumor of the liver), although possibility of malignancy couldn’t be excluded at all. Empiric antibiotic therapy for liver abscesses was administered with quick resolution of fever. Video-assisted laparoscopy failed to obtain larger biopsy specimens from the lesions because of the presence of easily bleeding inflammatory adhesions among the inferior face of the liver, stomach, omentum and duodenum. During surgery, ultrasound revealed complete resolution of the V segment lesion.

These results confirmed us the diagnosis of IPT of the liver, caused by inflammatory/bacterial trigger from perforated peptic ulcer with localized peritonitis that occurred subclinically one year before, and that was masked by the intermittent administration of antibiotics for UTI. The patient was discharged from hospital with a 6-week oral course of levofloxacin and metronidazole with complete resolution of symptoms. Abdominal ultrasound and contrast-enhanced CT scan obtained respectively four and eight weeks from discharge showed complete resolution of the lesions and re-vascularization of the left portal branch.
A very uncommon cause of syncope mediated by a lung cancer

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A 69-year-old man, smoker (pack/years 45), was hospitalized in our Unit for syncope in November 2012 for a diagnostic work-up for syncope. The patient had been hospitalized in another Hospital for the same reason 15 days before, where a pacemaker had been implanted because of a sick sinus syndrome. Two days after the implantation, the patient relapsed with syncope. At the check, the functionality of PM was fine. So he decided to ask for help to our hospital. At admission the patient was in good clinical conditions, presenting only dry cough. Regarding to the syncope, he reported that he felt a pain at the left base of his neck, began to sweat and at the end he fell to the ground (with no neurological symptoms). His wife, a staff nurse, reported that she measured the blood pressure immediately after the loss of consciousness and noted a very low BP/80/50 mmHg (with a 45 pulse rate). Five minutes later the complete recovery of the patient BP was good again (110/80 mmHg, 82 pulse rate). Physical examination upon admission revealed a decreased thoracic breath sound, no-productive cough and reduced TVF on left apical. No other signs or symptoms to underline. His clinical history was about a major surgery on vessel’s right leg, a kinking of left carotid and a recent implant of a PM (see above). During the admission visit a syncope occurred: when the patient turned on his left side laying on the bed he had bradycardia (45 bpm even if a PM was implanted) and hypotension, which were treated with atropine, steroids, Trendelenburg position and fluids. No amnesia to declare.

We started with a check of the PM, indicating an incorrect setup. Then we made an ECG Holter that didn’t show any arrhythmia (no syncope occurred during Holter). The massage of carotid sinus showed a slowing pacing with the starting of PM function without any hypotension nor syncope. Echocardiography didn’t show any mechanical cause for syncope, with an EF% of 58. We studied the neck arteries by echo-color-doppler with dynamic proves that didn’t show any problem, nor subclavian steal syndrome, nor carotid’s kinking as cause for the syncope. Abdominal aorta and leg’s arteries were also studied and they were unremarkable. Since an episode of amnesia was reported by the patient, we did a neurological study with Brain CT Scan and EEG for epilepsy, both negative. The patient had other 3 synapses during the hospitalization: we realized that the patient’s position taken in bed could trigger the syncope. We made some attempts, discovering that each time the patient laid completely on his left side, the syncope started. For that reason we didn’t plan a TILT test. Then we thought about some mechanical cause that could trigger a vagus nerve dysfunction rousing the syncope. A thorax X-ray (done by the patient out of the hospital for other reasons) revealed a very small opacity on the apical of left lung with apparently no meaning (as radiologist reported), then we decided to extend CT scan from the brain to the thorax. The report described a small mass at apex of left lung. Contact with aorta (see Figures 1 and 2). We assumed that this mass could press on aortic arch and trigger baroceptors, causing bradycardia and hypotension due to Bezold–Jarisch reflex1. When the patient was laying on the left. We supposed the existence of a mechanical cause of syncope due to the internal compression of the lung’s mass on aortic arch. Therefore, we recommended to the patient to not take that position and synapses didn’t occur anymore. After a week, he underwent a thoracic surgery to remove the mass. The surgeon referred that the mass seemed to not infiltrate the aortic arch, but the vagus and the laryngeal nerves that were removed (now the patient has a two-tone voice). After some month we had the pathologist’s response: G3 adenocarcinoma, infiltrating not the aortic arch (even if the CT images seemed to show the contrary, see Figure 2), but the vagus and the recurrent laryngeal nerve, P4, N0, M0.

Fever of unknown origin and myalgias: unexpected diagnosis

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A 25-year-old man was hospitalized for recurrent attacks of fever (t 38°C without shivers), with the suspicion of endocarditis because of a 2/6 systolic mesocardial murmur.

The onset of the symptoms took place one month before with lower limbs arthromyalgias during the evening, with some benefit from the assumption of non steroid anti-inflammatory drugs (NSAIDs). Some days later, the symptoms increased and extended to the upper limbs and a transient erythematous-papular rash and purpuric lesions, neither painful nor itchy, involving the lower limbs. The pain required NSAIDs even during the day (average 4 tablets/day). During the weekend, after stopping these drugs the fever appeared again (t max 38°C), without either shivers or other symptoms, that responded to paracetamol. After a month he was admitted to the E.R. where the blood analysis showed: WBC 9.530/mm3, PLT 261.000/mm3, Hb 12.4 g/dl, CK 207 U/l, normal LDH and myoglobin, CRP 4.85 mg/dl. Chest x-Ray was negative. After few days from the discharge, he had other examinations: ESR 61 mm/h, TAS 179 U/ml, CRP 132 mg/l, a-1 acid-glycoprotein 259 mg/dl (n<130 mg/dl), Hb 10.9 g/dl, WBC 9520/mm3 (Neutrophils 83.3%) and hemoglobinuria. Rheumatic factor and Waaler-Rose were negative. He was treated with i.m. ceftazidime (1 vial twice a day) and oral methylprednisolon (starting with 48 mg/day and tapering until withdrawal within 9 days) with benefit, but at the end of the therapy he presented his symptoms again. For this reason he was admitted to our hospital after 2 weeks. The blood analysis confirmed a chronic inflammatory anemia (Hb 8 g/dl, MCV 70 fl, ferritin 324 ng/ml, transferrin 182 mg/dl), high inflammation markers (ESR 96 mm/h, CRP 58,7 mg/l), high creatinine blood levels (from 1,10 mg/dl it reached 1,78 mg/dl in about fifteen days). The urinalysis revealed: hemoglobinuria, albuminuria, red blood...
and white blood cells casts. Proteinuria was estimated as 1.07 g/l in 24 hours. Blood culture, urine culture and main viruses serologies were all negative. No valvular vegetations were detected at echocardiography. The serology excluded Leptospirosis (because of fever and myalgias and the patient lives in countryside) and other infections.

Because of the myalgias, another hypothesis was polyarteritis nodosa, whereas the glomerulonephritis were suggested by the high creatinine blood levels and the alterations in the urinalysis (hemoglobinuria, albuminuria, proteinuria, red blood and white blood cells casts). The anti-neutrophil cytoplasmic antibodies (ANCA s) showed high levels of c-ANCA (≥100 U/ml). Eventually the renal biopsy revealed a severe glomerulonephritis involving more than 90% of the glomerules and the presence of a great number of crescent formations.

Meanwhile the patient had a painless vegetant lesion of the hard palate and ocular involvement (episcleritis), too. All these evidences were suggestive for a diagnosis of Wegener’s granulomatosis. The thorax CT scan showed the presence of multiple bilateral non calcificated micronodules with sharp margins, focal ground glass areas in the lower lobes, and a focal pleuric thickening in the posterior segment of the right superior lobe (about 6mm). Even if it was not possible to administer the contrast media (because of the high creatinine levels), the presence of nodules fits with the clinical pattern of Wegener’s granulomatosis.

Therefore he started intravenous methylprednisolone (1 mg/Kg day) and pulse therapy with Rituximab (375 mg/m2), since the risk of long-term adverse events cyclophosphamide therapy (infertility and cancers) was refused by the patient. Within a few days, the patient obtained fast recovery of all the symptoms, disappearance of fever, myalgias, and healing of the lesion of the hard palate.

References:

Ascites of unknown origin: description of a clinical case


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A 54 year old woman was admitted to our unit in September 2012 because of ascites of unknown origin, appeared over the previous 2 years, with absence of biochemical signs of chronic liver disease, infection with hepatitis B or C virus, or ethanol abuse. The patient had no medical history, signs or symptoms suggestive of cardiac disease and showed a normal electro- and echo-cardiogram.

Autoimmune etiology was refuted based on serological markers (absence of ANA, AMA, SMA, anti-LKM and normal immunoglobulin levels). Diagnostic studies indicative of Wilson’s disease (ceruloplasmin, cupremia, cupuria) and primary or secondary haemochromatosis (transferrin saturation index, ferritin), were carried out with negative results.

Screening abdominal ultrasonography and upper gastrointestinal endoscopy showed no signs of portal hypertension complications. Ascitic fluid was examined for biochemistry, cytology and microbiology and appeared to be a transudate, without signs of infection or neoplastic spread (serum-ascites albumin gradient 2.2 gr, 80 leukocytes/ml, no malignant cells, no erythrocytes).

Because of the discrepancy between biochemical and clinical data, the patient underwent ultrasound-guided liver biopsy, that showed signs of inflammation (grading 5/18) and a stage 2, perportal and pericentral fibrosis, with mild dilatation of centrallobular veins and hepatic sinusoids.

To exclude a post-sinusoidal portal hypertension, we prescribed a triphasic, contrast-enhanced, abdominal CT scan. This showed a reduced size of juxta-caval hepatic veins, with constantly hypodense, not dulled, branching tributaries within liver parenchyma, a picture compatible with Budd-Chiari syndrome.

The coagulation parameters and the major clotting factors were studied and appeared to be within normal levels. Molecular diagnosis performed on patient DNA ruled out the presence of pro-thrombotic mutations, including G1691A factor V Leiden and G20210A prothrombin gene. Plasma homocysteine was normal in the absence of C677T methylene-tetrahydrofolate reductase gene mutation. Despite normal blood count, JAK-2 V617F mutation was sought in peripheral blood, but was found negative. No bone marrow exam was done.

The patient was put on maintenance diuretics and oral anticoagulant therapy under heparin priming, and was referred to a liver transplant center for possible transjugular intrahepatic portal-systemic shunting.

This clinical case suggests that in patients with ascites of unknown origin, in the absence of biochemical signs of chronic liver disease, serological evidence of chronic viral hepatitis, and no increase of hepatocyte damage indices, Budd-Chiari syndrome should always be suspected, especially in cases where CT or MRI show an uneven distribution of intra-hepatic arterial flow and/or post-hepatic venous obstruction.

Triphasic, contrast-enhanced, abdominal CT scan is a key investigation in order to obtain the diagnosis.

In the examined case, no apparent cause of thrombophilia was found upon medical history or laboratory investigations. Budd-Chiari syndrome is a clinico-pathological condition characterized by a heterogeneous group of disorders characterised by obstruction of the hepatic venous return at the level of the hepatic venules and veins, the supra-hepatic inferior vena cava or the right atrium. This pathophysiological state causes a progressive increase of sinusoidal pressure resulting in portal hypertension. Blood stasis and congestion produce an hypoxic damage of adjacent liver cells, eventually leading to hepatic necrosis, progressive centrilobular fibrosis, nodular regenerative hyperplasia and liver cirrhosis.

Anticoagulant therapy is indicated and beneficial in most cases. A porto-caval shunt may be taken into account early, if the portal vein and the inferior vena cava are patent. Conservative treatment with thrombolysis is reserved to patients who have incomplete obstruction of the hepatic veins or when clinical improvement is rapid. In those who have an acute, fulminant or end-stage disease, liver transplant is needed. Anticoagulant therapy often needs to be continued long-term.

Abdominal pain: from a misleading symptom to an unusual diagnosis


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Case presentation: A 46 years old woman, complaining of recurrent abdominal pain, underwent an ultrasonographic examination revealing a hypoechogenic mass, 15 mm in diameter, suspected for secondary lesion in the VI-II hepatic segment. The patient was therefore admitted to our hospital in December 2012 for further investigation. The physical examination was negative, blood cells counts and serum biochemistry, including liver function tests and tumor markers were all within the normal range. Hepatitis B virus
surface antigen and hepatitis C virus antibody were both negative. The breast cancer screening, panendoscopy and the EGDS were all negative. A further abdominal US with contrast revealed a well defined hypoechoic mass with a strong enhancement in arterial phase, a rapid wash-out in portal phase, isoechoic in delayed phase, suggestive for hypervascularized lesion such as neuroendocrine tumor metastases.

Searching for the primitive lesion, a thoraco-abdominal TC scan confirmed an isodense mass in arterial phase, with wash-out in portal phase, compatible with metastases. However, no primitive lesions were found. The 18F-FDG PET scan showed a mild positivity (SUV MAX 2.0) in the liver lesion; on the contrary, the 68Gallium PET was negative as well as neuroendocrine tumors markers.

Finally the patient underwent a percutaneous transhepatic needle biopsy, that showed a lymphoid infiltration of small T cells (CD3+), surrounding two lymphoid follicles with a polymorphic and polyclonal cells population composed of B lymphocytes (CD20+/BCL6+), mature plasmacells and stromal fibrosis. No nuclear atypia was found. Surprisingly reactive lymphoid hyperplasia (RLH) was diagnosed.

Discussion: Searching for abdominal pain causes, we found RLH, also known as pseudolymphoma, which is a rare benign condition characterized by marked proliferation of polyclonal lymphoid cells forming follicles with an active germinal centre. This extremely rare benign conditions may occur in the gastrointestinal tract, orbit, lung, skin and thyroid. Hepatic RLH is a benign focal mass that may mimic a malignat liver tumor, often posing diagnostic and management dilemma. It was firstly described by Snover et al. in 1981, so far, only 41 cases have been reported. According to literature, RLH has female predilection, the lesions are usually singular, small and well defined. Although it’s generally considered as a benign lesion, the risk of transformation into lymphoma has been speculated and supported by some cases of lung and gastric RLH. So far, no transformation has been described in liver RLH.

Conclusion: Due to the few cases reported, no guide-lines are available for the management of RLH and there is no agreement about the treatment. In literature the surgical approach has been described both for treatment and for histological diagnosis. In some cases, after a needle biopsy it was observed a decrease in size or a spontaneous regression during a radiological follow-up. In our case, since the histological diagnosis has been already made, RLH hepatic localization has not been so far reported to progress to malignancy, the lesion is small and there has not been any increase in size in the span of time of a few months observation, we have decided to have a wait and see approach in a patient in good physical conditions.

An unusual presentation of Crohn’s disease

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Clinical Case: A 61 year old man, smoker, with giant esophageal hernia arrives at the emergency room of the city hospital with burning pain in the chest lasting 2 hours. Blood tests showed elevation of troponin I, while at EKG inverted T waves in V5 and V6 and Q waves in DI and aVL were present. The pts was taken to the Coronary Care Unit of our Regional Hospital, where a severe microcytic anemia (Hb 7g/dl) was evidenced and at the echocardiography, the presence of areas of reduced mobility of the side wall and bottom of the left ventricle were shown. The diagnosis of Acute Coronary Syndrome was established, likely due to the anemia, and the patient was then transferred to our section of Internal Medicine.

Once restored the hemodynamic balance with blood transfusions and subsequent iron therapy, the possible cause of blood loss was investigated. The patient presented normal stools and reported that he had never noticed in the previous days feces with blood or melena.

The angioTC, done for the suspect of aorta lesions was negative, while the EGDS confirmed the presence of esophageal hernia but excluded the presence of erosive gastroduodenitis. The colonoscopy performed showed nothing of interest. The markers of neoplasias were negative and the stress EKG, performed after the correction of anemia, showed no signs of inducible ischemia. The diagnostic workup continued with the Pill cam to explore the small intestine. Twenty-five minutes after the ingestion of the Pill cam the presence of fecal material in the jejunum distal medium, which prevented the vision of the lumen, likely due to a fistula with the colon, was recorded. Therefore, an entero-magnetic resonance, which showed distension of a few ileal loops and thickening of the walls of the terminal ileum, was performed. The blood level of fecal calprotectin was high. It was therefore made the diagnosis of Crohn’s disease and the patient directed to an appropriate therapy.

Conclusions: Crohn’s disease is an inflammatory bowel disease that can affect any part of the gastrointestinal tract, commonly the terminal ileum and colon. It generally affects individuals between 15 and 30 years and the onset usually is abdominal pain, changes in bowel habit, weight loss, signs of malabsorption and, less frequently, extraintestinal manifestations. However, the current clinical case shows an unusually dramatic onset, with potentially dangerous consequences for the life of the patient.

Constrictive pericarditis due to AL amyloidosis: a case report

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Case report: A 69-year-old man was admitted to our department with a 10-day history of fever, dyspnea, fatigue, and dizziness. Physical examination revealed jaundice, lower limbs edema, jugular turgor, tachycardia, hypotension, bilateral basal crepitations on chest auscultation, hepatomegaly and splenomegaly on abdominal palpation, and dull percussion sound of lower abdominal quadrants. Routine laboratory investigations showed neutrophilic leukocytosis, increased bilirubin, increased transaminases, decreased serum albumin, increased INR and NT-pro-BNP (2901 pg/ml). Electrocardiogram showed Atrial fibrillation. Signs of chronic liver disease were described with Abdomen Ultrasonography. Chest CT scan demonstrated a retrosternal mediastinal mass containing calcifications and air bubbles. This mass did not show a cleavage plane with the heart, compressing and shifting it left. Bilateral pleural effusion was also found. Because of a rapid worsening of the vital signs and a strong decrease in blood pressure in particular, urgent pericardiectomy was performed. A constrictive purulent-like pericardium with calcifications was removed. Few days after surgery blood pressure and pulse rate became normal. On the contrary, no changes were found in lower limbs edema and albumin values. NT-pro-BNP and transaminases decreased. Anemia and thrombocytopenia became evident. A monoclonal band in gamma region on serum electrophoresis (23.3%; IgG-L) was found. A mild renal failure was demonstrated and Bence-Jones proteins in urine test were found (1.56 grams in 24 hours) as free Lambda chains. Markers for acute and chronic hepatitis and QuantiFeron were negative. All microbiological tests and cultures performed were negative. A plasmocytosis of 30% was found in bone marrow biopsy. No osteolytic lesions were described with radiology. Histopathological examination of the mediastinal mass showed an amorphous Congo red positive material that was apple-green birefringent under polarized light, with granulocytes and few plasmacells near to the vessels. A sample of periumbilical fat showed amyloid AL deposition near to the vessels. A treatment with Bortezomib and Dexamethasone was began.
An unusual cause of sixth nerve palsy

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Case Report: A 56 year-old-man presented to our Hospital for convergent strabismus of the left eye, diplopia and headache from about three days. He also reported a history of hypertension treated with beta-blockers, and diabetes mellitus type II in dietary therapy. The neurological examination confirmed the left convergent squint (Fig. 1), and did not reveal other findings such as weakness or abnormal tendon reflexes.

On admission to the ward, the blood pressure and pulse rate were 120/70 mmHg and 64 bpm, respectively. The blood tests were in the normal range (erythrocyte sedimentation rate, serum creatinine, blood urea nitrogen, serum electrolytes, GOT, GPT, cell blood count and lipidic profile), except for high values of blood glucose (363 mg/dl, HbA1c 12.1% and IFCC-GLAD 109 mmol/mol).

The ECG showed signs of left ventricular overload. Doppler ultrasound of carotid vessels showed myointimal thickening without significant atherosclerotic plaques.

Echocardiography showed a slight concentric hypertrophy with a preserved systolic heart function. Computer Tomography of the brain did not find acute lesions such as hemorrhagic or ischemic strokes. Chest x-ray and abdominal ultrasound were normal. The patient was treated with intravenous administration of fluids and insulin with improvement of the glycemic decompensation and resolution of the sixth nerve palsy (Fig. 2).

Discussion: The paralysis of the cranial nerves is a rare but established manifestation of diabetic neuropathy. It can involve one or more cranial nerves and the prevalence is highly dependent on the duration of the disease with values ranging between 0.4% and 0.97%. The ocular and facial nerves (III, IV, VI and VII, respectively) are the most frequently affected [1]. A proper diagnosis is essential, because an appropriate improvement of the glycemic decompensation can result in a resolution of the nerve palsy and prevent further episodes.

In vino veritas: a strange case of platelet dysfunction

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A 73 year-old male with a history of chronic alcoholic liver disease, was admitted to the Internal Medicine ward of our hospital because of ecchymoses appeared 4 days before admission on his left upper limb, not resulting from any trauma. The patient medications included spironolactone, esomeprazole, insulin aspart and insulin detemir. The patient reported that he had used acetylsalicylic acid in the last week (500 mg per day) for headache and that he had started drinking again about a month before admission after detoxification occurred two years earlier. On physical examination, body temperature was 36.5 °C, blood pressure was 110/70 mmHg, pulse was 95 beats/minute. Edema over his left forearm and left hand was noted. In the emergency room the venous and arterial echo-doppler were negative for thrombosis. Laboratory findings included bleeding time of 20 min, INR 1.48, hemo-
glocin 7.6 g/dl, slight thrombocytopenya (PLT 120000/ul); serum total, di-
rect and indirect bilirubine were 4,72 mg/dl, 2,43 mg/dl and 2,30 mg/dl re-
spectively, Gamma-GT was 302 U/L. Liver enzymes were within the nor-
mal range.

Despite the administration of fitomenadion and the following normalization of INR, ecchymoses on the upper left limb extended and grew into a hemATOMA, while spontaneous petechiae appeared in other areas of the limbs and on the thorax. When central venous catheter was placed because of peripheral veins unavailability, purpuric lesions arose on the neck and a thorax CT scan obtained in the third day, revealed spots in the sternoclei-
domastoid muscle due to blood extravasation. Although the patient was treat-
ed with red blood cell transfusion, anemia persisted. Blood chemistry (c-
Anca, p-Anca, cryoglobulins) tests were not suggestive of vasculitis.

To assess platelet function, the effects of ADP, epinephrine, collagen and
ristocetin were measured. In each test platelet aggregation induced by these
agonists was abnormal, indicating platelet dysfunction.

The investigations were repeated four days later (seven days from alcohol
and acetylsaliclic acid interruption) and the platelet aggregation curve re-
turned to normal.

The cause of the petechiae, ecchymoses and hemATOMA was then assumed
to be aspirin-induced platelet dysfunction enhanced by drinking alcohol.

After stopping the simultaneous ingestion of aspirin and alcohol for 5 days,
no new skin lesions appeared and the previous cutaneous manifestation due
to platelet dysfunction began paler and paler until they totally disappeared
after a month.

Alcohol alone has no effect on platelets but enhances the effect of aspirin
given simultaneously or up to at least 36 h after aspirin ingestion, pro-
longing bleeding time.

Since the magnitude of the augmentation varies independently from the re-
sponse to aspirin alone, it’s not possible to predict a given subject’s sensi-
tivity to simultaneous ingestion, which could range from a slight prolonga-
tion to a marked elevation of the bleeding time that may be sufficient to
provoke spontaneous bleeding. Although the simultaneous ingestion of aspirin
and alcohol is not a common cause of cutaneous manifestation as purpuric
lesions, ecchymoses and hemATOMA, this clinical presentation should al-
ways prompt the physician to make an accurate anamnesis including alco-
hol consumption in patients taking acetylsaliclic acid.

The last train out of my heart

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VA, a 55-years old man came to our attention referring the onset of sudden
neurological symptoms occurred 5 days earlier: during a journey in a
crowded and hot train (we were in summer) he started having trouble with
moving the right arm and losing the sensitivity. He also referred that diffi-
culties to speak appeared rapidly. The symptoms lasted almost 2 hours.
In the ED, the clinicians performed a cerebral magnetic resonance (MR) that
showed a hyperintense spot in the territory of left posterior internal cere-
bellar artery (PICA), associated with similar lesions in the right cerebellum.
He never had symptoms like that and suffered from arterial hypertension, he
never smoked, and referred a normal cholesterol blood level, he used to
practice physical activity as a professioner (former basketball player).

We started performing laboratory tests, obtaining normal serum levels of
electrolytes, cholesterol, normal renal and hepatic function, as well as red
blood cells count, hemoglobin and platelets. We looked for possible throm-
bophilia conditions, dosing lupus anticoagulans title, levels of antergic-
olipin, antiphospholipides antibodies and activated c-protein resistance: all
of the tests resulted negative.

We moved forward performing a bidimensional echocardiogram: the pa-
tient’s heart showed normal structure and function, with an altered relax-
ation diastolic pattern, typical of hypertensive patients. But, an anatomic al-
teration was found: the interatrial septum showed an aneurismic shape,
with its convexity passing form left-sided to right-sided during normal
breathing acts. Even though the Doppler analysis showed no apparent shunt
signals, we decided to go further performing a bubble test-echocardiogram:
during the echography, we injected intravenously about 10 milliliters of
shaked normal saline, in order to obtain microbubbles which appeared
markedly echogenic in the echo images, like a contrast-enhanced study.

During this procedure, bubbles showed a fast passage from the right to left
atrium, more pronounced after the Valsalva maneuver: We thus obtained
the diagnosis of a intracardiac shunt. To detect the actual position of the in-
teratrial defect, the patient underwent a transoesophageal echocardiogram
which showed the presence of an ostium secundum defect, and we reached
the diagnosis of Patent Foramen Ovale (PFO), which accounts for a signif-
icant proportion of acute cerebral ischaemic events, in young patients with
no other vascular risk factors. Some other evidences tell us that PFO can be
associated with stroke only in patients with other thrombophilia status, but,
when we re-examined VA’s clinical history, we obtained the ED’s blood
samples results, and we noticed a hematocrit rate of 54%, which, instead
was 46% in our tests. The patient also referred that in that period he was
following an hyperproteic slimming diet, which, in addition to the high en-
vironment temperature, resulted in a strong dehydration.

Patient’s PFO was not wide enough to recommend a percutaneous closure,
so our choice was to start antiplatelet therapy with acetylsaliclic acid 100
mg per day, reserving the opportunity of doubling with clopidogrel in high
risk conditions.

In conclusion, we could argue that, in patients with PFO and absence of
thrombophilia conditions, even hyperviscous blood can represent a risk
factor for the paradoxical embolism that results in acute ischaemic cerebral
events.

Get up on your feet again

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A 68-old man presented to our attention complaining with diffuse articular
pain, located especially to shoulders, hips and feet. The patient also referred
a worsening muscle weakness, and deambulation was almost impossible.
These symptoms were present from about a month.

He was affected by HBV, HbeAg positive chronic infection, which was
treated for 10 years with lamivudine, then, 5 years ago, he started therapy
with adefovir dipivoxil tablets, once daily, because of lack of viral re-
sponse.

At clinical examination, the patient presented diffuse pain on palpation
of shoulders, hips, ribs, and legs; diffuse muscle weakness was present, espe-
cially located in the lower limbs.

During ribs examination, we found several painful nodules along sixth and
seventh rib, bilaterally. He told pathological fractures were diagnosed,
through radiological imaging, and computed mineralometry showed os-
teopenia.

Blood laboratory testing showed: serum phosphate 1,2 mg/dl, blood urea
nitrogen 50 mg/dl, serum creatinine 1,5 mg/dl, alkaline phosphatase 306
U/L, PTH 9 pg/ml, blood Vitamin D3 level was 19.6 ng/mL.
Urinalysis: glicosuria > 1000 mg/dl, proteinuria 100 mg/dL, red blood cells 49/uL, urinary phosphate 0,5 mg/dl.
24 hours phosphate excretion was 10 mg/24h, urinary calcium excretion was 30 mg/24h, 24-h creatinine excretion was 92 mg/dl, within 2000 ml of urinary volume. Calculated phosphate Tm/GFR showed a value of 1,044.

The association between hypophosphatemia, glicosuria, proteinuria indicated kidney’s inability to reabsorb these compounds: patient had proximal tubulopathy.

This evidenced the presence of renal damage, which can be referred to iatrogenic aetiology: in fact, however rare, Fanconi’s syndrome is associated with long-term therapy with adefovir dipivoxil (our patient had been exposed to 1 tablet once daily for 60 months). The finding of a hypophosphatemia, instead of expected hyperphosphaturia could have been explained with the severe hypophosphatemia, and the consequent low concentration of phosphates in the patient’s peririne.

Our therapy started with the withdrawal of adefovir dipivoxil, switching to tenofovir disoproxil for hepatitis control, and oral supplements of 25-OH vitamin D and d-fructose 1,6-diphosphoric acid, providing 0,235 mEq/ml of phosphate.

At 1 month observation, however, the patient referred only poor resolution of the bony pain and muscular weakness.

We decided, indeed, to raise the level of phosphate supplements: tablets containing disodic hydrogenphosphate 360 mg + potassium dihydrogen-sulphate 602 five times a day.

After 1 month, blood phosphate raised to 2.1 mg/dl, creatinurina 55 mg/dL, urinary phosphate 4.0 mg/dl, and phosphaturia 64 mg/24h

The patient reported slight attenuation of bony pain, and muscular weakness.

The latter follow up showed normal blood levels of phosphate and phosphaturia. Patient could reduce supplementation therapy to three tablets a day, resuming all normal physical activities.

**Non-cirrhotic hyperammonemic encephalopathy (NCHE) in a patient with an abdominal abscess: a case report**


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**Case report:** We report the case of a 73-years-old Caucasian man admitted to our Unit due to colicky pain at the right upper abdomen. His previous medical history was unremarkable except for an ischemic stroke with left side weakness which occurred several months before our evaluation. Abdominal ultrasoundography showed gallbladder wall thickening, gallstones and a minimal intrahepatic bile duct dilatation. Endoscopic retrograde cholangiopancreatography (ERCP) was performed and revealed a prominent Vater’s ampulla, which was biopsied. Histology led to the high suspicion of Vater’s ampulla carcinoma. On January 2013, the patient underwent a Whipple’s pancreateicoduodenectomy: final histology confirmed the diagnosis of Vater’s ampulla carcinoma. As a post-operative complication, he developed fever. Analysis of fluid from abdominal drainages suggested a pancreatic fistula (amylose 25.198 U/L). A CT scan of the abdomen showed an abdominal abscess of 60x56 mm, localized below the anterior-inferior margin of the liver and with inter-aorto-caval extension. The abscess was promptly drained percutaneously and the cultures were positive for MDR Klebsiella Pneumoniae. As a consequence of infection, renal function gradually deteriorated but, surprisingly, while creatinine showed a progressive increase, urea plasmatic levels decreased to the lower limit of normal range. Liver enzymes and function tests (bilirubin, INR) were normal. The patient gradually developed altered mental status, alternating depression of consciousness and agitation, with fluctuation in cognitive performances during alertness. Behavioural symptoms were associated with slurred speech. He underwent brain MRI, showing only the old ischemic lesion (with sign of reperfusion), and a full neurological examination was performed. No focal signs resembling new cerebral ischemia were found. Electroencephalography (EEG) showed non-specific diffuse slow waves activity and rachicentesis ruled out any encephalic diffusion of infectious processes (chemical and cultural examination of cerebrospinal fluid resulted both negative). In spite of a preserved liver function, serial blood tests for venous ammonia concentration were finally performed revealing extremely elevated values (up to 264 uMol/L, normal ranges 18-72 uMol/L). The patient was promptly treated with branched chain amino-acids (BCAA) and enemas, with a rapid improvement in mental status and cognitive performances. Moreover, prolonged and definitive antibiotic treatment (Colistin, Vancomycin and Metronidazole) was able to manage infection with sepsis and access regression and a sustained improvement in mental and general conditions.

**Discussion:** Delirium is a serious and pervasive problem especially in critical ill patients. Even though a large number of aetiologies behind delirium remain poorly modifiable (e.g., environmental factors, surgery, drugs), an accurate investigation of all possible underlying metabolic disorders is recommended in order to avoid and treat potentially dangerous conditions. After deep investigation, non-cirrhotic hyperammonemic encephalopathy (NCHE) was recognised as the cause of delirium observed in our patient. NCHE is a potentially life-threatening condition which can result mainly from infections, inborn errors of metabolism, porto-systemic shunts, haematopoietic disorders, drugs and starvation. Klebsiella Pneumoniae is a Gram-negative, non-motile, encapsulated, urease producing bacterium that often causes nosocomial ATB resistant infections. The urease enzyme hydrolysates urea to ammonia and carbon dioxide [(NH₂)₂CO + H₂O = CO₂ + 2 NH₃], increasing the circulating level of ammonium (NH₄⁺). The presence of low plasmatic urea levels, despite high creatinine, corroborates our hypothesis. In the setting of normal liver functioning, clinical suspicion is the most important diagnostic element because neurological procedures such as EEG and lumbar puncture could be ineffective or non-specific in order to discover this condition. Therefore, NCHE should be considered in the differential diagnosis of altered mentation, particularly in patients infected by urease-producing bacteria.

**Rapidly progressive liver failure in a breast cancer patient with negative hepatic imaging**

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**Case Report:** We describe the case of a 58-year-old Caucasian woman who was referred to our Unit due to ascitic decompensation. Her medical history began several months before, when she underwent a FNAC of a breast lump, resulting positive for small groups of ductal cells and few atypical elements. Final histology evidenced grade II invasive lobular intraepithelial neoplasia (LIN sec. WHO), and immunohistochemistry yielded the following results: estrogen receptor = 90%, progesterone receptor = 90%, Ki67 = 3%, p53 = 30%, HER2 not overexpressed. A full-body CT scan was performed, revealing diffuse bone osteoblastic metastases, pleural effusion and ascites. She underwent three cycles of specific combined chemotheraphy and immunotheraphy with paclitaxel and bevacizumab (Avastin and Taxol) and subsequently began zolendronic acid (Zometa), monthly. After developing treatment-related neurological toxicity, she was started on fulvestrant (Faslodex), continuing the applications of Zometa. After a 8-month response, the follow-up blood tests showed raising tumor markers and she was given a single dose of vi-
norelbine and capecitabine (Vinorelbine and Xeloda). On admission to our Unit, she was hemodynamically stable and physical examination evidenced bulging of the flanks, shifting dullness of the abdomen and lower limb oedema. Blood tests showed an increased level of bilirubin (6.7 mg/dL) and INR (1.4), a moderate thrombocytopenia (61,000 u/L), together with mild elevation of hepatic enzymes (AST 45 U/L, ALT 44 U/L, GGT 340 U/L, ALP 109 U/L) and hypoalbuminemia (2.78 g/dL). Moreover she progressively developed altered mental status, lethargy and depressed consciousness. Results of serologic tests for hepatitis B and C were negative, autoimmune hepatitis was also excluded and she had no history of alcohol abuse. We performed a diagnostic paracentesis: 4 litres of yellow fluid were removed, the serum-ascites albumin gradient was > than 1.1 (SAAG>1.1), the cytologic examination of the ascitic fluid was negative for neoplastic cells and there was no evidence of spontaneous bacterial peritonitis. A CT scan of the abdomen with contrast medium was performed showing a normal liver in size and shape, a homogeneous parenchyma with no focal area of altered attenuation. A moderate splenomegaly was described (DM 14 cm).

**Diagnosis deepening:** The high gradient of SAAG (>1.1 g/dL) indicates the ascites is due to portal hypertension with 97% accuracy. Causes of portal hypertension can be divided into prehepatic, intrahepatic and posthepatic. Intrahepatic causes include liver fibrosis and cirrhosis; prehepatic causes include portal vein thrombosis or congenital atresia; posthepatic causes depend on obstruction, which may occur at any level between liver and right heart, including hepatic vein thrombosis, inferior vena cava thrombosis, inferior vena cava congenital malformation and constrictive pericarditis. All the possible diseases related to pre and post-hepatic causes of portal hypertension were excluded in our patient. There was no peritoneal diffusion of the carcinoma, and ascites and splenomegaly were therefore secondary to intrahepatic portal hypertension. Since all the possible causes of hepatic damage had been previously excluded (viral, autoimmune, toxic and metabolic), and since the raising of tumor markers was accompanied by rapid worsening of hepatic function and appearance of hepatic encephalopathy, we decided to perform a transjugular liver biopsy, which disclosed liver cirrhosis while showed a diffuse infiltration by poorly differentiated carcinoma with the following immunohistochemical results: CK7 +, GCDFP15, ER 40%, PGR 40%, CK20-, Ki67 Mib1 5%, c-erbB2 (CB 11 Novocastra) 20% (score test: 1+). The patient received best supportive care and died 40 days after admission due to terminal hepatic failure.

**Discussion:** Most liver metastases from breast cancer are apparent on contrast-enhanced CT imaging and rarely cause portal hypertension and progressive liver failure. This pattern of diffuse metastasis with negative imaging is rare and few case reports appear in the literature. The possibility of hepatic micrometastases must be suspected in patients with breast cancer who suddenly develop signs and symptoms of portal hypertension and liver failure, and posed in differential diagnosis mainly with hepatotoxicity from chemotherapeutic agents. In these cases, liver biopsy should be obtained to confirm diagnosis.

**Scleroderma-like lesions in a patient with Crohn’s disease**

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We report the case of a 85 years old woman admitted to our Institute for anemia of unknown origin. She had a history of right colectomy for colon carcinoma (1993). On admission: Hb 3.2 g/dL, MCV 63.4 fl, ferritin 11.1 ng/ml. Esophagogastroduodenoscopy and colonoscopy showed: “hyperemic ileostomie with multiple minimal ulcerations in the outcome of right hemicolectomy. Intencomitence of the cardia. Hiatal hernia. Moderate to severe edematous gastropathy watermelon type in the antrus.”

Histological examination of the ileal mucosa was compatible with the diagnosis of Crohn’s disease in the active phase.

Watermelon stomach is a gastric antral vascular ectasia and it is an uncommon cause of gastrointestinal bleeding and iron deficiency anemia. Two patterns of antral angiodysplasia have been described:

1. the classical form (type A), usually idiopathic, with hyperemic longitudinal stripes to antral origin, starting from the antrus and converging towards the pylorus. It mainly affects elderly women and is associated with autoimmune disease.
2. The diffuse form (type B), typical of patients suffering from portal hypertension and liver cirrhosis.

Neither case appears to be present in our patient, but the frequent association between “watermelon stomach” and autoimmune diseases prompted us to investigate in this direction. Interestingly we found a significant ANA positivity (titer 1/1280), showing nuclear centromeric pattern, associated with ENA CENP-B positivity (477.22 U/ml).

The capillaroscopic picture was suggestive for “late scleroderma pattern”. It is known that the Crohn's disease may develop skin manifestations; mostly erythema nodosum (present in more than 15% of patients with Crohn’s disease) and psoriasis (5-10%). Reported cases of scleroderma-like lesions in patients with Crohn’s disease are not common. Further studies will be needed to demonstrate the mechanism underlying the association between these two diseases.

**63 years old man with thyroid nodule**

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A 63 years old man presented with a thyroid nodule and right eye ptosis. His physical exam showed enlarged cervical, supraclavicular, right inguinal and occipital lymph nodes, two fibrotic lesions on the scalp and hepatosplenomegaly. The mass on the right side of the neck was mobile, soft, fluctuant with swelling. He was not jaundiced. The patient complained a loss of weight in the last two months, severe tiredness and evening fever. All the symptoms began in august 2012 when he had a TURP procedure for a local prostatic adenocarcinoma. Apart from a local pain in the right hip, he did not present any abdominal or cardiorespiratory discomfort. In january 2013 he felt a mass on the right side of his neck and asked for medical visit. When he was admitted to our department, he previously had neck ultrasonography and fine needle aspiration of the lesion. At that time cytological result was still in progress.

His routine laboratory investigations showed a mildly elevated level of ALT(92U/L),AST(110U/L),bilirubin(1.7 mg/dL), and high plasma levels of some neoplastic markers like (GICA 8731.52 U/mL, CA15-3 99.9U/mL, CEA, Ca 125 240.10). The thyroid profile showed high level of TSH(5.06microU/mL), decrease of FT3 level(2,54 pg/mL), normal FT4(1.18 ng/dL),negative thyroglobulin antibodies and high level of thyroglobulin(463,9ng/ml).

Thus clinical and laboratory data suggested the presence of a neoplasm. Ultrasonography of the neck showed a diffuse enlargement of submental, submandibular, cervical lymph nodes and enlargement of thyroid gland. Eight lesion in the right lobe and five in the left lobe were also noted. CT total body showed several lesions in the lungs, in pectoralis major and minor muscle, two in the iliac bone, multiple enlarged lymph nodes at thoracic-abdominal levels and a hypodense mass of 22mm in the pancreas. The brain CT showed a little lesion of inner acoustic meatus compatible with an acoustic neuroma. The brain NMR confirmed the hypothesis of neuroma. The result of the thyroid cytology revealed thyroid cells together with abnormal and necrotic cells, compatible with cancer(TIR 5).

Ultrasonography-guided biopsy of the liver showed a liver tissue infiltrated...
by an adenocarcinoma with sclerodermiform aspect and necrosis. Immuno-
histochemical analysis was positive for citocheratin 7 and Ca 125 and negative for ITF. This result suggested that pancreas was the primary site of the carcinoma. Thyroid biopsy showed thyroid tissue infiltrated by a low differentiated neoplasm and necrosis. The data were compatible with metastasis from pancreatic adenocarcinoma.

Malignancies of the thyroid are usually primary, although metastases should be considered in patients with a known malignancy. The most common non thyroid neoplasms that metastasize to the gland are kidney, colorectal, breast and lung carcinoma. The thyroid gland is believed to be rare site of metastases, possibly due to the high oxygen saturation and iodine content within the gland. Thyroid metastases from pancreas are extremely rare, since to our knowledge there are only three reported case of pancreatic tumors with clinically relevant metastases to the gland. The management of thyroid gland are not well defined and certainly it depends on clinical condition of the patient. According to some authors, although thyroidectomy may be useful to avoid further dissemination of the primary tumour in case of solitary thyroid metastasis, it does not contribute to prolong patients life.

Our patient was referred to the oncology unit of the department for palliative treatment since the advanced stage of the disease did not permit any other type of treatment.

An unexpected cause of fever of unknown origin (FUO)


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Introduction: Fever of unknown origin (FUO) in adults is defined as a temperature higher than 38.3°C that lasts for more than three weeks with no obvious source despite appropriate investigation. The four categories of potential etiology of FUO are classic, nosocomial, immune deficient, and human immunodeficiency virus–related. The four subgroups of the differential diagnosis of FUO are infections, malignancies, autoimmune conditions, and miscellaneous. Infections as extrapulmonary tuberculosis, culture-negative endocarditis and intra abdominal abscess account for about one-third of cases. We report a case of a 52-year-old man with FUO.

Case Report: a 52 year old man, was admitted to our Department because of fever (up to 40°C) that was onset about 3 weeks before. In his past medical history the patient reported that he had been hospitalized in the preceding year for the same reason at the Department of Infectious Diseases and was discharged with a diagnosis of “fever of unknown origin”, since infectious, hematological, oncological and immunological causes were ruled out. During hospitalization in our Department laboratory test demonstrated a severe increase of white blood cells and neutrophils (24,340 Neu 93%) and inflammatory index (PCR 24.9 mg/dl, VES 79 mm/h, PCT 1.95 ng/ml). IgG, IgA, IgM values and venous peripheral blood smear were within the normal limits, while lymphocyte subpopulations showed an increase of T4 lymphocytes (2.340 Neu 93%) and inflammatory index (PCR 24.9 mg/dl, VES 79 mm/h, PCT 1.95 ng/ml). Antistreptolysin titer were negative. Bence Jones, β2-microglobulin, serum and urinary immunofixation, Reumatoid Factor, Waaler Rose, ENA, ANA, C3, C4, antibodies to phospholipids, TSH, FT3, FT4 and tumor markers (CEA, CA 125, CA 15.3, CA 19.9,NSE, Cyfra, α-fetoprotein) were normal. EGDS, RSCD and thyroid echography did not point out significative alterations. TC–PET demonstrated a modest FDG uptake in the back-left corner of the jaw, laterocervical region contralateral, and pulmonary right hilum, in the first case compatible with overactive lymph node on the basis of inflammatory. Moreover modest hyperaccumulation of the radiopharmaceutical was detected in all skeletal segments examined. To complete diagnostic we performed an orthopanoramic x-ray that documented multiple root residue, carious lesions and periradicular inflammatory outbreaks. Therefore he was subjected to dental cleaning with disappeared of symptoms.

Conclusion: Because of their anatomic localization and their function teeth and their supporting structures are often prone to infections by pathogenic microorganisms. In literature are described different cases of patients in which an infective dental or parodontal outbreak has proved to be responsible of fever, initially considered FUO, without any other symptomatology. Therefore targeted investigations to exclude pathology of the oral cavity should be considered.

Electrocardiographic pattern ‘Brugada like’ caused by severe hyponatremia and antiarrhythmic drugs

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A 59-years old woman was admitted to our Clinical Unit due to a syncopal episode and an acute gastroenteritis with fever for two weeks. She had a past clinical history of hypertension and atrial fibrillation treated with cathether ablation. She was taking-over Flecaïnide 50 mg bid, Amiodarone, Irbesartan/Idroclorotiazide and Enalapril. There was not a family history of sudden death.

Laboratory investigations revealed hypokalemia (2.6 mEq/l) and hyponatremia (115 mEq/l). Electrocardiogram showed normal sinus rhythm at 72 bpm. QTc 482 mSec, ST-segment elevation associated with negative T waves in leads V1-V3, recognised as type 3 “Brugada like” pattern. Markers of myocardial necrosis were negative.

Based on the clinical symptoms and signs (syncopal episode during fever), the electrocardiographic pattern, the electrolyte disorder and the therapy with sodium- and potassium-channel blockers, we decided to suspend the antiarrhythmic drugs and correct the electrolytic disorder.

In a few days there was a general improvement in the clinical picture and the regression of electrocardiographic changes.

The Brugada syndrome (BS) is linked to a genetic mutation of the sodium channel in myocardioocytes, that causes a premature reduction and/or inactivation of Ina-late current during action potential phase 1. This electrical alteration is responsible for 3 different ECG pattern in the right precordial leads, so-called “coved-type” (pattern 1) and “saddle-back” >2mm or <2 mm (respectively pattern 2 and 3). The characteristic electrocardiographic pattern may be spontaneous or induced by fever, stress-test and sodium-channel blockers, that are used for diagnosis in the provocation test.

While it is known that antiarrhythmic drugs and hypokalemia can prolong QT interval and are proarrhythmic in BS, to our knowledge there are only three case reports showing the association between “Brugada-like” electrocardiography pattern and hyponatremia. In these papers the authors suggest that the reduction in transmembrane sodium gradient is responsible of this electrical alteration.

In our case we hypotized a role of both severe hyponatremia and antiarrhythmics, particularly flecaïnide, in reducing the Ina-late current, determining ECG changes and, finally, the syncpe. Although there were neither typical ECG pattern, i.e. the type 1 pattern, nor the other diagnostic criteria for the BS (documented ventricular arrhythmias induced by electrophysiologic examination, family history of early sudden death and typical ECG pattern), the suspension of drugs and the correction of electrolyte disturbances normalize ECG changes. Our report stresses the im-
portance, in patients treated with antiarrhythmics, of a careful monitoring of serum electrolytes and ECG, in order to early disclose unknown arrhythmogenic diseases.

An immunodeficiency... turning pale!


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AD, a female patient 38 years old, came to our attention for worsening dispnea wich started about three months before. In her medical history a diagnosis of Common variable immunodeficiency under intra venous immunoglobulin replacement; HBV+, CMV PCR+. At the admission to our department the patient appeared debilitated, pale, tachypnea, tachycardia (hr 115 bpm). Physical examination showed splenomegaly at the lower left abdominal quadrant. Blood tests showed normocytic normochromic anemia (hb 5,1 gr/dl); haptoglobin level was low; Suspecting autoimmune hemolytic anemia we required a direct antiglobulin test (coombs test) wich resulted positive. Due to the instability of the clinical set, we decided to perform transfusions with 2 compatible blood units, formerly washed by the trasfusional center and preceded by premedication with corticosteroids. Post transfusion Hb: 7,9 gr/dl. Reached the clinical stability daily desametasone 16 mg e.v. was promptly started beside antibiotic and anti-fungine profilaxis; in addiction a first infusion of AntiCD-20 monoclonal specific human Ig, avoiding valaciclovir side-effects. An abdominal ecography showed splenomegaly. six weeks from the admission, once hb stabilization was achieved, the patient was sent to the surgical department for splenectomy.

Erythema nodosum: a cutaneous sign of sistemic disease

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A 53-years-old man was admitted to our Department because of painful and tender erythematous nodules of recent onset. He was a former heavy smoker with a history of systemic arterial hypertension treated with losartan 100 mg/die. He had chronic hepatitis C treated with peg-interferon and ribavirin ten years before. He described asthenia, anorexia, weight loss and a lower fever in the last two months. Upon admission he had a body temperature of 37.7°C, blood pressure of 126/68 mmHg, a pulse rate of 89 bpm and a respiratory rate of 19 bpm. On physical examination, we noted the presence of symmetrical, tender, erythematous, warm nodules and raised plaques on the extensor surface of both lower legs. There were no others significant findings at clinical examination. He was quested for drugs usage, as well as preceding and concurrent systemic symptoms. The laboratory tests showed increased erythrocyte sedimentation rate and C-reactive protein. Whole blood count and blood biochemistry including renal and liver function and protein electrophoresis tests were within normal ranges as well as coagulation factors. Autoimmune markers, including anti-nucleus antibody, anti-citr-citrullinated peptide antibody, rheumatoid factor, lupus anti-coagulans were all negative. Angiotensin-converting enzyme dosage was within normal ranges excluding diagnosis of sarcoidosis. Antistreptolisyn O titer and oncomarkers were within normal ranges. Pharyngeal buffer and sputum microscopy were negative. He had anti-HCV antibodies and an absent viral load. Screening for Chlamydia Pneumoniae, Chlamydia Trachomatis, Salmonella, Brucella, Syphilys, Epstein-Barr virus, Hepatitis B and Human Immunodeficiency virus were all negative. Cryocrit lab test was negative too. Chest X-ray showed an accentuation of bronchovascular interstitial plot and absence of parenchymal infiltrative lesions. Thoracic computed tomo-graphic scans revealed a small nodule in right upper lung zone and mediastinal, sub-carinal lymfadenopathy. The Mantoux skin test was positive, with a skin reaction of induration more than 20 mm around the injection site. T-spot TB, a type of ELISpot assay used for tuberculosis diagnosis, was re-active, highlighting the presence of Mycobacterium tuberculosis infection. The lesion’s skin biopsy showed granulomatous septal panniculitis that was consistent with Erythema nodosum. On hystopathologic examination, there was fibrosis and granulomatous inflammatory cell infiltrate, primarily involving the thickened fibrous septa, but there was no evidence of vasculitis. The final diagnosis was: Primary Tuberculosis associated with Erythema nodosum. So, first-line therapy was: ethambutol 400 mg/die, isoniazid 300 mg/die and rifampin 600 mg/die for two months, followed by isoniazid and rifampin for four months. Primary tuberculosis is a common etiology of Erythema nodosum which may be the first sign of a systemic disease such as tuberculosis, bacterial or deep fungal infection, sarcoidosis, inflammatory bowel disease, or cancer. Differential diagnosis is mandatory when we find a case of Erythema nodosum.

Lymphadenopathy and aortitis: who are we to blame?


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Introduction: Aortitis is a general term which includes all inflammatory alterations of the aortic wall depending either on infectious or autoimmune or neoplastic causes. A number of organisms have been associated with infectious aortitis, such as Treponema pallidium, Koch’s Bacillus (BK), cytomegalovirus (CMV), Streptococcus pneumoniae, Salmonella and Staphylococcus species. Bacterial aortitis mostly occurs on preexisting atherosclerotic plaque or aneurism. Tuberculous aortitis occurs generally on the ascending aorta and may depend on a direct seeding from adjacent infected tissues such as lymphnodes, lungs or by miliary spread. Syphilitic or luetic aortitis typically involves the ascending aorta and is associated with thoracic aortic aneurysm. Infections can also trigger a noninfectious vasculitis by generating immune complexes or by cross-reactivity. Moreover aortitis may represent a paraneoplastic complication of an unknown neoplasia. The differential diagnosis between infective and autoimmune aortitis can be tricky. Here we report the case of a 79 year old man with ascending aortitis and diffuse lymphadenopathy.

Case report: A 79 year old male patient, was admitted to our Department because of malaise, weight loss, asthenia, anorexia nausea and vomiting which started one month before. In his past medical history: chronic atrial fibrillation (AF) treated with oral anticoagulant. A preceding total body CT scan documented aortitis and generalized lymphadenopathy (paracaval, inter-aortocaval, thoracic and abdominal paraortic, mesentery and bilateral inguinal lymph nodes). Laboratory tests showed increased C-reactive protein (CRP 2,6 mg/dl), an a slight increase of lymphocyte percentage. Considering aortitis Treponema pallidium and anti-CMV antibodies were searched for. Venereal disease research laboratory test (VDRL) was negative and anti-CMV resulted IgM+/- and IgG+. Quantiferon was negative. An autoimmune screening was therefore performed showing positive anti-nuclear antibodies (ANA 1:80) and rheumatoid factor (RF) (79 IU/ml),
Lymphocyte subpopulations documented an increase in T-CD4+ and in CD4/CD8 ratio. Since the patient did not report symptoms of autoimmunity in the suspicion of a paraneoplastic syndrome a total body contrast CT was performed confirming generalized lymphadenopathy, but not aortitis. Moreover a monoclonal rearrangement of TCR was found. Thus, a Total body CT-PET was performed showing no abnormalities. Because of worsening of his general conditions (neck rigidity, fever, tremors, nausea and vomiting), a viral encephalitis was suspected. Since the patients was under anticoagulant prophylaxis it was not possible to quickly perform a lumbar puncture, thus an empirical treatment with ceftriaxone and acyclovir was started. Since patient worsened within 24 hours, he was transferred to the Reanimation Department, where antiviral treatment was interrupted and hydration, dopamine and digoxin were started. Upon return in our Department, his general conditions were improved, but nausea and vomiting continued thus, an esophagogastroduodenoscopy (EGDS) was performed showing no relevant finding. During hospitalization a symmetric arthritis of the upper limbs was observed and gastrointestinal symptoms worsened. Since other neoplastic and infectious causes were excluded a diagnosis of undifferentiated connective tissue disease (UCTD) was performed and corticosteroid therapy was started with a quick improvement of the general condition and complete remission of the symptoms.

Conclusions: UCTD is a oligosymptomatic connective tissue disease (CTD) that does not meet the classification criteria of any specific systemic autoimmune disease, but has signs and symptoms suggestive of CTD. UCTD has a limited autoantibody repertoire, in particular ANA. Often in patients with active systemic autoimmune diseases an aspecific positivization of IgM anti-CMV is observed. Moreover the rearrangement of the TCR may occur as an epiphenomenon of the activation of the immune system and it is not necessarily an indicator of a lymphoproliferative disorder. Further confounding a possible differential diagnosis is that monoclonal TCR may occur during viral infections. This case therefore seems of particular interest since a systemic autoimmune disease was masked by aspecific symptoms and by positive infectious tests. However it could not be excluded that a reactivation of CMV infection may have triggered an immune mediated response accounting both for aortitis and arthritis.

An unusual case of polyarthritis

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A 55 years old man, living in rural area of Italy, was addressed to our clinic because of progressive multi-joint involvement and deterioration of the general conditions over the last 16 months despite the prolonged use of steroids and empiric therapy.

His medical history was poor: a partial gastrectomy for peptic ulcer when he was 30 years old and no further clinically relevant conditions up to 5 months earlier, when he was first admitted in hospital for worsening of general conditions, pain and swelling of the right sternoclavicular joint, abdominal pain, vomiting and asthenia. The patient was discharged without a definitive diagnosis, and continued therapy with steroids. In the following months he develops a severe polyarthritis, cough, fever, progressive severe weight loss, so he was hospitalized in our clinic for further medical examination. Physical examination revealed swelling of the right sterno-clavicular joint with tenderness during palpation, and multiple joint involvement (ankles, wrists and metacarpophalangeal of the right hand). Palpation of abdomen elicited pain in the epigastrium. Chest examination revealed moderate broncoostenosis. A weakness of right leg was also observed. Laboratory showed high Eritrocyte Sedimentation Rate (112 mm/1st hour), high C-reactive protein (8.5 mg/dl), low haemoglobin (9.8 g/dl), high leucocyte count with normal granulocyte distribution, thrombocytosis, low proteins (3.1 g/dl) with low albumin (1.7 mg/dl), low serum iron (22 µg/dl; normal values: 40-160), low transferrin (35 mg/dl; 200-360), high ferritin (357 ng/ml; 5-232), whereas vitamin B12 and folic acid levels were normal. For suspected inflammatory bowel disease occult blood test and calprotectin assay were performed and were not diagnostic. It was performed a parasitological examination of stools on multiple assays, and they were negative. To exclude malignancy a sampling was performed for cancer markers, that were negative. Anti-cyclic citrullinated peptide antibodies, rheumatoid factor, complement, immunoglobulin, antibodies for celiac disease and antinuclear antibodies tested were all negative. A workup for infectious agents including serology for Parvovirus B-19, Brucella, Borrelia, Salmonella, HCV, HBV, CMV, HIV, HZV, HSV, EBV, HTLV-1 was tested and was positive for HCV. Electroneurographic examination was performed to investigate the weakness of right leg revealing a mild neuropathy. Magnetic resonance imaging of the brain and spinal was not diagnostic.

To investigate occult malignancy, chest and abdomen computed tomography were performed revealing a thickening of right bronchial and of colonic mucosa.

To further investigate, also suspecting an intestinal lymphoma, the patient underwent to a colonoscopy that revealed mucosal edema and erythema, so multiple biopsies were performed. To exclude a bone cancer or repetitive lesions a scintigraphic skeletal examination was performed that showed an increased uptake of the right sternoclavicular joint and left shoulder. Finally, the istopathologic examination of the bowel biopsies described massive infestation of Strongyloides stercoralis. Albendazole 400 mg three times/day was consequently started.

Strongyloides stercoralis is an intestinal nematode; humans are generally infected transcutaneously, although infection has also been experimentally induced by oral administration of water contaminated with filariform larvae. The diagnosis could be difficult because the parasite load is low and the larval output is irregular. Albendazole may stimulate the excretion of larvae into stool allowing subsequent identification in the sample. After two days of therapy the parasite was detected in stool and sputum assays and after 15 days of therapy the parasitological exams of the stool did not identify parasites, articolar pain and swelling resolved and laboratory values were normalized. The patient has started to eat regularly and regain weight; laborat-

ory markers were then normalized. Patients under corticosteroid therapy have higher risk of being infected by Strongyloides stercoralis probably through its inhibitory action on eosinophils. Additionally, steroid may have a direct effect on the parasites, accelerating the transformation of rhabditiform to invasive filariform larvae or rejuvenating latent adult females thus facilitating their spreading. In uncommon feature of arthritis, some rare parasitosis have to be excluded before treatment with steroids avoiding a potentially lethal infection.

A case of hemolytic anemia

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A 59 year old woman went to the emergency room because of jaundiced sclerae, severe asthenia, leg myalgia, shortness of breath for moderate efforts, and right upper quadrant pain associated with diarrhea persisting for about a week. History revealed hypertension and chronic atrial fibrillation on oral anticoagulation in previous cardiac surgery for severe rheumatic mitral valve stenosis subjected first to commissurotomy and subsequently to replacement by a St Jude 27 mm mechanical valve. Cardiological follow-up had been regular since. Laboratory tests showed: Hb 9.9, MCV 88.3, Hct 30.8%, PLT 219000, total bilirubin 3.8, indirect bilirubin 3.3, direct bilirubin 0.5, AST 96. Chest X-ray showed congestion of the small circle and an
A 50 year-old Brazilian woman was admitted to our department because of pelvic pain irradiated to the lower left limb, associated to ipsilateral ankle swelling. Moreover, she reported a four-year history of constipation and post-prandial abdominal pain causing progressive weight loss due to a reduced amount of food intake (i.e. 7 kg in three years). An abdominal CT - performed in April 2009 to better investigate kidney stones - was substantially normal, except for the presence of a left ovarian cyst and uterine myomas. The patient had lived in Italy for ten years and her last trip to Brazil was six months before hospitalization. On admission, clinical examination evidenced mild hypogastric discomfort and blood tests showed normocytic anemia (Hb 10.5 g/dl), leukocytosis (WBC 13000/mmc), CRP 6 mg/dl, and increased D-dimer concentrations (923 mg/dl). Chest X-ray demonstrated a nodule in the upper right lung and Doppler-ultrasound a left deep venous femoro-popliteal thrombosis. Anticoagulant therapy with nadroprin was immediately started. Because of patient’s age, sex and the unusual presentation, a screening for the main forms of thrombophilia (Leiden factor V, prothrombin mutation) and autoimmunity (ANA, anti-phospholipid antibodies, rheumatoid factor) was performed and gave negative results.

In order to rule out the coexistence of pulmonary thromboembolism and to investigate thrombosis etiology (a pancoagulative origin was suspected), a thorax-abdomen CT was performed with evidence of multiple solid hypodense lesions in the upper and inferior lobes of the right lung characterized by contrast enhancement, a large hypodense lesion in the ilio-sous muscles bilaterally, and a complex cystoid lesion at the hepatic hilum, between pancreas, vena porta, and inferior vena cava. These findings were better characterized as active inflammatory colliquated lesions by positron emission tomography. We ruled out Toxoplasma gondii, T. solium, Cysticercosis, Trypanosoma cruzi, Trichinella spiralis, Histoplasmosa capsulatum, and HIV infections by serologic tests. Only previous echinococcal infection emerged. Since the abdominal lesions were highly suggestive for tubercular colliquated lymph nodes, Quantiferon-TB Gold In-Tube assay was assessed and suggested tubercular infection. Echo-guided percutaneous fine-needle aspiration of the left ilio-sous abcessual lesion finally allowed the diagnosis of tubercular infection with positive cultures for M. tuberculosis complex. A skeletal CT was negative for bone focuses. Drug susceptibility testing ruled out resistance to one of the first-line anti-tubercular drugs, i.e. isoniaizid, rifampin, pyrazamide, and ethambutol. Consequently standard quadruple antitubercular therapy (ethambutol 1200 mg, isoniaizid 250 mg, rifampin 600 mg, and pyrazamide 1500 mg po once daily) was started and the patient was referred to an infectious disease outpatient clinic.

Two weeks later she was admitted again to our department because of severe left lower limb pain and local paresthesias. CT-scan demonstrated an increase in diameter of the left ilio-sous abscess, abruptly enlarged probably in response to massive antitubercular therapy. To relieve symptoms, the lesion was percutaneously drained, with complete collapse. Electromyography diagnosed left femoral nerve suffering with active denervation, consequent to compressive psoas abcess injury. Metilprednisolone was immediately started, antitubercular drug dosages were reduced and ethambutol stopped. At discharge only mild paresthesias were still present. This case describes an unusual presentation of nodal tuberculosis in a Brazilian immunocompetent patient, characterized by skeletal muscles involvement without a bone focus.

### Chilaiditi sindrome complicating transthoracic lung biopsy

#### Case Report: A 84-years-old Caucasian man was admitted to our Department of Clinical Medicine - Sapienza University of Rome, for dyspnea becoming progressively severe in the last 2 days. His medical and surgical history was featured by mild hypertension (150/70 mmHg), chronic obstructive pulmonary disease (COPD), polycystic kidney disease and chronic kidney disease (CKD), post-ischemic dilated cardiomyopathy (ejection fraction, EF = 35%), implantation of a DDDR pace-
The patient was hemodynamically stable, without any obvious clinical signs on physical examination, apart from his medical history. Complete blood count, liver function tests and urinalysis were normal. Afterwards, chest X-ray and thorax computed tomography (CT) showed the COPD's signs and the presence of two bulk lesions respectively localized in the right lower lung and in the left lower lung. Lung needle biopsy confirmed the neoplastic nature of the lesions with histological diagnosis of squamous cell carcinoma. After biopsy, the patient complained of nausea, anorexia and mild non-specific abdominal pain becoming progressively stronger. Chest and abdominal X-ray revealed the presence of air in the right subfrenic region. In order to approach a correct differential diagnosis, an abdominal CT scan was performed, revealing hepatomegaly and the interposition of transverse colon segment between the diaphragm and the upper edge of the liver, the so-called Chilaiditi’s sign (Fig. A, Fig B). As neither clinical symptoms nor Chilaiditi’s sing were present before lung needle biopsy, post-biopsy Chilaiditi syndrome was the diagnosis made for such clinical presentation. Medical therapy was firstly based on anti-emetic drugs, protonic pump inhibitors and low-protein diet. In addition, according to literature evidences concerning the initial management of Chilaiditi syndrome, it was prescribed for bed rest, intravenous fluid therapy and laxative. In spite of slight improvements during the next 5 days, the patient cardiac function progressively deteriorated, the cardiomyopathy became unresponsive to any inotropic agents and the patient died from cardiogenic shock.

Discussion: Chilaiditi syndrome refers to a rare medical condition in which clinical symptoms are associated with the interposition of an intestine segment between the liver and the diaphragm (the so-called Chilaiditi’s sign). The main clinical symptoms are anorexia, nausea, vomiting, abdominal pain, abdominal distension, constipation and flatulence. Chilaiditi syndrome must be differentiated from bowel obstruction, volvulus, intussusception, ischemic bowel disease, diaphragmatic hernia and inflammatory conditions (such as appendicitis, diverticulitis, inflammatory bowel diseases). Although the mechanisms of Chilaiditi syndrome are largely unknown, several predisposing factors, numerous clinical conditions and various medical or surgical procedures (as reported in our case report) have been associated with its pathogenesis. No treatment is required when Chilaiditi’s sign is isolated or minimal symptoms are observed. In the presence of more serious clinical presentations, the management of Chilaiditi syndrome should be conservative, while surgical intervention should be reserved to refractory cases or complications.

An insidious cause of kidney failure in an elderly patient

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Introduction: An 83-year old woman was admitted to our hospital following the sudden onset of drowsiness. The patient’s medical records showed a condition of severe osteoporosis with multiple collapsed vertebrae, dysphagia and rapidly ingraescent cognitive impairment over the last 18 months. The patient appeared to be in generally serious conditions, Glasgow coma score (GCS) 11/15. A brain CT scan was negative as regards focal densitometric alterations and localised accumulation of blood. Blood chemistry analysis also showed: kidney failure (GFR 13 ml/min); anaemia (Hb 9.5 g/dl; n.v. 12-16 g/dl); hypercalcaemia (13.3 mg/dl; n.v. 8.40-10 mg/dl) and hyperphosphatemia (5.9 mg/dl; n.v. 2.8-4.6 mg/dl); increase of alkaline phosphatase (123 U/l; n.v. 35-104 U/l) and inflammatory markers (VES 69 mm/h; n.v. 0-35 mm/h; PCR 18600 µG/L; n.v. <5000 µG/L). Protein electrophoresis testing showed hypoalbuminemia (33.8 g/L; n.v. 40.2-47.6 g/L), increase of acute phase proteins and hypogammaglobulinemia (8% n.v. 11.1-18.8%). The concomitance of kidney failure and hypercalcaemia led us to suspect a condition of secondary hyperparathyroidism, but subsequent serum assays for parathormone (PTH) (40.7 pg/ml; n.v.15-65 pg/ml) and vitamin D (31 ng/ml; n.v. > 30 ng/ml) were normal in both cases.

Pathological findings: During the clinical course, the patient was less drowsy and suffered extremely painful symptoms, visual analogue scale (VAS) 10/10; worsening renal function was also noted. Even though drowsiness and painful symptoms could not be attributed to secondary hyperparathyroidism, was ingraescent kidney failure simply a concomitant pathological condition or was there a link between the clinical picture and renal dysfunction? A 24-hour urine collection showed significant proteinuria (2777 mg/24 hours; n.v. 40-150 mg/24). The finding of proteinuria in the absence of significant albuminuria, the electrophoresis of hypogammaglobulinaemia, the presence of extremely painful symptoms as well as the multiple collapsed vertebrae prompted us to perform immunofixation of both urine, which showed a significant level of Bence-Jones kappa proteins (1760 mg/litre with n.v. 69-93.4), and of serum, which showed a component with kappa immunoreactivity not associated with any immunoreactivity for immunoglobulin heavy chains. Hence the diagnosis was micromolecular kappa myeloma. A subcutaneous full body CT scan highlighted multiple, diffuse lytic bone lesions.

Discussion: The monoclonal plasmoproliferative disorders encompass a broad spectrum of diseases ranging from the often benign monoclonal gammapathy of undetermined significance to the potentially curable solitary plasmacytoma to the lifethreatening conditions of multiple myeloma. The micromolecular myeloma is a particular type of myeloma with not high frequency. In this form bone lesions are always early and extended, with bone marrow infiltration by plasmacells and course complicated by kidney failure. Extensive bone remodelling, as seen in the course of myeloma, as a result of an increase in the levels of ALP and alteration of calcium levels. The gold standard for screening for plasma cell disorders has been serum protein electrophoresis with immunofixation of the serum and the urine. Serum concentrations of immunoglobulin-light chain are dependent on the balance between production by plasma cells and renal clearance: although renal failure will increase the levels of both kappa and lambda serum immunoglobulin-free light chain in a given individual, it will not cause an abnormal kappa/lambda immunoglobulin-free light chain ratio. The clinical factors related with a shorter survival are: Bence-Jones proteinuria, high level of serum creatinine and serum calcium, low level of haemoglobin, widespread bone lesions, so that our patient has a poor prognosis.

References:
Twenty years of complications following a gunshot


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A 35 year old man was admitted to our unit because of high fever and cachexia. He had been accidently shot at the age of 13 with a shotgun. The bird-shots broke his right humerus and drilled through the right lung, leading to an urgent pneumonectomy and leaving his right arm parietic. Few weeks after surgery, the patient had the first episode of later constantly relapsing high fever. The bronchial stump underwent dehiscence giving rise to a bronchopleural fistula. He was treated with drainage and antibiotics without long-lasting benefit. After 8 months of hospitalization, while still suffering from recurrent fever due to empyema, he underwent bronchial fistula closure by median sternotomy. After being asymptomatic for the next 3 years, the patient developed a new pleural collection treated with chest tube placement. During the following 8 years, surgical site infections recurred innumerable times, requiring drainage and antibiotic courses. In 2002, to prevent further complications, he underwent a transdiaphragmatic omental harvest creating a newly-formed cavity draining pus outside the chest in the axillary region. Since then, the cavity remained patent, chronically draining purulent material. In 2009, the patient presented to another hospital due to leg edema, dyspnea on exertion, fatigue and palpitations. Heart failure, liver failure, anemia and uremia were ruled out. Within a month, urinary albumin excretion rose from 0.7 to 3.1 g/L (nephrotic syndrome). A kidney biopsy revealed the presence of glomerular amyloidosis type AA likely due to chronic inflammation.

He was started on colchicine. In May 2010, following partial right eye vision loss, a CT scan showed a temporal artery inferior branch occlusion. In October 2010, progressive kidney disease due to amyloidosis led the patient to end stage renal failure requiring hemodialysis. In January 2011, a small hemorrhagic stroke resulted in right hemi-paresis. Despite appearance of dysphonia, the patient denied any further medical care. After 30 months since the start of hemodialysis, the patient came to our attention. He showed shivering, high fever, unresponsive to amoxicillin, dehydration, lack of appetite and cachexia. After antibiotic wash out, we obtained blood cultures from peripheral veins and a newly placed central venous catheter and multiple swab cultures from the draining pleural cavity. A single blood culture drawn from the central catheter was positive for ESBL-negative Escherichia coli, whereas swab cultures were all positive for Pseudomonas aeruginosa. Among other blood cultures remained negative. We started the patient on cefazidime 1 gr bid and gentamicin 160 mg each after dialysis session. After 2 days of treatment, temperature went down. A further diagnostic work up was performed. Transthoracic echocardiography showed a calcified valve vegetation of 0.8 cm on the anterior mitral leaflet causing mild valve regurgitation. Thoracic CT scan with iv contrast showed the existence of a naturally formed duct linking the bronchial stump with the thoracic surface. To better evaluate the bronchial-pleural anatomy, a bronchoscopy was performed and showed the scar of the previous pneumonectomy but no fistula. As the actual condition was unclear, to explain how the lesion drained pus in the absence of a fistula, a fiberoptic scope examination of the open cavity was performed. With this procedure, the presence of an open, infected and draining bronchopleural fistula was confirmed. The patient started daily plugs of the wound under the care of our hospital thoracic surgeons. Still, no clear reason for an E.coli transient bacteremia was found, and echocardiography was not consistent with infective endocarditis. We therefore looked at a possible enteric portal of entry and scheduled a colonoscopy. On examination, the rectum and sigma were diffusely ulcerated and multiple biopsies were performed. The pathological report described a severe inflammation, with involvement of the muscularis mucosa, consistent with either Crohn’s disease or amyloidotic colitis. Low dose oral budesonide followed by mesalazine was started along with antibiotics. With daily medications of the wound, the pleural cavity under the armpit is eventually slowly healing. Bowel movements are regular and there is no fever. This case nicely illustrates how a chronic bacterial infection can lead to numerous and variable systemic complications (gunshot, pneumonectomy, bronchopleural fistula, pleural pyemysas, draining wound infection, AA amyloidosis, ischemic stroke, hemorrhagic stroke, dysphonia, kidney failure, dialysis, mitral valve calcification, colitis and E. coli bacteremia).

Gout and interstitial lung disease

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Introduction: Gout affects about 1-2% of the adult male population. Non-articular structures may sometimes be affected in the course of chronic gout and the most affected organs are the kidney and heart. Pulmonary involvement is rare. Only one case of uric acid crystal deposits in the lungs, which was identified by biopsy, is reported in the literature. Interstitial lung disease is equally rare. However it is a common complication in the course of connective tissue disease, although it is often not recognized or diagnosed late, especially when associated with rheumatoid arthritis.

Clinical case: We present the case of a sixty-year-old man, who came to our observation for light exercise dyspnoea and the onset of acute kidney injury, together with chronic symptoms of joint pain and swelling of the ankles and all the proximal interphalangeal joints of the hands. The patient had signs of frank arthritis and reported that his family doctor had diagnosed it as seronegative rheumatoid arthritis, which had never been treated with basic therapy. This diagnosis was immediately called into question when tophi were found upon physical examination (two large tophi on the right elbow and others on the left forearm and small hand joints). Bilateral dry basal crackles were found upon physical examination of the lungs. The patient had a medical history of kidney failure exacerbated by excessive use of NSAIDs, and essential hypertension, which was under treatment with angiotensin receptor antagonists and a thiazide diuretic.

The laboratory data showed mild anaemia, high inflammatory markers (ESR: 120 mm/h, CRP: 18 mg/L, variance < 3), hyperuricaemia (10.3 mg/dl), uricosuria (1088 mg/24 h), and negative rheumatoid factor and anti-citrulline antibodies. An ultrasound scan of the joints showed signs of active arthritis only in the metacarpophalangeal and some distal interphalangeal joints of the hands and feet and the presence of the “double track sign”, as found in gouty arthritis.

Worsening light exercise dyspnoea and hypoaemia in blood gas analysis in ambient air (pO2: 67.5 mmHg) prompted us to investigate the clinical condition with HRCT. This showed reticular intralobular interstitial thickening of the posterior basal segments bilaterally beneath the pleura (probable usual interstitial pneumonia, UIP) associated with areas with a ground glass appearance.

The patient was discharged with a diagnosis of chronic tophaceous gouty arthritis with pulmonary involvement, and began treatment with 1 mg of colchicine twice a day, 300 mg of allopurinol and 10 mg of prednisone, which brought about improvement in clinical and laboratory parameters.

Conclusions: We have described a case of interstitial lung disease in the course of chronic gout. In the absence of other possible causes of pulmonary fibrosis, it is likely to be a complication of the metabolic disorder.

References:
Posterior reversible encephalopathy syndrome

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40 year old man came to our attention because of fatigue, lack of strength in all four limbs, and vesiculo-bullous skin lesions of the lower limbs. His medical history was characterized by asthma and nasal polyposis. Routine blood tests showed leukocytosis, hypereosinophilia (14330 cells/ul), increase of inflammatory markers; p-ANCA were positive at high titer (100 UA/ml). A chest X-ray showed micro-nodular opacities in the right lung. Elecroneurography showed motor and sensory neuropathy with predominantly axonal character and asymmetric distribution, compatible with vasculitis. It was made diagnosis of Churg-Strauss Syndrome. The diagnosis was histologically confirmed by skin biopsy and muscle biopsy.

The patient was treated with intravenous methylprednisolone (1 gram per day for 3 days) with subsequent tapering. A week after the first treatment, he presented a generalized tonic-clonic seizure associated with hypertensive crisis. A brain MRI was performed and T2 weighted image showed bilateral high-intensity areas in the white matter of the occipital and parietal lobes (fig.1). These findings were suggestive of PRES (Posterior Reversible Encephalopathy Syndrome). He was treated with antihypertensive drugs and Diazepam with benefit and subsequent resolution of the clinical and radiological picture. The patient then continued maintenance therapy with low-dose steroids, azathioprine and rehabilitation.

PRES is associated with hypertension, eclampsia, renal insufficiency. Many autoimmune diseases have been described as systemic process in which PRES can develop. Most of cases of PRES associated with autoimmune diseases are described in patients with SLE and only few cases in patients with vasculitis.

In patients with vasculitis the endothelial damage may increase vascular permeability and high blood pressure can precipitate vascular injury. The use of high dose corticosteroid therapy may be a risk factor for PRES because of the elevation of the blood pressure. Thus in this group of patients blood pressure control can be very important in order to prevent this uncommon complication. However hypertension can be common even in young patients with Churg-Strauss Syndrome and it may be useful to start antihypertensive drugs before treating them with high dose corticosteroid therapy.

A case of pulmonary embolism in patient with bleeding gastric cancer


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In December 2012, a 72-year-old woman patient developed fever and severe dyspnea and was admitted to our emergency clinical department. Her past medical history was characterized from arterial hypertension, obesity class I (BMI: 34,5) and polyarthritis. Physical examination revealed the patient was suffering from acute distress with tachypnea at 26 respirations per minute and tachycardia of 120 beats per minute. She had her right leg swollen and hot. Laboratory test results were normal, except for mild anemia, neutrofilia and elevated D-Dimer. Arterial blood gas analysis revealed respiratory alkalosis with severe hypoxemia (PaO2: 59). Electrocardiogram revealed tachycardia sinus. Echocardiogram revealed dilatation of the right ventricle and mild pulmonary hypertension (PAPS: 49 mmHg). Chest X-ray revealed diffuse reticular shadows in both lung fields. Ultrasound color doppler of leg veins showed a popliteal right vein occlusion. For this reason, a thoracic CT-scan, using intravenous iodine contrast medium, was performed. The CT-scan revealed acute pulmonary thromboembolism and pneumonia. For this reason, she was transferred in our Department. The patient was given a full therapeutic dose of low molecular weight heparin, enoxaparin (8000 IU twice daily). After five days, she had melena and severe anemia. The patient was need for transfusion and enoxaparin was suspended. She was underwent upper endoscopy, that revealed active bleeding by advanced gastric tumor. Gastrointestinal bleeding is a contraindication to oral anticoagulant therapy, but because of her high thromboembolic risk, she was candidate to vena cava filter, that the patient refused. Because both the patient’s condition and the laboratory test improved, a pharmacologic thromboprophylaxis was administered until discharge. Then, in according to an oncologist, the patient was treated with neadjuvant chemotherapy to improve survival and with intermediate dose of enoxaparin every 12 hours. No new gastrointestinal bleeding and thrombosis occurred. After six months, the patient will be reassessed for surgery if a favourable response is achieved.

Discussion: Although the data available regarding the incidence, clinical characteristics and impact on survival of venous thromboembolism (VTE) in gastric cancer patients are very scarce, some studies showed that advanced stage and older age were independent risk factors for developing VTE and that the development of TVE was a significant predictor of early death. Then, gastrointestinal bleeding is no rare complication in patient...
A case report of mesenteric and splenic vein thrombosis in immunocompetent patient with acute CMV infection

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Case Report: A 40-years-old obese male was admitted at our Center on May 2012 for splanchnic and mesenteric vein thrombosis. He suffered by arterial hypertension, and was carrier of β-thalassemia trait. In the 2 weeks prior to the admission to our Department, he had fever and diarrhea unresponsive to antibiotic therapy. For severe abdominal pain, he was subsequently referred to an emergency department where laboratory investigations revealed an increase of D-dimers, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), amilase and lipase. The electrocardiogram and chest X-ray were normal. An IV-contrast enhanced computerized tomography (CT) of the abdomen and pelvis demonstrated extensive thrombosis of the superior mesenteric and splenic vein. For this reason, he was admitted to our Department. Laboratory analyses at admission showed leukopenia with a relative lymphocytosis (56 %), and confirmed the increase of cytolysis markers. Screening for thrombophilia was also performed and we excluded genetic (Factor V Leiden mutation, prothrombin G20210A mutation, antithrombin, protein C and protein S deficiency) or acquired (antiphospholipid antibodies, lupus anticoagulant, hyperhomocysteinemia) thrombophilic states. Cancer markers and hepatitis markers were negative. Viral test results for Herpes simplex 1 and 2, Epstein–Barr virus (EBV), human immunodeficiency virus (HIV)-1/2 and parvovirus B19 were all negative, while anti-cytomegalovirus (CMV) sierology was positive (IgM 82.5 IU/ml, and IgG 100 UI/mL), with CMV DNA PCR positive for a recent infection, leading to the diagnosis of acute CMV infection. Because both the patient’s clinical condition and laboratory test results improved, he wasn’t treated with antiviral therapy, and started treatment with therapeutic dose of low molecular weight heparin (LMWH): enoxaparin sodium 10000 IU sc twice daily, associated with warfarin 5 mg daily. He continued to receive warfarin, with a target international normalized ratio (INR) of 2.5, scheduled for the following 6 months. After 1 month, CMV sierology showed a total conversion to positive anti-CMV-IgG, with negative anti-CMV IgM and CMV DNA PCR. Abdominal ultrasound reported only the mesenteric vein thrombosis and showed the complete recanalization of the splenic vein. After 6 months, the abdominal CT-scan showed the resolution of the mesenteric vein thrombosis and the anti-coagulant therapy was withdrawn.

Discussion: CMV acute infection is associated with an increased short term venous thromboembolic risk. In particular, CMV seems to contribute to the development of venous thrombosis in immunocompromised patients where as data on the role in immunocompetent subjects are scarce. The definitive role of CMV in the development of abdominal vein thrombosis and the involved pathological processes have to be more extensively investigated. Physicians should be alert for symptoms and signs of thrombosis in patients with acute CMV infection, and for CMV infection signs in cases of patients with thrombosis.

Multifactorial headache in patient with chorio-retinal tuberculosis granuloma

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Patient L.F., 23 years old, North African, came to our Headache Center for the persistence of bilateral, frontal and temporal headache since the age of 20 years. Characteristics of pain: pulsating/oppressive, moderate-to-severe intensity, lasting a few hours, associated with nausea, photophobia and phonophobia. These symptoms were aggravated and sometimes unrelieved by physical activity.

Reason for the visit: in the last 6 months headaches had worsened in terms of intensity of pain and number of attacks.

The patient underwent medical examination that showed normal blood pressure (110/70 mmHg) and normal neurological examination but reduction in visual acuity in the left eye.

Family history was negative for headaches. Past medical history of the patient was positive for miliary Tuberculosis. Six months prior to our visit at the Headache Center, the patient had been examined in the Emergency department of the Hospital for acute onset of left eye pain associated with acute ipsilateral reduction of visual acuity; on that occasion ophthalmological examination had shown an exudative detachment of the retina.

Further diagnostic tests were performed: ocular bulb ultrasounds, retinal fluorescein angiography, indocyanine green angiography in addition to MRI of the brain, laboratory exams including QuantiFERON-TB Gold and Chest CT scan. A diagnosis of a chorio-retinal tuberculosis granuloma in patient with a positive history of miliary tuberculosis was performed. The patient underwent systemic therapy with Isoniazid 300 mg per day, Rifampicin 600 mg per day, Ethambutol 1500 mg per day and loco-regional therapy with Dexamethasone, Atropine, Ofloxacin, for 6 months, with net improvement of ocular symptoms and partial improvement of headache.

The described clinical case presents with a complex picture, both in terms of diagnosis and therapy. The etiology of the patient’s headache was multifactorial: Migraine without aura, Headache attributed to ocular inflammatory disorder and a possible worsening of the clinical picture by treatment with rifampicin, as a side-effect. Therapy with rifampicin made it very difficult to choose a drug for prophylactic treatment of the headache, since rifampicin metabolism via cytochrome P450 interferes with many of the drugs used in this case. Cinnarizine was chosen, at a dose of 24 mg/day for 3 months, together with paracetamol 1000 mg on demand for the acute phase. No further improvement of headache symptoms was however observed at a 3-month follow-up.

A young man with cough, fever and epigastric pain

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We report the case of a 25-year-old man who presented to the Emergency Department complaining about fever, productive cough, episodes of vomit and epigastric discomfort. These symptoms had started in the previous four – five days.

The past medical history was silent, except for a family history of coronary artery disease.
At presentation, symptoms, presence of pulmonary crackles at the right mediumlobe, elevated white cells blood count (25000/mm³, 86% neutrophils), and chest X-ray (CXR) showing a right perihilar inferior opacity supported a diagnosis of pneumonia. Therefore, an antimicrobial therapy with Levofloxacin was started and the patient was admitted to an Internal Medicine Division. The day after, a worsening respiratory distress with severe hypoxia was observed, and a second CXR showed an increased vascular redistribution. The ECG revealed sinus tachycardia, left atrial overload, incomplete right bundle branch block and atypical repolarization abnormalities. Cardiac ultrasound showed left ventricular global hypokinesia, with markedly impaired ejection fraction (10%) and right ventricle hyperkinesis. Respiratory failure in acute decompensated heart failure, possibly due to myocardiitis, was suspected and the patient was transferred to the Intensive Care Unit. The patient underwent non invasive mechanical ventilation with continuous positive airway pressure (CPAP), oxygen supply and antibiotic therapy (Levofloxacin and Azithromycin). A second cardiac ultrasound performed 4 days later showed a significant improvement of cardiac function (ejection fraction 40%). Autoimmunity, viral and bacterial tests, performed on the suspicion of acute myocardiitis, were negative. When clinical conditions improved, the patient was transferred to Cardiology Division, where he underwent a 24h Holter ECG, which was negative for significant arrhythmias, with a decreased circadian heart rate variability. To further investigate the hypothesis of myocardiitis, the patient underwent a cardiac MRI, demonstrating increased wall thickness consistent with myoccardial edema and late gadolinium enhancement more intense in the subepicardial layer of the lateral-inferior left ventricle segments. Incidentally, a right adrenal mass (35 x 25 mm) was detected, suggesting the hypothesis of pheochromocytoma and possible adrenergic myocardiitis. Significantly elevated urinary and plasma catecholamines levels confirmed the diagnosis: U-Epinephrine 138.7 μg/24h (n.v. 1.7-22.4 μg/24h); U-Norepinephrine 917 μg/24h (n.v. 12.1-85.3 μg/24h); P-Epinephrine 629 pg/ml (n.v. 10-196 pg/ml); P-Norepinephrine 6678 pg/ml (n.v. 80-520 pg/ml). Chromogranin A (655 μg/l, n.v. <94 μg/l) was also markedly above the upper reference limit.

Considering the patient’s young age and the possibility of pheochromocytoma being part of a familial syndrome as Multiple Endocrine Neoplasia (MEN), additional tests were performed. Increased serum calcitonin values (888.7 pg/ml, n.v. < 10 pg/ml) were consistent with medullary thyroid carcinoma (MTC), which was confirmed by thyroid ultrasound, showing multiple hypoechogetic nodules with peripheral and intra-nodular vascular pattern. A fine needle aspiration cytology was diagnostic for MTC.

PHT level was within normal range (42 pg/ml, n.v. 15-65 pg/ml), thus suggesting MEN type 2B.

In order to stage the disease, the patient underwent an abdominal CT which did not reveal any other mass. Genetic testing were performed to assess RET gene mutations and family members screening was suggested. Before surgery, a control cardiac ultrasound revealed a completely restored left ventricular ejection fraction. An α-blocker was prescribed for blood pressure control, without main adverse effects.

When the clinical conditions were stable, the patient underwent a posterior laparoscopic surgical resection of the adrenal mass and one week later a complete thyroidectomy with radical lymphadenectomy. No significant complications occurred neither during the surgery nor in the post-operative follow-up. Therapy with α-blocker was discontinued.

The patient has not complained about any symptom since the operation, calcitonin levels decreased as expected after MTC resection and his clinical conditions and biochemical parameters are stable.

This case report underlines that: a) common clinical presentations might sometimes be the atypical manifestations of a rare condition; b) myocardiitis can have a variety of underlying causes, which include catecholamine overproduction; c) pheochromocytoma, especially in young patients, can be part of a more complex syndrome and a thorough investigation is warranted to exclude/identify a MEN.

### Beyond the dyspnea: a dangerous liaison between heart and lung

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A 76-year-old man was admitted to our Institution for progressive exertional dyspnea during the last two months. He was a former heavy smoker, with a history of coronary artery disease treated with 3-vessel coronary artery bypass grafting in 1997. Physical examination revealed labial cyanosis, semiorthopnea, hepatomegaly, mild ankle edema, and bilateral basal crackles. Blood pressure was 110/70 mmHg, with a heart rate of 70 bpm (under treatment with beta-blockers), and oxygen saturation breathing room air was 88%. Whole blood count was within normal ranges. Arterial blood gas examination revealed mild hypoxemia, with hypocapnia, and normal pH and bicarbonates. A chest X-ray demonstrated fibrous-reticular thickening in the middle and basal fields, in the absence of infiltrative lesions. NT-proBNP levels were mildly increased. Transthoracic echocardiography showed normal size and ejection fraction of the left ventricle, with paradoxical diastolic movement of the interventricular septum. The right chambers were dilated and hypokinetic, tricuspid regurgitation was severe, and the estimated pulmonary artery systolic pressure was 80 mmHg. The inferior vena cava was dilated with reduced inspiratory collapse. Pulmonary function testing revealed normal lung volumes, while diffusing capacity for CO demonstrated severely impaired indices of gas exchange. The patient performed a full six-minute walk test stopping several times because of dyspnea, with a total walking distance of 180 meters. Pulmonary perfusion scan and pulmonary CT angiography ruled out chronic thromboembolic disease. The clinical and instrumental findings suggested a diagnosis of chronic partial respiratory failure and associated pulmonary hypertension with signs of congestive right heart failure. Initial treatment included loop diuretics, continuous oxygen therapy, and withdrawal of beta-blockers. Ankle swelling resolved, while exertional symptoms, as well as gas exchange parameters, remained unchanged. In order to assess hemodynamics and drive further treatment, right heart catheterization was performed. An invasive diagnosis of moderate pre-capillary pulmonary hypertension confirmed the echocardiographic suspicion. Because of bilateral basal crackles and reduced diffusion capacity, a high-resolution CT of the thorax was performed: mid-basal fibrosis with subpleural distribution, ground-glass opacities and small areas of honeycombing were noted, along with discrete centrilobular emphysematous changes involving the left apex. Therefore, our final diagnosis was: combined pulmonary fibrosis and emphysema (CPFE), complicated by WHO class III pulmonary hypertension. We decided to treat the patient with pulmonary vasodilator: ambrisentan 5 mg per os daily was started and than tadalafil 20 mg per os daily was added. After three months of combined therapy, clinical conditions and exercise capacity substantially improved. The improvements of clinical condition and exercise performance were sustained at 6, 9 and 12-months follow-up, with substantially stable clinical and instrumental findings. CPFE is a recently identified syndrome, probably related to tobacco use, characterized by the coexistence of upper-lobe emphysema and fibrotic changes of the lower lobes, preserved lung volumes, significant hypoxemia and a high prevalence of pulmonary hypertension resulting in severe dyspnea. In the literature, to our knowledge, there are only few cases reporting clinical improvement during pulmonary vasodilator therapy in a patient with CPFE.

### Atypical presentation of a common disease

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We report the case of a 66-year-old woman who was admitted to our Internal Medicine Unit with anterior chest pain in the right inframammary region and in the upper left hemithorax; she also complained of a dry cough for several days, without fever.

She had no significant medical problems until February 2012, when she was hospitalized for epigastric and chest pain and muscular pain in her legs; esophagitis (Grade A according to Los Angeles criteria) and infectious myositis were diagnosed. Blood tests showed: Hb 11.2 g/dL, MCV 88.5 fl, VES 51, AST 78 U/L, CK 217 U/L, LDH 1124 U/L; hepatic and thyroid indexes were normal.

After that she had several more admissions to the Emergency Department for the same symptoms; her blood tests revealed worsening anemia and high levels of LDH, AST and neoplastic markers [CA 19.9: 171 U/mL (normal value <35) CEA 364.3 ng/mL (n.v. <5)].

On admission to our Internal Medicine ward, physical examination revealed reduced breath sounds in the lower right lobe; chest and rib X-ray showed a dysventilation area in the lower right lobe of the lung, inhomogeneous bone loss and signs of a previous rib fracture.

Her blood tests revealed normocytic anemia (Hb 8.3 g/dL, MCV 89 fl), normal renal and hepatic function, LDH values at the higher limit of normal range, and increased levels of ESR and CRP. Microbiological tests were negative (urine culture and urine pneumococcal and Legionella antigens; HBV, HCV, CMV, EBV and Parvovirus serological tests).

Basing on her medical history, we investigated the source of anemia by upper and lower gastrointestinal tract endoscopy revealing mild chronic gastritis and some diverticula, with no signs of inflammation.

Further, abdomen and bowel ultrasounds (US) were normal.

So, no exam could explain her symptoms.

In view of the previous results of increased neoplastic markers, we repeated the tests, with the following findings: CEA: 182.4 U/ml (n.v. 0-34), CA 19.9: 192.5 U/ml (n.v. 0-27), CA 15.3: >3000 U/ml (n.v. 0-25) CA 125: 19.1 U/ml (n.v. 0-35).

Suspecting that a neoplastic condition could explain anemia and elevated ESR, we performed further diagnostic tests with the following results:

- Mammography and breast US: fibro-dysplastic areas but no sign of nodular lesions; bilateral reactive nodes in the axillary region.
- Gynecological evaluation: normal.
- Chest and abdomen CT: small (<1cm) lymph-nodes and slight pelvic fluid collection
- PET: weak capitation of spinal bone, humerus and femurs bilaterally, but not capitation areas suggestive of substitutive lesions.

At last, bone marrow biopsy was performed, showing diffuse osteomedullary localization of carcinoma; possible origins were both breast or upper gastrointestinal tract.

EGD negativity and the presence of estrogenic receptors in the bioptic samples made the breast origin more likely.

The patient underwent a complete breast examination with US and breast magnetic resonance without finding any pathological lump; biopsy of an unhomogeneous echogenic area demonstrated a lobular infiltrating carcinoma, with signet ring cells, positive estrogenic and progestinic receptors, and weak C-erb-B2 positivity.

After diagnosis the patient was referred to a specialized oncological center, where she underwent chemotherapy with Doxorubicin plus Placlitaxel.

Recent tests revealed disease progression with diffuse metastases (bone, lung, cutaneous and subcutaneous) and she has started a second line treatment with Vinorelbine plus Capecitabine.

**An atypical cause of urticaria**

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A 50-year-old woman presented to our department with a 7 days history of acute onset of urticarial rash, pharyngodynia, weakness, diffuse myalgia and remittant fever (above 38°C) despite 6 days of antibiotics. On admission she was febrile (37.7 °C), and presented diffuse red relieved and pruriginous skin lesions with Koebner response. She also presented some swollen cervical lymphnodes, a mild hepatomegaly and pharyngeal hyperemia. Laboratory findings included high WBC count (20.820/mm3), with 87.5% neutrophils, mild anemia, high inflammatory values (CRP...
He was already hospitalized in 2002, and discharged with the diagnosis of touch, and right dorsalis pedis artery was hyposphigmic. Associated with foot fingers' cyanosis, these areas showed hyperestesia at the foot.

At physical examination, right leg presented confluent purpuric lesions as - 300 mg/L, ESR 62 mm/h), mild elevation of transaminases (AST 44 U/L, ALT 62 U/L) and LDH (566 U/L) and a marked elevation of GGT (211 U/L); moreover, ferritin resulted very high (20,921 ug/L). As far as her medical history is concerned she reported a previous diagnosis of autoimmune thyroiditis, an history of allergic reactions to some medications and an elevation of the ESR value revealed in occasion of blood tests she had taken in the past. Her mother was affected of rheumatoid arthritis. She reported that the day before the onset of the above-described symptoms she had assumed a dose of desketoprefone for headache and she reported that in the last month she had been exposed to mononucleosis because of an outbreak in her son’s school. The hypothesis of an infection- either viral, fungal or bacterial- was ruled out by multiple blood, urine and sputum cultures, by serologic tests and by an echocardiographic assessment of the heart valves. The history and early laboratory findings weren’t suggestive for an adverse drug reaction and the most common autoantibodies were almost all negative, with the exception of a low titre positivity of ANA antibodies (1:20). Chest X-ray, ultrasound of abdomen and neck and total body CT scan ruled out the presence of malignancy. Her history and physical examination included no evidence suggestive for a connective tissue disease, systemic vasculitis or other chronic inflammatory diseases. At this point the most plausible diagnosis based on clinical and laboratory findings was Adult Onset Still’s Disease (AODS) (total 6 Yamaguchi’s criteria, 2 major, 4 minor). The diagnosis was finally supported by the finding of a low titre of glycosylated fraction of ferritin, which resulted 18%. This result, with a concomitant finding of a very high value of ferritin has a specificity of 92.9% for AODS Over the following days, despite the antibiotic therapy and the introduction of a corticosteroid therapy she kept being febrile (with spikes of 40 °C), she showed a change in the aspect of the skin lesions (with the appearance of the typical salmon pink rash) and started complaining about arthralgias of the large joints.

At this point antibiotics were suspended and the corticosteroids therapy was increased and cyclosporine was added 10 days after admission. After a week temperature had gone down and skin lesions were gradually improving. Two months after admission the patient presents no symptoms and is in complete remission. She gradually suspended the steroid therapy and is only on maintenance with cyclosporine. WBC, CRP, ESR and ferritin levels have all normalized.

A false friend diagnosis

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F.A., a 59 years old man, came to our attention complaining general weakness, diffuse myalgias, non-intentional weight loss, mild fever and onset of a skin rash consisting in erythematous confluent lesions on the plantar surface of right foot, associated with interdigital ulcers. These lesions caused intense burning pain, especially exacerbated in the late hours, spontaneously at rest or subsequent to walking and self-application of ice bags. Pain was so intense that patient had to stay in bed, having deambulation almost impossible.

The patient smoked about 30 cigarettes per day, he had arterial hypertension, occlusion of left dorsalis pedis artery treated with stenting of femoral artery, and history of HCV chronic hepatitis treated in 2003 with Interferon + Ribavirin, with no information added about sustained virological response. At physical examination, right leg presented confluent purpuric lesions associated with foot fingers’ cyanosis, these areas showed hyperestesia at the touch, and right dorsalis pedis artery was hypospigmic.

He was already hospitalized in 2002, and discharged with the diagnosis of “cryoglobulinemic polineuropathy in patient with HCV related chronic hepatitis.” He also underwent sural nerve biopsy that showed: “axonal degeneration with onion bulbs (expression of a chronic process of de- and remielization) likely secondary to cryoglobulinemic microangiopathy. At our admission, the pain therapy consisted in Fentanil 50 mcg 1 skin patch per day, Paracetamol 2000 mg per day, Gabapentin 375 mg per day, Amitriptiline 10 mg 3-5gtt/die, with just a little relief of the symptoms. We performed arterial Doppler ultrasound examination, negative for arterial obstructive disease.

Laboratory testings showed normal red blood cells count and Hemoglobin, normal kidney and liver function. Spot urine tests showed erythrocyturia and leucocyturia.

Research of rheumatoid factor, Ab anti PR3, MPO, was also negative. Otherwise, anti DSDNA-Antibodies had a level of 23.08UI/ml, with elevated CIC and C1Q (16.2 mcg/ml). Seriated blood samples failed to demonstrate the presence of circulating cryoglobulines. HCV Abs were present in the serum, but HCV RNA was not dosable.

The patient was indeed affected by a vasculitis, with dermatological and neurological involvement. We ruled out possible primary causes, such as infectious diseases (negative research for HBV, HCV, and HIV), haematologic neoplasias and drugs, defining it as a primary autoimmune process. To distinguish between possible hypotheses, we performed skin biopsy. Histologically, small vessels vasculitis was present, with segmental fibrinoid necrosis of the media, and infiltration with neutrophils, fragmented along the wall of postcapillary venules: leukocytoclasia (figure2). The leukocytoclastic angiitis is a common characteristic finding of the microscopic polyangiitis (MPA). It is noteworthy that in our patient, the research of p-ANCA anti MPO was negative, which is a rare finding in this disease (20%).

We started therapy with Ciclofosfamide 100mg daily and Prednisone 1 mg/kg/day, with prompt resolution of the painful symptoms.

Wegener’s granulomatosis after treatment with interferon-alfa for HCV infection

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We report the case of a 71-years-old patient who had been suffering for a year from temperature and it didn’t respond to a wide-spectrum antibiotic therapy. When he was admitted to our Unit general conditions were a bit lower and the patient showed respiratory failure and anemia. Inflammatory indexes were increased. The soon after follows a sudden bilateral hearing loss, signs of motor and sensory neuropathy to the legs, bilateral conjunctivitis and a complete atrioventricular block treated by pacemaker im-
An unusual case of refractory orthostatic hypotension

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A seventy-three year old Italian woman came under our attention for the persistence of severe refractory hypotension, fatigue, and loss of weight (i.e. 30 kg in the previous year). These symptoms had been investigated with endoscopic studies of the upper and lower gastrointestinal tract and abdomen ultra-sound, but none of them pointed out anything relevant correlated to the patient’s loss of weight. A thorax standard radiology and a mammographic screening were also performed, but they were unremarkable. Neoplastic markers were negative; cobalamine and iron profile values were in normal range.

Moreover, the patient complained of progressive hyporexia, dysphagia for solid foods, and xerostomia in the last two months. An ORL evaluation excluded organic disturbances and a neurologist, in the presence of a normal brain NMR study, concluded for a functional disease, suggesting antidepressant therapy with sertraline, which was of little benefit on the patient’s symptoms.

In the following weeks the presence of hypotension became more and more invalidating (systolic pressure values up to 60 mmHg), also determining frequent syncopes that caused several hospitalizations. During one of them, cardiac junctional rhythm was detected and a pace-maker was implanted. No improvement on pressure values were however observed.

On admission, clinical examination was substantially normal, apart for the presence of mild hepatomegaly and hypotension (PA 100/55 mmHg) with normal cardiac rate (80 bpm). No lymphadenopathy nor splenomegaly were objectivavle. Neurologic evaluation pointed out ptosis of the right eye, slight facial nerve deficit, and weakness of the right lower limb. Blood tests showed a mild normocytic anemia (Hb 11 g/dL), a rise in cholestasis indexes (alkaline phosphatase 201 U/L; gamma glutamyl transferase 328 UI/L with normal bilirubin) and a moderate hyperferritinemia (332 ng/mL). Furthermore, an important hypoalbuminemia (2.7 g/dL) associated to low total protein values (4.6 g/dL) was present.

In the suspect of a paraneoplastic syndrome, a thorax-abdomen CT scan was performed; due to the persistence of diarrhea and malabsorption, the evaluation was completed with an entero-CT to better investigate the bowel. Because of negative results of both exams and the persistence of dysphagia, endoscopic evaluation of the upper gastrointestinal tract was repeated. Hyperemic gastric antrum was showed and biopsy of the duodenal mucosa obtained and analyzed. Perivascular gastric and duodenal deposits weakly positive for Red Congo stain were detected.

A multisystemic disease became soon evident: renal involvement with signs of proteinuria (2.5 g/24 hours) and normal kidney function, autonomic and central nervous system involvement characterized by orthostatic hypotension, absence of baroreceptive reflexes and transient III and VII cranial nerve deficit, gastrointestinal disease in the presence of diarrhea, malabsorption and dysphagia for solid foods, cardiovascular disease (myocardial thickness and infiltration at echocardiography; increased pro-BNP levels) and bone femoral lytic lesions.

According to the clinical systemic presentation, the gastro-duodenal histology previously described became highly suggestive for amyloidosis. Moreover, Bence-Jones proteinuria was present and serum protein electrophoresis showed a small monoclonal component IgG kappa and monoclonal light chains lambda (kappa/lambda ratio 10/231 mg/L). Bone marrow biopsy evidenced the presence of 5-10% plasmacellular infiltrate and perivascular amyloid deposits. Besides, immunohistochemistry confirmed amyloid accumulation in the gastro-duodenal bioplic sample.

All these data allowed the diagnosis of AL amyloidosis and chemotherapy with reduced dosages of melphalan and dexamethasone was immediately started. Since its highly hypotensive effect, bortezomib was avoided.

During hospitalization the most invalidating symptom was severe refractory to volume expansion orthostatic hypotension. Therapy with fludrocortisone in association to midodrine had little benefits on pressure values and the patient remained unable to reach orthostatic position also after discharge.

This case describes an uncommon cause of orthostatic hypotension and urges to take amyloidosis into consideration in the differential diagnosis of autonomic disturbances, especially when a systemic involvement is present.
Electrolytes disorder: the hidden truth

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A 40-year-old Italian female was admitted to our ward with a 10-month history of retrosternal pain, hypotension and fatigue. Her medical history was consistent with GERD, chronic kidney disease, secondary adrenal glands insufficiency in therapy with fludrocortisone acetate; furthermore she was recently diagnosed of Gitelman’s Syndrome. She complained of 3 kg lost of weight and amenorrhea during the last six months.

On admission, clinical examination demonstrated an emaciated face, dry skin characterized by hypertricosis lanuginose, hypotension, abdominal pain, xerostomia and xerophthalmia, Raynaud phenomenon, generalized muscle wasting, anxiety and depression.

Laboratory analysis showed: Hb 11.7 g/dl; serum creatinine 1.98 mg/dl, Na+ 112 mmol/L, K+ 2.55 mmol/L, Cl- 82 mmol/L; serum magnesium 0.5 mmol/L; creatinine clearance 20.58 ml/min; urinary volume about 2000 ml/die; urinary sodium 87 mmol/L; urinary 24h sodium 174; urinary potassium 21 mmol/L; urinary 24h potassium 42; urinary clorur 86 mmol/L; urinary 24h clorur 172. FBG 65 mg/dl; alfa-2 globulin 13%; gamma globulin 7.7%; total cholesterol 232 mg/dl. We performed the Synacthen test that resulted normal. Schirmer’s test was positive and the salivary gland scintigraphy was negative. ANA and ENA screening were negative. Stool test for malabsorption demonstrated mucus 1+ and leucocytes 1+. Hormone test demonstrated: TSH 3.17 mcgU/mL, FSH 25 mUI/mL, LH 1.55 mUI/mL, PRL 10.41 ng/mL, 17 beta-estradiol < 5 pg/mL, ACTH 11 pg/mL.

Diagnostic Hypotheses were:
1) Hypokaliemia in patient with Gitelman’s Syndrome and secondary adrenal gland insufficiency in therapy with fludrocortisone acetate
2) Reumatologic disease such as connective tissue disease with Raynaud phenomenon.

During the hospital stay she was caught eating salt from a glass. Moreover we found in her locker about 20 blisters of furosemide and about 10 blisters of senna derived laxatives.

Our diagnosis was anorexia nervosa, while past diagnoses were more complex and uncertain, and brought the patient to take medications for secondary adrenal gland insufficiency (e.g. fludrocortisone acetate). The easiness in obtaining medications like furosemide and senna derived laxatives without any medical prescription emphasizes the ethical aspect of this case.

In conclusion, we point out that when a diagnosis doesn’t meet the expected course, clinicians should consider and explore not only the clinical and biochemical features of the patients, but also their daily habits.

Unexpected cardiac death in patient with excavated pulmonary lesion

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We report the case of a 34-year-old male who was admitted to our ward with a 20-days onset of fever after therapy with amoxicillin-clavulanic acid because of a tooth abscess. The patient reported no previous significant medical history except for smoking cigarettes (10 pack/years). On admission the patient was stable and afebrile. Clinical examination was consistent with muscle wasting and crackling in the upper right lung field with no cardiac pathological findings on auscultation.

Laboratory analysis demonstrated hemoglobin of 10.5 g/dl and white blood count of 18 \times 10^9/l. GOT was 58 U/L and GPT 93 U/L. Erythrocyte sedimentation rate was 90 mm/h and C-reactive protein was 20.8 mg/dl. The chest radiograph demonstrated an excavated opacity in the upper right lung field with normal cardiac silhouette. We put a differential diagnosis among: tuberculosis, lung abscess, staphylococcal pneumonia and lung cancer. A total-body CT-scan showed a cavitary mass in the apical segment of the right upper lobe, adherent to the pleura and the right atria, and other lesions with the same characteristics in the lower left lobe. The mediastinal lym-
A 72-year-old man, followed for hepatocellular carcinoma (HCC) arising in cirrhosis due to hereditary hemochromatosis and HCV infection, on December 2012 complained sore throat and diarrhea. His medical history showed a diagnosis of cirrhosis since 1999, and a recent percutaneous ethanol injection of two focal lesions of HCC in the right lobe in October 2012. After one month from treatment a computer tomography (TC) demonstrated complete necrosis of the lesions. In the past (1987) he underwent a partial pancreatectomy and splenectomy for complication of chronic pancreatitis, and he was also affected by a long-lasting obstructive pulmonary disease and diabetes.

At presentation physical examination was normal. The blood tests showed an increase of inflammatory indices and stoo l culture was positive for Campylobacter. An abdominal ultrasonography showed a new ipoanechoic lesion in 2nd segment, a MRN confirmed this new 5 cm diameter lesion in 2nd segment suspected but not typical for HCC. At the same time in the hypothesis of gastrointestinal infection by Campylobacter, he was treated with Levofloxacine for eight days with partial remission of fever and diarrhea. After two weeks from the end of antibiotic therapy the patient had again hyperpyrexia and blood tests showed an increase of inflammatory indices. Another abdominal ultrasonography showed the mass growing up to 8 cm diameter. The physical examination didn’t change with the exception of the presence of lower extremity edema. Blood tests showed presence of neutrophilia, increase of C reactive protein (3.7 mg/dL; reference value <1), reduction of liver synthesis (albumin 2.1 g/dL, INR 1.56, cholinesterase 453 U/L), and normal renal functional test. A differential diagnosis of fever and liver masses included: liver cancer complicated by infection, tuberculosis, Hydatid disease, Amebic abscess. Blood and stool culture were negative as well as anti Echinococcus and Entamoeba histolytica antibodies.

After three days of empirical treatment with intravenous carbapenem antibiotic, he continued to have fever, inflammatory markers remained high and Vancomycin was started. After few days the patient developed weariness, sweating, weight loss, dyspnea and abdominal pain; at physical exam showed tenderness and rigidity in right hypochondrium and left basal lung signs (reduction of the murmur associated with crackles). An abdominal ultrasonography showed: abdominal effusion with septa in the left hypocondrium, free abdominal effusion in the right side, edema and hypervascularization of the small bowel’s walls. MRN was again performed (25 January) showing: increase of the mass with dishomogeneous low signal intensity on T1 and high signal intensity on T2-weighted images, development of new small satellite lesions, ascites and left pleural effusion. Exploratory paracentesis was done showing exsudative fluid, but cultural exam was negative. Anti Entamoeba histolytica antibodies were already searched showing a positive result. A diagnosis of amebic hepatic abscess complicated by peritonitis was made. The patient was treated with metronidazole and paromicine with disappearance of symptoms, gradual reduction of the liver masses and normalization of inflammatory indices.

Nephrotic syndrome, acute renal failure and Henoch-Schönlein purpura in course of colorectal adenocarcinoma


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A 74-year-old man was admitted in our ward for a ten days history of incoercible diarrhea and macroscopic hematuria. The patient have been affected by a metastatic colorectal adenocarcinoma, recently treated with a third-line irinotecan- and cetuximab-based chemotherapy.

Patient lab tests showed increased inflammatory markers levels (CRP 1.62 mg/dL; LDH 455 U/L; Fibrinogen 610 mg/dL) and a slightly increased serum creatinine levels (1.3 mg/dL). An abdomen radiograph showed multiple small hydro-aerial levels, beaming right and left lower quadrants. No ascites, development of new small satellite lesions, ascites and left pleural effusion was present.

Looking forward to perform microbiological tests it was started an intravenous antibiotic therapy with ceftriaxone 2 gr/day and metronidazole 500 mg three times in a day. A symptomatic therapy with loperamide 2 mg at every diarrhea episode was also prescribed. In the second day of admission patient develops an inferior limbs palpable purpura, that rapidly involved all body. To exclude a primary autoimmune disease diagnosis, a complete immunitary, autoimmunitary and virological test panel was performed, resulting completely negative. Therefore the patient started a therapy with methylprednisolone 0.5 mg/kg per day.

Meanwhile, in consideration of all microbiological tests negative results and because of an oncological consultation that considered diarrhea as an irinotecan side-effect, antibiotics therapy was suspended. To explore possible causes of macroscopic hematuria a kidney ultrasound test was performed, describing: “Enhanced medullar parenchimal

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Liver mass in a patient with hepatocellular carcinoma (HCC) is not always a HCC recurrence


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A 72 years old man, followed for hepatocellular carcinoma (HCC) arising in cirrhosis due to hereditary hemochromatosis and HCV infection, on December 2012 complained sore throat and diarrhea. His medical history showed a diagnosis of cirrhosis since 1999, and a recent percutaneous ethanol injection of two focal lesions of HCC in the right lobe in October 2012. After one month from treatment a computer tomography (TC) demonstrated complete necrosis of the lesions. In the past (1987) he underwent a partial pancreatectomy and splenectomy for complication of chronic pancreatitis, and he was also affected by a long-lasting obstructive pulmonary disease and diabetes.

At presentation physical examination was normal. The blood tests showed an increase of inflammatory indices and stoo l culture was positive for Campylobacter. An abdominal ultrasonography was performed showing a new ipoanechoic lesion in 2nd segment, a MRN confirmed this new 5 cm diameter lesion in 2nd segment suspected but not typical for HCC. At the same time in the hypothesis of gastrointestinal infection by Campylobacter patient he was treated with Levofloxacine for eight days with partial remission of fever and diarrhea. After two weeks from the end of antibiotic therapy the patient had again hyperpyrexia and blood tests showed an increase of inflammatory indices. Another abdominal ultrasonography showed the mass growing up to 8 cm diameter. The physical examination didn’t change with the exception of the presence of lower extremity edema. Blood tests showed presence of neutrophilia, increase of C reactive protein (3.7 mg/dL; reference value <1), reduction of liver synthesis (albumin 2.1 g/dL, INR 1.56, cholinesterase 453 U/L), and normal renal functional test. A differential diagnosis of fever and liver masses included: liver cancer complicated by infection, tuberculosis, Hydatid disease, Amebic abscess. Blood and stool culture were negative as well as anti Echinococcus and Entamoeba histolytica antibodies.

After three days of empirical treatment with intravenous carbapenem antibiotic, he continued to have fever, inflammatory markers remained high and Vancomycin was started. After few days the patient developed weariness, sweating, weight loss, dyspnea and abdominal pain; at physical exam showed tenderness and rigidity in right hypochondrium and left basal lung signs (reduction of the murmur associated with crackles). An abdominal ultrasonography showed: abdominal effusion with septa in the left hypocondrium, free abdominal effusion in the right side, edema and hypervascularization of the small bowel’s walls. MRN was again performed (25 January) showing: increase of the mass with dishomogeneous low signal intensity on T1 and high signal intensity on T2-weighted images, development of new small satellite lesions, ascites and left pleural effusion. Exploratory paracentesis was done showing exsudative fluid, but cultural exam was negative. Anti Entamoeba histolytica antibodies were already searched showing a positive result. A diagnosis of amebic hepatic abscess complicated by peritonitis was made. The patient was treated with metronidazole and paromicine with disappearance of symptoms, gradual reduction of the liver masses and normalization of inflammatory indices.

Nephrotic syndrome, acute renal failure and Henoch-Schönlein purpura in course of colorectal adenocarcinoma


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A 74-year-old man was admitted in our ward for a ten days history of incoercible diarrhea and macroscopic hematuria. The patient have been affected by a metastatic colorectal adenocarcinoma, recently treated with a third-line irinotecan- and cetuximab-based chemotherapy.

Patient lab tests showed increased inflammatory markers levels (CRP 1.62 mg/dL; LDH 455 U/L; Fibrinogen 610 mg/dL) and a slightly increased serum creatinine levels (1.3 mg/dL). An abdomen radiograph showed multiple small hydro-aerial levels, beaming right and left lower quadrants. No ascites, development of new small satellite lesions, ascites and left pleural effusion was present.

Looking forward to perform microbiological tests it was started an intravenous antibiotic therapy with ceftriaxone 2 gr/day and metronidazole 500 mg three times in a day. A symptomatic therapy with loperamide 2 mg at every diarrhea episode was also prescribed. In the second day of admission patient develops an inferior limbs palpable purpura, that rapidly involved all body. To exclude a primary autoimmune disease diagnosis, a complete immunitary, autoimmunitary and virological test panel was performed, resulting completely negative. Therefore the patient started a therapy with methylprednisolone 0.5 mg/kg per day.

Meanwhile, in consideration of all microbiological tests negative results and because of an oncological consultation that considered diarrhea as an irinotecan side-effect, antibiotics therapy was suspended. To explore possible causes of macroscopic hematuria a kidney ultrasound test was performed, describing: “Enhanced medullar parenchimal

References:
3. Mikkel F et al. Increased morbidity from ischemic heart disease in patient with Wegener’s Granulomatosis & Arthritis & Rheumatism 2009; 60 (4), 1187-1192
echogeneity, with preserved corticomedullary thickness and renal pyramids marked evidence. Morphological appearance compatible with acute kidney injury (AKI). In order to deeply investigate the macroscopic hematuria origin, an abdomen CT-scan was performed, reporting: “Metastic V hepatic segment lesion dimensional growth (6 cm diameter), with VII hepatic segment and near-gallbladder lesions stable dimensions. None pathologic enhancement addressing kidneys, spleen and pancreas. Widespread bladder thickening without any evident lesion or pathological enhancement.”, documenting a recovery of the neoplastic disease.

Even in consideration of the rising serum creatinine level (1.7 mg/dL) and of a newly happened inferior limbs edema, a loop-diuretic therapy (furosemide 50 mg/daily and water restriction was administered. Moreover, biochemical analysis revealed hypoalbuminemia, low serum total proteins, and therefore 24 hours proteinuria was requested.

Even if purpura quickly retreat after glucocorticoid therapy begin and loop-diuretic doses increased in addition with potassium-sparing diuretic (spironolactone 200 mg per day), the patient presented a generalized edema and worsening of renal function (1.9 mg/dL fasting rising to 2.5 mg/dL).

A 24-hour proteinuria documented an heavy proteinuria (6935 mg/24h), making necessary a strengthening of the methylprednisolone therapy, rising to 1 mg/kg per day.

Thus, considering nephrotic syndrome and rapidly progressive renal failure, a kidney biopsy was performed. The histopathological report documented: “Renal tissue was processed and 25 glomeruli was found, two of which showed global sclerosis, whereas all the others show mild mesangial hypercellularity and 9 glomeruli with cellular crescents. Infiltration of inflammatory cells and were visible in the interstitium in association with a tubular atrophy. Immunofluorescence microscopy showed granular mesangial diffuse staining for IgA 2+, C3 2+, κ light chains 1+, λ light chains 1+. Thus, mesangial proliferative diffuse and focal extracapillary glomerulonephritis with focus on crescentic IgA nephropathy was diagnosed.”

Then the diagnosis was compatible with Henoch-Schönlein syndrome.

Nonetheless the potentiated glucocorticoid endovenous and diuretics therapy, serum creatinine levels rised up to 4.5 mg/dL until, after ten days of full therapy, started to decrease.

Patient was dismissed after twenty days of full therapy with a reduced serum creatinine level (3.2 mg/dL), a reduced 24-hour proteinuria level (1703 mg/24h) and almost negativity presence of hematuria.

In an ambulatory control, the patient demonstrate a great improvement of the renal function (serum creatinine level: 2.03 mg/dL; 24-hour proteinuria: 680 mg/24h), with a significant reduction in inferior limbs edema. In literature appears clearly that, even if in a small number of cases, Henoch-Schönlein vasculitis is somehow related to malignancy in adult patients. Despite that this association has been previously described, it appears as a new data the association with a colorectal adenocarcinoma.

Don’t stop search endocarditis in patients under immunosuppressive treatment

Don’t stop search endocarditis in patients under immunosuppressive treatment

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A 70-year-old female with diagnosis of rheumatoid arthritis presented fever associated with chills not resolving after repeated courses of empirical antibiotics therapy (cephalosporine and quinolone). These symptoms were associated with arthritis, fatigue, lymphadenopathy, skin purple lesions and erythema nodosum. The patient was in treatment with methotrexate, adalimumab and methyl prednisone since 2005.

The diagnostic hypotheses we considered were septic fever with reactive arthritis, rheumatoid arthritis reactivation (immunosuppressive therapy failure) and lymphoma.

Immunosuppressive therapy was stopped. Multiple sets of blood cultures were all negative. Laboratory data showed pancytopenia and high erythrocyte sedimentation rate (ESR), C-reactive protein within the normal range. A skin biopsy showed dermal perivascular inflammatory infiltrate with lymphohistiocytic cells and eosinophilic and neutrophil granulocytes. A PET-TC total body performed to exclude a lymphoma was negative.

A transthoracic echocardiogram (TTE) was performed and no vegetation was remarkable; a transesophageal echocardiogram (TEE) showed normal valve leaflet morphology with a small posterior leaflet valve vegetation, with mild mitral regurgitation.

The patient was started on treatment for culture-negative endocarditis consisting of vancomycin, gentamycin, and ceftriaxone. The following days she was tested for Q fever and serum samples were tested for possible etiologic agents of culture-negative endocarditis by PCR. PCR for Borelia burgdorferi and C. burnetii DNA were positive. Patient’s serum was positive for C. burnetii antibodies. According to these results and to international guide lines the antibiotic therapy changed to doxycycline and hydroxychloroquine [1-2].

After ten days from the beginning of therapy, the fever disappeared the patient experienced a progressive improvement of arthritis and skin lesions. Q fever serology regularly tested throughout the 12 months following the start of treatment showed an eightfold decrease in both phase I IgG and phase II IgG; thirty days after the start of therapy PCR for Borelia burgdorferi and C. burnetii DNA become negative.

Coxiella burnetii is the causative agent of Q fever, a zoonosis that occasionally manifests as culture-negative endocarditis, vascular infection, immune-mediated leukocytoclastic vasculitis, glomerulonephritis and arthritis [3]. Chronic Q fever develops when the immune system is unable to eradicate C. burnetii following an acute infection. Many conditions, including immunosuppression, can increase the risk of developing chronic Q fever [4], Borelia Burgdorferi is the causative agent of Lyme disease, multi-organ animal-borne disease that can affect the joints with chronically persistent joint swelling or recurrent inflammatory episodes [5] C. burneti and B. Burgdorferi can be both transmitted by ticks. Some studies have documented that both infections can be transmitted by the same species of arthropodes. [6]

We describe a rare case of co-infection of C. burneti and B. Burgdorferi, as a cause of relapsing arthropathy in a patient with rheumatoid arthritis under immunosuppressive treatment. This case report emphasizes the importance of excluding an infection as a cause of occurrence of unexplained fever and arthritis in patients with a diagnosis of rheumatic diseases.

References:


Thrombotic thrombocytopenic purpura in a woman with infiltrative cardiomyopathy

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Case report: In January 2013, a 49-year-old female was admitted to our Centre for Coagulation Diseases because of thrombotic microangiopathy of unknown origin and acute pulmonary embolism (PE). The patient, current smoker, had a past medical history characterized by arterial hypertension, hyperthyroidism and unspecified chronic urticaria. She had been treating with antihistamine drugs and methimazole.

In December 2012 the patient was admitted to another hospital because of fatigue, loss of appetite, evening fever, and progressive dyspnea. Laboratory tests showed hypereosinophilia, thrombocytopenia (20000/mm3) and involvement of the autoimmune system (complement C3 and C4 fractions consumption, ANA positivity, p-ANCA positivity). A thoracic computed tomography (CT)-scan showed PE and polyserositis, and the examination of the peripheral blood smear showed the presence of schistocytes.

Therapy with immunosuppressive doses of prednisone, IV fresh frozen plasma (FFP) and low molecular weight heparin (LMWH) was started and the patient was referred to our Centre. Additional laboratory tests confirmed thrombocytopenia, moderate renal failure, and involvement of the autoimmune system and showed increase in liver function tests, with the evidence of hepatosplenomegaly at the abdominal ultrasound. The presence of anti-ADAMTS 13 antibodies associated to low ADAMTS 13 activity leaded to a diagnosis of thrombotic thrombocytopenic purpura. Transthoracic echocardiography showed infiltrative biventricular heart disease with a severe restrictive diastolic pattern, severe pulmonary hypertension (about 50 mmHg) and moderate pericardial effusion. Cardiac magnetic resonance imaging confirmed the echocardiographic features, with the additional finding of left ventricular apical thrombus. The peribular fat biopsy excluded the diagnosis of amyloidosis. The thoracic CT scan confirmed the diagnosis of PE and showed diffused “frosted glass” areas. According to biochemical and morphological data we suspected Loeffler’s syndrome or Churg–Strauss syndrome and proposed a cardiac biopsy, unfortunately refused by the patient. A subsequent thoracic CT revealed disappearance of the “frosted glass” areas. This finding suggested diagnosis of Churg–Strauss syndrome (fleeting infiltrates). The patient refused to undergo further examinations and a month later she died because of a massive cardioembolic stroke.

Discussion: Churg–Strauss syndrome is a systemic small-sized vessel vasculitis, characterized by severe asthma, transient pulmonary infiltrates, and blood and tissue eosinophilia. This disease can affect several organs, including lungs, heart, kidneys and peripheral nervous system. p-ANCA are detected in about 40% of patients. Several studies have focused on venomous thromboembolic events, which are an emerging clinical condition in ANCA-associated vasculitis.

More is not better


*Clinica Medica “L. Condorelli”, Ospedale Vittorio Emanuele, Università degli Studi di Catania **UO di Anatomia Patologica, Ospedale Umberto I, Enna

Management of hepatitis C and progressive increase of serum alpha-fetoprotein levels may be challenging: a case report

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Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide and Chronic Hepatitis C is an independent risk factor for the development of HCC. Alpha-fetoprotein (AFP) is the most widely used biomarker in HCC for diagnosis as well as for surveillance. Persistently elevated serum levels of AFP are a risk factor for HCC. The main limitation of AFP for surveillance is that increased serum levels may reflect an exacerbation of liver disease rather than HCC development although the higher the cut-off value the higher the specificity for HCC is. AFP values higher than 20 ng/ml have good sensitivity but low specificity; while values higher than 200 ng/ml show a much lower sensitivity..
A previously fit and well 75-year-old woman was admitted to our hospital for the first time on April 8, 2013 with the chief complaint of purple-coloured spots and patches on lower extremities. Five days to admission she took an antibacterial (Amoxicillin/Clavulanate), prescribed by her primary care physician because of a febrile episode with no other signs or symptoms associated. Forty-five minutes after taking the second dose, she observed the sudden onset of a maculopapular rash on her legs, which became warm and swollen, but not itchy. The next morning she developed loose stools (she attributed to shellfish eaten) and arthralgia. She promptly consulted her physician who prescribed flavonoids as vasoprotector, without improvement. A chest x-ray and a transthoracic echocardiogram didn’t highlight anything wrong. Then hospitalization was advised for further investigations. On admission physical examination showed petechiae and maculopapular lesions on her legs, extending up from perimalleolar areas to her thighs. No prominent oedema nor other pathological signs were reported. Her past medical history wasn’t consistent with an allergic diathesis. She was an inactive HBsAg chronic carrier. Laboratory results include microcytic anaemia (without evidence of intra or extravascular haemolysis), thrombocytopenia and mild renal impairment. Viral screening was negative for HCV, EBV, CMV, HIV and Parvovirus infection. Other remarkable alterations in laboratory findings were C3-C4 complement consumption, hypogammaglobulinemia, rheumatoid factor expression (anti-citrulline antibodies were negative), beta2microglobulina very mildly increased. The other immunological tests were negative (ANA, ENA, c-ANCA, p-ANCA). Lymphocyte subpopulations showed no abnormalities. After the introduction of Methylprednisolone, we witnessed complete disappearance of the rash, improvement of anaemia and thrombocytopenia. Hypocomplementemia and hypogammaglobulinemia were persistent. Switching from intravenous to oral steroid therapy, new sporadic petechial lesions appeared and haemoglobin decreased again. A Fecal Occult Blood Test (FOBT) was obtained: the evidence of gastrointestinal bleeding made endoscopy examination mandatory. Esophago-gastro-duodenoscopy and colonoscopy were performed, but no relevant source of bleeding was discovered, except for haemorrhoidal piles congestion.

Suspecting a neoplastic condition, the patient underwent further investigations, with detection of Bence Jones proteinuria (k-type) and serum monoclonal protein of the same type. A CT scan from neck to pelvis highlighted pleural, pericardic and pelvic effusion. No pathological lymph nodes, nor other obvious abnormalities emerged. An immune complex syndrome was suspected and cryoglobulins were successfully detected. Though CT was negative, in order to rule out a lymphoproliferative disorder, a bone marrow biopsy was acquired. A bone marrow localization of mature B-cell neoplasm (CD23-, CD5-, cyclin D1-) was confirmed. We finally concluded for Cryoglobulinemia associated with HBV infection and with a lymphoproliferative disorder. The clinical findings we observed may be mediated by immune complex deposition and subsequent inflammatory vasculitis.

**Fever of unknown origin in a patient with diffuse atherosclerotic vascular disease and thoracic aortic graft:** from diagnosis to therapeutic approach

**Sartori F., Martinelli N., Olivieri O., Girelli D**

Department of Medicine, Section of Internal Medicine, University of Verona

A 83-year-old Caucasian woman was admitted to our department of Internal Medicine because of recurrent fever, general malaise, and mild weight loss. She had a medical history of diffuse atherosclerotic vascular disease, ischemic heart disease complicated by chronic heart failure (NYHA III), and previous endovascular repair of thoracic descendent aorta aneurysm. Since about 12 months she relayed every 10-15 days recurrent febrile episodes (>38°C), preceded by shivers, generally resolving spontaneously within a few hours or otherwise unresponsive to usual antibiotic therapies. On the other hand, no symptoms indicative of focal infection were reported and the physical examination was unhelpful. A complete diagnostic workup for fever of unknown origin was performed. However, beyond a persistent increase of inflammatory markers, no resolving findings were obtained from several laboratory and radio-

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**Table 1. Serum levels of HCV RNA, ALT and AFP during a 6 months course of PEG-IFN-a2b and ribavirin for CHC**

<table>
<thead>
<tr>
<th>Months of treatment</th>
<th>Baseline</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV RNA, log 10 IU/ml</td>
<td>5.89</td>
<td>5.44</td>
<td>5.37</td>
<td>-</td>
<td>4.96</td>
<td>4.86</td>
<td>4.86</td>
</tr>
<tr>
<td>ALT, X ULN</td>
<td>6.3</td>
<td>4.2</td>
<td>3.0</td>
<td>2.8</td>
<td>2.3</td>
<td>1.9</td>
<td>2.0</td>
</tr>
<tr>
<td>AFP, ng/ml</td>
<td>195</td>
<td>61</td>
<td>36</td>
<td>23</td>
<td>19</td>
<td>12</td>
<td>13</td>
</tr>
</tbody>
</table>

with high specificity. Moreover progressive increase of serum AFP values is more alarming than their fluctuation.

We report the case of a patient with Chronic Hepatitis C (CHC ) and increasing serum levels of AFP with no evidence of HCC on imaging studies.

**Case Report:** F. A. was a 62-old female who had been diagnosed CHC in 2000. She eventually experienced a reactivation of Pulmonary Tuberculosis which required prolonged specific treatment and therapy for HCV had to be postponed. In April 2008 the pulmonary disease was considered cured.

A liver biopsy was performed; histology was compatible with the diagnosis of chronic hepatitis: HAI 7, Fibrosis 3, steatosis 1 ( Ishak ) and the patient was given a 72 week treatment with PEG-a-IFN-2b,100 mg/wk and ribavirin, 1000 mg /d.

Treatment achieved EOT biochemical response without virological response.

In may 2010 biochemical relapse occurred with ALT values ranging between 6.4 and 9.2 X ULN , since February 2012 serum AFP levels progressively increased from 22 ng/ml to 195 ng/ml:US monitoring and CT scan showed no evidence of HCC.

Despite the virological no response to the previous treatment retreatment was considered. The aim was to decrease disease activity, in a manner similar to that observed with the first course of therapy , and thus to ascertain whether AFP values would continue to increase predicting a forthcoming HCC or rather they were associated with disease activity. Triple therapy was considered too risky due to the pulmonary history and in January 2013 the patient was restarted on PEG-a-IFN-2b and ribavirin for 6 months.

The table gives HCV RNA, ALT and AFP values during treatment.** Conclusions:** In CHC serum AFP levels may progressively increase up to alarming levels with no evidence of HCC on imaging study. In this setting antiviral therapy may cause decrease of disease activity along with AFP normalization. Such a response indicates that pre-treatment elevations of disease activity are more alarming than their fluctuation.

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**Rash after amoxicillin treatment: a simple reaction or something more?**


IRCCS Cu’ Granda Ospedale Maggiore Policlinico di Milano, Scuola di Specializzazione di Medicina Interna Università degli Studi di Milano

A fever of unknown origin in a patient with diffuse atherosclerotic vascular disease and thoracic aortic graft: from diagnosis to therapeutic approach

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**Sartori F., Martinelli N., Olivieri O., Girelli D**

Department of Medicine, Section of Internal Medicine, University of Verona

A 83-year-old Caucasian woman was admitted to our department of Internal Medicine because of recurrent fever, general malaise, and mild weight loss. She had a medical history of diffuse atherosclerotic vascular disease, ischemic heart disease complicated by chronic heart failure (NYHA III), and previous endovascular repair of thoracic descendent aorta aneurysm. Since about 12 months she relayed every 10-15 days recurrent febrile episodes (>38°C), preceded by shivers, generally resolving spontaneously within a few hours or otherwise unresponsive to usual antibiotic therapies. On the other hand, no symptoms indicative of focal infection were reported and the physical examination was unhelpful. A complete diagnostic workup for fever of unknown origin was performed. However, beyond a persistent increase of inflammatory markers, no resolving findings were obtained from several laboratory and radio-
logical examinations, including whole-body computed tomography (negative for occult neoplasia, abscesses or other forms of infection), echocardiography (negative for endocarditis), screening for autoimmune and oncologic markers (negative), and microbiological analyses (multiple blood cultures, performed even during febrile peaks and without concomitant antibiotic therapy, were negative). Finally, a positron emission tomography (PET) scanning revealed glucose hypermetabolism at the aortic vascular endograft, thus suggesting the diagnosis of endograft infection. Concomitantly, the positivity of antibodies against *Coxiella burnetii* was showed by serological analysis. *Coxiella burnetii*, a Gram-negative bacterium that cannot be isolated in standard microbiological media, is usually known as the etiologic agent of Q fever. Noteworthy, it is also recognized as an important pathogen for vascular infection, including vascular graft infection.

Taking into account patient’s comorbidities and the relative high operating risk, as well as according to her will, no surgical treatment (i.e. the removal of the infected vascular endograft) was accomplished. Instead, a long-term antibiotic therapy with doxycycline, initially associated with hydroxychloroquine, was proposed. After a few weeks with such medical treatment the patient remained asymptomatic and is still continuing doxycycline therapy.

### Preemptive tracheotomy in advanced thyroid cancer: time to consider timing?

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A 79 years old male patient was brought by sons to our observation for a suspected cognitive impairment, an unwitting weight loss of about 10 kg in 8 months and an increasing difficulty in breathing. He was a smoker (about 20 cigarettes per day) with a history of chronic obstructive pneumopathy disease, HCV-related hepatitis, Kyure’s disease, type-2 diabetes and chronic renal failure.

At physical examination he presented an asymmetric neck due to an increased thyroid volume with hard consistency at palpation. The ultrasound scan of the neck showed in the right lobe of the thyroid two mixed structure nodules (66x55 mm and 15x15 mm), one with a complex structure (21x16 mm) and a pronounced leftward deviation of the trachea. Bilaterally, in the latero-cervical areas, reactive lymph nodes were signaled. Echo-guided fine needle aspiration of the largest thyroid nodule revealed cells of primitive anaplastic thyroid cancer (ATC). Imaging was completed by a Total Body CT-scan showing a voluminous solid mass involving right lobe and isthmus (8x10x13 cm) with irregular structure and central colliquation, infiltrating surrounding tissue and vessels as brachiocephalic artery and vein and common carotid artery while there was thrombosis of the jugular vein. Noteworthy, thyroid function tests were normal accounting probably for the delay in the alert for the gland condition. Moreover, respiratory difficulties were underestimated too, because of previous recurrent episodes of bronchitis.

Surgical consult defined unrectactable the cancer so that the effective options for a therapy remained limited.

Targeted therapy (with Sorafenib, Gefitinib or Vandetanib) is an option for this advanced disease. Nevertheless, despite intensive treatment with multimodal therapy including cytotoxic chemotherapy and external beam radiation therapy, ATC outcome remains poor, with a median survival of approximately 5 months.

Considering the prognosis and symptoms we advanced the hypothesis of a preemptive tracheostomy in order to relieve the airflow impairment caused by tumor and securing the airway in case of critic obstruction of upper trachea particularly in emergency situations. There is neither scientific literature nor guidelines about timing of placement a tracheostomy in a non-intubated, spontaneous breathing patient. Preemptive tracheostomy is usually an elective procedure for airway management in patients with supraglottic obstruction undergoing general anesthesia for surgery (1). Furthermore, in spontaneous breathing patients tracheotomy reduces the work of breathing, probably by decreasing resistance and intrinsic positive end-expiratory pressure (2). These findings are consistent with benefit irrespective of upper airway obstruction. The risks in an individual patient are difficult to predict and often delayed, and are dependent on patient anatomy and comorbidities. Problems and acute and longer-term complications affect the balance with benefit but when preemptively placed, under the best conditions possible, success of the procedure could be optimized.

Therefore, after otolaryngologist and respirologist consultations, we agreed to judge the patient eligible for a preemptive tracheotomy.

Investigations should be performed in a prospective, randomized manner with a sufficient number of patients to enable clinicians to draw valid, concrete conclusions as to the optimal methods of evaluating these patients. In the meanwhile, with the lack of clear guidelines for selecting patients a multidisciplinary approach is recommended for balancing risks and benefits of preemptive thyroidectomy to determine if and when it should be placed.

### References:


### Comorbidity, aging and complexity are challenges in elderly patients admitted to Internal Medicine units: a case report

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In October 2012 a 85-year-old man came to our observation for abdominal pain radiating to lower back, anemia and prolonged PT (INR 6) in patient on long-term oral anticoagulant treatment. He had a history of left inguinal hernia, cerebrovascular disease, ischemic heart disease, permanent atrial fibrillation, diabetes mellitus, and chronic kidney disease. In 2007 he underwent aortic valve replacement with a bioprosthesis. In 2010 he was affected by pulmonary thromboembolism and in May 2012 he was hospitalized for heart failure followed by rehabilitation period. In the beginning of October 2012 the patient was brought to the emergency room with abdominal pain radiating to the thighs and with lower back pain worsened by movements and acupressure. He reported febrile episodes (max 39 °C) with vomiting of food over the last 15 days.

On physical examination a huge inguinal hernia and an acute retention of urine were detected.

Blood tests revealed microcytic anemia, high inflammatory markers with leukocytosis at the upper limits, alteration of coagulation, acute-on-chronic renal failure with hyperuricemia, high indices of cholestasis. (Abdomen US then revealed gallstones with mild dilation of biliary tract).
A 30 years-old man was admitted for recurrent fortnight high fever. The history was negative and his origin was in the South of Italy. He had visited many doctors before a diagnosis was finally reached. It took 10 years until the patient described developing all symptoms meeting the diagnostic criteria for the disease. He was initially treated with tramadol and fentanyl, oxycodone and naloxone; finally IV morphine was introduced with benefit.

To investigate anemia, esophagogastroduodenoscopy was performed and it showed an ulcerated lesion on the posterior gastric wall; bioplastic samples revealed a gastric adenocarcinoma. Disease staging was completed with CT brain scans that didn’t show any focal lesion. On PET no FDG uptake appeared in the stomach but there was an high uptake in L2/L3 vertebral disc level. On the eighteenth day of hospitalization there was a febrile episode with thrill (TC 38.8 °) and empirical antibiotic therapy with piperacillin/tazobactam was started. Then blood culture resulted positive for MRSA and antibiotic therapy in the course has been replaced with teicoplanin according to antibiogram (Vancomycin was excluded because of renal failure). During hospitalization our patient also developed hospital acquired pneumonia and UTI, that needed more intensive antibiotic therapy. Because of patient’s inability to maintain a supine position, MRI scan of the lumbar spine under sedation was finally performed: it finally revealed a spondylodiscitis at the level of L2-L3 associated with small abscesses with cystic components in the context of the psoas muscles. To investigate the cause of spondylodiscitis TT and TE echocardiograms were performed but they didn’t show any sign of intracardiac vegetation. After four weeks of therapy with teicoplanin low back pain had not improved as well as indices of inflammation; we repeated MRI scan that revealed an extension of inflammatory process to adjacent vertebral bodies and to the paravertebral musculature, interposed disc was also destroyed. To exclude tubercular origin of spondylodiscitis and/or spinal localization of adenocarcinoma CT-guided percutaneous biopsy of the intervertebral disc was then performed. The search for BK, culture and histology were all negative; also Quantiferon test was negative. In the light of these results and of persistent positivity of sputum culture for MRSA teicoplanin was therefore replaced with tigecycline obtaining clinical and biochemical benefit.

Beyond the criteria: think on this...

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Do we rely too heavily on diagnostic criteria for medical diagnosis? It took 10 years until the patient described develop all symptoms meeting the diagnostic criteria for the disease and it took him several years and multiple visits to many doctors before a diagnosis was finally reached. A 30-years-old man was admitted for recurrent fortnight high fever in the past two years and new onset of remitting right flank pain. The family history was negative and his origin was in the South of Italy. His only travel abroad was to Mexico when he was 23 years-old.

The past history was remarkable for:
- aphthous stomatitis since he was 15 years-old
- acute onset of focal distal atrophy of his left arm diagnosed at 20 years-old of age
- epilepsy, in complete remission under carbamazepine since he was 24 years-old without changes of cerebral MRI
- past calf edema and suspected phlebitis after surgery for traumatic knee tendon rupture at 28 years-old

Since 28 years-old he started to experience about every fortnight attacks of high fever, raising with chills and lasting 3 or 4 days, but remitting with NSAD or spontaneously. During attacks he complained of myalgia and sore throat and completely recovered between the two attacks. The first step extensive whole blood tests and radiological examinations showed high inflammation markers, mild monocytosis and subclinical thyroiditis. A two-weeks-course of steroids was prescribed. Behçet’s Disease was suspected out of recurrent aphthous stomatitis, fever, negative serological tests for infectious diseases and autoimmunity. The diagnosis was ruled out because HLA B51 and pathergy test were negative. Infectious diseases were considered, but urine, blood and stool cultures during fever attacks and between attacks were negative. Extensive serological and molecular tests for bacteria and virus, quantiferon and malariae plasmodium were negative.

Hereditary periodic fevers were hypothesized out of age, fever characteristics, geographical origin and exclusion of autoimmune and infectious diseases. No mutations on the genes of Familial Mediterranean Fever, TNFRSF1A associated periodic fever and Hyper IgD fever were found. Nevertheless, the patient was started with colchicine as adjunctive criteria and attacks became milder and shorter. Drug fever was also considered but we did not found reports of fever due to carbamazepine.

Total body CT-PET FDG scan revealed both epididymis uptake. Blood, urine and urethral fluids cultures were all negative. He had leukocytosis, high c-reactive protein and procalcitonin. He underwent wide spectrum endovenous antibiotics therapy. Despite a normal pelvis MRI, he was started with four-weeks course of TMP-SMX under suspicion of prostatitis, but fever relapsed. Based on past history, occult central nervous system affection was considered and spine MRI performed although no new symptoms appeared. Unspecific signal changes in the cervical spinal cord were observed from C4 to C7, the same findings observed when he was twenty. After discharge, he presented with a small superficial thrombophlebitis just in the site where was the peripheral device for intravenous therapy administration. Extraneural lymphoma was hypothesized. Brain and sinuses MRI as well as gastric endoscopy were normal. He underwent a second total body PET FDG scan that showed uptake of pleura, right lower parenchyma, both epididymis and of right leg muscles. CT-total body scan showed thrombosis of right lower lungs and extensive thrombosis of the inferior vena cava infra-hepatic up to the iliac veins. Finally the patient achieved the total of at least three points required for diagnosis according to “The International Criteria for Behçet’s disease” (ICBD 2006), although symptoms did not match the International Study Group (ISG) criteria, published in 1990, the most widely used and well-accepted criteria among experts in Behçet’s disease. Medical Science is complicated and each patient is unique and different.

An intriguing association between photosensitivity and iron deficiency

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We report the case of a thirty-year-old woman who came to our observation complaining photosensitivity since childhood. She had a history of iron deficiency anemia. Slight hepatomegaly was recorded in previous ultrasound scan (US). Her younger brother suffered from erythema, swelling, cutaneous burning feeling and pain with oedema at sun exposure since infancy and biochemical diagnosis of Erythropoietic Protoporphyria (EPP) was made. Our patient’s blood tests showed: haemoglobin value 9.7 g/dl; mean corpuscular volume (MCV) 74.6 fl; serum iron value 35 mcg/dl and serum ferritin 11 ng/ml. She had abnormal liver function tests (aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels: 213 U/L and 281 U/L respectively). Viral hepatitis serology (HAV, HBV, HCV, EBV and CMV) and Parvovirus antibodies were negative. She had no exposure to toxic or drugs and she didn’t take any herbs. On the basis of high free blood protoporphyrin IX (ZnPPIX) concentration with characteristic peak of fluorescence at 365 nm and high fecal (proto) porphyrins levels as well (total fecal porphyrins 104 mcg/g and protoporphyrins 92%). Diagnosis of EPP was made. To better characterize porphyrin molecular analysis was performed. Surprisingly, the sequence analysis of the ferrochelatase gene (FECH) was normal. Considering that the phenotype and the biochemical data were suggestive of EPP, the possibility of X linked EPP due to ALAS2 gain of function mutation was considered. ALAS2 gene analysis revealed a AGTG c.1706-1709 mutation in heterozygosis. The diagnosis was also supported by elevated zinc chelated-protoporphyrin (ZnPPIX) levels. Although very mild microcytic anemia may be associated to EPP, the iron deficiency in our patient was more than expected. Her menses and dietary iron intake were normal, celiac disease and bloody stools were excluded. In order to identify the etiology of anemia, the patient underwent esofagastroduodenoscopy with evidence of esophagitis and moderate antral gastropathy. Oral iron therapy was started, but without improvement in haemoglobin level and serum ferritin. An unusual cause of iron deficiency was suspected: TMPRSS6 gene analysis was performed revealing heterozygosis for the 911 C>T mutation associated to Iron-Refactory Iron Deficiency Anemia (IRIDA). IRIDA is an autosomal recessive disease caused by mutations in TMPRSS6 gene, which encodes a type II transmembrane serine protease (matriptase-2), produced by the liver, leading to iron deficiency non responsive to iron per os. She was treated with intravenous iron and her serum ferritin rose from 15 to 104 ng/ml and Hb up to 12.1 g/dl. Meanwhile transaminases were normalized.

Erythropoietic protoporphyria (EPP) is a rare inherited disorder of the haem pathway with a marked impact on quality of life. It consists of a painful dermatosis usually without blisters characterized by a life-long acute photosensitivity, due to excessive production of PPIX by erythrocytes and their accumulation mainly in skin, but also in liver and erythrocytes. Microcytic anemia occurs in 20% to 60% of patients. Hepatic disease may include cholelithiasis due to high protoporphyrin content in gallstones, in about 20% of patients and chronic liver disease, potentially evolving to rapid acute hepatic failure. The classical protoporphyria is caused by the partial deficiency of the terminal enzyme (FECH) of the haem biosynthetic pathway. Recently, it was discovered that, in about 4% of patients, EPP is caused by gain-of-function mutations within the C-terminal region of 5-aminolevulinate synthase 2 (ALAS). This form is named X linked recessive protoporphyria (XLPP). XLPP differs from EPP because the excess of PPIX is the zinc-PPIX rather than free PP. In presence of iron deficiency, as in our case report, ferrochelatase can use zinc instead of iron in order to create ZnPPIX. Iron repletion decreased protoporphyrin accumulation and corrected the anemia. Elevated ZnPPIX levels could indicate iron deficiency, but also X-linked EPP due to XLAS2 gain of function mutations. In conclusion, our patient had two problems: XLPP and IRIDA with elevated ZnPPIX levels. In XLPP, serum iron and soluble transferrin receptor are usually normal, only ferritin is low, but our patient had both serum iron and ferritin low levels because of IRIDA, a congenital microcytic anaemia with an abnormal iron absorption characterized by absent hematological response to oral iron treatment.

**An unusual case of urine bag discoloration**

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**Case report:** A 82 year-old-man, with a history of previous bladder cancer treated with cystectomy and subsequent ureterostomia, was admitted to our Department for asthenia, constipation and loss of appetite for about six months. The physical examination revealed tense and globose abdomen, diffuse pain on palpation and torpid peristalsis on auscultation. On the admission, bag from ureterostomy contained purple material mixed with cloudy urine (Fig. 1). The laboratory tests documented increased erythrocyte sedimentation rate (ESR), leukocytes and neutrophils. A mild normocytic and normochromic anemia (HGB 9,7 g/dl), with low reticulocyte index and high serum ferritin were also documented. Transferrin was within the normal range. Furthermore, fecal occult blood test, chest X-rays and abdominal ultrasound were negative. In view of the clinical findings, the pa-

**Figure 1. Bag from ureterostomy contained purple material mixed with cloudy urine**
test resulted positive, while specific tests for the detection of Mycobacterium tuberculosis (batterioscopic examinations from bronchiectasis. A total body scan resulted negative. At the same time, PPD high resolution chest CT showed a solid nodular lesion (20*20*20 mm) generally; diffuse ground glass bilaterally with mosaic distribution, multiple surgery complications or chronic inflammatory disease reactivation, a deep palpation of the lower right abdominal quadrant. Suspecting post-nation of the chest showed crackling at the right lung and a complete abolition of the murmur at the right base. Painful reaction evocable at the admission the patient appeared debilitated, BMI:15. Physical examination revealed increased muscle enzymes. A complete blood count (CBC) and urine culture. At the same time, the patient underwent frequent enemas with restoration of normal bowel function and yellowish straw color of the urine. The diagnosis was anemia from chronic phlegos secondary to multidrug resistant urinary tract infection (UTI), complicated by Purple Urine Bag Syndrome (PUBS).

**Discussion:** First reported more than 30 years ago, PUBS is an extremely rare condition characterized by a purple pigmentation of the urine, and has been attributed to the conversion by gram-negative bacteria of indoxyl sulfate (a chemical product of tryptophan metabolism) to indigo (blue) and indirubin (red) which combine to give purple appearance. Risk factors are female sex, advanced age, permanent indwelling urinary catheters, dehydration, renal failure, alkaline urine and constipation. The latter may indeed increase the absorption of tryptophan [1,2]. In asymptomatic patients, resolution of constipation and catheter replacement are usually sufficient to restore the normal urine color. An appropriate antibiotic treatment based on urine culture is also needed in symptomatic subjects. Our case is emblematic, because the detection of the abnormal purple pigmentation of the urine has revealed a chronic and multidrug resistant UTI, which resolved after appropriate antibiotic therapy and resolution of risk factors such as constipation.

**References:**

**When the imaging is... misleading**


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LM, a female patient 57 years old, came to our attention for intermittent fever, weight loss and weakness. These symptoms appeared about two weeks before. In her medical history a diagnosis of inflammatory bowel disease (M. Crohn) when she was 16 years old which required multiple small bowel resections (the last one two months before the admission in our department), now under treatment with high dose corticosteroids. At the admission the patient appeared debilitated, BMI:15. Physical examination of the chest showed crackling at the right lung and a complete abolition of the murrum at the right base. Painful reaction evocable at the deeply palpation of the lower right abdominal quadrant. Suspecting postsurgery complications or chronic inflammatory disease reactivation, a abdominal ecography was required which resulted substantially normal. A high resolution chest CT showed a solid nodular lesion (20*20*20 mm) partially colliquate, in the left lung, with mediastinal lymphnodes omolateraly; diffuse ground glass bilaterally with mosaic distribution, multiple bronchiectasis. A total body scan resulted negative. At the same time PPD test resulted positive, while specific tests for the detection of Mycobacterium tuberculosis (batterioscopic examinations from broncoalveolar lavage) were performed and resulted negative. The patient underwent paraciliary lung biopsy with histological examination of the nodular lesion: epithelioid, giant cell granuloma. The histological examination confirmed the clinical suspicion of atypical mycobacterium of the lung in a patient with IBD and isoniazide etambutol rifampicin pirazinamide were promptly started.

**Intravenous immunoglobulins used for treating esophageal involvement related to polydermatomyositis**

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A 61- year-old Caucasian woman came to our observation in March 2012 for erythematous lesions on the back, trunk and limbs, later extending to the face and hands. On the basis of the clinical picture she underwent laboratory and instrumental tests that showed increased muscle enzymes. A diagnosis of Polydermatomyositis (PM/DM) was made and therapy with steroids and azathioprine prescribed. This was integrated, when she developed asthenia and myalgia, with cyclophosphamide and cyclosporins, which induced a clinical improvement and reduction of CPK. In August 2012, due to ascites and a suspected adrenal neoplasm, she underwent hysterectomy, omentectomy, and removal of the vesico-uterine peritoneum and Douglas, as well as selective lymphadenectomy. Histology demonstrated a poorly differentiated tubal carcinoma. The immunosuppressive and corticosteroids therapy was suspended and in September 2012 she started cytostatic treatment with the Taxol-Carboplatin regimen. After a short period she again developed myalgia associated with exacerbation of the skin involvement: periortbital edema, heliotrope rash and Gottron’s papules. Steroid and immunosuppressive i.v. therapy was reintroduced and the symptoms improved, but then she developed progressively worsening dysphagia, gastroesophageal reflux and dysphonia, and we were obliged to start parenteral nutrition. Intravenous immunoglobulin (IVIG) therapy, 2 g/kg/month in two administrations was administered and after one week we observed an improvement of the esophageal symptoms, so oral nutrition could gradually be resumed. She underwent IVIG maintenance therapy, six infusions, with progressive tapering of the steroid and immunosuppressive therapy. In 30% of patients with PM/DM, severe esophageal symptoms occur six months after onset of the disease. According to the guidelines, first-line treatment is steroids, and second-line treatment immunosuppressive therapy. Currently IVIG are third-line treatment, associated with a resolution of symptoms in 82% of cases, especially if treated early. IVIG used as first-line treatment with high doses of steroids can be a viable therapeutic option in the management of severe dysphagia associated with PM/DM.

**Complications of a complex disease: spondylodiscitis in a patient affected by symptomatic acute intermittent porphyria**

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A 60-year-old woman affected by Acute Intermittent Porphyria (AIP) was admitted to our Unit (Internal Medicine 2, Policlinico Hospital of Modena) due to severe abdominal pain associated with nausea, vomiting, diarrhea, arterial hypertension and fever. These symptoms manifested after a short
course of treatment with corticosteroids and nonsteroidal anti-inflammatory drugs prescribed for a new-onset low back and leg pain that the patient had been experiencing for 4 weeks before the hospitalization. Physical examination showed a normal state of consciousness, hypertension (200/120 mmHg), fever (38°C) and diffuse abdominal tenderness. Laboratory tests showed a moderate increase in C-reactive Protein (8 mg/dl) and white blood cells count (14.00 migl/ul). The patient had a history of symptomatic AIP, currently treated with weekly hematine (Normosang®) intravenous infusion. Infusion was made through a central venous catheter (Porth-a-Cath®) currently poor functioning due to an extended thrombosis of the superior caval vein and the azygos system secondary to a prior CVC positioning.

Due to clinical suspect of an acute crisis of AIP, possibly triggered by the drug intake, we started a treatment with hematine infusion, achieving a fast normalization of ALA and PBG urinary levels in parallel with the remission of the abdominal symptoms. Due to persisting of severe low back pain after the recovery from the acute abdominal crisis, the patient underwent an NMR imaging of the lumbar spine with contrast enhancement. The T1-weighted contrast-enhanced MR images revealed a spondylodiscitis at the D6-D7 level. We obtained samples from the central venous catheter and from a peripheral vein for blood culture, prior to the initiation of antibiotic therapy, and we removed the central vein catheter, as a catheter-related infection complicated by bacteremia and spondylodiscitis was suspected. The blood cultures were positive for S.Epidermidis as the catheter culture was conducted after removal, even if the culture from the biopsy sample resulted negative.

Long term antibiotic therapy with Levofloxacin and Teicoplanine was started and continued for 2 months after the antibiogram results. The follow-up MR imaging after antibiotic therapy showed a normal chronic fibrotic evolution of the spondylodiscitis, moreover symptoms gradually resolved, blood cultures and inflammatory indexes normalized, with a complete resolution of the low back pain.

AIP is a rare and complex disease due its clinical pleomorphism. Diagnosis of an acute porphyric attack may be often difficult, even in patients with a previous diagnosed disease. Nevertheless, even in AIP patients, a documented acute attack may be triggered by many different conditions mandatory to look for.

**Acute kidney injury: NSAIDS abuse or more?**

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A 75 years old man with nothing relevant in medical history came to our observation because of severe fatigue, oliguria, neck pain and left arm pain. He reported NSAIDs abuse in the previous months. Routine blood tests showed severe renal impairment (creatinine 12 mg/dl), mild anemia (Hb 9 g/dl) and hypercalcemia. He was treated with fluid replacement, furosemide and intravenous bicarbonate supplementation with restoration of urine output, but the creatinine decreased less than we expected (8 mg/dl) according to the clinical suspect of NSAIDs abuse nephropathy. A kidney ultrasonography was unremarkable, thus it was mandatory to perform a kidney biopsy. Just before performing it, a 24 hours urine collection showed more than 3 g of protein in 24 hours and the serum protein electrophoresis showed severe hypogammaglobulinemia without any evident M-component. Anyway, a serum protein and a urine protein immunofixation were performed. Presence of free kappa light chains with suppression of nonmyelomatous immunoglobulin synthesis and kappa light chains in the urine were detected.

The patient didn’t undergo kidney biopsy but bone marrow biopsy was performed. Plasmacell infiltration >65% confirmed the diagnosis of multiple myeloma.

Patient was treated with high doses of dexamethasone and melphalan with improvement of bone pain and renal function. We suspect that the NSAIDs abuse precipitated a pre-existing undetected condition of myeloma kidney involvement.

**A case of renal tubular acidosis in Sjogren syndrome**

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A 31 years old woman presented to our observation with dyspnea, peripheral edema and severe headache not responsive to therapy with NSAIDs. She reported intensive use of NSAIDs in the previous 2 months with partial pain control. She suffered from Sjogren syndrome (SS), autoimmune hypothyroidism, and she reported a history of sensory disorders in both lower limbs. Her brain TC scan findings were normal. Her blood tests showed renal impairment (creatinine 1.9 mg/dl) and her arterial blood gas analysis showed severe metabolic acidosis (pH 7.12, pCO2 17 mmHg, pO2 90 mmHg, bicarbonate 5.5 mEq/l and BE -23 mEq/l) thus she was treated with intravenous bicarbonate supplementation with partial benefit. In order to investigate her symptoms and to rule out a neurological involvement of Sjogren Syndrome, a brain MRI was performed. Brain MRI showed no significant abnormalities. In order to study her renal impairment we performed a kidney ultrasonography that showed hyperechoic foci in the pyramids suggestive of nephrocalcinosis as it is seen in Type 1 Renal Tubular Acidosis (RTA). Even if the association between SS and type 1 RTA is well known, we decided to study her renal impairment we performed a kidney ultrasonography that showed hyperechoic foci in the pyramids suggestive of nephrocalcinosis as it is seen in Type 1 Renal Tubular Acidosis (RTA). Even if the association between SS and type 1 RTA is well known, we decided to perform a kidney biopsy because the renal impairment was not responsive to current treatment. The renal cortex showed a diffuse interstitial, predominantly mononuclear, inflammatory infiltrate suggestive of acute interstitial nephritis and signs of chronic interstitial nephritis such as interstitial fibrosis and tubular atrophy. Once ruled out infectious causes of acute interstitial nephritis, we suspected that kidney involvement related to Sjogren syndrome was worsened by NSAIDs abuse. Therapy with NSAIDs was immediately stopped and the patient was treated with potassium citrate. In few days the creatinine decreased and the arterial blood gas analysis showed a partial resolution of the metabolic picture. Headache improved after some weeks with the resolution of the metabolic acidosis.
A strange case of lower back pain

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A 49-years-old man was admitted to our ward because of the onset, several months ago, of lower back pain. This was stabbing, non-radiated, continuous, worsening during leg's movements and causing progressive impossibility of standing and inability to walk during last months.

This symptom was accompanied by asthenia, loss of appetite with weight loss and fever up to 40°C with chills which lasted about a week and disappeared without antibiotic therapy.

Case history revealed he was allergic to aspirin and paracetamol; he smoked 2 packs/day for 30 years until few days ago; he abused heroin, cocaine, amphetamines and cannabinoids both inhaled and intravenous until 3 years ago; he referred alcohol dependence with current consumption of 3 AU/day.

Since the youthful age he was diagnosed with bronchial asthma but he never took inhaled drugs; at the age of 23 he was diagnosed with schizophrenia and began taking neuroleptic drugs (currently haloperidol, olanzapine, risperidone and clonazepam) achieving a significant symptoms reduction; at the age of 45 he was diagnosed with diabetes mellitus whereby he began taking metformin with a good control of HbA1C levels.

Upon admission to our ward clinical examination showed lower limbs muscles' hypotrophy and hypotonia; general force reduction was observed and segmental tests revealed diffuse muscle involvement; knee, hell tap and achilles jerk were suppressed; both shallow and deep sensitivity were altered bilaterally with "sock" pattern up to knee; Babinsky, Lasegue and Wassermann signs were negative. We also appreciated mild force reduction in left cheek muscles and mild tremor during upper limbs movement.

Heart examination was normal; radial and pedidial pulses were symmetric. Auscultation of thorax showed mild diffuse and bilateral continuous sounds. Abdomen examination was normal.

Blood pressure was 150/90 mmHg, cardiac rate was 86 bpm, rythmic. Laboratory tests showed a normal blood cell count, ESR 51 mm/h, CRP 6.200 pg/ml, d-dimer 1.134 ng/ml, protein electrophoresis showed increase of α1 and α2 globulins, electrolytes were normal and renal, hepatic, cholestatic and metabolic markers were normal too; HbA1C was 6.3%.

Since we suspected a peripheral nervous system injury we performed backbone CT scan which showed presence of pathological tissue infiltrating and destroying intervertebral disc between L3 and L4, both the vertebrae in their front and rear side, the anterior epidural space and the psosas muscles bilaterally.

The same exam showed in the left ureter proximal tract a stone (11 x 21 mm) causing II stage hydronephrosis and other smaller stones both in the left and right ureter.

The bigger one was removed transureteral lithotripsy; the stone and the urine collected after the intervention underwent cultural assay which resulted negative.

To investigate the nature of the pathological tissue we performed brain and abdomen CT scan which were negative for malignancy; gastroscopy and colonoscopy were refused by the patient.

Intradermic Mantoux test was negative as TB gold assay; 3 urine and 3 sputum specimens were analized with Ziehl-Neelsen stain for AFB and were negative too. 6 blood specimens cultural exam was negative; Widal and Wright tests were negative too; transosephageal echocardiogram was not performed beacause of patient’s denial, but the trans thoracic one didn’t show any valvular vegetations.

Finally CT guided biopsy of the tissue was performed. The citologic specimen excluded the presence of neoplastic cells and Ziehl-Neelsen stain for AFB was negative too, instead the cultural assay showed growth of both methicillin sensible S. aureus and S. warnerii.

We decided to begin antibiotic therapy with ciprofloxacin and teicoplanin, an external corset was positioned and analgesic therapy with nimesulide, given in consideration of his allergies, was initiated.

Fifty shades of a shock

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A 54 years old man has been hospitalized for the appearance of fever from one week (38,5 °C), associated to diarrhea, abdominal pain, dysuria, anorexia, asthenia. Laboratory tests showed a rise in creatinine levels (from 3.6 mg/dL to 6.8 mg/dL in a month), increased white blood cells (11.01 x 10^9/L), significant increase in inflammatory markers; a blood gas analysis showed metabolic acidosis (pH 7.33; HCO3- 17.9 mg/dL).

In history: chronic kidney disease due to aseomul resepsive polycticid kidne y disease (ADPKD) diagnosed from the age of 41; Crohn’s disease complicated by multiple stenoses of the last ileal loop. Investigations showed a positive urine-culture for E.Coli; at abdomen ultrasound: presence of moderate ascitis, bilateral multiple kidney cysts and ileal wall thickening.

We treated the patient with Ertapenem for the urinary tract infection and Methylprednisolone in the event of a recurrence of Crohn’s disease, plus fluid and electrolyte replacement. In the first days we have witnessed an improvement of clinical and laboratory parameters.

After 5 days: sudden episode of shock (BP 80/50 mmHg) with no fever; abdomen diffusely tender; torpid peristalsis; metabolic acidosis at blood gas; lab analysis point out a new increase in creatinine levels associated to hypocalcemia, hyponatremia and hypoglycemia; abdomen x-ray showed a marked gaseous distension of ileal loops with multiple air-fluid levels; negative chest x-ray.

Diagnostic hypothesis: clinical deterioration could be primarily due to a worsening of urinary tract infection (hypotension of entero-vesical fistula or cyst infection); to a complication of Crohn’s disease or to a relative adrenal failure. An abdomen CT-Scan showed a marked thickening of the ileal walls and numerous renal cysts with fluid content. A new abdomen ultrasound showed some loops adherent to the bladder as for the presence of a entero-vesical fistula. We performed a MR-scan that showed no signs of fistula, but the presence of cysts with abscess content, as for acute pyelonephritis (Fig.1). We also investigated adrenocortical axis, resulted in the normal range. Our diagnostic conclusion was septic shock due to cyst infection.

Decision-making: the cyst was drained and a specific antibiotic therapy with meropenosum and fosfomycin was started (fosfomycin showed a synergic effect with meropenem – Int J Infect Dis. 2011 Nov, 15,11). The patient was subjected to dialysis with an improvement of clinical conditions. Indication for nephrectomy was placed due to the presence of recurrent infections (Clin Exp Nephrol 2012 16: 892-902). Suitability for kidney transplantation will be evaluated after the resolution of the infectious status.

Conclusions: Cyst infection is the second most common cause of death in patients with ADPKD. The clinical, radiological and therapeutic features are
Clinical Epidemiology

Clostridium difficile infection in patients hospitalised for pneumonia in the Internal Medicine Departments

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Introduction: Pneumonia is the most frequent cause of antibiotics prescription and hospitalization. It is still one of the main cause of mortality, especially in elderly. Clostridium difficile infection (CDI) is the most common infectious cause of antibiotic-associated diarrhea, and it is one of the most common health care-associated infection.

In elderly and physically disabled patients, CDI is a cause of increasing hospital morbidity and mortality, length of hospital stay and costs of hospitalization.

Up to date, few studies addressed the issue of CDI as a complication of pneumonia therapy.

Objectives: The aim is to compare the outcomes of hospitalised patients with and without Clostridium difficile infection occurred under treatment for pneumonia.

Methods: As a part of two continuing prospective observational studies, one on CDI and on Pneumonia (community acquired - CAP, health-care associated - HCAP, hospital acquired pneumonia - HAP) in hospitalised patients, we extracted two cohorts of subjects admitted from 15th March 2011 to 14 December 2011. We divided the population on the basis of CRP values at admission: group 1 with CRP ≥ 1.5 mg/dl (cases, n. 313) and group 2 with CRP <0.5 mg/dl (controls, n. 589). We also classified our population in seven subsets on the basis of the diagnosis formulated at the discharge according to the ICD-9-CM: infections (subset 1), rheumatic diseases (subset 2), neoplasms (subset 3), cerebro-cardiovascular diseases (subset 4), traumatic and mental disorders (subset 5), endocrine and metabolic diseases (subset 6);

Biohumoral and comorbidity determinants of low HDL-C during acute phase response in a setting of in-hospital patients


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Background: The acute phase reaction (APR) can be defined as the modifications occurring in response to an endogenous or exogenous injury, including infections, inflammatory processes, trauma, malignancies. APR is characterized, beyond other characteristics, also by alteration in lipid profile, particularly by a reduction of total cholesterol, HDL-C and LDL-C levels, while triglycerides concentrations remain normal or, in some cases, increase.

To evaluate the lipid profile modifications, mainly regarding HDL levels, at the time of hospitalization in a setting of in-hospital patients referred to our Department for different pathologies. Particularly we wanted to evaluate differences in HDL levels in subjects with and without APR and if HDL reduced on the basis of the hospitalization cause; finally we also tested the predictors of HDL reduction during hospitalization.

Patients and methods: In our retrospective cohort study we included 902 patients (aged between 20-80 yrs) in the period between January 2009 and December 2011. We divided the population on the basis of CRP values at admission: group 1 with CRP ≥ 1.5 mg/dl (cases, n. 313) and group 2 with CRP <0.5 mg/dl (controls, n. 589). We also classified our population in seven subsets on the basis of the diagnosis formulated at the discharge according to the ICD-9-CM: infections (subset 1), rheumatic diseases (subset 2), neoplasms (subset 3), cerebro-cardiovascular diseases (subset 4), traumatic and mental disorders (subset 5), endocrine and metabolic diseases (subset 6);
subjects with no significant morbidities were selected as subset 0. The following parameters have been determined: CRP, white blood cells count, serum alpha2 globulins, hemoglobin, platelets, total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, glyceremia, serum albumin, serum creatinine, ALT and AST.

Results: Comparing with the control group subjects with CRP ≥ 1.5 mg/dL were significantly older (p < 0.001), had significantly higher white blood cell count (p < 0.001), platelets (p = 0.001), alpha 2 globulins (p < 0.001), glyceremia (p< 0.001) creatinine (p< 0.001), AST (p = 0.003), ALT (p = 0.008) and lower hemoglobin (p < 0.001), albumin (p < 0.001), LDL-C (p < 0.001) and LDL-L (p < 0.001); also tryglicerides were lower; however not statistically significant. Regarding the differences of HDL-C and LDL-L among the seven subsets only subset 1 showed CRP significantly higher and HDL and LDL significantly lower than the other subsets. At correlation analysis HDL-C showed an inverse significant correlation with all acute phase parameters: CRP (\( \rho = -0.102 \), p < 0.001), WBC (\( \rho = -0.254 \), p < 0.001), alpha 2 globulins (\( \rho = -0.110 \), p = 0.001). LDL-C showed an inverse correlation with all acute phase parameters: CRP (\( \rho = -0.294 \), p < 0.001), WBC (\( \rho = -0.169 \), p < 0.001), alpha 2 globulins (\( \rho = -0.025 \), p = 0.462, not significant). Also creatinine showed an inverse correlation with HDL-C (\( \rho = -0.287 \), p < 0.001) and LDL-C (\( \rho = -0.042 \), p = 0.293), this last one however not significant, while albumin showed a significant positive correlation with both HDL-C (\( \rho = 0.305 \), p < 0.001) and LDL-C (\( \rho = 0.398 \), p < 0.001). Stepwise regression analysis showed that gender (\( \rho = -0.322 \), p < 0.001), albumin (\( \rho = 0.255 \), p < 0.001), tryglicerides (\( \rho = -0.219 \), p > 0.001) and CRP (\( \rho = -0.126 \), p = 0.001) were independent predictors of HDL-C levels (R of the model .285, p < 0.001). WBC, alpha 2 globulins, glyceremia and creatinine were also included in the model, but failed to enter the final equation.

Discussion: Our data although confirming that subjects with APR have total cholesterol, HDL and LDL levels lower than control subjects, extend this observation to a large setting of patients hospitalized for multiple morbidities, larger than previous studies. The greatest reduction of HDL levels was observed in patients included in subset 1 (infections), thus suggesting that a greater degree of inflammation cause a greater decrease of HDL levels. Among the APR parameters, PCR was the only one able to predict HDL levels reduction. Currently the physio-pathological role of lipid reductions has not been completely elucidated and particularly if lipoproteins may have a protective role in innate immunity.

Antibiotic prophylaxis in the laparoscopic cholecystectomy in patients at low-medium anesthetic and infectious risk


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Introduction: The incidence of surgical infections after laparoscopic cholecystectomy (LC) is reported to be <2%, because of the minimal trauma due to this approach. In LC, cephalosporins are the antibiotics most widely used in the prophylaxis of infections, even if laparoscopic surgery, among other advantageous techniques, resulted in a marker decrease in the incidence of perioperative septic complications.


Materials and methods. We studied 75 patients (26 M, 49 F, mean age 45 years) suffering from lithiasis (66 pt) and polypoid lesions (9 pt) of the gallbladder, divided randomly into 3 groups. The patients were at low-medium anesthetic risk (ASA I-III) and infectious (diabetes mellitus, kidney disease, COPD, congenital heart disease, previous malignancy).

Before anesthesia groups A (24 pt) and B (24 pt) received, respectively, sulfabtactam/ampicillin 3 g and ciprofloxacin 400 mg single dose intravenous infusion. In group C was not administered antibiotics. In all cases was performed cultural examination of bile from the gallbladder taken at the end of the intervention.

We evaluated: incidence of infections, circulating leukocytes, body temperature, pain, intestinal peristalsis, days of hospitalization, cosmetic damage and histological examination.

Statistics: for to compare the 3 groups we used One Way ANOVA for repeated measures with a p value of 0.05 considered significant.

Results: Infectious complications on-site umbilical fascial were 2 (8.3%) in group A and 4 (14.8%) in group C. Infections have not been registered in the group B, without any statistical significant differences between the 3 groups.

In the first day after surgery the value of circulating leukocytes was > 10x10/UL in 16/24 patients (66.6%) in group A, in 14/24 patients (58.3%) in group B, in 7/27 pt (25.5%) in group C (p = 0.016). The outcome occurred in II day after surgery in 8/24 patients (33.3%) in group A, in 9/24 patients (37.5%) in group B, in 11/27 patients (40.7%) in group C. The outcome In III days occurred in 14 patients of the group A, in 14 patients of the group B, in 14 patients of group C. The remaining patients were discharged on day IV after surgery, also in this case without any statistical significant differences between the 3 groups.

Discussion: The infections observed were limited only to the peri-umbilical site, never associated with fever and neutrophilic leukocytosis, with delayed intestinal duct, prolongation of the hospitalization, cosmetic damage, increased costs. The infectious complication did not correlate statistically significantly with BMI, duration of anesthesia, the surgical and histological examination.

In all patients, the bile culture was sterile and we found no correlation between positive bile cultures and surgical infections after LC, then the infection of the umbilical site is not due to bacterial infection from the gallbladder. It is possible that ischemia by repeated surgical trauma of skin margins of the site promotes contamination by pathogenic bacteria from the skin with not accurate antisepsis in pre-operative phase.

Conclusions: Antibiotic prophylaxis with sulfabtactam/ampicillin or ciprofloxacin did not affect the prognosis in patients undergone to LC. and we found no correlation in infectious complications statistically significant between the 3 groups. Therefore, antibiotic prophylaxis with cephalosporins, beta-lactamine, fluoroquinolones in the LC for benign disease, in patients with low-medium anesthetic risk and chronic diseases not seem to improve the infections or the outcome of the patients.

This study assesses the real efficacy of antibiotic prophylaxis in elective LC with respect to the postoperative infection rate and antibiotic treatment did not seem to affect the incidence and severity of infections.

High prevalence of hyperuricemia in apparently healthy people in current Italian urban setting

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Introduction: Uric acid has gained rising importance in the last decade. Serum uric acid (SUA) level is now recognized as an important marker and risk factor for many pathological conditions such as diabetes, hypertension, kidney disease and cardiovascular disease. However, SUA levels in healthy people and the relationship with other clinical markers have not been fully addressed yet, in current lifestyle and urban settings.
Methods and results: We enrolled 9369 apparently healthy people who passed clinical and haematologic screening before blood donation. Mean age was 45.26±10.67 years and 7361 (78.6%) were men. Mean body mass index (BMI) was 20.29±14.10, and mean creatinine level was 0.90±0.15 mg/dl. Mean SUA level was 5.15±1.20 mg/dl. Among our healthy population, 2738 (29.22%) patients had a SUA level over 6.0 mg/dl. Men had significantly higher levels of SUA compared to women (5.64±1.11 mg/dl vs 4.10±0.97 mg/dl, p<0.0001).

We divided our population in three groups according to age, BMI and creatinine level tertiles. Older people had significantly higher levels of SUA (5.21±1.23 mg/dl vs 5.34±1.26 mg/dl vs 5.38±1.26 mg/dl in 1st vs 2nd vs 3rd tertile, respectively; p<0.0001). SUA levels were also higher with increasingly higher creatinine levels (4.60±1.16 mg/dl vs 5.39±1.06 mg/dl vs 5.92±1.26 mg/dl in 1st vs 2nd vs 3rd tertile, respectively; p<0.0001) and BMI (4.97±1.31 mg/dl vs 5.20±1.14 mg/dl vs 5.76±1.19 mg/dl in 1st vs 2nd vs 3rd tertile, respectively; p<0.0001).

After univariate analysis, both age, creatinine and BMI were predictors of higher SUA levels. (all p<0.0001). After adjustment in the multivariable analysis they remained significant predictors of higher SUA values (age OR all p<0.0001).

Conclusions: In our apparently healthy population about 30% of subjects had a SUA above the currently approved cut-off of 6 mg/dl. This unexpectedly high prevalence might reflect the actual lifestyle habits in current Italian urban settings. We showed that SUA levels are higher in men as compared to women. We demonstrated that SUA levels are directly correlated to both BMI and creatinine levels. BMI is directly related to eating and lifestyle habits. Thus SUA seems to be correlated with various clinical and laboratory parameters even when they fall into a normal range. Whether higher SUA values in healthy subjects are correlated to a worse prognosis still remains to be defined by ad hoc studies.

Cardiovascular risk factors incidence in asymptomatic elderly patients in a mountain community. Preliminary data


More than 19 percent of Italy’s population is age 65 or older, making it the world’s “oldest” major country. Except for Japan, the world’s 20 oldest countries are all in Europe. Compared to the past decades population has undergone an aging which led, as a consequence, an increase in demand for health and social services. Aging and population growth both contribute importantly to the rise in health care costs and every year health care expenditures rise appreciably. Ageing populations are driving demand for healthcare services and pharmaceutical products around the globe. Older people tend to require more healthcare services and are subject to higher levels of chronic illness than younger people.

Some municipalities have organized monitoring and preventing services represented by the so-called neighbor clinics. In our Lepine mountain community neighbor clinic we analyzed the cardiovascular risk factors and diseases that occur in asymptomatic elderly subjects.

Patients were followed up from June 2012 to May 2013 after the first voluntary access to the clinic. At the beginning of the study over 65 patients were 961 equal to 19.7% of the whole population (in accord with Italy’s general value) During the follow up we examined 235 patients (133 F) equal to 25% of the elderly population with a mean age of 73.4±6.4 years for women and 74.0±6.1 for men.

188 patients (80%) were asymptomatic. The 47 symptomatic reported mainly exertional dyspnea (42) and palpitations (5) with no evidence of ischemic disease or heart failure except in 12 cases. Asymptomatic patients (60F and 61M) reported arterial hypertension in 63% of cases treated with various therapies but only 10 (6F) had uncontrolled blood pressure.

42 patients (21.3%) were being treated for lipid abnormalities (19F). 22 were diabetic (13F) equal to 11.7% and 22 were smokers (4F).

We analyzed also BMI and 88.8% of whole population was overweight with a BMI greater than 25. Furthermore our data show that these 46F and 32M (41.5%) showed an overt obesity with a BMI> 30.

59 patients had only 1 risk factor, 81 had 2 risk factors and 48 had 3 or more risk factors.

If we consider only the older asymptomatic population over 75 (70 patients with mean age 80.6±4.1 years - 25F) the data are similar to the data observed in all the patients population: obesity 84.3%, hypertension 67%, diabetes and dyslipidemia 15.7%.

In the follow up time 2 patients died, one for cancer. The surprising finding of this analysis in asymptomatic individuals, also in the oldest patients, is the lack of the manifestations of the classic cardiovascular diseases typical of the elderly, such as ischemic heart disease, arrhythmias, heart failure, despite the presence of multiple risk factors. In fact, we observed only few cases of ischemic cardiac diseases, all asymptomatic and only one case of atrial fibrillation.

An initial analysis leads us to suppose that our patient sample, based mainly on asymptomatic subjects, does not include critical patients followed in reference centers, or alternatively that in small community and municipalities social national health service is more effective.

Lifestyle analysis and eating habits of a working business community

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Introduction: The ‘analysis of the lifestyle is one of the most important aspects in terms of primary and secondary prevention of many chronic degenerative diseases such as diabetes, hypertension, coronary heart disease, cancer. The questionnaires are one of the most direct and most used methods for a first investigation devoted to the discovery of sedentary life and poor dietary habits. The aim of this study was to highlight, through the ‘use of validated international questionnaires, translated into Italian language, the prevalence of some non correct aspects of lifestyle and the prevalence of chronic degenerative diseases associated in a working community.

Materials and methods: It was investigated a sample from a working community of a pharmaceutical company in Tuscany-Italy. The adhesion to the completion of the questionnaire was voluntary and free. We used questionnaires translated into Italian language whose content was extracted from validated models in the international literature (ACSM guidelines) and which contained different types of topics, such as sports or physical activities, eating habits, estimation of chronic degenerative diseases and quality of life’s evaluation.

Results: The sample consists of 95 subjects with 61% female and 39% male average age 42±0.7. From the results, smokers were only 12%, the prevalence of chronic degenerative diseases (hypertension, diabetes, metabolic syndrome) was 55% with a distribution per sex: 67% in women and 33% men. The active population was 75% of the whole group, while only 25% were sedentary. The percentage of the gender into the active subjects was substantially similar: 50% males and 50% females. In 51% of cases’
physical activity was regularly practiced more than once a week, while 13% did it only once. Regarding the eating habits, food intolerances were declared in 8% of the cases analyzed, while the choice of the kind of food was characterized of an higher prevalence of consumption of fruits, cereals and dairy products, with low consumption of fish and alcohol. The meat consumption was in the middle. The analysis of the own perception of quality of life (QOL) showed a perception of the own lifestyle of high level. In the 70% of the community, the score reached was estimated in the highest range ( <60 < 90). For the other parameters, the greater average score was found in the question related with own cognitive abilities and the perception of the quality of the work. Also the questions regarding the time spent to the recreational and socialization activities have reached an high score level.

Conclusion: The lifestyle’s questionnaires represent now a valid system for the evaluation of risk factors closely related to cardiovascular risks. Questionnaires can be used for their positive implications for the educational role on the general population. The results obtained confirm the sensitivity of the working realities to undergo to these investigations. It has been also confirmed, in this context, the attention in respect of a adequate life style, in fact, the correct behaviors are those mainly represented.

Gastroenterology

The best tool to follow up coeliac patients? A duodenal biopsy!


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Background: Coeliac disease (CD) is a chronic enteropathy that 12-18 months after the start of a gluten-free diet (GFD) requires a close follow up. Despite this, the best way to follow up coeliac patients has not been established yet and different centres follow up coeliac patients in different ways [1]. In the last 14 years, we have been offering our coeliac patients a thorough 12-18 month follow up which includes both clinical, serological, and histological re-evaluation.

Aims: To retrospectively analyse the data we obtained to establish the best method to follow up coeliac patients. Patients and methods: the clinical notes of all the patients affected by CD on a GFD attending our clinic between Sept 1999 and March 2013 were examined. Sex, age at diagnosis of CD, clinical type of CD, result of histology, result of endomysial antibodies (EMA), and symptoms at time of follow up were collected. Patients with complicated CD, potential CD, CD diagnosed in the childhood, and CD patients on a GFD for fewer than 12 months were excluded. Results: 317 adult patients (236 F, age at diagnosis of CD 33.1±12.1) received a complete follow up, while 129 were lost to follow up (90 F, age at diagnosis of CD 32.1±13.7). Duodenal biopsy showed persistence of villous atrophy in 25/317 patients; EMA were still positive in 76, GFD adherence and clinical response were unsatisfactory in 58 and 97 respectively. Results of serological response, clinical response, and GFD adherence were analysed looking for correlations with histological response, assumed as golden standard. Sensitivity and specificity were therefore evaluated by means of Chi2 analysis. Although p-values were significantly different, from a clinical point of view sensitivity and specificity were very disappointing: 64% and 80% for serological response, 48% and 71% for clinical response, 56% and 85% for GFD adherence. A multivariate logistic analysis proved to be unable to foresee histological diagnosis with sufficient accuracy. Clinical and demographic characteristics of patients lost to follow up did not differ from those of the patients receiving follow up. Conclusion: Sensitivity and specificity were therefore evaluated by means of Chi2 analysis. The characteristics of patients lost to follow up did not differ from those of the patients receiving follow up. Only some of them could have been identified thanks to a serological and/or clinical follow up. Therefore, a follow up duodenal biopsy was the only tool that could identify those patients with persistent villous atrophy. However, one patient out of four was lost to follow up. Although the percentage of CD patients who receive follow up is unknown [1], it is theoretically possible that at least some of them were lost because they did not want to undergo a second duodenal biopsy.

References:

Interleukin (IL)-17A homodimer reduces pro-inflammatory cytokine production by inflammatory bowel disease mucosa cultured ex vivo

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Background & Aims: Interleukin (IL)-17A, which is up-regulated in inflammatory bowel disease (IBD) mucosal lesions, and IL-17F may form IL-17AA and IL-17FF homodimers or IL-17A/F heterodimers. The role of each IL-17 dimer in IBD is currently unknown. Therefore we studied the effects of IL-17AA, IL-17FF and IL-17-A/F in ulcerative colitis (UC) and Crohn’s disease (CD) mucosa.

Methods: Inflamed colonic biopsies from 17 IBD patients (6 UC and 11 CD) were cultured ex vivo with IL-17AA, IL-17FF or IL-17A/F (1 ng/ml). Mucosal myofibroblasts isolated from the inflamed colon of 4 CD and 4 UC patients were cultured with increasing concentrations (1-100 ng/ml) of each dimer. IL-8 and IL-6 were measured in culture supernatants by ELISA.

Results: IL-17AA, but not IL-17FF, significantly reduced both IL-6 and IL-8 production by inflamed IBD biopsies cultured ex vivo, whereas IL-17A/F decreased IL-8 release by IBD mucosa. No difference was observed between CD and UC. Neither IL-17AA, nor IL-17FF, nor IL-17-A/F exerted any effect on IL-6 and IL-8 production by IBD myofibroblasts.

Conclusions: IL-17AA exerts an anti-inflammatory action on inflamed IBD biopsies cultured ex vivo. Its action is not mediated by myofibroblasts, therefore further studies are underway to ascertain which cell type is the main target of IL-17AA in IBD mucosa.

Effects of sacral nerve electrostimulation on gastrointestinal motility in patients with chronic refractory constipation

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Background: Sacral nerve stimulation (SNS) has recently been proposed to treat unresponsive constipation despite its effects on gastrointestinal (GI) motility has never been confirmed.

Methods: 14 patients (12 females) affected by refractory constipation (lasting >12 months, n’evacuation/week=1.1±0.6, Bristol 1.5) entered the study. Gastric and gallbladder motility, orocecal transit time (OCTT), bowel...
habits, whole gut transit time (WGTT), autonomic neuropathy (AN), PAC-QoL, and upper/lower gastrointestinal symptoms were assessed before and during temporary SNS.

**Results:** Seven patients completed the evaluation and 3 underwent permanent SNS. AN was detected in all. Gastrointestinal symptoms significantly improved (P=0.03) during SNS, but gallbladder/stomach motility did not change (28.5±4.2 vs 35.2±4.5, P=0.07; 48.8±7.1 vs 43.5±7.4 min, P=0.23, respectively). OCTT was delayed at baseline compared to normal controls and did not change during SNS (141.7±102.6 vs 144±115.2, P=0.97). WGTT did not improve significantly although in two patients it improved from 90.6±75.5 to 52.8±59.4. Overall, the number of bowel movements/week was unchanged, however in three patients it improved from 1 to 2/week. PAC-QoL did not improve during SNS.

**Conclusions:** Temporary SNS does not affect upper/lower GI motility and QoL, however it can help a selected group of constipated patients and might represent an alternative treatment in patients candidate to colectomy.

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### New immunoassay tests for the detection of selective fecal occult blood (FOB) in patients with gastrointestinal (GI) lesions

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**Background:** Occult GI bleeding represents a daily challenge for physicians and can point to severe diseases including colorectal cancer (CRC). Screening strategies (FOBTs, colonoscopy and imaging) are therefore continuously being developed to detect the sequence adenoma-CRC as early as possible. FOBT represents a common noninvasive screening tool with high sensitivity and specificity.

**Aims:** We compared the diagnostic yield of two FOBTs, in patients screened for CRC. The double information about lower and upper GI bleeding provided by one FOBT were also integrated within the overall diagnostic pathway of the study group.

**Methods:** 41 patients (M:F=28:13, age 68.1±12.7SD, yrs) were referred for alarm symptoms including anemia, weight loss, fatigue, change in bowel habits. Two different immunochromatographic FOBTs, both based on a combination of mono-polyclonal antibodies were used: a) Colon Cancer Test® (FOBT-CCT, Sofar, Milano, IT) which separately identifies the hemoglobin-haptoglobin complex for upper bleeding and hemoglobin for lower bleeding, with a sensitivity of 25 ng Hb/ml; b) “Standard” FOBT (S-FOBT, Biolife, Milano, IT) which detects GI bleeding with a sensitivity of 50 ng Hb/ml. Both FOBTs were performed on the same stool sample. All pts. underwent subsequent (within one week) EGDS and colonoscopy; biopbies and histology were performed whenever a lesion was detected.

**Results:** FOBT-CCT was positive for lower bleeding in 22 (54%) out of 41 pts, including 3 (7%) cases with upper bleeding. S-FOBT was positive in 21 (51%) pts. Colonoscopy confirmed FOBT-CCT findings and diagnosed 20 (95%) adenocarcinomas and 1 (5%) adenomatous poly. In the S-FOBT false negative, a left-sided adenocarcinoma was detected. When FOBT-CCT and S-FOBT were negative, colonoscopy revealed non-bleeding lesions i.e., 4 (20%) adenocarcinomas, 3 (15%) adenomatous polyps, and 13 (65%) normal stomach and colon. For upper bleeding, all FOBT-CCT positive results were associated with gastric ulcerative lesions. Considering endoscopy as the golden standard, sensitivity was 76% (60-92%, 95%CI) (lower bleeding) and 100% (upper bleeding) for FOBT-CCT and 72% (56-88%, 95%CI) for S-FOBT. Specificity was 100% in both FOBTs.

**Conclusions:** Both FOBTs display almost similar diagnostic performance in the presence of lower GI bleeding, although S-FOBT might yield slightly lower sensitivity likely due to lower detection cut off (50 ng Hb/ml). An open issue remains the relatively high rate of false negative of both FOBTs due to non-bleeding lesions, including neoplasms. FOBT-CCT provides additional information because it can also detect upper GI bleeding, otherwise unrecognizable by other FOBTs.

### The liver as a new tissue source of thymidine phosphorylase for mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)


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**Background:** Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare autosomal recessive disease associated with mutations to the nuclear TYMP gene, which encodes for the thymidine phosphorylase enzyme (TP), converting thymidine (dThd) and deoxyuridine (dUrd) in thymin or uracil. The genetically-driven defect in MNGIE is such that the TP enzyme activity is completely lacking or markedly reduced. As a result, dThd and dUrd accumulate and this leads to an imbalance in the corresponding triphosphates pool. The resultant biochemical abnormality does not influence the nuclear DNA turnover, but it affects the mtDNA replication in high-energy dependent tissues, such as brain, skeletal and smooth muscle, thereby inducing mtDNA mutations and multiple deletions. On a clinical standpoint, MNGIE is characterized by severe gastrointestinal dismotility, in addition to neurological impairment, i.e. progressive external ophthalmoplegia, cachexia, peripheral neuropathy, and diffuse leukoencephalopathy. The severity of MNGIE depends on the entity of TP deficiency, i.e. a typical MNGIE patient has ~5% of TP residual activity and manifests with symptoms at a mean age of ~19 years and life expectancy is ~37 years. Interestingly, MNGIE relatives carrying heterozygous TYMP mutations have 25-35% of residual TP activity and remain asymptomatic for the whole life. Such threshold of enzymatic activity may be a target for therapeutic purposes. So far, there are no established therapeutic options for patients with MNGIE. Recently, in the attempt to restore a normal TP activity, allogenic hematopoietic stem cell transplantation (AHSC) has been performed as a cellular source of TP. Current data obtained on about 20 MNGIE patients underwent AHSC transplantation showed gastrointestinal and neurological improvement although 5-year survival rate is roughly 50%.

**Objective:** Since liver is the main organ for proteins biosynthesis, and the transplantation success is ~80%, the aim of this study is to test whether the liver tissue can be a new source of TP, providing a basis for the liver transplantation as an option for MNGIE patients.

**Methods:** A number of n= 11 patients (7 males; age range: 35-55 years) underwent hepatic resection for focal disorders (i.e., uncomplicated tumors in non-cirrhotic liver) were included. Margins of normal liver tissue were processed for a variety of methodological approaches aimed to identify, quantify and localize TP protein, i.e. WB, ELISA, and immunohistochemistry (IHC). TYMP mRNA specific expression has been evaluated via qPCR. Bone marrow and intestinal mucosa were used as positive controls while skeletal muscle as negative control.

**Results:** WB showed the presence of TP protein in ealty liver tissue with a densitometric ratio TP / GAPDH of 0.9±0.5 A.U. ELISA assay showed that TP content was 0.5±0.07 ng/µg total proteins. The liver localization of TP with IHC was identified in the nuclei and cytoplasm of hepatocytes and reticular cells. TYMP mRNA specific liver expression has been detected in...
the liver tissue, providing evidence of in situ synthesis. Moreover comparing results of bone marrow and liver, not only TYMP expression was similar, but TP was translated > 5 times in the liver (at the same amount of total proteins).

Conclusions: The results of this study provided evidence that the liver is an important tissue source of TP, which can be synthesized in situ. We propose that, likewise AHSC, orthotopic liver transplantation can be a therapeutic option for patients with MNGIE. Compared to AHSC, a better outcome in terms of survival rate is awaited.

The changing clinical profile of celiac disease: a 15-year experience of a referral center


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Background and Aim: Celiac disease (CD) is a multiform, challenging condition characterized by extremely variable features. We aimed to report the clinical, serological and histopathological aspects of adult CD patients diagnosed in an Italian referral Center during a 15-year period.

Patients and Methods: From January 1998 to December 2012, 770 patients (599 females and 171 males, F/M ratio 3.5:1, median age at diagnosis 36 years, range 18-78 years) were diagnosed as celiacs at the CD Center of St.Orsola-Malpighi Hospital (Bologna, Italy). The following parameters at diagnosis and during the follow-up were retrospectively evaluated: gastrointestinal (GI) and extra-intestinal (EI) symptoms along with laboratory abnormalities, serological tests, duodenal mucosa findings, associated disorders, response to gluten-free diet (GFD) and complications.

Results: The onset of CD was symptomatic in the majority of patients (78.1%). About half (53.2%) of CD patients had one or more GI symptoms, including diarrhea (26.7%), aphthous stomatitis (18.3%), irritable bowel syndrome (IBS) (14.6%), constipation (12.3%) and gastro-esophageal reflux disease (GERD) (11.6%). EI symptoms and laboratory abnormalities, alone or in combination with GI manifestations, were present in 45.4% of CD patients. The most frequent findings were osteopenia/osteoporosis (52.4%), anemia (33.9%), hyper-transaminasemia (28.6%), recurrent miscarriages (12.5%), allergic manifestations (9%), headache (5%) and fibromyalgia-like symptoms (2.2%). One hundred and sixty CD patients (21.9%) were completely asymptomatic. Tissue transglutaminase antibodies (tTGA) of IgA class were positive in 744 (96.6%) out of the 770 CD pts (associated with anti endomysial antibodies-EmA - IgA in 90.9%). Of the 26 pts without tTGA and EmA IgA, 15 had IgA deficiency and were positive for tTGA or deamidated gliadin antibodies – DGP - of IgG class, whereas the remaining seronegative cases (n= 11) were classified as celiacs based on villous atrophy responding to GFD and HLA-DQ2 and/or -DQ8 positivity. Duodenal biopsy showed villous atrophy in 87.5% of CD cases (3c in 36.1%, 3b in 26.4% and 3a in 25%), whereas the remaining 12.5% pts had a histological pattern of minor lesions consistent with potential CD (confirmed by HLA-DQ2 and/or -DQ8 and tTGA and/or EmA positivity). As for associated disorders, autoimmune thyroiditis was found in 26.3%, dermatitis herpetiformis in 4%, diabetes mellitus type 1 in 2.7%, neurological disorders in 2.2%, IgA deficiency in 1.9%, autoimmune liver disorders in 1.8%, connective tissue diseases in 1.7% and chromosomal disorders in 1.6% of CD patients. The response to GFD was considered satisfying in 75.3% of CD patients, whereas the remaining 190 cases were labeled as non-responsive CD, mainly for a poor compliance to GFD, IBS, GERD, nickel allergy and food (lactose and fructose) intolerance. Only 7 (0.91%) out of the 770 CD patients developed one or more complications of CD including refractory CD (three type 1 and one type 2), enteropathy-associated T-cell lymphoma (2 cases), small bowel carcinoma (2 cases) and ulcerative jejunoileitis (1 case). Patients developing complications had a delayed CD diagnosis (median age at CD diagnosis 55 years, range 42-66 years).

Conclusions: Our experience showed that overall clinical profile of CD patients changed over time. Specifically, about half of CD patients did not complain of GI symptoms, had a wide array of EI symptoms and >10% of cases were completely asymptomatic. Seronegative CD does exist, but it is a very rare finding. Although the majority of CD patients displayed a severe duodenal damage, in >10% of CD cases there were mild intestinal lesions consistent with potential CD. There was a close link between CD and autoimmune disorders, with autoimmune thyroiditis being the most common co-morbidity. Finally, the number of CD patients with an incomplete response to GFD was not uncommon, although cases with complicated CD occurred rarely.

Functional dyspepsia: is duodenal biopsy worthwhile?

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Background: Functional dyspepsia (FD) is defined as the presence of symptoms referable to the upper gastrointestinal tract without any organic, systemic, or metabolic cause. It is extremely common in the general population. Diagnosis of FD may be obtained only by exclusion criteria which require different tests, including endoscopy, even repeated over time. In this context duodenal biopsies are frequently taken; the histological examination often reveals the presence of duodenal intraepithelial lymphocytosis (DIL), defined as an “increased number of intraepithelial lymphocytes (IEL) with a normal villous architecture”. This condition has been described with different frequencies in duodenal biopsies of subjects undergoing upper endoscopy, but its role is not known.

Aim of this study was to evaluate whether the presence of DIL in duodenal biopsies may represent an organic cause for symptoms of dyspepsia. The presence of DIL has been analysed in duodenal biopsies of two groups of subjects, one including patients with symptoms of FD, the other including normal subjects without symptoms.

Methods: Prospective case-control study conducted in the GI unit of the University of L’Aquila in a 6 months period.

The study group (FD patients) included 39 consecutive patients (31F, 8M) admitted at our unit for the presence of symptoms of FD according with Rome III criteria. These patients were compared with a control group of 17 healthy subjects without any symptom (9F, 8M) (age 18-75 years in both groups). Both FD patients and healthy controls underwent upper endoscopy with 4 biopsies in the second duodenal portion and 3 biopsies in the gastric antrum. DIL was defined as a number of CD8+ intraepithelial lymphocytes > 25 every 100 enterocytes in the presence of normal villous architecture, identified by immunohistochemistry of duodenal biopsies. Conventional histopathology by H&E was performed in both duodenal and gastric biopsies; gastric samples were examined also for H. pylori infection. Fisher’s exact test was used for the statistical analysis.

Results: DIL was present in 20.51% of FD group (8 out 39 patients) and in 29.4% of control group (5 out 17 subjects). The difference was not significant.

In the FD group, DIL was significantly associated with the presence of H. Pylori infection (p=0.02). H. Pylori was present in 28.2% (11 out 39 patients) of FD group and in 29.4% (5 out 17 patients) of control group (n.s.).
Overall, all the subjects with the contemporaneous presence of DIL and H. Pylori infection were in the FD group. In the asymptomatic group none had contemporaneous DIL and H. Pylori.

Considering dyspeptic symptoms, bloating was the most frequent (referred 20 times), followed by epigastric pain (17), post-prandial fullness (9), heart-burn (5), early satiety (5), and nausea (1). No statistical correlation was observed with the presence of DIL.

Conclusions: DIL does not represent an organic cause for symptoms of dyspepsia, as it is present in duodenal biopsies of both patients with FD and healthy asymptomatic controls with similar frequencies. Considering the patients with symptoms of FD, DIL is associated with H. Pylori infection.

Patterns of clinical presentation of adult coeliac disease in a mediterranean population according to the age of onset

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Background and aim: Classical malabsorption syndrome is uncommon in celiac disease (CD) in adults, since most patients, when compared with children, present with nonspecific symptoms, such as abdominal discomfort and bloating, constipation or dyspepsia, and with anemia. Recent studies compared the clinical presentation between elderly and younger adults, with conflicting results. Our aim was to compare clinical, serological and histological characteristics in these two age groups of adult celiacs.

Materials and methods: data were extracted from clinical records of adult-onset biopsy proven celiac patients diagnosed in two referral centers from Sicily, Italy. Age at diagnosis, clinical presentation (classical, atypical, silent, according to National Institutes of Health Consensus Criteria), serological markers, i.e. tissue transglutaminase antibodies (tTGA) and anti-endomysium antibodies (EMA), degree of mucosal damage according to Marsh-Oberhuber classification (I-II minimal lesions or absent villous atrophy; III A/IIIB partial villous atrophy or PVA; III-C total villous atrophy or TVA), were registered on a shared database. Data were analyzed by the Statistical Package for Social Science (SPSS) version 13.0 for Windows. Differences were reported as statistically significant if the p value was <0.05.

Results: A total of 211 patients consecutively seen as out- or inpatients between January 2004 and April 2013 were enrolled. 77.6% were females; mean age was 40.6±14.80 (range 18 – 80). 7.6% of patients were ≥ 65 years old. 39.3% presented classic CD (C-CD); 41.3% showed an atypical presentation (A-CD); 19.4% had silent disease (S-CD). 22.7% of patients had a previous diagnosis of autoimmune disease. Patients were divided into 2 groups according to age at diagnosis: 18-64 years (n=195) and ≥ 65 (n = 16); no significant difference were observed in the two groups when comparing clinical presentation, laboratory data, autoantibodies titres and histological damage. Silent disease was significantly associated with more severe histological damage (P<0.05), as well as of other proposed drugs such as azathioprine, leukotriene receptor antag-
onists, antihistamines, and biological agents. In our patient as in other few cases presented in literature, steroid treatment, at dosages similar to those used in inflammatory bowel disease, resulted in an impressive symptomatology and radiological improvement. Nevertheless, we cannot exclude that the steroid therapy might have represented a risk factor for the subsequent recurrence of Clostridium difficile infection.

Effects of mesenchymal stromal cells on soluble factors released by T cells of Crohn’s disease patients

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Background: Mesenchymal stromal cells (MSCs) are multipotent non-haematopoietic stem cells able to promote tissue repair and to differentiate into several cell types. Recently, they have also been found to exert potent immunological effects by acting non-selectively on almost all cells involved in the immune response, including inhibition of T-cell proliferation mediated through several soluble factors. MSCs represent, therefore, an attractive novel source for treatment of conditions associated with harmful T-cell responses such Crohn’s disease (CD), a chronic inflammatory bowel disease characterized by loss of immune tolerance against microbial antigens, such as muramyl dipeptide (MDP), a peptidoglycan constituent of the bacterial wall that seems to play a crucial role in orchestrating the inflammatory cascade that leads to intestinal injury.

AIM: We aimed to investigate the in vitro effects of MSCs on mucosal T cells in terms of cytokine profile, Human Leukocyte Antigen-G (HLA-G) production and enzyme indoleamine 2,3-dioxygenase (IDO) activity upon specific antigen stimulation.

Patients and methods: Mononuclear cells were isolated from bone marrow blood samples of 3 adult CD patients, plated and expanded ex vivo until passage 3, when the adherent population underwent morphological and immunophenotypical characterization which confirmed an almost pure population of MSCs. For the generation of T cell lines, mononuclear cells were isolated from perendoscopic colonic biopsies from both inflamed and non-inflamed areas of 6 patients suffering from CD (F/M 4/2, median age: 32 years, range 8-56) and healthy mucosa of 4 control subjects (F/M 1/3, median age: 43 years, range 27-52) who underwent endoscopy for screening, by enzyme digestion. Afterwards, they were expanded in vitro through weekly cycles of antigen stimulation by MDP (10 mg/ml; Sigma-Aldrich) and cytokine stimulation with interleukin (IL)-2 (40 U/ml; Chiron). For each experiment, parallel cultures were settled in the absence or presence of allogeneic MSCs at MSC:T ratio (1:20), as well as in the absence or presence of MDP. The effects of MSC on antigen-reactive T-cell lines were evaluated on cell-free supernatants, in terms of cytokine profile by analyzing the levels of the following molecules: transforming growth factor (TGF)-β1, interferon (IFN)-γ, interleukin (IL)-6, IL-8, IL-10, IL-17A, IL-21, together with the levels of the HLA-G, by ELISA assay (SearchLight Tima Ricerca and Biovendor, respectively). Moreover, the IDO activity was indirectly evaluated by quantifying tryptophan and kynurenine concentrations by high-performance liquid chromatography, using the SCL-10 VP pump (Shimazu). The Mann-Whitney test was applied for statistical analysis, and a value of p<0.05 was considered statistically significant.

Results: When T cell lines were cultured in the presence of MDP, a significant modification of the cytokine pattern was found in terms of a reduction of the pro-inflammatory cytokines IL-17A, IL-21 (p<0.01 for both) and the immuno-modulating IL-10 (p<0.05) in both inflamed and non-inflamed mucosa, while the IFN-γ levels decreased only in non-inflamed mucosa (p<0.05). By contrast, in both inflamed and non-inflamed mucosa, an increase of the levels of the regulatory cytokine TGF-β1 (p<0.02) and the pleiotropic molecule IL-6 (p<0.05) was detected. No modification of IL-8 production was observed. Again, in the presence of MDP, an increase of IDO activity (p<0.003) and HLA-G levels (p<0.002) were clearly evident.

Conclusions: Bone marrow-derived MSCs exert a robust immune-modulant effect in vitro on antigen-reactive pathogenic T cells isolated from CD mucosa thus paving the biological basis for a future application as new therapeutic tool in this pathological condition.

Circulating levels of soluble rage as a predictive biomarker of activity in inflammatory bowel disease

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Background: The receptor for advanced glycation end products (RAGE) is a multi-ligand trans-membrane receptor of the immunoglobulin superfamily, whose cognate interaction with several pro-inflammatory molecules, including S100 proteins, results in an increased oxidative stress and activation of nuclear factor-k-B which ultimately lead to a sustained inflammation and tissue injury. The cleavage of its extracellular domain by matrix metalloproteinases causes the release of the soluble form (sRAGE) which plays a protective role thanks to the ability to capture and block RAGE ligands. The sRAGE has recently emerged as a reliable biomarker of inflammation in a number of chronic inflammatory disorders, such as rheumatoid arthritis, diabetes mellitus, atherosclerosis, and cancer. Crohn’s disease (CD) and ulcerative colitis (UC) are chronic relapsing inflammatory bowel disease (IBD) whose pathology is not completely understood, but preliminary data have suggested a potential role of RAGE and its ligands in sustaining chronic inflammation.

Aim: We investigated the level of sRAGE in the sera of a cohort of patients suffering from IBD, and its correlations with both clinical and serological indexes of disease activity.

Patients and methods: Peripheral blood and stool samples were collected from 60 patients with CD (M/F: 29/31; median age: 41.9 years, range 16-83), 67 with UC (M/F: 44/23; median age: 44.5 years, range 17-76), and 66 sex/age matched healthy controls (HC; M/F: 27/39; median age: 45.9 years, range 15-84). Clinical activity was assessed by measuring the levels of both serum C reactive protein (CRP) and faecal calprotectin, and by calculating CD activity index (CDAI) and Simple Index (SI) scores in CD and UC patients, respectively. For CD patients, the disease behaviour was also assessed according to Vienna classification as: inflammatory (B1), strictureing (B2), and penetrating (B3). Serum levels of sRAGE and S100-A12 were determined by ELISA using the QuantiKine Human RAGE Immunoassay kit (R&D System), and the S100A12 kit (USCNK), respectively. Statistical comparisons between mean values were performed with the Mann-Whitney U test for nonparametric data. The Kruskal-Wallis test was used for multiple group comparison. Correlations were searched by applying the Spearman rank correlation test. A level of p less than 0.05 was considered statistically significant.

Results: Serum levels of sRAGE were significantly lower in UC patients as compared to CD patients (mean values: 1030.7 versus 1373.2 pg/ml, respectively, p<0.03) and HC (mean values: 1030.7 versus 1346.9 pg/ml, respectively, p<0.01). By contrast, no clear difference between CD and HC was found. As regards the CD group, patients with a penetrating behaviour


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(B3) showed a significant decrease in sRAGE levels in comparison to those carrying an inflammatory and/or stricturing behaviour (B1/B2) (mean values: 1005.4 versus 1557.0 pg/ml, respectively, p=0.006). Moreover, a significant inverse correlation between the values of circulating CRP and sRAGE in CD patients (p=0.02, r=0.30) was found, but not in UC patients. Otherwise, in the UC group, sRAGE levels inversely correlated with those of faecal calprotectin (p=0.02, r=0.48). Finally, no correlation between sRAGE and activity disease indexes was observed in both patient groups.

**Conclusions:** Our study shows that serum levels of sRAGE displays a different pattern in patients with CD and UC, thus suggesting a different kind of involvement of RAGE in the pathogenesis of these diseases. These data also support a potential use of sRAGE dosage as an additional non-invasive laboratory marker in the diagnosis and monitoring of IBD patients.

A case of cachexia associated with vomiting: the afferent loop syndrome

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**Introduction:** A 68 years-old man suffering from cachexia and hypokinet-
ic syndrome is admitted after an accidental fall while he was sitting, with a radiological report of fracture of the posterior arch of the right XII rib. His medical history includes a Billroth II gastrectomy for a perforated ulcer about 40 years ago; hyporexia for nausea, lack of appetite, dyspepsia, a progressive decline of his general condition, weakness and a gradual reduc-
tion of gait up to his current hypokinetic syndrome have all been reported for the last two years. Moreover, 5 months ago he was diagnosed with colitis- 
itis and a giant post-anastomotic ulcer complicated by vomiting and cachex-
ia. On physical examination the patient presents with poor general condition, anelastic skin, diffuse muscular hypotrophy and weakness in the four limbs, especially the lower ones; cardiac, pulmonary and abdominal exams are all within normal range, as well as his vital signs (ABP 100/60 mmHg, HR 70 bpm). During the first days of hospital stay, the patient shows frequent episodes of post-prandial nausea and vomiting. Therefore, based on the labor-
atoristic exams, which show hypoproteinemia (protein level 5.1 g/dl), with severe hypoalbuminemia (albumin level 1661 mg/dl) and hypo-
oseridemia (29 mcg/dl), enteral nutrition support is started. The patient un-
dergoes an esophagogastroduodenoscopy (EGD), which turns out to be in-
conclusive, because both the esophagus and the gastric pouch are covered in food residues, and both the afferent and the efferent loops are consider-
ably ectatic and coated with food residues as well. Based on the endoscop-
ic report of possible intestinal subocclusion, an abdominal X-ray is per-
formed, which rules out this possibility. Therefore, considering his clinical status and his history of gastrectomy, the patient undergoes an enhanced ab-
dominal CT in order to evaluate possible abdominal neoplasms, which, how-
ever, does not show any mass in the gastric pouch and in the jejunal loops. Due to a progressive severe anemia (HB 7.7 g/dl), the patient is he-
motransfused with two IU of concentrated erythrocytes. A new esopha-
gastroduodenoscopy is performed, which shows multiple ulcers in the efferent loop, while the afferent loop cannot be viewed due to a considerable amount of kinking. Therefore, in order to evaluate the anastomotic function and to point out possible post-surgical stenoses, a Gastrofin-enhanced ab-
dominal X-ray is performed: it shows a dilation of both the gastric pouch and the afferent loop (the afferent loop syndrome). The patient is then trans-
ferred to the surgical ward for further treatment.

**Discussion:** The afferent loop syndrome (ALS) is a clinical condition which can occur as a complication in patients who previously underwent Billroth II gastrectomy. There are two types of ALS: the most common one is caused by bacterial proliferation in the afferent loop due to stasis; the patients may refer post-prandial abdominal pain, distention and diarrhea with concurrent fatty acids and vitamin B12 malabsorption. Cases not responding to antibi-
otics may require surgical treatment. The second type of ALS, which is less common, presents with abdominal pain and distention, which appears within in 20 to 60 minutes after eating; the pain is often followed by nausea and bil-
ious vomiting. Both the pain and the distention improve after emesis. The cause is the incomplete bile and pancreatic juice drainage from the partial-
ly obstructed afferent loop. Cases not responding to dietary measures may require surgical treatment.

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Higher number of enterochromaffin cells in refractory coeliac disease

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**Background & Aim:** In the gut serotonin-producing enterochromaffin (EC) cells are the prevalent neuroendocrine cell type, almost of all of which are characterised by the expression of the pan-neuroendocrine marker chromo-
granin A (CgA). Several immune-mediated gastrointestinal disorders, in-
cluding coeliac disease (CD), are associated with EC cell hyperplasia. However, neither number nor function of EC cells have been ever explored in refractory CD type 1 (RCD1) and type 2 (RCD2).

**Materials & Methods:** Seriate duodenal sections from 17 refractory CD pa-
tients (6 RCD1, 11 RCD2), 16 uncomplicated CD patients before and after gluten-free diet (GFD), and 16 control subjects (CS) were processed for the immunohistochemical detection of neuroendocrine markers CgA, serotonin and somatostatin. Mucosal tryptophan hydroxylase (Tph)-1 and serotonin-
selective reuptake transporter (SERT) transcripts were measured by quanti-
tative RT-PCR. Serum CgA and 24-h urine 5-hydroxyindoleacetic acid (5-
HIAA) were also measured. Uncomplicated treated CD biopsies were cul-
tured with serotonin or peptic tryptic digest of gliadin (PT-gliadin), and in-
terferon (IFN-γ) was detected by ELISA in culture supernatants.

**Results:** Both CgA-positive cells and EC cells, counted per 100 crypt cells, were significantly increased in RCD1 and RCD2 patients compared to un-
complicated CD patients before and after GFD and CS, with no difference be-
tween RCD1 and RCD2, whereas no change was found for somatostatin-pos-
itive cells amongst all groups. Raised transcripts of mucosal Tph-1, but not SERT, were found in RCD1 and RCD2 patients. Serotonin up-regulated the ex vivo production of IFN-γ at levels comparable to those of PT-gliadin. Serum CgA, but not urine 5-HIAA, was increased in RCD1 and RCD2 patients.

**Conclusions:** EC cells are increased in refractory CD mucosa. The up-regu-
lation of IFN-γ induced ex vivo by serotonin suggests that this monosamine may have a role in sustaining the local inflammatory response in CD.

Immune and fibrogenic mechanisms in the peridiverticular mucosa of patients with diverticular disease

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Background & Aims: Increased mucosal expression of pro-fibrogenic mediators such as collagen has been reported in diverticulitis and, to a lesser extent, in diverticulosis. While tumor necrosis factor (TNF-α) is overexpressed in diverticulitis, no information exists on other innate and adaptive pro-inflammatory cytokines in diverticulitis and diverticulosis. We therefore investigated the mucosal immunologic changes and the pro-fibrogenic response occurring next to inflamed diverticula.

Methods: Intestinal biopsies were collected from peridiverticular areas of 15 patients with diverticulitis and 15 with diverticulosis, from inflamed areas of 14 inflammatory bowel disease (IBD) patients, from strictured areas of 10 Crohn’s disease (CD) patients and from normal mucosa of 15 control subjects. After isolation, lamina propria mononuclear cells (LPMCs) were stimulated with pokeweed mitogen (PWM) or with anti-CD3/CD28 antibodies, whereas myofibroblasts were cultured with medium alone. Interleukin (IL)-1β, IL-6, IL-12, TNF-α, IL-17A, interferon (IFN)-γ and collagen were measured in culture supernatants. Mucosal transforming growth factor (TGF)-β1 transcripts were measured by quantitative RT-PCR and immunohistochemistry for smooth muscle actin (SMA) was performed on biopsy sections.

Results: PWM- and anti-CD3/CD28-stimulated LPMCs from diverticulitis and IBD patients produced significantly higher concentrations of IL-1β, IL-6, IL-12 and TNF-α, and IFN-γ and IL-17A, respectively, than uninfamed diverticula and control mucosa, with no difference between control and diverticular patients. Myofibroblasts from diverticulitis and strictured CD patients released significantly higher amounts of collagen than diverticulosis patients and controls. Raised transcripts of mucosal TGF-β1 were found in diverticulitis and strictured CD patients. SMA was overexpressed in the mucosa of diverticulitis compared to diverticulosis patients and controls.

Conclusions: Mucosa from diverticular inflamed areas is characterized by a marked pro-inflammatory immune activation and by an enhanced pro-fibrogenic response. The abnormal innate and adaptive immune response observed in diverticulitis is likely to amplify the aberrant process of fibrogenesis intrinsically associated to diverticulum formation.

Colonic bacterial fermentation and meal gluten content in healthy volunteers: preliminary data

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Background and aim: The existence of a heterogenous disorder called Non Celiac Gluten Sensitivity (NCGS) was recently proposed. The pathophysiology of this condition is unknown and many hypotheses were drawn. In healthy volunteers, an increase of colonic fermentation after complex carbohydrate ingestion was already shown many years ago; in particular, increased fermentation after gluten-containing products and absence of fermentation after both gluten-free products and gluten-free products to which gluten powder had been added was demonstrated. It was hypothesized that native gluten could cause an incomplete absorption of wheat starch. In healthy volunteers, it may be absent on waking and severe at the end of the day. The pathophysiology of bloating associated with functional gastrointestinal disorders has not yet been entirely clarified. Many mechanisms may have a role: besides alterations of muscular activity of the abdominal wall and diaphragm, visceral sensitivity, and intestinal gas production, alterations of gas handling at both small and large bowel level have been described. However, the phasic activity of the small and large bowel were studied: the role of intestinal tone is largely unknown. Patients with bloating may present a different clinical expression; for example, bloating may be related or not to food ingestion, it may be absent on waking and severe at the end of the day. Moreover, the presence of bloating is not associated with the visible distension of the abdomen. All these clinical differences indicate differences in the pathophysiology of the symptom. Accordingly, our aim was to verify the role of colonic activity in the onset of postprandial bloating in IBS patients.

Patients and Methods: A group of 11 healthy volunteers (9 female, mean age 27 ys, range 22-54) was enrolled. In a double-blind, crossover protocol, breath hydrogen and methane excretion were monitored (sampling every 15 min for 7 hours) after oral administration of three different meals, at least one week apart: (a) 95 g gluten-containing “pasta alla carbonara” (Antaars, PV, Italy) (63.5 g carbohydrates, 12.0 g protein, 5.9 g lipid); (b) 95 g gluten-free pasta (Antsares, PV, Italy) (66 g carbohydrates, 11.6 g protein, 5.1 g lipid); (c) 95 g gluten-free “pasta alla carbonara” and 7 g of gluten powder. The different content between the meals was offset by adding wheat starch, olive oil and albumin powder as needed. A questionnaire to check for gluten content recognition was administered. At the same intervals as breath sampling, patients filled in a visuo-analogic scale questionnaire to evaluate the presence and severity of heartburn, regurgitation, nausea, headache, belching, abdominal pain, abdominal distention, bloating, flatulence, and borborygmi.

Results: Seven out of 12 patients (58%) correctly recognized the gluten-free and gluten-containing meals. All patients proved to be breath hydrogen excretors, and 5 also excreted methane. Hydrogen peak (8±5 ppm vs 14±7 ppm, p=0.001) and cumulative breath hydrogen excretion (1122±682 ppm x min vs 2717±1736 ppm x min, p=0.02) were significantly lower after the gluten-free than after the gluten-containing meal. When gluten powder was added to gluten-free pasta, the results overlapped those obtained after the gluten-free meal. Meal ingestion did not modify breath methane excretion. Oro-cecal transit time was longer after the gluten-free than after the gluten-containing meal (389±58 vs 336±98 min). The occurrence of symptoms and their severity was negligible and not different among the three tests.

Conclusions: Gluten-containing foods may cause an increased intestinal fermentation. An increased fermentation of the gluten-wheat protein complex may explain these results. These mechanisms could be involved in the pathophysiology of the meteoric syndrome attributed to non-celiac gluten sensitivity.

In irritable bowel syndrome, postprandial bloating is associated with a reduction of postprandial colonic tone

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Background and aim: In irritable bowel syndrome (IBS) the prevalence of bloating is very high, even if its presence is not a key feature of the disease. The pathophysiology of bloating associated with functional gastrointestinal disorders has not yet been entirely clarified. Many mechanisms may have a role: besides alterations of muscular activity of the abdominal wall and diaphragm, visceral sensitivity, and intestinal gas production, alterations of gas handling at both small and large bowel level have been described. However, only the phasic activity of the small and large bowel were studied: the role of intestinal tone is largely unknown. Patients with bloating may present a different clinical expression; for example, bloating may be related or not to food ingestion, it may be absent on waking and severe at the end of the day. Moreover, the presence of bloating is not associated with the visible distension of the abdomen. All these clinical differences indicate differences in the pathophysiology of the symptom. Accordingly, our aim was to verify the role of colonic activity in the onset of postprandial bloating in IBS patients.

Methods: A group of 32 patients with IBS (mean age 38.4 years, range 21-60, IBS-C=16; IBS-D=4; IBS-M=12) diagnosed according to Rome III criteria and severe bloating were enrolled in order to consecutively select 16 patients with postprandial bloating and 16 patients with meal-unrelated symptoms. In all subjects, the recto-sigmoid barostat test was performed. After an overnight fast, a double lumen polyvinyl tube with an adherent, infinitely compliant plastic balloon was positioned at the recto-sigmoid junction and, at constant preselected pressure, recto-sigmoid volume was monitored during a 30-min fasting period and a 60-min period after meal con-
sumption (200 Kcal, 200 ml liquid meal). Every ten minutes, both during fasting and the postprandial period, the presence and severity of abdominal symptoms (abdominal pain, fullness, bloating, nausea) were measured by VAL.

Results: In postprandial bloaters, but not in the other group of IBS patients, meal intake induced an increase of recto-sigmoid volume, indicating a reduction of muscular tone. In particular, postprandial rectosigmoid volume modification was 4.69% to 30.86% (25°-75° percentile) in postprandial bloaters and -24.56 to 8.29% (25°-75° percentile) in the subgroup with non-meal-related bloating. Moreover, the severity of bloating paralleled colonic tone modifications.

Conclusions: In the subgroup of IBS patients with meal-related bloating, a reduction of colonic tone in the postprandial period may represent an important pathophysiological mechanism. This alteration should be kept in mind in the treatment of these patients.

**Background and Aims:** Celiac disease (CD) is frequently associated with bone mass and mineral metabolism alterations, often persisting despite a strict adherence to long term GFD. The incidence of fractures in CD is an incompletely clarified issue, as several studies reported an increased prevalence of fractures, but often at different skeletal sites. The FRAX score is a validated tool to estimate the risk of fracture in the general population. We therefore calculated the FRAX score in a group of celiac patients and calculated its correlation with indices of bone and mineral metabolism.

**Patients and Methods:** Thirty-six asymptomatic CD female patients (range 18-43 yrs) with a long history of GFD (> 8 yrs) were enrolled. Diagnosis was made in adult life, and no patient was in the menopausal or perimenopausal period. All patients showed strict adherence to GFD, according to a validated questionnaire. Lumbar and femoral BMD was measured by DEXA. Circulating serum levels of calcium, phosphate, parathyroid hormone, osteoprotegerin, RANKL, 1,25 OH 2vitamin D, 25 OH vitamin D, interleukin-1, interleukin-6, and TNF-alfa were evaluated. The OPG/RANKL ratio was also computed, as a marker of bone turnover. The FRAX score, a web-based clinical scale assessing the 10-year fracture risk, was evaluated according to http://www.shef.ac.uk/FRAX/.

**Results:** Thirty-five patients, the FRAX score indicated a low risk of fracture at 10 yrs and only one patient showed a moderate risk. All patients showed strict adherence to GFD, according to a validated questionnaire. Lumbar and femoral BMD was measured by DEXA. Circulating serum levels of calcium, phosphate, parathyroid hormone, osteoprotegerin, RANKL, 1,25 OH 2vitamin D, 25 OH vitamin D, interleukin-1, interleukin-6, and TNF-alfa were evaluated. The OPG/RANKL ratio was also computed, as a marker of bone turnover. The FRAX score, a web-based clinical scale assessing the 10-year fracture risk, was evaluated according to http://www.shef.ac.uk/FRAX/.

**Results:** In thirty-five patients, the FRAX score indicated a low risk of fracture at 10 yrs and only one patient showed a moderate risk. Eleven out of 36 patients showed a pathological reduction of the femoral T-score. The FRAX score was not correlated to lumbar BMD (r=0.30; p=NS), to OPG/RANKL ratio (r=0.58, p<0.001) or to serum TNFalfa levels (r=0.43, p<0.01).

**Conclusions:** The significant correlation between OPG/RANKL ratio and FRAX score could suggest its use as a biomarker of fracture risk in treated patients with celiac disease.

**Diarrhea: the tomb of the gastroenterologist**


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A 66-year-old woman was admitted to the Emergency Department of the St.Orsola-Malpighi Hospital because of vomiting and diarrhea lasting a few days. Physical examination of the abdomen was unremarkable (just slight abdominal tenderness at palpation). The X-Ray showed many air-fluid levels and significant meteorism. The patient was discharged with a generic diagnosis of “diarrhea-predominant irritable bowel syndrome” likely of post-infectious origin (the patient had a recent gastroenteritis episode probably of viral origin). She was prescribed PPI and probiotics. While at home, she had a new exacerbation of abdominal pain and because of this symptom associated to asthenia she returned to Emergency Department 5 days later. The patient was then admitted to our Unit. Her...
medical history included a previous appendectomy and tonsillectomy in young age, and (five years before this admission) a radical thyroidectomy preceded by neoadjuvant radiotherapy for a papilliferous carcinoma. She also had (two years before) a screening colonoscopy showing only colonic diverticulosis. Physical examination of the abdomen and the cardio-respiratory systems were unremarkable. Laboratory tests showed a slightly leukocytosis (WBC: 13,000/mmc, neutrophils 83%) and a mild increase of inflammatory indexes (PCR 2.62 g/dL, n.v. <0.80). Microbiological tests on fecal samples were repeatedly negative for bacterial, parasitological, mycotic infection, and C. difficile toxin-A. Compared to the previous exam, a new abdominal X-Ray was unchanged. An abdominal-US demonstrated only a few cysts on the left kidney. The patient was reassessed endoscopically with a gastroscopy (hiatal hernia and a chronic H. pylori-ve gastritis) and colonoscopy confirming a diffuse diverticulosis. The patient improved and was discharged with a treatment to be continued at home. However, due to sudden worsening of the clinical picture, she came back 6 days later for the appearance of a sub-occlusive episode (i.e., nausea, vomiting and severe obstipation for 3 days). Another X-Ray of the abdomen showed an important increase of meteorism and signs of bowel stretching, although an intestinal pull-through study with a water-soluble contrast substance (gastrographin®) demonstrated a patent small bowel with the contrast progressing from the ileocecal valve to the jejunum. The patient improved and was discharged with a treatment to be continued at home. However, due to sudden worsening of the clinical picture, she came back 6 days later for the appearance of a sub-occlusive episode (i.e., nausea, vomiting and severe obstipation for 3 days). Another X-Ray of the abdomen showed an important increase of meteorism and signs of bowel stretching, although an intestinal pull-through study with a water-soluble contrast substance (gastrographin®) demonstrated a patent small bowel with the contrast progressing from the upper to the lower gut. A transabdominal-US showed a pathological thickening of last ileal tract (6-8 cm). Finally, an abdominal CT with enteric reconstructions revealed a lesion situated 6 cm above the ileocecal valve associated with local lymph node abnormalities. Based on the clinical and radiological features, the patient was referred to surgery and underwent a right hemicolectomy with omentectomy, lymphoadenectomy (19 lymph nodes were removed) followed by ileo-colic anastomosis. The histological examination showed a moderately differentiated adenocarcinoma of the ileum (grade 2 WHO classification) with a pT4N1Ms,V1L1 stage. For this reason patient started an adjuvant FOLFOX chemotherapy for 6 month. This case was intriguing because brought up the differential diagnosis of functional vs organic intestinal sub-occlusion which still represents a challenge for the physicians. Moreover, this case was even more unusual as the tumor raised in a non-celiac patient. Overall, small-bowel tumors are rare, particularly adenocarcinoma. Its prognosis is poor and the lack of published data does not help its clinical management and follow-up. Thus a timely identification is needed to allow for early diagnosis and surgery.

The strange case of joint pain and erythematous nodules

Fabbri Dario, Zannetti Beatrice, Cevenini Monica, Casadei Beatrice, De Giorgio Roberto, Tomassetti Paola, Corinaldesi Roberto

Ospedale S. Orsola – Malpighi, Bologna

Case Report: A 70-year-old man was admitted to our Internal Medicine Unit in April 2013 for the onset of symmetric joint pain. He was a habitual alcohol drinker and a smoker. On admission, clinical examination revealed multiple cutaneous erythematous nodules (1-5 cm in size) localized to the lower extremities and gluteal region, with some of them evolving into necrotic abscesses, spontaneously ulcerating and exuding ‘fatty material’. Physical examination of the abdomen and the cardio-respiratory systems were unremarkable and vitals signs were normal. Laboratory tests showed a remarkable leukocytosis (WBC: 18,000/mmc, neutrophils 91%) and a prominent increase of inflammatory indexes (PCR 17.3 g/dL, n.v. <0.80). An autoimmune profile (ANA, ENA, anti-DNA, rheumatoid factor, anti-CCP, ANCA, C3 and C4, streptozyme test) and oncomarkers were all negative. He complained of severe pain involving bilateral ankles, knees, shoulders and elbows joints not associated with bone changes at the X-Ray evaluation. The arthrocentesis showed a yellowish synovial fluid, which turned negative for bacteria or other infections thus excluding a septic arthritis.

Systemic and local (infiltration) steroid therapy resulted in a modest improvement of pain. A few days later, the patient experienced an acute abdominal pain with a prominent localization to the mesogastrium. Serum amylase and lipase levels were ten (i.e.: 1037 U/L, n.v. <100) and sixty (3621 U/L, n.v. <60) times over normal value, respectively, thus indicating an acute pancreatitis. An abdominal CT showed a roundish formation of 55 mm in diameter in the head of the pancreas with necrosis and colliquation. This finding was associated with dilatation of the main pancreatic duct and thrombosis of the superior mesenteric vein. The pancreatic lesion was biopsied during an endoscopic ultrasonography (EUS) and the histopathological examination documented a chronic obstructive pancreatitis. Thus, we concluded that the patient had an acute pancreatitis developed on a chronic disease and complicated by a bulky pseudocyst. Meanwhile, the histopathological analysis of the erythematous nodules showed evidence of necrotic areas containing “ghost-like” fat cells, a typical feature of pancreatic enzyme-related panniculitis. Due to the poor response to the medical treatment (steroids) and the risk of a neoplastic component in the pancreatic lesion, the patient was referred to surgery. The laparotomic examination disclosed a chronic pancreatitis with acute exacerbations and a massive post-necrotic pseudocyst connected to the main pancreatic duct. An intraoperative US and histopathology confirmed the existence of a chronic obstructive pancreatitis. The procedure consisted of thorough drainage of pseudocyst content (mainly necrotic tissue) followed by a manual latero-lateral Wirsung-pseudocyst-jejunal anastomosis.

Discussion: Acute pancreatitis can be complicated by extrapancreatic tissue involvement, including the occurrence of panniculitis and arthritis: this triad is referred to as “pancreatitis, panniculitis, polyarthritics” (PPP) syndrome. In this very rare cases, the diagnosis of pancreatitis can be delayed because of the presence of mild abdominal pain and the predominance of cutaneous and articular manifestations. In the literature only 30 cases of PPP syndrome have been so far reported. The pathogenesis of this syndrome is still unclear, although it is widley accepted that pancreatic enzymes, released into systemic circulation, may lead to lipolysis and secondary inflammation in peripheral tissues, like subcutaneous tissues and joints. Pancreatic disease is, most frequently, an acute pancreatitis, although an association with chronic pancreatitis may occur as shown by this case. The treatment of PPP syndrome is aimed to resolve the pancreatic disese and that is why we referred our patient to surgery. In addition supportive measures are important and include fluid/electrolyte replacement, adequate pain control and, if necessary, nutritional support. Steroids and NSAIDs with can only alleviate symptoms related to skin lesions and arthritis. The experience emerged by this case suggests that a fast diagnosis and management of pancreatic disease is crucial to improve patient’s outcome.

An uncommon diarrhea

M. Ferrata, M.A. Baticchio, F. Murer, C. Martini

Scuola di Medicina Interna Università di Padova

Case description: A 65 years old Caucasian Italian male presented to our internal medicine department complaining diarrhea for 10-12 days and weight loss. The patient described the diarrhea as approximately 5-6 loose bowel movements per day of watery diarrhea, not associated with abdominal pain or cramping, nausea, fever, night stool and blood in stool. From the medical history, it emerged that the patient had a 12 kg weight loss in the last year (actual weight 48 kg) and polyarthralgia and fatigue in the same period.

Previous medical history included Helicobacter P. eradication therapy for a type B chronic gastritis. Surgical history included endoscopic resection of 2 colonic adenomas 4 years before. He reported to smoke 10 cigarette per day and to drink 1 glass of wine per day. Family history was non contribu-
tery. The patient denied any sick contacts or change in his diet. He reported no personal history of allergic disorders. The patient had not recently taken any antibiotics and his maintenance medications included Lometazepam, Amodlipine, Allopurinol, Rabeprazol, Cardioaspirin, Paracetamolo, Dutasteride, Silodisina, Furosemid.

Clinical examination revealed underweight (BMI 16.6), muscle hypotrophy, pale dehydrated skin, mild peripheral edema. Abdominal exam was unremarkable except for colonic mass on the right side and mild hepatomegaly. Routine chest x-ray was unremarkable with ECG showing only a right bundle branch block.

Laboratory findings demonstrated hypokaliemia (K 2.7 mmol/L, Mg 0.61 mmol/L, Na 134 mmol/L) and microcytic anemia (Hb 93 g/L, Iron 3.1 umol/L). White blood cell (WBC) count was 17.160 x 10^9/L and an eosinophil count 19.2%. SPEP revealed light increased light chain and IgA, hypoalbuminemia (26 g/L) while other serum immunoglobulins (included IgE) were normal. There was evidence of inflammation (ESR 67 mm/h, CPR 136 mg/L) and increased cholesterol parameters (GTT 351 U/L, ALP 294 U/L).

Because of the microcytic anemia associated with weight loss and polyarthralgia, a celiac disease screening (transglutaminase Ab) and an autoimmune assay (RF, ANA, ENA, ANCA Ab) were tested, resulting all negative. Thymus function was within the normal range. Mild increased gastrin (77 pmol/l) CgA after one week PPI withdraw (400 ug/l) and glucagon (172 ng/l) were found. In the normal range VIP, ACTH and cortisol (at 8.00 AM)

Stools studies were negative for fecal occult blood, C. difficile toxin, Widal-Wright test, Noro-Rotavirus, ova and parasites. Moderate WBC were present. Stool examination detected few vegetable fiber; with positive fecal calprotectin test (>1000 ug/g) as marker of bowel inflammatory level (IBD). Because of the past history of colonic adenomas, the calprotectin level suggesting inflammatory bowel disease (IBD), the detection of WBC in stools as well as the associated eosinophilia with the possibility of detecting eosinophil infiltration in the whole GI tract in eosinophilic gastroenteritis (EG), endoscopic examinations with random biopsies were planned. Colonoscopy examination was normal except for 3 colonic adenoma. EGD showed a healing middle esophageal ulcer and pale antro-pyloric mucosa. All collected biopsies were sent to pathologist. Active Crohn’s or Ulcerative colitis disease were excluded.

Histopathology remains the gold standard for eosinophilic gastroenteritis (EG) diagnosis, imaging investigations may help in early detection of this rare disease. MR enterography detected right colon thickened wall with early mucosal enhancement, thick gastric body and fundus without pathological contrast enhancement. Thicken gastric wall is a common find in EG. Meanwhile the Pathologist sent the histological findings: EGD: normal duodenal mucosa, gastric mucosa (pyloric antrum and transitional area) sight of lympho-monocyte inflammation in the lamina propria. Esophageal mucosa shows basal cells hyperplasia, parakeratosis and squamous epithelium. No HP like microorganism. No biotic detection of T. Whipplei-DNA. Colonoscopy: low-grade-dysplasia tubular adenomas. Intraepithelial CD 3+ lymphocytosis associated with primitive villous atrophy at ileum. The microscopic finding in colonic mucosa is diagnostic for microscopic colitis (MC) macroscopic normal colonic mucosa with intraepithelial lymphocytosis. MC explains the chronic watery diarrhea and weight loss. MC has never been associated with eosinophilia and most of all with pol iartralgia. MC is an IBD subtype and is often seen in 60–80yr old patients, does not present with fever, vomiting or hematochezia (in contrast to other IBD).

Studies on MC therapy: have proved Budesonide to be most effective so Budesonide was prescribed, well tolerated, with diarrhea regression and weight gain (2 kg). Under Budesonide therapy the patient reported an uncommon regression of polyarthralgia. The eosinophilia itself was properly investigated revealing to be a primitive eosinophilia. (Hematologic follow up was planned). The thick gastric wall is being controlled over time.

**Culture based triple therapy using levofloxacin or rifabutin in patients who fail initial therapy**

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**Background** Eradication of h pylori is extremely difficult when resistant strains are present. Aim To evaluate the success rate of targeted therapy directed by antimicrobial susceptibility testing in patients infected with resistant strains of H pylori.

**Methods**: Design: Single centre, prospective study. Patients: consecutive cases with H pylori infection persistent despite 1 or more treatment attempts in which bacterial culture documented resistance to at least one anti-microbial agent.

**Intervention**: Therapy with either a 10-day levofloxacin-triple (250 mg twice daily) or a 12-day rifabutin-triple (150 mg once daily), in addition to amoxicillin (1 g twice daily) and esomeprazole (40 mg twice daily).

**Outcome**: Eradication success was determined by 13C-urea breath test 6-8 weeks after therapy. Compliance and tolerance: Compliance and side-effects were determined by using a personal interview at the end of therapy. Rifabutin toxicity was monitored by blood counts.

**Results** A total of 290 patients were enrolled; 149 were levofloxacin susceptible and 141 had levofloxacin resistance. H pylori infection was cured in 128 (86%; 95% CI= 0.79 to 0.90; P< 0.0001) out of the 149 patients following levofloxacin triple therapy and 129 (91.5%; 95% CI= 0.85 to 0.95; P= 0.0565) out of the 141 patients with rifabutin triple regimen. In both groups, the cure rate did not significantly differ between patients infected with H pylori strains resistant to single or multiple antibiotics. Mild side-effects occurred in 15.5% and 14.9% of patients, respectively, and self-limiting neutropenia was observed in 1 (0.7%) case.

**Conclusions**: A culture-based triple therapy with either levofloxacin or low-dose rifabutin is highly effective in curing infection in patients with resistant strains to H pylori.

**Table 1. Clinical and demographic characteristics of the enrolled patients.**

<table>
<thead>
<tr>
<th>Mean age ± SD</th>
<th>Levofoxacin-amoxicillin therapy (N = 149)</th>
<th>Rifabutin-amoxicillin therapy (N = 141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>55±14</td>
<td>52±13,41</td>
<td></td>
</tr>
<tr>
<td>Male/Female</td>
<td>48/101</td>
<td>46/95</td>
</tr>
<tr>
<td>Smokers/Non smokers</td>
<td>28/121</td>
<td>30/111</td>
</tr>
<tr>
<td>Peptic ulcer/Non ulcer dyspepsia</td>
<td>2/147</td>
<td>4/137</td>
</tr>
<tr>
<td>Previous therapy failure</td>
<td>1 attempt</td>
<td>35</td>
</tr>
<tr>
<td>- 2 or &gt; more than two attempts</td>
<td>53</td>
<td>106</td>
</tr>
</tbody>
</table>

**Effect of the supplementation of a high-dose amoxicillin based triple therapy with fructooligosaccharides laocotterin and bacillus coagulans in patients undergoing H. pylori eradication**

**Franceschi Francesco**, **Tortora Annalisa**, **Di Rienzo Teresa**, **D’Angelo Giovanna**, **Giuseppe Zuccalà**, **Gasbarrini Giovanni**, **Gasbarrini Antonio**
Background: We have previously demonstrated that increasing the dosage of amoxicillin results in an increased performance of a standard first-line H. pylori eradicating triple therapy. Whether the supplementation of a high-dose amoxicillin eradicating regimen with a mix of fructooligosaccharides, lactoferrin and Bacillus coagulans may increase the eradication rate or reduce antibiotic-related side effects has never been studied.

AIM: To compare the efficacy and the occurrence of side effects of a standard first line triple therapy with a high-dose amoxicillin based therapy with or without a mix of fructooligosaccharides, lactoferrin and Bacillus coagulans.

Methods: 90 sex and age matched patients were randomized into 3 different therapeutic schemes (30 patients each): (1) standard LCA, lansoprazole 15 mg bid, clarithromycin 500 mg bid and amoxicillin 1000 mg bid for 7 days; (2) high dose LCA (HD-LCA), lansoprazole 15 mg bid, clarithromycin 500 mg bid and amoxicillin 1000 mg tid for 7 days; (3) high dose LCA plus a mix of fructooligosaccharides, lactoferrin and Bacillus coagulans for 7 days (HD-LCA-mix). Eradication was confirmed by 13C-Urea breath test. Occurrence of adverse effects was assessed by a validated questionnaire.

Results: Eradication rates were: LCA (53% PP; 50% ITT), HD-LCA (73% PP; 70% ITT), HD-LCA+mix (73% PP; 70% ITT). Eradication rates were significantly higher in HD-LCA and HD-LCA+mix group compared to LCA (p<0.01), while no significant differences were observed between HD-LCA and HD-LCA+mix group. Diarrhoea, dysgeusia, headache and nausea were the most common side effects recorded by patients. Adding a mix of fructooligosaccharides, lactoferrin and Bacillus coagulants to a HD-LCA therapy resulted in a reduced occurrence of diarrhea (9 of 30 vs 2 of 30; p=0.019), and nausea (8 of 30 vs 2 of 30; p=0.038).

Conclusions: High dose amoxicillin based eradicating treatment is superior to standard triple therapy. The supplementation with a mix of fructooligosaccharides, lactoferrin and Bacillus coagulants do not increase the eradication rate but significantly improves some antibiotic-related side effects.

Clinical importance of gastro esophageal reflux in patients with systemic sclerosis


S.O. C. Internal Medicine - AZ. OSP. Pugliese-Ciaccio – Catanzaro

Background: Systemic Sclerosis is an autoimmune rheumatic disease that is characterized by excessive collagen production resulting in skin and visceral fibrosis of various organs, such as the gastrointestinal tract. Reflux symptoms were defined as the presence of heartburn and regurgitation. Heartburn was subjectively assessed as pain behind the breastbone, and regurgitation was assessed as acid taste in mouth.

Objectives: to evaluate the impact of gastro esophageal reflux (GER) in a consecutive and non selected series of patients with Sclerosis Systemic and its clinical relevance with other manifestations of the disease.

Patients and Methods: a total of 142 (122Women-20Men) unselected consecutive pts with SSc were included in our study. They had mean age 51.2 years (range 13-84), disease duration 12.2 years±7.5 (range 1-24). All met the preliminary American College of Rheumatology classification criteria for SSc. And according skin cutaneous subsets: 16 pts (11.3%) with Early Sclerosis, 12 pts (8.4%) with intermediate cutaneous SSc, 72 pts (50.7%) with Limited cutaneous SSc, 42 pts (29.6%) with diffuse cutaneous SSc.

Laboratory findings, demographics, symptoms, and signs were collected from all patients. GER was diagnosed as mild heartburn or regurgitation ≥2 days/week, or moderate/severe heartburn or regurgitation ≥1/day a week. As expected all pts suffer from Raynaud’s phenomenon and nailfold videocapillaroscopy (NVC) was performed on all patients, and skin sclerosis was measured with Rodnan Skin Score (mRSS). All the patients with GER received an upper endoscopy or a double-contrast barium swallow.

Results: the prevalence of GER was 43,6% (62/142 patients). Among the 62 patients, by endoscopic examination, 57 were diagnosed with reflux esophagitis, the other five endoscopic negative patients were considered to have non erosive reflux disease. By HRCT of the chest only 15 patients (24,1%) had reflux in the upper esophagus and two patients had limited thickening of the esophageal wall. There was no significant difference in age, gender or disease duration between patients with GER (Group A) and without GER (Group B). Comparing 62 pts with GER (group A) vs. 80 pts without GER (Group B) we revealed: systemic blood pressure144.8±20.1 mmHg (A) vs. 143.3±20.4 (B) pNS; Body mass index 23.4±2.6 (A) vs 25.2±3.3 (B) p<0.32; SCL-70 70 pts (A) vs pts 8 (B) p<0.01; total cholesterol 213±28 mg/dl (A) vs 190±30 (B) <p0.32; LDL Cholesterol 130±30 (A) vs 129±31 (B) pNS; HDL cholesterol 39±14 (A) vs 43±15 (B) p<0.32; Raynaud’s phenomenon in 60 pts (96.7%) (Group A) vs 72 pts (90%) (Group B) p<0.045, Fingerpit Ulcers in 34 pts (54,8%)A vs 40 pts (50%) (B) <P 0.027, Rodnan Skin Score 22.3±5.3 (A) vs 9.6±2.5 (B) p<0.32. Comparing the 62 pts with GER, the nail fold capillaroscopic analysis revealed: 8 pts with capillaroscopic score <1 and mRSS 22.3±5.3; 26 pts with capillaroscopic score 1,5 and mRSS 14.9±2; 27 pts with capillaroscopic score 2,12 and mRSS 22.8. In this group we registered 6 deaths ( 4 male sex). Our study showed a correlation between capillaroscopic damage and a higher degree of skin score in pts with GER, a higher prevalence of Fingerpit Ulcers in pts with GER, and those patients had higher prevalence of diffuse cutaneous subset with anti-SCL-70 antibodies and cardiac and lung involvement.

Conclusion: GER is common in patients with systemic sclerosis and patients with GER are susceptible to micro vascular damage. Raynaud’s phenomenon, which reflects involvement of the vascular system in SSc, is usually the earliest clinical sign of the disease. As the disease progresses, complications with vascular involvement can be observed, such as fingerpit ulcers, watermelon stomach, PAH or renal crisis. Most of these events were more frequent in patients with SSc-related GER than patients without GER.

Fatal rhabdomyolysis after gastric endoscopy with midazolam in patient with chronic liver disease treated with statin

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Introduction: Statins are widely used to treat hypercholesterolemia reducing cardiovascular risk. Currently, there are no trials on the use of statins in chronic liver disease. Although hepatotoxicity during treatment with statins represents a rare event (<2%) and often it is dose-dependent, adverse effects or even death have been described in patients with liver disease. The concomitant use of other drugs that are substrates of the same isoenzymes can determine the increase of statin concentration in the blood and consequently the risk of myopathy. The most important side effect consists of increased creatinase levels, abdominal pain or muscle weakness, increased levels of creatinase, up to rhabdomyolysis.

Case report: A 67 years old man was admitted to our department of Internal Medicine for syncope. In the emergency Department the patient was oriented, no fever, pale skin, PA 90/50 mmHg, 80 bpm, AR; swollen abdomen, peristalsis present. Blood tests performed at the Emergency Department
were essentially normal except for ALT 146 IU/L, AST 125 IU/L, creatinine 1.2 mg/dl, D-dimer 2557, CK-MB 4.2 ng/ml, HB 15.1 g/dl, MCV 96.3 fl, platelets 115 x10^3/μl, glucose 195 mg/dl, myoglobin 175 mg/ml, Na+ 116 mEq/l, INR 1.75, PTT ratio 1.62, troponin T HS 0.022 mg/L. Chest X-ray and brain CT were performed resulting negative. Therefore he was admitted to our Department for investigation and treatment of the case. The patient reported recent hospitalization for myocardial infarction treated by PTCA with implantation of two drug-eluting stents, arterial hypertension, diabetes mellitus type II in therapy for about 7 years and recently finding of chronic atrial fibrillation (AF). The patient was treated with carvedilol 50mg/daily, digoxin 0.125 mg, ramipril 10 mg, duoplatvin 75/100 mg, furosemide 25 mg, canrenon 100 mg, pantoprazole 40 mg, insulin, atorvastatin 40 mg. In our Department presented arterial hypotension. Physiological anamnesis showed alcohol consumption of about 2 liters of wine for the last thirty years. ECG showed AF with frequency of 73 bpm and Holter ECG confirmed supraventricular ectopic activity consisting in total arrhythmia AF. An ambulatory blood pressure monitoring showed episodes of hypotension, ECD TSA and EEG showed no abnormalities attributable to syncpe. For this reason, we reduced antihypertensive therapy (ramipril 5 mg, carvedilol 25 mg). During hospitalization, for the detection of elevated transaminases, a hepatobiliary ultrasound was required showing increased liver size with heterogeneous echogenicity and irregular surface, without focal lesions. The average velocity in the portal vein was 8.2 cm/s (vn ≥ 14 cm/s). The spleen size was increased with ascites. Therefore hepatitis markers were required, resulting negative and so it was diagnosed with alcoholic liver cirrhosis. After two days from admission, the patient reported localized muscle pain in the lower limbs associated to intense weakness. In the suspicion of statin myopathy muscular enzymes were assayed resulting in normal range; however atorvastatin was stopped. The next day the patient underwent gastric endoscopy under sedation with midazolam showing congestive gastropathy in absence of esophageal varices. The day after the patient complained of a further increase of muscle pain with extension to the upper limbs with increased CK 3298 IU/L, myoglobin 22399 ng/ml, troponin HS 0.061 mg/L, ALT 70 IU/L, AST 191 IU/L, total bilirubin 3.39 mg/dl, direct bilirubin 2.12 mg/dl, alkaline phosphatase 192 IU/L. In the following days, despite discontinuation of statin, muscle pain not regressed, as well as muscle enzymes. In the suspicion of possible drug interactions, digoxin was suspend- ed because metabolized by the same isoenzyme of atorvastatin cytochrome (CYP 3A4). However, for the detection of myoglobinuria, oliguric-anuric phase, acute kidney injury, elevated levels of muscle enzymes, rhabdomyo- lysis was diagnosed with indication to hemodialysis (HD). HD treatment was continued for 5 consecutive days, followed by a further worsening of pain and muscle enzyme finally developing in disseminated intravascular coagulation (DIC). The patient was transferred in intensive care. Biochemical analysis showed: serum creatinine 2.5 mg/dl, BUN 14, 4 mmol/l, CK 1470 IU/L, CK-MB 68.72 ng/ml, myoglobin 714 mg/l, troponin T HS 1.53 g/l, LDH 1135 IU/L, ALT 827 IU/L, AST 2075 IU/L, total bilirubin 7.44 mg/dl, direct bilirubin 5.87 mg/dl, alkaline phosphatase 192 IU/L, ATIII 20%, INR 6.11, fibrinogen 0.58 g/L, PLT 40.000, D-dimer 9000 and lactic acidosis. The patient died the next day, after 9 days from diagnosis of rhabdomyolysis. The use of statins in the course of liver disease is not an absolute contraindication and it is recommended to start with low doses, making sure that the patient does not take alcohol and not have acute hepatitis. In literature there are rare cases of fatal rhabdomyolysis in patients with liver disease administered with statins. In our case, we assume that the development of rhabdomyolysis was related to several contributing factors such as the high dose of the statin in patients not previously diagnosed with alcoholic cirrhosis. The element trigger for the onset of rhabdomyolysis with subsequent DIC and multi organ failure, may have been caused by the use of midazolam, metabolized by the same isoenzyme of the statin. In conclusion, we must therefore pay particular attention to the potential risks of the association of statins with other drugs, especially in patients with chronic liver disease.

A combination of pre- and probiotics, vitamins, minerals, antioxidants and anti-inflammatory agents as a new therapeutic approach for increased intestinal permeability in patients with irritable bowel syndrome without constipation


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Introduction: Impairment of the intestinal barrier has been involved in the pathogenesis of several diseases. One of the most studied correlations is the one with irritable bowel syndrome (IBS). To date, there is no standard treatment for increased intestinal permeability.

Aims&methods: Our aim was to assess the efficacy of a dietary comple- ment containing pre- and probiotics, vitamins, minerals, antioxidants and anti-inflammatory agents in ameliorating the increased intestinal permeability and global state of health in subjects with IBS without constipation.

In this proof-of-concept study, a combination of pre- and probiotics (L. aci- dophilus NCFM, B lactis Bi-07), vitamins, minerals, antioxidants and anti-inflammatory agents (Nutritions®) was added to the common diet of 33 subjects (M/F=14/19, mean age 42 yo, range 19-72) with IBS-D or IBS-M and increased intestinal permeability (measured with 51 CrEDTA Test) at the dosage of 1 sachet per day for 60 days. After the treatment, each patient repeated the intestinal permeability test with 51CrEDTA. Global health state with a slightly modified version of EQ-5D VAS (0-100 mm) was evaluated at baseline and after the treatment.

Results: All the patients completed the treatment. Five patients were unable to repeat the 51CrEDTA Test and were withdrawn from the study. In the re- maining 28 patients, the mean 51CrEDTA score was respectively 7.43 (SD: ±2.75) at baseline and 5.93 (SD: ±2.7333) after the treatment (P=0.089). Mean EQ-5D VAS was respectively 40 (SD: ±14.86) at baseline and 64.61 (SD: ±9) after the treatment (P<0.0001).

Conclusion: Restroring the impaired gut barrier may be challenging, especially since there are several therapeutic targets to hit, as gut microbiota, intestinal mucus, intestinal immune cells, tight-junction function, et cetera. A multimodal approach, with a combination of different healing agents, seems to be effective both in improving intestinal permeability and in ameliorating symp- toms. Since this study has many limitations, further, randomized controlled tri- als, with an adequate sample size, are needed to confirm these results.

First impression, the best impression...?

Marco Vincenzo Lenti, Venerina Imbesi, Lucietta Ratta, Elena Strada, Alessandra Gallia, Paolo Gobbi, Gino Roberto Corazza

IRCCS Policlinico San Matteo - Università degli Studi di Pavia

A 67-year-old female was admitted to the Department of Internal Medicine of Fondazione Policlinico San Matteo (Pavia, Italy) because of dry cough, odynophagia, asthenia, lack of appetite, nocturnal fever and sweats. During the last 6 months she also lost 5 kilos for which she underwent diagnostic workup without a definitive diagnosis. Specifically, the routine laboratory exams resulted unremarkable and the chest X-ray was normal. Subsequently, an upper gastrointestinal endoscopy was performed showing large and deep ulcers with contiguous extended whitish membranes in the third upper-middle esophagus. Biopetic specimens were collected and re- vealed ulcerations with chronic inflammation, absence of granulomas or vi- ral inclusions, presence of Candida, without signs of malignancy. The pa-
Inflammatory bowel disease (IBD) are associated with an increased risk of early atherosclerosis: a cross-sectional study in young patients

Anna Licata, Maria Cappello, Ivana Bravati, Alessandra Aiello, Daniela Dab bene, Vincenza Calvaruso, Daniele Torres, Vittoriano Della Corte, Antonino Tuttolomondo, Giuseppe Licata, Antonio Craeli, Calogero Cammà

Sezione e UOC di Gastroenterologia; Sezione e UOC Medicina Interna e Cardioangiologia; DIBIMIS Università di Palermo, Palermo

Introduction: Inflammatory Bowel Disease (IBD) have been recently associated with an increased risk of cardiovascular events. Studies on surrogate markers for early atherosclerosis have led to conflicting results. Aim of this study was to examine whether carotid intima media thickness (IMT) and arterial stiffness are increased in young adults with IBD compared to matched controls.

Methods: Fifty consecutive IBD patients, 25 males, and 20 healthy controls (HC) comparable for age and sex were enrolled. Median age was 34 years (IQR 14), range 17-45. Thirty-six patients had Crohn’s disease (CD), 14 ulcerative colitis (UC). Median duration of disease was 4 years (IQR 6). IBD was active in 12 patients (10 CD, 2 UC), 13 were on steroids, 23 on immunomodulators, 12 on anti-TNF therapy (9 adalimumab, 3 infliximab). Fourteen patients presented extra-intestinal manifestations. Most of them were non-smokers (64%); 44% of the IBD patients had a familial history of cardiovascular events; one had hypertension, one diabetes. Data on clinical and demographic features, cardiovascular risk factors, personal and familial history of cardiovascular events, concomitant therapies were registered on a dedicate database. Leftand right carotid IMT was evaluated using high resolution B-mode ultrasonography. Arterial stiffness was assessed by measurement of carotid-femoral PulseWave Velocity (PWV) and Augmentation Index (AI).

Results: There were no significant differences in baseline characteristics between patients and controls when comparing smoking habits, BMI, lipid profile, blood pressure values. Right and left carotid IMT were significantly higher in patients compared to controls (0.5 versus 0.4 for both; p = 0.03 and n=0.015 respectively), 7 patients and no HC had evidence of atherosclerotic plaques. Carotid-femoral PWV median values were significantly higher in IBD patients than in controls (8.45 versus 8.3, p=0.007), as well as AI (122% in IBD, 112.5 in healthy controls; p=0.005). There was no association between type of IBD, disease activity and duration and both IMT and PWV, which instead were related to increasing age (p < 0.05).

Conclusion: In a homogeneous Mediterranean cohort of young adults, we found that IBD patients have an increased risk of early onset of atherosclerosis and alteration of arterial elastic properties, regardless of disease activity and of treatment. Clinical follow-up of IBD patients should include initial assessment and monitoring of IMT and arterial stiffness to keep cardiovascular risk under control.

Prevalence of irritable bowel syndrome in celiac patients on gluten free diet


 Policlinico di Bari

Background and aim: Irritable bowel syndrome (IBS) is a functional disorder of the gastrointestinal tract of unknown origin. The population prevalence in community surveys varies between 5% and 20% depending on the criteria used to define its presence, however, no data exist on the prevalence of IBS in patients with celiac disease (CD) on a gluten free diet (GFD). Aim of this study was to evaluate the prevalence of IBS in patients with CD on a strict GFD.

Materials and methods: 272 patients with CD, diagnosed according to ESPGHAN criteria, and regularly followed up in our Unit (Bari University Hospital) in the last year and regularly following the GFD (negative anti-transglutaminase-IgA in the last two scheduled visit) were enrolled in this prospective study. Of these, 122 were adults [90 F (74%); mean age 35 yrs (range 18-62)] and 150 were children [98 F (65%); mean age 9 yrs (range 2-17)]. As controls, we evaluated 615 non-celiac patients, 484 adults [234 F (48%); mean age 41.4 yrs (range 19-65)] and 131 children [68 F (51%); mean age 9 yrs (range 1-17)] enrolled among the first-degree relatives of celiac patients. All were prospectively evaluated for IBS diagnosis according to Rome III criteria.
Results: Our study shows that the overall prevalence of IBS is significantly higher in celiac patients as compared to healthy controls (39.7% vs 15.8%; p < 0.001). The prevalence of IBS was higher in celiac patients both in children ([37.33% vs 15.3%; p < 0.001); RR 2.4; CI95%: 1.6-3.8] and adults ([42.6% vs 15.9%; p < 0.001); RR 2.7; CI95%: 2.0-3.6]). No difference was found according to sex. No correlation was found between the prevalence of IBS and the CD presentation, duration of disease and histological damage.

Conclusion: Our study shows that patients with CD have an increased risk of developing IBS: the risk is doubled in children and tripled in adults. In view of these results, we believe that new strategies aimed at the prevention/treatment of irritable bowel syndrome in celiac patients should be planned.

Irritable bowel syndrome and correlation with affective disorders

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Irritable bowel syndrome (IBS) is a functional disorder of the gastrointestinal tract to multifactorial etiology, including psychosocial factors, organic and neuromotor dysfunction. The prevalence in the general population ranges between 5 and 20% in relation to the criteria used for diagnosis. Currently, with the Rome III criteria, the prevalence is between 25 and 50%. The etiology of IBS is multifactorial, including psychosocial factors, organic (inflammation and infection) and neuromotor dysfunction. The aim of this study was to correlate the pathology in question with alterations of the profile psycho-emotional and social stressors. The study was conducted on 56 patients (M 14, F 42, mean age 45±3 years), with IBS, diagnosed according to the Rome III criteria. The control group consists of 45 subjects (15 F 30 M, mean age 35±2 years), free from gastro-intestinal diseases. All patients were subjected to clinical evaluation and administration of the following questionnaires: SF-36 for the quality of life, Toronto Alexithymia Test (TAS-20), Middlesex Hospital Questionnaire (MHQ). From the questionnaire SF-36 scores emerge to clinical evaluation and administration of the following questionnaires: SF-36 for the quality of life, Toronto Alexithymia Test (TAS-20), Middlesex Hospital Questionnaire (MHQ). From the questionnaire SF-36 scores emerge. From MHQ questionnaire showed that subjects with IBS have score ≥ 8 (presence of noise) for the following psychoneurotic disorders: anxiety, obsessiveness, depression, and somatic anxiety. In contrast, subjects in the control group, present score <8 for all disorders mentioned. From the TAS-20 questionnaire, it was found that among the subjects in the control group, 1 and 3 are borderline alexithymia presents, while among subjects with IBS have alexithymia 11 and 18 are borderline. Our study shows that patients with IBS have a worse quality of life, with disturbances such as anxiety, obsessiveness, depression, anxiety and somatic trait alexithymia overt or borderline compared with the control group. For this reason, it is necessary to identify the impact of the emotional profile of somatic health status in order to delineate the role of possible intervention strategies designed to favorably influence the prognosis of this disease so frequent.

Alpha-fetoprotein (AFP) but not TGF-β is correlated with the stage of disease in hepatocellular carcinoma (HCC): a clinical study in 149 patients

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Background: TGF-β1 is considered an attractive target for the development of new biological therapies. In fact, different therapies for inhibiting TGF-β are currently under evaluation in clinical trials, in patients with advanced stage of HCC. Alpha-fetoprotein (AFP) has been proposed as an indirect indicator of TGF-β pathway activation.

Aim of the study: The aim of this study was to analyze the circulating levels of TGF-β and AFP in patients with HCC in different stage of disease in order to verify which patients would be most suitable for receiving anti-TGF-β therapy.

Methods: 149 patients with HCC, including 113 male (75.8%) and 36 females (24.2%) were studied. Age, sex, etiology, Child-Pugh (CP), BCLC, CLIP score and the presence of portal vein thrombosis were considered as variables and the degree of correlation between AFP and TGF-β compared to these variables were analyzed. Comparison between independent groups were evaluated using Wilcoxon or Kruskal Wallis tests as appropriate. The correlation between AFP and TGF-β were evaluated with Spearman correlation Coefficient. A p-value <0.05 was considered as statistically significant.

Results: According to the Child-Pugh score, 63.5% patients (94/148) were in stage A, 31.1% (46/148) in stage B and 5.4% (8/148) in stage C, whereas according to the BCLC classification, 27.5% (41/149) patients were in BCLC 0, 26.9% (40/149) in BCLC A, 25.5% (38/149) in BCLC B and 1% (30/149) as BCLC C. According to the CLIP classification, 33.8% of patients (50/148) were scored as CLIP 0; 29.7% (44/148) of patients as CLIP 1, 18.9% (28/148) as CLIP 2, 8.8% (13/148) as CLIP 3, 6.8% (10/148) as CLIP 4, 1.4% (2/148) as CLIP 5 and 0.7% (1/148) as CLIP 6. Portal vein thrombosis was observed in 10.5% of patients (15/143). AFP values were significant when considering the presence of portal vein thrombosis (p <0.0001), Child-Pugh stage (p = 0.0195), BCLC stage (p <0.0001) and CLIP (p <0.0001). By contrast, TGF-β1 levels were not significantly different in any of the score systems, nor was the coefficient of correlation between AFP and TGF-β statistically significant.

Portal vein thrombosis was observed in 10.5% of patients (15/143). The coefficient of correlation between AFP and TGF-β1 was not statistically significant in any of the categories tested.

Conclusions: Lack of correlation between TGF-β1 and stage of disease defined by any of the clinical staging scores suggests that is necessary to measure circulating levels of TGF-β1 to identify patients susceptible to anti-TGF-β treatment in order to tailor the therapy according to the biological characteristics of the tumor. Furthermore, AFP is not a surrogate of activation of the TGF-β signaling pathway but is positively associated with more advanced disease and likely of shorter survival in patients with HCC.

A strange case of portal vein thrombosis

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We present the clinical case of a 35 year old man, affected by Crohn’s disease since the age of 20 years, come to our attention in Internal Medicine Ward of the University Hospital of Bari to the appearance of fever, asthenia and diarrhea. We diagnosed by CT scan an ileal abscess treated with antibiotics. It was recommended an abdomen CT control to be carried out 20 days after initiation of therapy. Abdomen CT performed to control ileal abscess, showed the following reports: “... marked absence of opacification of the left branch of the portal vein extended in the segmental branches. It should be noted the absence of partial opacification of the left renal vein and a posterior hilar branch as par-
tial thrombosis. Therefore, the patient was sent to our attention and was immediately taken therapy with low molecular weight heparin at a dose of 100 IU/kg × 2/day.

At admission to the ward, the patient was alert, oriented, afebrile, asymptomatic; cardiac auscultation, showed tachycardia; chest auscultation showed nothing pathological; abdomen examination was negative, except for the presence of a tender palpable in right iliac fossa, with a diameter of about 2 cm, smaller than the previous hospitalization.

Blood tests showed neutrophil leukocytosis, iron-deficiency microcytic anemia, thrombocytosis, increased inflammatory markers, hyperfibrinogenemia, hypoalbuminemia, positivity of dimers, faecal occult blood positive, folic acid deficiency and hyperhomocysteinemia.

Colonoscopy performed concluded that: “Substenosis of the ileocecal valve in Crohn’s disease.”

To investigate the pathogenesis of portal and renal vein thrombosis, were assessed genetic testing for thrombophilia; it was not possible to run a thrombophilia screening of level I and II for heparin therapy in place. These tests showed a heterozygous mutation in the gene encoding MTHFR (methylene tetrahydrofolate reductase).

The occurrence of renal and portal thrombosis in patients with inflammatory bowel diseases is very rare; although Crohn’s disease is an independent risk factor for the development of venous thrombosis, especially for deep veins of the lower limbs, other prothrombotic factors may contribute to the development of the clinical picture. Therefore, thrombophilia study is appropriate in these patients, in order to not only attributed to the underlying disease the etiopathogenesis of the thrombotic process that is, on the contrary, multifactorial.

Alternative treatment in refractory coeliac disease type II

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Case presentation: a 54 years old woman, affected by coeliac disease diagnosed 5 years earlier. The patient followed a strictly gluten-free diet, but she never attained a complete clinical, endoscopic or histological improvement. The patient came to our attention because of worsening diarrhea (up to 20 discharges/day), and severe weight loss (13 Kg) in the last three months.

Clinical course: on admission the patient underwent blood tests and clinical evaluation, which showed severe malnutrition (albumin 2.9 g/dl, creatinine 0.24 mg/dl, cholesterol 53 mg/dl, BMI 14, percentage of ideal body weight: 65%) and systemic inflammation (CRP 6.6 g/dl, erythrocyte sedimentation rate 17 g/dl, serum ferritin 1287 mcg/l, Hb 10.4 g/dl, MCV 86 fl). An abdomen ultrasound examination showed hepatosteatosis, severe ileitis with mesenteric satellite inflammation and intramesenteric adenopathies. A restaging EGDS showed hypotrophic gastric and duodenal mucosa with scalloping. Histological examination showed pseudopyloric and intestinal metaplasia of the gastric fundus with severe glandular atrophy; duodenal biopsies showed severe villous atrophy with crypt hyperplasia and glandular atrophy; intraepithelial T lymphocytes were more than 40/100 cells, with a monoclonal TCRR rearrangement and an aberrant phenotype. A diagnosis of type II refractory coeliac disease was established. A positron emission tomography excluded the presence of intestinal lymphoma; the patient was treated with high dose steroid therapy, parenteral nutrition and albumin supplementation. She maintained a stable body weight, with improvement of inflammation and nutritional status, but only a mild reduction of stool frequency (about 8/day). Given the high risk of progression to lymphoma associated with azathioprine treatment, the patient was treated with cladribine, 0.1 mg/kg per day for 5 days; a second cladribine course was administered 4 weeks later. The patient had no significant side effects. Clinical conditions remained substantially unchanged, with persistence of about 8 evacuations/day, but the patient reported subjective improvement, which allowed us to progressively taper steroid treatment.

Conclusions: the treatment with cladribine allowed to reduce the dose of the steroid without clinical deterioration. The general conditions of the patient remain severely compromised by the underlying disease and its complications. For a proper evaluation of the effectiveness of the drug we should evaluate the patient in the course of time and monitor for the possible occurrence of enteropathy-associated T cell lymphoma. The presentation of this case aims to extend the knowledge about alternative therapeutic strategies in the treatment of patients with refractory coeliac disease unresponsive to steroids.

Fluconazole related toxic epidermal necrolysis: a case report

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A 51 year old caucasian man, affected by decompensated sclerosant cholangitis, was admitted to hospital S. Donato (in Arezzo) with painful generalized body rash. The rash involved greater than 70% of the body surface area, included oral mucosa and conjunctiva and occurred four days after beginning treatment with 50 mg bid of oral fluconazole prescribed for esophageal candidiasis. Medications prior to admission included lansoprazole 30 mg, uricosuric acid 450 mg tid, low dose methylprednisone 4 mg and carnitine 100 mg; he had taken for at least six months these drugs without adverse events. Firstly, the rash showing as macular rash, involved anterior trunk and then face included oral mucosa and conjunctiva, palms, soles and extremities. Over a course of a week, the macular rash developed to spread blisters. A diagnosis of fluconazole related toxic epidermal necrolysis was made based on clinical criteria. Dermatologist consult was performed: specialist didn’t believe helpful doing cutaneous biopsy to confirm diagnosis. The patient begun high dose prednisone, five days immunoglobulins infusion and antibiotics prophylaxis with slow progressive resolution. After 30 days from hospital admission, he developed fever and respiratory failure related to Acinetobacter pneumonia MDR and he died. Toxical epidermal necrosis (TEN) and Stevens-Johnson syndrome (SJS) are two forms of a life-threatening skin condition, related to immunological mechanism leading to extensive detachment of the epidermis. The first one is most aggressive disease, with severe systemic symptoms and involved more than 30% of the epidermis; the second one is soft form and involved less than 10% of the epidermis. First cause of TEN/SJS is drug related but also infection are responsible to possible disease development. In case reports and studies, more than 100 drugs have been described as causes of SJS and TEN; but a limited number of drugs, including allopurinol, sulfonamides and anti-convulsants (carbamazepine, barbiturates, hydantoin). Immunoological underlying disease as Lupus or AIDS increased the risk to develop TEN/SJS. Fluconazole induced very rarely TEN/SJS; the most common adverse events are hematochemical, metabolic, hepatic and gastrointestinal side effects. Muco-cutaneous reactions are generally mild like as rash, pruritus or urticaria. Only few cases of fluconazole related TEN/SJS are described in general population, usually the most affected people are patients with HIV or liver related diseases. Fluconazole is eliminated from the skin at a slower rate than in plasma and it is possible detecting in skin after 10 days after therapy stop. Metabolism of this drug is primarily hepatic, only 10% of fluconazole is metabolized and the rest is excreted by urine in unchanged form. Liver failure could be responsible of slowing metabolism and so of drug accumulation in skin, leading of longer exposition of a drug antigens to immunological cells. So liver failure could increase the risk of fluconazole related TEN/SJS; in patients with liver disease fluconazole should be used only if nearly indicated.
Whipple’s disease: easy diagnosis, when considered

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We report the case of a 48-year-old white man, smoker, who presented with abdominal complaints, mild diarrhea and progressive weight loss combined with asthma and diffuse arthropathy, only partially controlled with corticosteroids therapy, which were observed 3 months previously. There was no past or family history of gastroenteric or joint disorders, or drug abuse and no history of any recent illness, trip or contact with an infectious disease. The patient referred little benefit after therapy with metronidazole. He was admitted for a recrudescence of symptomatology with low-grade fever, fatigue, severe abdominal pain, nausea, vomiting and diarrhea (8-10 stools/day), resulting in a severe malabsorption syndrome with about 10 kg weight loss in the previous week. Laboratory tests displayed an increased C-reactive protein level and an elevated leukocyte count, mild anemia, hypoalbuminemia, hyponatremia, low total seric protein and folate deficiency. All other routine laboratory results were within normal limits, but, in few days, he developed an acute renal failure because of dehydration with serum creatinine 4.0 mg/dl. Physical examination revealed only bilateral inguinal lymphadenopathy and dehydration signs. Rehydration with electrolytic supplement was started.

Abdominal US-scan showed paraortic and mesenteric lymph nodes with reactive aspects. In the suspect of Inflammatory Bowel Disease or tuberculous enteritis or malignancy an upper gastrointestinal endoscopy investigation that showed an erythematous and edematous aspect of the duodenal mucosa, with villous atrophy and velvet-like aspect. Histological HE stain revealed the presence of foamy cells and abundant peroxidase acid Schiff (PAS) positive macrophages were seen on duodenal of biopsy samples, suggestive for Whipple’s disease diagnosis. The macrophages were negative for Alcian blue and Ziehl Nieelsen stain. It was started Ceftriaxone 2g/once a day ev for two weeks and than trimetroprim-sulphamethoxazole x os (160/800 mg bid), that he is still receiving after 4 months. The patient referred little benefit after therapy with metronidazole.

A rare cause of infertility and neural tube defects during fetal growth: a case report

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Background: Autoimmune atrophic gastritis (AAG) is characterized by the destruction of the gastric body and fundus mucosa, leading to hypoachlorhydria and lack of intrinsic factor. Vitamin B12 deficiency has severe clinical consequences, including complications in fetal development such as neural-tube defects and low birth weight. There are no studies on the role of AAG in fertility and miscarriage. We here describe a case of a woman affected by AAG.

Case: FC is a 37 years-old woman. In 2010 she referred to our Centre for Medically Assisted Procreation because of longstanding infertility (7 years), and underwent In vitro fertilization and embryo transfert (FIVET) five times and all the attempts ended up in early miscarriage. Past medical history was recorded. FC is affected by undifferenziated connective tissue disease, Hashimoto’s thyroiditis in replacement therapy, hetherozygosity of the MTHFR gene and hyperhomocysteinemia. A severe vitamin B12 deficiency (76 pg/mL) was assessed. She was then referred to our gastroenterological outpatient clinic because of dyspepsia and abdominal pain and in the suspicion of malabsorption. Gastric biopsies were assessed and AAG was diagnosed. We prescribed vitamin B12 injections and after only 6 months FC naturally became pregnant but the ultrasound morphology scan revealed a severe neural tube defect (myelomeningocele, open spina bifida).

Conclusions: AAG and vitamin B12 deficiency may be cause of infertility and may lead to neural tube defects and miscarriage. In this case report, probably, vitamin B12 supplementation was necessary for starting the pregnancy, but not enough to avoid vitamin B12-related complications. Gynecologists should be aware that vitamin B12 deficiency may manifest with blurred clinical symptoms and all pregnant women should be assessed for the deficiency. Further studies are needed to better highlight the crucial role of AAG in infertility, miscarriage and fetal growth abnormalities.

Autoimmune atrophic gastritis may predispose to the development of small intestinal bacterial overgrowth

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Background and aim: Gastric acidity plays a crucial role in the stomach homeostasis. In particular, the low pH of the gastric juice (<3.0) is responsible for its bactericidal properties. Exogenous bacteria introduced into the stomach when the pH is less than 3.0 are usually destroyed within 15 minutes. It is well known that conditions characterized by the lack of gastric acid output, such as
gastrectomy, are associated with small intestinal bacterial overgrowth (SI-BO). In autoimmune atrophic gastritis (AAG) the destruction of the gastric body and fundus mucosa leads to hypo-achlorhydria, therefore, aim of the study was to assess the possible role of AAG in predisposing to SI-BO.

Material and methods: We enrolled 23 patients (mean age 58±17 yrs, 14 females) affected by AAG with severe gastric atrophy in corpus and fundus (group 1). None of them were assuming acid suppressor drugs or antibiotics. Patients with other possible causes of SI-BO were not included. A statistically homogeneous group of patients that underwent total or partial gastrectomy (N=20, mean age 63±19 yrs, 10 females, group 2) was used as control. A H2 glucose breath test was performed according with international criteria. Gastrointestinal symptoms were recorded using the Gastrointestinal Symptom Rating Scale (GSRS). Statistical comparison was made with unpaired t test.

Results: Among patients of the first group, three (7.6%) showed a positive H2 glucose breath test. All of them did not complain gastrointestinal symptoms (GSRS<0). In the second group, 18 patients (90%) had a positive test and all of them had at least 2 or more symptoms, in particular, bloating (65%), diarrhea (42%) and weight loss (17%). SI-BO is statistically associated with the second group if compared to the first one (p<0.0001).

Conclusions: In our series, SI-BO seems to be more prevalent in gastrectomized patients than in AAG patients. Further studies (pH-metry, analysis and culture of gastric juice) are necessary to better define the association between the gastric acid output and bacterial overgrowth.

Autoimmune atrophic gastritis: what about the homocysteine?

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Background & Aim: Hyperhomocysteinemia (hyper-Hcy) is reported as an independent risk factor for thrombo-embolic disease. In autoimmune atrophic gastritis (AAG) the malabsorption of B12 determines alterations of methionine metabolism and increased homocysteine (Hcy) serum levels. The aim of this study is to evaluate the prevalence of hyper-Hcy in AAG patients and the correlation to cardiovascular disease.

Methods: An AAG population-based cohort [N =129, mean age 62±17 yrs, 95 females (mean age 61±17 yrs), 34 males, (mean age 67±15 yrs)] was screened for Hcy at the time of diagnosis (normal if <14.5 µmol/L). Cardiovascular and thrombo-embolic accidents were recorded and monitored during a median follow-up interval of 3 years (T0−T1−T2−T3: enrollment-1°-2°-3° year). Vitamin B12 and folic acid supplementation was administered when depleted. Data were described as mean and standard deviation (SD) if continuous and as counts and percent if categorical, a student’s t-test was performed.

Results: At the time of diagnosis mean Hcy was 14.8±8.7 µmol/L. Forty-five patients (34.8%) presented hyper-Hcy (mean Hcy 22.8±10.5 µmol/L, mean age 64±13 yrs, F 29), 3 of them evidenced MTHFR gene mutations. Men had higher Hcy concentrations than women (16.3±9.17 µmol/L vs 14.2±8.5 7 µmol/L, p<0.049). Vitamin B12 deficiency was confirmed as risk factor for hyper-Hcy (OR 3.2, 95% CI 1.4-7.2, p 0.004). In the hyper-Hcy group the incidence of cardiovascular diseases was higher than in the normal Hcy group (57% vs 41%). During the next three years, Hcy levels significantly decreased (mean Hcy T1: 12.1±5.1 µmol/L (p<0.001), T2: 12.44±3 µmol/L (p<0.001), T3:11.42±4.1 µmol/L (p 0.005)) and only 1 cardiovascular event (2%, myocardial infarction) occurred.

Conclusions: Our data show an increased prevalence of hyper-Hcy in AAG patients and suggest that vitamins supplementation may modify the influence of hyperHcy in predisposing to cardiovascular events. All AAG patients should assess Hcy levels and should be treated with vitamins supplementation, if depleted. Other studies are needed to better clarify this association.

Evaluation of the iron status in patients with autoimmune atrophic gastritis: a retrospective study

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Background & Aim: Clinical presentation of autoimmune atrophic gastritis (AAG) is unspecific. Pernicious anemia is considered the most distinct feature because of vitamin B12 deficiency; however, iron malabsorption can also occur resulting in stores depletion. Aim of this study is to evaluate the iron status in AAG patients.

Methods: In a single-center study (Fondazione IRCCS Policlinico San Matteo), all the subjects who received the diagnosis of AAG from January 2007 to April 2013 were enrolled. We evaluated biochemical parameters performed at the time of diagnosis: complete cell blood count, serum iron (normal if ≥25 µg/dL), ferritin (female 5-204 ng/mL, male 22-270 ng/mL) and vitamin B12 (normal <240 pg/mL). Exclusion criteria were incomplete data and previous support therapies. Moreover, for each subject, we excluded other causes of iron depletion (gastrointestinal bleeding, celiac disease, intestinal infections, inflammatory bowel diseases, chronic disease). Data were described as mean and standard deviation (SD) if continuous and as counts and percent if categorical, a student’s t-test was performed.

Results: The study cohort was of 191 subjects (137 females, mean age 62±17 yrs). Complete data were available only for 135 patients (99 females, mean age 61±17 yrs, 36 males mean age 66±16 yrs). As shown in Figure, anemia occurred in 75 patients (55%), 41 presented a clear pernicious anemia while 18 (13%) lone macrocytosis, 14 (10%) a microcytic anemia. Decreased serum iron was present in 21 (25%), concomitant depletion of storage in 16 (11%). To note that 7 of the 16 with low levels of serum iron and ferritin showed macrocytosis, almost all (14/16) anyscrosis. There was no significant difference of iron levels between genders; female had lower storage levels (F 45.8±75 ng/mL vs M 111.8±199 ng/mL; p<0.001) while men showed lower levels of vitamin B12 (M 229±210 pg/mL vs F 325±695 pg/mL; p<0.001).

Conclusion: Data suggest that iron malabsorption is an important feature of AAG that can often coexist with vitamin B12 deficiency. Therefore, iron status should always be included in the laboratory evaluation of AAG patients, even in the absence of anemia or macrocytosis.

### Table 1.

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Long-term follow-up study of autoimmune atrophic gastritis patients: a single-center experience

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Background & Aim: Autoimmune atrophic gastritis is an organ specific disease that results in systemic involvement from pernicious anemia to neurological symptoms; moreover it is considered a preneoplastic condition. No data are available on its long-term course or on the impact of vitamin B12 treatment. In this study, we evaluated the natural history of AAG reporting a comprehensive clinical, analytical, endoscopic and long-term follow-up.

Methods: We designed a prospective study to analyze the incidence of the development of neoplastic lesions in the stomach, the biochemical trend and the response to supplementation therapy. From 2009 to 2012 we enrolled 180 AAG patients (130 females, mean age 62±16 yrs) and met them twice a year for a clinical and laboratory evaluation. We performed an endoscopic surveillance in a time interval ranging from 6 to 24 months (T0-T1-T2-T3: enrollment-1°-2°-3° year). Patients with vitamin B12 deficiency were treated with cyanocobalamin and folic acid.

Results: Hemoglobin levels significantly increased after a year of vitamin B12 supplementation (T0 Hb 11.6±2.2 g/dl vs T1 Hb 13.2±1.5 g/dl; p<0.001), in parallel with the rise of vitamin B12 serum levels (T0 263±187 pg/ml vs T2 501±308 pg/ml, p<0.001). Mean corpuscular volume significantly decreased during the study period (T0 MCV 92.6±13.5 fl vs T3 MCV 88±4.4 fl, p<0.001). At the moment of the diagnosis 11 patients (6%) showed immature lesions of the gastric mucosa, during the follow up period 6 patients (3%) developed gastric dysplasia and 4 of them microcarcinoids.

Conclusion: Supplementation therapy is crucial to prevent hematological complications. Furthermore, endoscopic surveillance is mandatory to identify early gastric lesions. Other studies should be performed in order to assess factors that impact on morbidity and complications.

A long-term follow-up of laryngo-pharyngeal reflux (LPR) in professional singers: impact of inappropriate lifestyles and drug consumption

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Background: The performance of professional singers can be negatively affected by Laryngo-Pharyngeal Reflux (LPR) symptoms due to inappropriate dietary-lifestyle habits and self-administered medications. Aim of the study was to evaluate, in this group of selected subjects and in the absence of PPI therapy, the role of an educational program and the adequacy of the compliance on the long-term clinical outcome.

Methods: Twenty adult singers (age 29±4 yrs, 5M) with symptoms suggestive for LPR were enrolled. Subjects were assessed by a validated Reflux Symptom Index (RSI, 9 items scored 0-5, max. score=45). Validated questionnaires exploring dietary-lifestyle habits (Medstyle), medical history and pharmacological therapies were administered at enrollment (T0), at 12 (T12) and at 24 months (T24). At the same time points a Visual Analogue Scale (VAS, 0-100mm) was employed to measure compliance to a correct dietary style and self-administered drugs (steroids, NSAIDs, anti-histaminics, long acting beta2 agonists). During the first year, subjects underwent a close monthly follow-up and an educational program with specific dietary modifications and information about negative effects of inappropriate self-medication. Subsequently, (from T12 to T24), subjects were left free to choose lifestyles, therapeutic and alimentary behaviors.

Results: The RSI was 13.6±1.8 at T0, 6.3±1.8 at T12 and 10.7±2.5 at T24 (P<0.05, ANOVA). The compliance to a correct dietary style as measured by VAS (mm) was 2.5±2.3 at T0, 70.3±3.9 at T12, and 64.5±4.7 at T24 (P<0.0001, ANOVA). The VAS (in mm) of self-administered drugs was 39.0±2.7 at T0, 1.5±1.9 at T12, and 33.0±4.4 at T24 (P<0.0001, ANOVA). At the end of the study (T24) only two subjects were under PPI therapy. A multivariate analysis confirmed that RSI was significantly influenced by the consumption of junk food, by self-administration of inappropriate drugs and by the presence of a close follow-up (P<0.05).

Conclusions: (i) In a selected group of singers, bad alimentary habits and inappropriate self-administered drugs are significantly linked to LPR symptoms; (ii) symptoms strongly ameliorate during a strict follow-up by an educational program and the elimination of inappropriate drugs, also in the absence of PPI therapy; (iii) at the end of the close follow-up (free-living subjects) LPR symptoms worsened, mainly due to reversal of inappropriate self-medication, even in the presence of correct dietary lifestyles.

The assessment of psychical and affective traits in a cohort of patients with liver cirrhosis

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Background: Numerous studies have reported the presence of psycho-affective disorders in the chronic organic diseases, emphasizing the need for a specific therapeutic approach. Also, more recently, additional data have shown the ability of psycho-affective disorders, in the past interpreted as essentially phenomenon “reactive” organic pathology to chronic, to condition both the evolution of both the drug response; in fact, psycho-affective disorders assume the role of real potential “risk factors.” Liver cirrhosis, a disease with chronic evolution, and progressive worsening, characterized by a high potential disabling (dependence on drugs, doctor, periodic checks clinical, biological and instrumental) is, in our opinion, an outstanding model for the study of these issues.

Aim: The aim of our study is to verify in patients with liver cirrhosis both the presence of psycho-affective disorders and that of the alexithymia. Materials and methods. We studied 51 subjects, including 15 female and 36 male, aged between 45 and 75 years, with liver cirrhosis undergoing fluid and electrolyte imbalance, hospitalized at the Internal Medicine Unit of the Policlinico di Bari. The subjects were scored with the following tests: the Zung A & D test, for the evaluation of Anxiety Disorder and Major Depressive Disorder, and the TAS 20 test for the evaluation of alexithymia. The control group, homogeneous by sex and age, is made up of 48 subjects not affected by chronic organic diseases, by functional disorders and psycho-affective disorders.

Results: The Zung A & D test has shown in patients with liver cirrhosis both the presence of psycho-affective disorders and that of the alexithymia.

Conclusions: Our data, in addition to signaling the presence of important psycho-affective and alexithymia (is it conceivable a “secondary” to organic disease with chronic evolution Alexithymia form?) in subjects with liver cirrhosis, indicate the presence of psycho-affective disorders and of the alexithymia.
hepatic cirrhosis, reproduce strongly the need for a “holistic” evaluation of such patients in the light of recent data that allow us to hypothesize, through the intermediary of a stress pathological reaction, pathophysiological plots among the diseases in question. Finally, the particularly disabling characteristics of Liver Cirrhosis, suggest the utility of technical support such as counseling, educational approach in order to ensure an even from the subjective point of view of their disease (optimized adaptation) with inevitable positive impact on their quality of life.

Is the autonomic nervous system dysfunction a biomarker of functional digestive disorders?

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Introduction: Autonomic nervous system (ANS) regulation may be altered in functional/organic digestive disorders, but published data are not clear cut to date. Different and not consistent methodologies may account for controversial results.

Aims & Methods: To analyze ANS function with a standardized technique in three subgroups of patients with (i) endoscopic and/or clinical gastrointestinal reflux disease (GERD), (ii) irritable bowel syndrome (IBS) according to Rome III criteria, and (iii) inflammatory bowel disease (IBD) in clinical and endoscopic remission complaining of IBS-like symptoms. Results were compared to healthy matched subjects. ANS activity was evaluated by autoregressive spectral analysis of RR interval and systolic arterial pressure variabilities. Cut-off values for pathological findings were identified by comparing ROC curves between all patients and healthy subjects. Analysis of variance was performed by one-way ANOVA. Statistically significant difference was set as a p<0.05.

Results: We enrolled 42 patients (28 F, age 41±2 yrs) and 42 healthy matched controls. Total variance of RR interval variability was lower in patients than controls (188±313 vs 4185±650 msec2; p<0.01) as well as alpha index (18±2 vs 29±3 msec/mmHg; p<0.01). ROC curves analysis showed that an alpha index ≤ 21 (sensitivity 76%, specificity 60%, PPV 65%, NPV 71%) and total variance RR ≤ 2896 identified subjects with disease (sensitivity 86%, specificity 55%, PPV 66%, NPV 79%). Specifically, in GERD patients, an alpha index ≥ 18 (sensitivity 92%, specificity 64%, PPV 30%, NPV 98%; p=0.001) and variance RR ≤ 608 identified subjects with disease (sensitivity 58%, specificity 94%, PPV 64%, NPV 93%; p=0.001).

Conclusion: Patients with functional diseases show a significant reduction of variance RR and alpha index, which is an established marker of cardiac baroreflex, compared to controls. ANS evaluation is a useful test which correctly identifies patients, especially those with GERD.

Cough as first symptom of inflammatory bowel disease

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We report the case of a 54 year-old white woman, ex smoker, with history of chronic autoimmune thyroiditis, low back pain, plantar fasciitis, who reported the onset of non-productive cough and low grade fever, especially in the evenings. Laboratory examination revealed mild normochromic normocytic anemia, iron and folate deficiency, normal liver and kidney functionality, increased levels of CRP, VES and leucocyte count with prevalence of neutrophils. She took antibiotic therapy without benefit. For this reason, she did a chest X-ray that showed three rounded cavitary lesions, in the medium lobe on the right lung and in the medium and inferior part of contralateral one, not only referable to inflammatory areas. Chest-CT confirmed the presence of multiple spherical, regularly delimited, lesions localized bilaterally, especially in peripheral areas, variably sized (from few mm to 30 mm in the maximum diameter). The core area was composed of air or air-fluid-level and some of them presented a solid peripheral rim with little contrast enhancement. There were also some subcentimeters lymph nodes in Barety’s space. Pulmonary functional testing revealed a restrictive pattern with reduced diffusing capacity, while bronchoscopy with lung biopsy was normal. All infectious and microbiological screens were negative, such as Quantiferon TB-gold, Galactomannan, Anaplasma Phagocytophilum, Ehrlichia Canis, Coxiella Burnetii, Rickettsia, Leishmania, Toxoplasma. Serum anti-Bartonella Henselae IgG and IgM were first low titer positive but the second confirmatory test was negative. Cultures of sputum were unreaviling. Screening for malignancies and autoimmune diseases were negative and there was not an increase in peripheral eosinophils.

During the observation, she experienced abdominal pain and bloody diarrhea so she did a colonoscopy that revealed distortion of crypt architecture, inflammation of crypts, frank crypt absceses and inflammatory cells in the lamina propria, suggestive for ulcerative colitis in activity phase. She started Mesoalazine with rapid improvement of intestinal symptoms. EGDS did not show any pathological feature. Cough, though, was still present. She did a X-ray and CT follow up which showed new consolidative opacities in the same radiological features. She repeated bronchoscopy which revealed diffuse airway inflammation, a lymphocytic BAL fluid and lung biopsy with histological findings of fibrosis and inflammatory infiltration referable to constrictive bronchiolitis during ulcerative colitis.

She started steroid therapy (Methylprednisolone per os 32 mg/die) with dramatic improvement of symptoms. Radiological exams showed the disappearance of the cavitary lesions, substituted by fibrotic areas. However, during steroid-tapering, she had a relapse in pulmonary and gastroenteric symptoms, with systemic involvement (fever, arthralgias and fatigue), and a chest-CT showed the reappearance of previous and new excavated lesions. A second colonoscopy revealed an acute, left sided, colitis. It was reintroduced high-dose steroid therapy and after some months she started also Azathioprine as sparing agent. During follow-up, radiological findings showed initially a partial regression but relapsed when corticosteroid was tapered to 12.5 mg/die. At the moment, the patient is asymptomatic for abdominal symptoms but she is still presenting dry hacking cough. Because of the poor response to AZA, we are planning to start a therapy with anti-TNF agent. Involvement of the respiratory tract, although relatively rare, has been increasingly recognized in patients with IBD, although it is more frequently associated with Crohn’s disease rather than ulcerative colitis.

It can be due to the same pathogenetic factors (e.g. common embryogenic origin from the primitive foregut) or can be related to the medications used to treat that disease, but the latter hypothesis can be excluded in our case since the IBD treatment was started afterwards. In fact, most cases of respiratory tract disease occur years after the diagnosis of IBD, but occasionally, can precede the diagnosis like in our case. The activity of underlying IBD does not always correlate with the activity of lung involvement.

We want to remark especially the radiological pattern of this case, which is not frequently described in IBD lung involvement, showing usually bronchitis, bronchiectasis, fibrosing alveolitis, eosinophilic pneumonitis, non specific interstitial pneumonia, thromboembolic disease, pulmonary vasculitis, serosis.
A severe clinical picture of pancreatitis in a young nurse disclosed an underlived Wilkie’s disease


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Introduction: Wilkie’s syndrome (WS) or Superior mesenteric Artery Syndrome (SMA), first described by Rokitansky in 1861, is a rare condition due to congenital or acquired factors and characterised by arteriomesenteric obstruction of the duodenum. It occurs when the third portion of the duodenum is entrapped under the superior mesenteric artery due to alteration of the angle between the superior mesenteric artery and the aorta (which is normally 45°) and presents with abdominal pain, vomiting, weight loss, progressive deterioration of digestive functions, pancreatitis and in few cases acute course with ileus. Initially, conservative treatment including intravenous and oral fluids, nutrition, decompression, and proper positioning after food intake is recommended. Enteral feeding by nasogastric tube can be helpful as part of the treatment of severe weight loss. Medical treatment on eukinetics may be beneficial as well as parenteral nutrition in the most severe cases. Surgical treatment consists in duodenojunostomy.

Case Report: A 22-year-old woman working as nurse in our Hospital, was admitted to our Dept due to severe and acute abdominal pain associated with incoercible vomiting. Since the last six months she had experimentally relapsing abdominal pain and weight loss of about 4 kg. At word history appendectomy at the age of 13 y. The patient appeared suffering with incoercible vomiting and deep abdominal pain. Normal BP, body temperature, HR and EKG. At abdomen evaluation presence of pain at epigastrium, normal liver and spleen. Laboratory data pointed out leukocytosis and slight anaemia (WBC 13.500, RC 3.900/mmc, Hgb 11.5 g/dl, Htc 32.9%); rise of ALT and AST, amylasis and lipasis, LDH, normal bilirubin and negative EMA and tFG. Abdomen-X-ray resulted negative. Gastroscopy showed obstruction of the duodenum as in aortomesenteric compasses. Abdomen echo-color-doppler and duodenography and CT scan of abdomen disclosed the presence of a Superior mesenteric Artery Syndrome and confirmed the oedema of pancreas as in pancreatitis. After the supportive therapy on fluids, fast, antibiotics and PPI we obtained the amelioration of the clinical picture as well as the laboratory parameters, and discharged the patient with diagnosis of pancreatitis in subject afflict-ed with Wilkie’s syndrome on eukinetics therapy.

Discussion: Wilkie’s syndrome, probably underestimated, can have wide range of clinical presentation, from subtle to devastating, and acute or chronic course owing to the grading of the duodenum obstruction. It is quite rare although its precise incidence is unknown. No racial differences have been identified and usually it occurs in older children and adolescents and it seems to strike women about twice as often as men. Moreover, sometimes it can cause severe clinical pictures of pancreatitis as in our patient. Delay in the diagnosis of acute or chronic SMA syndrome can result in malnutrition, dehydration, electrolytes disorders and death! Abdomen ultrasonography color-doppler with mesenteric-aorta angle evaluation and gastroscopy represent simple, economic, with good compliance for the patients, without side effects, and over all, non-invasive methods useful to demonstrate the important reduction of the corner between meseraic artery and aorta (<20°) and to diagnose Wilkie’s syndrome.

From Schatzki to Barrett: a long story

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Introduction: Schatzki ring is a smooth, benign, circumferential tissue in the lower end of the esophagus just above the junction of the esophagus
with the stomach. These rings are very common, occurring in more than 6% of the population. The pathogenesis is not clear, and patients typically present intermittent nonprogressive dysphagia for solids. Most patients respond well to initial and repeat dilatation therapy. A small number of patients may have stubborn rings that require more aggressive endoscopic or surgical intervention. In some studies, the severity of symptoms has clearly been demonstrated to correlate with the luminal diameter. Dysphagia predictably occurs in patients with a luminal diameter less than 13 mm and depending on the size and type of bolus. The pathogenesis of Schatzki rings is not clear. Different hypotheses have been proposed: a pleat of redundant mucosa, congenital origin, consequence of gastroesophageal reflux disease or pill-induced esophagitis. The presence of Schatzki ring could determine the prevalence of Barrett’s esophagus. Barrett’s esophagus is a common condition, with a prevalence that most likely ranges from 2% to 6% in Western countries (1). In a retrospective case-control study (2), Barrett’s esophagus is less prevalent in patients with Schatzki ring, compared to patients without Schatzki ring, and long segment Barrett’s esophagus was not observed. That suggest a possible not enough explained protective mechanism against Barrett’s esophagus. In a case-control study (3) H. Pylori colonization were inversely associated with a new diagnosis of Barrett’s esophagus, suggesting a protective action partially mediated through HP. In a prospective study (4) H. Pylori appears to have a protective effect against Barrett’s high-grade dysplasia and adenocarcinoma.

**Case-Report:** Man, 63 years-old, until early childhood complaints sticking sensation in the chest with swallowing, chest pain, solid dysphagia, regurgitation and vomiting. At 39 years-old barium esophagus x-ray examination showed the presence of Schatzki ring. Endoscopy diagnoses Schatzki ring, instead the biopsies demonstrated a long Barrett’s esophagus and gastric H. Pylori colonization. The patient was treated with endoscopic dilatations, PPI and HP eradication therapy. For 25 years annual endoscopy and histology follow up confirmed a long Barrett’s esophagus without dysplasia but, the last endoscopic evaluation showed a high-grade dysplasia. The patient undergoes esophageal thoracic resection and Gastric ciprofloxacin for a concomitant urinary tract infection. After about two weeks since feomoral endoprosthesis, this patient was transferred to a rehabilitation unit. There he was submitted to clinical examination and abdominal X-ray confirming the presence of an abnormal gaseous distension of the colon and small bowel with air-fluid levels compatible with intestinal obstruction, without free air. Therefore, he was sent to our hospital. At admission, the patient showed signs of a markedly relaxed abdomen for bloating, however treatable without pain elicited on palpation. Peristalsis was torpid with metallic tones and Blumberg sign resulted negative. From nasogastric tube, entero-biliary material was not leaked but there was typical gastric retention. It was reiterated that barium enema confirmed the presence of a distal sigmoid volvulus. A rectal probe was placed with escape of gas and liquid stool and initial regression of abdominal distension. Laboratory testing indicated the presence of hypokalemia because of abundant faecal losses. However, persisting a sub occlusive state, abdominal CT with contrast showed mega colon and ectasia of the sigmoid colon (antero-posterior diameter of 19 cm and transverse one of 13 cm) without anatomic stenosis. Instrumental tests were useful to exclude major diseases. On evaluation by our team, his clinical picture was that of an “Ogilvie syndrome”. Our patient was subjected to several colonoscopic de-compressions in addition to the rectal probe and he started treatment with laxatives, stool softeners and neostigmine, an acetylcholinesterase inhibitor, working on the basis of the theory that this disease is caused by an imbalance between the parasympathetic and sympathetic nervous systems. So our patient presented a drastic decrease in abdominal girth. Ogilvie syndrome is a massive dilatation of the colon in absence of mechanical obstruction which may develop in hospitalized patients consequent to prolonged bed rest, high doses of narcotics, sepsis, surgery, electrolyte and metabolic imbalances. In conclusion, this case shows that the differential diagnosis in present of an abdominal distension may be a challenge and a failure in the diagnosis can lead to serious complications such as perforation and ischemia.

**What lies behind an abdominal distension?**


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An 83-year-old Caucasian man was admitted to our emergency department with a 30-day history of abdominal distension. His past medical history was significant for permanent atrial fibrillation, blood hypertension, hypothyroidism, a past hospitalization for pulmonary thromboembolism, a previous prostatectomy for a carcinoma, obstructive sleep apnea syndrome in a severe obesity. His medications included a beta-blocker, spironolactone, levothyroxine, furosemide, fraxiparine, vitamins. Specifically, one month before, the patient was admitted to the surgical division of another hospital to undergo a biarticular left femoral endoprosthesis following to a traumatic subcapital fracture of his femur. During his hospital stay, there was the onset of a sub occlusive abdominal framework. So the patient was transferred to the geriatriac ward, where he underwent abdominal x-ray which showed a gaseous distension of the loops of his small intestine and colon with air-fluid levels and a barium enema showing a clouding of the sigmoid and descending colon up to the left flexure with no further progression of the contrast medium without evidence of stenosis. The surgeon did not pose an indication for surgery and he was treated with enemas, nasogastric tube and rectal probe with partial benefit. Furthermore, he took ciprofloxacin for a concomitant urinary tract infection. After about two weeks since feomoral endoprosthesis, this patient was transferred to a rehabilitation unit. There he was submitted to clinical examination and abdominal X-ray confirming the presence of an abnormal gaseous distension of the colon and small bowel with air-fluid levels compatible with intestinal obstruction, without free air. Therefore, he was sent to our hospital. At admission, the patient showed signs of a markedly relaxed abdomen for bloating, however treatable without pain elicited on palpation. Peristalsis was torpid with metallic tones and Blumberg sign resulted negative. From nasogastric tube, entero-biliary material was not leaked but there was typical gastric retention. It was reiterated that barium enema confirmed the presence of a distal sigmoid volvulus. A rectal probe was placed with escape of gas and liquid stool and initial regression of abdominal distension. Laboratory testing indicated the presence of hypokalemia because of abundant faecal losses. However, persisting a sub occlusive state, abdominal CT with contrast showed mega colon and ectasia of the sigmoid colon (antero-posterior diameter of 19 cm and transverse one of 13 cm) without anatomic stenosis. Instrumental tests were useful to exclude major diseases. On evaluation by our team, his clinical picture was that of an “Ogilvie syndrome”. Our patient was subjected to several colonoscopic de-compressions in addition to the rectal probe and he started treatment with laxatives, stool softeners and neostigmine, an acetylcholinesterase inhibitor, working on the basis of the theory that this disease is caused by an imbalance between the parasympathetic and sympathetic nervous systems. So our patient presented a drastic decrease in abdominal girth. Ogilvie syndrome is a massive dilatation of the colon in absence of mechanical obstruction which may develop in hospitalized patients consequent to prolonged bed rest, high doses of narcotics, sepsis, surgery, electrolyte and metabolic imbalances. In conclusion, this case shows that the differential diagnosis in present of an abdominal distension may be a challenge and a failure in the diagnosis can lead to serious complications such as perforation and ischemia.
A 81 years-old woman was admitted to our Division of Internal Medicine for acute abdominal distention with pain in the right side and watery diarrhea. She had a clinical history of ischemic heart disease and of recent traumatic fracture of D12. Home therapy for this fracture was Enoxaparina (2,5 mg/dl). We decided to start liquids and potassium supplementation with improvement in symptoms. More likely, the increase of the anticoagulant therapy, due to pulmonary embolism, has induced an ischimia or perforation. Initially, our patient presented an acute bowel dilation without mechanical obstruction. The pathogenesis of OS is not completely understood, although more likely result from an imbalance in the autonomic regulation of colon motor function. Trauma, infection, cardiac diseases, abdominal or pelvic surgery, orthopedic surgery and neurologic diseases may alter the autonomic regulation of colon function, leading to excessive parasympathetic suppression or sympathetic stimulation. Clinical features include abdominal distention, abdominal pain (80%), nausea, vomiting and watery diarrhea (40%). The mortality rate is estimated at 40% when ischemia or perforation occurs. The best treatment of OS is intravenous neostigmine. In patients failing or having contraindications to neostigmine, colonoscopic decompression is the active intervention of choice. Surgery is reserved for those patients with peritonitis or perforation. Initially, our patient presented an acute bowel dilation without mechanical obstruction and so we decided to undergo her to colonoscopic decompression with improvement in symptoms. More likely, the increase of the anticoagulant therapy, due to pulmonary embolism, has caused the growth of a hematoma of the psoas muscle and induced an ischemia of the right colon, favoring a worsening of OS. We conclude that OS should always be suspected in patients with an acute large bowel dilatation without mechanical obstruction.
with resolution of hallucinations and stability of the MMSE (NPI 12/144). This is a fundamental aspect as the use of acetazolamide may be an alternative to shunting procedures to improve cognitive symptoms in patients with normal pressure hydrocephalus.

**Case report: fronto-temporal dementia in patient with secondary polycythemia**


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We report the case of a 79 years old male patient, who came to our observation for an assessment of the cognitive. The patient and the caregiver reported mnesic deficits associated with mild behavioral disorders, mood depression, asthenia, headache and episodes of vertigo. The patient was suffering from chronic respiratory failure, osteoporosis, osteoarthrits of the lumbarosacral spine, coxofemoral joints and of the right elbow. The patient reported a 7 year schooling, he denied alcohol consumption, tabagism. An I level multidimensional assessment was performed: the patient came out to be quite well oriented in time and space; he showed a small deficit in recording, no impairment in language and in tests evaluating the praxic and constructive ability; serious impaired in short-term memory (MMSE 21/30, corrected for age and education 20,7/30); he was self-sufficient in the basic activities of daily living (ADL 6/6 level A of Katz); he appeared partially independent in the instrumental activities of daily living (IADL 2/5); it was evident a mood depression (GDS 5/15), and finally the patient and the caregiver reported the almost constant presence of delusions, hallucinations and agitation of moderate severity and the almost constant and severe presence of euphoria/elation. The blood pressure was 140/90 mmHg.

The first diagnosis was: moderate dementia of mixed origin with predominantly vascular component. A therapy with cholinomimetics and promazine (5 drops) was started to treat the psychomotor agitation and the aggressive behavior; blood tests also were required together with ECG and brain MRI to investigate the cause of the dementia more accurately, in order to exclude secondary and reversible causes and to decide the most appropriate therapeutic strategy.

The follow-up, after 3 months, showed a persistence of behavioral disorders, hyperactivity and agitation so evident to make it very difficult to perform any tests. The patient was disoriented in time and space, he had a small deficit in recording, no impairment in language, serious deficits in tests evaluating attention and calculation, the praxic and constructive ability, the short-term memory (MMSE 12/30, corrected for age and education 11,7/30). The electrocardiogram underlined a normal sinus rhythm, 79 bpm, RBBB, left anterior hemiblock, not extrasystoles. Blood tests were compatible with polycythemia and hyperviscosity; RBC=5.72, HGB=17.4 g/dl, HCT=51.9%, vit B12=211.7 pg/ml, folate=4.7 ng/ml, iron=171 µg/dl, PLT=213, WBC=7.86. The MRI revealed: “The presence of a discrete leukoencephalopathy probably of ischemic and chronic cerebrovascular origin, in gliotic and cicatricial evolution, stabilized in the context of the white matter of the radiated crowns of semiolateral centers, deep of both frontal lobes with extension to the paratrigonal region. Discrete cerebral cortical atrophy in both hemispheres in supratentorial region with characteristics of asymmetry of development, extended in correspondence of the temporal lobes with involvement of the islets, of their polar portions and of the hippocampi “.

After analysing these tests the diagnosis was: fronto-temporal dementia of vascular secondary origin of blood hyperviscosity polycythemia. A therapy with acetylcholinesterase inhibitors (Rivastigmine patch 4.6 mg) was started and a hematology consultation was required to identify the pathogenesis of Polycythemia.

At the next monitoring the caregiver brought the haematochemical checks which underlined an increase in RBC, HGB, HCT, MCH and high values of ferritin (922 ng/ml) and erythrocyte sedimentation rate (42); the hematology consultation pointed out a non-suggestive outline for Polycythemia Vera, but secondary in nature. The hematologist then began a treatment with Hydroxyurea (500mg) and Allopurinol (300mg). The patient went on with the rest of his therapy.

At the next check, after 3 months, tests were performed but they were not very reliable because of the patient’s awareness of his own deficit and because of his poor control of the behavior disorders: agitation, irritability, euphoria. However, the patient appeared to be improved cognitively, well oriented in time and space (MMSE 16/30 corrected for age and education 15,7/30). The caregiver reported a better control of some behavioral disorders: delusions and hallucinations (2 frequency, severity 1). Blood tests pointed out a good control of the hematologic disease: RBC = 4.57, HGB = 16.5, HCT = 48.2, MCV = 89.9, MCH = 30.7, PLT = 234, WBC = 5.6, as well as a decrease in ESR (14). The therapy continued with acetylcholinesterase inhibitors (Rivastigmine 4.6 mg patch), promazine (5 drops), Acetylsalicylic acid 100mg, Allopurinol 300mg. Hydroxyurea 500mg.

The combined drug treatment with acetylcholinesterase inhibitors on cognitive impairment (Rivastigmina patch 4.6 mg) and with Hydroxyurea (500 mg) on hematological disease was able to counter the effects of hypoxic-ischemic degeneration and to reverse the decline in cognitive performance that seemed to be strongly worsening; a control of hematologic disease and a regression of inflammatory markers were observed.

**Resistant hypertension in the elderly**

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**Objective:** Resistant Hypertension (Clinical Blood Pressure > 140/90mmHg, 24-h Ambulatory Blood Pressure Monitoring (ABPM) > 135/85mmHg and Day ABPM > 130/80mmHg in spite of relevant changes in lifestyle and the concurrent use of three different antihypertensive drugs at optimal doses, including a diuretic agent) is a public health problem because patients suffering from it are more prone to cardiovascular events, especially older people because of aging, the risk is even greater. The findings suggest that the prevalence of resistant hypertension accounts for 8-12% of adult patients with hypertension. Nevertheless, there are no data on the prevalence of resistant hypertension in the elderly. And so we wanted to assess the prevalence of elderly patients resistant to antihypertensive treatment.

**Methods:** 271 hypertensive patients related to our Geriatric Hypertension Unit (mean age 76±8 years, 150 females and 121 males) with a low salt diet intake and treated with antihypertensive medications underwent clinical measurement of blood pressure (Clinical BP), 24-h Ambulatory Blood Pressure Monitoring (ABPM), according to ESH guidelines, and determination of the Body Mass Index (BMI), to investigate the percentage of resistant patients and the prevalence among these of “non dippers” (less than

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<th>Clinic BP</th>
<th>24 h ABPM</th>
<th>Day ABPM</th>
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<td>Resistants</td>
<td>17%</td>
<td>12%</td>
<td>15%</td>
</tr>
<tr>
<td>Overweight</td>
<td>59%</td>
<td>60%</td>
<td>56%</td>
</tr>
<tr>
<td>Dipper</td>
<td>63%</td>
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<tr>
<td>Non dipper</td>
<td>37%</td>
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</table>
10% reduction in SBP and DBP from day to night) and overweight (BMI>25kg/m²). Exclusion criteria were: secondary hypertension, cancer, haematological, endocrine, cardio-respiratory diseases, vasopressor therapy and nonsteroidal antiinflammatory drugs.

**Conclusion:** Our data confirm that the prevalence of hypertensive mirrors that of the general population and that the “white coat” effect is more common in the elderly. The non dipping pattern seems to be frequently associated to therapy-resistance as the high body mass index may indicate an influence on the resistance to antihypertensive therapy.

**Pathological gambling: a case of a frontal syndrome**


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**Case presentation:** A 79 years old patient came to our department complaining about cognitive impairment associated with mood depression and obsessive-compulsive disorder (pathological gambling), starting approximately three years before following a cerebral ischemic event and worsened in the last three months. The patient was affected by hypertension, ischemic heart disease with episode of angina pectoris at the age of 35 years, chronic obstructive bronchitis, bilateral sensorineural hearing loss, hyperuricemia, previous ischemic stroke with right hemiparesis in 2008, two episodes of transient ischemic attack with deviation of the rhyme buccal in 2012, angious-depressive syndrome with SSRI. In our physical examination, the patient was alert, cooperative, with mild cognitive impairment (MMSE roughly 10/30; corrected according to age and schooling=11,4/30) Routine laboratory tests (blood count, levels of electrolytes, B12 vitamin, folic acid and thyroid hormones) were in normal range. A sovraortic echodoppler showed absence of hemodynamically significant stenosis. A without contrast magnetic resonance (MRI) brain revealed cortical and sub-cortical atrophy of the frontal lobe. An electroencephalogram showed diffuse minor anomalies. The spirometry showed a slight reduction in pulmonary volumes. A neuropsychological evaluation with second level tests showed attention disorder (double Barrage), deficit of the praxic functions (copy of figures), language deficits (production semantics), and deficits in executive functions (Raven Progressive Matrices); we performed the Frontal Assessment Battery (FAB), a screening test used to assess the integrity of frontal functions, which confirmed a deficit of frontol-executive functions (FAB 11.2/18), especially deficiency in the conceptualization, planning motor and a slight deficit in mental fluidity and inhibition control. We therefore placed diagnosis of Frontal Syndrome and our patient was treated with paroxetine and mood stabilizers.

**Disscusions and conclusions:** Frontal Syndrome, that can manifest itself with the pathological gambling, is characterized by cognitive impairment associated with structural injury of frontal lobe. The patient showed behavioral disorders (changes in personality with compulsive behavior and impaired social interaction) and disability of frontal executive functions that had induced us to diagnosis of Frontotemporal Dementia but the anamnesis and the associated MRI report induced us to a vascular pathology’s diagnosis. These symptoms can not be attributed to neuropsychiatric disorders like bipolar disorder and personality disorder, since our patient had not had a history of psychiatric disorders, with the exception of pathological gambling, appeared in elderly, after an ischemic stroke. Pathological gambling should be a potential adverse effect associated with the use of dopamine agonists in Parkinson disease and in Restless Legs Syndrome, including others compulsive disorders such as pathological shopping, overeating, hypersexuality. Our patient, however, had not used use dopamine agonists and he had no symptoms of Parkinson disease or Parkinsonian syndromes. MRI of the brain showed no evidence of other structural abnormalities like trauma, Normal Pressure Hydrocephalus or tumors, moreover there was no clinical evidence of motor neuron disease (Amyotrophic Lateral Sclerosis). The framework therefore led us to a diagnosis of vascular disease, referred more precisely to a Frontal Syndrome. We treated our patient with selective serotonin reuptake inhibitors (paroxetine) in order to reduce behavioral disorders. Atypical antidepressants in small doses could be also effective, but we avoided them because of their potential adverse effects, such as extra pyramidal symptoms. We used as well mood stabilizing medications (carbamazepine) which can reduce long-term emotional fluctuations and produce positive results in patients with pathological gambling.

**Brain microbleeds and MTHFR polymorphism a clinical case of cerebral amyloid angiopathy**


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Brain microbleeds (BM) are small dot-like lesions appearing as hyposignal on gradient echo T2 MR sequence; They represent microscopic areas of old haemosiderin deposits. They are now accepted as a manifestation of cerebral small vessel disease pathologies, including hypertensive small vessel disease and cerebral amyloid angiopathy. A lobar distribution of BM is considered to relate to cerebral amyloid angiopathy, while BM located in the basal ganglia or in infratentorial brain regions are thought to relate to hypertensive vasculopathy. BM are often detected in patients with stroke, Alzheimer’s disease, and mild cognitive impairment, although they are also present in 5 % of healthy adults. BM might reflect the risk of vascular events, but their diagnostic and prognostic value has still to be proved.

We report the clinical case of a 86-years-old male patient, five years of schooling, come to our attention for an evaluation of his cognitive status. His caregiver reported a symptomatology characterized by mnesic gaps as early as one year linked to dysarthria and loss of balance. In ananmesis prostatica curative in terapia farmacologica, pregresso ascesso polmonare da aspergillo; the caregiver denied other diseases and vascular risk factors. The patient was evaluated with a multidimensional cognitive test of first level that showed disorientation in time and space, serious deficiency in those items concerning attention and calculation, registration, recall and in the ability to perform complex commands (Mini Mental State Examination, roughly 10/30; corrected according to age and schooling=11,4/30), The patient showed also some dependence in basic life activities (ADL 3/6) and in instrumental activities (IADL 0/5), some neuropsychiatric alterations came out, such as sleep disorders, apathy and indifference (NPI= 10/144; GDS: 1/15).

A brain RM was performed; it showed diffuse chronic cerebrovascular leukoencephalopathy associated with multiple lacunar lesions at the level of brainstem, basal ganglia region and thalamus, including the full thickness of the cortex and immediate subcortical white matter. Haemosiderin accumulations were also detected in the frontal, parietal and temporal lobes bilaterally; further deficit in the insulae and cerebellar regions at cortical and sub-cortical level.
The radiological description, supported by clinical history, allowed us to make two diagnostic hypotheses: encephalopathy linked to thromboembolic cardiopathy or amyloid angiopathy. The second level diagnostic tests, such as Doppler ultrasonographic evaluation of cervical and legs vessels, electrocardiogram, transthoracic echocardiogram were normal. Laboratory tests were normal except for homocysteine value (28.6 mc-mol/L). The C677T polymorphism of the methylenetetrahydrofolate reductase gene was detected. The localization of the MB and the collateral framework of marked atrophy associated with severe cognitive impairment (CDR 3), directed our diagnosis in favor of MS by angiomioptia amyloid (CAA) with degenerative character. The most effective method, after the biopsy, of determining amyloid deposits in the blood vessels and brain parenchyma is the study with PIB PET (Positrion Emission 11C-Pittsburgh compound B), which can’t be applied on a regular basis yet. Patient underwent brain SPECT with 99mTc-esametazime. It reported a diffuse thinning of the cortical component with hypoperfusion in the frontal, parietal and temporal lobes bilaterally mainly in the left hemisphere. A therapy with memantine (20 mg / day), nicergoline (30 mg/day), calcium folinate (15 mg/day) and cyanoecobalamin (2000 micrograms/week) was set. After six months, we repeated the evaluation that showed a slight improvement in MMSE (13,4/30), ADL and IADL unchanged. Laboratory tests showed homocysteine levels equal to 14 micromol/L, which is therefore within the normal range and a brain MRI control showed a picture unchanged from the previous year. This case that we have explained demonstrates how MS brain and high levels of homocysteine can be correlated with pictures of amyloid angiopathy.

AIDS dementia in elderly patient with E.coli urinary infection. A case report


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AIDS dementia complex (ADC) is a rare condition that leads to the loss of intellectual abilities such as memory, judgment, abstract thinking and changes in personality usually occurring in advanced stages of AIDS. ADC develops principally in the context of late HIV-1 infection and associated severe immunosuppression. With the advent of highly active antiretroviral therapy (HAART), the incidence of ADC has declined in developed countries, although its prevalence is increasing. A 75-year-old caucasian woman with medical history of breast, thyroid cancer, colon diverticulosis, chronic vascular encephalopathy and mild cognitive impairment was admitted to our hospital for fever preceded by shaking chills, weight loss, and chronic anemia. The patient was previously evaluated for myeloproliferative syndrome, which was excluded with bone marrow aspirate blood. An increase in inflammatory markers, anemia and leucocytopenia. Urine culture was positive for E. Coli. A chest X-ray showed no active infiltrates and was otherwise normal. The computer tomographic (CT) scan of the thorax showed no other focus of infection, while a CT scan of the abdomen and pelvis revealed a heterogeneous hypodense mass, indicative of an extensive unilateral pyelonephritis. The patient was then treated with piperacillin and tazobactam, which led to a complete recovery and discharged in discrete clinical conditions. A week later, the patient was re-hospitalized for fever. The urine culture was positive for E. Coli but antibiotic therapy did not change the clinical picture of the patient characterized by persisting anemia, leukopenia lymphocytopenia and a rapid cognitive decline with gradual changes in the personality and loss of bowels control. Finally, diagnosis of ADC was made with anti-HIV test, HIV-RNA levels in bone marrow aspirate and by the presence of lymphocyte subpopulations. The present case report strongly suggests that HIV-related dementia should be included in the differential diagnosis of dementias, particularly in immunocompromised patients with rapid cognitive decline.

Atrial fibrillation as presenting symptom of celiac disease. A case report


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Celiac disease (CD) is an immune-based reaction to dietary gluten that occurs in genetically predisposed people of all ages. CD primarily affects the small-bowel tissue, causing an inflammatory reaction and resolves with gluten-free diet. Over the last 50 years, the prevalence of CD is dramatically increased as well as an the rate of diagnosis in the last 10 years. CD is characterized by a variety of signs and symptoms, including typical gastrointestinal symptoms (e.g., diarrhea, steatorrhea, weight loss, bloating, flatulence, abdominal pain) and non-gastrointestinal abnormalities (e.g., abnormal liver function tests, iron deficiency anemia, bone disease, skin disorders). CD impaired electrolytes and carbohydrate absorption and irregular heart rhythms may also result from inadequate levels of potassium and other electrolytes. A 55 years-old caucasian women with autoimmune thyroiditis was admitted to our hospital for arhythmia, preceded by incoercible vomit for the last three months. EKG showed U-waves and Q-T interval prolongation. At the time of admission, blood tests revealed hypokaliemia (2 mEq/l) associated with metabolic acidosis. Kidney function tests and urinalysis were negative. Ultrasonography of the abdomen and abdomen CT scan showed no abnormalities while the abdomen MRI showed a parietal accentuation of the small intestine. Total body PET scan showed an increase of the tracers captation at the abdomen level related to the small intestine suggesting a non-specific captation and/or an inflammation disease. The patient underwent gastroscope which showed a small erosion at the level of the 4th portion of duodenal mucosa and the histological analysis confirmed celiac disease (3rd type sec. Mars). Gliadin and transglutaminase antibodies were negative. Gluten-free diet reversed the general disease symptomatology and the cardiac arhythmia. This case report may provide a further information of the presenting symptoms of CD.

Retroperitoneal fibrosis. A case report


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Retroperitoneal fibrosis (RPF) is a rare condition characterized by inflammation and tissue fibrosis in the retroperitoneal space, which wraps the abdominal aorta and the iliac arteries and often leads to the involvement of the...
Interventions used by nurses in multidisciplinary team to enhance adherence to medication in older patients

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**Background:** Approximately 20% to 50% of patients are not adherent to medical therapy. Elderly patients are at an increased risk of poor adherence, because of long term medical conditions, multiple comorbidities and cognitive and functional impairments. The World Health Organization identified medication non adherence as one of the major causes of morbidity, mortality and health care costs. There are many factors that can contribute to non-adherence such as: frequent changes to drug regimen, misunderstanding prescribing instructions, limited education about the medication and forgetfulness. Different multidisciplinary interventions are used for improving the knowledge and the medication adherence in the elderly patients.

**Research questions:** The question was: which intervention approaches are used by nurses in multidisciplinary team and which of them are effective by improving medication adherence in elderly patients aged 65 years or over?

**Methods:** A literature search was conducted in the medical and nursing literature databases (PubMed, Cinahl, Cochrane) in April 2013, beginning from 2007. Systematic reviews on the basis of randomized controlled trials (RCT) and reviews concerning the interventions effect to enhance adherence, were included in the evaluation.

**Results:** Four systematic reviews with data for 83 RCT were included in the evaluation and others three reviews were included. A significant positive effect on the enhancing of knowledge and adherence was reported in 4 RCT. The interventions used were: behavioral (e.g. drug compliance aid, calendars, reminders charts, programmed devices, pill boxes, dosage simplification, repeated assessment of medication use with feedback), information/educational, (e.g. individual and group teaching, verbal written or visual, medication cards, counseling about the patient’s target disease, pharma-directed care programs) and combined informational, behavioral and/or social investigations (e.g. patient education programs, medication review, domiciliary visits, manual telephone follow up, family interventions, monitoring specific health outcome, pharmacy-driven medication review). Interventions approaches used are complex and multifaceted and heterogeneous in the effects and they did not seem to work consistently across all studies.

**Discussion:** There is uncertainty about which elements of the intervention processes constitute success in improving appropriate adherence because of the differences in how the interventions were provided, in timing, or follow up measurements, in background practice and culture and in variable processes in delivery of care. Furthermore the methodical shortcomings restrict the reliability of the conclusions of the studies.

**Conclusions:** In drug therapy some adherence enhancing interventions with concomitant positive effect on the treatment outcome may be used but priority should be given to applied research concerning innovations to assist patients to follow medication prescriptions for long term medical conditions.

The evaluation of frailty by different scales in aging

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Frailty has been defined as a physiological syndrome characterized by decreased reserve and diminished resistance to stressors, resulting from cumulative decline across multiple physiological systems, causing vulnerability to adverse outcomes and high risk of death.

Fried and colleagues proposed specific diagnostic criteria (Fried's criteria) combining information on weight loss, fatigue, impaired grip strength, diminished physical activity and slow gait. Rockwood and colleagues proposed the frailty scale (Canadian Study of Health and Aging- Clinical Frailty Scale, CSAH-CFS) based on the presence of disability and polypathology. Recently, the Silver Code (Di Bari M et al 2010) has been developed as a prognostic tool that identifies older patients at an increased risk for 1-year mortality considering as predicting variables the age, the gender, the marital status, the number of drugs, the admission to a day hospital/hospital in the previous 6 months.

The aim of this study was to investigate the relationship between the different scales of frailty and the Silver Code in aged subjects.

We enrolled 85 elderly patients (mean±standard deviation, 72±6 years, n=62 women and n=23 men) coming to our Geriatric Unit. Every patient received a multidimensional geriatric assessment, including the evaluation of frailty by the means of Fried's criteria (score 0-5, frailty ≥3) and CSAH-CFS (1-7 levels, frailty >4th level) and the determination of the Silver Code (0-30 points, in four classes ranging 0-3, 4-6, 7-10 and ≥11, respectively). A statistical analysis by the linear regression analysis was performed between the scales. A p<0.05 was considered as significant.

The frailty syndrome was present in 50% of elderly subjects. The correlation between Fried’s scale and CSAH-CFS was statistically significant (r=0.867 p<0.0001). The Silver Code was significantly related to Fried’s scale (r=0.960 p<0.0001) and CSAH-CFS (r=0.399 p<0.001). The gait speed was negatively related to Fried’s scale (r=0.702 p<0.0001), CSAH-CFS (r=-0.689 p<0.0001) and the Silver Code (r=-0.385 p<0.01), respectively.

In conclusion, we showed a statistically significant correlation between the main frailty scales (Fried’s criteria are considered as the gold standard of the frailty evaluation). The gait speed represents a simple index of frailty, similar to the extensive scale from which it has been derived (Fried’s scale) and therefore it has an...
important role in the setting of care where the evaluation of frailty has to be immediate. The Silver Code was significantly related to the frailty scales, since it investigates several parameters common to the frail phenotype (such as age, polyopathy and number of administered drugs). The Silver Code can be considered in the frailty evaluation, with the advantage of requiring few simple variables of measure.

References:

Agreement between MNA, must and NRS in the evaluation of nutritional risk in elderly institutionalised subjects

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Introduction: Malnutrition occurs frequently in the elderly with important consequences in clinical and functional domains. Moreover, the treatment may be effective if we face up to malnutrition in the early stages of it. Therefore we have the need to highlight precociously the risk of malnutrition using validated and handy tools. Mini Nutritional Assessment (MNA) was validated for this purpose since many years: the “original” version consists of 18 questions grouped into 4 parts: anthropometry [body mass index (BMI), weight loss, mid upper arm and calf circumferences], clinical status [medications, mobility, pressure sores and skin ulcers, lifestyle, psychological stress or neuropsychological problems], dietary assessment (autonomy on feeding, quality and number of meals, fluid intake) and self perception about health and nutrition.

Malnutrition Universal Screening Tool (MUST) is a five-step screening tool to identify adults, who are malnourished, at risk of malnutrition (under and over-nutrition). It also includes management guidelines which can be used to develop a care plan. It is for use in hospitals, community and other care settings and can be used by all care workers.

Nutrition Risk Screening tool (NRS) was developed by the European Society for Clinical Nutrition and Metabolism and may be used to identify nutrition concerns and potential risk for poor nutrition. The questions asked address eating behaviours, food choices, food resources, weight and body image, physical activity, and the client’s readiness for making changes in these areas.

MUST and NRS were validated in acute care. In particular in surgical and cancer patients.

The aim of this study was to assess the agreement between MNA, MUST and NRS in the evaluation of nutritional risk in elderly institutionalised subjects.

Methods: a total of 250 subjects, 168 women and 82 men (respectively 82.4±10 and 76.2±11 years old), were recruited from nursing homes in Italy. All subjects underwent a multidimensional geriatric evaluation, addressed to nutritional status, cognitive and functional impairment, depression, clinical status and comorbidity. MUST and NRS results were compared to MNA scoring and classification.

Results: according to MNA, a high prevalence of malnutrition (21%) or risk of malnutrition (58%) was found. MUST an NRS provided consistently similar results. The diagnostic accuracy of MUST and NRS compared to MNA (calculated from a 2x2 table through the evaluation of efficacy, sensitivity, specificity, positive and negative predictive values) was very high.

Conclusion: although the data must be confirmed in larger samples and different settings, our first results suggest that MUST and NRS can be useful tools also in the evaluation of nutritional risk in elderly institutionalized subjects.

Does good clinical practice really modify prognosis?

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A 85 years old man was admitted to the emergency room complaining asthenia, diarrhea and left lower anterior thigh pain associated with progressive difficulty on walking and standing up from about two weeks. Laboratory tests showed mild normocytic anemia (Hb 9 g/dl,MCV 81 fl), neutrophilic leukocytosis (WBC 18000/mm³, N 15520/mm³), increased level of C-reactive protein (CRP 17.8 mg/dl, normal value < 0.4 mg/dl) and creatinine (2 mg/dl). Chest X-ray and abdominal X-ray weren’t diagnostic for acute disease; so the patient was admitted to our ward. His medical history was relevant for several comorbidities: type 2 diabetes, arterial hypertension, coronary artery disease (NSTEMI treated with PCI two years before), peripheral obliterative arteriopathy (treated with left external iliac artery PTA), previous urinary bladder cancer treated with radical cystectomy and ileal neobladder reconstruction, left nephrectomy due to recidivant pyelonephritis, chronic kidney impairment, colic diverticulosis, polidistrectual arthrosis.

His physical examination was remarkable for fever (38 °), abdominal tenderness localized to left iliac fossa, left groin pain and an anterior and lateral hip pain aggravated by direct pressure without signs of flogosis. The lower extremity pulses were palpable and the evaluation of the thigh mobility was limited by the general conditions associated to the preexisting ankylosis of the left knee. As initial investigation an abdominal ultrasonography (no signs of diverticulitis or other significant findings) and plain radiographs of the pelvis and femurs (no signs of bone disease) were performed.

So we were facing a patient with recent onset of loss of range of motion of the left hip joint, abdominal pain and history of diarrhea and clinical features compatible with sistemic inflammatory response syndrome. May we put these all together in one clinical condition like sepsis? Immediately after obtaining blood and urinary sample for cultute we started a course of treatment with empiric antibiotic therapy with ciprofloxacine. Clinical course was complicated by onset of tachypnoea, hypoxemia and increased heart rate (110 bpm, ECG finding of atrial fibrillation). To rule out diagnosis of pulmonary thromboembolism, we performed a venous ultrasound study of the legs that showed right soleal vein thromboses and because of the kidney impairment a pulmonary perfusion scintigrapy that was negative. Low molecular
weight heparin therapy, according to the kidney function, was started and dual antiplatelet treatment was interrupted. To better understand the clinical findings despite a positive urinary culture for Candida albicans that could have explained the sepsis, the patient underwent a thoracoabdominal computed tomography (CT) that showed a large fluid mass (7.5 x 20 cm) in the left iliopsoas muscle compartment, compatible with a large abscess extending to the pelvis without evidence of adjacent infected focus. Considering the clinical comorbidities we choose as first treatment an echo-guided drainage that was successfully performed obtaining 300 cc of purulent material. A culture exam of the purulent material was positive for methicillin-resistant Staphylococcus aureus and according to the antibiogram a course of therapy with vancomycin and metronidazole was started. Nevertheless, we assisted to a progressive worsening of clinical conditions and another abdominal CT scans showed the persistence of the wide partial fluid mass in the iliopsoas muscle compartment. The patient was transferred to the Surgery Department and underwent exploratory laparotomy and evacuation of large abscessural retroperitoneal left iliopsoas hematoma. At a more accurate anamnesis, no traumatic events appeared, but we knew the patient received an overlased antiplatelet treatment at home, thus increasing risk of bleeding. Postoperative course was characterized by a slow progressive improvement of clinical conditions and hematocrit levels. The final diagnosis was sepsis in patient with spontaneous hematoma with secondary development of abscess of iliopsoas muscle compartment. The patient received a physical rehabilitation and after two months of hospitalization, he was discharged at home. Nevertheless, the patient died three days later probably for a myocardial infarction. This clinical case offered several clinical considerations. First of all it reinforces the difficulty of promptly hypothesize the presence of iliopsoas abscess on the sole basis of the clinical picture. The incidence of psosas abscess is rare and the median time between the onset of symptoms and diagnosis is 22 days. Second, the clinical course of the patient highlights the need for better prognostic stratification tools in order to guide our clinical decision making process and optimize health care utilization in the complex geriatric patient.

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A study with the calcaneal ultrasound in elderly patients at risk of osteoporosis and falls

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The aging population has placed the urgent need for innovative health planning in relation to disability. In 2011, after a program agreement between the Department of Geriatric Acute Care Hospital S. Eugenio ASL RMC and the Department of Social Policy and Health Promotion, city of Rome, has launched a project for the prevention of impaired balance, falls, fractures and osteoporosis, which are made available to users of senior centers, free of charge, the equipment of the Day Hospital of Geriatrics, for screening of osteoporosis and assessment of balance disorders. Numerous studies have given impetus to the application of the U.S., with the commercialization of various devices for quantitative ultrasound. The used device available to the Day Hospital of Geriatrics was Achilles GE Lunar, when measured at the calcaneus, which is considered valid. It was developed a brochure entitled “You’re a tough cookie,” which provides actionable information on osteoporosis and falls, along with advice. We prepared various modules (inform ered consent, test information on the presence of risk factors and 3 tabs: one of physiotherapy assessment, a master, one with the results of densitometric, diagnosis and recommendations for appropriate further investigations, treatments and controls). The multidisciplinary team consisted of a geriatrician, a nurse and a physiotherapist. The project was developed between January 1 and July 1, 2011. A total of 37 access centers Elderly were carried out with conducting multidisciplinary interventions and prevention of 1396 subjects. The total sample of subjects was divided into two large clusters on the basis of diagnosis (patients divided in osteopenic, or osteoporotic healthy) and age (<65 years, 65-75 years, >75 years). The sample mean age was 73.14±6.7 years (maximum 98, minimum 53), 200 males (14.3%) and 1126 females (85.7%). The mean age was 72.74±6.6 years for women (maximum 98, minimum 53) of 75.5±6.36 for men (maximum 90, minimum 60). Sample screened (n=1396), 489 subjects were diagnosed with osteoporosis, accounting for 34.95% of the total, from osteopenia 657 (47.06%) and healthy 250 (17.91%). Ultrasonography in the total sample showed a T-score -1.99±1.6, with values -1.11±1.21 for males, -2.13±1.09 for females. The evaluation of gait showed total values of the scale Tinetti 25.38±2.95, for males 25.83±2.59 and females 25.31±2. The subjects, stratified by diagnosis, were further characterized. The osteopenic subjects (n = 657) were 83 males (12.63%) and 574 females (87.37%) age was 72.42±6.46, 75.48±6.25 for males, 71.98±6.37 for females. In this subset ultrasonography showed a T-score -1.77±0.44, with values worse in women than in men. Of the 657 osteopenic subjects, 37% (newly diagnosed) did not make any treatment, which was recommended for prophylaxis with calcium and vitamin D, as well as suggested dietary advice and environmental hygiene. The osteoporotic subjects (n = 489) were 24 males (4.91%) and 464 females (94.89%), age 74.39 ±6.58. Healthy subjects (n = 250) were 92 males (36.8%) and 158 females (63.2%), age 72.59 ±6.9. The number of subjects screened (1396) was high, and the range of age variable (maximum 98, minimum 53). The 9.31% of the total sample, 137 subjects, was made up of younger people, as is explained by the success of the initiative, which led him to request an evaluation also several companions of the original recipients of screening, including relatives and carers, of which only 24 (the 17.51%) were “healthy”, as only 250 subjects (17.91%) of the total sample. In contrast, 657 subjects were osteopenic and osteoporotic 489. Of the 657 subjects, 37% osteopenic (newly diagnosed) was not in therapy, as 21% of those with osteoporosis. The difficulty in walking demonstrated in the value of the Tinetti total score were higher in osteoporotic subjects (mean score 24.9), compared to osteopenic (25.53), compared to healthy subjects (Tinetti total score average 25.7), and this difference was significant. Osteoporosis can be prevented: for this reason, the World Health Organization has included in all programs for lifestyle-related diseases, like hypertension, diabetes, obesity. Were collected several interesting data on interventions, both with regard to motor skills that the clinical conditions, with particular reference to osteoporosis of the subjects, which may, after further statistical analysis, provide further information. In conclusion we can say that the ultrasonometry bone can be considered a valid diagnostic instrumental in osteoporosis and that this method can be applied on a large scale mainly in general screening programs, as well as our study has shown.

A not frequent adverse event of the oral anticoagulant therapy in an old patient

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The oral anticoagulant therapy (OAT) is the preventive strategy for patients at high risk of thromboembolism [atrial fibrillation (AF) and/or valvular heart disease treated surgically] against ischemic stroke and peripheral arterial embolism. However, it has several limitations, including the risk of bleeding, increased significantly for INRs above 5.0 and proportional to the duration of OAT and the time spent with high INR values. An 88 years
old patient was suffering from hypertension, chronic ischemic heart disease, hypothyroidism with thyroid nodules to the right thyroid lobe, chronic obstructive pulmonary disease, permanent AF, previous cardiac surgery (coronary bypass, aortic valve replacement with bioprosthesis). Home therapy consisted of protonic pump inhibitor, nitrates, ACE inhibitors, diuretics, calcium channel blocker, warfarin, thyroxine, SSRI. The patient came to the emergency department for abdominal pain occurring on the previous day and worsening. The general conditions was expired; the patient was alert, dyspnoeic; the abdomen was poorly treatable with generalized pain on all quadrants (Visual Analogue Scale 10/10: very severe pain). The total body CT with contrast medium (CM) showed the presence in the context of the rectus abdominis muscle of the right of a voluminous collection of high density (60 UH), diameter about 7 cm, length 20 cm, with marked hyperdensity the surrounding tissue. After contrast it signaled in the context of the collection as small spots of contrast material for minimal bleeding, most evident in the venous phase. The arterial catheterization (selective procedure for the right common femoral artery and a super-selective catheterization for the ipsilateral deep epigastric artery) and angiography were performed with documentation of a micro-hemorrhage oozing in the context of the abdominal wall to the right, stopped by embolization with microspheres (Embozene) and release of metal coils. Then, the patient was transferred to our department. At the multidimensional assessment ADL 5/6, IADL 6/8, MMSE (score 19/30), Mini Nutritional Assessment 21. The ECG showed FA at 70 bpm, complete left bundle branch block, previous inferior infarction. The chest radiography showed a reticular interstitial thickening associated with areas of confluent alveolar filling compatible with acute pulmonary edema, bilateral pleural effusions. The echocardiogram showed a dilated left ventricle with markedly concentric hypertrophy and an ejection fraction 55%, markedly dilated atrium (area 31 cm2), mild to moderate aortic stenosis. For severe anemia (Hb 7.3 g/dl), the patient was subjected to transfusion; we treated heart failure (oxygen, then suspended; clonidine 5 mg/kg, pantoprazole 40 mg/day, furosemide 50 mg, 100 mg spironolactone, losartan 50 mg, amiodipine 5 mg), dyspnea (salmeterol/fluticasone 50/500 mg, 18 mg tiotropium), AF (digoxin, then suspended), pain (acetaminophen 1000 mg, ketoprofen 160 mg as needed), agitation (promazine 14 mg as needed) and depression (escitalopram 5 mg), the dysthyroidism (50 mcg), the entrapment (enoxaparin 4000 IU), the constipation (lactulose, lactis ferments). Treatment consisted of protonic pump inhibitor, nitrates, ACE inhibitors, diuretics, calcium channel blocker, warfarin, thyroxine, SSRI. The patient was discharged to home under medical therapy and oxygen, activating the Center for Home Care for local dressings and physiotherapy, recommending the ambulatory monitoring of the abdominal wound. The hematoma of the rectus abdominis muscle is a rare cause of acute abdomen and an infrequent adverse event in the course of OAT; but unfortunately more common in elderly patients. The abdominal pain and anemia in an elderly subject in OAT pose the suspect, with a sonographic or better TC diagnosis. Transcatheter embolization is effective in interrupting the bleeding. Topical negative pressure therapy is acute skin lesions and promotes healing of chronic ones. An elderly patient with comorbidities is at risk of defective and delayed healing of these lesions, also subject to infectious complications. VAC therapy can be effective: the negative pressure removes the extracellular fluid and exudate, reduces edema, improves blood flow, providing oxygen and nutrients to the tissues at the site of injury, accelerating the healing process while also reducing the bacterial load.

Effect of 90-day supplementation with alfa-lipoic acid and a multivitamins complex on cognitive functions of a group of elderly patients with Alzheimer disease

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Background: Alzheimer’s disease (AD) is the most common and most frequent form of dementia throughout the world. It affects 35 million of people and the cost of managing the disease is estimated at 604 billion US dollars annually. AD is characterized by two major neuropathological hallmarks. The deposition of neuritic, beta-amyloid peptide containing senile plaques in hippocampal and cerebral cortical regions of AD patients is accompanied by the presence of intracellular neurofibrillary tangles. Inflammation is another hallmark of AD. Inflammation, including superoxide production (oxidative burst) is an important source of oxidative stress in AD patients. Lipoic acid (LA), a critical component of the antioxidant network, exhibits anti-amyloidogenicity for beta-amyloid fibrils in vitro. Many studies suggest that LA has the following anti-AD properties: to increase acetylcholine production by activation of choline-acetyltransferase; to increase glucose uptake, supplying more acetyl-CoA for the production of acetylcholine; to chelate redox-active transition metals, inhibiting the formation of hydrogen peroxide and hydroxyl radicals; to scavenge ROS increasing the level of reduced glutathione and down-regulating inflammatory processes. Recently, the use of antioxidant therapy has shown a slight ameliorating effect on the progression of AD. This study aims to analyse the therapeutic effect on cognitive functions of a compound with LA 600 mg and multivitamins complex, administered daily for 90-day, in a group of patients with mild AD.

Material and methods: 106 subjects, aged 70 or older, were selected in our Alzheimer Unit, to take part in the study, who met inclusion criteria: diagnosis of mild AD (DSM IV and NINCDS-ADRDA criteria) >6 months; MMSE >19/30; drug treatment by rivastigmine patch 9.5 mg/die and memantine 20 mg/die from at least 12 months; brain MRI that showed hypopacalymal atrophy. Final determination for inclusion was based on a consensus diagnosis based on clinical, functional and neuropsychological informations, laboratory test results, and MRI clinical report. Laboratory test included: homocysteine, blood glucose and insulin (0’ and 120’ after breakfast), glycated haemoglobin, PCR and VES. The randomisation procedure was conducted by a computerized system. The subjects were randomised consecutively into two different groups:
- LA Group (n=53): patients treated with LA 600 mg and multivitamins complex (carnosine, zinc, group B vitamins) daily for 90 days.
- No-LA Group (n=53): patients who had not been treated with LA.

The subjects were assessed at baseline (T0) and after 90-day follow-up (T1). All the patients were evaluated through comprehensive geriatric assessment methods: Mini Mental State Examination, Activities of Daily Living, Instrumental Activities of Daily Living, Hamilton Scale, Alzheimer

![Graph](https://via.placeholder.com/150)

Figure.
The palliative care need of people in the terminal phase of dementia: prevalence study in the hospital setting of INRCA


* I.N.R.C.A. Fermo, ** I.N.R.C.A. Ancona

**Introduction:** Dementia is a progressive terminal illness for which there is currently no cure. However health care professionals not perceiving people with dementia as having a terminal condition. People with dementia have cognitive, functional and physical impairment, which gets progressively more severe, often over a prolonged period of time (1). The number of symptoms is similar to that of people with cancer, but people with dementia experience them for longer. The care of older patients with dementia is widely inadequate: too much intervention with little benefit (tube feeding and laboratory tests, the use of restraints and intravenous medications) or too little (poor symptoms control and support for family caregivers) (2).

**Aims:** To describe the characteristics of hospital care in patients affected by severe Dementia: prescriptions of procedures with increased distress for patients, inappropriate medications use (3) and the presence of discomfort symptoms with specific scale Discomfort Scale-Dementia of Alzheimer Type (DS-DAT) (4); to identify the presence of primary and secondary clinic criteria for patients with need of palliative care in hospital setting (5) in prevision of defining “the INRCA care pathway for geriatrics patients with palliative needs”.

**Methods and Results:** The study was conducted in the Geriatric Units (Ancona and Fermo), Internal Medicine, Neurology, Long-term care Units of INRCA in a specific data: 18 patients were identified with advanced dementia using FAST scale > 7 (24% of hospitalized patients), 11 females and 7 males, mean age 84 years (DSa5 years); at the time of observation average time of hospitalization was 12 days. All patients showed clinical criteria of the Consensus report Weissman and Meier used to identify persons with advanced dementia: Identifying appropriate medications use.


**Weakness and CPK: beyond the statins**


Sapienza Università di Roma

A 74 year old woman presents with fatigue and mild weakness of both lower limbs for five years, worsened in the last two months. In 2008 she had a diagnosis of essential hypertension, in treatment with ACE Inhibitor therapy, and hypercholesterolemia. She started a HMG-CoA reductase inhibitors (statins) therapy, interrupted after a few months because of the increase of creatine phosphokinase (CPK) serum value. She had no history of cardiac disease, diabetes or neurological pathology, nor smoke or alcohol addiction; her family history showed the presence of cardiovascular diseases and diabetes. Her CPK value has always been high during these years, despite of statins interruption; she also referred weight loss. No certain information about her sleep habit and quality.

Her medical examination showed a regular cardiac activity, 68 bpm, blood pressure 150/90 mmHg, no abnormalities in lungs and abdomen, waist circumference 84 cm, with BMI score = 29. Lower limbs examination showed mild hyperalgesia and hypotonia, no fasciculations or wasting, normal reflex response, no sensation impairment. Cranial nerves and upper limbs showed no abnormalities. She underwent blood tests, EKG, echocardiogram and 24 hours blood pressure monitoring.

The results excluded any cardiovascular event or organ damage, but CPK resulted increased (630 U/l); fasting plasma glucose (FPG) was 110 mg/dL, glycated hemoglobin (HbA1c) 6%. According to international criteria (NCEP ATP III), we diagnosed Metabolic Syndrome.

We excluded chronic disease anemia (RBC 5000 x 10³, Hb 14.2 g/dL, MCV 87 fL, HCT 44%), and iron deficiency anemia (serum iron 61 μg/dL, transferrin 2.99 g/L). White blood cells, vitamin B-12, folic acid, CRP,
Pleiotropic effects of rosuvastatin on blood pressure in elderly patients with hypercholesterolemia


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Introduction: Elderly patients are often characterized by comorbidities. Hypercholesterolemia and hypertension are two of the most common pathologies in these kind of patients, especially important for cardiovascular risk. Hydroxy-methylglutaryl coenzyme A reductase inhibitors (statins) are used as lipid lowering drugs, but recent clinical trials have shown that they have other pleiotropic effects, for example on endothelial function and inflammation. The aim of this study was to determine the efficacy of rosuvastatin in lowering blood pressure, and so in providing an additional cardiovascular protection. We studied rosuvastatin because it is the most prescribed statin in our Day Service.

Materials and Methods: In this open label and prospective clinical trial we studied the effect of rosuvastatin on hypertension in elderly patients with hypercholesterolemia. Twenty-nine patients, 62% females and 38% males, with a mean age of 78.8 ± 7.24, were recruited. They had a mean serum LDL cholesterol. Twenty-nine patients, 62% females and 38% males, with a mean age of 78.8 ± 7.24, were recruited. They had a mean serum LDL cholesterol, mean systolic blood pressure of 133.9 ± 8.0, mean diastolic blood pressure of 80.8 ± 5.9 mmHg. We measured the 24 hour blood pressure mean with a 24 hour ambulatory blood pressure monitoring. During this clinical trial, patients continued to be in therapy with their antihypertensive drugs. The P value was considered significant when inferior to 0.05.

Results: After 3 months, the 24 hour systolic blood pressure mean showed a significant reduction to 127.9 ± 7.2 mmHg (P < 0.01, t-test 2.99), while the 24 hour diastolic blood pressure mean did not showed a significant modification (81.8 ± 2.99, P > 0.05, t-test 0.5). In fact systolic blood pressure was reduced by 6 mmHg, while diastolic blood pressure was increased by 1.4 mmHg. After 3 months LDL cholesterol levels were significantly reduced (2.9 ± 0.5 mmol/L, P < 0.001, t-test 13.9), with a difference of 1.7 mmol/L.

Conclusions: In this clinical trial we showed that rosuvastatin therapy can determine a significant reduction of 24 hour systolic blood pressure mean in elderly patients with hypercholesterolemia. This can be considered another statins pleiotropic effect, maybe related with an anti-inflammatory action, independently of their lipid-lowering activity.

Effectiveness of standardized care plans in health outcomes in patients with type 2 diabetes mellitus in residential care for elderly people (RSA)


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Background: Type 2 diabetes prevalence increases with age and is especially high in Residential Care (R.S.A.). In addition to the traditional cardiovascular complications, diabetes has been associated with excess risk of a number of clinical conditions typical of the geriatric population including, physical disability, falls, fractures, cognitive impairment, and depression. These conditions are common and will profoundly affect the quality of life of older patients with diabetes.

Sophisticated approaches are needed to improve the quality of care for elderly people living in residential care. We determined the effects of multidisciplinary integrated care on the quality of care and quality of life for elderly people in a Residential Care. The treatment of diabetics in R.S.A. should be improved avoiding ageism or lack of attention, improving elderly quality of life.

Materials and methods: Baseline data was collected on patients living in RSA with type 2 diabetes enrolled in a study that examined the effectiveness of diabetes care managers. The “Diabetes Study” focused on four aspects: recognition, assessment, management and monitoring. The intervention, inspired by the disease management model, consisted of a geriatric assessment of functional health every three months. The assessment included use of the Basic Activities of Daily Living Scale, Sandoz Clinical Assessment Geriatric (SCAG), Geriatric Depression Scale (GDS), Tinetti Balance and Barthel Index and a seminal nursing record. To determine the effectiveness of study we compared the data obtained with those of previous years.

Results: A total of 110 patients were included, of which 51.6% were female, mean age 69.7 years (SD = 14.5). Patients had a higher prevalence of poorer personal health habits (drinking and sedentary physical activity), dyslipidemia and diabetes complications. Patients received more treatment for diabetes (oral antidiabetic and insulin) and for cardiovascular disease, with poorer HbA1c (7.25% vs. 7.12%; p < 0.001), and better LDL cholesterol (115 mg/dL vs. 119 mg/dL; p < 0.001), than patients of the previous years. The new protocol showed a significant reduction of functional decline in ADL (p < 0.001), a reduction in the prevalence of pressure ulcers (p < 0.05), dehydration (p < 0.005) and malnutrition (p < 0.001). The prevalence of hypo/hyper glycaemia, diabetic foot, poly pharmacy, disability and depression in this population was decrease. The relationship between old treatment and new treatment was significant (p < 0.05), indicating treatment satisfaction.

Discussion: The attitude much more methodical treatment of the frail el-
Infectious Diseases

Infective endocarditis due to multidrug resistant Gram-negative pathogens: single centre experience over five years

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Background: Infective endocarditis (IE) is a severe clinical condition characterised by high morbidity and mortality rates. The vast majority of IE cases is currently caused by Gram-positive cocci. In contrast, Gram-negative bacilli account for only a small number of cases of IE. Interestingly, during the last few years, the rate of Gram-negative bloodstream infections is on the rise, and among these microorganisms multi- or extensively-drug resistant (MDR/XDR) pathogens are a growing concern. Notwithstanding, there are at present very few data about MDR Gram negative IE (MDR GNIE). In this study, we present our centre experience with the aim to improve the current understanding of the clinical characteristics, course and outcome of MDR GNIE.

Methods: Included in this study were five subjects, from October 2007 to October 2012 because of MDR GNIE. All patients (pts) were managed according to a predefined clinical protocol employed in our unit. Data were prospectively collected and are now retrospectively analysed. MDR and XDR pathogens were defined as microorganisms showing resistance to at least three different classes of antimicrobials. All pts. fulfilled the modified Duke’s diagnostic criteria for definite infective endocarditis (Li, et. al. Clin. Infect. Dis. 2000;30:633-8). Outcomes were assessed at the end of hospitalization and at the latest available follow up. Response to treatment was rated as follows: complete response was defined as resolution of clinical signs and symptoms, clearance of blood cultures and no recurrence during follow up; microbiological response as clearance of bacteremia without resolution of clinical signs and symptoms during antimicrobial treatment; treatment failure as persistence of fever and/or bacteremia by the causative pathogen, despite ongoing targeted treatment; infection-related death as patient decease in the presence of persistent symptoms and/or signs of infection. On admission, at least two sets of blood cultures were obtained from each patient irrespective of prior treatment or the presence of fever. Moreover, all included pts. underwent trans-thoracic and trans-esophageal echocardiography. After treatment start, surveillance blood cultures were drawn.

Results: pts. had been admitted to the hospital during the 6 months before IE onset. The place of acquisition of IE was deemed to be the hospital in 3 of the 5 cases. At the onset of IE 2 subjects were on antibiotics whereas all had intracardiac prosthetic devices. The causative pathogen was MDR P. aeruginosa in 2, and in one case each MDR A. baumannii, MDR B. cepacia and E. coli producing extended spectrum beta-lactamases (ESBL). Each pathogen had a broad drug resistance pattern, in particular, 3 cases fulfilled criteria for XDR, the other 2 for MDR. Co-pathogens were isolated in 4 of 5 pts., all were MDR bacteria. Treatment was based colistin use or on carbapenems. In pts. with XDR pathogen infection, meropenem was added to colistin, despite of its documented in vitro inactivity, in the attempt to obtain a synergistic effect. Coverage for co-pathogens was given, mostly with a carbapenem. Cotrimoxazole was used against the single case of Stenotrophomonas maltophilia bacteremia whereas vancomycin or daptomycin were administered for S. aureus. With these treatments, a complete response was obtained in one pt, microbiologic response was obtained in 3. Definite treatment failure in 2 pts. with persistently positive cultures despite intracardiac device removal or valve replacement. In-hospital infection-related death occurred in these two pts.. One pt. died in hos-
hospital after transvenous pace-maker catheter extraction. One pt. was discharged from hospital in the absence of persisting signs of infection and after resolution of the IE episode, but died shortly after due to cardiopulmonary complications. 4 pts. underwent cardiac surgery. Two pts. underwent transvenous pacemaker lead extraction. One pt. underwent open-heart surgery with aortic valve replacement combined with splenectomy due to a spleen abscess. One pt. was considered unfit for surgery.

**Conclusions:** MDR GNIE is mostly a heath-care related disease, associated with intra-cardiac devices, with a high mortality rate. Antibiotic options available, either as monotherapy or in combination, appear poorly active. The lack of knowledge regarding the emerging issue of MDR pathogens and the low rate of MDR GNIE likely contributed to the poor observed outcome.

### Carbapenemase producing klebsiella pneumoniae: incidence and prevalence in a single Internal Medicine unit

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**Clinica di Medicina Interna 3 – IRCSS AOU San Martino IST – Genova**

**Background:** Multiresistant drug germ infections are an important cause of morbidity and mortality. These infections also have an important impact on sanitary costs due to the need of aggressive therapy and days of hospitalization. Moreover patients in internal medicine units are often elderly and frail, with two or more comorbidities; infections in this subset of patients increase the number of hospitalizations which lead to a higher risk of producing more antibiotic resistance. Bacterial resistance to antibiotics is a worldwide health problem, in particular Klebsiella pneumoniae producing carbapenemase (CRKP) seems to be the most concerning challenge to clinicians, especially in Italy where the bacterium seems to be endemic and where colistin resistance is more often frequent.

**Methods:** We retrospectively collected isolations of of CRKP from inward patient of our unit in year 2012. We considered data about comorbidities, antibiotic susceptibility of the isolated strains and response to therapy with evaluation of outcome.

**Results:** We collected 57 isolations of CRKP from 21 patients. Mean age was 77 (range 59-89). Cultures were positive from urine (64.9%), blood (17%), upper respiratory tract (8.77%), infected wounds (8.77%). Antibiotic therapy was tailored on single patient according to our infectious diseases clinicians, especially in Italy where the bacterium seems to be endemic and where colistin resistance is more often frequent.

**Conclusions:** CRKP isolations are increased in our unit in 2012, while in 2011 they were reported as occasional. Rapid identification and isolation of CRKP colonized or infected patient seems to be the better strategy in order to prevent epidemic clusters in hospital wards. Very few antibiotics are effective on these germs; colistin resistance is another important matter of concern; combination therapy could be a valid option to avoid development of other resistance. Moreover, we suggest a carbapenem sparing strategy when possible, in order to reduce the incidence of new carbapenemase producing bacteria.

### Anaerobic pericarditis: an unusual cause of fever and chest pain in a patient with unrecognized Waldenstrom’s disease with AL amyloidosis


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**Introduction:** Pericarditis caused by anaerobic bacteria is a rare condition, but it can be serious and life-threatening.

Here we present the case of a patient with pneumopericardium successfully treated with prompt antibiotic therapy in the diagnostic suspicion of anaerobic pericarditis.

**Case report:** A 67-years-old man came to our Emergency Ward in the June of 2012 for fever of 4 days duration with posteriorly irradiated chest pain, that was exacerbated by deep inspiration. His past clinical history was significant for: permanent atrial fibrillation; mi-
tral valve replacement with a Starr Edwards prosthesis in 2005: IgM monoclonal gammopathy (3 g/dL) diagnosed since June 2010; acute myocardial infarction undergone percutaneous treatment (primary angioplasty and bare metal stent implantation on the middle tract of the anterior descending artery) in December 2010; elective percutaneous angioplasty and stenting of the proximal tract of the anterior descending artery, and intrastent angioplasty of the middle tract of the same artery in December 2011. In the February 2012 he had an episode of acute heart failure during a febrile affection with thrombophlebitis of the right great saphenous vein.

In our Emergency Ward he was febrile with blood pressure 80/60, heart rate 77 bpm, peripheral oxygen saturation 98% while breathing room air. The ECG showed atrial fibrillation, low voltages in peripheral leads, left anterior hemiblock and signs of previous anterolateral necrosis. Among the blood tests, white blood cells were 6.860/mm3 (75.2% neutrophils), C-reactive protein was 10.65 mg/dL (n.v. <0.5), creatinine 1.38 mg/dL (n.v. 0.67-1.17), INR was in therapeutic anticoagulant range with normal serum electrolytes and liver function. A chest CT-angiography excluded pulmonary embolism and aortic dissection, but documented the presence of mild pericardial effusion with small bubbles inside the pericardium, anteriorly the right atrium.

Then he was admitted to the Internal Medicine Department and he was promptly treated with intravenous meropenem 1 g t.i.d. and metronidazole 500 mg t.i.d. The patient presented rapid defervescence and disappearance of the chest pain; a new a chest CT performed on the 2nd day of hospital stay showed almost complete disappearance of the pericardial bubbles. Blood cultures (executed after initiation of antibiotic therapy) resulted negative. An esophagus-pericardial fistula was excluded by means of double-contrast esophagography and esophagogastroduodenoscopy. During the hospital stay, also the diagnosis of a previously unrecognized Waldenstrom’s disease due to lymphoplasmacytic lymphoma with associated AL amyloidosis was substantiated.

The patient was then referred to the amyloidosis regional center where a cyclic treatments consisting of cyclophosphamide (then substituted with bortezomib), rituximab and dexamethasone was prescribed.

Conclusions: The case presented illustrates a rare case of acute pericarditis due to anaerobic bacteria successfully treated with prompt initiation of appropriate antibiotic therapy, that likely resulted life-saving. Often the initial source of the infection in anaerobic pericarditis remains undetermined; in our case we speculate an odontogenic spread, having excluded also an esophagus-pericardial fistula. Finally, it is likely that the anaerobic infection was facilitated by the relative immunodeficiency owing to the underlying and previously unrecognized Waldenstrom’s disease.

A long history of infection

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A 61-year old man, suffering from chronic pyrosis, hypertension and vascular encephalopathy, was referred to our unit for anorexia, altered mental status, diarrhea and seizures successfully treated with diazepam. Blood tests showed acute renal failure with hyperkalemia, so that was necessary the placement of a central venous catheter (CVC) in the left internal jugular vein for subsequent hemodialysis treatment. During hospitalization, the patient presented recurrent febrile episodes, CVC malfunction with pus leakage, whereby CVC was removed. Culture tests performed on catheter tip showed Staphylococcus auricularis, treated with amoxicillin and clavulanic acid for a week with defervescence. Another CVC was positioned in right internal jugular vein to continue hemodialysis for two weeks, until partial renal function recovery, despite the presence of bilateral hydronephrosis and macroematuria. Subsequently, the patient presented oedema to the upper right arm: CT examination showed extended thrombosis of right subclavian, axillary and humeral veins with minimal thrombotic apposition in left internal jugular vein and superior vena cava, despite of therapy with low molecular weight heparin. Further examinations showed a malignant thickening of the posterior bladder wall. Hospitalization was again complicated by fever with increased inflammatory markers, treated with empirical large broad-spectrum antibiotic therapy with tetracyclines and carbapenems, switched to vancomycin after Staphlococcus aureus isolation from blood cultures. The patient presented also Clostridium difficile diarrhea and worsening anorexia. Accordingly,a total parenteral nutrition was at first administered through the apparently working CVC, despite the thrombotic process. Fever persistence during large broad-spectrum antibiotic therapy has raised fungal infection suspicion. Consequently, empirical therapy with echinocandin was begun. Cultures performed on CVC’s tip and blood cultures taken before and after CVC removal, respectively, 50 and 55 days of hospitalization showed Candida albicans and Candida glabrata. Despite antibiotic treatment adjustment and continuation of antifungal therapy, patient died by septic shock 77 days after admission. Thrombosis and candidemia are frequent complications in patients with central venous catheter (CVC). The incidence of this disease has increased in recent decades due to diagnostic improvement and the increased use of CVC. The onset of Candidal Thrombophlebitis of Central Veins (CTCV) frequently causes a prolonged hospitalization and increased incidence of mortality (40%). Prolonged antibiotic therapy, total parenteral nutrition, immunosuppression, surgery, dialysis, extensive burns and the presence of CVC represent the major risk factors for CTCV. In our opinion this is an emblematic case: a more and more frequent reality in internal medicine departments related to frail patients with multiple comorbidities, CTCV to date is almost always fatal despite appropriate and timely therapy.

Old problems with new problems

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Backgroud: Sepsis is a potentially deadly medical condition characterized by a systemic inflammatory state (SIRS) due to infection. Each year sepsis causes more deaths than prostate cancer, breast cancer and HIV/AIDS combined. Furthermore, sepsis involves huge economic costs, regarding hospitalization and long-term sequelae, in addition to the costs in terms of human lives. The greater proportion of septic patients comes from internal medicine units, and we also observed an increased incidence of sepsis in the last year, with a high mortality rate. According to recent studies, the incidence of the condition is increasing due to the aging of the population, the large use of high-risk interventions in all age groups and the development of certain infections more virulent and drug-resistant. The infectious agents are usually bacteria but can also be fungi and viruses. While gram-negative bacteria were previously the most common cause of sepsis, in the last decade, gram-positive bacteria, most commonly staphylococci, are thought to cause more than 50% of cases of sepsis

Aim of the study: The aim of our study was to identify which factors might be possibly involved in the onset of sepsis in patients admitted to our department. Another aim of the study was to outline a risk card intended to classify patients at high or low risk of developing sepsis and rationalize blood cultures use.

Patients and methods: All consecutive patients admitted at Clinica di

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Medicina Interna 1 (Azienda Ospedaliera Universitaria San Martino e IST – IRCCS) from January 2009 to December 2012 were included in the study. Of these 1378 patients, 136 presented a diagnosis of sepsis, with a cumulative incidence of 9.86% and a crude mortality rate of 41.91% (57/136). Of all these patients, 86 (63%) were admitted for sepsis and 50 (37%) developed the clinical features of sepsis during hospitalization. 31 patients (36%) admitted for sepsis died despite of therapies, but mortality rate was higher in the group who developed sepsis during hospitalization (52%). The mean age of patients was 75.36 years old, 73 were men (54%), with a mean stay of 34.57 days. The mean stay decreased over the years from 49.75 days in 2009 to 24.22 in 2012. In 2009, patients admitted for sepsis had a lower mean stay compared to those who developed sepsis during hospitalization, but over the years this difference was almost canceled. Of all the patients examined, only 60% had positive blood culture at diagnosis. For each patient were defined the main clinical features and reported personal data, all comorbidities, blood exams and cultural isolation.

Results and Conclusions: Neoplastic patients, with increasing trend during the last year, seem to be at high risk of developing sepsis, but a recognition and early treatment of sepsis would allow to obtain a better outcome in terms of survival in this group of people. The widespread use of central venous catheters, and total parenteral nutrition, although sometimes necessary, it would seem also involved in promoting a greater incidence of septicemia, and same goes for the presence of pressure ulcers, which often turn out to be the start of the outbreak of septic phenomena. The type of germ involved does not seem to affect significantly mortality rates, as opposed to sites of infection, for which we found a higher mortality in patients with lung infections or pressure sores. Sepsis diagnosis was made by blood cultures (in accordance to the criteria of Sepsis Survival Campaign 2012) which resulted positive in approximately 60% of cases, but only if drawn in the first 72 hours of symptoms onset. Platelets and inflammation are closely related and the mean platelet volume, in particular, has recently been correlated with the risk of sepsis and a high MPV seems to correlate with a worse outcome in terms of survival. Early recognition of the septic state is crucial to improve the survival of these patients and identifying patients at high risk for sepsis in an attempt to implement simple, low cost measures, can have a huge impact in terms of spending on health and survival of these patients.

Rhabdomyolysis and pancreatitis: an unusual association
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U/O Semiotica Medica Università D’Annunzio Chieti

Case Report: A 88-year-old-man was admitted to our Department for non-bloody diarrhea and fever, not associated with abdominal pain, treated at home with Loperamide without significant improvement. The patient had a history of permanent atrial fibrillation in antiplatelet therapy, previous ischemic stroke and Parkinson’s disease treated with carbidopa/levodopa. He denied raw meat, fish and spoiled food consumption. On the admission, physical examination showed only dryness of mucous and skin, signs of dehydration. The vital signs and remaining physical examination were substantially normal. Laboratory tests revealed: serum creatinine 3.27 mg/dL, blood urea nitrogen (BUN) 42 mg/dL, D-Dimer value over 2000 ng/mL, Troponin 10,109 ng/mL, myoglobin 1897 ng/mL. During the first days of hospitalization laboratory tests also showed signs of rhabdomyolysis (myoglobin over 2000 ng/mL, CK-MB max 14,1 ng/mL, and troponin 1 0,264 ng/mL) complicated by acute kidney failure without electrolyte abnormalities (serum creatinine max value 4,95 mg/dL), systemic phlogosis (CRP 17.60 mg/dL, Procalcitonin 19.9 ng/mL) and mild lymphopenia. In view of the clinical findings, a Widal Wright test was performed and resulted in the normal range. Furthermore, because of the history of Parkinson’s disease treated with levodopa and persistent diarrhea and fever, a neuroleptic malignant syndrome [1] cause was suspected. The patient was treated with massive intravenous administrations of fluids associated with urinary alkalization with resolution of laboratory findings of rhabdomyolysis. Furthermore, during the hospital stay we observed a significant but asymptomatic increase of amylase and lipase, and ultrasound showed signs of edematous pancreatitis without gallstones. The patient underwent strict fasting without improvement. After a week, coprocultures and blood culture results were obtained and resulted positive for a Salmonella group B infection.

Discussion: A diagnosis of Salmonella group B infection was made. The patient was treated with appropriate antibiotic therapy with resolution of clinical and laboratory findings. Salmonellosis usually manifest with self-limiting enterocolitis, but rarely can cause a persistent bacteremia with extra-intestinal manifestations particularly in debilitated patients [2]. Every organ can be affected, but sites of preexisting structural abnormalities are the most vulnerable although the underlying pathophysiology is not completely understood. To our best knowledge, this is the first case of pancreatitis caused by an infection by Salmonella group B associated with severe rhabdomyolysis.

References:

Infective endocarditis: definite, possible or rejected?
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A 76 year-old man presented to our Emergency Department on April 2013 for fever and low pack pain; two days before admission the patient developed acute urinary retention, which was treated with bladder catheterization. No other acute event was reported, but his wife reported “difficult speech” in the last weeks. In his past medical history the following diseases were reported: mechanical aortic valve replacement surgery in 1991; replacement of the aortic root for aneurysm in 2012; chronic low back pain due to arthrosis and multiple spinal disc herniations, with sensorimotor polyneuropathy of the legs; mild anemia and thrombocytopenia associated with spleen enlargement, in periodic hematologic follow-up; benign prostatic hyperplasia. His medications included acenocumarol, bisoprolol, furosemide, tamsulosin, pregabalin and vitamins. At admission physical examination revealed spleen enlargement and dysarthria; laboratory tests confirmed anemia (hemoglobin 9 g/dl), mild thrombocytopenia (platelet 133000/mmc) and increased reactive C protein (14.7 mg/dl, normal value < 0.5 mg/dl); PT INR 4.2. Brain CT scan excluded acute events. The patient was treated with levofloxacin in the hypothesis of urinary tract infection, with normalization of body temperature and of reactive C protein levels. Acenocumarol was replaced with heparin at therapeutic dosage, to perform invasive investigations. The patient was diagnosed as having a mature B-cell neoplasm associated to myelodysplastic syndrome, with spleen involvement (bipolar diameter 17.5
Erysipelas: non-trivial diagnosis of non-trivial disease


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We describe the case of a 38 year old man who came in emergency room for continuous-remitting fever with maximum bets of 40 ° C, associated with shaking chills and diffused arthralgias, lasting from about 24h. Came to our observation the patient had heart rate 140 bpm, blood pressure 95/60 mmHg, respiratory rate 22 breaths / min, columnar left lower limb edema, splenomegaly, lateral cervical and inguinal lymphadenopathy. The first blood chemistry investigations showed leukopenia (2.660/uL) with 95/60 mmHg, respiratory rate 22 breaths / min, columnar left lower limb edema, splenomegaly, lateral cervical and inguinal lymphadenopathy. The weak positivity for ANA (1/80) and AMA (1/80), the absence of rheumatoid factor, the positive result for TAS, and the septic fever suggested more a reactive arthritis than a primitive immunological disease.

On the other hand, the sepsis, the inflammation of the left lower limb, and the inguinal reactive lymphadenopathy indicated strongly the possibility of an infectious disease. Serological and direct testing for the most likely infectious agents was performed. The clinical manifestation and discovery of 4 positive blood cultures for the presence of group A Streptococcus pyogenes have allowed us to make a diagnosis of Erysipelas, and, given the patient’s history, of recurrent Erysipelas complicated by reactive arthritis. The patient was treated with Ampicillin 12 g/die, Methylprednisolone 10 mg/die, Acetylsalicylic acid 4 g/die followed by prophylaxis with Penicillin G benzathine 1.200.000 UI every 3 weeks. The fever disappeared after two days of targeted antibiotic therapy; systemic inflammatory indicators and the arthritis gradually reduced and the patient showed no recurrence of symptoms during 6 months of surveillance.

Erysipelas is commonly an infectious disease with easy diagnosis and therapy, but sometimes occurs with the grave clinical picture of sepsis or recurrent Erysipelas –both present in our patient- so configuring a not-trivial condition.

A sever misdiagnosed urinary tract infection

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We describe a case of a 75 years old woman which underwent neurosurgery intervention in April 2012 for meningioma complicated by triventricular hydrocephalus, treated with implant of ventriculoperitoneal derivation. In May 2012 she hospitalized for urinary sepsis, unresponsive to empiric antibiotic therapy with ceftriaxone and levofloxacin, with detection of E. faecalis on blood cultures, treated with meropenem. She also had abdominal pain with diarrhea caused by C. difficile, treated with vancomycin. A month later, she had a new hospitalization for the persistence of fever, dysuria, strangury and abdominal pain, treated with ceftriaxone and levofloxacin, with recurrence of diarrhea and a new isolation of C. difficile-related toxin, treated with metronidazole. In July 2012, for the recurrence of fever and widespread abdominal pain with headache, she performed brain CT, which resulted similar to the previous one, and a transesophageal echocardiogram, which showed no vegetations. Therapy with levofloxacin and metronidazolo was continued. Because of the persistence of symptoms, the patient was hospitalized and admitted to our department.

The patient had altered mental status with Glasgow Coma Scale (GCS) 14. She had fever (38.9°), with normal vital signs. Blood tests showed leukocytosis (13000/mm3) with neutrophilia, mild microcytic anemia, normal procalcitonin (0.26 ng/mL) and elevated C-reactive protein (82 mg/L). Hepatic and renal function were normal. Urine examination was suggestive for urinary infection. For the persistence of fever and worsening of abdominal pain, differential diagnosis included a complication related to C. difficile infection, infection of ventriculoperitoneal derivation and pielonephritis, and abdominal CT scan with contrast media was performed.
It showed multiple fluid collection of mesentery, which was suggestive for septic emboli abscesses. Transesophageal echocardiography was performed again, with detection of aortic endocarditis. During hospitalization, no microorganism was isolated from 10 blood cultures. On the basis of the previous antibiogram for *E. faecalis* performed during the first hospitalization, therapy with imipenem, daptomycin and ampicillin was started, without further clinical improvement. After few days, we found the results of an urine culture performed as outpatient just before the admission to our department, showing the isolation of *Klebsiella pneumoniae* carbapenemase producing (KPC). On the basis of antibiogram, we started therapy with tigecycline and gentamicin. Because of further neurological worsening with coma (GCS 6), we performed a brain CT, which showed tetra-ventricular hydrocephalus. External ventricular drainage was positioned and the bacterial culture on cephalorachidian fluid confirmed the presence of KPC. However, it was resistant to tigecycline. Intratecal administration of gentamicin was then started, but no clinical improvement was observed. *Klebsiella Pneumoniae* is an opportunistic pathogen for human mainly related to a nosocomial infections of urinary tract and pneumonia. The major risk factors for infection are: long hospitalization stay (especially in intensive care units), immunosuppression, elderly patients, prolonged antibiotics therapy and invasive medical devices. The clinical presentation is highly variable: patients can be asymptomatic or can present the clinical features of sepsis. The incidence of multidrug-resistant *Klebsiella Pneumoniae* (resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides) is increasing and since 2009 also carbapenem resistance has developed. Carbapenems are last-line antibiotics for treatment of infections with multidrug-resistant Gram-negative bacteria, including those which produce an extended-spectrum beta-lactamase (ESBL). Treatment options for patients infected with carbapenem-resistant *K. pneumoniae* or other carbapenem-resistant bacteria are severely limited. In these cases is indicated a multi-drug therapy with colistin, rifampicin, tigecycline and meropenem. Despite this therapy the mortality exceeds the fifty per cent.

**Renal mycetoma: a severe complication in a diabetic patient with poor glycaemic control**

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A 63yr-old woman was referred to our Department of Internal Medicine because in the last two months had had asthenia, fever, profuse sweating, polyuria, polydipsia and stranguary. Her medical history was relevant for hypertension, diabetes mellitus, COPD, uterine prolapse with urinary incontinence. At the admission in our Department, physical examination revealed harsh breath sounds, pain in the left iliac fossa, peripheral edema, upper limb weakness and bilateral lower limb pain. Blood chemistry showed increased rates of cell lysis (CPK: 21,273 U/L, myoglobinemia: 2059 ng/mL, LDH: 1610 U/L), positive inflammatory markers (CRP: 20.380 mg/dl, ESR: 67, ferritin: 460 ng/ml, white blood cells: 15.100/microliter) and urinalysis with marked leukocyturia and presence of nitrates. During hospitalization a positive urine culture for *Candida albicans* was obtained and renal ultrasonography showed the presence of multiple oval hyperechoic lesions with parenchymal localization in the right kidney. CT and MRI scan confirmed the existence of multiple nonhomogeneous cortico-medullary lesions of triangular form. The evidence of these injuries in the context of acute inflammation, associated with *Candida* infection and rhabdomyolysis, brought to a diagnosis of acute fungal pyelonephritis. Hyperglycaemia, the frequent use of corticosteroids and urinary incontinence were likely responsible for the development of renal parenchymal mycetomas. The patient was given antifungal treatment with fluconazole 400 mg daily for one month, followed by an improvement of symptoms and CT imaging, associated with normalization of blood chemistry and urine culture.

**Carbapenemase-producing Klebsiella pneumoniae (KPC) infection in elderly frail patients with multiple comorbidities: report of an experience in a subacute critical care unit of a large regional hospital**

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**Background:** Carbapenemase-producing Klebsiella pneumoniae (KPC) is an emerging multidrug resistant nosocomial pathogen, described for the first time in the United States in 2001. It may cause epidemic outbreaks of serious systemic infections in hospital in-patients with a high degree of frailty and clinical complexity and a large number of comorbidities. Its intrinsic resistance to almost every antibiotic therapy makes these infections particularly difficult to treat, with a documented mortality rate next to 60%. The first epidemic outbreak in Italy was described in 2009, while our hospital was involved for the first time in July 2011.

**Aims:** The aims of our research were to describe the characteristics of a KPC outbreak in a subacute critical care ward and to assess the effect of sanitary measures (bed isolation vs cohort isolation).

**Materials and methods:** At Internal Medicine and Critical Subacute Care Unit of Parma University Hospital (94 beds managed by care intensity) we consecutively studied all patients infected by KPC (133 patients, M 75, F 58, mean age 79±12 years) from August 2011 to May 2012. We recorded main diagnosis, comorbidities, length of hospital stay, outcome (discharge or death), anatomical district of KPC isolation for all patients. Following Emilia-Romagna Regional Guidelines, all infected patients, all contacts of these patients and all bedridden patients of the same ward were subdued to a rectal tampon for KPC detection every 7 days until discharge or death. From September 2011 to February 2012 we also activated a 14-bed isolation ward applying a staff cohorting management. In the previous and following period we instead applied the traditional contact isolation approach.

**Results:** During the first two months of epidemic outbreak with the traditional contact isolation approach we observed 41 new cases (23 in the first month and 18 in the second month). The cases were limited to an average of 8 cases per month (range 3-13) in the following 5 months after the activation of the 14-bed staff cohorting ward. After the restoration of the usual contact isolation measures, we initially observed a maintainance of incidence rates (9 new cases in March 2012), followed by a new increase (respectively 15 and 18 cases in April and May 2012). Mean length of hospital stay of KPC-positive patients was significantly longer than that of other patients admitted to our unit (35±2 vs 18±1 days, p<0.001). In most cases, KPC was isolated in rectal tampon cultures and only in few cases in other biologic fluid cultures. 29 patients out of 133 (14%) deceased during hospital stay. Most of the deaths were attributable to septic shock and occurred in the first two months of the epidemic outbreak. The most prevalent comorbidities were cardiopathies (84/133 patients, 64%) and COPD (72/133 patients, 54%).

**Conclusions:** KPC infection is quickly emerging as a relevant health issue, especially in elderly frail inpatients with multiple comorbidities. Mortality in our setting has however been lower than that described in literature. Staff cohorting isolation measures may be effective to limit the epidemic spread, al-
though a periodicity in KPC infections, like the one observed for other Enterobacteriaceae, cannot be excluded.

An addicted staphylococcus


University of L’Aquila - Department of Life, Health and Environmental Sciences

A 46-year-old male patient, 20 cigarettes per day smoker, HCV+, with an history of toxic substance abuse and recent previous traumatic fractures of right arm, both limbs and nasal septum, was admitted to our Department for intense back pain extended from the lumbar to the cervical tract, also involving scapular girdles and arms. Moreover, he complained of limb weakness and walking difficulties. One week before for the same symptomatology he was unsuccessfully treated with non-steroidal anti-inflammatory drugs. At the admission the physical exam was negative, except for a moderate hepatomegaly; neurologic evaluation revealed no cranial nerve abnormalities, dysesthesia with dorsal sensory levels at the ninth and tenth dorsal somites, lack of coordination, negativity of Mingazzini’s sign, reduced deep tendon reflexes, ataxic gait and sphincter disorders. Laboratory tests showed neutrophilia with high ESR and CRP. Blood cultures were negative. Therefore, investigation on infective, immunological and/or neoplastic causes were ruled out. In particular, a neurophysiopathological evaluation showed signs of dorsal myelopathy or secondary myelopathy, thus further diagnostic tests were performed: somatosensory and motor evoked potentials and electromyography described an injury of the pyramidal tract prevalent at the upper limb level. A full spine MRI showed an anterior epidural fluid collection of 4 mm of maximum thickness determining a reduced amplitude of the cervical spinal canal; between the fifth and the eighth dorsal vertebral bodies a corpuscular collection of 9 mm of maximum thickness in the rear epidural space was showed, resulting in compression and signs of ischemic injury of the bone marrow as well as a voluminous ovoid mass at the left side (42 x 60 x 36 mm), with intense peripheral enhancement and wide central area of colliquation; transverse process of the sixth dorsal vertebral body and the posterior arch of the sixth rib revealed alteration of signal intensity due to infiltrative process. All of these signs were suggestive for an infectious-inflammatory disease. A CT-guided percutaneous spinal biopsy of the sixth dorsal vertebral body was performed: the histological examination only showed striated muscle tissue with hemorrhagic extravasation, otherwise bacterial culture revealed Staphylococcus aureus infection. Targeted broad-spectrum antibiotic therapy was started (imipenem/cilastatin and teicoplanin). A chest-CT confirmed the MR, showing the thickening of soft intercostals tissues, ground-glass opacity at both lung bases, numerous enlarged mediastinic lymphnodes (max 18 mm). An echocardiogram evidenced tricuspid posterior leaflet prolapse; a pulsed Doppler study showed tricuspid insufficiency, but endocarditis was ruled out. We diagnosed a paravertebral abscess by Staphylococcus aureus infection, so he was transferred to the Thoracic Surgery Unit and underwent surgical debridement of the epidural abscess.

Discussion: Cervical localization of vertebral osteomyelitis is relatively uncommon, excepting for toxic substance abusers, due to injection of infected material into the forearm veins and the local spread of infection to the paraspinous venous plexus in the cervical region. In adults, the disc is avascular and the organisms invade the end-arterial arcades in the metaphyseal region adjacent to it. Subsequently, the infection spreads by direct extension with rupture of the infective focus through the endplate into the disc. It may extend from the vertebral body to the subligamentous paravertebral area, the epidural space and contiguous vertebral bodies. Spinal instability after destruction of the disc, bone and posterior elements may cause compression of the spinal cord or nerve root. Common organisms include Staphylococcus aureus and streptococcus species, but gram-negative bacilli are also frequently isolated in intravenous drug abusers. Neurological deficit is related to a spinal epidural abscess in about one-third of cases, resulting from the occlusion of the blood flow to the spinal cord, thrombosis of the venous drainage system or an abscess-induced vasculitis. However, it seems likely that the primary etiology of neural damage is a mechanical compression, playing the vascular injury a secondary role.

Mononucleosis-like syndrome: a misleading condition


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A 29-year-old woman came to our attention for fever and rash. A week before hospitalization, because of the rapid onset of fever up to 38 °C, sore throat, lateral cervical lymphadenopathy and diarrhea, amoxicillin clavulanate therapy was prescribed. The therapy was suspended at day 4 for the appearance of erythematous-drus, not itching, rash at the trunk and at the root of the limbs. Antibiotic therapy was then replaced with clarithromycin, without benefit. The patient was then admitted to our Hospital. Physical examination was unremarkable, except for hard-elastic, painful, mobile, about 1 cm of diameter lymphadenopathy in the right lateral cervical, right supravclavicular, bilateral axillary and bilateral preauricular sites. Skin examination revealed a non-pruritic erythematous-drus rash at the head, trunk and root of the limbs. The tongue was coated, pharyngeal tonsils were erythematous. Chest radiograph and abdominal ultrasound were performed to evaluate an infectious etiology and resulted normal. Laboratory tests showed: leukocytes 8300 cells/μl (6800 neutrophils, 1080 lymphocytes with some reactive ones, 400 monocytes), elevation of inflammatory markers (C Reactive Protein 112 mg/dL, normal values < 6 mg/L) and transaminases (SGOT 14 times the upper limit of normal, SGPT 40 times the upper limit of normal). Blood cultures, throat swab and stool cultures were collected and resulted negative. Soon after admission antibiotic therapy was stopped. Patient denied unprotected intercourses, contact with children or travels abroad. Considering the hypothesis of a mononucleosis-like syndrome with rash appearance after amoxicillin clavulanate therapy and the increase in liver enzymes, serology for EBV, CMV, HIV and HCV, HBV, HAV was obtained. Moreover, in consideration of the presence of erythematous-drus skin lesions in patient non vaccinated for rubella and measles, serology for these two viruses was performed. Antibody assays showed a serology consistent with previous infection with EBV, negativity for CMV, HCV, HBV, HAV, HIV and rubella; whereas measles antibodies were consistent with recent infection (IgM positive, IgG negative).

We therefore concluded for acute measles infection complicated by hepatitis. Few months later, a 40-year-old woman was admitted to our Hospital with similar clinical conditions: fever, erythematous-drus not itching rash after amoxicillin therapy located at the trunk and limbs, erythematous pharyngeal tonsils, lateral cervical and inguinal microlymphadenopathy. Laboratory tests showed: leukocytes 3700 cells/μl, elevation of inflammatory markers (C Reactive Protein 97 mg/dL, n. v. < 6 mg/L) and transaminases (SGOT 25 times the upper limit of normal, SGPT 18 times the upper limit of normal). In consideration of the previous clinical case and a confirmed professional exposure, we supposed acute measles infection with hepatitis. Nevertheless, serology for EBV, CMV, HIV, HCV, HBV, HAV, rubella and measles was obtained and it showed recent measles infection (IgM positive, IgG negative).

Actually, even thought measles virus infection is not considered common in adulthood, it should always be supposed in the presence of the typical char-
acreristics, because measles outbreaks involving people over the age of 20 years have been reported in the U.S., with 25% of total cases in 2008 [1]. Furthermore, measles hepatitis is generally underdiagnosed because often it is asymptomatic or presents with nonspecific symptoms, but its incidence is considerable, in some reports estimated up to 80% [2]. The course of measles hepatitis is benign and it resolves in few weeks without sequelae.

**References:**

**Clinical features of pyogenic liver abscesses in a northern Italy hospital**

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Pyogenic hepatic abscesses are relatively rare, though untreated are uniformly fatal. The aim of this pilot study was to review pyogenic liver abscess clinical features in our Northern Italy hospital.

**Methods:** We reviewed the data of a consecutive series of patients, examined at S. Croce Hospital in Cuneo, Piedmont, with a diagnosis of pyogenic liver abscess between 1st January 2009 to 31st December 2011.

**Results:** Of 23 cases reviewed, 13 were male. The mean age was 66 years. The most common symptoms were fever (91.3%) and right upper quadrant pain or tenderness (69.5%). The most common laboratory abnormalities were an elevated white blood cell count (in 73.9% of cases), a low albumin level (91.3%), and an elevated Gamma-glutamyl transpeptidase level (86.9%). Only 21.7% of patients had an elevated alkaline phosphatase level. 43.5% of patients had diabetes. The median abscess number was 1.5 for patient. 33.3% of blood culture were positive: Staphilococcus epidermidis was identified in 42.86% of cases in which a contaminated blood culture was suspected; Escherichia coli was identified in 14.28% of cases. 21.7% of the be the etiologic organisms: 40% had Escherichia Coli isolated, 20% had Klebsiella pneumoniae isolated.

Fifty-two percent of cases involved treatment with percutaneous drainage.

**Conclusions:** This is a pilot study to identify pyogenic liver abscess patients clinical patterns. Our preliminary data suggest that, in our hospital too, Escherichia Coli is the predominant etiology.

**An epileptogenic bacillus**


University of L’Aquila - Department of Life, Health and Environmental Sciences

A 30-year-old female patient, affected by psoriasis and systemic erythematosus lupus, previous smoker, was admitted to our Department for a three-months symptomatology characterized by recurrent evening fever, fatigue, weight loss and a two-months intense lumbar backache resulting in walking limitation. Three months earlier she was admitted to another hospital due to two episodes of generalized seizure, intense fronto-orbital headache, severe low back pain and acute pericarditis. During the hospitalization chest x-rays was negative and echocardiogram demonstrated moderate pericardial effusion. Bronchoscopy with cytologic examination of the bronchoaspirate revealed numerous macrophages (68%), polymorphonuclear leukocytes, bronchial epithelial cells and necrotic areas. Cultural examination of the bronchal lavage fluid for common bacteria, mycobacteria common bacteria, mycobacteriumtand fungi and fungi was negative. Laboratory exams showed neutrophlic leukocytosis, increase of the inflammation markers (erythrocyte sedimentation rate > 100 mm/h); blood and urine culture were negative. Moreover a dorso-lumbar spine-CT was carried out, demonstrating multiple lesions of vertebral bodies (between the eleventh thoracic and the first sacral vertebra) compatible with abscesses. At the admission to our Division the physical examination showed mild neck stiffness and cervical, thoracic and lumbar spine tenderness to touch, lack of sensory-motor deficits, lower extremities weakness and bilaterally positive Laségue’s sign. Tumor markers as well as infective and immunological tests were performed: PSA, CA-125, CA 19-9, AFP and Mantoux tuberculin skin test were negative, while interferon-gamma release assays was undetermined. A brain and full spine MRI was performed, revealing a T2-wighted hypointense brain area (17x15 mm) with intense nodular enhancement on post-contrast images, surrounded by hyperintense edema and infiltrating both tentorium cerebelli and transverse sinus; solid lesions appearing isointense, with large ring enhancement and surrounded by hypointense edema, extended between the eighth thoracic to the fifth lumbar vertebral body, also involving sacrum and iliac wings. In order to further investigate these findings, a whole body-CT was performed, showing spread subpleural nodules, mild left pleural effusion, multiple hilar, para-aortic and mediastinic lymph nodes, some of which presenting central colliquiative necrosis, minimal pericardial effusion, osteolytic lesions at the iliac wings, right ilio-pubic branch, ischial tuberosities, several dorsal and lumbar vertebral bodies, the body of the sternum, the anterior arch of the right second rib and the left scapula. A whole body bone scan demonstrated multiple areas of intense activity in the appendicular and axial skeleton, suggesting metastatic involvement. The biopsy of the patient’s skin lesions revealed a pattern of granulomatous osteomyelitis with Langhans-type giant cells, and the Ziehl-Neelsen staining technique detected some acid-fast bacilli with absence of neoplastic epithelial cells. Based on clinical presentation and laboratory, radiological and scintigraphic findings, a presumptive diagnosis of tuberculosis was made. Thus, anti-tubercular therapy with rifampicin, ethambutol, isoniazid and pyrazinamide was started.

**Discussion:** Extrapulmonary manifestations of tuberculosis involving the central nervous system (CNS) due to haematogenous spread are not a rare entity. Tuberculoma is a granulomatous inflammatory process rarely mimicking a malignant neoplasm in the radiological study. Our case is an unusual presentation of a giant brain tuberculoma interpreted as a malignancy by the MR, while CT revealed bone infiltration. Diagnosis could be established on the basis of the pathology results of a brain biopsy or detection of DNA of Mycobacterium tuberculosis in the PCR study. Our case revealed atypical disseminated lesions located in the axial and appendicular regions. In this case there were multiple lesions in the small bones of the hands and feet, as well as in the wrists, distal forearm and legs. This pattern of lesion distribution is less likely to be related to a primary or secondary skeletal tumor, therefore other possibilities (like tuberculosis) should be considered, especially in the endemic areas.

**An unusual case of sinusitis**

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**Case report:** We present the case of a 59-year-old white woman with a history of uncontrolled diabetes mellitus type 2 and hypertension who was admitted to our Department because of persistent right hemifacial pain asso-
associated with homolateral periorbital edema, exophthalmos, ptosis and blurring of vision. No history of traumatic head injury was reported and a head CT scan showing sinusopathy with complete destruction of the medial wall of the right maxillary sinus and sphenoidal sinus and nasal fossa involvement was performed at the onset of clinical manifestations, one month before hospital admission. Neither thrombotic lesions in intracranial vessels nor aneurysms in ophthalmic artery were demonstrated. Seven day antifungal treatment with ceftazidime and moxifloxacin was implemented with no apparent clinical benefit. The patient had been getting progressively worse with right visual field loss and increasing right hemifacial pain and swelling. Blood tests were unremarkable except for high fasting plasma glucose and elevated inflammation markers. The patient underwent fiberoscopic right sphenoidal sinus debridement and therapy was shifted to fluconazole and ceftazidime. One week later a head CT-scan evidenced further disease progression with pterygopalatine fossa and orbital apex involvement. A head-MRI scan confirmed complete right sinususes and homolateral extracranial muscle involvement. The patient underwent sinus surgery and ethmoidectomy and biopptic samples were sent for microscopic analysis. Therapy was empirically shifted to intravenous liposomal amphotericin B (L-AmB) and ceftazidime. Patient was finally moved to our Department to carry on antibiotic therapy and to monitor general status, especially worsening renal function, plasma glucose levels and fluid and electrolyte balance (because of the onset of amphotericin-related hypokalemia). Physical examination confirmed local edema and right visual loss. Blood tests showed elevation of inflammation markers, high fasting plasma glucose (332 mg/dl), abnormal glycated haemoglobin (12%), increased serum creatinine (1.74 mg/dl) and blood urea nitrogen (77.3 mg/dl) levels. Complete blood count demonstrated normochronic normocytic anemia (haemoglobin 10 mg/dl) with normal leukocyte count (6240/µl). Antibodies to human immunodeficiency virus (HIV) were negative. Fluid balance was carefully monitored to prevent acute renal injury and hypokalemia was corrected. Multi-kinetic insulin regimen was implemented. According to pathognomonic morphologic findings of right-angle branching irregular hyphae with only occasional septae, definitive diagnosis of mucormicosis was possible and posaconazole 400 mg bid on full meals was added. After 10 day-course of antimicrobial chemotherapy, the patient was able to lift the eyelid up and periorbital edema was significantly reduced. Because of substance increase in serum creatinine levels (up to 2.65 mg/dl) L-AmB was withdrawn deescalating therapy to posaconazole alone. After 26 days of hospital stay the patient was discharged. Clinical examination showed eyelid function recovery, complete resolution of periorbital edema but no improvement in visual field loss. A head-MRI scan confirmed extracranial muscle and retroorbital fat amelioration with persisting lesions at the lateral wall of the ethmoid sinus. After 12 month-course of antifungal therapy, posaconazole was discontinued.

Discussion: Mucormycosis is an uncommon invasive fungal infection (IFI) caused by ubiquitous fungi of the Mucorales order. Immunocompromised patients are at increased risk of developing the disease. Diabetes mellitus is considered a major risk factor: high glucose plasma levels are reported to induce qualitative abnormalities of neutrophil functions. Kno-orbito-cerebral disease can be rapidly fatal with a mortality rate of 40% despite adequate antimicrobial treatment. This IFI must be excluded in all patients with known risk factors showing persisting nasal obstruction and discharge, facial pain and headache with or without signs of orbital and CNS involvement. Pathognomonic and early signs such as palatal necrotic eschar are present in a minority of patients (20-40%), while other patients have signs of direct invasion of the CNS. In the past survival was critically linked to aggressive surgical procedures such as exenteratio orbitae. Now, computed tomography and magnetic resonance imaging allow early diagnosis. This, combined with the availability of new antifungals, might reduce the importance of surgery. L-AmB (5-10 mg/kg daily), is less nephrotoxic and has better pharmacokinetic properties compared to conventional amphotericin B and is therefore considered the first line antifungal option for mucormicosis. Reconstituted L-AmB must be diluted with 5% dextrose so that adequate adjuvant of insulin regimen could be required. Renal function and serum potassium must be closely monitored. An orally administered antifungal triazole, posaconazole, alone or in combination with L-AmB, is reported to be effective for the treatment of mucormicosis and it can be considered as a valuable alternative to L-AmB in case of resistance or toxicity. Long-term antifungal regimens should be continued up to 12-18 months. Data are lacking and further studies are needed to evaluate duration of treatment regimens along with the impact of posaconazole in mucormicosis therapy.

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Clinical Pharmacology

Use of proton pump inhibitors in elderly population: risk of clinical adverse events and possible underlying mechanisms

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Background: Despite the effectiveness of proton pump inhibitors (PPIs), high exposure and/or inappropriate treatment period have been associated in older individuals with fractures, infections, pneumonia, mortality and lower insulin-like growth factor-1 (IGF-1) levels. However, the impact on mortality and potential underlying mechanisms are poorly understood. We investigated the relationship between PPI use and mortality, bone quality and IGF-1 levels in 3 populations of elderly.

Methods: PPIs use and risk of 1-year mortality and rehospitalization was tested in 491 patients (80.1±5.9yrs) discharged from 11 acute care Italian wards, using time-dependent Cox proportional hazard regression. The relationship between PPI and IGF-1 and bone quality was tested, respectively, in 938 (536 women, 402 men, 75.7±7.4 yrs) and 1038 subjects (452 men, 586 women, 75.7±7.4 yrs), of the InCHIANTI study by multivariate-adjusted linear regression analysis.

Results: PPI use was independently associated with mortality (HR, 1.51 [95%CI:1.03-2.77]), but not with the endpoint death-rehospitalization (1.49 [0.98-2.17]). An increased risk of mortality was observed in patients with high doses of PPI (HR, 2.59 [95%CI 1.22-1.76]). In 938 subject of the InCHIANTI study, 35 PPI users, after adjustment for age, PPI male users (107.0±69.6 vs 127.1±55.8, p<0.001) and female (87.6±29.1 vs 107.6±52.3, p=0.03) had lower IGF-1 levels compared to non-users. In the whole population, after adjustment for age and sex, PPI users had lower IGF-1 levels 81.9±61.1-113.8 vs compared with non-users 110±77.8-148.6, p=0.02. After adjustment for multiple confounders, the relationship between PPI and IGF-1 remained statistically significant (β±SE=18.09±9.38, p=0.05). In 36 PPI users of total 1038 subjects, we found a significant lower vBMDc after adjustment for age, sex and compared to non-users (180.5±54.8 vs 207.9±59.4, p=0.03) but not significant differences in total BMD and vBMDc.

Conclusions: In the elderly, inappropriate PPIs use is associated with mortality, low trabecular BMD and low IGF-1 levels.

References:

**Emergency Medicine**

**Cardiocerebral resuscitation for out-of-hospital cardiac arrest**

Astazi P., Bianchi A., Masi P., and Sciannamea L.

*Azienda Regionale Emergenza Sanitaria 118 – Regione Lazio – Italy*

**Introduction:** Cardiocerebral resuscitation (CCR) has been shown to improve neurologically intact survival from cardiac arrest (CA). This protocol emphasizes high quality minimally interrupted chest compressions, delayed active ventilation and early epinephrine administration. It was adopted by several Emergency Medical Services (EMS) and by A.R.E.S. 118 – Regione LAZIO.

**Case report.** A 62-yr-old male suddenly became unconscious without breathing effort. EMS’s dispatchers provided telephone instructions for bystander cardiopulmonary resuscitation (CPR). A.R.E.S. 118 EMS’s team managed a witnessed CA by ventricular fibrillation (VF), according to CCR protocol. A shock at 360 J was immediately delivered (Fig.1), continuing continuous-chest-compressions and bag-mask O₂ ventilation a bradycardia pulseless electrical activity during anaphylaxis

Astazi P., Pistellini B., Masi P., and Sciannamea L.

*Azienda Regionale Emergenza Sanitaria 118 – Regione Lazio – Italy*

**Introduction:** Anaphylaxis is a sudden-onset, immediate or retard allergic reaction that sometimes implies a risk of death. Fatalities can be due to asphyxiation from laryngeal swelling, to the collapse from hypotensive shock, to cardiac arrest (CA), or to acute severe bronchoconstriction causing respiratory failure.

**Case report:** A 41-yr-old male was found unconscious with stridor and agonal breathing in the countryside where he was working alone. Emergency Medical Service’s team (A.R.E.S. 118 – Regione LAZIO) managed a not witnessed CA (Fig.1) by pulseless electrical activity (PEA). Hypoxia (Sat.pO₂:<50%, visible cyanosis, swollen lips-tongue) and distributive shock were immediately considered. Established a venous access, adrenaline 1 mg every 3 minutes, fluid therapy (1 litre NaCl), corticosteroids, antihista-mines were administrated, continuing high quality continuous-chest-compressions and bag-mask O₂ ventilation. Direct laryngoscopy showed laryngeal swelling and intubation was achieved without stopping chest compressions, obtaining an oxygen saturation of 98% with a rapid reduction of cyanosis. A tachycardia soon appeared and radial pulse became palpable.
Paraparetic syndrome of lower limbs

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The authors want to propose a clinical case represented by a young woman who came to their attention for paraparetic syndrome of lower limbs suddenly arose after reported sudden movement of the spine with sensory motor syndrome, paraparesis, anesthesia and hypesthesia with D8 spine level. Blood tests, CT scan and MRI without contrast, PEM, PESS, neurological and neurosurgical consultations were performed, on suspicion of mielie disease. All tests were normal, in particular spine MRI has highlighted only a small herniated discs median-paramedian bilateral L5-S1 with modest compression on front side of dural sac that did not justify the syndrome. Then was considered the presence of a somatoform symptom. Symptoms were so described as medically unexplained, nonorganic, psychogenic, hysterical, conversion, or functional. In the case of psychogenic movement disorders frequently physical injury has been reported as a recent antecedent of motor and sensory conversion symptoms in modern reports and the clinical characteristics of patients with conversion symptoms are associated with physical injury. It was not possible to seek associations between types of injury and symptoms, as the nature of the injury was often not clearly stated. We proceeded to an in-depth medical history with family members who reported an abortion with surgical intervention, anxiety disorders linked to emotional problems associated with behavioral abnormalities for which the patient since the age of 4-5 years was followed by a specialist in family counseling center. The suspension of treatment for about 1 year, the change of the school, the exit of father with affective abuse from family, the loss of baby produced manifestations of conversion disorder particularly striking. So the patient returned home with prescription of psychological support.

Is the patient’s anamnesis and physical examination still useful or valid in emergency department activity??


*S. Camillo-Forlanini RM; **ARES 118 Lazio

The anamnesis (AN) and the physical examination (PE) let the physician to diagnose the illness at the bedside of patient in 76-88% of cases and this is more simple for cardiac and respiratory pathology than for others. Also in real or estimated critical conditions seen in Emergency Department (ED) the anamnesis and the physical examination, completely performed (survey, palpation, percussion, auscultation, sensitivity and mobility) on the undressed patient, did demonstrate to be the essential basis of physician activity: -to make a diagnosis, even if they can be imbricated and extremely concise as in the cardiac arrest or in the trauma (ABCDE); -to prescribe the right examinations and the correct therapy Moreover the same physician or others can repeat again an AN and a PE on the patient along the time and the data found in these occasions help them to confirm the diagnosis or to correct a possible discordance. This is not only an index of collaboration among fel-

Conclusions: Anaphylaxis is a rare but dramatic medical emergency.


*S. Camillo-Forlanini RM; **ARES 118 Lazio

The anamnesis (AN) and the physical examination (PE) let the physician to diagnose the illness at the bedside of patient in 76-88% of cases and this is more simple for cardiac and respiratory pathology than for others. Also in real or estimated critical conditions seen in Emergency Department (ED) the anamnesis and the physical examination, completely performed (survey, palpation, percussion, auscultation, sensitivity and mobility) on the undressed patient, did demonstrate to be the essential basis of physician activity: -to make a diagnosis, even if they can be imbricated and extremely concise as in the cardiac arrest or in the trauma (ABCDE); -to prescribe the right examinations and the correct therapy Moreover the same physician or others can repeat again an AN and a PE on the patient along the time and the data found in these occasions help them to confirm the diagnosis or to correct a possible discordance. This is not only an index of collaboration among fellows. Indeed, this last one can derive from the PE different executions and can be ascribed to: -the presence of different pathologies in the same patient; -the variability and/or the evolution of symptoms; -the different place where the PE is made (noise, light, etc); -the insufficient or incomplete execution of PE. This last occurrence can happen: for the influence of time factor (overcrowding); for the inexperience and/or the occasional use of specific manoeuvre or approximately; for the expectation to find an objective datum estimated from AN or derived from Triage. All this happens daily in ED,
Severe hypoglycemia requiring admission in an emergency department is associated with poor outcome in patients with type 2 diabetes

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Background and aim: Hypoglycemia is a relatively common event in patients with type 2 diabetes. Few studies investigated the long-term outcome among patients who experienced an episode of severe hypoglycemia. Recently some investigations showed that hypoglycemia is associated with adverse clinical outcomes. However most of these studies are based on post-hoc analyses of randomized controlled trials, which included selected patients with strict treatment schedules so that they may not reflect what happens in a setting of everyday clinical practice. Patients requiring admission in an emergency department for severe hypoglycemia might represent a particularly fragile population at risk of more frequent adverse events. Aim of the present study was to evaluate long-term outcomes in patients with type 2 diabetes who experienced an episode of severe hypoglycemia requiring hospital admission in an emergency department of a tertiary hospital.

Methods: We retrospectively retrieved all patients with age >18 years admitted to emergency department of our hospital from 1st January to 31st December 2011 for an episode of hypoglycemia.

Severe hypoglycemia was defined as a transient dysfunction of the central nervous system requiring help from health service with evidence of decreased plasma glucose concentration and rapid attenuation of those symptoms by correction of the low glycaemia. We adopted a recall strategy by physician telephone interview addressed to patients, relatives, institutions or local administrations to collect data on clinical outcomes. Primary outcomes were considered death, readmission in emergency department, hospital admission and falls at home.

Categorical and continuous variables are expressed as number (percentage) and mean +/- standard error, respectively. Actuarial probability analyses were performed using Kaplan-Meier method.

Results: During one-year period, 64 patients experienced an episode of severe hypoglycemia. Five patients had not diabetes while 12 patients had type 1 diabetes. In 4 cases we were unable to provide data on clinical outcomes. The remaining 43 patients had type 2 diabetes and were included in the present study. Twenty-six (60.5%) patients were male and age was of 79 +/- 2 years. Thirty-three patients assumed oral hypoglycemic agents whereas 14 patients used insulin (four patients used both drugs). Twenty-eight (65.1%) patients had a history of cardiovascular disease, 10 (23.3%) cerebrovascular disease, 6 (14.0%) cancer, 5 (11.6%) dementia and 7 (16.3%) renal failure. Seven patients experienced at least a previous episode of hypoglycemia. The glucose level at the moment of the diagnosis of hypoglycemia was 39 +/- 3.7 mg/dl.

During a mean follow up of 57.8 +/- 4.2 weeks, 11 (25.6%) patients died. Mortality at 12, 24 and 52 weeks was 7.0%, 14.0% and 20.9%, respectively. The actuarial probabilities to survival were 85% and 77% at 24 and 52 weeks, respectively. During follow up, 22 (51.2%) patients needed a new admission in the emergency department and 15 (34.9%) patients required hospital admission. Five (11.6%) patients experienced a fall at home reporting bone fractures in 3 cases.

Conclusions: Patients with type 2 diabetes who experienced an episode of severe hypoglycemia requiring admission in an emergency department have considerable long-term mortality. Moreover, these patients show significant morbidity requiring frequent hospital readmissions. Further prospective studies should be performed to investigate about predictive factors associated with poor outcomes in such a population.

A really unusual chest pain

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Sometimes common symptoms of a cardiopulmonary emergency can hide a complex pathology. A 35 years old woman came to the Emergency Room for symptoms such as recurrent chest pain and upper left limb paraesthesias, persisting from more than five months. These symptoms occurred frequently when she was working and coughing whereas they regressed with rest. She attended several admissions to various hospitals and she was subjected to routine blood tests and heart checks, always resulting in the standard. Furthermore, X-rays of the chest, cervical spine and left shoulder exams were carried out all resulting negative as well as she was visited by various specialists Orthopedics, Rheumatologists, without any conclusive diagnosis. When we saw the patient she was alert and oriented, with normal vital parameters; abdominal,
The Syndrome of Arnold Chiari I is a posterior fossa malformation characterized by the lack of development of the bony structures and the herniation of the structures contained therein. Hence both the cerebellum and brain trunk displace through the foramen magnum into the spinal canal. It is often associated myelomeningocele, syringomyelia, spina bifida and hydrocephalus. Symptoms such as cranial nerve involvement (dysphagia, dysphonia, etc.), spinal cord compression (paresesias, spasticity, loss of ambulation and fine movements), the brain trunk involvement (palpitations, sleep apnea and more rarely chest pain), intracranial hypertension (headache, neck stiffness) are resulting. It is a rare malformation, in 2% of cases is familiar.

Conclusions: Although the majority of chest pain faced at the Emergency Room are cardiopulmonary emergency, sometimes it’s necessary to broaden the diagnostic spectrum as the mentioned case demonstrated. Early diagnosis allow to intervene promptly arresting the progression of syringomyelia.

Multi-organ dysfunction in heatstroke: case report

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A 46 years-old man with no significant previous medical history presents with an episode of loss of consciousness while running the eleventh kilometer of a half marathon; reportedly, the patient is unconscious for about 30 minutes before regaining consciousness on his own. On paramedics’ arrival, the patient is conscious with the following vital signs: ABP=100/60 mmHg, HR=120 bpm, sO2= 95%, blood glucose concentration=55 mg/dl, no significant focal neurological deficit. Later in the ER, the patient is still conscious but disoriented and dehydrated (serum creatinine level=2.08 mg/dl, blood sodium level=154 mmol/l, Hct=54%, Hb=18.2 g/dl); the arterial blood gas (ABG) shows metabolic acidosis (pH 7.309, pCO2 43.6 mmHg, pO2 70.4 mmol/l, sO2 92.4%, HCO3: 18.0 mmol/l). Then the patient exhibits a sudden deterioration: in fact he becomes unconscious and agitated, and shows signs of tachypnea, tachycardia and muscle rigidity with ischemic, isocyclic and normally reactive to light pupils; he also develops a febrile peak (39.5°C) on the first day. Despite this rapid improvement, alterations of the laboratory studies persist: hypertransaminasemia (GOT=3748 U/L, GPT=6773 U/L), coagulation panel (INR=2,14 PTL=70000/ul ATIII 54% D-dimer>2000 ng/ml APTT 39,1sec PT 35%), renal function (creatininemia 2,13 mg/dl BUN 31 mg/dl), hypernatriemia (Na+=154 mmol/l), high levels of hematocrit and hemoglobin (HCT 54% Hb 18.2 g/dl), neurophilic leukocytosis (WBC= 15820/ul neutrophils 90.5%), increased necrosis enzymes (Tnl=7,564 ng/ml Myoglobin 1410 ng/ml CMK 43.8 ng/ml), increased LDH (9648 U/L) and CPK (2985 U/L). The urinary toxicology test, thoracic RX, ECG and echocardiogram are negative. Based on this clinical status, the patient is administered a hydroptic therapy, vitamin K, vitamin B and ATIII; on the third day of hospital stay in the ICU, he is transferred to the internal medicine ward and in the following days he is asymptomatic and shows good hemodynamic parameters (ABP 110/70 mmHg, HR 55 bpm, good urine output) with no fever. The arterial blood gas (ABG) and the laborotistic studies show gradual improvements (pH 7.402, pCO2 40.1 mmHg, pO2 89.3 mmHg, sO2 98%), with the exception of the hypertransaminasemia (GOT 50 U/L, GPT 174 U/L on patient’s discharge). The instrumental exams (abdominal ultrasound, echocoldoppler of supra-aortic vessels, EEG, Holter ECG, repeated brain CT, brain MRI, MRA of the intracranial circulation).

Discussion: Intrinsic factors, such as an inadequate hydration before the race and a suboptimal training, and extrinsic factors, such as the environmental conditions (i.e. high environmental temperature) all lead to the initial heatstroke with the subsequent increase of metabolism, body temperature, cutaneous blood flow and decrease of splancnic perfusion. These alterations then lead to the uncompensated stage; in fact the dehydration and the energy depletion cause an exaggerated inflammatory response, cellular anoxia and further elevation of the body temperature, leading to heatstroke with multi-organ dysfunction.

References:


Time of admission from the emergency department and outcome of internal medicine patients: association with in-hospital mortality


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Background: Patients are more likely to die when admitted through the emergency department (ED) on the weekend (Bell et al, N Engl J Med 2001; Sharp et al, Am J Emerg Med 2013). Several possible explanations have been given, such as medical understaffing (number and expertise), and reduced availability of diagnostic facilities (Lee et al, Med J Malaysia 2012; Smith et al, Emerg Med J 2013). On the other hand, these data have not been confirmed in intensive care units (Ensminger et al, Chest 2004; Luyt et al, Crit Care Med 2007). Moreover, it has been observed that in-hospital mortality and length of stay depend on the duration of the visit in the ED (Singer et al, Acad Emerg Med 2011). The aim of our study was to assess which factors, related to evaluation in the ED, were associated to in-hospital mortality in patients admitted to the medical department.

Patients and methods: We analyzed age, sex, time of arrival to the ED, waiting time, and color code of all patients admitted to the medical department of the Azienda Ospedaliera-Universitaria di Ferrara, Italy, during the
period from 01/01/2010 to 31/07/2012. Our Medical Department includes four Internal Medicine and two Infectious Diseases units, Geriatrics, and Gastroenterology, and accounts for more than 25% of all hospital admissions. Time period was classified into holidays (weekends + festive days) and weekdays, and day-time (08:00-20:00) and night-time (20:00-08:00). The end point was in-hospital mortality.

**Results:** We evaluated 13237 consecutive patients (43% males), with a mean age of 76±13.5 years. The majority of admissions occurred during the day-time (71.6%) and in the weekdays (73.9%). The more frequent color coding of hospital admission was yellow (69.2%), followed by green (24.6%), and red (6.2%). Of total sample population, 1336 (10.1%) died after an average hospital stay of 8.2 days.

As for univariate analysis, in-hospital mortality was related to time of admission (day-time 74.5% vs. 71.3%, night-time 25.5% vs 28.7%, p = 0.015), day of the week (weekends 28.6% vs 25.8%, weekdays 71.4% vs 74.2%, p = 0.026), and during holidays (holidays 30.4% vs 27.4%, no holidays 69.6% vs 72.6%, p = 0.021). Furthermore, in-hospital mortality depended on both color code of admission (9.5% for green, yellow for 64.8%, 25.7% for red, p < 0.001), and patients’ age (76±14 vs. 80±12, p < 0.001). Multivariate analysis showed an independent association between in-hospital mortality and color code of admission (yellow: OR=2.5 [CI 2.06-3.026], p<0.001, red: OR=17.1 [CI 13.6-21.5], p<0.001, age (OR=1.024 [CI 1.019-1.03], p<0.001), male gender (OR=0.844 [CI 0.75-0.95], p<0.001), and day-time hospitalization (OR=0.773, [CI 0.67-0.89], p<0.001).

**Conclusions:** This study shows that periods classically at risk for in-hospital mortality, i.e., night-time, weekends and holidays, are not independently associated with it. Differences with previous findings may depend on different health service organization in different Countries. In Italy, in fact, even on holidays, night-time and weekends, the medical staff, albeit reduced in number, is equally competent and experienced. Again, diagnostic and specialist facilities are equally available at any time. In-hospital mortality appears rather to depend on non-modifiable factors, i.e., disease severity at the time of hospitalization, age, and sex.

**Time of admission from the emergency department and outcome of internal medicine patients: association with hospital length of stay**


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**Background:** Due to the significant paucity of economical resources, hospital length-of-stay (LOS) is a crucial point. LOS has been reported to be related to different patients’ features, such as sex, age, type of disease, and time of admission. Admission during weekends and night-time seem to be independently associated with higher LOS [Earnest, BMC Health Serv Res 2006]. However, data about LOS in Italian hospitals are very limited.

The aim of this study was to assess the relationship between emergency department (ED) evaluation and LOS in patients admitted to the Dedical Department of a general hospital.

**Patients and methods:** We analyzed age, sex, time of arrival to the ED, waiting time, and color code of all patients admitted in the medical department of the Azienda Ospedaliera-Universitaria of Ferrara, Italy; during the period from 01/01/2010 to 31/07/2012. Our Medical Department includes four Internal Medicine and two Infectious Diseases units, Geriatrics, and Gastroenterology, and accounts for more than 25% of all hospital admissions. Time period was classified into holidays (weekends + festive days) and weekdays, and day-time (08:00-20:00) and night-time (20:00-08:00). The main end point was length-of-stay.

**Results:** We evaluated 13237 consecutive patients (43% males), with a mean age of 76±13.5 years. The majority of admissions occurred during the day-time (71.6%) and in the weekdays (73.9%). The more frequent color coding of hospital admission was yellow (69.2%), followed by green (24.6%), and red (6.2%). Mean LOS was 8.9±8 days. As for univariate analysis, LOS > 7 days was related to time of admission (day-time 75.7% vs. 68.4%, night-time 24.3% vs 31.6%, p<0.001), day of the week (weekends 24.7% vs 27.2%, weekdays 75.3% vs 72.8%, p=0.001), and during holidays (holidays 26.3% vs 28.8%, no holidays 73.3% vs 71.2%, p = 0.002). Furthermore, LOS > 7 days depended on both colour code of admission (21.5% for green, yellow for 72.6%, 5.9% for red, p<0.001), and patients’ age (78±12 vs. 76±14, p<0.001).

**Conclusions:** The data from our study in a tertiary level Italian general hospital seem to show that LOS may be related with time of admission. However, differences among results of published studies should take into account the significant differences in health service organization of different Countries.

**Emergency department and acute renal failure requiring hemodialysis after suicidal attempt**


**Background:** Data from the National Poison Data System reported that more than 2 million cases of exposure to toxic agents occur annually in the United States, and about one half is due to suicidal episodes [Bronstein et al, Clin Toxicol 2011]. In many cases, substances used for suicidal intent are nephrotoxic, and the development of acute renal failure is common. The aim of this study was to review the literature to evaluate the outcome of subjects who attempted suicide and developed renal failure.

**Patients and methods:** We performed a systematic search of medical literature focused on case reports of acute kidney injury (AKI) secondary to voluntary intake of toxic agents for suicidal intent. For this search, performed across the major medical databases, PubMed and Embase, the Medical Subject Headings (MeSH) terms used were: Acute Kidney Injury – Renal Insufficiency – Suicide – Suicide, attempted – Emergency service, hospital. We recorded age and sex, type of substance used, type of therapy for renal failure and clinical outcome. Statistical analysis was performed in order to compare survivors with deceased subjects.

**Results:** Total sample consisted of 108 cases of attempted suicides. Mean age was 35±15 years. The majority of patients were aged between 20 and 30 years (28.7%), with no sex predominance. However, females attempted suicide at a younger age than males (32±16 vs. 37±14 years, p:NS). The preferred route of administration was oral (94.5%). The most widely used substances were toxic agents (69.4%). Males used more frequently drugs acting on Central Nervous System (CNS) (9.7% vs. 8.7%) and toxic agents (79% vs. 56.5%), while females more often used cardiovascular (CV) drugs (15.2% vs. 1.6%), and analgesics (19.6% vs. 9.7%). We found the presence of outcome reports in 75% of cases. Univariate analysis, comparing groups
Tab.1. Univariate analysis comparing males and females, and fatal and nonfatal cases.

<table>
<thead>
<tr>
<th></th>
<th>Females</th>
<th>Males</th>
<th>Fatal outcome</th>
<th>Nonfatal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxic substances</td>
<td>26 (56.5%)</td>
<td>49 (79%)</td>
<td>21 (28%)</td>
<td>54 (72%)</td>
</tr>
<tr>
<td>CV drugs</td>
<td>7 (15.2%)</td>
<td>1 (1.6%)</td>
<td>1 (12.5%)</td>
<td>7 (87.5%)</td>
</tr>
<tr>
<td>Analgesics</td>
<td>9 (19.6%)</td>
<td>6 (9.7%)</td>
<td>2 (13.3%)</td>
<td>13 (86.7%)</td>
</tr>
<tr>
<td>CNS drugs</td>
<td>4 (8.7%)</td>
<td>6 (9.7%)</td>
<td>3 (30%)</td>
<td>7 (70%)</td>
</tr>
<tr>
<td>p</td>
<td>0.015</td>
<td>0.522</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis therapy</td>
<td>32 (69.6%)</td>
<td>42 (67.7%)</td>
<td>13 (17.6%)</td>
<td>61 (82.4%)</td>
</tr>
<tr>
<td>Medical therapy</td>
<td>14 (30.4%)</td>
<td>20 (32.3%)</td>
<td>14 (41.2%)</td>
<td>20 (58.8%)</td>
</tr>
</tbody>
</table>

by gender and outcome, is reported in Table 1. Multivariate logistic regression analysis showed that dialysis was negatively associated with death (OR=0.254 [95% C.I. 0.074-0.434], p=0.006).

Conclusions: Although in the presence of a selection bias limitation (search focused on patients with AKI after suicidal attempt referring to the ED, so excluding not-hospitalized fatal cases), the high mortality of self-poisoning and the importance of hemodialysis is confirmed. Internists operating in the ED should have also some nephrologic knowledge, to early suspect a potential risk for AKI, and provide immediate treatment.

A retrospective study on intervention times and procedures of pre-hospital and in-hospital integrated emergency care activities in acute coronary syndromes, heart failure and arrhythmias

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It is generally recognized that emergency medical activities are nowadays an essential component of health care provision. These activities, managed by a single Emergency Medical System (EMS) in any regional area, begin out of hospital, and continue in hospital Emergency Department (E.D.). Observational studies put in evidence that these activities reduce the mortality and the complications of every pathology especially, for cardiovascular ones (acute coronary syndromes, heart failure, arrhythmias).

Sample: We have retrospectively studied 422 out-of-hospital emergency medical interventions, made from 2001 until 2004. All these interventions were managed by an emergency ambulance (ALS mobile unit) of the Addolorata Institute of Rome, one time of A.O. San Camillo-Forlanini and later of ARES 118 Regione Lazio. The composition of this sample (221 m, mean age 72 years, and 201 f, mean age 80 years: all delivered alive to the E.D. of San Giovanni Hospital) has been determined to compare the selected variables, for both the out-of-hospital interventions and the in-hospital interventions at the ED.

Objectives – study methodology – results: Essentially, our aim was to evaluate a total of 40 parameters related to the interventions carried out for every patient have been considered and the corresponding relationships have been calculated. Overall, the sample of this study included 16880 in/out-of-hospital interventions parameters [age; sex; time on the scene: clinical signs (pain, dyspnea, arrhythmia, other symptoms); diagnostic procedures (physical examination, electrocardiogram, oxygen saturation); clinical conditions (stable or critical); diagnosis (acute coronary syndromes, heart failure, arrhythmias, other, none); therapy (number of drugs administered); out-of-hospital intervention time (hours minutes); time in E.D: clinical conditions (unchanged, improved, deteriorated); diagnostic procedures (physical examination, electrocardiogram, ultrasonography, x-ray, laboratory tests, consultations); diagnosis (confirmed, different, none); therapy (continued, implemented, changed, none); time of E.D stay (hours and minutes); outcome (discharge, admitted, refuses admission, deceased, transferred). Given the large amount of these data, in order to estimate the comprehensive interrelated behavior of the modalities of the evaluated variables, we have used the Main Components Analysis. This method permits the study of relationships between a large number of variables by assembling them into few factors which are tightly correlated to these variables allowing an easier understanding of the studied events graphically too (Figure 1). The results have shown: -a reverse relationship between the out-of-hospital intervention time and the in-hospital intervention time; -a positive relationship between number of drugs given, out-of-hospital time and patient’s age; -location of indexes of in ED procedures and clinical signs observed in the out-of-hospital intervention; -a correlation of the indexes of out-of-hospital procedures with the time and the number of supplied drugs. Among the studied variables, it appears that the out-of-hospital intervention time, here intended as “time spent at the patient’s side” is important (golden hour). This variable seems to affect: -the diagnostic accuracy of the first survey; -the administered therapy, which may support the preservation of patient’s organ reserve (stabilization); -the patient’s clinical conditions resulting from the intervention, considering that any individuals and particularly the patients with heart disease are negatively affected by the subsequent transport; -the clinical picture of the patient that has to be reported to ED colleagues who will continue the treatment.

When a common pain of the right scapula can change a “green code” in a “red code”

Di Matteo R, Iascone E, Picciarella A, Scarponi V, Zulli L

ACO San Filippo Neri Roma UOC MUPS

Background: venous thromboembolism (VTE) is the third most common cause of death from cardiovascular disease after heart attack and stroke (1) with an incidence of 100/100000 persons each year particularly in elderly. Almost one third of patients with symptomatic VTE manifest pulmonary
embolism (PE) whereas two thirds manifest deep vein thrombosis (DVT) alone with a recurrence rate of 7% at 6 months after the first event despite anticoagulant therapy. Death occurs in 6% of DVT cases and 12% of PE cases within 1 month of diagnosis. (2) VTE is often asymptomatic and mis-diagnosed and consequently its incidence results underestimated (3) as many cases of unsuspected no clinically PE found on up to 3.4% of inpatient and 0.9% of outpatient CT scans (4). CASE REPORT: a 55-year old caucasian man was referred to our Emergency Department due to a persistent and sub-continuous twinge localized to the right scapula (NRS scale 10). He had no medical history, no history of smoking and he was a sportsman. At Triage a green code was attributed according to the “Triage Lazio protocol” On admission he was hemodynamically stable with following vital signs: blood pressure of 145/75 mmHg without significative difference between right and left arm; a heart rate of 80/min, a respiratory rate 16/min, saturation 99%. The physical examination showed valid peripheral pulse status, height 175 cm and body weight 65 Kg, temperature of 36.2°C and GCS 15 without any neurological deficits; chest examination showed absence of bronchial breathing murmur on lower right part of the chest. No swelling of the legs or edema were found. ECG showed sinus rhythm with delay of right conduction and no ischemic sigs. Blood tests showed increased white blood cells (15,000/ml) and PCR (3.09 mg/dl) (0.0-0.8), no increasing of p-troponin. Because of this findings a EGA (respiratory alkalosis) and a chest radiography (presence of small lung consolidations in the lower right part of the lung) were performed. The Wells score was zero and the revised Geneva score (5) was 3 and a D-dimer done to rule out was positive 1.29 (0.5-ug/mlEIA). A CT scan of the chest was guided by the hypothesis of a diagnosis of pneumonia. Computed tomography angiogram showed multiple intraluminal filling defects that occlude the sub-segmental branches of the pulmonary arteries directed to both lower parts of the lungs. No pleural effusion was revealed. En extended CT scan to the legs revealed DVT of the right deep and superficial femoral veins. At this point an anticoagulant therapy associated to antibiotics was started and the patient admitted to the craniological department where he was further diagnosed as having no cancer or any positive blood testing for thrombophilia.

Discussion and conclusion: pulmonary embolism (PE) is a common cardiovascular emergency clinically described in the early 1800s. From 2000-2007, the incidence of PE increased from 0.69 to 0.91 per 100 admissions, in strong correlation with increased use of pulmonary CT scan (7). Clinical manifestations of VTE are heterogeneous and often absent. The actual diagnostic score are not always suitable with the heterogeneous clinical presentation and the real medical perception of this pathology is still low. This case is an emblematic and unsuspected case of PE who could have been undervalued. At the Triage, a green code was attributed with possible consequences from a delay to the medical visit. Later a misdiagnosis of pneumonia was done with potential therapeutic missing. Both clinical score for the probability of having a VTE indicated a low risk for the patient. Our considerations on this case are open questions: firstly, the actual scores can suit with the heterogeneous presentation of TEV in order to direct the diagnostic choice? Secondly, should EGA be considered in the Triage evaluation at Emergency Department door together with the ECG to increase the sensibility of chest pain stratification risk? In conclusion, we suggest to consider always TEV in the differential diagnosis of chest pain even if without anamnestic and clinical data of predisposition.

References:

Intracranial haemorrhages: observational study in an emergency room

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IRCCS Fondazione Ca’ Granda Ospedale Maggiore Policlinico, Milano

Intracranial haemorrhages (ICH) are a group of potentially life-threatening pathologies with a very high morbidity and mortality. Antithrombotic therapy and head trauma are important risk factors for these events.

Materials and methods: We performed an observational study enrolling all consecutive patients with ICH admitted to the Emergency Room (ER) of IRCCS Policlinico Hospital of Milan from January 1st, 2010, to March 31st, 2013. 530 patients with ICH were enrolled (52% males, mean age 70.4 yrs).

Results: At the admission to the ER, 33% of patients was registered as red codes, 48.8% as yellow codes and 18.1% as green codes. A significant number of patients (202, 38.1%) was on antithrombotic therapy. Of these, 65 (12.2%) were treated with Vitamin K antagonists (VKA), 139 (26.2%) with anti-aggregants (AA), 18 patients (3.3%) with heparin (15 low-weight molecular heparin, 3 unfractioned heparin), while 18 patients had a combined therapy (anticoagulants+antiaggregants or 2 antiaggregants). An elevated number of patients (162, 30.6%) had a history of head trauma in the hours or days before the arrival to the ER. The different types of haemorrhages are reported in table 1 (17 patients had more than one type).

<table>
<thead>
<tr>
<th>Type of ICH</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subdural haemorrhage</td>
<td>136</td>
<td>25.7</td>
</tr>
<tr>
<td>Intraparenchymal haemorrhage</td>
<td>303</td>
<td>57.2</td>
</tr>
<tr>
<td>Subarachnoid haemorrhage</td>
<td>97</td>
<td>18.3</td>
</tr>
<tr>
<td>Extradural haemorrhage</td>
<td>11</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Of the 530 patients, 16 died in the ER (3.0%). Surgical operation or admission to Neurosurgery Unit for observation and eventual surgery was indicated for 198 (37.3%) patients, while 205 (38.7%) were admitted to medical divisions in the absolute absence of surgical indications. 99 (18.7%) were admitted to the Intensive Therapy Unit. Only 11 patients (2.1%) were discharged and sent home directly from the ER and 1 refused the admission to the Hospital. In patients receiving VKA, therapy was performed in 47/65 subjects (72.3%) with vitamin K, factor VII, prothrombin complex concentrate, fresh frozen plasma in various combinations. In total, 43 patients were treated with vitamin K, 21 with prothrombin complex concentrate, 15 with factor VII, 1 with fresh frozen plasma, 3 with the complex including prothrombin, factor VII, and c+s proteins. INR values at arrival to the ER are reported in table 2. 95% of patients had an INR>1.5.

<table>
<thead>
<tr>
<th>INR value</th>
<th>Number of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR &lt; 2</td>
<td>11</td>
<td>16.9</td>
</tr>
<tr>
<td>INR between 2 and 3</td>
<td>30</td>
<td>46.1</td>
</tr>
<tr>
<td>INR &gt; 3</td>
<td>24</td>
<td>36.9</td>
</tr>
</tbody>
</table>
Conclusions: Intracranial haemorrhages are a group of life-threatening pathologies whose clinical presentation and prognosis can be worsened by the assumption of antithrombotic therapy. In patients treated with VKA, reversal therapy with prothrombin complex concentrate is necessary but still underused.

A woman with psychomotor agitation and hepatic injury


IRCCS San Martino Genova

A 56-year-old caucasian woman was admitted for jaundice and psychomotor agitation. She had no important medical history. Psychomotor agitation associated with hallucinations, confabulation, tremulousness, tachycardia, anxiety (sympathetic overdrive, autonomic hyperreactivity) required rapid therapy with diazepam, beta blocker and thiamine.

Upon physical examination she appeared alert, disoriented for place, time and person, tachycardic, with high blood pressure, jaundice, ascites. Also the patient had retropulsion the upright stance. Laboratory tests detected important hepatic impairment (AST 153 U/I, ALT 55 U/I, GGT 856 U/I, INR 3.06, ATIII 5%, total bilirubin 28mg/dl, albumin 2.1g/dl), thrombocytopenia, elevation of inflammatory markers (protein C reactive 41mg/dl), neutrophilia, acute renal failure, hyponatremia. Ammonium dosage was normal.

The liver function tests, refractory ascites and hepatorenal syndrome imposed a strict monitoring and dedicated therapy. After a few days the adrenergic component decreased but the confusional state still remained. During hospitalization Electroencephalography and brain CT were performed. EEG showed abnormalities of relevant degree with widespread bilaterally and rhythmic simultaneous high amplitude sharp waves mainly with prevalence in temporal and frontal lobes and whole brain diffusion. Brain CT scan showed enlarged subarachnoid spaces, particularly at the level of basic brain; hypodense areas borne by the parietal bilateral frontal white matter, encephalic blood collections were not observed.

Condition to consider in the differential diagnosis include the following: hepatic encephalopathy, Wernicke encephalopathy, pycnosis, raised intracranial pressure, intracerebral hemorrhage, subdural hematomas, infectious diseases (sepsis, meningitis, encephalitis, epidural and subdural infections), metabolic disorders (hypothyroidism, thyrotoxicosis, diabeties ketoacidosis), vitamin deficiency, cerebral tumors, drugs, hypocalcemia, hypomagnesemia, status epilepticus, substance intoxication and withdrawal (alcohol, drugs).

Based on the EEG, CT brain, the response to the administration of benzodiazepines, the most likely hypothesis diagnostic is status epilepticus in alcohol withdrawal.

Lampedusa emergency: prevalence, treatment and brief review of hypothermia in a in a cohort of migrants

Grembiale A, Carullo G, Leo E, Scicchitano M

3° Reparto Corpo Militare del Sovrano Militare Ordine di Malta

Introduction: Each year, tens of thousands refugees and migrants arrive in Italy, in the context of so-called “mixed migration flows.” From 2006 to 2009 in the Strait of Sicily have passed more than 60,000 migrants, of whom more than 90% departed from the Libyan coast. Following the evolution of the “North African crisis” in spring 2011, a massive influx arrived on the Sicilian coast and in particular on the island of Lampedusa. In this context, the Military Corps of the Italian Knights of the Sovereign Military Order of Malta (ACISOMOM) work, always at the forefront in emergency, to give health care to hundreds of thousands of migrants. This paper presents a report on the activities conducted by our association, analyzing the clinical conditions and diseases necessary intervention of our medical staff.

Method: we analyzed the end service reports of the ACISOMOM volunteer doctors operating in Lampedusa in the period April 2011 - March 2012.

Results: during the reporting period were rescued about 6975 migrants, most of them males (90%), while 2% were under 18 years old. 75% presented no active problem, in 23% of cases could be found a migratory related diseases, while in the remaining 5% of the cases was found a reproductive and/or infectious diseases. At first contact, there were 31 deaths. 6 red codes, with ready shelter in a protected environment and resolution of problems, while 21% and 34% respectively, had a yellow and a green code. The main medical intervention concerned cases of severe dehydration with shock (65%), hypothermia (10%), heat stroke (22%), pregnancies and abortions (2%) and infectious diseases (1%). Almost all of those rescued had also skin lesions caused by caustic, while only 20 cases have been reported blunt trauma, one in serious condition, immediately transferred by helicopter to a hospital.

Conclusions: our data confirm the theory of “healthy migrant”, i.e. people who in most cases was healthy in their own land but could lose this condition for the violence before boarding, for travel conditions but also by the socio-economic and health conditions in the new country. The relief activities of migrants is therefore an important both medical and human commitment. Very often we work in adverse conditions, with few human and material resources and with a huge influx of patients.

The theoretical and practical preparation is a vital resource to provide an effectively and efficiently aid. The clinical characteristics of migrants on arrival and completeness of internal medicine training, allows this type of specialty as the most useful to be able to provide adequate relief.

Lampedusa emergency: experience and report by physician of association of the Italian Knights of the Sovereign Order of Malta

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Introduction: Each year, tens of thousands refugees and migrants arrive in Italy, in the context of so-called “mixed migration flows.” From 2006 to 2009 in the Strait of Sicily have passed more than 60,000 migrants, of whom more than 90% departed from the Libyan coast. Many of the trips take place at night and in winter, with potential risk of hypothermia. Hypothermia exists when the body core temperature is below 35 °C and is classified arbitrarily as mild (35—32 °C), moderate (32—30 °C) or severe (less than 30 °C). Hypothermia can occur in people with normal thermoregulation who are exposed to cold environments, particularly wet or windy conditions, or following immersion in cold water, like migrants. In this paper we report the experience of physicians of Military Corps of the Italian Knights of the Sovereign Military Order of Malta (ACISOMOM) and conduct a brief review to evaluate the best treatment for this condition.

Method: we analyzed the end service reports of the ACISOMOM volunteer doctors operating in Lampedusa in the period April 2011 - March 2012. The MESH term “rewarming” and “accidental hypothermia” in PubMed (until May 2013) were searched with no language restrictions.

Results: during the reporting period were rescued about 6975 migrants, most of them males (90%), while 2% were under 18 years old. 75% pre-
sent no active problem, in 23% of cases could be found a migratory related diseases, in particular the 10% of them was in hypothermia. 120 were mild and 40 moderate hypothermia needed immediate hospitalization. Given the large number of patients and the smaller areas of intervention (patrol boats or migrant boats), migrants with mild hypothermia treated by remove cold or wet clothing as soon as possible and cover the dry casualties with blankets and keep them out of the wind and administration of hot drinks. Moderate hypothermia was treated with infusion of warm fluids and with heated blankets, all patients were carefully monitored to prevent the development of cardiac arrhythmias. Most serious were transferred immediately to local hospital.

The best treatment of this condition seems to be removal from the cold environment, prevention of further heat loss and rapid transfer to the hospital. Rewarming may be passive external, active external, or active internal. Passive warming is achieved with blankets and a warm room, and is suitable for conscious victims with mild hypothermia. In severe hypothermia or cardiac arrest, active warming is required, but this must not delay transport to a hospital where more advanced rewarming techniques are available. Several techniques have been described, although there are no clinical trials of outcome to determine the best rewarming method. Studies show that forced air rewarming and warm IV fluids are effective in patients with severe hypothermia and a perfusing rhythm. Other warming techniques include the use of warm humidified gases, gastric, peritoneal, pleural or bladder lavage with warm fluids (at 40 °C), and extracorporeal blood warming with partial bypass. Obviously these techniques are not applicable to rescue large numbers of victims aboard patrol boats.

Conclusions: migrants rescue is therefore an important both medical and human commitment. Very often we work in adverse conditions, with few human and material resources and with a huge influx of patients. The theoretical and practical preparation is a vital resource to provide an efficiently and efficiently aid. Many migrants arrive in hypothermia, especially in winter, therefore it is necessary to begin an immediate and careful heating of the victims to avoid fatal consequences of this condition.

Abstract-to-publication ratio for papers presented at Italian emergency medicine meeting: a retrospective study

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Objective: To determine the publication rate of abstracts presented by Italian emergency physicians at major emergency medicine meeting in 2008, and to identify the publication site of papers.

Methods: All abstracts presented to the annual scientific meeting of the Italian Society of Emergency Medicine in 2008 were identified retrospectively from the conference programme. To identify whether the work relating to the abstract had been published in a peer-reviewed journal, the Medline database was searched using the first and the last author as well as key words from the abstract. A series of evidence-based recommendations were used in order to verify the methodological quality of unpublished abstracts.

Results: Of the 298 abstracts identified, 41 (14%) had been published as full articles. For abstracts presented in the oral sessions, 15 (22%) resulted in a publication. Positive predictive factors for future publication of the presented abstracts were the kind of the study, both RCT (RR=11.76; 95% CI 2.69 to 51.31) and basic research (RR=9.79; 95% CI 4.30 to 22.27), and the study population > 100 patients (RR=5.57; 95% CI 2.77 to 11.19). The majority of the unpublished abstracts had poor methodological quality.

Conclusions: The abstract-to-publication ratio for Italian emergency medicine was lower than other countries in 2008. We hope that the introduction of the school of Emergency Medicine in Italy in 2008 has encouraged an improved research output from the emergency medicine within Italy. A subsequent work will be needed to analyze this topic.

Serum glial fibrillary acidic protein as a sensitive and specific marker for the identification of intracerebral hemorrhage in acute stroke patients: results of improved assay performance

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Objectives: The prognosis of acute stroke has been improved by the use of very early therapeutic interventions. Biochemical markers that could allow a rapid and accurate diagnosis differentiating between intracerebral hemorrhage (ICH) and ischemic stroke (IS) have recently been identified. This study was designed to evaluate plasma concentrations of glial fibrillary acidic protein (GFAP) in acute stroke patients and the accuracy for distinguishing ICH from IS using a current-generation sensitive assay.

Methods: This prospective case control study enrolled in 45 controls and 33 stroke patients. ICH (n = 6) and IS (n = 27) were diagnosed using brain imaging. Blood samples were taken from each stroke patient at admission (mean122 minutes after stroke symptom onset) and measured by ELISAs, using an ultra-sensitive assay detecting GFAP.

Results: Levels of GFAP in serum were significantly increased in ICH compared to control subjects and IS (median, 2.25 vs 0.06 vs 0.07 ng/ml, P<0.0001 and P=0.0002, respectively). GFAP concentrations in IS patients were not significantly different compared to controls (p=0.12). ROC curve analyses showed high sensitivity and specificity in differentiating between ICH and IS (AUC = 0.99; cut off=0.33 ng/ml; sensitivity 100% specificity 96%) (Figure). Concentrations of GFAP did not correlate with time to sample withdrawal. GFAP values in ICH were almost significantly correlated with the NIHSS score on admission (r = 0.9, p = 0.08).

Figure 1.
Conclusions: Our pilot study indicates that plasma GFAP could be a reliable biomarker of intracerebral hemorrhage in acute stroke, accurately distinguish between ICH and IS and thereby facilitate the hyperacute delivery of stroke therapies. In addition, these findings support the incremental value of newer, more sensitive assays in stroke patients. Further investigations in a large cohort of patients are needed.

Early performance of blood cultures in the emergency department: an essential procedure in septic patients

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ACO San Filippo Neri Roma UOC MUPS

Background: Blood cultures in the emergency department are, actually, an unusual procedure in patients with suspected sepsis. The Surviving Sepsis Campaign recommend obtaining appropriate cultures before antimicrobial therapy, if such cultures do not cause significant delay (> 45 minutes) in the start of antimiicrobial administration. To optimize identification of causative organisms, is also recommend obtaining at least two sets of blood cultures (both aerobic and anaerobic bottles) before antimicrobial therapy, with at least one drawn percutaneously and one drawn through each vascular access device, unless the device was recently (<48 hours) inserted. These blood cultures can be drawn at the same time if they are obtained from different sites. The aim of this study is to evaluate our experience in the emergency department during the last 4 years.

Methods: This is a retrospective, observational study conducted in the Hospital “San Filippo Neri” of Rome. All blood cultures performed in the Emergency Department (emergency rooms number 1-2), from January 2009 to December 2012, were included in the study. The cultures were obtained from patients with signs and symptoms of sepsis, as reported from anamnesis, physical examination, blood exams and radiological findings. Two sets of blood cultures (both aerobic and anaerobic bottles) were obtained before antimicrobial therapy, in the first 45 minutes; in patients with vascular devices (as central venous catheter, port-a-cat) were also obtained samples from these sites. All the cultures were sent to the Department of Microbiology of our hospital.

Results: In the study period were performed 83 blood cultures. Out of these, 0 were obtained in 2009, 3 (3.6%) in 2010, 22 (26.5%) in 2011 and, finally, 58 (69.8%) in 2012. The blood cultures resulted positive in twentytwo patients (22% of the total blood cultures), as reported in Figure 2; from 18 cultures (82% of the positive blood cultures) grew aerobic bacteria (11 gram-positive pathogens and 7 gram-negative pathogens); from 4 cultures (18% of the positive blood cultures) anaerobic bacteria. In all patients the antimicrobial therapy was confirmed or modified on the basis of the cultures.

Discussion: This study is a report on the appropriateness and importance of blood cultures performed in the first 1 hour from the admission in the Emergency Room. Of interest, we report a case of a 86 years-old woman admitted at 10 p.m. in the Emergency Room for fever with chill and dysuria, with signs and symptoms of severe sepsis. Two sets of blood cultures were performed in the first 30 minutes, and was started an empirical antibiotic therapy with amoxicillin/clavulanate and ciprofloxacin. At 16 p.m. of the next day we was contacted from our Microbiology unit for the grown from the blood cultures of Escherichia coli producing extended spectrum beta-lactamases (ESBL). The antimicrobial therapy was modified according with the antibiogram, using a carbapenem. At 8 pm the patient was admitted in internal medicine division with an etiological antibiotic therapy. Although sampling should not delay timely administration of antimicrobial agents in patients with severe sepsis, obtaining appropriate cultures before administration of antimicrobials is essential to confirm infection and the responsible pathogens, to detect multidrug-resistant pathogens and to allow de-escalation of antimicrobial therapy after receipt of the susceptibility profile.

Conclusion: early in the Emergency Room all the patients with signs or symptoms of sepsis must be submitted to two sets of blood cultures (both aerobic and anaerobic bottles) before antimicrobial therapy. The point is to achieve timely the etiological diagnosis in order to start a specific antibiotic therapy, particularly in case of multi-drug resistant pathogens (MDR). As matter of fact, inappropriate therapy is recognized as one of the most important risk factor associated to unfavorable outcome in patients with severe sepsis or septic shock.

A shakespearean dramatic disease....The Cotard syndrome!


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Introduction: Cotard’s syndrome, also known as Walking Corpse Syndrome, first described by Jules Cotard as “le délire de negation”, a French neurologist in 1880, represents a very rare mental disorder in which people hold a delusional belief that they are dead (either figuratively or literally), do not exist, are putrefying or have lost their blood or internal organs. In rare instances, it can include delusions or immortality. The syndrome has degrees of severity that range from mild to severe. The central symptom in Cotard’s syndrome is the delusion of negation. The disease has three distinct stages (germination, blooming, chronic). In the first stage the patients exhibit psychotic depression and hypochondria. In the second stage they present with the full expression of delusions of negation. In the third stage they present with severe delusions and chronic depression.

Case report: A 38-year-old male patient was admitted to our Department because of onset of delusion of negation. At history oropharyngeal cancer treated by surgery and radiotherapy two years before and episode of encephalitis treated on acyclovir one month before. Moreover, he was an alcoholic abuser and strong smoker. He appeared in faded clinical conditions, very pale, tachycardic and polypnoic, particularly anxious for his clinical conditions and deeply conscious to be dead, smelled like rotting flesh and wanting to be taken to a morgue so that he could be with dead people, with hopelessness, low energy, decreased appetite, and somnolence. Normal resulted neurological evaluation with no signs of encephalitis and no fever as well as the cardiac evaluation and EKG, except for sinus tachycardia, BP 100/65 mmHg. The laboratory data no pointed out any alterations. Brain Magnetic Resonance and chest-radiography no showed pathologies. After organic causes were ruled out, treatment with quetiapine and bupropion SR was started. The patient was initially reluctant to take medication or eat and he appeared isolative, spending much of the day in bed and neglecting his personal hygiene and grooming. With his family’s support, the decision was made to take the patient to court for treatment over objection. Subsequently, the patient’s medication regimen was bupropion SR and olanzapine (intramuscular since he refused the oral form). He showed improvement in symptoms over one month on olanzapine 25 mg daily, and lorazepam 2 mg daily. At discharge he denied nihilistic or paranoid delusions and hallucinations and expressed hopefulness about his future and a desire to participate in psychiatric follow-up care. Now he is in quite clinical conditions although in follow-up for oro-pharyngeal disease.

Discussion: The underlying cause of Cotard’s syndrome appears to be a misfiring in the fusiform face areas of the brain, which recognises faces, and also in the amygdale, which adds emotions to those recognitions. The result is a lack of emotion when viewing familiar faces and the result disconnection can result in complete detachment. Viewing ones own face in this condition
can lead to a lack of association between their reflections or projected self and their own sense of self, leading to a belief that one doesn’t exist. Treatment of Cotard’s syndrome is tricky as it can be very difficult to treat the cause and instead efforts are made to control the symptoms. Antidepressants and antipsychotics have been shown to help as has electro-convulsive therapy but we are still very much in the dark on this fascinating and intriguing disease.

The mysterious life of a self-bleeding nurse ....A unique case of hemorrhoidal disease!!


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Introduction Lathénie de Ferjol syndrome (LF) is a rare psychiatric pathology (presently classified among Fictitious Troubles, in conformity with DSM V) of which very few cases are described in the literature characterised by deep and relapsing anaemia due to self-induced and repeated blood lettings.

Clinical case A 59 year-old woman, working as a nurse in a Surgery Division of a little hospital of Sicily, was admitted to our Emergency Department because of deep asthenia, cardiopalms and dyspnea after very moderate efforts. At history father dead at 35 years for hypertrophic cardiomyopathy and mother alive but afflicted with alcoholism; two brothers and one sister apparently healthy. She was no married and had no any son or daughter, no smoker and no alcohol drinker, but she was suffering with hemorrhoidal syndrome since the age of twenty-three and with repeated admissions to various hospitals for severe anaemic syndrome in last years for hypocromic anaemia, hiatal hesofagus hernia, gastritis by reflux, treated on iron, B12 vitamin and folic acid. Later, during a further anamnesis (got through a confidential dialogue) she revealed that she had been self-inducing blood lettings stingingly her hemorrhoids with a syringe (more than an half of liter each time). The patient appeared in too faded clinical conditions, with deep pallor of dehydrated skin and mucosae, subcutaneous pad scarcely represented, jaundice and oedema absent. At cardiovascular evaluation: B.P. 100/75 mmHg; H.R. 100 B/min; sweet and systolic heart murmur of mitral valve, 2/VI Levine, irradiated to all auscultation cardiac foci. Nothing important at respiratory, abdominal (normal liver and spleen) and urogenital apparatuses evaluation, but presence of many pinprick signs of emorhoids. Haematocrit and blood iron tests, urgently executed, pointed out an hypochromic, microcytic, iron-less anaemia (R.C. 2.400.000/mm³, Hb 4,5 g/dl, Hct 13,7%, MCV 57m³, iron 22 mg/ml, ferritin 10 ng/ml). Normal glycohaemia, urea, creatinine and serum electrolytes. Normal chest-X-ray, echocardiography and gastroscopy. On the grounds of the deep anaemia and the accurate history, which permitted us to learn that our patient was inducing blood-letting herself, and, since we excluded all the other possible causes of such a deep haematic despoliation, we suspected a Lathénie de Ferjol syndrome. As we had already administered the urgent supporting therapy (blood transfusion and physiological salt solution 2 L/IV), we suggested a therapy based on iron iv, folic acid per os, B12 vitamin IM and further concentrated red cells transfusions (in consequence of daily haematoctrite checks) and obtained a fairly good improvement of anaemia (Hgb 8g/dl, R.B.C. 3.270.000/mm³). Moreover we requested a psychiatric consultation which confirmed our diagnosis of LF. According to the psychiatric’s advice the patient started psychotherapy and in the same time were programmed ambulatory successive controls. Six months later, our patient appeared ameliorated with dramatic remittance of anaemia. She told us that with the help of psychotherapy she had improved considerably and experienced no more self-induced blood-lettings.

Discussion: Lathénie de Ferjol syndrome is a very rare psychiatric pathology characterised by an important and relapsing anaemia due to repeated haemorrhages that the patient secretly procures to him or herself. The modality of self blood-lettings can vary from a patient to another and even within the same patient and in the course of time if she or he thinks she/he could be discovered. The bleedings can be caused by venous drawings, and/or by self-inflicted vesical or vaginal traumas, or, very rarely, they can be induced by other people for example by frequent blood donations in different places. Somatic therapy is fundamental but palliative, while psychotherapy (particularly behavioural) is the most useful of all therapies and it should begin in a very short time so as to avoid the illness to become chronic, or even lethal. Given all this, the global management of these patients ever and necessarily requires a close team-work of Internists or Haematologists and, above all, Psychiatrists.

A very tasty rhadomyolysis!


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Introduction: Licorice extracts and its principle component, glycyrrhizin, have extensive use in foods, tobacco products, traditional and herbal medicine. Licorice is also found in some soft drinks and in some herbal teas. It has also been used as a medicinal agent in ancient Egypt and China. Medicinal uses have included cough suppression, gastric ulcer treatment, treatment of early Addison disease, treatment of liver disease, and as a laxative.

Case Report: A 52 year-old woman with history of allergic rinitis, was admitted to our Dept for severe asthenia and important generalized muscle weakness although she referred no any particular trigger. However, when we kept further her word history, we learned that she was drinking daily licorice herbal tea after the lunch since six months. She presented very suffering with deep muscle weakness. Normal resulted body Temperature, Blood Pressure and Heart Rate, Respiratory Rate and EKG. Laboratory data pointed out slight leukocytosis, rise of urea and creatinine, important increase of AST, ALT, LDH, CPK and serum myoglobin, hypokalemia (2.8 mEq/l). Normal chest radiography and BMR. The patient was alert, cooperative and orientated but afflicted with a severe weakness although the systemic and neurologic examinations were normal. She was asked to bring a sample of her special licorice tea which at examen really contained glycyrrhizic acid. We hypothesized a severe case of licorice-induced rhabdomyolysis and promptly administered iv fluids and implementation of iv potassium (10 mmol of potassium chloride per hour-KCL-) with gradual improvement of our patient’s clinical conditions. The patient was discharged with recommendations of taking 1 tablet of oral potassium per day.

Discussion: The physio-pathogenesis of licorice-induced rhabdomyolysis is related to the presence of glycyrrhizic acid which inhibiting 11β-hydroxysteroid dehydrogenase and inducing excess mineralocorticoid production, with consequent hypokalemia, causes a muscle weakness until the possible paralysis and death due to ventricular fibrillation. For treatment, licorice consumption should be restricted and potassium loss should be replaced. Potassium sparing diuretic, spironolactone and dexamethasone administration should be considered.
Modified D-dimer cut-off values to rule out pulmonary embolism in the emergency department safely reduce the need of computed tomography angiography in the elderly


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Background: acute Pulmonary Embolism (PE) is the third largest cause of cardiovascular death after coronary artery disease and stroke. Diagnostic strategies in patients suspected of having PE initially focus on identifying patients in whom PE can be ruled out. The assessment of clinical probability using scores (Wells, Geneva, etc) or clinical judgment (Gestalt) in combination with D-dimer and pulmonary computed tomography angiography (CTA) have been proved valuable tools for the diagnosis of PE especially in the setting of the Emergency Department (ED). However, CTA confirms the presence of suspected PE in only 5 to 25% of cases. D-dimer concentration increases with age, therefore its specificity for PE decreases. A higher well defined and an age adjusted D-dimer cut-off point have been proposed to increase the proportion of elder patients in whom PE could be safely excluded, to avoid contrast agent and radiation risks and reducing the length of hospital stay and cost.

Purpose: to evaluate whether increasing the standard threshold value of serum D-dimer to a higher well defined cut-off or an age-adjusted one could safely reduce the utilization of pulmonary CTA to exclude PE in the elderly ED patient population.

Material and Methods: the study was performed in Vimercate’s Hospital, a 500-bed general hospital with 120,000 ED visits per year. All patients with a CTA performed in the ED from 2010 through 2012 for clinical suspicion of PE were included in a retrospective study. Helical CT scans were performed on Philips CT and General Electric CT which included 64-detector capability. D-Dimer was measured with particle enhanced immunoturbidimetric assay Innovance DDIMER on the Behring Coagulation IL, USA) normal value: less than 490 ng/mL. Sensitivity (S), Specificity (SP), and Negative Predictive Value (NPV) were calculated for the D-dimer cut-off value of 1000 ng/mL, and for age-adjusted cut-off value (defined as the patient’s age x 10) in patients aged 75 or more years and 80 or more years.

Results: a total of 481 patients underwent pulmonary CTA and had a D-dimer measurement performed. The number of CTA carried out for clinical suspicion of PE grew over the years (2010: 94; 2011: 165; 2012: 222), while the percentage of diagnosis of PE remained substantially stable (2010: 22.3%; 2011: 20.0%; 2012: 24.3%). In patients aged >=75 years (n=282) the number of diagnosed PE was 62 (28.2% of total). D-dimer cut-off of 1000 ng/mL yields S, SP and NPV values of 100%, 9%, 100%. In subjects aged >=80 years (n=191; PE=37; 19.4% of the total) values were 100%, 8%, 100%, respectively. By using age-adjusted D-dimer cut-off in subjects >=75 years, S was 100%, SP 7%, and NPV 100%, while for those who had >= 80 years 100%, 7%, 100%, respectively. Compared with the standard 490 ng/mL D-dimer cut-off value, the use of a cut-off of 1000 ng/mL would lead to a saving of 18 CTA’s (6.4% of total) in patients aged >=75 years and 11 (5.8% of total) in those aged >=80 years. Results for age-adjusted cut-off were 14 (4.9%) and 9 (4.7%), respectively (percentage difference: p=non-significant).

Conclusion: in elderly subjects referring to the ED with clinically suspected PE, adjusting the D-dimer cut-off value either according to a definite higher (1000 ng/mL) or an age-adjusted cut-off of D-dimer increases the specificity of D-dimer assay for the exclusion of PE without reducing sensitivity. Using these cut-off values would lead to a substantial reduction of the number of CTA with patient benefits and cost savings.

A new computer aided detection for pulmonary embolism

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Background: Pulmonary embolism (PE), a life-threatening cardiological emergency, is still underdiagnosed because of a non-specific clinical presentation. First-level examinations, such as clinical examination, electrocardiography and blood gas analysis and other laboratory tests have low sensitivity and specificity. Clinical prediction rulers (CPRs) have been derived from the combination of first-level exams. CPRs are currently validated to weight the pretest probability of PE and choose the next-step diagnostic strategy. The most frequently used CPR are the Wells rule and the Geneva Revised rule[1].

Aims: our aims are to perform a comparison between the two score systems in our population and to derive a new Clinical Predictive Rule (CPR) model using an Artificial Neural Network (ANN).

Methods: We enrolled 987 consecutive outpatients with suspect of PE (mean age 71 years ±14). From each patients we synthesized 26 clinical, electrocardiographic and laboratoristic variables, obtaining Wells and Geneva scores. We evaluated the diagnostic reliability of these scores in our population performing ROC curves computation. To derive the new classifier, first we splitted the dataset (in the supervised classification step) into a train and a test subset (respectively containing about 2/3 ad 1/3 of the patients’ dataset). To find the optimal configuration of the new classifier we tested two different ANNs: a non-linear feed-forward ANN with back-propagation and a Levenberg-Marquardt network. For both networks we fixed the topological configurations of the connections (one hidden layer, one output neuron) and we stressed the system to find the optimal number of neurons in the hidden layer for the best configuration among highest AUC with the highest number of hit in the validation process and the minimum epochs. We repeated this study changing the dimension of the input dataset in three ways: excluding interactively some features (age, Wells, Geneva scores), performing the reduction of the dimensionality of the feature space (at the same time eliminating redundancy of information) with Principal Component Analysis and performing the features selection with Aysadi-IRIS[2,3]. The application of the trained network to a new set (“map set”) returns for each patient the probability of belonging to the “pathological” or “healthy” class, thus obtaining the new CPR model. The automatic classifications were compared with the manual ones by calculating the Jaccard similarity coefficient (its range value is from 0 to 1), giving a measure of the system quality[4]. The ANN has been implemented by the Rulex software suite. The comparative study of three AUCs comparative study has been made with the software MedCalc.

Results: in our population, Wells discriminated better than Revised Geneva (Wells AUC 0.75%, Rev. Gen. AUC 0.63%). Our CPR by a feed-forward ANN with back-propagation obtained an average AUC of 0.86% and Jaccard coefficient=0.86 from the map set, the optimal configuration of the ANN is with 3 neurons in the hidden layer. IRIS detected some sub-groups among healthy patients, which present other diseases to be diagnosed properly even though they are not affected by PE.

References:
Pulmonary embolism: score use

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Introduction: A pulmonary embolism (PE) represents a frequent pathology, often not diagnosed especially in elderly patients, worsened by high morbidity and mortality if it is not treated in time. In recent years notable progress has been made in the diagnostic field and interesting diagnostic strategies have been proposed. More recently the assessment of the clinical pre-test probabilities in PE has been validated with the elaboration in scales in which a certain, anamnestic, clinical and laboratory finding is given a score that in the final analysis is generally identified within 3 classes of patients who have different probabilities of having this pathology. The first valid models were those of the Wells score, carried out by a group of Canadian researchers and the Geneva score carried out by Swiss researchers. Since 2010 the Padua Prediction Score has been validated and has been recommended by the American college of Chest Physicians as an instrument for evaluating the necessity of prophylaxis in order to avoid thromboembolism.

Materials and Methods: The purpose of our research is to evaluate the efficiency in an emergency of two scores i.e. Wells (1998) and the Padua Prediction Score (2010) and compare the two scores and verify which appears more reliable in a welfare context, like that of emergency medicine. Our assessment study is based on patients who had been to the emergency department in 2011 with suspected diagnosis of PE. In all of them we have found the following parameters: age, sex, D-Dimer, fibrinogen, troponin I, creatinine, CK-MB, LDH, EGA, TC thorax- abdomen, RX- Thorax, Eco-Doppler, risk factors, echo cardiogram, ECG. The probability index pre-test of the PE was analyzed in each patient with the Wells score and Padua Prediction Score.

Results: 29 patients of which 19 men and 10 women were hospitalized in the Medical Emergency Department (ED) of suspected PE in 2011. The patients in our study are between 19 and 90 years old (average age 69.27) and we evaluated the pre-test probability of PE with the Wells score and PPS on them. According to the Wells 55% of the patients showed high probability of disease (62% according to the modified Wells) and 35% intermediate probability, 10% low probability of PE (according to the modified Wells 37.93%). According to PPS 52% of the patients had high risk of PE, 48% had a low risk of PE. Deep Vein Thrombosis was presented in 48.27 cases: 6.8% of the patients had suffered a trauma with a fracture of the lower limbs, 31% had an oncological pathology. At the end of the diagnostic workup of the 29 patients admitted to ED with suspected diagnosis of PE, all of them resulted positive of the disease. In 75.8% of the cases patients were discharged from ED after an average hospital stay of 13.6 days. 20.6% of the PE patients in our department were transferred to another hospital where they remained an average of 35.3 days before being discharged. Deaths were equal to 1.8%: 1 patient died in our department, another died after being transferred. Note that in both cases, the Wells score gave a low risk assessment while the PPS gave a high risk assessment.

Conclusions: Still today PE represents a clinical challenge above all in elderly patients with pluripathologies. However nowadays much better diagnostic tests are available and more importantly have been coded and proposed...according to quite simple algorithms potentially applicable to minor centres. Knowledge of this diagnostic algorithm is fundamental in carrying out the diagnosis quickly, establish an adequate therapy, reduce errors and contain the -cost which are primary requisites of current orientations of disease management. The stratification of risk allows the identification of subjects who need pharmacological treatment and a more aggressive monitoring. In our study we have applied both the Wells score and the modified one i.e the PPS and we have been able to verify their overlapping in patients being examined, even though PPS is more complete in that it takes into consideration more data from the patient being examined. It has been found, if only in a few cases (13.79%) the results were higher in respect of Wells. It is also true that, in an emergency situation, like those that can be revealed in Emergency Room, Wells gives less data which is more practical for the doctor also considering that when a patient is admitted a lot of information cannot be found.

Troponin I as marker of systemic involvement in septic shock: a case series

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Introduction: Sepsis and septic shock are severe medical conditions, often observed in Internal Medicine Departments. Several clinical scores are currently used to assess the extent of the end-organ dysfunction and predict the risk of mortality. Even if not recognized by some authors as an additional risk factor (1,2), troponin I (TnI), can represent an early marker of cardiac microvessels derangement and septic cardiomyopathy (3,4), but is not included in the common scores used to assess prognosis in septic shock.

Objective: Our aim was to examine the association between SOFA score, a common index used to stratify the prognosis in septic shock, and TnI.

Patients and Methods: We retrospectively collected data from patients’ files treated in our Internal Medicine Department for severe sepsis/septic shock. Age, sex, SOFA score, TnI and in-hospital death were considered for the analysis. Troponin I was treated as a binary variable (cutoff 0.08 ng/ml), while SOFA score was analyzed both as an ordinal variable and a binary variable (cutoff at 9 points). The association between the two variables was assessed with an ordinal regression model using a complementary log-log link function, obtaining a significant model (p<0.05). Risk of in-hospital death was analyzed with chi-squared statistics. Analysis was performed with SPSS 13.0 for Windows Systems.

Results: We enrolled 20 patients affected by septic shock (males 42.1%) with a mean age of 75.84 years old (SD±13.89 years). TnI resulted positive in 64.2% of the sample. As in literature, higher SOFA scores (>9 points) resulted significantly associated with an increased risk of death (OR 3.00; 95%CI 1.10-9.30; p<0.05). We calculated the odds ratios of obtaining different SOFA scores depending on the absence of TnI: a negative TnI was highly predictive of lower SOFA scores (SOFA = 1: OR 5.89; 95%CI 2.99-11.6; p<0.05), while was negatively associated to the prediction of higher SOFA scores (SOFA = 13: OR 0.07; 95%CI 0.03-0.14; p<0.05) Our analysis outlined an inverse-exponential relationship between the odds ratios (r²=0.992, p<0.05), as shown in Figure 1.

Conclusions: In this small case series, SOFA score was confirmed as a good prognostic tool in severe sepsis/septic shock, and its values are associated to TnI. The presence of a negative TnI is strongly associated to a low end-organ damage in this patients. A positive troponin could be a marker of systemic involvement and septic cardiomyopathy, and could be useful to further stratify septic patients identifying the ones at higher risk. These data need validation in larger cohorts.
Rapid intensive observation: one year-experience of an acute medical unit in an internal medicine ward


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Background: the overcrowding of the Emergency Department is an increasing problem, with growing rates of admission to the wards, length-of-stay, more difficult discharges and readmissions. We needed a new way to evaluate and manage the patient, entering the Emergency Departments for peculiar acute medical problems. Rapid Intensive Observation within an Internal Medicine Department is a project proposed in Anglo-Saxon countries and adopted in the Internal Medicine ward (Clinica Medica I, Azienda Ospedaliera- Università di Padova) in close collaboration with the Emergency Department.

Objective: The purpose of this study was to evaluate the effectiveness of Rapid Intensive Observation in Internal Medicine, in terms of quality, reliability and adequacy of the project. Patients and Methods: During the first year of the project (February 1, 2011 - February 1, 2012), 729 patients were admitted in our unit. Inclusion criteria, defined between the Emergency Department and the Internal Medicine staff, were the following: low-intermediate risk TIMI score chest pain; syncope; stable supraventricular arrhythmias; pulmonary embolism high risk deep veins thromboses; electrolytic disorders and dehidratation; ostoheporotic vertebral fractures; dif-ficult management of oncological and non oncological pain; allergies; ab-trolytic disorders and dehidratation; ostheoporotic vertebral fractures; differ -rhythmias; pulmunary embolism high risk deep veins thrombosys; elec-

Results: Of the patients admitted, 60% had been managed within 72 hours, with a mean hospital stay of 2.3±0.8 days. The likelihood of needing more than 72 hours of hospitalization was significantly affected by disability (Barthel Index) and the age at admission, after adjusting for gender, CIRS (comorbidity and severity), number of previous medications and admissions. The majority of the patients was admitted for chest pain (46%), syncope (15.6%) and arrhythmias (8%). 18.93% of the patients were readmitted within 90 days to the Emergency Department for a medical problem linked to the previous hospitalization reason, 55.8% of them were discharged and 44.2% were rehospitalized.

Conclusions: The Rapid Intensive Observation has significantly reduced the length of hospital stay, was not associated with increased readmission rates after discharge. Patients discharged within 72h were younger and with less disability and comorbidity. In conclusion, the Rapid Intensive Observation seems to be a new and effective modality for Internal Medicine in-patients, able to reduce hospital stay, without affecting the efficiency of the diagnostic and therapeutic approach to the patients.

Sports Medicine

Physical activity reduces blood pressure variability in hypertensives


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Introduction and aim: For many decades, the main goal of antihypertensive treatment was to lower blood pressure (BP) to a defined level. Recently, several investigators have shown that BP variability (BPV) is another critical cardiovascular risk factor, which should also be emphasized in the treatment of hypertension. Mancia et al were the first to report a close association of BPV, assessed by 24-hour ambulatory BP monitoring (ABPM), with target-organ damage in hypertensive patients, carotid artery damage and increased left ventricular mass index. Aim of our study was to analyze the effects of 24 weeks of physical activity in hypertensive patients on BPV.

Materials and Method: We enrolled 158 stage I ESC-ESH hypertensive subjects (72 men and 86 women, mean age 58.8±13.38 years), referring to the UU.OO. of Fisiopatologia Circolatoria and Medicina Interna e Cardioangiologia of the University of Palermo for ambulatory examination in the period between 01/01/2006 and 31/09/2010. In all subjects enrolled, before the beginning of training, was performed a 24-hour Ambulatory Blood Pressure Monitoring (ABPM) using a TM – 2430 Recorder by A & D Company Limited of Tokyo, Japan. This device provides an oscillometric record. The home-based program of physical activity was conducted evaluating the degree of activity and the distance walked through the periodic analysis of data registered by a step counter provided to every patient. We used an OMROM step counter type Walking Style II. Patients were invited to walk for one hour every day. The walking velocity was required higher than the one retained “comfortable” by the patient, previously assessed in the run-in visit inviting the patient to walk “normally” in a 10-meters walkway under chronometric control. To every subject enrolled was asked to register in a diary the daily activity. Every week, during the periodic visit due to data input and storage for the later analysis, was performed a comparison between patient’s diary of physical activity and speed counter data. Walking velocity during training period was obtained analyzing the separate aerobic distance covered recorded by step counter and comparing it with the time spent walking aerobically as reported in the patient’s diary. Weekly, during the periodic control of data, patients enrolled were required to modify walking velocity and/or walking distance to adhere the protocol. The total duration of home-based fast walking programme was...
set in 24 weeks. After the end of the intervention period the anthropometric data and laboratoristic determination were repeated as well as a 24 hour ABPM was performed.

Results: After the 24 weeks of training the BP variability (measured as one Standard Deviation of the mean value) changed as follows: 24 hours PAS variability: 16.82 mmHg vs 14.12 mmHg (P < 0.001), 24 hours PAD variability 11.86 mmHg vs 10.16 mmHg (P < 0.001), diurnal PAS variability 17.86 vs 15.47 mmHg (P < 0.001), diurnal PAD variability 13.43 vs 11.87 mmHg (P < 0.001), nocturnal PAS variability 10.47 vs 7.79 mmHg (P < 0.001), nocturnal PAD variability 8.44 vs 6.58 mmHg (P < 0.001). All the results obtained maintained the statistical significance after correction for age, sex, and anti-hypertensive therapy.

The correlation between VO₂max and baroreflex gain: preliminary non-invasive study in clinical context


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Introduction: It is well known that an improvement of fitness parameters, particularly aerobic fitness, is associated to an improvement of the profile of autonomic nervous system indexes. There are however few data addressing directly the influence of aerobic fitness on the autonomic nervous system control in a clinical context, among general population.

Objective: analyse the correlation between VO₂max (Maximal Oxygen Uptake) and autonomic nervous system descriptive variables, above all the Alpha Index (Index of Baroreflex Gain).

Methods: We studied 200 healthy subjects: 95 males (average age: 38.2±1.6 years) and 105 females (average age: 39.7±1.2 years). The study consisted of a medical examination, an evaluation of the autonomic nervous system functionality, an analysis of the body composition, a cardio-pulmonary bicycle exercise test and a questionnaire about lifestyle.

Results: Both in men and women we found a significant correlation between VO₂max and Alpha Index (Male group: 0.524 – p < 0.001, Female group: 0.426 - p < 0.001). This significance remained even when we corrected for the age influence on the two parameters (Male group: 0.418 – p < 0.001, Female group: 0.226 - p = 0.03). We further divided our two groups in four subgroups according to the subjects’ age and VO₂max, and we found again significant correlations in each group, suggesting that the influence of aerobic training on baroreflex gain control may be stronger than age impact.

Conclusions: The results of our study suggest a possible clinical use of the autonomic nervous system indexes to monitor the effects of a rehabilitation, training or exercise prescription program.

Assessment of the influence of prolonged experimental hypoxia on autonomic cardiovascular modulation in normal volunteers: insight from spectral analysis of cardiovascular variabilities

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Long term reduction in levels of physical activity and Hypoxia (Hpx) may be a critical component of several extreme environmental conditions, ranging from high altitude to space flights, interfering with health and well-being of participants as well as with working performance.

The autonomic nervous system represents, together with the hormonal and the immune systems, a key element in the chain of adaptive responses to prolonged environmental stress.

In this study we specifically tested the adaptation of autonomic cardiovascular regulation in response to the exposure of 15 healthy male volunteers (age 24±1) to three periods of 10 days duration, in which they were subjected to Hpx alone, or combined with bed rest induced inactivity (BRHpx) and bed rest only (BR). In all these periods subjects were housed in a controlled, low altitude, environment, thus avoiding the confounding effect of high altitude. Hpx was obtained by setting partial oxygen pressure to the equivalent of about 4000 meters of altitude (12.5 kPa oxygen, as compared to a normoxic environment of 21 kPa).

Autonomic regulation was inferred from mono and bivariate autoregressive spectral analysis of RR and systolic arterial pressure variabilities, selected non linear indices of RR variability were also obtained (conditional entropy, RR Ro).

Results show significant changes in HR, RR entropy, the alpha index and the low frequency component of systolic arterial pressure variability (LF SAP, an index of sympathetic arterial regulation), but not in arterial pressure or RR variance.

Overall data suggest that Hpx is a stronger stimulus than BR for reducing the spontaneous baroreflex gain (from 29.3±4.8 to 19.73±2.7 ms/mmHg, p < 0.05 ) and increasing LF SAP (from 4.6±1.4 to 16.5±4.8 mmHg², p < 0.05). The combination of hypoxia and bed rest does not appear to have an interactive effect (Repeated measure and Mixed model analysis, SPSS version 19).

In conclusion, prolonged exposure to Hpx in a closed, controlled, environment induces profound changes in autonomic cardiovascular regulation, characterized by reduced baroreflex gain and increased sympathetic vaso-motor regulation, which can be assessed non invasively with spectral analysis of cardiovascular variabilities. These changes are not further affected by the combination of BR. The potential implication for subjects’ performance and safety under the stress of prolonged Hpx in altered gravity justifies further investigations.

Non invasive autonomic profile in élite athletes


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Introduction: It is well known that heart rate is lower in athletes than in normal subjects. However the reasons for training bradycardia are incompletely understood, although an important role is attributed to autonomic nervous regulation of the SA node, mostly via vagal drive. Very few studies compare athletes and normal controls using spectral analysis of RR interval variability that is a convenient non-invasive method furnishing reliable proxies of sympathetic and vagal regulation of heart period.

Objective: to assess whether there is a difference in cardiac autonomic proxies obtained from RR variability in trained athletes and controls considering rest and the response to an excitatory stimulus such as standing up.

Methods: We examined a group of 102 top level male athletes of different sports – formula 1 drivers (n=2), Italian national badminton team (n=4), Italian national basket team (n=15), a premiere league basket team (n=9), a premiere league (n=22) and a junior league (n=18) football team – and a control group of 106 male subjects of similar age (24.77±0.32 versus 24.36±0.46; p<0.462) and BMI (23.32±0.26 versus 23.76±0.30; p<0.329).

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We obtained indirect indices of autonomic cardiac regulation with non-invasive method based on autoregressive spectral analysis of RR interval variability (\(\sigma^2_{RR}\)). Recordings were performed at rest (5 minutes lying down) and subsequently during active standing (5 minutes). We assessed low and high frequency oscillations in RR interval (RR-LF and RR-HF, in absolute and normalized units, \(nu\)) and the difference between RR-LF nu in resting condition and standing (\(\Delta LF_{stand-rest}\)).

**Results:** Overall data show a significant difference between athletes and control subjects. In particular: Heart Rate (50±1 versus 66±1, \(p<0.001\)) \(\sigma^2_{RR}\) (8221.6±1367.64 ms\(^2\) versus 3604±333.2 ms\(^2\); \(p=0.001\)), RR-LF (35.9±1.86nu versus 52.07±2.14nu; \(p<0.001\)), RR-HF (59.35±2.03nu versus 42.85±2.15nu; \(p<0.001\)), RR-LF/HF (0.98±0.16nu versus 2.35±0.33nu; \(p<0.001\)), \(\Delta LF_{stand-rest}\) (48.96±2.15nu versus 34.39±2.17nu; \(p<0.001\)).

**Conclusion:** Data show a difference in indirect autonomic proxies of SA node regulation between athletes and controls, suggesting a prevailing vagal modulation at rest, which may be a component of training bradycardia. In addition the greater increase in LF/nu with active standing suggests a more marked capacity to enhance sympathetic modulation. This particular autonomic profile might be part of the greater heart rate reserve typical of competing athletes.

**Physical activity assessment in healthy Italian population with 3 simple questions**

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**Introduction:** The evaluation of exercise capacity through Cardiopulmonary Exercise Test is fundamental in clinical practice, particularly for exercise prescription, however among practical limitations we must consider that this test is time consuming and expensive. To address, at least in part, these limitations the International Physical Activity Questionnaire (IPAQ31 items in long version, 9 in short one) was proposed, to estimate the level of physical activity in general population. Its validity was assessed against accelerometer determination of objective activity. Three simple questions from the questionnaire may be used in practice to estimate daily activity.

**Objective:** The aim of the study in a group of apparently healthy Italian people was to verify whether three simple questions about the weekly amount of physical activity, correlate to exercise capacity as assessed objectively by VO2max.

**Methods:** We examined a total of 88 apparently healthy subjects, 28 men and 60 women (mean age 45). They were asked about the time (min/week) they used to spend practising low (3.3 METs/min), moderate (4 METs/min) and vigorous (8 METs/min) physical activity, in order to compute an estimation in everyday clinical practice.

**Results:** We found a significant correlation (0.427; \(p<0.001\)) between METs and VO2max.

**Conclusions:** Our results suggest that the use of these three simple questions from the IPAQ could provide an initial estimate of the performed physical activity also in a healthy Italian population, that well correlates with fitness. Further research is warranted to test the validity of this instrument in everyday clinical practice.

**Myocardial performance in breast cancer survivors athletes**

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**Background:** The upper limbs edema in breast cancer survivors is a frequent side effect, often controlled with sport activity as Dragon Boat. Few information are available on the cardiovascular performance when this sport is regularly practiced. The study aims to evaluate in a group of survivors breast cancer women (BC), the effects of Dragon Boat sport on the myocardial performance during 4 years of follow up.

**Methods:** Since 2006 to 2010, one year after the diagnosis of breast cancer, a group of 55 women, previously treated with adjuvant therapy without evidence of metastasis, has been consecutively enrolled in a Dragon Boat competitive team. They were yearly submitted to an ergometric test, and to a 2D echocardiographic exam (MayLab 50 -ESAOTE) to evaluate the hemodynamic, morphological and functional cardiac parameters. All data have been matched with a group of 36 healthy women (HW).

**Results:** Both groups have maintained a normal systolic function during all the period, despite the CMi and BMI and EF values were higher in HW. At the onset of the study, the diastolic function of the BC group turns out to be compatible with an initial diastolic dysfunction, if compared with the HW group. After 4 years of sport Dragon Boat activity, the diastolic parameters resulted to be improved in both, but specially in BC group (A peak: from 68.5±15.1 cm/sec to 50±14.1 cm/sec with \(p<0.05\); E': from 9.3±2 cm/sec to 11.89±1.7 cm/sec with \(p<0.001\)). The data obtained from the ergometric test showed in both normal values despite in HW group, the

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<tr>
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<td>28.66±2.3</td>
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<td>95.52±15.1</td>
<td>NS</td>
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<td>EF %</td>
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<td>65.13±3.3</td>
<td>NS</td>
</tr>
<tr>
<td>AOR (mm)</td>
<td>29.98±2.52</td>
<td>26.50±2.5</td>
<td>NS</td>
</tr>
<tr>
<td>LA (mm)</td>
<td>33.89±3.50</td>
<td>33.47±3.1</td>
<td>NS</td>
</tr>
<tr>
<td>RV (mm)</td>
<td>20.75±1.9</td>
<td>21.4 ± 2.7</td>
<td>NS</td>
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<tr>
<td>E peck (cm/s)</td>
<td>71.5± 12.2</td>
<td>73.05±14.8</td>
<td>NS</td>
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<tr>
<td>A peck (cm/s)</td>
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<td>57.19 ± 16.8 a</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVRT (ms)</td>
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<td>78.59±10.97</td>
<td>NS</td>
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<td>DTe (ms)</td>
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<td>E/A ratio</td>
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<tr>
<td>Ea (cm/s)</td>
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<td>Aa (cm/s)</td>
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<td>7.25±1.9 a</td>
<td>6.57±1.3 a</td>
<td>&lt;0.05</td>
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</table>
data were significantly higher than in BC (Double Product 23870±3190 in HW vs BC 22785.8±276 with p<0.005)

Conclusions: The results obtained demonstrate significant improvement of the diastolic function in BC survivors after four years of Dragon Boat sport training with an excellent effort’s tolerance. Competitive sport activity, does not seem to have any negative impact on the myocardial performance in patients previously treated with chemotherapy.

Exercise prescription program to reduce cardiovascular risk factors: comparison between cancer and hypertensive patients

Stefani L, Mascherini G, Scacciati I, Francini L, Petri C, Galanti G

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Background: Despite the positive effects of the exercise as prescription therapy in patients with chronic disease has been well demonstrated, however the global response and any possible differences among different kinds of diseases after a short period of an unsupervised program it has not yet well investigated. The study aims to verify the effects of fast walking associated to a resistance exercise to improve the anthropometrics and water distribution parameters.

Methods: Two groups of subjects (10 cancer survivorship aged 48.8 yrs and 19 hypertensive aged 54.3 yrs) were submitted to an evaluation of the anthropometrics parameters consisting of a BMI and waist circumference measurement. A complete evaluation of cardiovascular performance and of exercise tolerance, including 6-Minute walking test, with the evaluation of the heart rate (HR), respiratory rate (RR) and systolic and diastolic blood pressure at rest and at the end of the exercise, was also performed. The bioelectrical impedance analysis to measure Total Body water (TBW), extracellular and intracellular water (ICW, ECW), and the flexibility (Sit & Reach Test) and strength test for the upper limbs (hand-grip) and lower ones, (30’ Chair Test) were also performed. From the 6MWT data, the intensity and the duration of exercise was established per each patients. The exams were performed at the initial phase of the study and after 3 month of regular physical exercise.

Results: From the data obtained a significant reduction of anthropometric parameters it has been observed (BMI T0 = 29.2±6.8 vs T3= 27.4±4.4 p<0.001) in the hypertensive population, in addition to a reduction of the waist circumference ( T0=92.5±14.1 cm vs T3=92.1±12.8 cm, p<0.05). A significant improvement in tissue water distribution was also observed (ECW T0= 17.5±3.7 vs T3= 17.2±3.9 p<0.005). A predominant improvement of the cardiovascular parameters was on the contrary observed in cancer group (DBP T0=76.4±6.5 vs T3=72.2±7.1 p<0.05; 6MWT meters T0=487.8±116.0 vs T3=525.6±117.3 p<0.05). In the same group the flexibility tests resulted to be also improved (sit and reach test : T0=0,4±7.4 cm vs T3=4,1±6.1 cm p<0.05).

Conclusions: A combined aerobic and resistance exercise program can induce a predominant modification of the cardiovascular risk factors (waist circumference and BMI) in a hypertensive population. On the contrary it is more evident in a population affected of cancer, the improvement of the exercise tolerance and the flexibility parameters more frequently related to the muscles fatigue. The same program seems to be therefore adequate for both, despite in presence of different kind of chronic disease and with apparent different risk factors. Further studies will be anyway necessary to investigate the main cause of this diverse sensibility.

Effects of resistance and aerobic exercises on physical capacity and quality of life outcomes in cancer patients

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Background: Exercise as therapy is normally used in patients with cancer to reduce the fatigue and to improve quality of life. The effects of a mixed exercise, aerobic and of resistance, after a short period of training, it has not been well investigated. The study aims to verify the effects of the combination of fast walking and resistance exercise, to improve the cardiovascular, anthropometrics and water distribution parameters.

Methods: A group of 10 survivors cancer subjects (breast and colon) were submitted to a mixed exercise program composed of three times of physical exercise of fast walking and three times a week of resistance exercise. Before to start, they were all evaluated for the cardiovascular and exercise tolerance. The exams performed were BMI (Body Mass Index) and waist circumference (WC), 6-Minute walking test (6MWT), with the evaluation of the heart rate (HR) and systolic (SBP) and diastolic blood pressure (DBP) at rest and at the end of the exercise, the bioelectrical impedance analysis to measure Total Body water (TBW), extracellular and intracellular water (ICW, ECW), the flexibility test (Sit and Reach test) and strength test for the upper limbs (hand-grip test) and for lower one (stand chair test). From the 6MWT were obtained the parameters to establish the intensity and the duration of exercise per each patients. These exams were performed at the beginning of the study and after 3 months of exercises. Despite the program is non supervised, a wearable accelerometer was also positioned at the waist of the subjects at the end of the study for at least 1 week in order to count the number of the steps.

Results: Among the anthropometrics parameters the BMI and WC showed a trend toward a reduction despite non significant (BMI T0: 30.3±10.3 ;T3 :29.8±9.8 p=NS- WC T0: 92.4±19.2; T3: 90.9±17.3 cm p<0.05), on the contrary the TBW has showed a significant reduction (T0: 38.1±8.2; T3: 37.0±7.9 p<0.05). From the 6MWT data, the distance results to be significantly longer after 3 months (T0: 487.8±116.0 m; T3: 525.6±117.3 m p<0.05), as well as the mean value of the rest DBP( T0: 76.4±7.1 mmHg vs 72.2±7.1 mmHg p<0.05). The flexibility evaluated using the “sit and reach” test, is significantly improved (T0: 0,4±7.4 cm vs T3: 4,1±6.1 cm p<0.05) while the SBP mean value and and the data of the hand grip test did not show any significant variation. The number of the daily steps and the daily distance run, from the accelerometers report did not show any substantial modification.

Conclusions: The combination of resistance and aerobic exercises determine a significant improvement in a short time, of the principal parameters strongly related with the quality of life and with the cardiovascular risks.

Figure 1.
Is there an association between different morphological BAV patterns and LV dimensions in athletes from different kinds of sports?

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Purpose: BAV is a common congenital cardiac disease. It is normally represented in two different morphologies: “typical (rare) or atypical (no-rare)”. It has been demonstrated as specially in regularly trained athletes, BAV can be associated to a progressive enlargement of LV chamber. The exact prevalence of the two BAV patterns in athletes and the possible association with the increase of the LV dimensions in them, is not yet investigated.

The study aims to verify in a large group of BAV athletes from different kinds of sports, and mild valve dysfunction, the prevalence of the two main morphological BAV patterns and also the eventual association with the LV dimensions.

Methods: from 2000 to 2011, a group of 292 BAV subjects, (athletes, sedentary and ex-athletes), were investigated. All they were submitted to an 2D echo exam (MayLab 50-ESAOTE) to classify the BAV morphologies and to measure the standard LV sisto-diastolic parameters (LV diameters, wall thickness and CMI). Then their LV dimensions were compared with a significance at P<.005. The Student Test and ANOVA test were used to compare the data with a significance at P<.005.

Results: The typical BAV was more represented in all the groups (68%, 67%, 63%) than atypical. Within the typical BAV pattern the form due to the fusion of the right cusp with the left one, was more common (70%, 73%, 62%) in all the groups. In athletes only, typical BAV was found in 51% of soccer players, in 10% of basketball players, in 8% of cyclists, 6% swimmers, and 15% rugby players. All the echo parameters didn’t show any statistical differences with respect of the different morphological BAV patterns and also to the different kind of sports.

Conclusions: The results are in agreement with the current literature and confirm the prevalence of BAV in athletes is similar to the general population. Despite the LV diameters found were at the upper limits of the normal range, however there are no significant differences for this aspect among the diverse BAV patterns associated.

Assessing the autonomic response to repeated bouts of exercise below and above respiratory threshold: insight from linear and non linear analysis of RR variability

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a)IRCCS Istituto Clinico Humanitas, Rozzano; b)CTNV Università degli Studi di Milano; c)AMPS, NY; d) Ospedale L. Sacco, Milano

Background: RR variations during successive transients of pulses of submaximal exercise might provide information on dynamics of vagal withdrawal (onset of exercise) and reactivation (offset of exercise). It is likely that load intensity and exercise duration might influence autonomic adaptation, as expressed by multiple indices from RR variations.

Methods: We recorded single lead ECG during a series of five successive short bouts of submaximal exercise (at 40 and 70% of VO2max, different days). Autonomic responsiveness was inferred from analysis 1. of the baseline and after-bouts rest tachograms with autoregressive spectral and symbolic algorithms, and 2. the quantification of the onset and offset of RR dynamics of each individual bout with an ad hoc software.

Results: RR interval reduction and sympathetic oscillatory modulation enhancement is observed already at preexercise rest (baseline vs preexercise: HR 65.97±2.09 vs 78.50±2.34 b/min; LF RR 41.88±4.78 vs 82.25±2.87 nu; p<0.001). During 5 subsequent exercise bouts of 2’ duration Indices from tachycardic and bradycardic transients, reflecting vagal withdrawal and reactivation are lower in response to higher exercise loads and longer duration (reactivation speed: first vs last bout 9.97±0.91 vs 6.76±0.75, p<0.002). Signs of sympathetic overactivity and vagal inhibition are also evidenced by non linear indices of RR variations obtained from after-bouts rest segments (Poincare’ plot: first vs last bout: 161.02±30.20 vs 26.87±3.88, p<0.001). The information provided by different indices appears congruent.

Conclusion: Our indirect data suggest that intensity and time modulate vagal withdrawal and reactivation, in combination with signs of sympathetic activation. These data suggest that analysis of RR variations, initiated by short exercise bouts at different intensity, may be performed using multiple methods, which could be useful for a more detailed study of autonomic response to exercise bouts also in clinical conditions.

Metabolism, diabetes and clinical nutrition

Role of autophagy in the pathogenesis of muscle wasting in cancer cachexia


*Department of Clinical Medicine, Sapienza, University of Rome, Italy; **Department of Clinical and Biological Sciences, University of Torino, Italy; ***St. Maria alle Scotte Hospital, Siena, Italy
Cancer cachexia is a complex multifactorial syndrome characterized by anorexia, body weight loss, muscle wasting, fat tissue depletion and metabolic alterations. Cancer cachexia has serious clinical consequences as it can affect quality of life, response to anti-neoplastic treatments, morbidity and mortality rates. Muscle wasting is the most relevant phenotypic feature of cancer cachexia and the principal cause of fatigue, function impairment and respiratory complications. Despite the relevance of cachexia to patient outcome, effective treatments are still lacking, and only recently cancer-induced muscle wasting is becoming to be considered as a prognostic tool. The mechanisms underlying muscle wasting are still unclear, although the ubiquitin-proteasome system has been involved in the degradation of bulk myofibrillar proteins. Recently also autophagic degradation has been proposed to play a role in the pathogenesis of muscle wasting. Autophagy is a homeostatic mechanism involved in the degradation of cellular constituents that is enhanced by stress conditions leading to organelle damage or by marked nutrient restriction (starvation) to recycle biomolecules for the synthesis of essential constituents. The PI3K/Akt/mTOR pathway is an important regulator of autophagy.

Aim of our study was to investigate the influence of a six month vibration-exercise period on glycaemic control, body composition, physical performance in the vibration group (VG) and 23 in the control group (CG), were subjected to vibration provided by a commercial device twice a week, 10 minutes each session, with frequency vibration of 25 Hz. The assessment includes: routine biochemical tests, evaluation of physical performance, evaluation of body composition by total body dual X ray absorptiometry (DEXA) and peripheral Quantitative Computed Tomography (pQCT), blood pressure control and structural/functional echocardiographic parameters.

**Results:**

1. Effects on glycaemic control: at baseline (bs) fasting glucose (FG), blood level of insulin (Ins) and HbA1c were similar between two groups (VGbs vs CGbs: FG 9.1+2.4 vs 8.5+2.6 mmol/L; Ins 13.2+8.2 vs 13.9+21.6 mmol/L; HbA1c 7.9+1.3 vs 7.4+1.2 %) while FG and HbA1c did not differ significantly after six months (VGF vs CGF: 7.8+1.8 vs 7.7+1.8 mmol/L; HbA1c 7.2+1.1 vs 7.2+0.8 %). FG and HbA1c decreased in both groups at final visit with consensual significant reduction of Ins only in VG (Ins 9.6+4.5 vs 18.5+32.6 mmol/L, p=0.027).

2. Effects on body composition: After intervention no significant changes in two groups were observed nor in weight nor in BMI. A significant change in total body mass were measured with DEXA, with an increased mass in cases and a decreases mass in CG (p=0.0005). In VG a significant change in total mass, total fat mass and regional and fat mass were reported. Precisely, fat mass in the trunk and in both legs decreased significantly (p=0.0008, p=0.05, p=0.002). Lean total mass did not change in both case and control. There were no effects on bone and muscle parameters measured by DEXA and pQCT, with the only exception of marrow density that showed increased values after intervention in vibration group.

3. Effects on performances status: it was shown a significant improvement in six minute walk test in VG (p=0.03), while the results in the CG were similar at baseline and at final visit. Other performances status test, as balance in standing and ability to rise from a chair did not significantly differ.

4. Effects on cardiovascular parameters: diastolic blood pressure differed significantly at baseline in two groups (VGbs vs CGbs: 84+10 vs 78+7 mmHg, p<0.05), while no significant difference in systolic pressure was observed (VGBs vs CGbs: 159+28 vs 144+20 mmHg). Diastolic blood pressure decreased in both and was significantly lower in VG after vibration (VGF vs CGF: 75+12 vs 77+8 mmHg, p=0.04). Systolic blood pressure tended to be lower in VG after vibration (VGF vs CGF: 137+19 vs 138+12 mmHg). Echocardiographic diastatic parameters did not differ in both groups at baseline and at final visit.

**Conclusions:** Overall our study demonstrated that six months of whole body vibration determine changes in body composition by decreasing fat mass as well as a better trend of metabolic / blood pressure control and an improved physical performance in the vibration group than in the control group. Echocardiographic diastatic features changes were not appreciated after the training, probably due to the length of the exercise session. Accordingly in future more studies are required to determine the real effects of vibration on metabolism and cardiovascular control and to understand the different underlying mechanisms that may contribute.

**Methods:** 42 type II diabetes post menopausal women on oral antidiabetes agents, insulin therapy or only on a specific diabetic diet, including 19 in the vibration group (VG) and 23 in the control group (CG), were subjected to vibration provided by a commercial device twice a week, 10 minutes each session, with frequency vibration of 25 Hz. The assessment includes: routine biochemical tests, evaluation of physical performance, evaluation of body composition by total body dual X ray absorptiometry (DEXA) and peripheral Quantitative Computed Tomography (pQCT), blood pressure control and structural/functional echocardiographic parameters.

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**Whole body vibration as exercise model: effects upon glycemic control, body composition and cardiovascular parameters**

Paola Bigolin, Paola Siviero, Francesco Bolzetta, Giuseppe Sergi, Stefania Maggi, Alois Saller

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**Background:** Vibration exercise is still largely unknown to the scientific community and the notion that vibration can be beneficial is relatively emerging profile of applications of this exercise modality also if clearly more research is needed in order to better understand the specific therapeutic potential of vibration as an exercise model. Aim of our study was to investigate the influence of a six month vibration-exercise period on glycaemic control, body composition, physical performance and cardiovascular parameters including echocardiographic diastolic pattern in type II diabetes post menopausal women compared to a control group.
Aims of the study: To assess the relationships between micro and macrovascular complications and diastolic dysfunction in patients with type 2 diabetes.

Methods: 92 T2DM patients with diabetes duration of at least five years and with normal ejection fraction were included in this study. In order to assess the presence of microvascular complications, every patient had glomerular filtration rate (GFR) measured by iohexol plasma clearance, albumin excretion rate (AER) and a fundoscopic examination. The presence of macrovascular complications was determined based on the history of events and an echocoloruldopplerography was performed to measure intima-media thickness and patency of carotid and femoral arteries. An echocardiogram was performed to assess diastolic function, and the E/E’ (the most specific echocardiographic index of diastolic dysfunction), was used. Patients were categorized as follows: based on diastolic dysfunction in 4 groups (absent, stage I, II, III), based on GFR in 3 groups (≥90 ml/min/1.73 m², 90-60 ml/min/1.73 m², <60 ml/min/1.73 m²), based on AER in 3 groups (<30 mg/24 h, 30-300 mg/24 h, ≥300 mg/24 h) and based on retinopathy in 3 groups (absent, background, proliferative). In order to enhance the power of the study, further analysis was carried out considering the dichotomy (absent vs present) for each diabetic complication and the different distributions of continuous values related to diabetic complications (i.e. GFR, AER, E/E’, blood pressure, HbA₁c, lipids, diabetes duration, age) among the aforesaid subgroups. For the macrovascular complications, patients were divided according to presence/absence of cerebrovascular and cardiac events in their history; peripheral artery disease was scored into 4 stages according to the estimation of luminal arterial patency (Stage 0: stenosis< 20%, stage I: 20–40%, stage II: 40–60%, stage III: >60%).

Results: The categorization of patients based on diastolic dysfunction severity was significantly associated with both stages of severity of albuminuria (p = 0.048) and dichotomy of presence/absence of abnormal albuminuria (p = 0.009) and with systolic arterial blood pressure (p = 0.014).

As far as microvascular complications, the categorization of patients according to the dichotomy of normal/abnormal E/E’ (The most specific echocardiographic index of diastolic dysfunction), was associated with pathological AER (p = 0.012) and pathological GFR (p = 0.01); these relationships have proven to be statistically significant also when considering the severity stages of albuminuria (p = 0.05) and of GFR (p = 0.022). A trend for significance was found testing the association of diastolic dysfunction (presence of abnormal E/E’) with diabetic retinopathy (p = 0.065).

As far as macrovascular complications, diastolic dysfunction (presence of abnormal E/E’) was related with history of ischemic stroke (p = 0.015).

Conclusions: This study demonstrates significant relationships between diastolic dysfunction and diabetic microvascular complications, especially nephropathy (both AER and GFR); for retinopathy here was a trend towards significance. There was also a relationship with a positive history for stroke. This is suggestive of a role of microangiopathy in the etiology of diastolic dysfunction and of diabetic cardiomyopathy in diabetes. These data suggest performing a diastolic function echocardiographic assessment in diabetic patients with impaired renal function and/or abnormal AER in order to assess their burden of cardiovascular risk. The tight relationship between diastolic dysfunction and diabetic nephropathy suggests the usefulness of performing a diastolic function echocardiographic assessment in diabetic patients with impaired renal function and/or abnormal AER in order to assess their burden of cardiovascular risk. Further longitudinal studies are needed to better understand these relationships.

Beginning a basal plus meal-time insulin regimen using prandial insulin aspart in insulin naive adults with type 2 diabetes: results from the A1chieve study


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| Tab.1. Baseline demographics and clinical outcomes after 24 weeks of treatment |
|-------------------------------|-----------------|-----------------|
|                               | > 65 years      | ≤65 years       |
|                               | (n=1967)        | (n=9890)        |
| Baseline characteristics      |                 |                 |
| Age (years)                   | 71.5 (5.0)      | 50.5 (8.6)      |
| Male (%)                      | 42.6            | 57.3            |
| Body mass index (kg/m²)       | 26.8 (5.0)      | 28.4 (5.3)      |
| Duration of diabetes (years)  | 11.2 (7.3)      | 6.9 (4.8)       |
| Clinical outcomes             |                 |                 |
| A1C (%)                       | Baseline        | Change          |
|                               | 9.5 (1.7)       | –1.9 (1.6)*     |
|                               |                 | –2.1 (1.6)*     |
| FPG (pre-breakfast) (mg/dL)   | Baseline        | Change          |
|                               | 197.8 (62.0)    | –71.4 (64.8)*   |
|                               |                 | –75.7 (56.7)*   |
| PPPG (pre-breakfast) (mg/dL)  | Baseline        | Change          |
|                               | 260.9 (79.2)    | –80.6 (83.1)*   |
|                               |                 | –101.0 (73.8)*  |
| Hypoglycemia (overall)        | Baseline        | Final visit     |
| (event/ person-year [% with event]) | 1.22 (4.1)   | 1.76 (6.0)†     |
|                               |                 | 1.27 (4.2)²     |
| Bodyweight (kg)               | Baseline        | Change          |
|                               | 70.0 (14.6)     | 0.4 (3.7)*      |
|                               |                 | –0.5 (4.1)*     |
| Insulin dose (U/kg)           | Day 1           | Final visit     |
|                               | 0.23 (0.13)     | 0.35 (0.19)     |
|                               |                 | 0.35 (0.18)     |
| Quality of life (VAS 0-100)   | Baseline        | Change          |
|                               | 61.6 (17.3)     | 12.3 (18.5)*    |
|                               |                 | 16.0 (18.3)*    |

Mean (SD) or %; *p<0.001 from baseline; †p=0.007; ‡p=0.481. FPG, fasting plasma glucose; PPPG, postprandial plasma glucose; VAS, visual analog scale.
Bioelectrical phase angle on hospital admission as predictor of short- and middle-term mortality in elderly medical patients

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Malnutrition in elderly hospitalized patients is a significant public health problem affecting 60-70% of this subpopulation. In fact, it is recognized as an important independent risk factor for morbidity and mortality. To date there are no well-defined clinical, instrumental and blood markers to diagnose malnutrition in this specific group of patients and to allow adequate follow-up of nutritional treatment as well as to predict events. The bioelectrical impedance analysis (BIA) is now a widely used method for the evaluation of body composition. In particular, the phase angle (PA), a BIA derived indicator based on body resistance and reactance and resistance, is assumed as an indicator of cellular membrane integrity and water distribution between the intra- and extra-cellular spaces and for these reasons it has also been used as an indicator of general and nutritional wellness. Moreover, even the Mini Nutritional Assessment (MNA) is a test that has been used for the assessment of nutritional status in the elderly. This study was carried out to evaluate longitudinally the ability of BIA and MNA tests to predict mortality in the short and medium term beyond the traditional anthropometric and laboratory measurements in a group of hospitalized elderly patients.

One-hundred-fifty patients aged 73.5±7.9 years (mean ± sd) admitted to the internal medicine ward were included in the study regardless of the admitting diagnosis. After discharge clinical informations were obtained via telephone contact every 4 months with a maximum follow-up duration of 16 months (4 months: n = 130, 8 months: n = 94, 12 months n = 24, 16 months: n = 7 patients). At the end of the observation period 12 deaths were recorded. The definition of malnutrition according to the MNA was not able to predict mortality (P= 0.73). According to the median values of PA (4.0°), MNA (22) and serum albumin concentration (2.7 g/dl), the values of these variables were dichotomized as “low” or “high” respectively when below or above the median value. A low PA value was able to predict mortality (figure 1A) and even more when a cluster that aggregates low PA, low MNA and low albumin concentrations was considered (figure 1B).

Although the preliminary results of this study need to be confirmed in a larger sample of patients and for a longer follow-up period, it seems that BIA is a good candidate for the diagnosis of malnutrition and to predict mortality.

References:

Indirect calorimetry demonstrates that resting energy expenditure is increased in patients with poorly controlled diabetes and is normalized by insulin bolus

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It has been suggested that an increase in energy expenditure may promote the body weight reduction which is usually observed in diabetic patients with poor metabolic control. Therefore, the resting energy expenditure (REE) was measured using a ventilated hood system of indirect calorimetry (Quark RMR; Cosmed, Roma, Italy) in 20 patients (8 males, 12 females) with poorly controlled type 2 diabetes (body mass index -BMI-: 34.3±2.1 kg/m²; fasting plasma glucose -FPG-: 11.1±0.5 mmol/l), treated with oral hypoglycemic agents (n=14) or nutritional treatment alone (n=6). A group of non-diabetics (n=14, 8 males and 6 females) with similar age and body size to that of the diabetic group (BMI: 35.2±1.9 kg/m², P= 0.76; FPG: 4.8±0.2 mmol/l, P< 0.001) was included as control group. The diabetic group exhibited a REE normalized for the fat-free mass size (FFM, bioelectrical impedance; BIA-103, RJL, Detroit, MI, USA/Akern, Florence, Italy) higher by 6.8% (+123 kcal/24h, P = 0.04) than that of non diabetics.

Furthermore, the value of normalized REE for FFM was significantly correlated to the value of FPG (r= 0.58, P= 0.04) in diabetic patients, suggesting that the higher REE is dependent on glycemic control. As known, the value of FPG is strongly influenced by the gluconeogenesis, an energetically wasteful metabolic process. Therefore, the high REE observed in diabetic patients might be in consequence of the increased gluconeogenic metabolism. In order to verify this hypothesis, it was administered an IV bolus of regular insulin (0.2 IU kg body weight; Actrapid®, NovoNordisk, Denmark) in 5 diabetic participants. Following the insulin bolus a progressive reduction of REE was observed as follows (REE change): 10 min: -11.6%; 20 min: -17.4%; 30 min: -19.9%; 45 min: -22.0%; 60 min: -20.1%, (P = 0.04), similar reductions of blood glucose and lactate concentrations were observed. In conclusion, diabetic patients with poor metabolic control have a higher energy expenditure probably in consequence of a significantly higher activity of gluconeogenesis. This study may contribute, at least in part, to recognize the nature of body weight reduction that occurs in concomitance with poorly controlled diabetes and of body

Figure 1. Kaplan-Meyer curves describing the probability of surviving of resident elderly medical patients according to (A) the value of PA (≤ 4.0°, red –lower- line; >4.0°, blue –upper- line) or (B) a combination of PA ≤ 4.0° + albuminemia ≤ 2.7 mg/dl + score of MNA test < 22 (red –lower- line) or, respectively, > 4° + > 2.7 mg/dl + ≥ 22 (blue –upper- line).
weight gain as that commonly observed when the hypoglycemic treatment with, in particular, sulphonlureas and insulin is started.

**References:**

**The BIA vector in obesity and diabetes**

The BIA vector in obesity and diabetes

1. Buscemi S, 2Sprini D, 3Migliaccio S, 3Cianferotti L, 3Brandi ML, 2Lenzi A, 2Rini GB

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Although the assessment of body water compartments is of great diagnostic value, appropriate methods are not readily available for routinely clinical application. Bioelectrical impedance analysis (BIA) is a safe, non-invasive, rapid and highly reproducible procedure that is strongly influenced by body water and intra-extra-cellular distribution. Four-hundred-fifty-six adults (224 males and 232 females) were enrolled and divided in subgroups on the basis of the presence of obesity and diabetes (type 1 and type 2). The aim of the study was to investigate if different BIA measurements in terms of resistance (R), reactance (Xc) and phase angle (PA) were associated to body characteristics that expressed in terms of BIA vector may be useful to diagnose and monitoring imbalances of body water compartments.

**References:**

**Identifying predictors of response to liraglutide in type 2 diabetes using recursive partitioning analysis**

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Randomized clinical trials provide unbiased databases for comparative effectiveness analyses to see which patients respond best to available interventions. We evaluated patient-level data pooled from 7 phase 3 clinical trials with liraglutide to examine responder subgroups, as defined by those achieving a composite endpoint of A1C <7%, no weight gain and no hypoglycemia (episodes requiring assistance or self-treated with PG <56 mg/dL) over 26 weeks. Overall 34% of individuals on liraglutide 1.8 mg achieved the prespecified composite endpoint: the highest response rate among compared therapies. Candidate predictor variables included baseline age, sex, ethnicity, BMI, A1C, beta-cell function, FPG, insulin resistance, previous treatments, and diabetes duration. Using recursive partitioning to create classification trees, baseline A1C was the most significant predictor, with a probability of achieving the composite outcome of 46% with baseline A1C <8.5% as opposed to 19% if baseline A1C ≥8.5% (p<0.0001). Subsequent splits (with p-values <0.05) produced a subgroup within pa-
Type of insulin and age are predictors of hospitalization due to severe hypoglycemia: the ephiphoto study

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Incidence and recurrence of severe hypoglycemic (SH) events among patients with diabetes mellitus (DM) was evaluated in a retrospective nationwide register-based linkage study in Finland. SH was defined as a hospitalization or a secondary health care visit due to DM with severe hypoglycemia (ICD E10.00 or E11.00). Total population (n=140,035) comprised patients who purchased insulin during 2000–2009 and were followed-up for SH events until end of year 2009 or death. The present analysis comprised those 77,046 patients who had not used insulin glargine (IGla), insulin detemir (IDet) or NPH insulin (NPH) before year 2000. Stratified incidence rates with 95% CIs were calculated. Hazard ratios (HR) were estimated by Cox’s proportional hazards model. 9716 SH events were identified. Type of DM (type 1 or 2) was not associated with risk of SH. Compared to IGla, risk of SH was lower during use of IDet (HR 0.76, CI 0.67–0.87), and higher during use of NPH (HR 1.19, CI 1.11–1.28) (Figure: upper panel). Female gender predicted lower risk (HR 0.93, CI 0.88–0.98), and increasing age predicted higher risk of SH (Figure: lower panel). Risk of SH recurrence was lower during IDet (HR 0.60, CI 0.52–0.69), and higher during NPH (HR 1.58, CI 1.46–1.71) compared to IGla.

In conclusion, our data show that increasing age and type of long-acting insulin are predictors of hospitalization due to SH. Risk of hospitalization due to SH could potentially be modified by selection of long-acting insulin.
Methods: We enrolled 122 hypertensive subjects (71 men) that underwent OGTT and endothelial function assessment at baseline by using peripheral arterial tonometry (PAT) with EndoPAT 2000 (Itamar Medical Inc., Israel) device. The average age was 55.4±10.1 years (mean±SD) and none of the patient had a previous CV event. RHI was calculated as the ratio between the digital pulse volume during reactive hyperemia and at baseline.

Results: Among participants, 48 were NGT with PLPG <155 mg/dl, 29 were NGT with PLPG ≥155 mg/dl, 28 had impaired glucose tolerance (IGT) and 17 had a T2D diagnosis. NGT≥155 had a worse RHI comparing with NGT<155 (1.98±0.54 vs. 2.20±0.38 respectively, P=0.04) and similar to IGT (1.94±0.28, P=0.728). A stepwise regression analysis showed that 1h PLPG was the strongest predictor of RHI variation justifying a 15.2% (P <0.0001) of its variation.

Conclusions: Endothelial function assessed by RHI, shows a reduction with the impairment of glucose tolerance status, in particular, NGT≥155 subjects, compared with NGT<155, have a lower RHI mean value, similar to that of IGT and diabetic subjects. On the basis of these results, we suggest to consider also NGT ≥155 subjects at high cardiometabolic risk.

NOX2 generated oxidative stress is associated with severity of steatosis in patients with non-alcoholic fatty liver disease


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Background and aim: Nonalcoholic fatty liver disease (NAFLD) includes a wide spectrum of liver diseases ranging from simple fatty liver to non-alcoholic steatohepatitis (NASH), which may progress to fibrosis and even cirrhosis and hepatocellular carcinoma. Chronic oxidative stress is considered one of the key mechanisms responsible for liver damage and disease progression in non-alcoholic fatty liver disease. However, so far, no study has been performed with newer markers of systemic oxidative stress. Aim of this study was to assess the relationship between urinary 8-iso-prostaglandin F2α (8-iso-PGF2α) and serum soluble NOX2-derived peptide (sNOX2-dp) and the severity of liver steatosis in subjects with non-alcoholic fatty liver disease in different clinical settings.

Methods: The study has been performed in 264 consecutive patients referred for suspected metabolic disease. Metabolic syndrome was diagnosed according to the modified criteria of the ATPIII Expert Panel of the US National Cholesterol Education Program. Liver steatosis was defined according to Hamaguchi ultrasonographic criteria. Oxidative stress was assessed by urinary 8-iso-PGF2α and serum sNOX2-dp levels.

Results: Patients with NAFLD had significantly higher (p<0.001) mean values of urinary 8-iso-PGF2α, and serum sNOX2-dp, ALT, and cys-teratine-18 and HOMA-IR and lower values of serum adiponectin as compared to those without. Prevalence of MetS and of most of its clinical features was significantly higher in patients with NAFLD. The same findings were also observed after the exclusion of obese subjects, or subjects with diabetes or with metabolic syndrome and in those not taking statin medication. In addition, the levels of urinary 8-iso-PGF2α were independent predictors of NAFLD and a strong association of urinary 8-iso-PGF2α and of serum sNOX2-dp with the severity of liver steatosis at ultrasound examination was also observed.

Conclusions: We demonstrated an increased NOX2 generated oxidative stress in subjects with NAFLD. Oxidative stress was independent from obesity, diabetes and metabolic syndrome and increased with the severity of liver steatosis at ultrasound.

Disease-specific nutritional support in malnourished pressure ulcer patients: a randomized, controlled trial

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Background and aim: Malnutrition is a common comorbidity among pressure ulcer (PU) patients and nutritional support has been found to be effective in improving healing. Preliminary trials suggest that supplementation of arginine, zinc and antioxidants contributes to faster healing, but evidence from high-quality trials is lacking.

Objective: To investigate whether a disease-specific oral nutritional supplement is beneficial to the healing of PUs.

Methods, setting, and patients. Multicenter, randomized, controlled trial conducted from February 2010 to November 2012 in adult (≥18 year-old) malnourished patients with stage II, III and IV PUs; 200 long-term care residents and patients at home-care services were randomized and 157 included in the intention-to-treat analysis.

Interventions: An energy-dense, protein-rich oral formula (400 mL per day) enriched with arginine, zinc and antioxidants vs. an equal volume of an isocaloric, isonitrogenous formula for 8 weeks.

Main outcome measures: The primary endpoint was the percentage of change in PU area. Secondary endpoints included: complete healing and reduction in area ≥40%, incidence of wound infections, total number of dressings at 8 weeks and percentage of change in PU area at 4 weeks. A cost-effectiveness analysis was also carried out.

Results: Intention-to-treat analyses were based on 157 patients. Supplementation with the enriched-formula (N=78) resulted in higher re-daction in PU area vs the use of control formula (N=79): 62.9% vs 43.4%; mean difference, 19.5% [95%CI, 9.6, 29.4]; P<0.001. Reduction in area ≥40% was more frequent in enriched-formula group (73.1% vs 51.9%; difference, 21.2% [95%CI, 6, 35.3]; P=0.008). There was no difference in complete healing (15.4% vs 7.6 %; difference, 7.8% [95%CI, -2.5, 17.7]; P=0.141). Intervention with an enriched formula at 8 weeks was found to be cost-effective, required a lower number of dressings and resulted in larger reduction in PU area also at 4 weeks. There was no significant difference between groups in incidence of wound infections at 8 weeks.

Conclusion and relevance: Among malnourished patients with PUs, 8 weeks of supplementation with an oral energy-dense formula enriched with arginine, zinc and antioxidants resulted in better healing and was found to be cost-effective.

Trial registration. ClinicalTrials.gov Identifier: NCT01107197

Case report: endothelial dysfunction in obese patient

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Introduction: Few studies have investigated whether endothelial dysfunction, assessed through the measurement of the Flow Mediated Dilatation (FMD) of the brachial artery, is directly associated with measurements of obesity. A study conducted in Boston showed a direct correlation between FMD value and obesity, whereas no correlation with Body Mass Index (BMI) was found; particularly, it has not been shown yet a relationship between FMD reduction and weight gain. The endothelium plays a key role in biolog-
Perticone F.

Endothelial cells mediate dilation of the brachial artery. The brachial artery was visualized by high-resolution ultrasoundography with a high-frequency probe (7-12 MHz). The sphygmomanometer is placed on the proximal artery, in correspondence of the arm. After a one minute basal acquisition of the diameter of the brachial artery and arterial flow, the cuff is inflated for 5 minutes at a pressure 50-70 mmHg greater than the resting systolic blood pressure, generating a transient downstream ischemia. A short period of artery dilation follows to the cuff deflation (compensatory reactive hyperemia) induced by metabolites released during the stress phase. A few seconds after the restoration of the blood flow, the maximum diameter of arterial dilation is measured. The image of the artery is then continuously recorded until the initial diameter of the artery is restored. Few studies tried to establish the normal values of FMD in a sufficient sample of patients free from diseases and cardiovascular risk factors. In a Review published in 2005, Moens et al. considered all the published studies, and proposed as normal FMD range value an interval of 7-10%.

Clinical case: We studied a 57 years old men referred to the ambulatory of Predictive Medicine of the Policlinico Umberto I in Rome, in March of 2013. The patient also had systemic hypertension, treated with ARBs, and hepatic steatosis. She denied smoking status and followed a diet abundant in quantity and little variety. The anthropomorphic data collected at the first visit were: weight 115.5 kg, height 161 cm, BMI 44.6, waist circumference 125 cm, hip circumference 122 cm, PA 130/80 mmHg; FMD examination showed a complete lack of vasodilation in the test of brachial artery, which maintained an unchanged caliber of 5.0 mm for the duration of the examination (30°, 60°, 90°, 120°). FMD = 0% (v.n. 7-10%). The patient underwent a low-calorie diet of 1400 kcal, with lipids and carbohydrates reduction and increase of vegetable and protein portion, especially white meat, fish and vegetable proteins (pulses). This diet was also associated with mild-moderate physical activity (45 minutes a day of fast-paced walking). The patient attended the 3 months follow-up, reporting he had strictly complied with our instructions. The collection of anthropometric data recorded a weight loss of 14.5 kg (weight: 101 kg) associated with a reduction of the BMI (BMI: 39). The patient underwent a second FMD examination which showed a marked improvement of the endothelial response with gradual increase in the caliber of the brachial artery as the sleeve deflates: T0°: 4.5 mm, T30°: 4.6 mm, T60°: 4.8 mm, T90°: 4.9 mm, T120°: 5.0 mm. FMD = 11% (v.n. 7-10%).

Conclusions: This clinical case shows that, in the evaluation of best therapy in obesity, realized in the first instance through diet and lifestyle changes, the examination of FMD, for its simplicity and non-invasiveness, can be useful as additional parameters to achieve therapeutic benefit in these patients. In our case, the low-calorie diet associated with mild-moderate physical activity has lead not only in reduction of body weight, BMI, waist circumference and hip circumference, but also in improvement of endothelial function. In just 3 months the patient lost 14.5 kg of body weight with a reduction of BMI from 44.7 to 39. Also there was a net improvement of endothelial function, assessed by FMD, exceeding the normal range (7-10%). Therefore we can confirm that non-pharmacological therapeutic interventions, designed to reduce body weight and BMI, also brings benefits on endothelial function and cardiovascular risk reduction. The FMD can be considered an additional marker of atherosclerosis for ease of execution, correlation with clinical endpoints and ability to predict the onset of benefits in clinical trials.

Essential amino acids and insulin signaling in human endothelial cells

Cimellaro A, Tassone EJ, Presta I, Hribal MI, Sciacqua A, Sesti G, Perticone F.
12.4±4.5, \(p<0.0001\) for D3), and a decrease thereafter, but the baseline difference was still significant up to d 90 for po D3 only (7.1±5.7, \(p<0.01\)). On the contrary, D2 and D3 im administration determined a slow increase during the observation period, reaching a peak at d 120 (11.1±6.5 for im D2 and 11.1±2.8 for im D3, \(p<0.0001\) for both). Concerning serum 1,25(OH)\(_2\)D, a significant increase of mean values after po D2 was observed; interestingly, a decrease of serum total 1,25(OH)\(_2\)D was observed by RIA. By LC-MS/MS the po D2 determined a significant decrease in serum 1,25(OH)\(_2\)D and an increase in 1,25(OH)\(_2\)D\(_2\) throughout the observation period. The AUC of total 1,25(OH)\(_2\)D was higher for D2 vs D3 (po D2 6833 vs po D3 4879 and im D2 6671 vs im D3 5453, \(p<0.0001\) for both). Both po D2 and D3 determined a significant increase in 24,25(OH)\(_2\)D\(_2\) (2.5±1 ng/ml, \(p<0.001\)) and 24,25(OH)\(_2\)D\(_3\) (4.6±1.4, \(p<0.001\)) at d 30 in the subgroup of 3 patients. A significant decrease in PTH serum levels was detected only after po D3 at d 30 (\(p<0.05\)). In conclusion, 1) A single dose of 600,000 IU of po D2 and D3 is initially more effective in increasing total 25(OH)D serum levels than the equivalent im dose; the last instead determined a sustained and gradual increase. 2) Regardless the way of administration, D3 has a greater effect than D2 in raising serum total 25(OH)D. These differences in pharmaceutical bioavailability should be taken into account when treating or preventing vitamin D deficient states. 3) Our RIA assay for 1,25(OH)\(_2\)D may not recognize 1,25(OH)\(_2\)D\(_2\), thus underestimating the concentration of the active metabolite in D2 treated patients. 4) Following high doses of both po forms of vitamin D there is a rapid conversion in both active and inactive metabolites.

### Dietary integration with Grana Padano cheese lowers blood pressure in hypertensive patients

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Cow-milk protein fermentation by proteases from *Lactobacillus helveticus* can produce peptides with sustained ACE inhibitory activity, mainly due to 2 tripeptides [valyl-prolyl-proline (VPP) and isoleucyl-prolyl-proline (IPP)] that have shown to lower blood pressure (BP) in experimental animals and in humans. Grana Padano cheese is an Italian semi-fat hard cheese which has shown a potent in-vitro ACE-inhibitory effect (spectrophotometric assay). Aim of study was to test the hypothesis that a dietary integration with a small amount of Grana Padano cheese was able to reduce BP in mild hypertensive patients. The randomized, open-label, controlled study has been concluded in 45 patients (59.3% male, aged 74.2±6.0 years) with a diagnosis of type 2 DM attending our clinical unit was included in the study. Information on clinical, functional, nutritional status, comorbidities, medications, and social support network was used to calculate MPI. Based on the predictive value of MPI, all subjects were stratified in two groups: the low-risk group (MPI mean value > 0.33) and the moderate/severe risk group (1 < MPI mean value > 0.33). The statistical analysis was performed using IBM SPSS Statistics software.

### The multidimensional prognostic index (MPI): a new measure of frailty in elderly diabetic out patients?


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**Introduction:** Frailty is an important and problematic issue that affects elderly people. It is an expression of high vulnerability for adverse health outcomes, including disability, dependency, falls, and mortality. Recently a Multidimensional Prognostic Index (MPI) was developed for evaluation of frail elderly hospitalized subjects. MPI predicts 1-year mortality risk in elderly hospitalized patients. **Aim:** To evaluate the efficacy of MPI in predicting mortality risk in elderly out-patients with type 2 diabetes mellitus (DM) and to assess the correlation between MPI score, HbA1c values and eGFR (CKD-EPI). **Methods and results:** A sample of 118 patients aged \(\geq\) 65 years and older (59.3% male, aged 74.2±6.0 years) with a diagnosis of type 2 DM attending our clinical unit was included in the study. Information on clinical, functional, nutritional status, comorbidities, medications, and social support network was used to calculate MPI. Based on the predictive value of MPI, all subjects were stratified in two groups: the low-risk group (MPI mean value > 0.33) and the moderate/severe risk group (1 < MPI mean value > 0.33). The statistical analysis was performed using IBM SPSS Statistics software.

Results demonstrated that higher scores on MPI carried a greater short-term mortality risk were more likely to be associated with increasing age (\(p = 0.0018\)). Moreover, lower MPI mean values were found in men than in women, i.e. men have a less risk of mortality than women (0.32±0.14 vs 0.42±0.21, \(p = 0.003\)). A significant correlation was observed between MPI mean value and HbA1c (\(p = 0.022\)): the mean value of HbA1c was respectively 7.14±1.31 in the low risk group patients and 8.13±2.12 in the moderate/severe group. Similarly, a significant association was found between eGFR and MPI mean value (\(p < 0.001\)).
**Discussion:** MPI is a useful tool in stratifying elderly out-patients with chronic disease, such as diabetes, into groups at varying risk of mortality, and it is helpful in setting the making decision of the clinical plans. We highlight that MPI is a good care approach to the frail elderly people because it mirrors the multi-dimensional domains of frailty providing further opportunities and strategies for prevention, treatment and intervention in both older hospitalized and out-patient subjects.

**Liraglutide is safe and effective in mild or moderate renal impairment: the association of british clinical diabetologists (ABCD) nationwide liraglutide audit**

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We evaluated the safety and efficacy of liraglutide among patients with mild or moderate renal impairment. Data was obtained from a nationwide audit of liraglutide use in UK. Among 4129 patients, we excluded patients with follow-up <6 months, previously on exenatide, used liraglutide 1.8 mg (too few to analyse), or lacked baseline data to estimate creatinine clearance (CrCl) using the Cockcroft-Gault formula. Remaining 1081 patients were divided into CKD group 1 (normal, CrCl>90 ml/min) (n=872), CKD group 2 (mild renal impairment, CrCl 60-90 ml/min) (n=169) and CKD group 3 (moderate renal impairment, CrCl 30-59 ml/min) (n=40).

Effect of CKD group on changes of A1c, weight, systolic blood pressure (SBP) and creatinine (Cr) at 6 months were analysed using ANCOVA using baseline values as covariates, while proportion of patients reaching A1c ≤7% (glycaemia (adjusted for insulin and sulfonylurea use) using logistic regression. A1c and weight reduction for all three groups were significantly reduced from baseline; CKD group 1, -1.0% (0.1) and -3.6 kg (0.2), CKD group 2, -0.9% (0.1) and -3.3 kg (0.4), and group 3, -0.8% (0.2) and 2.5 kg (0.9). There were no influences of CKD group on A1c reduction (p=0.46) or weight reduction (p=0.95).

Similarly, no effect of CKD group was seen on SBP reduction (-4 mmHg v -3 mmHg v -6 mmHg; p=0.74), rates of GI side effects (15.3% v 12.4% v 17.5%, CKD 2 v 1 OR [95%CI] 0.8 [0.5;1.2], p=0.26) or rates of reported hypoglycaemia (1.7% v 1.2% v 0%, CKD 2 v 1 OR 0.5 [0.1;2.2] (p=0.36). A small but significant reduction of Cr was observed with advancing CKD group (+1 µmol/L v -3 µmol/L v -7 µmol/L, p=0.02). A case of acute renal failure attributed to dehydration from prolonged vomiting was reported in CKD group 2.

We conclude that liraglutide 1.2 mg is safe and effective in real life clinical practice among patients with mild or moderate renal impairment.

**Prospectively planned meta-analysis comparing hypoglycaemia rates of insulin degludec with those of insulin glargine in all patients and an elderly (≥65 year) subgroup**


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**Introduction:** Hypoglycaemia and the fear of hypoglycaemia are significant barriers to achieving glycaemic control with insulin. The introduction of basal insulin analogues, such as insulin glargine (IGlar) and insulin degludec (IDeg), a new basal insulin that forms soluble multimers after subcutaneous injection, has an ultra-long and stable glucose-lowering effect, with low day-to-day and hour-to-hour variability.1–4 This prospective meta-analysis aimed to demonstrate the superiority of IDeg over IGlar in terms of hypoglycaemic episodes at equivalent HbA1c using pooled, individual patient-level data from all phase 3a trials in the IDeg clinical development programme that compared IDeg once daily (OD) with IGlar OD in patients with type 2 or 1 diabetes (T2D/T1D).

**Methods:** Two major strengths of this meta-analysis are the inclusion of all phase 3a trials comparing IDeg OD with IGlar OD and its prospective design. All seven trials (five T2D and two T1D) were randomised, controlled, open-label, multicentre, phase 3a, treat-to-target trials of 26 or 52 weeks’ duration.1,2,3–10 IDeg and IGlar doses were titrated according to the same algorithm to the pre-breakfast self-measured blood glucose targets calibrated to plasma glucose of >3.9–<5.0 mmol/L (>70–<90 mg/dL).1,2,3 Self-reported confirmed hypoglycaemia (requiring assistance or confirmed by plasma glucose of <3.1 mmol/L [<56 mg/dL]) and nocturnal confirmed hypoglycaemia (00:01 through 05:59 hours) were analysed with a negative binomial regression model. Treatment difference in hypoglycaemic rate was compared during the titration period (0–15 weeks of treatment) and the maintenance period (from 16 weeks to the end of treatment, when most patients had achieved stable insulin doses and stable glycaemic control).

**Results:** This meta-analysis analysed 4330 patients (2899 IDeg OD vs.1431 IGlar OD, reflecting the unequal randomisation ratio in different trials [1:1, 2:1 or 3:1]). Withdrawal rates (16.6% [IDeg OD] and 13.8% [IGlar OD]), baseline characteristics, and demographics were similar between treatment groups. Insulin glargine was previously used by 30–40% and 60–70% of T2D and T1D insulin-treated patients, respectively. A total of 21% of all patients were ≥65 years of age.

- Insulin-naïve patients with T2D who were treated with IDeg experienced significantly lower rates of overall confirmed (lower by 17%), nocturnal confirmed (lower by 36%) and severe hypoglycaemic episodes (lower by 86%) compared with patients treated with IGlar in the total treatment period
- In the overall population with T2D, patients who were treated with IDeg experienced significantly lower rates of overall confirmed (lower by 17%) and nocturnal confirmed hypoglycaemic episodes (lower by 32%) during the trial compared with IGlar; these treatment differences were greater during the maintenance period.
- In the overall population with T1D, the estimated rate ratio (IDeg:IGlar) of nocturnal confirmed hypoglycaemic episodes during the trial was 0.83 (not significant). The rate of episodes was 25% lower with IDeg than with IGlar during the maintenance period (significant).
- Elderly patients treated with IDeg experience a numerically (18%) lower rate of confirmed hypoglycaemia and a significantly (35%) lower nocturnal hypoglycaemia rate with IDeg versus IGlar, confirming the results of the total population included in the IDeg clinical programme.

**Conclusions:** This meta-analysis confirms the findings of the individual trials that similar improvements in HbA1c can be achieved with fewer hypoglycaemic episodes with IDeg than with IGlar across a broad spectrum of patients with diabetes and insulin regimens. Lower rates of hypoglycaemia associated with IDeg may be of particular importance in the elderly population on insulin.
Starting insulin detemir in older vs younger adults with type 2 diabetes (T2D): results from the A1chieve study


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A1chieve® was a 24-week, non-interventional study evaluating the safety and effectiveness of starting an insulin analog in people with T2DM (n=66,726) in routine clinical care in 28 countries across four continents. The present subgroup analysis investigated the effectiveness of starting insulin detemir (detemir) in older (>65 yr; n=1967) and younger (≤65 yr; n=9890) insulin-naïve adults with T2DM. Baseline characteristics are shown in the Table. The majority of people in both subgroups were using two oral glucose-lowering drugs at baseline (56% ≤65 yr, 55% >65 yr). A1C was poor for both age groups (9.5%) but significant improvements in fasting plasma glucose (PG) and postprandial PG in both subgroups (p<0.001) at 24 weeks (Table). The overall incidence of hypoglycemia decreased from 0.07 (≤65 yr) and 0.09 (>65 yr) to 0.00 events/person-year (p<0.001 and p=0.003 respectively). Quality of life and health, as assessed by the EQ-5D 100-point visual analog scale, reported significant improvement at 24 weeks in both age groups (p<0.001) (Table). Thus, starting treatment with insulin detemir in both older and younger insulin-naïve adults with poorly controlled T2DM was associated with improvements in glycemic control without increased risk of major hypoglycemia at 24 weeks.

Tab.1. Glycemic control, bodyweight & quality of life after treatment with aspart plus basal insulin

<table>
<thead>
<tr>
<th></th>
<th>Younger participants (n=1317)</th>
<th>Older participants (n=2444)</th>
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<tbody>
<tr>
<td>A1C (%)</td>
<td>Baseline 10.2 (2.0)</td>
<td>10.0 (2.5)</td>
</tr>
<tr>
<td></td>
<td>Change -2.8 (2.0)*</td>
<td>-2.8 (2.1)*</td>
</tr>
<tr>
<td>FPG (pre-breakfast)</td>
<td>Baseline 216.4 (72.8)</td>
<td>202.9 (78.0)</td>
</tr>
<tr>
<td>(mg/dL)</td>
<td>Change -90.1 (74.1)*</td>
<td>-80.3 (79.7)*</td>
</tr>
<tr>
<td>PPG (pre-breakfast)</td>
<td>Baseline 283.9 (88.8)</td>
<td>275.3 (92.4)</td>
</tr>
<tr>
<td>(mg/dL)</td>
<td>Change -121.0 (89.3)*</td>
<td>-115.2 (95.5)*</td>
</tr>
<tr>
<td>Hypoglycemia (overall) (event/ person-year [% with event])</td>
<td>Baseline 1.43 (4.9)</td>
<td>2.88 (8.2)</td>
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<tr>
<td></td>
<td>Week 24 2.89 (8.4)*</td>
<td>3.49 (10.6)*</td>
</tr>
<tr>
<td>Bodyweight (kg)</td>
<td>Baseline 75.5 (17.1)</td>
<td>70.3 (12.1)</td>
</tr>
<tr>
<td></td>
<td>Change -0.4 (4.2)</td>
<td>0.5 (4.0)</td>
</tr>
<tr>
<td>Quality of life (VAS 0-100)</td>
<td>Baseline 65.7 (17.5)</td>
<td>65.1 (18.0)</td>
</tr>
<tr>
<td></td>
<td>Week 24 77.9 (11.9)*</td>
<td>77.6 (12.3)*</td>
</tr>
<tr>
<td>Insulin dose (U/kg)</td>
<td>Day 1 0.60 (0.25)</td>
<td>0.57 (0.24)</td>
</tr>
<tr>
<td></td>
<td>Week 24 0.65 (0.29)</td>
<td>0.60 (0.27)</td>
</tr>
</tbody>
</table>

Mean (SD) or as started; *p<0.001; †p=NS; insulin dose was not analyzed statistically; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; VAS, visual analog scale.

Omental adipose tissue fibrosis does not impact on insulin-resistance in morbid obesity

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Introduction: In chronic obesity, fibrosis accumulation occurs in adipose tissue limiting adipocyte fat buffering capacity. So far the clinical impact of adipose tissue fibrosis remains unclear. The aim of our study was to investigate whether omental adipose tissue (OAT) fibrosis may account for a more severe insulin-resistance in morbidly obese population.

Methods: OAT biopsies were obtained from 27 obese subjects (age 41.9±1.6 y; BMI 48.5±1.4 Kg/m²) undergoing bariatric surgery. The patients, characterized by anthropometric, biochemical and oral glucose tolerance test evaluation were divided in two age-, waist- and BMI-matched groups (Group A: n=14; Group B: n=13) according to the severity of insulin-resistance assessed by hyperinsulinemic euglycemic clamp (Group A, M=4.34±0.4; Group B, M=2.14±0.2 mg·kg⁻¹·min⁻¹ p<0.001). OAT expression of Collagens 1, 3 and 6, pro-fibrotic mediators (TGF-β, Actinin A, CTGF), hypoxia (HIF-1α), inflammation (IL6) and macrophage infiltration (CD68, MCP-1) and polarization (M1: CD86, CD206; M2: CD150) markers was analyzed by Real Time PCR. Sections of OAT biopsies fixed and paraffin-embedded, were hematoxin- and eosin-stained to assess morphometry.

Results: The groups did not differ in any gene analyzed. Notably, in all subjects, Collagen 6, the most highly enriched collagen in adipose tissue, significantly correlated with Collagen 1 (r=0.72; p<0.001) and 3 (r=0.82; p<0.001), HIF-1α (r=0.62; p<0.001), TGF-β1 (r=0.48; p<0.05), CD68 (r=0.64; p<0.001), MCP-1 (r=0.38; p<0.05) and CD150 (r=0.40; p<0.05) mRNA levels, supporting their relation with fibrosis development. The mean adipocyte area was not different between the low and the high Collagen 6 mRNA tertiles and resulted not affected by collagen expression in a waist circumference-adjusted model.

Conclusion: These findings suggest that, within morbidly obese population, OAT transcription levels of fibrogenic proteins do not explain a more severe peripheral insulin-resistance. Meanwhile, our results highlight the link between OAT fibrosis and both tissue hypoxia and alternatively-activated macrophage accumulation.

Micro RNA 21 is up-regulated in obese adipose tissue in type 2 diabetes

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Introduction: MicroRNAs (miRNAs) are a class of short, single-stranded non-protein coding gene products known to post-transcriptionally regulate the expression of target genes through interactions with specific messenger RNA. There is growing evidence for an important role of miRNAs in regulating the pathways in adipose tissue that control a range of processes including adipogenesis, insulin resistance and inflammation. In particular,
miR21 showed a positive correlation with BMI in human subcutaneous adipose tissue (SAT) and was demonstrated to affect the proliferation but not the differentiation of human adipose mesenchymal stem cells through the modulation of Transforming Growth Factor-β signaling and negatively correlate with adipocyte number in epididimal fat of high fat diet-induced obese mice.

The aim of this study was to investigate miR21 expression in obese omental and subcutaneous adipose depots and in type 2 diabetes (T2DM).

**Methods:** Subcutaneous and omental adipose tissue (OAT) biopsies were obtained from 12 obese subjects (age 41.7±2.6 y; BMI 46.9±2.4 Kg/m²; waist 149.7±6 cm) undergoing bariatric surgery. The patients, characterized by anthropometric, biochemical and oral glucose tolerance test evaluation were divided in two age-, waist- and BMI-matched groups (n=6) according to the presence of T2DM. Expression levels of miR21, Tumor Necrosis Factor-α (TNF-α), Monocyte Chemoattractant Protein-1 (MCP-1) and TGFB-β were quantified using Real Time Polymerase Chain Reaction.

Results: The expression of miR21 was not different in OAT compared to SAT in all patients and did not correlate with any gene analyzed. Interestingly, in diabetic subjects, miR21 expression was 2 folds greater than in those not affected by T2DM.

**Conclusion:** These findings show that human adipose tissue expression of miR21 seems to not contribute to intrinsic differences between human OAT and SAT. Notably, the up-regulation of miR21 in SAT of diabetic patients suggests that its expression levels play a role in the pathophysiology of obesity-related metabolic dysfunction, putatively impairing the obese SAT fat buffering capacity.

**Impact of malnutrition on survival rates and hospital readmission in internal medicine patients**

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**Rationale:** Malnutrition is commonly observed in hospitalized patients ranging from 20% to 50%. Although it is frequently associated with chronic and severe diseases with a relevant impact on quality of life, morbidity and mortality, the inclusion of malnutrition in the clinical charts remains limited. Further, it is still matter of debate which functional, biochemical or screening tool is superior in identifying clinical risk.

In our study, we aimed at evaluating the role of malnutrition in survival rates, hospital readmission and working days lost, after a period of 90-days follow up.

**Methods:** Patients consecutively admitted to the Internal Medicine ward at our institution, and who gave their consent, were screened for malnutrition using NRS-2002 (the Nutritional Risk Screening 2002), MNA (the Mini-Nutritional Assessment), and MUST (the Malnutrition Universal Screening Tool). Causes of hospitalization, clinical course, length of hospital stay and clinical outcomes were recorded. After a period of 90-days from nutritional screening, patients who had accepted to be enrolled in the study were contacted by re-call. Data have been statistically analyzed by non-parametric test (Wilcoxon–Mann–Whitney test). Results are reported as Mean±SD.

**Results:** 151 patients (79M:72F; 71±15 yrs) were studied. The prevalence of malnourished patients was 51.1% (73/151) by NRS-2002, 16.3% (22/151) by MNA and 29.9 (41/151) by MUST. Malnourished patients screened with NRS-2002 and MNA were older than non-malnourished patients (p<0.001 and p=0.006, respectively). Length of stay was significantly correlated with MNA (r=0.19; p<0.05), but not with MUST and NRS-2002. Well-nourished patients screened by MNA present a median hospital stay 6 days shorter than malnourished patients (12 vs 18 days, respectively). 77 of 151 patients were eligible for the follow up, but 2 patients deny their consent.

After 90 days, 13 patients (17%) were dead, with an hospital death rate of 46% (n=6, mean hospital stay 23±19 days). 20 patients (26%) were readmitted to the hospital and 2 patients presented more than one readmission. Malnourished patients with lower survival rate were significantly detected by MNA (p<0.01) and MUST (p<0.01). Only MNA was able to identify in-hospital mortality in malnourished patients (p<0.05).

Whereas, no screening tool was able to predict hospital readmissions at 90-days follow up.

Moreover, 8 of 75 patients (11%) were active workers, 2 of which were malnourished, losing 43.34±39.28 days because of their disease, after the follow up period. No statistical differences were observed between active workers and no workers.

**Conclusion:** Malnutrition is highly prevalent in internal medicine patients. Not one single screening or assessment tool is capable of adequate nutrition screening as well as predicting poor nutrition related outcome. However, assessing malnutrition appear extremely important in order to identify patients with longer hospital stay and lower survival rates. Inpatient malnutrition screening along with appropriate nutritional intervention appear extremely important in order to improve clinical outcome and to save healthcare costs.

**Comparison of the performance of different screening tools in identifying malnutrition and functional impairment in hospitalized patients**


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**Rationale:** The prevalence of malnutrition in hospitals is high ranging from 20% to 50% upon admission. The most common nutritional tools recommended for screening hospitalized patients for nutritional risk are: the Mini-Nutritional Assessment (MNA), the Nutritional Risk Screening 2002 (NRS-2002) and the Malnutrition Universal Screening Tool (MUST). Our aim was to assess which tool better identifies malnutrition and functional impairment in hospitalized patients.

**Methods:** Patients consecutively admitted to the Internal Medicine ward at our institution, and who gave their consent, were screened for malnutrition using NRS-2002, MNA, and MUST. Handgrip strength (HG; kg), CRP levels (mg/dL), phase angle (PhA) and body composition (by BIA 101 of AK-ERN SRL), were assessed upon admission. Data have been statistically analyzed by non-parametric test (Wilcoxon–Mann–Whitney test). Results are reported as Mean±SD.

**Results:** 151 patients (79M:72F; 71±15 yrs) were studied. The prevalence of patients at nutritional risk was 44.1% (63/151) by NRS-2002, 37.0% (50/151) by MNA and 27.0% (37/151) by MUST. However, the prevalence of malnourished patients was 51.1% (73/151) by NRS-2002, 16.3% (22/151) by MNA and 29.9 (41/151) by MUST. Malnourished patients screened with NRS-2002 and MNA were older than non-malnourished patients (p<0.001 and p=0.006, respectively). Moreover, compared with non-malnourished patients, malnourished patients screened by NRS-2002 showed: lower BMI (p=0.004), lower fat mass index (FFMI) (p=0.003) and increased C-reactive protein (CRP) (p=0.039). In addition, malnourished patients screened with MNA and MUST reported a significant reduction in HG (p=0.01 and p=0.004, respectively).

**Conclusion:** Malnutrition is strongly associated with metabolic and body composition alterations. The screening and the assessment of malnutrition appear extremely important in order to identify patients able to benefit from a nutritional intervention. The more suitable nutritional screening tool should be chosen considering its ease to perform, the patient population and the care
setting. Our study confirms that NRS-2002 is superior in detecting body composition alterations and patients at nutritional risk, whereas MNA and MUST showed a better association with functional impairment.

Nutritional status, functional assessment, inflammatory status and phase angle as predictors of clinical outcome


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Rationale: Although hospital malnutrition is frequently observed, its inclusion in the clinical charts is limited. Also, which functional, biochemical or screening tool is superior in identifying clinical risk is still matter of debate. We assessed the consistency between the presence of nutrition risk and its inclusion in the charts. Further, we compared the predictive value of accepted screening tools, phase angle, handgrip strength, and CRP levels, in identifying patients with longer hospital stay.

Methods: Patients consecutively admitted to the Internal Medicine ward at our institution were considered for the study. After giving their consent, patients were screened for nutrition risk by using NRS-2002, MUST and MNA. Handgrip strength (HG; kg), phase angle (PhA), and CRP levels (mg/dL) were measured upon admission. Length of stay and the inclusion of malnutrition in the diagnosis reported in the chart were recorded. Data have been statistically analyzed by Students’ t-test and Spearman correlation.

Results: 151 patients (79M:72F; 71±15 yrs) were studied. 73 patients (44M:29F; 75.1±14.4 yrs) were at nutrition risk based on NRS-2002 (>3), but malnutrition was reported in the charts in only 3 cases, whereas nutritional consultation was requested for only 20 patients. Well-nourished patients (32M:38F) were significantly younger (66.5±15.3 yrs; p<0.01), and the malnourished patients screened by MNA (N=22, 13M:9F) presented a median hospital stay shorter than 6 days compared with non-malnourished patients (18 vs 12 days, respectively). Length of stay was significantly correlated with MNA (r=-199; p<0.05), PhA (r=0.272; p=0.05), CRP levels (r=0.287; p<0.01), but not with HG, MUST and NRS-2002.

Conclusion: Malnutrition remains under-reported in clinical charts, thus contributing to lack of awareness. Besides, MNA, PhA and CRP appear superior to other screening tools and functional assessment in predicting clinical outcome. Inpatient malnutrition screening along with appropriate nutritional intervention appear extremely important in order to improve clinical outcome and to save healthcare costs.

Pre-cachexia, cachexia and body composition in cancer patients

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Introduction: Cachexia is a devastating condition resulting from the complex interplay between the presence of a tumor, the inflammatory response and the metabolic alterations in the host. Altered body composition, in particular reduced fat-free mass (FFM), is a hallmark of cachexia. Loss of FFM is an independent predictor of morbidity, increased chemotherapy toxicity and mortality in cancer patients. With the recent availability of criteria for classification and staging of cancer cachexia (i.e. pre-cachexia, cachexia), the attention has focused on early detection and prompt interventions aimed at prevention and early treatment of cancer cachexia. However, it is not clear whether the new clinical criteria reliably reflect changes in body composition occurring in cancer cachexia. Recently, it has been proposed that computed tomography scan could be a reliable tool for the assessment of FFM in cancer patients. However, this technique is complicated, requires a dedicated interpretation software and is not yet validated in large clinical trials. Phase angle (PA), as determined by Bio-impedance Analysis (BIA), has been shown to be influenced by changes in nutritional status and body composition and to be a reliable prognostic indicator in several chronic diseases. PA reflects the relative contribution of fluid, tissue interface and cellular membranes of the human body. Data on the clinical value of PA in cancer patients are lacking. The aim of this study was to assess whether the classification of cancer patients according to the new criteria is reflected by changes of PA and other BIA measurements and to verify if PA may represent a reliable tool to assess for body composition assessment in cancer patients.

Methods: After written informed consent was obtained, forty-two consecutive surgical cancer patients (24M:18F; age 68.6±11.13 yrs; 21 colon, 6 gastric, 5 pancreatic, 3 kidney, 2 gallbladder, 2 ovary, 1 duodenal GIST, prostate and bladder cancer) were enrolled between March 2011 and February 2013. Immediately before surgery, all patients were evaluated for the presence of anorexia and the presence of pre-cachexia or cachexia, according to the current classification. Anthropometric measurements (body weight, BMI), body composition analysis (BIA) and measurement of serum C-reactive protein (CRP) serum levels were performed in all patients. Individual phase angle values were also standardized according to the reference value as follows: standardized phase angle (SPhA)=(observed phase angle – mean phase angle)/SD of the phase angle, where the mean and SD are from sex-, age-, and BMI-stratified reference values.

In 20 patients, handgrip muscle strength (HGS) was also assessed by means of a hand-grip dynamometer. ANOVA, two-way Dunnnet post-hoc analysis, Kruskal-Wallis test and Spearman test were used, as appropriated, for statistical analysis.

Results: Anorexia was present in 23 patients (54.8%). Pre-cachexia was present in 6 patients (14.3%), cachexia in 15 patients (35.7%), while 21 (50.0%) patients did not match either criteria. Body mass index (BMI) was decreased in cachetic patients with respect to no pre-cachetic/cachetic (p<0.001). Fat-free mass (FFM) and fat-free mass index (FFMI) were decreased in cachetic vs pre-cachetic and no pre-cachetic/cachetic patients (p=0.005 and p<0.001, respectively). Total body water (TBW) and intracellular water (ICW) were significantly reduced in cachetic patients vs pre-cachetic and no pre-cachetic/cachetic patients (p=0.014 for both parameters). Although there were not statistically differences among cachexia staging groups, PA was significantly reduced in anorectic patients vs non anorectic patients (5.1±1.20 vs 6.0±1.41, p<0.01). HGS was negatively correlated with age (r=-0.739; p<0.001) and CRP (r=-0.686, p<0.01), while it was positively correlated with FFM (r=0.516, p<0.05) and SPhA (r=0.468, p<0.05). PA was inversely correlated with age (r=-0.436; p<0.01).

Conclusions: This study suggests that pre-cachexia and cachexia are highly prevalent in pre-surgical cancer patients. Pre-cachexia and cachexia are associated with decreased FFM and FFMI. Changes in PA and its standardized value (SPhA) did not correlate with stages of cachexia, whereas a significant association was found with functional assessment. Further studies are needed to evaluate the relationship between cancer cachexia staging and body composition with surgical outcome in cancer patients.

A “magnetic” case of diabetes

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D.V. male, 28 yrs, was admitted to our department with a income diagnosis of uncontrolled Diabetes Mellitus type 1. The clinical history of the patient was silent until December 2012 when after a weight loss of about 15 Kg in the last 3 months, he went to hospital for asthenia and dehydration. The laboratory exams showed hyperglycemia (350 mg/dl) glycosuria, elevation of ALT (x3) and AST (x2.5), hematic PH 7.21. A diagnosis of DM type 1 complicated with metabolic acidosis was made. The patient was discharged with insulin therapy.

At admission in our Clinic, the patient told us he felt asthenic and that he had great difficulties to obtain a good glycemic control.

At a first evaluation his face looked infantile without barb and he has a mild hyponutrition aspect. The skin appeared dehydrated, with a rare distribution of hair.

The abnormal findings in the clinical examination were hepatomegaly and low development of the testes. An Ultrasonography of abdomen revealed hepaticomegaly with staeotic aspect, a light splenomegaly, reduction in caliber of hepatic veins and concluded for chronic epatopathy. The association of supposed hypogonadism, the presence of diabetes and a chronic hepatopathy prompted us to hypothesize a hemochromatosis.

The laboratory exams showed ferritinitemia over 4000 ng/dl, a transferrin saturation over 70%, elevated AST (x3) and ALT (x2), HBA1c 10%.

A liver biopsy was made and it revealed a serious iron accumulation in the liver and a severe fibrosis compatible with hemochromatosis.

Ormalon exams showed the reduction of all the pituitary hormones. The virological markers were negative.

A diagnosis of hemochromatosis was made. The study of HFE gene did not reveal mutations, other genetic studies to find other mutations of the genes involved in the iron metabolism are still now in progress because in the absence of other risk factors for a pathologic iron accumulation a diagnosis of congenital hemochromatosis has to be searched and confirmed.

This medical case demonstrated that a systemic approach to the patient problems is mandatory for a correct diagnosis elaboration.

The diabetes in this patient was only one and probably not the worst component of a more complex syndrome not recognized at the first evaluation because the severe hyperglycemia was more impressive than the hypertransaminasemia or facies and the clinical aspect of the patient.

Iron has magnetic properties when a magnetic field is applied. Our observation capability is the magnetic field that the iron of our patient needed to be track down.

**Effects of febuxostat vs allopurinol on the urinary uric acid excretion in patients with idiopathic calcium nephrolithiasis: a pilot study**


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**Background:** Nephrolithiasis is a disease with a high prevalence in industrialized countries. The most frequent form is calcium nephrolithiasis (80%), leading to the formation of either calcium oxalate (CaOx) or calcium phosphate (CaP) stones. Uric acid nephrolithiasis has a prevalence of about 8% of all stones, although mixed calcium-uric acid stones are frequent. High urinary uric acid excretion is a relevant lithogenic risk factor both for patients with uric acid stones and for patients with calcium stones. The first-choice treatment of this disorder is allopurinol, a purine analogue with competitive inhibition effect on xanthine oxidase. Febuxostat is a new non-purine xanthine oxidase inhibitor, already shown as effective in hyperuricemia treatment of patients with gout. Comparison studies with allopurinol in nephrolithiasis treatment are lacking.

**Aims:** To compare the effect of a therapy with allopurinol and febuxostat on uricemia, urinary uric acid excretion and other urinary factors of lithogenic risk in patients with idiopathic calcium nephrolithiasis with hyperuricosuria.

**Materials and methods:** At the Kidney Stone Clinic of Clinical and Experimental Medicine Department of Parma University Hospital we enrolled 20 patients (18 M, 2 F) with idiopathic calcium nephrolithiasis and elevated urinary uric acid excretion (>750 mg/day). They were randomly assigned to receive allopurinol 100 mg/day (11 patients, 10 M, 1 F) or febuxostat 80 mg/day (9 patients, 8 M, 1 F) for 5 weeks. Before and after the treatment a 24-hour urine sample was collected in order to determine the urinary profile of lithogenic risk and a blood sample was obtained to determine serum uric acid.

**Results:** At the basal profile the febuxostat group had a higher mean urinary volume (229±855 vs 1546±381 ml/24 hr, p<0.001) and a lower relative supersaturation for calcium oxalate (5.2±3.35 vs 10.10±4.56, p=0.02). There were no differences for urinary uric acid excretion (864±268 vs 970±157 mg/24 hr, p=ns) and uricemia (5.6±1.64 vs 6.34±1.23, p=ns). At the end of the 5-week treatment period a significant decrease in urinary uric acid excretion was observed in both groups (febuxostat group 581±328 mg/24 hr [-42%], allopurinol group 558±161 mg/24 hr [-42%], p=ns between two groups) without variations in serum uric acid (febuxostat group 6.3±0.74 mg/dl, allopurinol group 5.63±0.74 mg/dl). The urinary profiles of lithogenic risk did not show significant differences between the two groups, except for a higher potassium (78±27 vs 56±14 mEq/24 hr, p=0.04) and oxalate excretion (39±9 vs 31±6 mg/24 hr, p=0.029) in the febuxostat group. No patient reported adverse effects from each treatment.

**Conclusions:** Allopurinol and febuxostat seem to demonstrate a similar effect in patients with idiopathic calcium nephrolithiasis and elevated urinary uric acid excretion. More in-depth studies are needed to assess renal physiopathology of febuxostat and its long-term effects on kidney stone relapses.

**Ultra-long pharmacokinetic properties of insulin degludec in younger adults are preserved in geriatric subjects with type 1 diabetes**


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**Introduction:** Insulin degludec (IDeg) is a new generation basal insulin in the late stages of development. Previous pharmacokinetic (PK) and pharmacodynamic (PD) studies have shown IDeg to have an ultra-long (>42 hours), flat and stable action profile with low hour-to-hour and day-to-day variability.1–3.

Non-clinical studies show this to result from a unique mechanism of prolonged absorption.3 This ultra-long and stable action profile may increase dosing flexibility, thus allowing patients to adapt injection timing to suit their daily activities.

**Aim:** To assess steady-state PK and PD properties of IDeg in geriatric (≥65 years) versus younger adult (18–35 years) subjects with type 1 diabetes (T1D).

**Methods:** Study design and participants

This was a single-centre, randomised, double-blind, two-period crossover, multiple-dose study in geriatric and younger adult subjects with T1D. Subjects were randomly allocated to two treatment periods of 6 days each of once-daily subcutaneous dosing with IDeg and IGlar (0.4 U/kg). The steady-state PD response was evaluated during a 24-hour manual euglycaemic glucose clamp (clamp blood glucose level: 5.5 mmol/L [100 mg/dL] starting af-
ter the last dose at the end of each treatment period on Day 6). Blood samples for assessment of steady-state pharmacokinetics were drawn before the last investigational product administration and frequently thereafter for 24 hours (IGlar and IDeg).

Statistical analysis
The log-transformed PK and PD endpoints (AUCDeg,r,SS, Cmax,IDeg,SS, AUGCIR,t,SS) for the IDeg treatment were analysed using an analysis of variance (ANOVA) method with age group (young/geriatric) and treatment period (period 1/period 2) as fixed factors.

Results: Fourteen geriatric and 13 younger adult subjects participated in the study. Baseline characteristics are shown in Table 1. The mean IDeg concentration–time profile at steady state was similar in geriatric and younger adult subjects (Figure 2).

Total exposure to IDeg was similar for geriatric and younger adult subjects (Table 2). There was no statistically significant difference in total exposure (AUCIDeg,r,SS) or maximum concentration (Cmax,IDeg,SS) of IDeg between groups (Table 3).

Mean estimates (mg/kg) of AUGCIR,t,SS were comparable between groups (Table 4). The ratio (95% CI) of AUGCIR,t,SS for geriatric/younger adult subjects was 0.78 (0.47:1.13).

Conclusions: The ultra-long PK properties of IDeg observed in younger adults were preserved in geriatric subjects with T1D. Total exposure to IDeg was similar between geriatric and younger adult subjects. There were no differences in the glucose-lowering effect of IDeg between geriatric and younger adult subjects.

Oxidative stress induces liver cell apoptosis in patients with nonalcoholic fatty liver disease


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Background and aim: Nonalcoholic fatty liver disease (NAFLD) represents the most common form of chronic liver disease worldwide. Recent data suggest that hepatocyte apoptosis may play a major role in disease progression in NAFLD. It has been reported that cytokeratin-18-M30 (CK-18) fragment levels correlate with the magnitude of hepatocyte apoptosis and independently predict the presence of nonalcoholic steatohepatitis (NASH).

Currently, NAFLD is regarded as the liver manifestation of the metabolic syndrome (MetS) and is associated with systemic inflammation and oxidative stress. Oxidative stress is considered a major player triggering the progression of steatosis to NASH. The aim of this study was to determine the role of oxidative stress in the prediction of liver damage expressed by CK-18 levels in a population of NAFLD patients.

Methods: The study has been performed in 209 consecutive patients referred for suspected metabolic disease and with a liver ultrasonographic scan (US) positive for NAFLD. Severity of liver steatosis was defined according to Hamaguchi ultrasonographic criteria. All subjects underwent routine clinical and biochemical evaluation. Serum levels of CK-18, urinary 8-iso-prostaglandin F2α (8-iso-PGF2α), soluble NOX2-derived peptide (sNOX2-dp) and adiponectin were measured.

Results: Median serum CK-18 values progressively increased with NAFLD severity [from 169.5 (129.3/183.8) to 176 (140/190) and 180 (169.5/192.5) in mild, moderate and severe steatosis, respectively; p < 0.01]. Stratifying population by CK-18 tertiles, a significant progression of BMI, HOMA-IR, triglycerides, prevalence of diabetes and severe NAFLD, urinary 8-iso-PGF2α [616.7±122.9 vs 727.5±82.1 vs 800.9±82.1; P=0.001], sNOX2-dp [49 (40/58.3) vs 60 (50/66) vs 67 (64/71); P<0.001] was found. Instead, HDL-cholesterol and adiponectin [12 (10/4/14.1), vs 7.5 (5.5/10.5) vs 5 (4/7); P<0.001] progressively decreased. Linear bivariate regression confirmed a positive correlation between CK-18 and BMI (r=0.58; P<0.001), HOMA-IR, Hamaguchi’s score. Urinary 8-iso-PGF2α (r=0.61; P<0.001), sNOX2-dp (r=0.45; P<0.001) and a negative correlation between CK-18 and HDL-cholesterol and adiponectin (r=−.45; P<0.01).

Conclusion: We demonstrated a worse metabolic profile and higher levels of oxidative stress in NAFLD patients with a more severe liver damage, as expressed by higher levels of serum CK-18. Levels of CK-18 were predicted by serum adiponectin and sNOX2-dp levels. Our results suggest that increased oxidative stress may play a role in the promotion of apoptosis in patients with NAFLD.

Relation between type 2 diabetes and depression in elderly out-patients

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Introduction: Depression and diabetes are two major public health problems associated with significant burden and their prevalence is growing significantly in elderly people. Studies show that depression may affect and be affected by diabetes and that older subjects with diabetes are almost twice as likely to suffer from depression. Moreover, the combination of diabetes and depression in elderly individuals has been shown to increase the risk of complications of diabetes and the likelihood of death.

Aim: To assess the prevalence of depressive symptoms among elderly patients with type 2 diabetes and find out its relation with HbA1c values and the Multidimensional Prognostic Index (MPI) score.

Methods: 118 elderly out patients (59.3% male, aged 74.2±6.0 years) with type 2 diabetes attending our Clinical Unit in the last year were included in the study. All subjects received a comprehensive clinical history and physical examination. HbA1c level and diabetes mellitus (DM) related complications were assessed. Depressive disorder was assessed using the Geriatric Depression Scale (GDS) and defined as a GDS score > 10. MPI was evaluated and based on MPI score all subjects were classified in two classes: subjects with a low risk (MPI score ≤ 0.33), and subjects with moderate/severe risk (<1 MPI score >0.33). The statistical analysis was performed using the IBM SPSS Statistics 19 software.

Results: The prevalence of depression among our elderly community with type 2 diabetes was 47%, and women were more likely to have depression than men. The presence of depression was found to be significant associated to MPI score (p<0.001), i.e. patients with diabetes and depression had a worse MPI score compared to patients without depression. No correlation was observed between depression and HbA1c.

Conclusion: Depression is high prevalent in elderly people with type 2 diabetes and can strongly impact the quality of life of these subjects with negative effects on medical outcomes and diabetes self-care. Whatever the underlying cause of the relationship between diabetes and depression, our study underline the importance of a clinical approach to the patients with DM that includes a screening for detection and treatment of depression. Moreover, we support the concept that it is important in elderly subjects with chronic conditions, such as diabetes and depression, taking in account the multidimensional aggregate information for predicting short- and long-term all-cause mortality and for identification of a better management of treatment.
Impact of laparoscopic sleeve gastrectomy on metabolism, adipokines and liver structure

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Rationale: Bariatric surgery represents an effective option for the management of metabolic syndrome in morbid obese patients, by contributing to reduce the risk of cardiovascular diseases and related mortality.

Methods: To assess the effects of Laparoscopic Sleeve Gastrectomy (LSG) on some biochemical parameters, serum adipokines, proinflammatory cytokines, and liver structure by ultrasonography have been evaluated.

Results: The two patients’ groups were statistically different as far as weight (98±26.6 kg in LSG vs 127.9±23.8 kg; p=0.001) and BMI (p=0.001), serum triglycerides (86.3±29.6 in LSG vs 148.7±79.3 mg/dL; p=0.005), HDL Chol (62.2±11.7 vs 46.2±13.4 mg/dL; p=0.001), AST (17.7±4.0 vs 23.6±10.1 U/L; p=0.030), ALT (15.9±5.6 vs 34.1±18.1 U/L; p=0.001), GGT (20.5±2.5 vs 33.7±19.7 U/L; p=0.049), Hb (13.1±1.5 vs 14.2±0.9 g/dL; p=0.015), Hct (40.2±4.3 vs 43.4±3.0 %; p=0.010), CK (87.7±26.2 vs 157.2 vs 84.7 U/L; p=0.003), butyrylcholinesterase (7446±1674 vs 13846±2787 U/L; p=0.015), leptin levels (15.9±11.7 vs 23.5±7.7 p=0.05) and BMR (1911±399 vs 1322±281 kcal/day; p=0.015), were significantly lower in LSG, as well as fecal Short Chain Fatty Acids were not significantly different in the two groups.

Prevalence of liver steatosis was 46% in OB (10% mild, 30% moderate, 6% severe) and 45% in LSG (35% mild, 10% moderate).

Total body fat free mass (60,2±14,7 in LSG vs 74,7±13,3 kg in OB; p=0.014) and fat mass (40.6±19.9 vs 58.3±17.2 %; p=0.022) were different in the two groups.

Reported calorie intake was not significantly different in the two groups, whilst protein (69±24 vs 106±36 g; p=0.01), disaccharide (170±80 vs 292±109 g; p=0.007) and total fiber (14±8 vs 25±12 gr; p=0.024) intakes were reduced in LSG.

Conclusions: After 1 year follow-up LSG has produced positive effects on metabolic parameters and fatty liver disease so improving prognosis in severely obese patients.

Impaired beta cell function and preserved incretin effect in subjects with prediabetes


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Objective: New recommendations for the use of glycated haemoglobin A1c (HbA1c) for diagnosis of diabetes resulted in the establishment of a new cluster of subjects with pre-diabetes that comprehends subjects with HbA1c levels above the laboratory normal range but below the diagnostic cut point for diabetes (5.7 to 6.4%). We aimed to investigate whether the reduced incretin effect (the phenomenon that oral glucose elicits a higher insulin response than intravenous glucose at identical plasma glucose (PG) profiles) observed in patients with type 2 diabetes, is already present in subjects with pre-diabetes, according to HbA1c. Furthermore, we aimed to investigate b cell function (disposition index (DI)), in these subjects.

Research Design and Methods: Ten subjects with pre-diabetes according HbA1c (5.7 to 6.4%), eight newly diagnosed patients with type 2 diabetes (HbA1c ≥ 6.5%), and ten controls (HbA1c <5.7%), were studied. Each participant underwent to a four hours 75-g oral glucose tolerance test (OGTT) and an isoglycemic intravenous glucose infusion (IIGI). Incretin effect was calculated by relating the difference in integrated beta cell secretory responses (insulin and C-peptide responses) between stimulation with oral and isoglycemic i.v. glucose to the response after oral glucose, which was taken as 100%, using the following formula: 100% x (AUCOGTT – AUCIIGI)/AUCIIGI). DI has been calculated as the product of measures of insulin sensitivity and first phase insulin secretion.

Results: The incretin effect (C-Peptide response) was significantly (p<0.05) higher in patients with pre-diabetes (43,4%±5) and in controls (51,5%±4,2), in comparison to patients with diabetes (19,5%±6,7). GLP-1 and GIP plasma levels did not differ across the groups. DI was significantly lower (p<0.05) in pre-diabetes (0,3±0,0) and diabetes (0,1±0,1), than controls (1,0±0,3).

Conclusions: Pre-diabetes subjects are characterized by preserved incretin effect compared to diabetes subjects, and an impaired b cell function compared to control subjects. Additional work is necessary to determine how these abnormalities may be related to the progression to diabetes.

Liraglutide + metformin in type 2 diabetes: clinical benefits associated with switch or use early in the disease process

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Metformin (Met) is generally considered the most appropriate first-line pharmacotherapy for type 2 diabetes (T2DM). When Met becomes insufficient, however, there is no general consensus on how to intensify treatment. This post-hoc analysis compared clinical benefits achieved by adding liraglutide in patients previously receiving Met only (Met-add-on) vs substituting liraglutide for sulfonylurea (SU) in subjects previously receiving Met + SU (SU-switch). Data were obtained from a large clinical trial (n=988) in which patients receiving met alone or Met + SU had their therapy changed to Met + liraglutide 1.8 mg. Baseline age (mean [SD]): 58 [9.3] vs 56 [9.8], respectively and A1c (Table) were similar, while duration of diabetes was significantly longer in the SU-switch subjects (9.0 [6.2] vs 6.5 [5.4]; p<0.0001). Among subjects who completed 12 weeks of treatment, the SU-switch group lost more weight, likely due to the termination of SU treatment, and subjects in the Met-add-on group had a greater reduction in A1C. These data are consistent with greater clinical efficacy of liraglutide among patients with less advanced T2DM, with ~70% of the Met-add-on group reaching a target A1C of 7%. The further reduction in mean A1C among the SU switch-subjects, with ~45% reaching the glycemic goal, suggests benefits of liraglutide vs SU. These findings support the conclusions that the glycemic response to liraglutide varies across the spectrum of diabetes progression, and that changing from SU to liraglutide can bring additional benefits to some patients.
**Differences in serum uric acid between metabolically healthy obese (MHO) subjects, obese insulin resistant (IRO) and normal weight subjects**

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**Introduction:** It is known that high values of uric acid are associated with obesity, metabolic syndrome, insulin resistance and cardiovascular disease. There is a growing body of evidence indicating that a subset of obese subjects appears to be protected against obesity-related cardio-metabolic abnormalities. Metabolically healthy but obese (MHO) subjects are relatively insulin sensitive and have a favorable cardio-metabolic risk profile, but is not known whether they have high values of uric acid.

**Aim:** Aim of this study was to evaluate the uric acid levels in a group of MHO subjects and compare them with those of a group of insulin resistant obese (IRO) and of a group of normal-weight subjects.

**Patients and Methods:** The study group consisted of 815 Caucasian subjects, aged between 20-70 years. Subjects were excluded if they had a history of chronic gastrointestinal diseases associated with malabsorption, chronic pancreatitis, history of any malignant disease, history of alcohol or drug abuse, liver or kidney failure, and treatments able to modify glucose metabolism including lipid-lowering and antihypertensive therapy. All the subjects underwent a complete anthropometrical evaluation and a venous blood sample was drawn for laboratory determinations. A 75 g oral glucose tolerance test (OGTT) was performed with 0, 30, 60, 90 and 120 min sampling for plasma glucose and insulin. The ISI index, derived from OGTT, was used to estimate insulin sensitivity. According to BMI the subjects was divided in obese (BMI ≥30 Kg/m²) (n=584), and normal weight (BMI ≤25 Kg/m²) (n=231). The obese subjects were stratified into quartiles according to their insulin sensitivity: subjects in the upper quartile were categorized as metabolically healthy but obese (MHO) (n=145), while subjects in the two lower quartiles were defined as insulin-resistant obese (IRO) (n=291).

**Results:** There were no differences in age and sex in the study groups. MHO subjects exhibited significant lower waist, triglycerides, fasting glucose and insulin, glucose and insulin 2 h during OGTT and higher HDL cholesterol as compared with IRO subjects. MHO subjects exhibited also significantly lower serum uric acid levels and lower levels of hs-C-reactive protein (hs-PCR) as compared with IRO subjects. There were no differences in the levels of both fasting glucose and 2 h during OGTT, insulin and triglycerides between MHO and normal weight subjects. MHO subjects showed significant higher waist, BMI, uric acid levels and hs-PCR and lower HDL cholesterol as compared with normal weight subjects. In a logistic regression model IRO showed an increased risk of having serum uric acid levels in the highest quartile (OR 1.43, 95.0% C.I. 1.13-1.83; P=0.003) as compared with normal weight subjects. No differences in uric acid levels were observed between MHO and normal weight subjects.

**Conclusions:** These results indicate that MHO subjects showed lower serum uric acid levels as compared with insulin resistant obese subjects. IRO showed an increased risk of having higher serum uric acid levels as compared normal weight subjects. Metabolically healthy but obese, also, exhibited a metabolic and cardiovascular risk profile intermediate between insulin resistant obese and normal weight subjects.

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**Possible role of bioenterics intragastric ballon (BIB) on glucose tolerance, insulin sensitivity and entero-hormonal axis**

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**Introduction:** BioEnterics Intragastric Balloon (BIB) is the less invasive, temporary and safe surgical procedure to obtain a significant weight loss. BIB is used in severely obese patients to induce weight loss before subjecting them to the intervention of bariatric surgery or other surgical procedures. Several evidences have demonstrated in obese patients an improvement in insulin sensitivity and incretin axis following treatment with the different bariatric surgery procedures. Conversely, there are few data on the effect of BIB on insulin sensitivity and modifications of entero-hormonal axis in obese subjects.

**Patients and Methods:** For this purpose, we have studied 6 obese subjects (4 men and 2 women), aged between 20-60 years, with BMI > 45 Kg/m² underwent to BIB. Subjects were excluded if they had secondary causes of obesity, previous bariatric surgery, presence of esophagitis, hiatal hernia, peptic ulcer. In basal condition and 3 and 6 months from BIB placement, all the patients underwent a complete anthropometrical evaluation and a venous blood sample was drawn for laboratory determinations. Similarly, 75 g oral glucose tolerance test (OGTT) to 5 hours was performed with sampling for plasma glucose, insulin, C-peptide. After OGTT, 2 patients showed a type 2 diabetes (DM2), 2 an impaired glucose tolerance (IGT), the remaining patients had normal glucose tolerance (NGT). In addition, in two patients we have investigated also GLP-1 and glucagon levels during OGTT. The ISI index, derived from OGTT, was used to estimate insulin sensitivity.

**Results:** After 6 months from BIB placement was observed in all the patients a 12% mean reduction in the body weight and a reduction in both BMI and waist circumference when compared with baseline. These reductions were already present after only 3 months. The insertion of the BIB was able to induce an improvement of glucose tolerance. In fact, at 3 and 6 months from BIB placement, all the patients
showed normal glucose tolerance with a significant reduction in fasting glucose and glucose 2 h during OGTT. In addition, the patients exhibited also a reduction of fasting insulin, insulin 2 h during OGTT and insulin mean levels during OGTT with an improvement of insulin sensitivity, assessed by ISI index. Moreover, patients that had hypoglycemia during initial OGTT, showed at 3 and 6 months from BIB placement disappearance of hypoglycemic episodes. The patients in which we studied the levels of glucagon and GLP-1 during OGTT, showed after 6 months of BIB placement a reduction of both basal and during OGTT GLP-1 levels and an increase in the mean levels of glucagon during OGTT.

**Conclusions:** These preliminary data indicate that in obese subjects BIB placement was able to induce: 1) a reduction in body weight, BMI and waist circumference; 2) an improvement of tolerance glucose; 3) an improvement of insulin sensitivity; 4) modifications of entero-hormonal axis, characterized by a reduction of GLP-1 levels and increase of glucagon levels during OGTT.

**Hypovitaminosis D and clinical nutrition in post-menopause woman: a pilot study**


“Science of Aging” Interdepartmental Research Center - Sapienza University of Rome

**Introduction:** Post-menopausal women represent one of the groups most at risk of hypovitaminosis D. Despite the oral vitamin supplementation is often unable to achieve optimal values of 25(OH)D3. The present study was aimed to explore whether personalized diet and contemporary oral supplementation of vitamin D is more efficacious of only oral supplementation for to achieve normal vit.D plasma values.

**Materials and methods:** Were selected women in post-menopause, with BMI ≥ 25 and deficiency of vitamin D. The patients were divided into 2 groups: group A was treated with personalized diet and contemporary oral supplementation of vitamin D; the control group (B) was treated only with oral supplementation of vitamin D according to the same dose of the first group.

**Results:** Twenty-seven postmenopausal women, between the ages of 53 and 78 years, completed all elements of the study assessment. Table 1 shows the average scores that resulted from the plasma value of vitamin D into the group A (10 patients) and into the group B (17 patients), at the start of the study (T0) and after two months (T1). The average values of vitamin D before and after treatment were significantly higher in the first group of patients (p<0.001). Into the first group we observed also a significant reduction in total cholesterol (p<0.001) and triglycerides (p=0.026).

**Conclusions:** These data have shown that a proper rotation of foods improves the intestinal absorption of micronutrients such as vitamin D.

**Seriate determination of urinary porphyrins and porphyrins precursors and assessment of PBGD mutations and PBGD activity to predict disease severity in patients affected by acute intermittent porphyria**


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**Background:** only few data are available regarding biological parameters able to predict severity of disease in patients affected by acute intermittent porphyria (AIP). If identified, these predictors may be useful in defining patients appropriate for more intensive or continuative therapeutic approach.

**Aim:** to assess and compare the possible role of genetics (mutation of Porhobilinogen deaminase (PBGD) gene), enzymatic [erythrocyte PBGD deaminase activity (ePBGDa)] and biochemical [urinary levels of ALA and PBG and porphyrins (as total or fractionated)] in predicting severity of disease (measured in terms of severity/number of crisis in the lifetime) in patients carriers of PBGD mutation documented for AIP.

**Materials and methods:** 23 italian patients with documented mutation of PBGD gene (from 20 unrelated families; 15 female, age range 35-62

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that 82.3% of our study population had 25(OH)D <30 ng/ml; of these, all who had osteoporosis. By assessing plasma levels of 25(OH)D, we found subjects who were already on vit. D supplementation therapy and those

May 2011 we enrolled 243 patients (aged 26-93; 67 males). We excluded vascular risk (CVR). We are going to exhibit some interesting results derived from this study. In recent times further vitamin D (vit.D) pleiotropic effects have been observed, together with genetic scoring may represent simple and reliable predictors of severely symptomatic disease in AIP patients.

The relationship between vitamin D and arterial hypertension: preliminary results of a study on effects of oral supplementation therapy


“Science of Aging” Interdepartmental Research Center - Sapienza University of Rome

In recent times further vitamin D (vit.D) pleiotropic effects have been observed (1). Currently our Department is pursuing a study in order to investigate the effects of calcitriol supplementation therapy on cardio-vascular risk (CVR). We are going to exhibit some interesting results derived from preliminary data at baseline and after 6 months of follow up. From May 2011 we enrolled 243 patients (aged 26-93; 67 males). We excluded subjects who were already on vit. D supplementation therapy and those who had osteoporosis. By assessing plasma levels of 25(OH)D, we found that 82.3% of our study population had 25(OH)D <30 ng/ml; of these, almost 1 out of every 4 patients had 25(OH)D <10 ng/ml. These results clearly show that hypovitaminosis D has a high prevalence though in a city like Rome, that is the second sunniest city in Europe (1687 hours of sunshine/year). Moreover we observed that vit.D deficit seems to affect both older than younger subjects (75.6% in the patients aged <65 yrs and 86.5% in those aged >65 yrs). A sedentary lifestyle and poor dietary habits could be the main determinants of vit.D deficit. Mean systolic (SBP) and diastolic (DBP) blood pressure levels of the patients with vitamin D deficiency (VDD) were significantly higher than those without VDD. The importance of keeping sufficient plasma levels of vitamin D is a matter of fact, however there is no consensus on the way to achieve this goal. The minimum recommended dose in the elderly is that of 800 IU/day of Cholecalciferol (vitamin D3), though doses of 1.500-2.000 IU/day are usually tolerated. Higher daily doses could be more likely to exert pleiotropic effects. A recent report emphasizes that vitamin D doses of more than 4.000 IU/day could give side effects, and that more than 10.000 IU/day may lead renal failure (4). In a recent investigation the authors recommended to keep plasma vitamin D >30 ng/ml by administration of small daily or weekly or monthly doses of vit.D, in order to minimize the likelihood of side effects (5). In our sample, 73 patients with hypovitaminosis D received 25.000 IU (Cholecalciferol) per os twice a month (Tp.A), but we have not achieved satisfactory results: hypovitaminosis persisted in 60% of the subjects after 6 months. For this reason, we decided to administer in 51 patients (Tp.B) a loading dose of 50.000 IU once a week for 8 weeks, followed by a maintenance dose of 25.000 IU twice a month. The results at 6 months show that almost 75% of patients achieved plasma vit D >30 mg/dl, without side effects. In addition, at the end of follow-up we found that, in the patients with normal plasma levels of 25(OH)D after oral supplementation therapy, both SBP and DBP were significantly reduced (p=0.000 and p=0.008 respectively). All in all, hypovitaminosis D is a widespread condition even in young/adult people. There is still no consensus on the dose to supplement in order to produce pleiotropic effects but we believe it is important to quickly achieve normal vit.D plasma values, also in order to decrease CVR.

References:


Miscellanea

Lung ultrasound performed at discharge: a prognostic tool to predict 90-days death and readmission in patients hospitalised for heart failure

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Background: Heart failure (HF) is one of the most important causes of morbidity and mortality in the industrialized world, representing the leading cause of hospitalization for patients older than 65 years, with a combined mortality and readmission rate of 30% within 90 days post-discharge. Several factors have been evaluated to stratify prognosis, such as ejection fraction (EF), NYHA class and nt-proBNP; however timing of readmission and risk for major clinical disease events in a community-based population of older adults: a cohort study. Ann Intern Med. 2012 May 1;156(9):627-34.}

Conclusions: B lines at discharge may represent a prognostic factor for readmission and death at 90 days in HF patients.

Approach to the health system of a third world country: experience in Kenya

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In the Italian system, the National Health Service (NHS) is the complex of functions and welfare activities carried out by the regional health services, bodies and institutions of national importance and by the State, to ensure the protection of health as a fundamental right of individual and collective interest, while respecting the dignity and freedom of the human person. This conception of health is purely European-American, and does not find a counterpart in the health systems of developing countries, the so-called Third World. For example, the NHS of Kenya is organized in multiple structures with an increasing amount of services. The first level corresponds to the Community Unit (CU), a first aid care center run by volunteers, spread over the territory (in private clinics, in schools, in places with particular social problems), but still partially paid, the equivalent of the European first aid point. The second level is the Dispensaries and Health Center where nurses are qualified to make a first triage and prescriptions of medicines for common diseases, but they don’t have the opportunity of making any diagnostic test. The third level is the GOK Hospital (Governmental Hospital of Kenya) that provides obstetrical assistance, basic health services, primary care and laboratory services, and in which there may be some diagnostic tools (ultrasound, X-ray). The last level is the DISTRICT HOSPITAL in which the specializations converge. This kind of hospitals are the equivalent of our DEA of first and second level. Around these governmental structures a number of private companies flourishes. These companies are recognized from the NHS and they variably integrate into it, trying to cover the lack of qualitative and instrumental state reality. We report the experience of a CU at the Takaye Primary School, a government school in which a clinic, that corresponds to a European territorial point of first Aid, is present. This CU is managed by the Kenya Pole Pole Onlus, an association born in Italy in 2006 and run by a board made up of Kenyans. In the clinic works a Kenyan nurse and, for short periods, physicians from Italy (for the most part of the time interns). Access to the clinic is designed for school students (about 2000 students from baby class to stranded 8th grade, from 3 to 19 years old) and school teachers. The clinic is open only during school hours. This structure responds to urgent, but not major, health needs that can be solved without immediate recourse to instrumental examinations, specialist visits or hospitalization. If the doctor estimates a critical case, the patient can be transferred to the closer district hospital but transportation is not provided since there is not a widespread territorial emergency system, although there is the International Red Cross. The medical support is provided for small wounds, minor trauma, insect bites, burns or rashes, minor advice on maternity, substance abuse and addiction. It is also organized a service of health education with periodic meetings held in order to train students and teachers, and opened also to parents and the local population. The integration between local staff and Italian physicians allows mutual training, with the passage of new knowledge and skills to local health and the approach to culture by doctors guests. This point is essential to establish a relationship of trust and respect between the physician and the patient/tribal culture. A good knowledge of English is not enough to obtain a good communication because most of
the population speaks only local dialects. The scarcity of resources and the presence of a health care system for an additional fee, introduces the relevance criteria in the selection of diagnostic and therapeutic procedures, often overlooked in Italy, as well as tight control of health spending. In this situation it is even more necessary for the physician to rely on clinical method and not merely on instrumental diagnostics.

Comparison among patients of REPOSI project affected or not by atrial fibrillation

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Introduction: REPOSI (Register Polipathology SIMI) is an epidemiological study that evaluates the frequency of several diseases and therapies in elderly patients (age >65 years) admitted to the departments of the network SIMI (Italian Society of Internal Medicine).

Aims: The aim of this study was to assess the anthropometric and biochemical statistically significant data in patients of “Reposi Project 2012” affected or not by AF (atrial fibrillation), admitted to the Clinica Medica “A. Murri” in the Policlinico Hospital of Bari.

Materials and methods: We enrolled 20 patients (13 M, 7 F, median age 75 yrs± 5 SD, 5 with AF, 15 without AF). For each patient we assessed the following data: body mass index, systolic and diastolic blood pressure, heart rate, blood glucose, serum triglycerides, serum total cholesterol, HDL cholesterol, LDL cholesterol. We compared each variable between the two groups of patients (one group with AF and the other one without). We used the Wilcoxon rank sum test for statistical analysis.

Results: The plasmatic levels of total cholesterol were significantly lower in patients affected by atrial fibrillation in comparison to the other group (mean 139.7 mg/dl, median 137 mg/dl).

Discussion: If the values of plasma total cholesterol are lower than 137 mg/dl, it’s more likely that patients suffer from atrial fibrillation. We could use the total cholesterol as an additional marker for prediction of atrial fibrillation.

Tab. Anthropometric and biochemical data analyzed, statistically significant and not statistically significant.

<table>
<thead>
<tr>
<th>Data</th>
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<tbody>
<tr>
<td>Body Mass Index</td>
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<tr>
<td>Systolic Blood Pressure</td>
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<td>Diastolic Blood Pressure</td>
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<td>Serum Triglycerides</td>
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<td>Blood Glucose</td>
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Management of cigarettes dependence in schizophrenic smokers with e-cig

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Background: Cigarette smoking is a tough addiction to break. This dependence is the most common dual diagnosis for individuals with schizophrenia. Currently three effective drugs are approved for smoking cessation: nicotine replacement therapy (NRT), varenicline and bupropion. However, some serious side effects of varenicline have been reported, including depression, suicidal thoughts, and suicide. The use of bupropion also has side effects. It should not be used by people who have epilepsy or any condition that lowers the seizure threshold, nor by people who take a specific class of drugs called monoamine oxidase inhibitors. Hence, there are pharmacodynamic reason to believe they could precipitate or exacerbate psychosis. For its capacity to deliver nicotine and provide a coping mechanism for conditioned smoking cues by replacing some of the rituals associated with smoking gestures, electronic-cigarettes may reduce nicotine withdrawal symptoms without serious side effects. Our recent work with ECs in healthy smokers not intending to quit consistently show surprisingly high success rates. We hypothesised that these positive findings could be replicated in difficult patients with schizophrenia. This tool may help smokers with schizophrenia remain abstinent during their quitting attempts or to reduce cigarette consumption. Efficacy and safety of these devices in long-term smoking cessation and/or smoking reduction studies have never been investigated for this special population.

Methods: In this study we monitored possible modifications in smoking habits of 14 smokers (not intending to quit) with schizophrenia experimenting with the “Categoria” e-Cigarette with a focus on smoking reduction and smoking abstinence. Study participants were invited to attend six study visits: at baseline, week-4, week-8, week-12 week-24 and week 52. Product use, number of cigarettes smoked, carbon monoxide in exhaled breath (eCO) and positive and negative symptoms of schizophrenia levels were measured at each visit. Smoking reduction and abstinence rates were calculated. Adverse events were also reviewed.

Results: Sustained 50% reduction in the number of cig/day at week-52 was shown in 7/14 (50%) participants; their median of 30 cig/day decreasing significantly to 15 cig/day (p = 0.018). Sustained smoking abstinence at week-52 was observed in 2/14 (14.3%) participants. Combined sustained 50% reduction and smoking abstinence was shown in 9/14 (64.3%) participants. Nausea was observed in 2/14 (14.4%) of participants, throat irritation in 2/14 (14.4%) of participants, headache in 2/14 (14.4%) of participants, and dry cough in 4/14 (28.6%) of participants. However, these adverse events diminished substantially by week-24. Overall, one to two cartridges/day were used throughout the study. Positive and negative symptoms of schizophrenia are not increased after smoking reduction/cessation in patients using e-cigarettes.

Conclusions: We have shown for the first time that the use of e-cigarette substantially decreased cigarette consumption without causing significant side effects in chronic schizophrenic patients who smoke not intending to quit. This was achieved without negative impacts on the symptoms of schizophrenia as assessed by SAFS and SANS symptoms scales.

Teaching of internal medicine and simulators devices

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Simulation means a technical model of reality that allows to assess and predict the unfolding dynamic of a series of events or processes subsequent to the imposition of certain conditions by the analyst or the user. It’s an experimental tool of analysis very powerful, used in many areas, imposed by the difficulty or impossibility to reproduce physically, in a real laboratory, the actual terms to be studied and that takes advantage of the great opportunities offered by information processing advanced. The simulation, in fact, is the...
transposition in logical-mathematical procedure of a “conceptual model” of reality, such a conceptual model or mathematical model can be defined as the set of processes that take place in the system evaluated and which together allow to understand the logic of the operation of the system and to adapt to these practices related to achieving the mission. It therefore qualifies as a sort of virtual laboratory that often allows a reduction of costs compared to study complex experiments carried out in the real laboratory. This use is widespread in the analysis of dynamic systems such as those characterized by high biological complexity, both structural and dynamic-interactive, high impact of risk factors of heart failure, for frequency and magnitude, related, also, to the stochasticity of the variables system. In order to develop a simulation model effectively and efficiently you need to follow a conceptual process whose progression is dictated by the interaction of the 9 competencies required to achieve the mission. Simulation has always been used in health education and improvement of the techniques has made it possible an ever greater realism. In particular, in the simulation teaching in academic medicine Mission is to: promote cultural initiatives in innovation and training essential, particularly in cognitive systems-operating, highly specialized and rapidly changing as the various professions in health care, use of new methodologies, technologically advanced and high impact, such as modern teaching techniques based on simulation systems, a system of “training” totally interactive, based on the use of educational tools and educational innovation, placed in the context of a clinical scenario absolutely realistic; systems make use of both macro and micro simulation of both systems of “virtual reality” and “augmented reality”; propose and implement programs and research projects with the possibility of the development of both hardware and software systems, to produce packages of training, information and updates, accredited by the Ministry of Health; stimulate a culture of prevention, health education and health promotion; accomplish the above in collaboration with the Ministry of Health, the regions, local health authorities, other organizations and public institutions. The complexity of the relationship between teachers and learners is not resolved, but, rather, is exacerbated by the availability of tools and technology. In practice, through the Macrosimulation, both screen-based, both full-scale, re-creating an environment equipped to simulate, in a more realistic and accurate as possible, many clinical situations are recreated (emergency room, hospital ward, operating room, hemodynamic environment, radiological, medical, scenes of places of disasters of various kinds, etc.); Microsimulation use in a clinical simulation software platform of third-generation highly innovative and sophisticated, allowing the creation of clinical cases in a virtual environment with high realism. The management of the virtual patient is in a totally interactive, real-time the learner attends the pathophysiological response arising from its diagnostic and therapeutic choices. At the end of the performance the diagnostic-therapeutic-welfare is proposed and all the choices you make can be assessed and commented upon with the instructor, to the sharing of a plan of optimal intervention. The software can be used in different therapeutic areas and fully customized.

Sub-acute beds in internal medicine wards: a single-center one-year experience

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The so-called model of “graded care hospital” is currently being proposed to enhance the efficiency and efficacy of patient-centered care, and to reduce the health-related costs. In the second half of 2011, the Public Health Service of Lombardy transformed part of acute beds in sub-acute ones, intended for patients who still require some medical intervention, but below the level of an acute care institution, for a period no longer than 40 days. To be eligible for the sub-acute area, patients have to satisfy the following criteria: to be clinically stable, with a Modified Early Warning Score ≤ 2 (MEWS is a tool for bedside evaluation based on five physiological parameters: systolic blood pressure, pulse rate, respiratory rate, temperature and AVPU [Alert, Reacting to Voice, Reacting to Pain, Unresponsive]); absence of Systemic Inflammatory Reaction Syndrome (SIRS criteria include body temperature, heart rate, respiratory rate, white blood cell count); a Care Nursing Index ≥ 2 (CNI rates the needs of 10 functions [physiological and related to diagnostic/therapeutic procedures] according to a 4-point scale, from 1 = no need to 4 = completely dependent). While acute beds are reimbursed by the DRG system, sub-acute beds are paid on a fixed per day reimbursement: a CNI of 2 was reimbursed by a daily rate of 150 €, a CNI of 3 or 4 by 190 €. Here we analyze the experience of our hospital, where such an innovation consisted in transforming 10 beds (about 15%) of the internal medicine ward in 10 sub-acute beds, activated in a contiguous area, still charged to the patient. In 2012, 140 patients were discharged from the sub-acute area, all coming from the acute ward, i.e. about 9% of the discharged from this ward in the same period. Their median age was 81 years (range 46-101), with a little predominance of females (53%). They had been admitted to hospital, through emergency, for respiratory (29%), circulatory (17%), digestive and hepato-biliary (11%), musculoskeletal and connective tissue (10%), kidney and urinary tract (9%), infectious and parasitic diseases (9%), and other causes (15%). Their average length of stay (LOS) in the acute area had been 12.58 days (range 2-37). At admission to the sub-acute area, CNI values were 2, 3 and 4 in 24%, 54% and 22% of patients, respectively. The average LOS in the sub-acute area was 14.61 days (range 2-41). Ninety-six patients were discharged to their home (24 with home care assistance), 27 to a nursing home, long-term or hospice care facility. Nine patients returned to the acute area, for unexpected complications; eight patients died. The actual overall payment for these patients was calculated by adding together, for each patient, his/her fixed DRG-based reimbursement (for the acute phase) with his/her daily-based reimbursement obtained according to his/her CNI and LOS values (for the sub-acute hospitalization): this actual overall payment was of 959,386 €. Then, we simulated the reimbursement we should have obtained if these patients had remained in the acute ward until conclusive discharge: for each patient the DRG-based payment was calculated by the 3M APR-DRG grouper software, according to the same patient specific diagnosis (DRG code) and global (acute + sub-acute) LOS. By this simulation, the overall payment should have been of 751,422 €. Our results suggest that, in our Internal Medicine ward, having transformed 10 acute in 10 sub-acute beds was not so cost-effective as expected. A first possible explanation refers to how these beds have been used. While originally intended for patients not requiring acute care (i.e. not requiring “classical” hospitalization, reimbursed by the DRG system), in our experience they had been used for patients coming from the acute ward, thus leading to a post-acute rather than a sub-acute context; but none of our patients, at admission, was so clinically stable, according to MEWS, to avoid a period of hospitalization in the acute ward. A second, not mutually exclusive explanation refers to the actual LOS in our acute ward: in 2012, considering all the 1,504 patients discharged, the average LOS was 10.59 days. When the Public Health Service introduced the innovation of sub-acute beds, the amount of beds to be transformed from acute to sub-acute was calculated on a regional basis (not related to a single hospital and/or ward), taking into account the percentage of patients with LOS longer than 11 days. Therefore, our already short acute LOS may have reduced, at least partially, the potential advantage of having a sub(post)-acute low-cost area. We cannot exclude that the opportunity to shift these patients to an extra-period of hospital care may have increased their overall hospital stay. However, thanks to this opportunity our patients were discharged to a more appropriate setting of long-term care, as suggested by the increased numbers of patients entrusted immediately to nursing homes, rehabilitation facilities, social and/or home care services.
(17% in 2012 vs 9% in 2010, evaluating the total population of our ward). Indeed, we cannot forget that these patients were mainly older subjects, with many comorbidities and higher levels of disability, often with social problems, such as lack of appropriate housing and community care services.

**An uncommon case of orbital emphysema**

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**UO Semeiotica Medica PO SS Annunziata Chieti**

Orbital emphysema is an uncommon condition occurring because of air trapped into loose subcutaneous tissue around the orbit, commonly seen in cases with history of sinusitis, facial trauma or surgery. Lamina papyracea is the most common site of bony defect for passage of air from paranasal sinuses. Orbital wall fracture is a common cause. Other causes include forceful nose blowing, post-surgical and pressure changes during air travel. Treatment options include observation as it is usually benign and spontaneous resolution occurs in two to three weeks. However, it can cause ischemic optic neuritis and central retinal artery occlusion and may lead to visual loss. Hence when orbital emphysema shows signs of pressure effect like restricted ocular motility, sluggish pupillary reaction, disc edema or decreased visual acuity, then drainage of trapped air in the subcutaneous tissue should be considered. It can be done effectively by simple underwater drainage of air by 24-gauge needle or lateral canthotomy and cantholysis.

Here we present a case of a 28-year-old woman presented with sudden and painless onset of peri orbital emphysema particularly pronounced at left side. There was no history of sinusitis, facial trauma or previous surgery. On examination there was massive non-tender peri orbital swelling with crepitus on palpation suggestive of subcutaneous orbital emphysema. On lid retraction, there was mild proptosis with conjunctival congestion. Ocular movements, pupillary reactions and dilated fundus examination were normal. The visual acuity was 20/20. Right eye examination was normal. Toracic tomography showed the presence of a small blebs in the apical left region but revealed no mediastinic emphysema. Facial tomography showed the presence of dilatation of the lacrimal sac with radiologic signs of dacryocystitis; that’s why we administered a topic therapy with tobramicina and washing frequently the eyes by a solution of i aluronico acid and mineral salts. After 7 days of therapy, we observed a prompt improvement of the emphysema and of the flogistic parameters.

This case show a singular etiology of orbital emphysema that is important to remember as differential diagnosis.

**Guillain-Barré syndrome**

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Guillain-Barré syndrome (GBS) is a complicated degenerative neurological disorder which can present in acute or chronic fashion. It is an acquired condition which is characterized by progressive, symmetrical, proximal and distal tingling and weakness. Muscle stretch reflexes are decreased to absent and loss of sensation is common. Etiology remains unclear but pathophysiology includes demyelination of spinal nerve roots. Death is rare. Early diagnosis and prompt referral should occur in severe cases due to the incidence of potential ventilatory failure and cardiovascular instability in some patients.

Here we present a case of a 80 years old man who was admitted to the internal medicine department with a history of dyspnea and chest pain. In the anamnesys he refers good clinical condition exceptly for a low renal impairment and a surgery procedure for cholecistectomy three weeks before the admission. A diagnosis of pulmonary embolism was made supported by the clinical manifestations and the elevation of D-Dimer, the results of the echocardiography and X-ray. During the observations in hospital the patients begins to present a sinthermatology characterized by progressive, symmetrical, proximal and distal tingling and weakness with decreased stretch reflexes, affecting the legs first and then the arms.

After two days the patient wasn’t able to stand up alone. A prompt electromyography was done that showed the presence of a motor sensitive polineuropathy; a tentative diagnosis of GBS was made. We begin a therapy with immunoglobulins without improvement of the symptoms and the patients died for respiratory disorders.

A common misconception is that the Guillain-Barré syndrome has a good prognosis — but up to 20% of patients remain severely disabled and approximately 5% die, despite immunotherapy. In this case one of the problem was the delayed observation of the patients who has presented, on admission, one of the first complication of Guillain-Barré syndrome, the pulmonary embolism.

**A woman with persistent orthostatic headache and diplopia**

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We describe a case of a 56-years-old woman with sudden onset of severe, continuous vertix headache, which was worsened when getting into upright position and immediately relieved by lying down. After few days headache was irradiated to the neck and the patient developed diplopia. She denied nausea, vomiting or fever. The patient has never suffered from headache before. She has never smoked and she was natural menopause. No other cardiovascular risk factors were reported. She was allergic to pollen and took homeopathic products. Medical history included tonsillectomy and a recent bronchitis, spontaneously resolved. For the persistance of headache and transient diplopia she presented to emergency department where vital signs were normal and there were no pathological findings on the neurological examination. Also the ophthalmologic evaluation was normal. CT angiography of the intracranial vessels showed no parenchymal nor vascular abnormalities. Headache resolved after analgesics and the patient refused hospitalization. She performed a Doppler ultrasound of the neck vessels as outpatient, which was negative for carotid stenosis. After four days, because of the persistence of headache, only partially responsive to analgesics, and recurrence of diplopia, the patient came back to the emergency department. Encephalic CT scan was normal. Vital signs and neurological examination were normal, except for oblique binocular diplopia on the stare of only far objects (more than one meter), brisk reflexes and mild neck stiffness. There was no gaze palsy, ptosis, or nystagmus. The remainder of the physical examination was normal. The chest X-ray and laboratory investigations (full blood count, erythrocyte sedimentation rate, glucose, liver and renal function) were normal.

The differential diagnoses included meningoencephalitis, subarachnoid hemorrhage, a venous sinus thrombosis, vertebralbasilar dissection or an episode of migraine with aura. The patient had never suffered from headache and had no trauma. CT angiography of the intracranial vessels had shown no vascular or parenchymal abnormalities, as well as Doppler ultrasound of the...
From bedside ultrasound to diagnosis

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A 83 years old man came to our attention for pain in the left hypochondrium, exacerbated by breathing and movement, appeared about 10 days before. Patological history: arterial hypertension and chronic renal failure. On the first consultation, the patient presented with pain in the left hypochondrium, especially with deep inspiration and with some diaphragmatic movements. The physical examination revealed a left hypochondriac mass, the size of which was about 10 cm. The patient was scheduled for an ultrasound test, which showed a solid mass in the left hypochondrium, with a diameter of 12 cm, with a heterogeneous echostructure. The patient was referred to the Department of Internal Medicine for further diagnostic tests. In the department, the patient was found to be normocytic and normochromic anemia. During the recovery the patient manifested febrile episodes, associated with nocturnal sweating so we decided to perform a peripheral blood smear that showed atypical lymphocytes. To exclude an infectious etiology we performed the serological tests for EBV, CMV, Leishmania, found all negative. Suspecting a lymph/myeloproliferative disease we executed bone marrow biopsy and lymphocyte subpopulations analysis; due to bone marrow biopsy we were able to make a diagnosis of diffuse large B-cell non-Hodgkin Lymphoma. A PET limited whole body showed massive splenic involvement with multiple infarction and pathological lymph-adenomegaly above and below diaphragm. The patient was treated with R-CHOP chemotherapy with improvement of his clinical condition.

We have decided to describe this case due to under light usefulness of bedside ultrasound which allowed us to explain the cause of pain in the left hypochondrium (multiple splenic infarctions), addressing the following diagnostic tests and enabling us to achieve an early diagnosis of systemic pathology.

Is it really a Sjögren’s syndrome?

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Sjögren’s syndrome (SS) is an autoimmune systemic disease characterized by lymphocytic infiltration of the exocrine glands. It manifests clinically with xerostomia, xerophthalmia and recurrent swelling of parotid glands and it is more frequent in women.

We report a case of a 22-year-old woman with prominent bilateral and indolent swelling of parotid glands and xerostomia lasting a year prior to her presentation to our Centre. Her main concern was the related aesthetic abnormality. In her past history autoimmune thyroiditis. Principal blood exams were normal, in particular blood cell count, except for slight ipokaliemia and metabolic alkalosis. Anti-nuclear autoantibodies (ANA) and specific autoantibodies, such as anti-SSA and anti-SSB, were negative. Also Schirmer’s test was normal. The patient has undergone parotidoid ultrasound that showed marked homogeneous increase of the glands.

The tests did not confirm the clinical suspicion of SS. However, a repeated analysis of her medical history revealed that the patient has recurrent episodes of binge eating, with regular use of self-induced vomiting, in the last two years.

Bulimia nervosa is an eating disorder characterized by self- compulsive vomit after taking huge amounts of food. Occasionally parotid swelling could be present because of autonomy neuropathy with altered secretion of the acinar cells. There is an accumulation of zymogenes, resulting in glandular hypertrophy.

In conclusion, since patients with bulimia tend to be secretive about their purging, it is important that physicians should be alert for medical compli-
Cardiac hypertrophy predicts toxicity in head & neck cancer (H&NC) patients receiving combined radio-chemotherapy

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Rationale: Cardiac mass as measured by echocardiography correlates with body mass index (BMI) and muscle mass. Sarcopenia predicts complications in cancer patients receiving chemotherapy. We evaluated whether cardiac mass predicts toxicity in H&NC patients receiving radio-chemotherapy.

Methods: H&NC patients undergoing radio-chemotherapy were considered. Before starting treatment, anthropometrics were measured. Cardiac mass (g/m2), as expressed by the Devereaux formula and normalized by body surface, and ejection fraction (EF; %) were measured by echocardiography. During treatment, toxicity was recorded using the RTOG scores. At the end of treatment, measurements were repeated. Data obtained were statistically analyzed by Student’s t-test and Spearman correlation. Results are presented as M±SD.

Results: As of March 30, 2013, thirteen H&NC patients (8M:5F) have been considered. Five patients dropped out because of tumor progression/refusal to continue treatment. Eight patients (5M:3F; BMI: 24.4±5.3), mean age 55.3±10.3 yrs, completed the study. At baseline, cardiac mass was 105.9±32.1 which negatively correlated with BMI (r=-0.35) and EF (r=−0.83; p<0.05). During treatment, patients developed toxicity ≥G2 grade, and cardiac mass was greater than in patients with toxicity ≤G2 (122.1±32.6 vs 96.1±29.3, respectively; p>0.05), but EF was lower (36.6±11.5 vs 51.4±9.1, respectively; p<0.05). Also, 2/3 of the patients in the high toxicity group met the echocardiographic criteria of cardiac hypertrophy, whereas cardiac mass was hypertrophic only in 2/5 of the patients in the low toxicity group. At the end of treatment, 7 patients had lost body weight, but no significant changes in cardiac mass were observed in the high or the low toxicity group.

Conclusion: Cardiac hypertrophy, as measured by echocardiography, may represent an easily available marker of radiochemotherapy induced toxicity. Disclosure of Interest: None Declared

An ancient hypothyroidism

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A 24 year-old Pakistani patient was admitted for a meal-evoked, ‘colicky-like’ abdomen primarily localized to the right hypochondrium and epigastrium. The clinical (including family and drug) history was unremarkable. On admission, the patient’s clinical parameters were normal, i.e. BP 105/60 mmHg, HR 58 bpm, SpO2 96%. Physical examination showed a swollen face, sparse hairs; the abdomen was flat and tender with a positive Murphy and negative Blumberg sign. Cardio-respiratory examination was unrelevent. The neurological evaluation revealed numbness associated with bradialia. Cutaneous and tendon reflexes were slow although symmetrical.

CD and bed-side ultrasonography

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A 40-year-old man diagnosed with Crohn’s disease (CD) in 2003, was afflicted by persistent diarrhea despite ongoing Infliximab treatment. At previous hospitalization he was in good clinical condition despite Abdominal US showed a thickened, dyshomogeneous colonic wall, with loss of the echogenic wall structure and preserved peristalsis. At pancolonoscopy performed in that occasion, the endoscopic encountered a difficult passage through the ileo-cecal valve due to edema and signs of active disease. Adalimumab therapy was prescribed. After a few days, because of the onset of mild abdominal pain associated with fever and marked asthenia, he was urgently hospitalized again in our unit. The patient was pale and unwell, but BP and vital parameters were within normal limits. Physical examination did not reveal any signs that could indicate CD complications: a tender abdomen only at deep palpation, negative Blumberg, preserved peristalsis and passage of wind. Emergency blood tests showed mild neutrophilic leukocytosis, increased inflammatory indexes, microcytic anemia. Due to the development of mild but progressive hypotension, bed-side US
was performed, that revealed dilated bowel loops containing fluid material, with hypometabolity but no sign of swelling. At ileocecal level the loss of the normal bowel wall architecture persisted, showing multiple hypoechogenic images and endoabdominal leakage. An ultrasound diagnosis of acute abdomen due to a suspected perforated bowel was made and the patient underwent emergency surgery, after CT confirmation, for resection of the right colon and terminal ileal loops.

In this patient the poorly specific clinical picture did not allow an immediate diagnosis. The use of US as the “new stethoscope”, not to replace but to integrate traditional semiotics, allowed us to make a bedside diagnosis of a critical condition. This method, that has become routine in the follow-up of patients affected by Crohn’s disease because it is non invasive and highly specific, can be of great aid to the clinician also in an emergency situation.

CPK increase as marker of occult cerebrovascular disease: a case report

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As regards the great family of kinases, creatine phosphokinase (CPK) has surely a remarkable importance for several reason. Expressed by various tissues and cell types, CPK catalyses the conversion of creatine and consumes adenosine triphosphate (ATP) to create phosphocreatine and adenosine diphosphate (ADP). This particular reaction is reversible, such that also ATP can be regenerated from phosphocreatine and ADP. Assay of CPK serum level, has a significant clinical role as marker of myocardial infarction (heart attack), rhabdomyolysis (severe muscle breakdown), muscular dystrophy, the autoimmune myositis and in acute renal failure. Furthermore, the existence of three different isoenzymes, with different localization, is useful to guide the diagnostic process: CPK-MM with a predominant localization in muscle tissue, CK-BB in nervous tissue (this one cannot be identified in systemic circulation unless of blood-brain barrier injury) and CPK-MB with a myocardial localization. Differential diagnosis of a hyper-CPKemia can, however, be extremely intricate and, as usual, the medical history collection is fundamental. Here we report the clinical case of a 65 years old non-smoker woman, who had an isolated creatine kinase and lactate dehydrogenase increase, due to several syncopal episodes with consequential ground drop, by pre-existing impaired cerebral blood flow.

References:

Seek and ye shall find...not always

Masala M., Ruggia M., Pinna M., Pisanò M., Prettì V., Deltàla G.

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A 65 years old woman was admitted to the our department presenting with fever over 39°, productive cough, and dyspnea since 10 days. No personal history for significant diseases. Her pharmacology history was negative. No smoke, no use of alcohol, no asthma, no occupational risk. At the admission the patient complaining weakness and asthenia. On physical examination the patient was eufono, pyretic (38,5 C°), blood pressure 130/70 mmHg, heart rate 110 b/min, O2 saturation was 96% AA. Were notable breath sounds diminished with faint, high pitched rhonchi towards the end of expiration. Heart and abdomen examinations were negative, no superficial lymphadenopathy.

The neurological examination revealed weakness and tingling sensations in her legs and hands, unsteady walking and numbness in her extremities. She presented also some petechial lesions in her legs. No other significant findings. Arterial blood gas was normal.

On admission laboratory findings revealed a leukocytosis with hypereosinophilia (2500/mm3) confirmed in the smear blood test, normochromic and normocytic anaemia (Hbg: 11,5 g/dl), increase of inflammatory markers: C reactive protein (15 mg/dl), VES and IgE.

Other laboratory tests (test of renal, liver, thyroid and renal function, electrolytes) result negative. To clarify the hematologic, cutaneous and neurologi
cal scenario and suspecting immunemediated, infectious/parainfectious or paraneoplastic vasculitis, were tested: autoimmune serum markers (ANA, ANCA, ENA, ASCA, complement components C3 and C4), parasitic markers (absence of helminth infection: Trichinella Spiralis, Schistosoma, Echinococcus, Filaria, Tenia, etc.), mycobacterial serum markers (quantifier, TBC, etc.), fungal infection (absence of Aspergillus, Coccidiodomyces, etc.), viral infection (absence of HIV). She performed also cultural test on blood, urine, feces. All these examinations did not reveal any alteration. She performed ECG: normal, except for I degree AV block; chest X-ray that showed faint diffuse fibrosis, confirmed by chest CT scan. Pulmonary function testing was normal except for a mild diffusion impairment. The patient underwent a fibrobronchoscropy with bronchoalveolar lavage (BAL) that showed high number of eosinophilis cells and biopsy that excluded neoplast origin. Were also performed TC total body, abdominal, breast and cardiac ultrasound, and mammography.

The results were negative. During the hospitalization for the persistence of the fever and for the worsening of the hypereosinophilia we started broad spectrum antibiotic therapy without any advantage. She started to complain diarrhea. She performed gastroscopy and colonoscopy with biopsy resulting negative. Suspecting a medullary origin a fine needle aspiration and osteomendullary biopsy was performed: FLPL1-PDGFR, BCR/ABL, P210 JAK2 mutation were negative. In order to exclude an occult lymphoma we performed PET scan resulted negative.

A brain MRI was performed that showed disuse vasculitis lesions. She performed also nerve conduction study that showed weakness and sensitive deficit in the lower limbs. Excluded all cause of hypereosinophilia we decide to start steroid therapy with 80 mg/die of prednisone. The patient showed a decrease of the hypereosinophilia, improvement of the symptoms and the remission of the fever. After 2 months we started gradually to reduce the dose of the steroids but we attend to a new increase of the eosinophilia and of the symptoms.

We decide to associate the steroid therapy with Imatinib Mesilato (Glivec) in off label scheme with remission of all syntoms. The patient is monitoring in our service and is still treated with top down corticosteroids therapy and Glivec. The patient was discharged with the diagnosis of idiopatic hypereosinophilia.

Conclusion: it does not exist a codified therapy for idiopatic hypereosinophilia. Glivec can be a new effective therapy. Obviously we need other medical evidence.
Aim: We tested a checklist for patient discharge from hospital in order to:
1) improve continuity of care from hospital to community; 2) improve safety of frail elderly patients with multiple comorbidities; 3) improve hospital and community care integration; 4) identify near-miss events and incidents for every kind of health professional; 5) standardize the discharge process; 6) measure the level of care needed by patients with multiple comorbidities.

Materials and Methods: We adapted to the Italian setting a discharge checklist already validated in literature. It contains two sections: one for transport organization (part A) and one encompassing both specific professional items (i.e., notice to the patient's general practitioner, last clinical evaluation by physicians, handling of medical devices by nurses, toilet by healthcare assistants) and relational items (i.e., medical and healthcare information, contact numbers, greetings) for physicians, nurses and healthcare assistants (part B).

Results: During a seven-month period 658 checklists were filled in by the healthcare professionals involved in the study (330 in the high-intensity area, 144 in the mean-intensity area and 184 in the low-intensity area), 78.6% of which were complete in all parts. Physicians appropriately filled in 97.6% of all checklists, while nurses 98.5% and healthcare assistants 90.7% (p<0.05). A non-conformity was pointed out in 67.8% of all checklists, thus preventing a possible error, with a prevalence significantly higher for nurses (17%) and healthcare assistants (12.5%) than physicians (5.7%, p<0.001).

Non-conformity concerned mainly professional items (i.e., missed activation of home nursing services for physicians, missed compiling of nursing discharge forms for nurses and missed patient toilet performing for healthcare assistants). Our survey also highlighted a heavy healthcare need of studied patients (58.4% of them had invasive devices, were totally dependent in ADL and needed community nursing support and anti-decubitus systems.

Checklist for frail multiple-disease patient discharge from hospital: pilot study of a new tool for assuring continuity of care from hospital to community and for improving patient safety


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Background: Internal medicine practice is being more and more characterized by a massive increase in the number of frail multiple-disease elderly patients, with frequent relapses of chronic diseases, prolonged hospital stays, readmissions and difficulties in discharge from hospital to community. Discharge is indeed a critical process for these complex patients. Moreover, an excessive fragmentation and insufficient cooperation between hospital and community care are often the main causes of a delayed or unsafe discharge. Checklists are simple tools allowing to manage high-complexity multi-professional processes, improving safety and effectiveness.

Setting – Internal Medicine and Critical Subacute Care Unit of Parma University Hospital is a large internal medicine area (94 beds) whose mission is the care of frail elderly patients with multiple comorbidities. It is managed by care intensity encompassing three different wards: high-intensity (mean length of stay < 5 days), mean-intensity (mean length of stay < 20 days) and low-intensity nurse-managed ward (mean length of stay < 20 days).
Conclusions: Checklists may be a valid tool to improve continuity of care from hospital to community and discharge safety. Their correct application need consciousness and adequate education for all the healthcare professionals involved.

The intensity-of-care model in an internal medicine ward: a proposal for the characterization of acutely ill patients

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Background: The organization of hospital, departments and wards on the basis of the so-called “intensity-of-care” model represents one of the most interesting proposal in the last years in the field of health system. On-going experiences in internal medicine units require the implementation of section of the wards assigned to a higher level of care and differently denominated on the basis of tipology of patients problems (e.g. sub-intensive units, stroke units, high dependance units). The real impact of these special areas in the organization of internal medicine wards needs to be well defined in order to plan appropriate choices on human and material resources.

Objective: To characterize and to quantify the real need of intensive care in a ward of internal medicine.

Materials and Methods: The study has been conducted in the internal medicine ward of “Clinica Medica “A. Murri”, allocated in a university hospital in Bari.

We have monitored almost one hundred consecutive patients admitted during the last month (of which 90% admitted through the Emergency Department and 10% from on a basis of non urgent programmation list). Each day, each patient has been labeled as having “urgent” or “emergency” clinical problem on the basis of the ABCDE approach proposed by the Resuscitation Council (2006) in order to recognize the acutely ill patient (A= air way obstruction; B= breathing problems; C= circulation and cardiac problems; D = disability, including most of severe neurological deficiencies; E= exposure, refering to trauma, bleeding, skin reactions (rashes), needle marks, etc.). Several indicators have been then calculated.

Results: We have observed 96 patients (mean age 71.5yrs, M/F: 43/51). Main indicators are the following: total number of hospital stays examine: 696; average duration of stay: 7,4days; number (%) of patients positive to the ABCDE approach: 67 (9,6%); average daily number of patients positive to the ABCDE: 2,3; total number of urgeny criteria: 81; average number of urgeny criteria for patient: 1,2.

The distribution of the criteria were: A = 0; B = 27 (33,3%); C = 33 (40,7%); D = 17 (20,9%); E = 4 (4,9%). In 14/67 cases more than one criteria was positive. During the observation period, we had two exitus in which 69% of days of the lenght of stay (16/23) were positive for ABCDE protocol.

Conclusion: The introduction of the ABCDE approach to the characterization and quantification of acutely ill patients in an internal medicine ward may be useful for both clinical and organizational purposes. In our experience, main prevalence of circulation problems and breathin disorders imply the availability of appropriate human and material resources as well as the planning of educational activities of the personnel.

Migraine without aura and disability: the MIDAS questionnaire

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Introduction: Migraine without aura is “a recurring, 24-72 hours, headache-related disability,” frequently overlapping with a number of internal medicine diseases - such as essential hypertension, ischemic heart disease, or metabolic syndrome. Although considered by the World Health Organization among the top nine most disabling diseases, it is still widely diagnosed – either by general practitioners or by internal medicine specialists – as a “simple headache” which can be successfully treated by means of an “ordinary painkiller.”

Objective: To quantitatively assess the quality of life (QoL) impairment in patients suffering from migraine without aura, due to the latter’s remarkable disabling effects, and to point out the severity of a disease which can affect individuals on several levels (psycho-physical, familiar, social, job-related, etc.).

Materials and methods: We enrolled 58 subjects, 49 females and 19 males, aged between 22 and 71 years, suffering from migraine without aura diagnosed according to IHS criteria, 2004, previously admitted to the Headache Study Center of the Department of Internal Medicine of Bari Teaching Hospital. As a background control group, homogeneous as to age and sex, we enrolled 35 patients suffering from diabetes mellitus during the metabolic control stage. All patients were administered an ad hoc questionnaire named MIDAS (Migraine Disability Assessment Scale).

Results: The use of the MIDAS questionnaire showed a significant impairment in three main areas: “school and work,” “housework and family life,” and “social and leisure time,” albeit with different degrees of severity. Specifically, the most significantly compromised areas were those related to school/work proficiency and production capacity. Interestingly, the disability/work activity vs. disability/work inactivity ratio pointed out a higher disabling potential of the disease during “work inactivity” rather than during “work activity.” As final confirmation of the disabling capability of this migraine-related disease, the background control group suffering from diabetes showed overlapping disability levels in the three areas involved in the study.

Conclusions: Our data confirm the disabling potential of migraine without aura and stress the highly negative impact of the disease on the patient’s overall quality of life. Moreover, the disabling potential of the disease bears no significant relation to diabetes mellitus, the latter being a chronic disease involving significantly more complex diagnostic and therapeutic assessment. In our opinion, our data should draw heighten the level of attention to the complex pathophysiological and clinical issues relating to “chronic non-organic pain”, of which migraine is the more frequent expression, and not just “a simple headache”.

Single nucleotide polymorphisms (SNPs) of pro-inflammatory/anti-inflammatory and thrombotic/fibrinolytic genes in patients with acute ischemic stroke in relation to toast subtype

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Background: The genetic basis of complex diseases like ischemic stroke probably consists of several predisposing risk factors, such as genes involved in inflammation and thrombotic pathways. On this basis the aim of our study was to evaluate the role of SNPs (single nucleotide polymorphisms) of some pro-inflammatory/anti-inflammatory and coagulation/fibrinolytic genes in patients with acute ischemic stroke.
Methods: The study population consisted of 144 consecutive Caucasian adult patients who were hospitalized in the Internal Medicine Department at the University of Palermo between November 2006 and January 2008, and who met inclusion criteria. The cases were patients admitted with a diagnosis of acute ischemic stroke, and age-matched (±3 years) control subjects: patients admitted to our Internal Medicine Department for any cause other than acute cardiovascular and cerebrovascular events and for routine check-up examinations. Molecular analysis of alleles at the -308 nucleotide (−308GA/Ga, -1082/-819 haplotypes of IL-10 gene, IL-1RN exon 2 VNTR polymorphism, alleles at the -174 nucleotide (−174G/C) of IL-6 gene, PAI-1675 5G/4G polymorphism, alleles at the -7351 nucleotide (−7351C/T) of tPA gene were undertaken in both patient groups.

Results: We analyzed 96 subjects with acute ischemic stroke and 48 control subjects. We observed a significantly higher frequency of IL-10 1082 AA genotype in stroke patients with a significant risk trend. We also reported a higher frequency in stroke patients with a significant risk trend of the TPA 7351-CT genotype and of IL-1RN VNTR 86bp/2/2 genotype. Moreover, we observed a significant relationship with TOAST subtype only with regard to CC TPA genotype and 1/1 IL-1 VNTR 86bp and lacunar strokes.

Conclusions: Ischemic stroke is a common multifactor disease, which is affected by a number of genetic mutations and environmental factors. Our findings showing a relationship between pro-inflammatory/anti-inflammatory and thrombotic/fibrinolytic genes SNPs and ischemic stroke may contribute to delineate a possible stroke risk profile in subjects with cerebrovascular risk factors.

CD4+CD28- cell peripheral frequency in subjects with acute ischemic stroke: relationship with TOAST subtype and prognostic indicators

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Background: Ischemic stroke is characterized by a cytokine cascade that represents the first step of the progressive “cellular recruitment” that brings the inflammatory cells in the cerebral ischemic injury through the damage to the blood-brain barrier. On this basis, we therefore designed a study to analyze the frequency of peripheral CD4+CD28-cells (CD28 null cells) in patients with ischemic stroke in relation to TOAST subtype diagnosis and to evaluate the relationship with some prognostic indicators and their predictive towards ischemic stroke and TOAST subtype diagnosis.

Methods: We enrolled consecutive hospitalized subjects with acute ischemic stroke at between 1 June 2011 and 1 October 2012. From blood samples of 3 ml of venous blood collected at 72 h after the onset of symptoms was evaluated total and differential white cell component. By mean flow cytometry CD4+ cell and CD4+CD28 null cell frequency was evaluated.

Results: Patients with ischemic stroke compared with controls showed a significantly higher frequency (%) of CD4 + cells in comparison to control subjects and similarly the percentage of peripheral CD4 + CD28- T cells was significantly higher in patients with ischemic stroke compared with control subjects. Patients with cardioembolic stroke also showed a significantly higher frequency (%) of CD4 + cells than those with LAAS and lacunar TOAST subtypes and CD28 null cells compared with control subjects. With regard to the relationship with outcome indicators we observed a significant relationship between peripheral percentage of CD4-CD28 null cells and SSS and NIHSS scores. In order to evaluate the predictive role of peripheral CD4-CD28 null cells towards stroke and TOAST subtype diagnosis, ROC curves showed that CD28- cells are significantly associated with the diagnosis of stroke and we also observed a significant association between the frequency of peripheral CD28-cells and the diagnosis of cardioembolic stroke.

Discussion: Findings of this study confirm the results of a research line concerning immunoinflammatory activation of the acute phase of ischemic stroke, emphasizing a role, as yet not clearly shown, also of the cell-mediated component. Therefore our results allow to extend what has already been reported by our group and by several other research groups as regards the immunoinflammatory activation in terms of inflammatory cytokines, selectins, and adhesion molecules characteristic of the acute phase of ischemic stroke also to the cellular component of inflammation and in particular to the T-cell subpopulations such as CD4+ and in particular CD28 null cells.

A difficult diagnosis in few laboratory tests

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Introduction: Often the correct interpretation of a few laboratory tests avoids expensive instrumental tests. The authors describe an emblematic case report.

Clinical Case: Woman, 44, non-smoker, hypertensive. Five months before hospitalization, because of atypical chest pain she underwent:
- chest X-ray (CXR): fibrotic basal stria;
- thoracic CT: pleural effusion;
- ECG: limits;

Fifteen days before hospitalization, due to the recurrence of symptoms, she underwent:
- CXR: left basal pleural effusion;
- Spirometry: limits;

She is then hospitalized because of swoon and mild dyspnea. Blood tests: PTT: 67s; aPTTr: 2.31; fibrinogen and INR: limits A/B balance: PH 7.5, PCO2 30, PO2 82, SBC 25; (A-A)DO2 30.5

Assuming Pulmonary embolism (PE) in LAC syndrome, we subjected the patient:
- Lung Scintigraphy: suggestive for pulmonary microembolism;
- Thrombophilia tests: DRVVTi 1.87 (Normal Value <1.2), aPC resistance (factor V Leiden) 0.46 (NV >0.7); ACL IgG: 453 (NV <10) Anti-IgG-beta-1GPI: 790 (NV <10) ANA: 5120 (NV <80).

Final diagnosis: Pulmonary microembolism in a patient with thrombophilic syndrome (LAC and factor V Leiden positivity) in SLE.

Discussion: LAC syndrome, often secondary to autoimmune diseases (SLE), is characterized by arterial and venous thrombosis; frequent abortions. Laboratory: LAC positivity or elevated ACA or anti-beta2-GP1 positivity. It should be suspected when there’s an unexplained increase in aPTT with symptoms of VTE.

In our case report, chest pain, swoon, respiratory alkalosis and increase of AaDO2 of the patient are suggestive of PE.

In addition, she has a further increase of thrombophilia: positivity of aPCR coagulation test, to be confirmed by genetic test for factor V Leiden (G1691A mutation).

Conclusions: The prudent request and proper interpretation of few laboratory tests often improve the effectiveness of medical intervention avoiding dangerous delays and and overspending.
Feasibility of a focused ultrasound training course for medical undergraduate students

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Purpose: Ultrasonography, performed by clinicians at the bedside, is a useful tool to answer focused clinical questions, a practice termed “echoscopy”. Undergraduate ultrasound training has not been uniformly formalized yet in this setting. Aims of the study were to assess feasibility of a focused ultrasound training for undergraduate students and the possibility to deliver effective teaching by condensed courses.

Material and methods: A 12 questions questionnaire on theoretical knowledge and image interpretation skills was administered to 58 late-year medical students, who then attended either A) a condensed 4-hour ultrasound course (35 students) addressing suspected pleural/abdominal fluid and abdominal pain in a medical division or B) a 16-hour course (23 students) on the same topics, but with more extended technical, anatomical, clinical information. The same 12 questions questionnaire was administered at the end of the courses. Students undertaking the extended course underwent a practical ultrasound examination on human volunteers. A survey on students’ opinion on ultrasound in undergraduate training was collected.

Results: Pre-course median correct answer rate was 66.7% (range 25-91.7) and 58.3% (41.7-91.7) respectively in the “condensed” and “extended” teaching groups, which increased to 91.7% (66.7-100) for both groups (p < 0.0001) after the courses. Although overall skills improved, this improvement was greater for theoretical knowledge than for image interpretation capability, without significant differences between the two groups. No significant effects on scores of potential previous ultrasound training (surveyed by pre-course questionnaire assessment) were observed. At practical test, 91% students correctly completed abdominal aorta scans and 80% completed scans of hepatorenal/ splenorenal space. At the survey 97% students believed ultrasound was relevant for their training and should be a regular component of their curriculum.

Conclusion: An introductory ultrasound course is effective in improving medical students’ skills, but image interpretation requires more extensive education. Undergraduate ultrasonography training is a feasible goal highly desired by medical students.

The emiss study: Epidemiological Multicenter Italian Stroke Statins study


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Background: Statins have been claimed to be effective in the acute phase of ischemic stroke. The potential positive actions of statins during an acute cerebrovascular ischemic event are two-fold: a neuroproprotective effect, limiting damage and improving recovery; and a preventative effect on early recurrence. To quantify the potential benefits and harms of statins in the acute treatment of cerebrovascular ischemic events, we planned a multi-phase project. Aim of the current paper is to present the second phase of the project, the Epidemiological Multicenter Italian Stroke Statins (EMISS) study.

Methods: EMISS is designed as a multicenter retrospective cohort study. Consecutive adult patients admitted for acute ischemic stroke from January 2010 till December 2011 were included. Primary outcome of the study was rate of statins prescription during hospital stay (any type and any dosage) and identification of any predictor of statin prescription. Secondary outcome was mortality during hospital stay associated with statin use. Univariate and multivariate logistic regression analyses were applied.

Results: On March 2013, a total of 267 patients were included. Mean age was 75.6 years (±12.4, standard deviation). Median hospital stay was 12 days (range, 1-60). One hundred and four (38.9%) patients received statin during hospital stay. Thirty seven (35.6%) started statin the same day of stroke occurrence. At the multivariate logistic regression analysis, statin administration is more frequent in male patients (odds ratio [OR] 2.71, 95% confidence interval [CI] 1.23-5.94), in previous statin users (OR 23.87, 95% CI 7.30-78.04) and in patients admitted in Internal Medicine Departments (OR 5.57, 95% CI 2.50-12.40). Thirty one (11.6%) patients died during hospital stay. Statin use compared to non-statin use was associated with statistically significant reduction of mortality (hazard ratio 0.15, 95% CI 0.03-0.66) at the multivariate Cox regression analysis (adjusted for gender, chronic liver disease, aspirin and Oxford Community Stroke Project classification).

Conclusions: Our data suggests that only a minority of patients admitted with acute ischemic stroke receive statin. Most of them had an atherothrombotic stroke and receive statin for acute treatment more than for secondary prevention. Moreover, the striking better survival associated with statin use suggests an healthy-users effect.


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Mrs S.A. 75 years old
Close pathological anamnesis: lethargy and numbness for a few days. Normal physical examination. Neurological examination: soporose state and temporal-spatial disorientation. Mild arms hypertonia. Normal laboratory exams, except for Na (101mmol/L), K (3.2 mmol/L), natriurina (8mEq/die), kaliuria (3 mEq/die), CPK (1018 U/L), CK-MB (15ng/ml), LDH (622U/L), mild iron deficiency anemia. Normal CT brain, chest X-ray and abdominal ultrasound exam. Thyroid ultrasound: micronodular goiter. Therapy: physiological solution 250 ml containing 2 vials of sodium chloride bid and physiological solution 250 ml containing 1 vial of potassium chloride od.

on the second day: Na+ 107 mmol/L; K+ 3.2 mmol/L;
on the third day: Na+ 123 mmol/L; K+ 3.5 mmol/L;
on the fourth day: Na+ 129 mmol/L; K+ 4.0 mmol/L;
on the fifth day: Na+ 129 mmol/L; K+ 3.8 mmol/L;
on the sixth day: Na+ 139 mmol/L; K+ 3.3 mmol/L;
on the seventh day: Na+ 133 mmol/L; K+ 3.0 mmol/L;
on the eighth day: Na+ 134 mmol/L; K+ 3.6 mmol/L;
on the ninth day: Na+ 138 mmol/L; K+ 3.8 mmol/L;

Profiling of circulating microRNAs in migraine


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Background: MicroRNAs are short, non-coding RNAs and represent a new class of post-transcriptional modulators of gene expression. Several evidences have found a link between the deregulation of miRNAs and human diseases, including cancer, inflammatory diseases, cardiovascular disease and atherosclerosis. The aim of this study was to identify differentially expressed circulating miRNAs in migraine patients.

Methods: 15 female migraine patients and 13 sex and age-balanced healthy controls underwent a circulating microRNA expression profiling. MiR-22, miR-26a, miR-26b, miR-27b, miR-29b, let-7b, miR-181a, miR-221, miR-30b, miR-30e were selected for validation by quantitative Real-Time Polymerase Chain Reaction (qPCR). Furthermore, modulated microRNAs were also evaluated in peripheral blood monocytes from the same patients.

Results: In migraineurs vs controls, a significant expression was found for 4 miRNAs: miR-27b was significantly up-regulated (p<0.001), while miR-181a, let-7b and miR-22 were significantly down-regulated (p≤0.01). Moreover, miR-22 and let-7b down-regulation was also confirmed in blood monocytes. A logistic regression model based on microRNA expression data showed an high accuracy for identify migraine (AUC of ROC curve: 0.960; p<0.001) in our population.

Conclusion: a peculiar circulating miRNAs profile is associated with migraine. Remarkably, these miRNAs were known to be modulated in the setting of atherosclerosis and stroke in humans. The identification of these miRNAs is a first important step towards further profiling of different subgroups of migraineurs, in relation to both the severity of the disease and the response to specific therapies.

Rubella infection during the first 8-10 weeks of gestation?

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A 30-year-old woman is referred to by her gynecologist because she has a suspected rubella infection during of gestation. On examination, the patient was afebrile, well appearing, slightly anxious with a blood pressure of 120/80 mm Hg and heart rate of 85/min. She denies having had before a brief illness with a low-grade fever, lymphadenopathy, and a maculopapular rash that began on the face and spread to the rest of her body resolving spontaneously; and do not vaccinate against rubella.

Rubella in early pregnancy bears a high risk for congenital defects (e.g., cataracts, hearing loss, and heart disease) and for long-term sequelae in the newborn. Therefore, accurate diagnosis is vital if unnecessary abortion is to be avoided.

Results:

- Rubella –Antibody (01/03/2013) Value: Normal value
- Rubella Antibody IgG Method: CMIA Value: Negative
- Rubella Ab IgM Method: ELFA Value: Borderline
- Blood:01/03/2013 Rubella Virus RNA Method: quality PCR Value: Negative

IgG negative and IgM positive indicate possible recent infection. Given this finding and the fact that the patient is asymptomatic, after weeks 2, we have repeat serology that confirm the IgM result.

For investigating this result, suspecting a false positive test, we used modern analytical technologies as ELFA, a reverse transcriptase PCR for detection of rubella virus.

Conclusions: While current anti-rubella IgM ELISAs are relatively sensitive, their specificity are may be limited by cross reactivity with other viruses, i.e. parvovirus B19 and Epstein-Barr virus. Presence of rubella-specific IgM antibodies must be interpreted with caution.

Improving quality is not simple: results of a clinical audit project about patients with community-acquired pneumonia (CAP)

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Aim/Objectives: in-hospital management of Community-Acquired Pneumonia (CAP) patients is affected by high variability leading to both clinical and economical poor outcomes. Scientific literature provides high quality evidence-based documents which can be used to implement quality improving planes based on a clinical audit methodology.

A clinical audit cycle has been created in order to: improve relevant clinical outcomes of CAP patients admitted to Clinica Medica ward; minimize hospital stay-related adverse events; reduce improper use of organizational resources, length-of-stay and overall costs; train medical and nursing staff.

Material and Methods: bidirectional pre-post study: 1.usual practice data retrospective review; 2.implementation of recommendation and training; 3.prospective post implementation data collection and analysis. Inclusion criteria: patients admitted with CAP diagnosed according to IDSA 2001 criteria from April 2011 to April 2013. Exclusion criteria: cancer chemotherapy or immunosuppressive treatment, age ≤18, HIV or A/H1N1 influenza, transplant recipients. Referral guideline: IDSA/ATS Guidelines 2007. Quality indicators: 8 process and outcome indicators were defined and monitored. Implementation tools: training-retraining, use of ad hoc pocket reminders, posters. A dedicated website (www.polmonitiancona.net) was built too.

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**Results:** Clinical practice between the two periods of this study got only poor improvements, both for the process and for the outcome indicators. The relative low number of cases (~40/y), the particular setting of this study (teaching hospital) and the probably too soft implementation tools are the main obstacles to the generalizability of results.

**Discussion and Conclusion:** 1) Light implementation tools could be more effective if used in easier settings and with a more prevalent disease, otherwise more invasive tools could be used; 2) the employment of audit instruments in modifying usual practice is difficult; 3) with the aim of verifying these points, the extension of the experimentation to other setting is in progress.

**Charcot neuroarthropathy in a patient with chronic alcohol abuse**


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**Introduction:** Charcot neuroarthropathy is a destructive condition producing joint instability, a rocker-bottom foot deformity with development of bony prominences. It is often associated with diabetes mellitus and leads to ulceration and, ultimately, to lower extremity amputation (1). Here we describe a case of a patient with Charcot neuroarthropathy due to chronic alcohol abuse.

**Case:** A 43 years old male, with a history of alcoholism lasting more than 20 years, hepatitis C infection, liver cirrhosis (Child A5, MELD 9), and ulcers of the lower limbs since 5 years, was admitted to our Internal Medicine inpatient unit because of the onset of fever (max 38 °C) since two days. His medications included omeprazole, spironolactone and diazepam. Family history was not significant. The amount of alcohol consumed was about 10-12 drinks per day since about 20 years. Clinical examination revealed flatfoot, lateral deviation of toes, two deep granular ulcers on plantar surface of left foot, and one on right plantar surface. Pedal pulse was palpable, capillary fill time was immediate, and abnormalities in sensory were present. Blood tests showed microcytic anemia, thrombocytopenia, and normal renal function. Hepatitis C viral load was 295.858, other tests such as serum electrophoresis, cryoglobulinemia, B9 and B12 levels were normal. Arterial, venous and soft tissue ultrasonography were negative respectively for arterial stenosis, thrombotic and inflammatory events. The patient was subject to plain radiographs that excluded signs of osteomyelitis and showed osteo-articular deformity of the foot, just like a picture of Charcot neuroarthropathy. Intravenous cefazidime and vancomycin was started with regression of fever. No effects on ulcers were reached. After consulting the orthopaedist, we decided for the amputation of left foot. After amputation the patient was discharged in good clinical conditions and started a rehabilitation program.

**Discussion:** The pathogenesis of Charcot neuroarthropathy includes osteopenia, bone destruction and joint subluxation, due to abnormal stress on the bones and joints related to muscle imbalances (1). Chronic alcohol abuse has been described to be a cause of Charcot neuroarthropathy due to alcohol-induced osteopenia, impairment of bone repair and alcoholic neuropathy (alcohol toxicity, malabsorption of thiamine and other vitamins). A limited number of case of alcohol-induced Charcot neuroarthropathy have been described, being a rare complication of chronic alcohol abuse. First sign of Charcot arthropathy is a “red, hot and swollen” foot, usually painless, mimicking cellulitis or deep venous thrombosis (2). The treatment includes interventions to reduce alcohol intake and promote abstinence, vitamin supplementation (thiamine, folates and B12), protective footwear and routine foot care. Clinicians with expertise in alcohol-related diseases should screen alcoholic patients chronic with severe neuropathy for Charcot arthropathy, to prevent feet ulcerations, soft tissue or bone infection and amputation.

**References:**


**Nephrology**

**Urinary albumin excretion is associated to the presence and the onset of renal cysts in patients with essential hypertension**

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Studies on association between simple renal cysts and essential hypertension are controversial and mechanisms of this association are not clear. The aim of this study was to investigate clinical and biochemical differences between subjects with or without simple renal cysts in a large group of essential hypertensive patients. In 783 patients with essential hypertension (55% treated) we evaluated clinical characteristics, anti-hypertensive drugs, renal function, urinary albumin excretion, plasma aldosterone and active rennin levels. Presence of simple renal cysts has been established by renal ultrasound or CT scan. In 80 patients the same evaluations have been repeated after a follow-up of 7±2 years. Simple renal cysts have been documented in 203 (26%) of subjects, and was independently associated with age (P<0.001), male gender (P=0.008), urinary albumin excretion (P=0.014) and use of angiotensin II receptor blockers (P=0.035). These associations were founded even in the subgroup of 355 never treated patients. There was no association between presence of simple renal cysts and blood pressure levels, glomerular filtration rate, aldosterone and renin levels. The onset of new simple renal cysts was independently associated with plasma creatinine at the baseline and urinary albumin excretion at the end of follow-up. In conclusion, in patients with essential hypertension presence of simple renal cysts is independently associated with urinary albumin excretion level but not with blood pressure severity, renal function or parameters of renin-angiotensin-aldosterone system.

**Renal function and in-hospital mortality due to acute cerebrovascular events: the database of hospital admissions of the Emilia-Romagna region of Italy**


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**Background:** Stroke is a major medical and social problem, and represents a major cause of death and of disability both in the developed and developing countries [Norrving & Kissela, Neurology 2013]. In the period of time included between 1990 and 2010, the years of life lost due to premature mortality due to stroke increased by 17-28% [Lozano et al, Lancet 2012].
Although the relationship between renal dysfunction and stroke is well known [Fabbian et al, Clin Appl Thromb Hemost 2012], precise data about in the Italian clinical practice is still matter of debate. The aim of this study was to evaluate in-hospital mortality due to stroke and renal dysfunction in the Emilia-Romagna region of Italy.

**Methods:** We considered all cases of stroke (first event, both ischaemic and haemorrhagic) recorded in the database of hospital admissions for the Emilia-Romagna region, Italy, from 1999 to 2009. The inclusion criterion was the presence, as a main discharge diagnosis, of acute stroke according to International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Age and diagnoses of chronic kidney disease (CKD), end-stage renal disease (ESRD), atrial fibrillation (AF) were collected. In-Hospital mortality for stroke was the main outcome indicator considered. For statistical analysis, Charlson comorbidity index (CCI) for administrative database was used for statistical calculations, with the exclusion of renal dysfunction and cerebrovascular disease, and multivariate logistic regression analysis were used.

**Results:** Along the considered period, 186,219 cases of first episode of stroke were recorded, of whom 1,626 (0.9%) had CKD, and 819 (0.4%) had ESRD. The main age of subjects without renal dysfunction, with CKD, and with ESRD was 76±12, 75±13 and 76±12 years, respectively (p<0.001).

In-hospital mortality in the three groups of patients was 11.6%, 33.9% and 30.6% (p<0.001) respectively.

In-hospital mortality was independently associated with age (OR 1.001 [95% CI 1.000-1.003], p=0.017), CKD (OR 3.715 [95% CI 3.346-4.125], p<0.0001), ESRD (OR 3.413 [95%CI 2.938-3.964], p<0.0001), AF (OR 1.611 [95%CI 1.551-1.673], p<0.0001), CCI (OR 1.078 [95%CI 1.062-1.094], p<0.0001).

**Conclusions:** In agreement of our previous findings from our group, demonstrating an association between in-hospital mortality due to myocardial infarction and renal impairment [Fabbian et al, Int Urol Nephrol 2012 Epub], this seems to be true also for in-hospital mortality due to acute cerebrovascular events. Moreover, patients with renal impairment have multiple co-morbidities, especially in elderly subjects, capable either to worsen diseases and be worsened in their renal function at the same time [Smyth et al, Age Ageing 2013]. In addition, many general medical inpatients (approx. 30%) have just a reduced kidney function on admission, and mortality rises with it [Yong et al, QJM 2013]. In conclusion, as for our data, acute stroke, both ischaemic and haemorrhagic, was independently associated with age, comorbidity, atrial fibrillation, and different degree of renal dysfunction.

**ANCA-negative pauciimmune crescentic glomerulonephritis in a 69 year-old patient: an unusual case**

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In the majority of patients pauci-immune crescentic glomerulonephritis is a manifestation of ANCA-associated vasculitis. However, in 10-30% of patients circulating ANCAs are negative. These patients are usually younger, and present a different clinical spectrum characterized by fewer constitutional (e.g. fever, weight loss, myalgia and arthralgia) and extrarenal symptoms than those who are ANCA-positive.

We report the case of a 69 year-old woman who presented to our department with diarrhea and vomiting lasting 5 weeks associated with increased serum creatinine and blood urea levels at routine blood examinations. Her family history was positive for cardiovascular and immunological (SLE) diseases. The patient referred hypertension in therapy with ace-inhibitors, dyslipidemia in the pathological anamnesis and, about 20 years before, an episode of idiopathic alopecia associated with cutaneous lesions, then spontaneously regressed. Routine blood and urine tests showed normal renal function and negative urinary sediment up to 2009. She occasionally assumed nefrotic drugs (NSAIDs) over the last two months to alleviate pain due to a knee replacement. At the First Aid Department, laboratory findings showed as follows: serum creatinine 12.8 mg/dL, BUN 57 mg/dL, Na 134 mmol/L, K 4.44 mmol/L, P 8 mg/dL; emogasanalysis revealed pH 7.35, HCO3 18.6, BE -9. Renal ultrasonography showed “normal size of kidneys, with a cortical-medullary thickness preserved and absence of dilatation of the urinary tract”. For the occurrence of progressive dyspnea, anuria and more severe hypertension, renal replacement therapy by femoral central venous catheter was started. Upon arrival at our department, the patient was in critical clinical status, the high blood pressure level was treated with nitrates therapy and it was necessary to continue with a three time a week renal replacement therapy, which led to improved clinical conditions. During the hospital stay, a second kidney Doppler ultrasonography showed hyperchoic bilateral parenchyma with reduced thickness and increased resistive index. Repeated urine tests revealed persistent active sediment and proteinuria 1656 mg per 24 hours. Autoimmunity profile (ANA, ds-DNA, ENA, LAC, p- and c-ANCA, C3, C4) showed a rise of C3 component with IgE and IgM increased serum level. Renal biopsy was performed showing diffuse extracapillary proliferative glomerulonephritis, cellular crescents (13%), cellular and fibrionic crescents (74%), areas of interstitial fibrosis, tubular atrophy and lympho-mononuclear infiltration (Fig.1). Direct IF resulted negative. ANCA test was appraised for a second time by both Indirect Immunofluorescence assay and antigen-specific ELISA resulting negative. High-resolution chest CT was also performed in order to evaluate a systemic involvement of the disease, with a negative result. The diagnosis was ANCA-negative pauciimmune crescentic glomerulonephritis (renal vasculitis). Two doses of steroid bolus (1 gr) were administered monitoring urinary sediment and proteinuria/24h, progressively reduced. This case is an unusual presentation of ANCA-negative pauciimmune crescentic glomerulonephritis in a 69 years old woman with acute kidney disease onset. Anamnesis was negative for vasculitic manifestations and only the renal biopsy highlighted an already advanced stage of renal damage. A pre-existing but undiagnosed renal injury has likely developed insidiously as evidenced by the prevalence of fibrionic crescents at biopsy with the superimposed recent active lesions.

ANCA negativity seems to be associated with increased severity of glomerular and poor renal outcome. It is reported a more aggressive clinical course in advanced age at onset of disease. Therefore the high mortality rate, especially in older patients with ANCA-negative vasculitis, underlines the importance of an early and accurate diagnosis.

![Figure 1. Renal biopsy PAS staining](image-url)
Gender difference in diagnosis of acute kidney injury in cirrhotic patients: AKIN versus conventional criteria

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Acute kidney injury (AKI) has a negative impact on both pre and post-transplantation outcomes, associated with increased morbidity and mortality.

Conventional diagnostic criteria for AKI in patients with end-stage liver disease awaiting liver transplantation (ESLD-wOLT) include an increase in serum creatinine (sCr) >1.5 mg/dL. (International Ascites Club Criteria). The MELD score, used to prioritize allocation of liver grafts, including INR, total bilirubin and sCr, sets sCr=1 mg/dL as standard value. Several studies have confirmed that sCr in patients with ESLD-wOLT is influenced by several underlying factors, such as decreased hepatic creatine synthesis and reduced muscle mass, and may be subjected to inaccuracy depending on the assay method and validation. This variability may be magnified in women because for a given level of creatinine, on average, women have a lower glomerular filtration rate than men due to their reduced muscle mass. This sex-related difference in creatinine concentrations may partially account for gender disparities in outcomes on the waiting list in the MELD era.

AKIN criteria (KDIGO 2012) have been validated to define and stratify AKI on the basis of deviation of sCr from baseline rather than absolute values: increase in sCr≥150% from baseline or ≥0.3 mg/dL (Stage1), sCr≥200% from baseline (Stage2), sCr≥300% from baseline or sCr≥4 mg/dL (Stage3).

The aim of the study was to compare the prevalence of pre-OLT AKI in patients with ESLD-wOLT based on AKIN vs conventional and MELD criteria.

This is a single-centre retrospective study of 77 patients (63M/14F), mean age 55±9y, assessed from listing to transplant (2008-13). Eleven and 6 patients presented undiagnosed AKI with conventional and MELD criteria respectively vs. AKIN criteria (negative predictive value was 82.5% and 89.7%, respectively). Among these patients, women were 45% and 50% vs 14% and 16% among patients diagnosed with conventional and MELD criteria respectively (p 0.006 e p 0.024). No differences were detected for age, BMI.

AKIN criteria improve diagnosis of AKI as compared to conventional criteria. The diagnosis of AKI in ESLD based on AKIN criteria was implemented especially in women: about 50% of them would have not been recognized outside AKIN criteria.

Female gender is recognized to be disadvantaged in the MELD era because of reduced serum creatinine concentrations with increased short-term mortality vs men and lower MELD scores and priority for transplantation.

Prevention of kidney injury following crush syndrome: best approach on the field

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Introduction: The crush syndrome is the second most frequent cause of disaster-related mortality after earthquakes. The incidence of this syndrome can rise up to 2–5% overall in disaster victims, whereas it takes a lot of effort to extricate them from the rubble. Hence, it would be deplorable and even counter productive if the proper therapeutic possibilities would not be offered, especially in the case of acute kidney injury (AKI), which is one of the most common potentially lethal but also frequently reversible complications. The clinician should be prepared to address issues of crush syndrome proactively and aggressively. In this paper we conduct a brief systematic literature review to evaluate evidence-based recommendations for the prevention of rhabdomyolysis-associated acute renal failure (ARF) in the field hospitals.

Method: the MESH term “crush syndrome” in PubMed (until May 2013) were searched with no language restrictions. Studies selected dealt with treatment of rhabdomyolysis (crush syndrome) or prevention of ARF in patients with rhabdomyolysis.

Results: Twenty-seven studies met the inclusion criteria. No controlled trials compared intravenous fluid administration plus sodium bicarbonate to fluid administration alone. Three concluded that there was no significant difference in the rates of ARF between patients receiving and those not receiving sodium bicarbonate; however, urine alkalinization was not documented. Eight investigations concluded that delayed fluid administration increased the risk of ARF. No controlled study compared volumes of fluid administered or targeted urine output goals. Fluid type, therapy duration, and monitoring parameters varied widely; 4 used a urine output goal in adults of more than 300 mL/h or 300 mL/h or more. No evidence supported a preferred fluid type or that sodium bicarbonate with or without mannitol was superior to fluid therapy alone.

Conclusions: Intravenous fluids should be initiated as soon as possible, preferably within the first 6 hours after muscle injury, at a rate that maintains a urine output in adults of 300 mL/h or more for at least the first 24 hours. Sodium bicarbonate should be administered only if necessary to correct systemic acidosis and mannitol only to maintain urine output of 300 mL/h or more despite adequate fluid administration. Currently the guidelines suggest: Before extrication: even while the victim is still under the rubble initiate isotonic saline at a rate of 1000 mL/h in adults and 15 to 20 mL/kg/hr in children for 2 hours; then, reduce to 500 mL/hr in adults and 10 mL/kg/hr in children, or even lower. Avoid solutions containing even small amounts of potassium. During extrication: Administer intravenous isotonic saline at a rate of 1000 mL/hr during the period of extrication (usually 45-90 min). If extrication takes longer than 2 hours, reduce the rate of fluid administration so as not to exceed 500 mL/hr, and adjust its rate depending on age, body weight, trauma pattern, ambient temperature, urine production, and amount of overall estimated fluid losses. Bring to the field hospital as soon as possible. After extrication in ROLE2 o ROLE3: Check the victim for a six hour period regularly while administering 3 – 6 L of fluid. Check the victim for a six hour period regularly while administering 3 – 6 L of fluid. Individualize volume of fluids considering demographic features, medical signs and symptoms, environmental and logistic factors. Evaluate urinary volume and hemodynamic status to determine further fluid administration.

Left ventricular hypertrophy, cardio-thoracic ratio and hyperparathyroidism in patients with end stage renal disease undergoing hemodialysis and peritoneal dialysis


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Introduction: Cardiovascular disease is the most common cause of morbidity and mortality in patients with end-stage renal disease (ESRD) treated with dialysis. Hypertension in dialysis patients is an important risk
Personalized nutritional therapy in patients with chronic kidney disease: metabolic state, body composition, inflammation and atherosclerosis markers

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Introduction: Chronic kidney disease (CKD) alters the metabolism of several minerals, thereby inducing bone lesions and vessel-wall calcifications that can cause functional impairments and excess mortality. Factors that affect bone include acidosis, chronic inflammation, and nutritional deficiencies. The Malnutrition-Inflammation-Atherosclerosis (MIA) syndrome is already a tendency when the Glomerular filtration rate (GFR)< 50 mL/min, Protein-energy wasting (PEW), a term proposed by the International Society of Renal Nutrition and Metabolism (ISRNM), refers to the multiple nutritional and catabolic alterations that occur in CKD and associate with morbidity and mortality. This syndrome is caused by uremia-induced alterations such as increased energy expenditure, persistent inflammation, acidosis, and multiple endocrine disorders that render a state of hypermetabolism leading to excess catabolism of muscle and fat. Related studies also support that correction of metabolic acidosis with dietary acid reduction slows CKD progression.

Aim: The purpose of this study was to verify the effects of a personalized nutritional intervention in patients with CKD stages III/IV KDOKI.

Materials and methods: We have studied 16 patients (9 female and 7 male) with an average age of 53.7 (±12.9 years). These patients have been visited before the nutritional intervention and in a later stage, after 3,6,9,12 months of treatment. We have evaluated and measured the lipid, inflammatory markers, electrolytes, mineral metabolism serum, renal function, proteinuria, azoturia 24h and markers of atherosclerosis (carotid intima media thickness (cIMT) and flow mediated dilation brachial artery (baFMD)). Furthermore we have done a Blood gas analysis, evaluated the anthropometric parameters and body composition by DEXA. The data was subjected to a statistical analysis with SPSS software version 17.0.

Results: A decline of the values of blood urea nitrogen have been observed (F=8.186, P=0.008). Furthermore it is also observed that the phosphate serum (\( \chi^2=8.73, p=0.068 \)) and the C-reactive protein (\( \chi^2=12.71, P=0.013 \)) have reduced. The levels of serum creatinine, albumin and total serum proteins have remained constant and IMT (F=0.621, P=0.562) and

![Figure 1. Profile Plots. A repeated measures ANOVA(Sphericity Assumed) determined that mean of HCO3- (mmol/L) concentration differed statistically significantly between time points (F(4,36)=4.680, P=0.004).](image-url)
FMD (F=0.460, p=0.764) have remained unchanged in the follow-up. No modifications have been observed regarding the values of the pH (F=0.866, p=0.493), however there was an improvement of the values of the bicarbonate (F=4.680, p=0.004). The muscle strength assessed by Hand Grip has improved and the bioimpedance and the DEXA have revealed a non-significant reduction in fat mass and maintenance of lean mass.

**Discussion:** The nutritional intervention has been developed by adopting the prescription to the degree of renal dysfunction, but also adapting it to the BMI and the case history of every individual patient. By differentiating the degree of restriction of protein and energy intake, a greater compliance can be achieved and therefore a greater efficiency and effectiveness of the treatment, preventing the MIA and PEW-syndrome, the bone lesions and vessel-wall calcifications. Recent studies suggest that metabolic acidosis mediates nephropathy progression, and its treatment with the comparatively inexpensive and well tolerated intervention of dietary acid reduction holds promise to be an additional kidney-protective strategy in CKD management.

**Conn’s disease misdiagnosed in diabetic patient with severe hypokalemia and asthenia**

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Primary hyperaldosteronism (PHA) consisted in an increased aldosterone synthesis which is independent of the Renin Angiotensin Aldosterone System (RAAS). PHA is due to the overproduction of the mineralocorticoid hormone aldosterone by the adrenal glands from adrenal hyperplasia, adrenal adenoma (Conn’s disease) and adrenal carcinoma. Patients may present without the classical Conn syndrome trias (hypertension, hypokalemia, metabolic alkalosis) and hypernatremia. The PHA, considered by many physicians as a rare form of hypertension, is the most common cause of secondary hypertension. The plasma aldosterone to plasma renin activity ratio (ARR) revealed that PHA prevalence in hypertensive patients is approximately 5-13%. We report a case of PHA in a 50-year-old man who presented to our observation with uncontrolled hypertension (administrated amlodipine 10 mg daily), severe asthenia, polyuria, nycturia and surprisingly with hypokalemia (2.9 mEq/L) despite 5 KCl 600mg tablets daily supplementation therapy. Anamnesis revealed that patient was previously gone to emergency department with asthenia and limbs pain. The laboratory examinations showed extremely low serum potassium (1.5 mmol/L), metabolic alkalosis (pH 7.55, HCO3- 38mmol/L, pCO2 42 mmHg). Electrocardiogram (ECG) showed Q-T interval elongation and abnormal U wave. During hospitalization serum 8:00 AM cortisol levels resulted in range (20.9 µg/dL) but assessment of ARR was not performed. The histological report confirmed that also the young age of the patient alone should raise the promptly research of Conn’s disease.

**A patient with renal artery fibromuscular dysplasia and hyperaldosteronism. Never judge a book by its cover**

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We have studied a 37 years old Caucasian woman was admitted of the hospital with high blood pressure values of about 140/100 mmHg four months ago, associated with intense frontal headache. As clinical history she referred maternal familiarity for arterial hypertension. The patient was already receiving therapy with ramipril 10 mg and bardipine 10 mg without succeeding in lowering the blood pressure. In the meanwhile of these months of therapy the patient also reported an episode of chest pain associated with short-term dyspnea, non radiating and regressing spontaneously. Therefore a performed ECG and echocardiography excluded a cardiac origin of the chest pain. Noticing that the blood pressure was not influenced by the therapy with 2 different classes of antihypertensive drugs and also the young age of the patient, we decided to perform a screening for the secondary causes of hypertension. Thus a color-Doppler ultrasonography of renal arteries and serum and urine research for aldosterone, renin, cortisol, catecholamines, thyroid hormones, vanil mandelic acid and metanephrines were prescribed. In order to not influence this screening a therapy modification was done as follows: ramipril intake was interrupted and doxazosin 2 mg/day was initiated, bardipine dosage was increased to 20 mg/day. The color Doppler ultrasonography of renal arteries showed a fibromuscular dysplastic process of the right renal artery with a good perfusion of the renal parenchyma. The blood and urine analyses showed an increased concentration of serum and urinary aldosterone of 475 pg/ml and 31 µg/24h respectively and a decreased value of renin concentration of 6 pg/ml. Serum thyroid hormone and urinary vanil mandelic acid concentration were in normal ranges. After 3 weeks of this therapy the patient refered to have voluntary interrupted the intake of doxazosin and reduced the dosage of bardipine for the occurrence of fainting episodes. Thus at this point having the clinical basis for hypothesizing a diagnosis of an adrenal adenoma, a new therapy modification was made initiating spiranolacete 25 mg/day and reincreasing the dosage of bardipine to 20mg/day, furthermore also a MRI examination was prescribed. An ABFM was then performed showing a normal 24h blood pressure control. The MRI examination confirmed our hypothesis showing the presence of a nodular formation of 9 × 16 mm at the right adrenal gland. We decided then to repeat the blood and urine analyses that reconfirmed the increased concentration of serum and urine aldosterone of 548.3 pg/ml in orthostatism and 278.4 µg/24h respectively with the serum renin activity in orthostatism decreased to 0.21 ng/ml/h. The serum and urinary catecholamines’s concentrations were normal. We proceeded then to schedule a surgical operation of right adenectomy. The histological report confirmed the nature of the nodular formation as an adenoma. Although, primary hyperaldosteronism is frequently associated with resistant hypertension (defined by the 2013 ESC guidelines as type of hypertension refractory to treatment that includes attention to lifestyle measures and the prescription of at least 3 different drugs including a diuretic in adequate doses), this case demonstrates that also the young age of the patient alone should raise the clinical suspicion of primary hyperaldosteronism. By this way we suggest that an adequate research for secondary causes of hypertension should al-
ways be done in young patients even if they have familiarity for it or don’t present a resistant form.

**Type of cardiorenal syndrome and clinical outcome:**
a follow-up study of a cohort of elderly subjects admitted to an internal medicine unit


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**Background:** The cardio-renal syndrome (CRS) is a heart and kidneys disorder in which the acute or chronic dysfunction of one can induce an acute or chronic dysfunction of the other [Ronco, J Am Coll Cardiol. 2008]. This syndrome is divided into 5 types in relation to the interaction between two organs, that is due to hemodynamic and neurohumoral factors [Gil, Curr Opin Hypertens 2005]. In a previous study we described the clinical features of CRS, and type 1 appeared to be more frequent than the other types [Fabbian, Open Cardiovasc Med J 2011]. The aim of our study was to evaluate the prognosis of different types of CRS in a cohort of patients discharged from an internal medicine unit.

**Patients and methods:** We followed-up patients discharged from June 2007 to December 2009 with diagnoses of CRS type 1 to 5. All-cause mortality was our end-point, and mean follow-up was 2.42±1.37 years. Factors independently associated to all-cause mortality were analyzed.

**Results:** 374 patients (51.9% males) were included. Their mean age was 79.5±7.8 years, and 144 deaths (38.7%) were recorded. Survivors and deceased subjects, with different types of CRS, are reported in the table. Cox regression analysis showed that all-cause mortality was independently associated with age (HR=1.049, 95% CI 1.023-1.075, p <0.001) and glomerular filtration rate calculated at the time of admission (HR=0.972, 95% CI 0.957-0.988, p <0.001).

<table>
<thead>
<tr>
<th>Type</th>
<th>Deceased</th>
<th>Survivors</th>
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<tbody>
<tr>
<td>Type 1 (44.9%)</td>
<td>93</td>
<td>74</td>
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<tr>
<td>Type 2 (23.2%)</td>
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<td>Type 4 (7.5%)</td>
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<td>10</td>
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</tr>
<tr>
<td>Type 5 (3.5)</td>
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<td>8</td>
<td>0.085</td>
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</tbody>
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**Conclusion:** Even if different types of CRS appear to have different survival curves, in these groups of elderly patients the main risk factors for all-cause mortality remain age and severity of renal failure.

**Chronic kidney disease in subjects with acute ischemic stroke:**

**Introduction:** Chronic kidney disease (CKD) might be an independent risk factor for stroke, especially for cardiogenic and atherosclerotic subtypes (1). Patients with CKD, in particular the ones affected by end-stage renal disease (ESRD) have markedly advanced vascular disease if compared to the general population. Dialytic support has been shown to be an additional risk factor for stroke (2). Moreover, incidence and prevalence of atrial fibrillation in ESRD patients are higher than in the general population and associated with an increased risk of stroke and mortality (3). Several authors reported more severe atherosclerotic disease of the carotid arteries among ESRD patients than in subjects with normal renal function.

**Objective:** Our aim was to examine the association between estimated glomerular filtration rate (GFR) and ischemic stroke outcome and to assess whether CKD and its severity affect stroke outcomes in a small cohort of unselected patients with acute stroke.

**Patients and methods:** We retrospectively collected data from patients’ files discharged with “stroke” as first diagnosis from our Internal Medicine Department in the period between 01/01/2012 and 30/04/2013. Age, sex, length of hospital stay (LOS), renal function (expressed as creatinin clearance)
and in-hospital death were considered for the analysis. The association between renal function and LOS was explored with multiple regression models.

**Results:** We enrolled 149 patients affected by ischemic stroke (47% males) with a mean age of 81.66 years old (SD ±8.72 years). CKD was found in 119 patients (79.86%). Our analysis outlined an inverse logarithmic relationship between creatinin clearance and LOS ($r^2=0.915$, $p<0.05$). We did not find any relationship between CKD, stroke and death in this series, probably for the short outcome period (from admission to discharge) and the small dimensions of the analyzed cohort.

**Conclusions:** In this case series, CKD has been found to be an important predictor of increased and complicated LOS in patients affected by acute ischemic stroke. These results confirm the importance of this condition as a marker of comorbidity, especially among elderly subjects.

**References:**

**A complicated kidney**

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Patient of 62 years old admitted at the hospital for persistence from 8 days of diffuse abdominal pain associated with fever (38 ° degrees), an episode of hematuria with dysuria, nausea and vomiting. Patient history is characterized by recent episode of femoral fracture treated with prothesis, polymyalgia rheumatic in steroid therapy, primary hyperparathyroidism complicated by nefrocalcinosis, bilateral inguinal hernia, paramedian supra umbilical hernia, bilateral adrenal adenomas, splenectomy for angiomatosis and cholecystectomy. In the light of the clinical context suggestive of cholangitis (WBC 34,000, GOT 122 U/L, ALT 135 U/L, GGT 291 U/L, Bil.Dir. 0.77 mg/dL, CRP 10.2 mg/dL, Procalcitonin 6.3 mg/mL, ALK 198 U/L) patient is treated with piperacillin/tazobactam obtaining a partial benefit. Subsequently is replaced initial therapy with meropenem thanks to a single positivity of blood culture for E.Coli (negative in subsequent blood cultures). Meanwhile we are observing an acute episode of anemia without significant sources of macro and microscopic bleeding (negative EGDS, SOF negative and colonoscopy positive for diverticulosis of the sigma) and left lower limb thrombosis. For the persistence of fever and symptoms without any laboratory, culture and instrumental test that find the origin of the infection we execute an MRI that showed abdominal polycystic disease widespread, accordingly we have enhanced the antibiotic therapy inserting levofloxacin and achieving a rapid clinical and instrumental improvement. After a few months the patient performed an abdomen MRI of control that showed that the reduction in volume of some renal cysts and the appearance of proteinaceous material inside other; therefore the final diagnosis is: polycystic kidney disease complicated by anemia, sepsis and cholangitis. Polycystic kidney disease is associated with extrarenal alterations so should be considered a systemic disease. Are documented cysts in other organs, especially the liver, the gastrointestinal abnormalities such as inguinal hernias diverticulosis of the colon and cardiovascular abnormalities, intracranial aneurysms and valvular abnormalities. The clinical picture is dominated by changes in renal function such as hypertension, hematuria but often have anemia without hematuria as the cyst does not communicate with the urinary tract, urinary tract infections especially by E. coli species, nephrolithiasis, renal pain and kidney failure. At diagnostic completion the patient has performed brain MRI which showed the presence of some intracranial aneurysms and renal cysts were found also to the relatives of the first degree.

**Non-adherence to immunosuppression in an asian living donor renal transplant recipient: is just a rejection problem?**

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Non-adherence to immunosuppression is a common and significant problem in renal transplant recipients accounting for one of the major causes of early and late renal acute rejection and allograft failure. In renal transplantation it has been shown that recurrence of the primary nephropathy occurs in 10-20% of kidney grafts and accounts for graft failure in up to 50% of the cases. Recurrences mainly concern glomerulopathy such as IgA nephropathy, particularly common in Asian countries. We describe the case of a 52 years old Asian woman who received a related living donor kidney transplantation in October 2006. She began immunosuppressive therapy with mycophenolate, steroids and cyclosporine, replaced with tacrolimus in December 2006. From January 2007 the patient is followed by our outpatient nephrology, blood tests and imaging showing good function of transplanted kidney (serum creatinine 0.5-0.7 mg/dL). Since 2011 the patient did not longer perform outpatient visits. In February 2013 she was admitted to the emergency department for anuria and a general maculopapular pruritic rash and came back to our attention. Laboratory findings showed: serum creatinine 20.8 mg/dL, BUN 148 mg/dL, Na 126 mmol/L, K 5.0 mmol/L, P 9.2 mg/dL, glucose 132 mg/dL. The emogas analysis revealed severe metabolic acidosis (pH 7.13, HCO3- 8.5 mEq/L). Chest x-ray showed multiple nodular thickening partially confluent in the right lung. Metabolic acidosis was corrected, antibiotic and renal replacement therapy (by femoral central venous catheter) were started, with improvement of blood test during the following days. By a further anamnestic investigation, the patient reported that she had independently stopped all immunosuppressive maintenance therapy since 3 months. We performed a Doppler ultrasonography of the transplanted kidney that showed increased size (maximum longitudinal diameter of 143.3 mm) and regular shape. Reduction of cortico-medullary differentiation with hyperechoic cortex. No urinary tract dilatations. Patent renal vein with normal flow in the absence of wall alterations. Iliac-renal anastomosis and renal artery were patent. IR 0.70. PCR analysis for HSV, CMV, EBV, VZV, BKV resulted negative and the cross match was negative too. In the suspicion of acute allograft rejection a first renal biopsy was performed. It showed the presence of acute T-cell mediated rejection (t3, i3, v1, g0) with mild/moderate intimal arteritis and negative immunofluorescence (IF). C4d staining was negative. (Figure 1) A first high dose steroid bolus was administered with resumption of diuresis and reduction of the transplanted kidney size (maximum longitudinal diameter of 133.3 mm). At the same time immunosuppressive therapy was reintroduced, maintaining tacrolimus and mycophenolate levels into the therapeutic range. The patient underwent to a second high dose steroid bolus with improvement in overall clinical condition and blood tests (creatinine 5.3 mg/dL, BUN 61 mg/dL, Na 130 mmol/L, K 4.56 mmol/L). One more renal Doppler ultrasonography showed a further reduction of transplanted kidney size compared to the previous control (maximum longitudinal diameter of...
133.3 mm). Moreover renal replacement therapy was stopped. After a third high dose steroid bolus, however, serum creatinine increased again. A second biopsy of the transplanted kidney showed partial resolution of T-cell mediated rejection features (grade borderline: I1, I1, V0, G0) associated with interstitial fibrosis. IF negative in the previous biopsy, showed the onset of diffuse mesangial granular IgA deposits as for diffuse proliferative IgA glomerulonephritis. C4d staining was occasionally positive in peritubular capillaries in the context of the major areas of fibrosis. (Figure 2) Despite improvement in the rejection features, the second biopsy showed IgA nephropathy, probably as recurrence of the kidney native IgA nephropathy. On the basis of this result and the persistent poor patient’s compliance we suggested chronic renal replacement therapy after arteriovenous fistula creation. In conclusion the non-adherence to immunosuppressive therapy is not only the major cause of rejection but it can lead to recurrence of the primary nephropathy resulting in a synergic negative impact on outcome.

Oncology

A very big neck

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A 73 years old man was admitted to our department because of a sudden and rapid enlarging neck mass. The patient reported a starting enlargement 40 days before. He lived in a rural village, was a farmer and a 20 cigarettes per day former smoker for 2 years. Physical examination revealed a very large painless neck mass, swelling of the face, upper extremities and trunk, with hoarseness and dysphagia; dullness on thoracic percussion with absence of vesicular murmur at the lung left base. There were no other symptoms such as fever, weight loss, cough or asthenia and his vital signs were normal. The results of routine laboratory findings were within normal ranges, except for a neutrophil leukocytosis (WBC: 18540/mmc, neutrophils: 15230/mmc), an α1 and α2 increase and a C-reactive protein 2.64mg/dl. Thyroid function tests and tumor markers were normal, only serum thyroglobulin was 1077 ng/ml (reference range: 1.4-78 ng/ml). Chest X-ray documented the presence of opacity in the base of the right lung and a small pleural effusion on the left side. Thyroid ultrasound revealed several small laterocervical lymph nodes and a diffuse thyroid enlargement with dishomogeneous pattern for various nodules, the mayor one (greater diameter 10 cm) with mix ecotexture, that extends until the mediastinum, and tracheal compression and deviation. A ultrasound-guided needle aspiration of the thyroid showed partial resolution of T-cell mediated rejection features (grade borderline: I1, I1, V0, G0) associated with interstitial fibrosis. IF negative in the previous biopsy, showed the onset of diffuse mesangial granular IgA deposits as for diffuse proliferative IgA glomerulonephritis. C4d staining was occasionally positive in peritubular capillaries in the context of the major areas of fibrosis. (Figure 2) Despite improvement in the rejection features, the second biopsy showed IgA nephropathy, probably as recurrence of the kidney native IgA nephropathy. On the basis of this result and the persistent poor patient’s compliance we suggested chronic renal replacement therapy after arteriovenous fistula creation. In conclusion the non-adherence to immunosuppressive therapy is not only the major cause of rejection but it can lead to recurrence of the primary nephropathy resulting in a synergic negative impact on outcome.

Malignant pheochromocytoma: current problems for its diagnosis and management


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Introduction: Pheochromocytomas and paragangliomas are rare tumors that can be life-threatening because of excessive catecholamine secretion. Approximately 10-20% of pheochromocytomas and paragangliomas are malignant, and they carry a poor prognosis. Despite the increasing availability of diagnostic histopathologic, biochemical, molecular and genetic markers, standardized criteria to precisely define malignancy are still lacking. Also the therapeutic strategies to manage malignant pheochromocytoma are under evaluation, with limited results up to now.

The Authors describe a case of recurrent pheochromocytoma with multiple bone metastasis that became evident 20 months after an apparently successful primary surgery.
Case report: A 59-years-old woman in April 2011 underwent left adrenalectomy for a norepinephrine-secreting pheochromocytoma (tumor diameter: 47 mm). At the histological examination tumor cells infiltrated the capsule (without passing it) and stained positively chromogranin, neurofilaments, S100,NSE, synaptophysin. One year after the intervention, the patient was well and abdominal CT as well as serum markers (NSE, chromogranin A) and urinary catecholamines/metanephrines resulted negative for recurrence. In November 2012 at an abdomen radiograph performed for an atypical abdominal pain an osteolytic lesion with swelling of the VII right rib on its dorsal portion was incidentally discovered. The chest and abdominal CT that were subsequently performed revealed the presence of a mass (diameter: 10 mm) in the place of previous left adrenalectomy, a 2-cm osteolytic lesion at the right ischium and confirmed the osteolysis with swelling of the VII right rib. The PET-CT demonstrated accumulation of the radiotracer at the level of cervical vertebrae, D2, D3, D6, L3, sacrum, multiple ribs, iliac crest, right acetabulum, right ischium, proximal portion of both femurs, proximal portion of both humerus. The MIBG scintigraphy showed accumulation of the radiotracer at the level of the lower right ribs, right ischium, right femur. At that time, the laboratory examinations showed normal values of serum NSE as well as of urinary dopamine, epinephrine and metanephrine; instead urinary norepinephrine was 675 μg/24h (n.v. 12-85), urinary normetanephrine 2289 μg/24h (n.v. 105-354), serum chromogranin A 86.6 U/L (n.v. 0-20).

She then started cyclic oral therapy with the tyrosine kinase inhibitor sunitinib 50 mg o.d., and local radiotherapy at the level of the right ischium and femur has been prescribed for pain relief.

Conclusions: The case presented confirms the current problems for the diagnosis of malignant pheochromocytoma. Although several scoring systems considering invasion, histologic growth patterns, cytologic features, or mitotic activity have been proposed to predict the risk of malignancy, they are probably understudied and further evidence of their prognostic significance is needed. This underscores the importance of careful and close follow-up of patients, that should continue also in the long-term, since recurrence may become apparent even several years after the initial diagnosis, as described by other Authors. Once recurrence or metastatic spread has been demonstrated, the current therapeutic options include radiometabolic treatment with 131-I-MIBG, chemotherapy with cyclophosphamide, vincristine and dacarbazine and more experimental targeted therapies. Sunitinib, an inhibitor of the tyrosine kinase, that has shown good response in phase II studies as well as in single case reports, was chosen in this specific case. Further studies are needed to achieve a satisfactory treatment for affected patients.

Secondary pulmonary thromboembolism in an old woman


IRCCS San Martino Genova

A 73 year old woman was admitted to hospital because of intense shortness of breath. Her medical history was silent for important illness and she didn’t usually take drugs. Upon physical examination in the emergency department she appeared to be suffering from shortness of breath; blood pressure was normal but saturation of oxygen was significantly reduced. Her left leg was swollen, hot and painful on palpation. The ultrasound examination demonstrated the presence of deep thrombophlebitis and the computed tomography images of chest after the intravenous administration of contrast material showed the presence of lung thromboembolism at the level of the pulmonary trunk common, the right pulmonary artery and the left and all of their branches. TC imaging demonstrated also multiple suspected lesions in correspondence of liver.

Patient received an anticoagulant therapy and she was transferred to our unit. Upon her arrival, she appeared on fairly good conditions, she breathed better- without pain or fatigue- and her saturation of oxygen was normal. Laboratory test didn’t detected inflammatory signs (C reactive protein 32.5 mg/L), indices of necrosis (LDH 289 U/L) and tumor markers CEA and CA19.9 and thrombophilia screening tests were negative. The troponin dosage was normal.

Most likely diagnostic hypothesis was thrombophlebitis paraneoplastic but the absence of associated symptoms imposed a careful differential diagnosis also to establish a correct therapeutic approach and prognosis. However there was a contradiction between the lack of patient’s symptoms and the dramatic appearance of the TC imaging. In addition, in spite of discontinuation of proton pump inhibitors therapy, the value of Chromogranin A was significantly altered (182.6 ng/ml)

A TC total body reevaluation showed, in addition to an improvement of the pulmonary embolism, an exophytic lesion of the pancreatic body and multiple liver secondarism.

She underwent liver biopsy because it was more accessible in comparison of pancreatic ones; but it was not diagnostic. Then we decided to subject the patient to a positron emission tomography with octreotide in the hypothesis of neuroendocrine pancreas tumor. This exam confirmed the presence of tissue with high receptor density for somatostatin in correspondence with the already demonstrated liver and pancreatic lesions.

At this point, it was necessary to decide whether to start immediately a radionuclide therapy or to seek a more definitive histological diagnosis. We opted for the second solution and a needle biopsy of pancreas lesion was performed: the histological diagnosis was neuroendocrine well differentiated tumor of pancreas G2. At this moment the patient is clinically stable, she continues anticoagulant therapy and she has been evaluated for surgery.

Living with a stranger


University of L’Aquila-Department of Life, Health and Environmental Sciences

A 36-year-young man with no past medical history and no risk factors was referred to our Department of Internal Medicine for investigation of diffuse neuropathic pain with spasms involving axial and limb musculature, paresthesias and fasciculations in the upper and lower extremities, non-specific abdominal pain and fatigue to usual physical activity occurring over the last year. He also presented nocturnal diaphoresis, fever, insomnia and weight loss. The symptoms had progressively worsened during the last weeks with no response to pharmacological pain treatment. The clinical exam did not show significant abnormalities except high blood pressure (180/110 mmHg), diffuse hypeflexia and fasciculations at upper and lower extremities. The laboratory examinations evidenced high levels of lactate dehydrogenase (1365 IU/L), creatine phosphokinase (460 IU/L), aldolase (26.1 mIU/mL), myoglobin (190 ng/mL) and a slight increase of C-reactive protein (4.16 mg/dl), erythrocyte sedimentation rate (21 mm/h) and fibrinogen (449 mg/dl). Blood cell count, renal function, protein electrohoresis and immunoglobulins were normal. ANA, ENA, ANCA, blood cultures and tumor markers (apart from a little increase of neuron specific enolase, 19.6 μg/L) were negative and urinalysis showed abnormal hypercalcuria (1935 mg/24 hours) and hyperphosphatemia (5859 mg/24 hours) with normal blood calcium (9.4 mg/dl), phosphorous (3.8 mg/dl), magnesium (2.4 mg/dl) and parathormone (43.4 μg/mL) levels. We performed a lumbar sacral spine MRI that revealed minimal C5-C6, C6-C7 and D11-D12 disc herniations, but no brain and spinal alterations after contrast
enhancement. Electromyography revealed fasciculations, doublets and triplets suggestive for nerve hyperexcitability and signs of C7 radicular involvement. As part of the evaluation, US imaging of the abdomen was performed, revealing an 8-cm mass posterior to the left kidney. Based on these findings, we decide for a total body CT that showed a well enhanced giant mass (8 x 7 cm in diameter) at the left side of the anterior mediastinum, locally invasive with circumferential parietal pleural thickening and nodularity. It also showed a subdiaphragmatic paravertebral mass of 7 cm in size posterior to the left kidney and signs of mediastinal lymph node enlargement. Therefore, we performed a CT-guided fine needle aspiration biopsy of the mediastinal mass. Histopathological examination found out lobules composed of scant oval epithelial cells with pale nuclei and small nucleoli and predominantly small thymic medullary and cortical T lymphocytes. At immunochemistry the epithelial cells were cytokeratins AE1/AE3+, the cortical lymphocytes were CD1a+, CD99+ and CD5+ and the medullary lymphocytes were CD5+ and CD3+. The epithelial cells of the tumor were all CD20-. These histopathological findings indicated that the tumor was a type B1 thymoma according to the World Health Organization classification and Masaoka stage IVB. We referred our patient to a specialist center where neoadjuvant chemotherapy and surgical intervention were performed. Currently, the patient is starting on consolidation chemotherapy. Half of thymomas present asymptomatically and are detected incidentally on radiographic imaging while half present with symptoms associated with a paraneoplastic syndrome, as in our case, or with symptoms due to the local mass effect. This report describes the unusual case of a giant pleural-based thymoma with subdiaphragmatic diffusion diagnosed through clinical manifestations of multiple neurologic paraneoplastic syndromes that occur rarely in patients with thymoma (Stiff-Person syndrome and Isaac’s syndrome) in association with uncommon laboratory findings showing a remarkable muscle damage and singular alterations in urinary calcium and phosphorus.

Environmental liability
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In March 2013 a 76-year-old man was admitted to our hospital because of peritoneal cavity fluid. At the physical examination abdomen was swollen for ascites, legs were swollen for edema, the left arm appeared hardened and painful. Blood tests showed elevation of C reactive protein (226 mg/L, normal values <6 mg/L), a mild anemia and a mild chronic kidney disease. Compression ultrasonography (US) of the left arm showed the presence of deep vein thrombosis. His medical history was unremarkable, except for arterial hypertension, treated with olmesartan 20 mg/day. At the admission, the physical exam was significant for erythematous macules and papules localized on the back, abdomen and anterior chest, without signs of lymphadenopathy or hepatosplenomegaly. Complete blood count, immunoglobulin (IgA, IgG, IgM, IgE), serum protein electrophoresis, liver and kidney function tests, glico-lipid profile, and urinalysis were normal. The antinuclear antibodies were negative. Abdominal ultrasound and chest X-ray showed no abnormalities.

Skin biopsies showed plaque parapsoriasis with atypia, also intraepidermal, and lymphocytes CD3+, CD4+. These findings were compatible with mycosis fungoides in early stage. To assess the systemic involvement, a total body CT was performed. It revealed the presence of a nodular area (13 mm) in the left lower lung, adherent to the mediastinal pleura, and of a carinal lymph-node (14mm). A bronchoscopy showed no significant alterations. Accordingly, the patient was submitted to surgical treatment of right lower lobectomy with mediastinal linof adenectomy; histologic examination revealed small and big cell neuroendocrine cancer. Mediastinal lymph nodes were disease free. The diagnosis was small and big cells neuroendocrine lung cancer, CD56+, CK7-, ITF1+, p63- (T1a, N0, M0, Stage 1A) and did not require further treatment. Mycosis fungoides is currently in PUVA treatment and an appropriate cancer follow-up is planned.

Mycosis fungoides is the commonest cutaneous T cell lymphoma (CTCL) and is usually characterized by a favorable outcome, absence of systemic involvement and good response to local therapies. An association between mycosis fungoides and second malignancies is well known. In particular, lung cancer has been often reported in two large cohorts of patients affected by CTCL. The diagnosis of lung cancer was made quite shortly after CTCL diagnosis, as in our patient. A sequential accumulation of multiple genetic mutations may involve some regions common for the progression of both cancers. Smoke, occupational exposure and topic therapies do not seem to be responsible of the development of both CTCL and histological examination confirmed epithelioid mesothelioma while the PET scan showed pathological uptake in peritoneum, in several lymph nodes (cervical, mediastinal, mammary, retrocrural, peri diaphragmatic, lomboaortic, paracaval) and in pericardial adipose tissue. Morphine and anticoagulant therapy were started. Considering elevated inflammatory markers and supposing spontaneous bacterial peritonitis, antibiotic therapy with ceftriaxone was started but elevated inflammatory markers, probably due to neoplasia, did not decrease and antibiotic therapy was discontinued.

Peritoneal mesothelioma is a rare malignancy of the peritoneal serous membrane, associated to asbestosis exposure (even if the association is less strong than in pleural mesothelioma)[1]. The patient denied personal or professional exposure to asbestos fibers, but reported that 10 years before, his wife died for pleural mesothelioma.


The odd couple
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A 79-year-old female patient, was admitted to our department of Internal Medicine for a 1-year history of itchy and erythematous eruptions on the trunk, associated with night sweating and fever. She had a clinical history of hypertension, treated with olmesartan 20 mg/die. At the admission, the physical exam was significant for night sweating and fever. She had a clinical history of hypertension, treated with olmesartan 20 mg/die. At the admission, the physical exam was significant for night sweating and fever. She had a clinical history of hypertension, treated with olmesartan 20 mg/die. At the admission, the physical exam was significant for night sweating and fever.
lungs cancer. Therefore, early and serially malignant screening in patients affected by mycosis fungoides may caus a significant benefit in terms of mortality.

A clinical experience of treatment of the pain in a patient with poor prognosis

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The taking care of the elderly with advanced stage disease and limited life expectancy raises the issue of the pain therapy for optimal quality of care. The pain is a common manifestation of myeloma and its evaluation/optimal treatment are part of the Venice Declaration (Fourth Research Forum of the European Association for Palliative Care). The management is complex due to the characteristics of the cancer patient, suffering from myeloma and to the specific bone pain (cancer-induced bone pain-CIBP). The analgesic to use and the best route of administration are subject to different variables: pain intensity, patient’s clinical condition, comorbidities, drug addiction, tolerance. A patient of 67 years was suffering from hypertension and myeloma treated with various chemotherapies, the last suspended for cardioxicity. She came for a fever that arose from 2 days, dyspnea, productive cough. The general conditions were expired: The patient was alert and dyspnoeic; she pains in upper limbs and spine (VAS-Visual Analogue Scale 9/10: very severe pain). We treated the acute heart failure (oxygen at 2 liters/minute, nitroglycerin 15 mg), the dyspnea (beclometasone 0.8 mg in aerosol), the pain and the emesis (acetaminophen, methylprednisolone 40 mg and ondansetron 4 mg intravenously, morphine hydrochloride 10 mg intramuscularly). Blood tests were performed. White Blood cells were 18.71×10^{9}/liter, neutrophils 12.87×10^{9}/liter, platelets 587000, D-dimer 1958 mg/liter, PCR 11.85 mg/dl, LDH 495 IU/liter, TcT 0.062. The radiography of the chest showed a thickening parenchymal peri-ilar lower right accentuation of the design broncho-vascular hilum-periilar bilateral pleural breasts cost-free. An increased image of heart size: cefazolin was initiated at a dose of 1 g/day. The patient presented a suffered facies, poor appetite, diffuse atrophy, dehydration. Vital Signs were GCS 15, apyrexia, PA 160/90 mmHg, heart rhythm action with 102 bpm, parafonic tones, SpO2 91% on room air. Hypoexpanselfe chest, low transmission of the thrill tactile voice, harsh murmur spread, abolished in the mean field on the right, crackles in the lower left field. Presence of spontaneous pain in the right upper limb and to the thoraco-lumbar spine, chest widely (VAS 9, Number Rating Scale NRS-10), with greater mobilization and acts of breathing. Karnofsky 20 (severe impairment of one or more vital functions with irreversibility of the clinical picture). ECG sinus rhythm, sporadic supraventricular ectopic beats. Radiological studies showed multiple osteolytic lesions in the spine, upper limbs, signs of previous pathological fracture of the surgical neck of the right humerus (already treated with osteosynthesis), multiple rib fractures. We continued the antibiotic therapy and oxygen (2 liters/minute at need-target SpO2>92%), the anti-thrombotic prophylaxis (patient bedridden), the optimization of the heart failure therapy (esmepazole 40 mg, 12.5 mg carvedilol, furosemide 50 mg, ramipril 2.5 mg, amiodipine 10 mg). For pain control, we continued therapy with morphine crafting an elastomer for 48 hours (daily dose: morphine 100 mg, metoclopramide 10 mg betamethasone 8 mg, ranitidine 100 mg) subcutaneously by continuous infusion, associating an adjuvant therapy (prednisone 50 mg/day and predgalbin titrated up to 375 mg). Because of difficult for the control of pain (VAS 8; NRS 9) and the occurrence of repeated intense episodic algic pain, the opioid therapy was modified in oxycodone 80 mg/day (titrated up to 160 mg) and transmucosal fentanyl (600 mcg 3 times per day, and 800 mcg at bedtime). There was a significant reduction of peri-ilar parenchymal thickening, an unchanged Karnofsky scale, the stabilization of the clinical picture and the vital signs (GCS 15, PA 110/70 mm Hg; FC 81 bpm SpO2 94% in oxygen), a satisfactory, improved pain control (VAS 4/10; NRS 5=moderate pain), a fewer episodes of breakthrough pain. We resigned the patient entrusted to the continuity service of home care for the continuation of laboratory monitoring and therapy. The overall approach of just Geriatric Medicine must take into account both the setting of an effective and personalized pharmacotherapy, in accordance with the dictates of scientific societies (in addition to those mentioned, it should be rebemered the American Society of Clinical Oncology, the Italian Society of Anaesthesia Analgesia Resuscitation And Intensive Care and the Italian Society of Palliative Care) both realistically achieved in the seriously ill patient: the preservation of residual abilities and the control of the most disabling symptoms of daily life. The use of morphine (gold standard) and oxycodone have been implemented on the instructions of the Society Guidelines of the World Health Organization, the American Geriatric Society, the British Committee for Standards in Haematology, the UK Myeloma Forum, the Italian Association of Medical Oncology. We have been associated with adjuvants (corticosteroids, gabapentinoid, diphasphonates), though the evidence is less consistent and sometimes not. The breakthrough pain in opioid takes advantage of immediate availability used drugs (fentanyl oral transmucosal or transnasal). The pain and disease with fatality outcome are devastating emotional experiences, in elderly patients, often with comorbidities, depression, social and psychological situations particularly labile. Maintaining a decent quality of life is the therapeutic goal. In addition, the relational aspect with the patient: the need to provide to him, family members and caregivers information about the state of the illness, prognosis, interventions to be implemented and where to implement them (home, hospice, Integrated Home Care, nursing homes, hospital). In this management, set the effective analgesic therapy and having organized the continuation of care with a view to transition ospital Territory, also discharge appears as an act appropriately and ethically. The accompaniment of the patient, no more suffering, preferably at their home, and the treatment of pain of the elderly, is a definite clinical and ethical task, which can contribute to improving the quality of life of these individuals and to the relief of their suffering.

BRAF V600E: one gene mutation for two tumors


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Introduction: BRAF gene, which belongs to the Ser/Thr protein kinase family, when mutated, plays a key role in inducing melanoma and papillary thyroid carcinoma. BRAF gene mutations promote a constitutive activation of both mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3-phosphate kinase (PI3K/Akt) signaling pathways, resulting in uncontrolled tumor growth and survival. The most frequent (80%) BRAF mutation carries the pVal600Glu (V600E), resulting in the substitution of glutamic acid for valine at codon 600. Recent studies have shown that melanomas with the BRAF V600E mutation are more aggressive and less sensitive to chemotherapy than BRAF wild-type melanomas. Here we report the case of a 73-years-old woman carrying BRAF mutation and with co-existing metastatic melanoma and papillary thyroid macrocarcinoma.

Case Report: A 73-years-old woman was admitted to our Department because of dyspnea and subcapsularis right back pain, which had occurred 1 week before. The patient, affected by severe obesity (BMI 52 kg/m²), chronic kidney failure (III stage /DOQI), recurrent kidney stones, chronic obstructive pulmonary disease, reported a history of cutaneous epithelioid...
melanoma excised from her upper back in 2000, and a previous papillary thyroid macrocarcinoma treated by total thyroidectomy and radio-iodine-therapy in 2007. The total body CT-scan showed a pulmonary consolidation with irregular margins occurring in the posterior basal segment of the right lower lobe and infiltrating the adjacent parietal pleura; it showed also osteolytic bony lesions of the right costal arches with pathologic fractures from the IV to the VIII ribs. Thus, a biopsy of the lung lesion was performed showing epithelioid neoplasia positive for S100 protein and negative for panCK and panLEU. Results from immunohistchemistry were consistent with the diagnosis of pulmonary metastatic lesion of epithelioid melanoma. The research of BRAF mutation, determined by direct sequencing of the BRAF gene exon n.15 performed on the tissue extracted DNA, resulted positive for V600E. During hospitalization because of the occurrence of nausea, vomiting and epigastric pain, although analgesic morphine therapy reduction, was performed an esophago-gastro-duodenoscopy which reveals multiples mucosal lesions presenting central umbilication and showing signs of recent bleeding in the fundus and in the body of the stomach, attributed to mucosal melanoma metastases.

Conclusion: Because of the high incidence of BRAFV600E mutation in both malignant melanoma and papillary thyroid macrocarcinoma, and its importance as prognostic and chemotherapy response index, there could be a proper indication of BRAFV600E mutation testing in all cutaneous melanomas, in papillary thyroid macrocarcinomas or in fine-needle aspirates of thyroid nodules >1 cm in size. Furthermore, it could be useful to suggest a dermatological visit to all patients with thyroid carcinomas in search of suspected skin lesions to be examined.

**Neuroimaging of hypothalamic activity in cancer anorexia evaluated by functional magnetic resonance**

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**Introduction:** Anorexia, i.e., the loss of the desire to eat, is a frequent feature in cancer patients, its presence negatively impacting on patients’ morbidity, mortality and quality of life. Recent evidences indicate that energy homeostasis, i.e., the control of energy intake and expenditure, is largely mediated by the hypothalamus, and centrally produced inflammation is involved in triggering the molecular changes of anorexia and cachexia. Recently, a sophisticated neuroimaging technique to study in vivo neurophysiology, including hypothalamic activity, has become available, i.e., functional magnetic resonance imaging (fMRI). Aim of the present study was to determine the specific patterns of the brain activation after assumption of a standardized meal in both anorexic (A) and non-anorexic (NA) cancer patients to reveal potential differences.

**Materials and methods:** Patients with confirmed lung cancer diagnosis were enrolled before the initiation of any anti-cancer treatments. The presence/absence of anorexia was investigated using a specific questionnaire. On the same day, hypothalamic activation patterns were evaluated in A and NA patients by fMRI, before and after administration of 200 mL of an oral hypercaloric nutritional supplement providing 300 Kcal (1.5 kcal/mL). Using a computerized software, the average value of the grey for the hypothalamus was calculated, and normalized for the one obtained in the basal condition. Data obtained were statistically analyzed using the Student and Bonferroni tests.

**Results:** Eleven lung cancer patients were enrolled (6M, 5F), 7 were A, 4 NA, as revealed by the questionnaire. Anorexic cancer patients presented a lower hypothalamic activity respect to NA group in basal condition (evaluated by fMRI, % of signal intensity change) (573±46 vs 669±27, p=0.004, respectively), immediately after the standard meal assumption (520±60 vs 610.5±25.6, p=0.02, respectively) and after 15 minutes from meal assumption (543.4±49.1 vs 623.4±60.5, p=0.039, respectively). No differences in hypothalamic activity were observed within the A group during the time of observation, whereas NA patients significantly reduced the hypothalamic signals from basal condition to the period immediately after the meal assumption (669.3±27.2 vs 610.5±25.6, p=0.01, respectively).

**Conclusion:** Our results show for the first time in humans that in A cancer patients hypothalamic activity is depressed and does not respond to oral challenges. We therefore speculate that the gut-brain axis is impaired in A cancer patients. Our study also confirms the diagnostic accuracy of the anorexia questionnaire and the reliability of fMRI in studying brain activity in vivo.

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**A woman with fever, gluteal and perianal ulceration**

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A 52-year-old Caucasian woman was admitted to our hospital for asthenia and general malaise. The patient had a history of breast cancer with bone metastases subjected to chemotherapy, hormone therapy and radiotherapy, presently in experimental protocol. Over the last week she suffered from high spiking fevers, exceeding 39°C, general myalgias and worsening of motor and sensory deficits. Therefore, oral antibiotic therapy with azithromycin had been administered.

On first assessment she appeared alert, oriented and cooperative, suffering from pain in the spine and sacrum, feverish. Upon physical examination we noted normal blood pressure and oxygen saturation, elevated heart rate and ulcerated deep lesions in the perianal and gluteal region. Laboratory tests detected severe piastrinopenia, macrocytic anemia, altered liver function tests (gGl 307 U/L, AST 52 U/L, ALT 77 U/L), LDH (757 U/L), systemic inflammatory indicators (C reactive protein 320 mg/l, fibrinogen 8.74 g/L). White blood cell count was normal. Blood cultures and urine culture were sterile. Swabs of wounds were positive for E.Coli and E.Faecalis she was treated with endovenous antibiotic therapy with metronidazolo and ceftriaxon. TC evidenced no colic or bones abscesses and no fistulous route as cause of skin lesions.

Considering the available data, fever and infection were caused by this lesion, but the wounds could not be caused only by the decubitus, considering also the position and that the patient was not bedridden but she could change positions and turn with a wheelchair.

Among the drugs taken by the patient everolimus was also present, in experimental protocol, an mTOR inhibitor that has immunosopressive properties and may give mouth ulcerations. This particular adverse effect isn’t described in literature, but we had discontinued this therapy, assuming that it was the responsible factor.

In fact, after a few days, the patient was afebrile and ulcers showed granulation tissue, low residues of fibrin and sovinfection signs were reduced. Laboratory tests also detected a progressive rise in the platelet count.

We describe in this case report ulcerated lesions in gluteal and perianal region as an unknown everolimus adverse effect.
The top of the iceberg

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In April 2013 a 59 year-old man was admitted to our hospital because of fever and edema in the right forearm and in the right leg. He denied any traumatic event. His medical history was unremarkable, except for carotid endarterectomy for right carotid stenosis and ulcerative ileitis. In January 2012, because of abdominal pain, ultrasonography (US) of abdomen was performed but it did not show any pathological findings affecting abdominal organs except for increased echogenicity of hepatic tissue, suggestive of nonalcoholic fatty liver disease. In July 2012 he repeated US of the small intestine that confirmed previous abdominal US findings. When the patient arrived at the emergency department of our hospital, his body temperature was 38°C. At the physical examination the right calf appeared swollen and painful with negative Homans’ sign; the right forearm was swollen and warm. Blood tests showed mild elevation of muscle enzymes: CK 370 U/L (n.v. 20-195 U/L), SGOT 1.5 times the upper limit of normal, SGPT at upper limit of normal, LDH 449 U/L (n.v. 125-220 U/L). Inflammation markers were slightly altered: C Reactive Protein 43.9 mg/L (normal values <6 mg/L), fibrinogen 458 mg/dL (n.v.150-400 mg/dL), ESR 15 mm/1h (n.v. 1-15 mm/1h), while blood count values were normal except for mild anemia and eosinophilia (1400 cells/μL). Serum levels of thyroid hormones were normal. ANA were positive but in low titer (1:80), with speckled pattern. Tests of blood coagulation were normal. Compression US of upper and lower limbs was normal. Soft tissue US showed that mediasl gastronomicus muscle of the right leg and medial muscle fascicles of the right forearm were increased in volume with no fluid collections or hematomas. Medial gastrocnemius of the right leg was dishomogeneous with increased vessel density. In the following days, there was a clinic and biochimico spontaneous remission but the patient began complaining of abdominal pain. Our first diagnostic hypothesis was deep vein thrombosis, but compression US did not support it. Soft tissue US findings were suspicious for myositis. However, neither clinical findings nor medical history were suggestive of polymyositis. We hypothesized the presence of an infectious myositis linked to parasitic intestinal infestations, but stool tests resulted negative. Eosinophilia suggested an allergic manifestation but serum levels of total IgE were normal and also serum levels of C3, C4, C1q were normal. Finally, considering patient’s history of ulcerative ileitis, we supposed Ciuffini-Pancoast syndrome, and therefore we performed:

- Chest-X-ray: apical parenchimal thickening on the right side;
- Chest-CT: solid mass in soft edges on the right apex;
- Bone scintigraphy: artrosis.

Finally he underwent Bronchoscopy: “Poorly differentiated squamous cell carcinoma”.

Discussion: It is very important suspecting Bernard-Horner syndrome in front of chronic brachial pain, resistant to treatment; and then we have to look for other typical signs, such as eyelid ptosis, enophthalmos and miosis (due to damage to cervical sympathetic nervous system, resulting in a prevalence of parasympathetic), especially in the presence of story of smoking, which is the main risk factor for lung cancer. When a tumor of the lung apex compresses the nerve plexus causing also arm pain, there is Ciuffini-Pancoast syndrome.

Conclusions: Clinical history, adequate attention to the risk factor “smoking” and thorough clinical examination are essential for making diagnosis in the presence of generic symptoms such as chronic pain. The holistic management of the patient is essential to achieve this goal.

Increased risk of chemotherapy-associated venous thromboembolism in elderly patients with cancer

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Cancer has becoming an increasingly common problem in elderly patients and the number of older adults seeking treatment for cancer is considerably increasing. Due to advanced medical technology, cancer patients are surviving health conditions that would have proven fatal years ago. However, the number of medically fragile patients has increased, as aging is associated with multifaceted changes in physiology and is accompanied by an increase in co-morbidities, which may have independent prognostic implications that can substantially impact clinical decision making. This,
in turn, results in alterations in pharmacokinetics and adverse effects related to many commonly used anticancer agents. Among these, venous thromboembolism (VTE), including either deep vein thrombosis (DVT) or pulmonary embolism (PE) could be particularly challenging, as its incidence dramatically increases with age and approximately two-thirds of patients with VTE are older than 70 years. Beyond age, VTE is a frequent complication of cancer treatment, especially in the first 3-6 months of chemotherapy. Therefore, elderly patients affected by cancer and treated with chemotherapy should be at further risk of VTE than younger cancer patients, but available data are sporadic and contrasting.

In light of these considerations, we sought to evaluate the risk of chemotherapy-associated VTE in young-middle-aged (YMA) and elderly cancer patients, and to analyze the VTE-free survival time in both groups. Patients with histological confirmed diagnosis of solid malignancy receiving any type of systemic chemotherapy; no clinical diagnosis of VTE before chemotherapy initiation; and Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2 were enrolled in this study. Of the 486 consecutive patients included in the study, 380 (78%) were classified as YMA (≤70 years of age) and 106 (22%) as elderly (>70 years of age). At a median follow-up of 1 year, the incidence of VTE events was almost two-fold greater in elderly than in YMA (11% vs. 6%). Age (≤ 70 years vs. > 70 years; HR, 2.42; 95% CI, 1.15-5.06; p=0.020), ECOG-PS (HR, 6.54; 95% CI, 3.10-13.8; p<0.0001), and platinum-based chemotherapy (HR, 2.46; 95% CI, 1.06-5.69; p=0.035) were independent risk factors for VTE.

In the elderly subset, a trend towards an increased risk of VTE in patients receiving a platinum-based chemotherapy when compared with a non-platinum containing regimen was observed (15% vs. 9.1%). The Kaplan-Meier analysis showed that elderly patients had a significantly shorter VTE-free survival time compared with younger cancer patients (log-rank test=2.0; p=0.045). Our study reports an increase incidence of VTE in elderly cancer patients treated with chemotherapy compared with the younger group, suggesting that aging is one of the most important risk factor for VTE. Based on the results of the present study, we believe that a validated predictive model including age, ECOG-PS and type of chemotherapy (platinum vs. non-platinum containing regimen) would enable clinicians to target thromboprophylaxis to those patients considered to be at greatest risk.

This work has been carried out within the PhD program in “Physiopathology” (XXVI cycle - Medical Oncology Course), University of Rome Tor Vergata. This work was partially supported by the Italian Ministry of Health Grant MERIT RBNE08NKH7. Authors declare that no competing financial interests exist.

Figure 1.

Pneumology

Unusual etiology for pleural effusion


SC Medicina Interna ASO Santa Croce e Carle Cuneo

A 36 years old male was admitted from Emergency Department for chest pain with pleural effusion. He had a 1 year history of left hemithorax chest pain, unresponsive to anti-inflammatory therapy (a clinical evaluation performed six months before demonstrated a normal chest radiography and normal serum troponin levels). The patient described the pain like a stab lasting about two hours each time. In the last few days a syncopal episode occurred too and moreover appeared orthopaen.

Chest X-ray showed left pleural effusion. Patient’s clinical history included depressive syndrome treated with Sertraline, plausible sequel of a road accident trauma occurred at age of 16, with multiple fractures and head trauma.

Considering chest pain and pleural effusion among the possible diagnostic options there were: pneumothorax, coronary artery disease, aortic valve stenosis, chronic pericarditis, aortic dissection, pulmonary embolism and pneumonia.

Blood tests revealed peripheral eosinophilia (14%). A chest TC was performed: it showed a massive left pleural effusion but ruled out pulmonary embolism. A small lung fibrotical nodule and a atelectasic area were also detected. A pleural drainage was positioned and eosinophilic cells resulted marked – increased in pleural effusion too.

Possible causes of peripheral eosinophilia and pleural effusion included: Hodgkin Lymphoma, sarcoidosis, leukemia, bronchogenic carcinoma, mastocytosis, parasitic infections, fungal infections, HIV, Churg Strauss syndrome, drugs.

Peripheral blood tests were normal except for eosinophilia; HIV test, co-procurulture, uroculture, BAAR, HBV, CMV sierology, Aspergillus and mycoplasma sierology were all negative. Autoimmunity tests were normal. An abdominal ultrasound exam was performed to rule out presence of haepatic lesion or adenopathy.

A total body positron emission tomography revealed subcarineal ad paramedian adenopathy with low SUV, compatible with aspecific inflammactory finding.

Sertralina was stopped, in the suspect of iatrogenic cause of iper eosinophilia and eosinophilic pleural effusion and patient started a new therapy with Venlafaxina.

Patient’s clinical conditions rapidly improved and chest’s radiography confirmed a reduction of pleural effusion; on the third day, the pleural drainage was removed and the patient was discharged with the diagnosis of peripheral pleural effusion. At follow up after three months patient was asymptomatic, peripheral eosinophilia and pleural effusion were no more present.

Drug reactions should be considered as a potential cause of pleural fluid accumulation in all patients with eosinophilic pleural effusion (EPE). However, drug-induced EPE should be considered on a broad basis of EPE aetiology. Since a specific cause of EPE can be identified in the majority of cases, all patients with this type of pleural effusion require rigorous and full diagnostic algorithm (1).

References:
Retrospective study on the use of ultrasound at the bedside of patient for early diagnosis of pneumonia


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Introduction: we evaluated the diagnostic pathway of the patients hospitalized in the Medical Clinic III of San Martino Hospital (Genoa, Italy) in the period from January to December 2012 and discharged with a diagnosis of pneumonia.

Case Study: the incidence of diagnosis of pneumonia was 16.3%, out of a total of 312 hospitalized patients, patients discharged with a diagnosis of pneumonia were 51; the patients who died, in which diagnosis of pneumonia was made, were 7 (2, 2%) The mean age was 72.9 years, a neoplastic disease was present in 27% of patients. Nosocomial pneumonia was found in 8 of 44 patients discharged (18%) and in 3 of the 7 patients died (42.8%). Hypoxemia at the time of diagnosis was present in 35 of the 44 discharged patients (79.5%) and in 100% of patients died during hospitalization.

Method of lung ultrasound: the instrument used was Esaote MyLab with 5.0-10.0 MHz linear probe and 3.5-5 MHz convex probe. All examinations were performed at the bedside, with oblique and longitudinal scans (intercostal) in the anterior, lateral and posterior areas of the chest, examining the patient supine, lateral and sitting. In normal conditions, the lung ultrasound showed only echogenic pleural line, visible shadows between two ribs, and his slider (sliding) with breaths. Ultrasound diagnosis of pneumonia was based on the presence of subpleural pulmonary consolidation or focal interstitial syndrome.

Results: The diagnosis of pneumonia was made with chest radiography at the time of the admission in hospital in 31 of 44 patients discharged and in 4 of 7 patients who died of pneumonia. Chest radiography performed after a few days in patients with a negative initial chest radiograph allowed to make the diagnosis in a further 2 patients discharged. Lung ultrasonography was performed in 12 patients with clinical suspicion of pneumonia, but negative initial chest radiography, and was positive in all cases. In addition, lung ultrasonography was performed in 24 patients with positive initial radiography. Among these cases, pleural effusion was mild in 17 patients and massive in 3 patients. CT chest scan was performed in 30 patients, including 19 with positive initial radiography, 6 patients with initial negative radiography, but positive lung ultrasound, and in 5 patients with negative radiography and ultrasound not performed. In search of complications of pneumonia, we used ultrasound for research (and possibly guided puncture) of the pleural effusion, for the evaluation of its characteristics (in particular, highlighting a case of pleural empyema), and to monitor the size of pulmonary consolidation, and finally, in patients with hemodynamically compromised, we applied the integrated ultrasound according to the protocol ALS, in particular with the indirect assessment of Central Venous Pressure and the search for signs of ARDS.

Conclusion: Our study confirms the feasibility and reliability of lung ultrasonography performed at the patient bedside for the diagnosis of pneumonia.

Effectiveness and tolerability of electronic cigarette in real-life: a 24-month prospective observational study


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Background: Electronic-cigarettes (e-Cigarette) are battery-operated devices designed to vaporize nicotine that may aid smokers to quit or reduce their cigarette consumption. Research on e-Cigarette is urgently needed in order to ensure that the decisions of regulators, healthcare providers and consumers are evidence based. Here we assessed long-term effectiveness and tolerability of e-Cigarette use in a ‘naturalistic’ setting.

Methods: This prospective observational study evaluated smoking reduction/abstinence in smokers not intending to quit using an e-Cigarette (‘Categoría’; Arbi Group, Italy). After an intervention phase of 6-month, during which e-Cigarette use was provided on a regular basis, cigarettes per day (cig/day) and exhaled carbon monoxide (eCO) levels were followed up in an observation phase at 18- and 24-months. Efficacy measures included: a) ≥50% reduction in the number of cig/day from baseline, defined as self-reported reduction in the number of cig/day (≥50%) compared to baseline; b) ≥80% reduction in the number of cig/day from baseline, defined as self-reported reduction in the number of cig/day (≥80%) compared to baseline; c) abstinence from smoking, defined as complete self-reported abstinence from tobacco smoking (together with an eCO concentration of ≤10 ppm). Smoking reduction and abstinence rates were computed, and adverse events reviewed.

Results: Of the 40 subjects, seventeen were lost-to-follow-up at 24-months. A >50% reduction in the number of cig/day at 24-months was shown in 11/40 (27.5%) participants with a median of 24 cig/day use at baseline decreasing significantly to 4 cig/day (p=0.003). Smoking abstinence was reported in 5/40 (12.5%) participants while combined >50% reduction and smoking abstinence was observed in 16/40 (40%) participants at 24-month. Five subjects stopped e-Cigarette use (and stayed quit), three relapsed back to tobacco smoking and four upgraded to more performing products by 24-months. Only some mouth irritation, throat irritation, and dry cough were reported. Withdrawal symptoms were uncommon.

Conclusion: Long term e-Cigarette use can substantially decrease cigarette consumption in smokers not willing to quit and is well tolerated. (http://ClinicalTrials.gov number NCT01195597).

Community acquired pneumonia and anemia occurrence

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Background: Anemia is common in patients with occult and overt inflammatory stressors, and when severe, anemia exacerbates an already existing symptom burden. Hepcidin is an IL-6-induced key modulator of inflammation-associated anemia. The association between inflammation, hepcidin release and anemia has not been investigated in patients with pneumonia.

Aim: We explored the relationships between hepcidin and pneumonia-associated anemia.

Methods: Sixty consecutive patients were enrolled after presentation for acute inflammatory illness on the emergency ward of a university hospital. Inflammation was indicated by the presence of a proven or suspected infection and elevated C-RP (≥ 3 mg/dl). Patients with, creatinine > 2 mg/dl, any cancer, any hematological diseases, cirrhosis, active bleeding, last month received blood transfusion were excluded. Blood was drawn at day 1 and 6 after admission for the measurement of hepcidin-25, cytokines profiling, inflammation markers and iron status. Systemic inflammatory response syndrome (SIRS) and Pneumonia Severity Index (PSI) have been assessed at admission.

Long term e-Cigarette use can substantially decrease cigarette consumption in smokers not willing to quit and is well tolerated. (http://ClinicalTrials.gov number NCT01195597).
Results: Patients with pneumonia were 27 and 33 patients had other acute diseases (bacteremia, urinary tract infections, acute exacerbation of COPD). Patients with pneumonia were older (75 yrs ±13.4) than the patients without (67 yrs ±21).

At presentation, the group of patients with pneumonia had higher mean levels of serum C-RRP (16.9 mg/dl) and IL-6 (87.9 pg/ml) compared with the other patients (C-RRP 10.4 mg/dl, p<0.001; IL-6 54.6 pg/ml, p=0.048).

In all patients, IL-6 and C-RRP concentrations positively correlated with hepcidin serum levels and hepcidin correlated with the rate of decrease of hemoglobin (Spearman’s r -0.330, p = 0.009).

Conclusion: These data suggest that, in patients admitted with pneumonia, hepcidin-25 could predict anemia occurrence just in the first week whatever their PSI score.

Bedside transthoracic ultrasound and chest radiography in the clinical evaluation of patients with acute dyspnea: a multicenter study


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Transthoracic ultrasound (TUS) currently stands out as a useful technique for the clinical assessment of different pleuro-pulmonary disorders. To the best of our knowledge, at present no data are available on the clinical application of methodologically standardized TUS technique in a large sample of patients with acute dyspnea from different causes, compared to the posterior-anterior (PA) chest radiography (X-ray). We therefore performed a multicenter study aimed to evaluate the possible role of TUS as a complementary technique, in association with PA chest X-ray, in the differential diagnosis and clinical management of patients with acute dyspnea.

We studied 359 patients (178 male and 181 female, age range 26-87 years) with acute dyspnea. A TUS with a convex probe and an anteroposterior chest X-ray were performed in all the subjects at bedside. All the US machines were set for transthoracic study. The ultrasound parameters considered for each lung were: pleural effusion, pleural sliding or gliding sign, pleural line thickening, subpleural nodule and/or consolidation. The percentage of the different causes of dyspnea assessed using TUS and X-ray and compared to the definitive diagnosis was evaluated.

We found a statistically significant difference in the percentage of pleural effusion and pulmonary consolidation assessed by US (100% and 93%, respectively), compared to X-ray (35% and 43%) (p<0.001 for both). There was a significant difference between the two techniques in the percentage of pleural effusion caused by acute pulmonary edema, heart failure, hydrothorax secondary to liver cirrhosis (p<0.001 for all), pneumonia (p<0.05) and neoplastic lymphangitis/lung cancer (p<0.001). Among the different causes of consolidation, we found a significant difference in the percentage of pneumonia detected by TUS (100%) and by X-ray (33.3%) (p<0.001). No difference was found in the percentage of pulmonary cancer between the two techniques (TUS: 80.7 and X-ray 71%), as well as of severe pulmonary fibrosis (TUS: 94.4%; X-ray: 72.2%). Nevertheless, inflammatory subpleural consolidation was detected in 11/33 (33.3%) patients with pulmonary fibrosis and 9/30 (30%) patients with COPD exacerbation using TUS method, compared to none using X-ray.

The impact of dyspnea as one of the most frequent clinical issue in the emergency setting has been widely reported. The clinical usefulness of noninvasive techniques has been investigated as well, in order to further increase accuracy and rapidity of the diagnosis. Our results demonstrated that bedside TUS represents a useful complementary tool, in association with bedside PA chest X-ray, in the differential diagnosis of acute dyspnea. Moreover, TUS has a higher sensitivity, compared to X-ray, in the detection of pleural effusion and pneumonia, as well as of subpleural consolidation in patients with pulmonary fibrosis and COPD exacerbation in the acute setting.

A rare lung disease

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Introduction: The authors describe a clinical case of a rare lung disease, which is peculiar for its epidemiological characteristics and anatomical aspect.

Case report: FM, male, 31 y.o., non-smoker, hydraulic comes to our attention because he complains of fever and non-productive cough for several months.

He undergoes:

• Chest X-ray: right basal mass (which remains unmodified after steroid and antibiotic therapy for 10 days);

• Thoracic CT: solid rounded mass with sharp margins, projecting into the lumen of the right bronchus;

• CT angiography: nodule, in the context of the intermedius bronchus, with intense opacification in the arterial phase, compatible with endobronchial carcinoid; atelectasis of the middle lobe.

• Bronchoscopy: intraluminal obstruction of the right bronchus

• Histological examination: low-grade neuroendocrine carcinoma; histochemical study positive for NSE, chromogranin, synaptophysin and CD57, low mitotic activity (<1/HPF).

Diagnosis: low-grade neuroendocrine carcinoma (atypical carcinoid tumor).

Therefore the patient undergoes lobectomy and extensive ilo-mediastinic lymphadenectomy.

Discussion: The case described is not frequently observed both for the rarity of pulmonary atypical carcinoid (pulmonary carcinoids are neuroendocrine tumors that make up 1% to 2% of all lung tumors, typical 80% and
Chronic respiratory diseases and real life: a clinical study

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Introduction: Chronic respiratory diseases are extremely frequent. According to World Health Organization, in 2020 COPD will become the third leading cause of mortality in the world, while asthma are currently between 100 and 150 million people.

Objectives: Primary: evaluating sensibility of patients and doctors to prevention and instrumental diagnosis (spirometry) of such diseases. Secondary: evaluating the reliability of the screening test, the effective control of such diseases, by means of validated questionnaires, and the contribution of spirometry in the differential diagnosis (DD).

Methods: 10 medical general practitioners (GPs) were invited to send 5 respiratory patients for each of them, to internal medicine visit, after collection of personal data, medical history, GOLD questionnaire for suspected COPD, ECRHS (European Community Respiratory Health Survey) questionnaire for suspected asthma, COPD Assessment Test (CAT) for patients already treated for COPD, and Asthma Control Test (ACT) for those already treated for asthma.

Results: Of the 50 expected, 30 were evaluated: all were subjected to visit and spirometry. Some GPs did not send patients or they sent less than expected. From screening questionnaires: 13% suspected COPD, 57% suspected asthma, and 30% both possible. From CAT test in COPD: clinical and spirometry together) of the patients suspected for COPD was: 75% COPD, and 25% neither asthma nor COPD. Final diagnosis of the suspected for asthma, was: 94.1% asthma, and 5.9% neither asthma nor COPD. So validity of the screening questionnaires was confirmed. Definitive diagnosis of the patients suspected for both diseases was: 55.6% asthma, 33.3% COPD, 11.1% neither asthma nor COPD, confirming the central role of spirometry in D.D.

Conclusions: This study, despite the small number of patients, shows:

- inadequate sensibility of physicians to respiratory diseases
- usefulness of screening questionnaires
- central role of spirometry for the evaluation of patients too often underdiagnosed or inadequately treated (results of CAT and ACT).

Evaluation of intrarenal hemodynamic parameters and oxidative stress in patients with obstructive sleep apnea syndrome

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Background: The increased risk, sustained by endothelial dysfunction, of developing hypertension, cardiovascular disease and cerebrovascular events has been extensively documented in patients with obstructive sleep apnea syndrome (OSAs).

Some studies demonstrated a significant incidence of OSAs in patients with alterations of renal function. In 2011, Buchner et al. documented an increase of renal resistance index (RRI) in patients with mild-to-moderate OSAs. Furthermore, a recent study by Chou et al. showed a relation between OSAs and development of chronic kidney disease (CKD). However, the underlying mechanism causing renal dysfunction is still unclear.

Aim of the study: To evaluate endothelial dysfunction and intrarenal hemodynamic parameters in patients with OSAs at baseline and at follow-up after 30 days therapy with continuous positive airway pressure (CPAP).

Methods: Sixteen patients, median age 59.5 (45-70) were evaluated with polysomnographic study and enrolled in a monocentric, longitudinal, prospective study, before and after a month of treatment with CPAP. No patient had chronic renal failure and median filtration glomerular rate was 91 ml/min. Exclusion criteria were diabetes, cancer, COPD, immunologic disorders, cardiac failure and smoke.

Polysomnographic study estimates apnea hypopnea index (AHI) that represents a severity index of OSAs. All subjects underwent ultrasonographic examination to assess endothelial dysfunction and intrarenal artery stiffness, by collecting brachial flow-mediated artery dilation (FMD) and intrarenal hemodynamic parameters such as RRI and S/D.

Results: All patients improved endothelial dysfunction and intrarenal artery parameters after a month of treatment with CPAP. We observed a significant reduction of RRI (p<0.001) and S/D (p<0.01). Moreover, a significant increase of FMD (p<0.001) was demonstrated in our patients. The AHI showed a negative correlation with delta FMD (r = -0.52, p <0.05).

Conclusions: Both intrarenal arterial parameters and FMD improve with CPAP therapy in OSAs patients. In our study, an effective treatment of OSAs patients with CPAP resulted in a decreased RRI and S/D, suggesting an improvement in renal perfusion. Also CPAP may specifically improves endothelial function. Oxygen desaturation and re-oxygenation related to intermittent hypoxia (IH) cycle is a major pathophysiologic character of OSAs and it is thought to be responsible for its association with increased cardiovascular morbidity and mortality. Endothelial dysfunction results from IH, representing an important pathogenic factor of atherosclerosis. The endothelial dysfunction was demonstrated both in OSAs patients and in IH animal models, providing a major link between acute cyclical IH during sleep and the increased prevalence of chronic vascular diseases. Further studies are needed to elucidate the role of CPAP therapy on the renal hemodynamic parameters and oxidative stress in OSAs patients.

A rare lung nodule

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Introduction: The authors describe a case of occasional diagnosis in the context of pulmonary nodules.

Case report: GG, male, 60 y. o. comes in our observation because a chest radiograph shows a rounded radiopaque image in the mean field of the right lung. Smoker of more than 60 p/y, for several months he has difficulty breathing in normal activity. He complains little morning cough with seromucous sputum. Chest examination shows a diffuse reduction of the auscultatory findings. The SO2 at rest on room air is 93% and the curve flow/volume shows: mild bronchial obstruction in the absence of bronchus...
Be careful to dysphonia!

Schiavo A*, Renis M**


Introduction: Detailed clinical history and careful physical examination of the patient are essential for correct diagnosis. The authors describe an emblematic case report.

Case report: C.C. female, 66, smoker (40 p/y), came to our attention because of dysphonia from 6 months. She had already practiced ENT visit: “paresis of the left vocal cord”, and therefore she had taken steroid and mucolytics without success.

We practiced chest examination: signs of pleural effusion, then confirmed by CXR. Thoracic CT: “left lesion invading the mediastinum and atelectasis of the lobar bronchi; abundant pleural effusion”. Echocardiogram: circumferential pericardial effusion; A/B balance: mild hypoxemia; Ultrasound abdomen and ECG within the limits; Spirometry compatible with functional alteration of restrictive type of moderate degree; Thoracentesis: exudative fluid; NSE: 35 (normal up to 12.) Bronchoscopy with biopsy in the left main bronchus: small cell lung cancer (SCLC).

Discussion: The symptoms of lung cancer may be missing for a long time. Dyspnea, cough and hemoptysis may not be present, as in the case described. It is necessary, therefore, investigate very carefully cigarette smoking because it can lead to exact diagnosis, avoiding delays. 15-20% of pleural effusions has cancer etiology, especially if exudative, and in a smoker. The sudden dysphonia in a smoker suggests a laryngeal pathology but, in the presence of pleural effusion and paresis of vocal cord, we have to imagine a disease which, invading the mediastinum, may damage laryngeal nerve. SCLC is a lung cancer that originates from neuroendocrine cells of the lobar bronchi; abundant pleural effusion”.

Conclusions: Smoking remains an independent risk factor for respiratory and cardiovascular disease. The case shows how much is still limited awareness among the people, and sensitivity among physicians, about this issue. At the age of 60 years and at an advanced stage of disease, this patient, in a fortuitous manner, comes to the diagnosis of COPD already in the respiratory failure. Despite its low frequency, the pulmonary nodule, in this clinical case, has allowed the diagnosis of an important and extremely widespread disease, as COPD.

Rheumatology

Worsening back pain after delivery: a case of pregnancy-induced severe osteoporosis

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A 37-year-old Caucasian woman during the last month of her first pregnancy had non-traumatic moderate low back pain. After the delivery, she was threatened with paracetamol and physiokinesis therapy. Three month after, she was referred to our clinic for persistence and increase of the back pain. She had difficulties with her daily activities and to carry her baby. At the physical examination, thoracic and lumbar vertebrae were tenderness on percussion, without focal neurological signs. She reported she was completely healthy before pregnancy. She was a non-smoker and there was no positive family history for osteoporosis or related risk factors. She never was exposed to corticosteroids or thyroid hormones, and her story was free from endocrine and ovariic disorders. However, it was noted that she take calcium supplementation during her pregnancy. The laboratory assessments revealed only a mild leucocytosis without other abnormality. Radiological examinations were conducted: on dorsolumbar spinal radiographs there was subsidence of the upper limiting somatic L1, anterior wedging of D11 and D9. There was adjustment in alignment on the coronal and sagittal planes with preserved Kyphosis-lordosis thoracolumbar curvature. Not evident alterations in character osteolytic/osteothickener. These results are consistent with the magnetic resonance imaging that showed also the involvement of the dorsal vertebral bodies from D6 to D10 and at the level of L1 with discal protrusion at D11-D12. Bone mineral density was measured by using a dual-energy X-ray absorptiometry: the results showed that L3 T score was -3 and total femoral T score was -2.6 that indicated severe bone loss. There were no signs of metabolic, metastatic or infectious bone disease based on laboratory and radiological findings. According to these findings she was diagnosed as pregnancy-induced osteoporosis. The patient was put on calcium carbonate 1,500 mg/day, vitamin D3 400 IU/day plus 25000 UI/monthly and strontium ranelate 2g/day were started immediately. Analgesics were recommended for pain management. In addition, she was advised to bottle-feed her baby. A rehabilitation program including muscle strengthening, range of motion and relaxation exercises as well as weight-bearing exercises was started. Actually, after 3 months of therapy the back pain has gradually decreased but still remains. She is in a program of continuous follow up every 3 months. Prevalence, etiology and pathogenesis of osteoporosis associated with pregnancy and lactation (PLO) is unclear, however seem to have a role family history, genetic, dietary habits, endocrine factors (like augmented levels of PTHrP, a low estradiol levels, an alteration of calcitonin or its receptor, an increase of calcium requirement) but their contribute in skeleton anomalies remains unclear. Cases of hip localization of transient osteoporosis are also described. Majority of the cases are seen late pregnancy or the first several months of lactation in women who never had a baseline measure of bone density, consequently in most cases remains unclear whether these fractures occurs in a previously abnormal skeleton or if during pregnancy and lactation bone strenght become compromised. Differential diagnosis in PLO are: inflammatory joint disorders, avascular necrosis of the hip, reflex sympathetic dystrophy. It’s possible in some cases to identify secondary causes like: anorexia nervosa, hyperparathyroidism, osteogenesis imperfecta, corticosteroid or heparin therapy. PLO is a rare condition and there are no specific recommendations in the Italian and international guidelines. In literature are described cases of resolution of back pain and reconstitution of bone mass by replacement and antiabsorbitive therapy. This case highlights
the importance of suspecting PLO in young pregnant/recent delivery women with severe and progressive back pain to treat quickly and prevent severe sequela that may occur.

References:

"amorphous material in the context of which are observed abundant red blood cells, macrophages, neutrophils, detection of neoplastic cells. was at the level of both the femoral condyles and the medial tibial plateau in part."

CRP 4.6 mg/dl (NV 0-1), ESR 75, fibrinogen 486 mg/l (NV 170 -410), total protein 6.4 g/dl;
Alpha 2 16.4 (7.1-11.8), 6,200 WBC, platelets 335,000. The urinary examination showed the presence of nitrates, ricketsaluminaurina and abundant microbial flora, fungi, red blood cells and leukocytes. Therapy was intravenous ciprofloxacin 400 mg/die. On February 26, arthrocentesis was performed and result: "cloudy appearance of synovial fluid, neutrophils and carpet of red blood cells are present and there are no neoplastic cells."

For the persistence of joint effusion and pain symptoms and suspicion of osteomyelitis, has been set therapy with Teicoplanin 400 mg (2 x 1 for 2 days) and then 600 mg/day, Meropenem 1g (1 x 3), Ciprofloxacin 400 mg (1 x 2), Metronidazole 500 (1 x 4), the latter subjected for the onset of dizzy syndrome. On March was performed further arthroscopy of the right knee: ".... presence of pannus which limits the motion and severe osteochondral damage. Synovecctomy and regularization of the meniscal margins with special instruments, was done. Microscopic examination of synovial fluid showed "amorphous material in the context of which are observed abundant red blood cells, macrophages, neutrophils, detection of necrotic cells, was negative. The anaerobic bacterial culture was negative; aerobic bacterial culture was positive for Staphylococcus capitis. Laboratory tests have documented subsequent negativity inflammatory markers and patient began a cautious rehabilitation. During the hospitalization the patient has performed TC right knee: "signs of bone resorption at the level of both the femoral condyles and the medial tibial plateau in part characterized by the presence of thin cortical erosions of the box with greater involvement of the slope where endosteal appreciates trabecular bone architecture rarefaction, to a lesser extent these findings can be appreciated even at the apex of the ridge and medial patella. It is associated with marked inflammatory joint commitment with distension fluid in the re-

A case of iatrogenic osteomyelitis after exploratory puncture joint

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Patient, female aged 49 with history of goitre and IDDM, was studied for inflammatory process of right knee, fever. In December 2012 she made MRI of right knee which evidence of “patellofemoral chondropathy with sub-chondral bone ischemic lesions affecting joints and ridge of patella; coexists area of bone marrow edema..... “. The recommended therapy at the time was NSAIDs But patient had no improvement. Blood examination for autoimmunity result normal. Persisting pain, functional impairment, and joint effusion, the patient underwent to a second RM: “normal appearance of the posterior cruciate ligament and anterior; degenerative phenomena are appreciated to load structures without evidence of meniscal lesions ; widespread alteration signal from bone marrow edema affects the tibial and femoral condyles ....”. Therapy was prednisone without benefit.

The patient was then admitted to our unit in February 2013. The inflammatory markers were:

CRP 4.6 mg/dl (NV 0-1), ESR 75, fibrinogen 486 mg/l (NV 170 -410), total protein 6.4 g/dl;
Alpha 2 16.4 (7.1-11.8), 6,200 WBC, platelets 335,000. The urinary examination showed the presence of nitrates, microalumunirina and abundant microbial flora, fungi, red blood cells and leukocytes. Therapy was intravenous ciprofloxacin 400 mg/die. On February 26, arthrocentesis was performed and result: "cloudy appearance of synovial fluid, neutrophils and carpet of red blood cells are present and there are no neoplastic cells."

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Effects of an individualized specific rehabilitation program on hand function and quality-of-life in long standing scleroderma patients: preliminary results

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Systemic Sclerosis (SSc) is a chronic connective tissue disorder, with skin and musculoskeletal involvement that may compromise global ability leading to a progressive disabling condition.

In SSc patients hand function may decline over time because of skin tightening and arthropathy and this has been identified as a major source of difficulty in activities of daily living.

The aim of our observational study was to evaluate the effectiveness of an individualized specific rehabilitation program of the hands in patients affected by Long-Standing Scleroderma, in order to reduce and prevent the cutaneous and musculoskeletal limitations.

We enrolled a group of 10 female SSc patients, mean age 56.0±16.3 years and mean disease duration 15±4.3 yrs. All of them fulfilled the ACR criteria for progressive SSc and each nail-fold capillaroscopy was classified as Scleroderma pattern1, late (70% of patients) and active (30%). Throughout the period of the observation they continued their own pharmacological treatments with no changes.

SSc patients were assessed at baseline (T0), at the end of each rehabilitation period (T1) and after a 24 months follow up (T2), by Hand Mobility in Scleroderma Test (HAMIS), Finger to Palm distance (FTP), Global disability and QoL. They were treated 3 times in a year, for 5 weeks, twice a week for 1 hour, with district specific techniques for hand involvement, manual lymph drainage, finger stretching and therapist-guided exercises.

The treatment was effective in improving hand mobility, exercise tolerance and quality of life. Range of motion gains were present in each finger after 3 months and maintained for 2 years, and afterwards HAQ score for hand functions, such as eating and gripping, was significantly decreased.

At the end of the 24 months treatment period, patients were asked to fill in a questionnaire about their level of overall satisfaction for treatment. Our SSc patients presented prominent hand disabilities that affect global disability and QoL. The encouraging outcomes obtained suggest that a specific manual rehabilitation program could play an important role in the treatment of SSc improving "physical activity" of the hands, with the maintenance of good Activity Daily Living (ADL) and a positive influence on the Quality of Life (QoL).

At this time, no home self management program has been prescribed, but evidence of results support the hypothesis that continuity of care is mandatory in the rehabilitation of SSc patients.

References:
Thrombotic thrombocytopenic purpura and Systemic Lupus Erythematosus: a rare association

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Case Report: We report the case of a 32-year-old woman, admitted to our clinical unit with purpura in the lower limbs and severe thrombocytopenia (PLT 9 × 10^9/L). She was suffering from systemic lupus erythematosus (SLE) since she was 12 years old (with skin involvement and positive anti-nuclear and anti dsDNA antibodies, treated with steroids and immunosuppressive therapy). The first episode of Thrombotic thrombocytopenic purpura (TTP) was at the age of 25 years and relapse in January 2013. When she was admitted, laboratory tests showed anemia (Hb 10.6 g/dl), reticulocytosis, thrombocytopenia (PLT 13 × 10^9/L), slight increase in bilirubin and LDH (408 U/L) and negative direct Coomb’s test. On the second day the patient presented intense headache, vomiting and schistocytes in peripheral blood (5 for field). The patient was treated with plasma exchange with improvement of symptoms, but persistence of mild thrombocytopenia and schistocytosis. Since there was an incomplete response to the treatment, we proposed to the patient a new treatment with anti-BLyS Belimumab human monoclonal antibody, recently approved for severe forms of SLE. The patient gave consent and she will start the therapy in a few days.

Discussion: TTP is a clinical syndrome characterized by microangiopathic hemolytic anemia, thrombocytopenia, fever, neurological symptoms, and renal involvement. The association between TTP and SLE has been recognized in the medical literature since 1939, and the incidence of this association is 0.5%. The coexistence of these two diseases causes high mortality. The differential diagnosis between these two conditions is often difficult because they have similar autoimmune pathogenetic mechanisms and clinical features. The mainstay to recognize TTP in the context of active SLE is the presence of helmet red cells, marked reticulocytosis, and negative direct Coomb’s test. As we know from scientific literature, TTP usually precedes overt forms of SLE but sometimes it occurs in the advanced stages of SLE with severe renal manifestations. Instead, in our case, the TTP appeared after 13 years from the diagnosis of SLE, when the disease was clinically silent. This new episode of TTP is maybe due to a poor control of the underlying disease (high value of anti dsDNA antibodies and reduction of complement fractions). Furthermore, considering the severity of the TTP and the increase in the risk of mortality resulting from the presence of the two diseases, we re-evaluated the background therapy of SLE, choosing as a therapeutic option the Belimumab, that is indicated as adjunctive therapy in adults patients with active SLE, autoantibody-positive, high degree of activity. Our goal was to obtain a resolution of the episode of TTP, a better control of the SLE and the prevention of future relapses that would compromise the life expectancy of the patient.

Handgrip and phalangeal ultrasound are predictive of fracture risk in postmenopausal women screened for osteoporosis

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Osteoporosis and fractures increase with aging and lifespan is increasing worldwide. To promote early diagnosis of osteoporosis and reduce the related social burden, we screened all the postmenopausal women referring to our Centre during the last World Osteoporosis Day. We announced the initiative by a single communicate via local newspaper and television, and by a locandina affixed to the entrance of the Outpatients Clinics the day before. The invitation was targeted to postmenopausal women who had never been diagnosed nor treated for osteoporosis and who intended to know the health status of their bones and their fracture risk. Screening was based on a personal interview focused on clinical risk factors (CRFs), and the risk of major osteoporotic and hip fractures over ten years was estimated using the online version of the FRAX (Fracture Risk Assessment Tool) algorithm. Phalangeal quantitative ultrasound (QUS) and handgrip, which are indicator of bone and muscle strength respectively, were also evaluated and correlated to fracture risk. Eighty-six subjects (mean age 61.2±8.7) were screened. The median risk of major osteoporotic fracture (%) in the whole population was 6.3 (3.6-10) and the risk of hip fractures was 1.1 (0.4-3). The median risk of fracture increased with the number of CRFs (p<0.001). Women over 65 years were found to be at higher risk in comparison with subjects under 55 years: the median risk of major osteoporotic fractures was 12 (8-19) and 3.1 (2.5-3.9), while the risk of hip fracture was 3.9 (1.8-10.5) and 0.4 (0.3-0.5) respectively. QUS values and handgrip were both significantly inversely related to fracture risk evaluated by FRAX (p<0.05).

As clinically appropriate, further investigations (e.g. DXA, RX, lab tests) were advised to women at higher fracture risk, in accordance to current Italian guideline. Application of FRAX combined with QUS and handgrip could be clinically useful to select women at risk for fracture suggesting further investigations, finally reducing social costs.

Noninvasive evaluation of conduction disturbances and cardiac arrhythmias in patients with sclerosis systemic

S.O.C. Internal Medicine - AZ. OSP. Pugliese-Ciaccio – Catanzaro

Background: Arrhythmias, conduction disturbances, and cardiac autonomic nervous system dysfunction are the most frequent cardiovascular complications in systemic sclerosis. Atrial and ventricular arrhythmias are common among asymptomatic patients with SSc and may be associated with poor outcome. Microangiopathy is the main histopathologic feature that is early detectable in the course of SSc and conduction disturbances in SSc are mostly due to the fibrosis of the sinoatrial node, but direct involvement of the cardiac conduction tissue and its arterial blood supply has also been reported. Patchy myocardial fibrosis provides an ideal substrate for tachyarrhythmias dependent on re-entrant circuits.

Objectives: to assess conduction disturbances and cardiac arrhythmias in a consecutive and non selected series of patients with Sclerosis Systemic. Patients and Methods: a total of 142 (122Women-20Men) unselected consecutive pts with SSc were included in our study. They had mean age 51.2 years (range 13-84), disease duration 12.2 years ±7.5 (range 1-24). All met the preliminary American College of Rheumatology classification criteria for SSc. And according skin cutaneous subsets: 16 pts (11.3%) with Early Sclerosis, 12 pts (8.4%) with intermediate cutaneous SSc, 72 pts (50.7%) with Limited cutaneous SSc, 42 pts (29.6%) with Diffuse cutaneous SSc. As expected all pts suffer from Raynaud’s Phenomenon and nailfold videocapillaroscopy (NVC) was performed on all patients, and skin sclerosis was measured with Rodnan Skin Score (mRSS). All the patients were assessed for cardiac complaints according to the World Health Organization (WHO) functional class, electrocardiogram (ECG) abnormalities, trans-thoracic echocardiography (ECHO) and N-terminal pro-brain natriuretic peptide (BNP).
with vasodilators and/or immunosuppressors. Among analyzed parameters, a total number of 57 new DU were observed in our patients’ series (38/142; 26.7%). There was also present in 7 patients (4.9%). During the 18-month period, a total of 13 patients had normal recording, 16/49 pts (11.2%) abnormal recording. The most common finding was an increased number of extrasystoles, 87% had >1000/24h, 7 pts had non-sustained ventricular tachycardia, 3 pts atrial arrhythmias, 2 pts AV II block.

**Conclusion:** AV conduction abnormalities and septal q wave/flow R pattern without QRS prolongation are common ECG findings found in SSc patients. Despite the mild clinical complaints, cardiac abnormalities in EchocG were found in 49.2% of pts, these findings reinforce the need to increase awareness of cardiac involvement in order to implement adequate prophylactic and therapeutic measures.

Clinical burden of digital vasculopathy in patients with systemic sclerosis

S.O.C. Internal Medicine - A.Z. OSP. Pugliese-Ciaccio – Catanzaro

**Background:** Vascular involvement plays a decisive role in SSc pathogenesis; it is responsible of some important clinical manifestations of the disease; more frequently Raynaud’s phenomenon and digital ulcers (DU) with a deep impact on patients’ quality of life, as well as scleroderma renal crisis and pulmonary arterial hypertension, associated to very poor prognosis. The management of DU is very challenging, risk factors are not well defined and the possibility to predict their appearance remains scarce. Objectives: to determine the clinical burden of severe digital vasculopathy we have reviewed hospital–based treatment for this important complication of SSc in a single centre cohort and we aimed to elaborate risk factors for developing new DU within six months from baseline evaluation taking into account demographic, clinic-serological, and capillaroscopic parameters.

**Patients and Methods:** a total of 142 (122Women-20Men) unselected consecutive pts with SSc were included in our study, and were reviewed during an 18-month period. They had mean age 51.2 years (range 13-84), disease duration 12.2 years ±7.5 (range 1-24). All met the preliminary American College oh Rheumatology classification criteria for SSc. And according skin cutaneous subsets: 16 pts (11.3%) with Early Sclerosis, 12 pts (8.4%) with intermediate cutaneous SSc, 72 pts (50.7%) with Limited cutaneous SSc, 42 pts (29.6%) with diffuse cutaneous SSc. As expected all pts suffer from Raynaud’s phenomenon and nailfold videocapillaroscopy (NVC) was performed on all patients, and skin sclerosis was measured with Rodnan Skin Score (mRSS). A wide patient’s anamnesis, with particular attention to previous history of DU, was also recorded, as well as ongoing treatments, mainly vasodilator or immunosuppressive therapies, and the presence of comorbidities potentially responsible for digital ischemia.

**Results:** 38 patients (29 F and 7 M) with SSc were affected by DU, PAH was also present in 7 patients (4, 9%). During the 18-month period, a total number of 57 new DU were observed in our patients’ series (38/142; 26.7%). There was not significant association between DU and treatment with vasodilators and/or immunosuppressors, Among analyzed parameters, cutaneous SSc subsets, disease duration, history of DU in the last year, smoke, DLCO, CSURI, ESR, and CRP showed a significantly positive association with DU. The frequency of DU was significantly higher among the patients with diffuse cutaneous subset of SSc compared with the patients with limited cutaneous SSc (p<0.001). More Digital Ulcers were present at the end of the cold season from February to May. The average number of DU episodes over the 18-month period in these patients was 1.4, while the average number of ulcers they had was 2.1. Sixteen patients (11.2%) developed digital gangrene, in seven patients (4.9%) this resulted in auto or required surgical amputation. All the 38 patients (26, 7%) were admitted to hospital at least once to receive intravenous prostacyclina or immunosuppressors during the 18 month window.9 patients (6, 3%) required multiple admissions; there were a total of 62 admissions with a mean duration of 9 days, which accounted for a total of 358 bed-days, 3 patients were died for PAH, all the patients required parenteral antibiotic for infected digits and needed opioid analgesic for DU-related pain.

**Conclusion:** DU represents a burdensome clinical manifestation in course of SSc, digital vasculopathy is a serious complication of SSc contributing significant morbidity and often requiring hospital admissions and management. The systematic evaluation of capillaroscopic findings, ESR, and clinical examination could help to identify patients at risk to develop DU and to optimize the therapeutic approach including preventive vasoactive therapy.

Capillaroscopic analysis in patients with Raynaud’s phenomenon

S.O.C. Internal Medicine - A.Z. OSP. Pugliese-Ciaccio – Catanzaro

Raynaud’s phenomenon (RP) is essentially an exaggerated vasospastic response to cold or emotion, and is the earliest clinical symptom of digital microcirculatory involvement and can be considered one of the risk factor for the development of a connective tissue disease. Nail fold capillaroscopy is a useful non invasive tool to evaluate micro vascular involvement, and is the most reliable method to distinguish between primary and secondary Raynaud’s phenomenon.

**Objective:** to describe our single centre experience in the use of nail fold capillaroscopy.

**Methods:** Review of the all nail fold capillaroscopies done in our centre between January 2009 and December 2012. Nail fold capillaroscopy(NFC) was performed using a Videocap 3.0 (DS Medica) with magnification 200x. NFC examinations were performed by the same experienced investigator, four consecutive fields were examined bilaterally in the middle of the nail fold for any single finger (2,3,4,5). The following NFC findings interpretation was accepted: capillary density was calculated as the number of capillaries in the distal row on the non dominant hand, an avascular area was defined as the lack of two or more consecutive capillaries, neovascularization was defined as bushy,branching,ramified and coiled capillaries, giant capillaries as a homogeneous enlarged diameter of both afferent and efferent limb>50 micron, enlarged capillaries was defined as homogeneous enlarged diameter of both afferent and efferent limb>50 micron, enlarged capillaries was defined as homogeneous enlarged diameter (> width >30 and < 50 micron, were also recorded microhaemorrhages and microaneurysm.

**Results:** 3978 nail fold capillaroscopies were made in patients who had RP (89% females, 11% males). The mean age of these patients was 48, 2 (range 5-79) years. In 227 pts (5, 7%) was found the scleroderma pattern: 82 (36, 1%) could be classified as having early pattern, 102 (44, 9%) as having active pattern, 43 (19%) as having late pattern. Others 272 pts (6, 8%) were classified as having secondary RP fitting the classification of a specific rheumatic disease: 84 (LES), 58 (Sjögren’s Syndrome), 74 (RA), 26 (MCTD), 30 (UCTD). In 404 pts (10, 1%) were found some capill-
laroscopic abnormalities (hemorrhages and dilated and winding capillar-
ies) and were classified as suspect secondary RP without yet fitting the 
classification of a specific rheumatic disease. 3075 exams (77.4%) were 
considered normal capillaroscopies and corresponded to patients that did 
not have any diagnosed disease (primary RP).

**Conclusion:** Nail fold capillary microscopy is a very useful method in the early diagnosis of some CTDs, nail fold capillary microscopy detects the early micro vascular involvement that characterize secondary RP and the changes are quantifiable.

**Association between acro-osteolysis and severity of digital ulcers in patients with systemic sclerosis**

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S.O.C. Internal Medicine - Az. Osp. Pugliese - Ciaccio – Catanzeno

Digital ulcers reflect the vascular abnormalities and fibrosis that charac-
terize the disease process of SSC. The bony resorption of terminal digital 
tufts (acro-osteolysis) is a under-researched manifestation of SSC. Objectives: to investigate the association between acro-osteolysis, the presence of calcinosis and the severity of digital ulcers; to assess the vari-
ation of digital ulcers number in SSc patients receiving a combined thera-
py with prostanoids and endothelin receptor antagonist Methods: Data 
were collected retrospectively from patients with DU, with and without 
pulmonary arterial hypertension, who were initiating bosentan and prosta-
noïds therapy in 2004 (8 patients), in 2005 (6 patients), in 2006 (4 pa-
tients), in 2007 (10 patients), in 2008 (10 patients) and followed until 
December 2012. Relevant measures included number of DU; occurrence 
of new DU, overall DU clinical status: improved, stabilized, and worsened. 
We explored associations of disease subset, antibody profile, organ in-
volvement, season, time interval after onset of Raynaud’s phenomenon 
with development of DU and we describe potential risk factors for DU. All 
the patients underwent a hand radiographs and for the purpose of the study 
a grading scale for acro-osteolysis was developed: 0= normal bone struc-
ture, 1 = resorption of most of the distal tip of the terminal tuft, 2=resorp-
tion of most of terminal tuft, 3 = severe penciling of the terminal pha-
langes. Calcinosis was subdivided into mild, moderate and severe de-
pending on the density of calcinosis and the number of separate sites of 
calcinosis. Results 38 patients (29 F and 7 M) with SSC and DU were in-
cluded. PAH was also present in 7 patients (18.4%). At the start of com-
bined therapy (bosentan + iloprost), the median number of DU was 3.0. 
More Digital Ulcers were present at the end of the cold season from 
February to May (p 0.036). Of 38 patients, 28 (73.6%) had an acro-os-
teolysis rating of 0-1 (normal/minimal), 2 (5.1%) patients had a rating of 2 
(moderate) and 8 (21.3%) patients had a rating of 3 (severe). 16 patients 
(40.2%) had radiographic calcinosis; although patients with acro-osteol-
sis were more likely to have severe calcinosis, this association was not sta-
tistically significant. With the combined therapy 32 patients (84.2%) im-
proved, in these patients digital ulcers healed within an observational pe-
riod of 2.80 months (min 1,max 6 months), 3 patients (7.8%) stabilized, 
3 patients (7.8%) had soft tissue infection requiring antibiotics, followed 
by gangrene and finally by surgical amputation. At 24’ month of combined 
therapy 24 patients (63.1%) did not develop any new DU. After the follow-
ups at December 2012, of 8 patients with severe acro-osteolysis: 3 patients 
were died for PAH, 3 patients underwent surgical amputation, 2 pts ( 
5.1%) had active digital ulcers. Conclusion Our study suggests that acro-
osteolysis is another ischaemic manifestation of SSC and may also be as-
associated with calcinosis. Acro-osteolysis is associated with severity of 
digital ulcers. A validated acro-osteolysis scoring system could become a 
marker of digital vascular disease progression and of treatment response.

**IMPRESS 2 (International Multicentric Prospective study on Pregnancy in Systemic Sclerosis), Prospective, case-control study of pregnancy in systemic sclerosis**

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University, Washington DC; Policlinico Federico II, Napoli

**Background:** Systemic Sclerosis (Scleroderma, SSC) has its usual onset in 
the mid-forties, but it is not unusual to find Scleroderma women wanting 
a child, especially nowadays where a great number of women delay preg-
nancy. Data on pregnancy in SSC are limited. We recently published a 
large retrospective study: IMPRESS: Italian Multicentric study on 
PREgnancy in Systemic Sclerosis, partially supported by Italian patients 
associations, that studied 99 SSC women and their 109 pregnancies, ad-
mitted in 25 Italian centers within the years 2000-2011, compared with a 
general obstetric population (GOP). In SSC women preterm deliveries 
(25% vs. 12%) and severe preterm deliveries (<34 weeks) (10% vs. 5%), 
intrauterine growth restriction (IUGR, 6% vs. 1%) and very-low-birth-
weight babies (5% vs. 1%) were significantly more frequent than in the 
GOP. Multivariable analysis found that corticosteroid use was associated 
with preterm deliveries. The disease remained stable in most SSC patients, 
but there were four cases of progression within one year from delivery.

**Aim of the study:** to plan a new fully prospective study: IMPRESS 2 
(International Multicentric ProSpective Study on PREgnancy in Systemic 
Sclerosis).

**Patients and methods:** we are planning a fully prospective, case-control 
study of 3 groups of people, enrolled at an International level: 1. 100 preg-
nant SSC patients, 2. 200 non-pregnant matched SSC women, 3. 200 
healthy pregnant women. Their children will be studied at birth and at 1 
and 3 years of age. IMPRESS 2 study will prospectively investigate dis-
ease activity of SSC during and after pregnancy, pregnancy complications 
and outcome in patients with SSC, children outcome at 1 and possibly 3 
years, and the modern incidence of renal crisis, severe cardiac involvem-
ent and pulmonary hypertension in women with SSC, both pregnant and non-
pregnant. Papa Giovanni XXIII ethical committee has approved the study, 
and enrolment is started: 14 pregnancies worldwide are currently ongoing.

**Expected results and Conclusion:** IMPRESS 2 will answer to the fol-
lowing important questions. 1. are complications of SSC more frequent 
during pregnancy than in the non-pregnant state? 2. Which is the current in-
cidence of renal crisis, cardiac involvement, and pulmonary hypertension 
development in scleroderma women, both pregnant and non-pregnant? 3. Is 
folic acid use protective for prematurity? 4. Are some autoantibodies pro-
tective for prematurity? 5. Which is the impact of prematurity on children 
development? Which is their IQ at 3 years? These data will be extremely 
important for counseling fertile SSC women contemplating a pregnancy.

**Haemostatic and fibrinolytic changes in subjects with psoriatic arthritis. The effect of the treatment with TNF-α inhibitors**

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**Objective:** To prospectively evaluate the effect of TNF-α inhibitors on haemosta-
static and fibrinolytic variables in subjects with Psoriatic Arthritis (PsA).
Methods: Among PsA subjects under traditional DMARDs, 98 patients with an active disease switching to a treatment with TNF-α inhibitors were enrolled in this study (Group 1). In parallel, 98 matched subjects in minimal disease activity (MDA) and continuously treated with DMARDs were enrolled (Group 2). In all patients, haemostatic and fibrinolytic variables were evaluated at enrolment and after a 6-month follow-up. Results were stratified according to treatment and to MDA achievement.

Results: Seventy-six Group 1 and 80 Group 2 subjects completed the 6-mo follow-up. During the follow-up, significant changes in haemostatic and fibrinolytic variables were found in Group 1, but not in Group 2 subjects. At the end of the follow-up, patients treated with TNF-α inhibitors showed significantly lower levels of haemostatic and fibrinolytic variables as compared to those continuously treated with traditional DMARDs. Among Group 1 subjects, changes in haemostatic and fibrinolytic variables levels resulted significantly higher in those achieving MDA than in those that did not. Multivariate analyses showed that a treatment with TNF-alpha blockers impacted on fibrinolytic parameters (PAI-1 and t-PA) and on some acute phase proteins (D-Dimer, FVIII and vWF). In contrast, the MDA achievement during treatment with TNF-alpha blockers maximally impacted on fibrinolytic parameters (PAI-1 and t-PA).

Conclusion: TNF-α inhibitors determined a significant improvement of haemostatic and fibrinolytic balance in PsA subjects, maximal changes being found in patients achieving MDA.

Lipid profile changes in patients with rheumatic diseases receiving a treatment with TNF-α blockers: a meta-analysis of prospective studies

Matteo Nicola Dario Di Minno[1], Pasquale Ambrosino[1], Rosario Peluso[1], Gaia Spadarella[1], Alessandro Di Minno[1], Roberta Lupoli[1], Francesco Dentali[2]


Background: TNF-α blockers improve the cardiovascular (CV) risk profile in rheumatic patients. Although some studies showed an anti-atherogenic effect of TNF-α blockers on lipid profile, these data have been challenged.

Objective: To perform a meta-analysis on changes in lipid profile after treatment with TNF-α blockers in patients with rheumatic diseases.

Methods: Electronic databases were searched to identify prospective studies on rheumatic patients treated with TNF-α blockers and providing values before and after treatment of triglycerides (TGs), total cholesterol (TC), HDL-cholesterol (HDLc), LDL-cholesterol (LDLc) and atherogenic index (AI) were included. Lipid profile changes were analyzed at short-term (2–12 weeks), mid-term (13–24 weeks) and long-term (25–52 weeks). Analysis of standardized mean differences (SMD) was carried out and random effects model was used to take into account the heterogeneity among the studies.

Results: A total of 30 articles (1707 patients) were included in the analysis. A treatment with TNF-blockers determined a significant increase in TC at short, middle and long term assessments (SMD: 0.20 mmol/l; 95%CI: 0.04, 0.35; p=0.01, SMD: 0.27 mmol/l 95%CI:0.08,0.46; p=0.005 and SMD: 0.22 mmol/l; 95%CI:0.01,0.43; p=0.04). A significant increase was found in HDLc at the short term (SMD:0.19 mmol/l; 95%CI:0.10,0.28; p<0.001) but not at the middle and long term assessments. TGs levels showed a progressive increase overtime, achieving a significant increase at the long-term assessment (SMD:0.19 mmol/l; 95%CI:0.04,0.34; p=0.02). In contrast, LDLc and AI were not affected by TNF-α blockers treatment.

Conclusions: Slight but significant increase in TC occurred without any significant change in LDLc and AI. Changes in HDLc and TGs were not consistent among the different time-point assessment. These quantitative changes in lipid profile do not seem to be able to explain CV risk improvement reported in patients receiving TNF-α blockers. Further studies on other mechanisms should be assessed to address this issue.

A case of fever and weight loss

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A patient of 81 yrs, male, was admitted to our Emergency Room for the presence of fever for one week, associated only to to a slight headache and cough. The patient had a prostatic cancer in hormonal therapy and a non-critical carotid artery stenosis treated with acetylsalicylate and he had a history of gastric ulcer related to non-steroidal anti-inflammatory drugs. The fever was scarcely responsive to paracetamol. The patient had been treated with amoxicillin/clavulanate and successively with ceftriaxone, without clinical improvement. At arrival to the Emergency Room, physical examination was normal. The patient performed blood exams showing an increase of CRP (10.3 mg/dl), a CT of the brain and a chest X-ray, both negative. The patient was therefore admitted to our Emergency Medicine Division. During the in-hospital stay, blood exams showed a persistent elevation of CRP (maximum 13 mg/dl) without leukocytosis, normal function of liver, kidney and thyroid, normal red cell count, negativity of tumor markers and autoantibodies. An empyrical therapy with levofloxacin was started. Multiple specimens for culture were examined (urine, blood, upper airways tampons), all with negative results. For the presence of pain in the lumbar sacral region a bone scintigraphy and a magnetic resonance were performed, showing only the presence of arthrosis. For the persistence of fever, the patient underwent further exams: a total body CT-scan, a gastroscopy and a colonoscopy, an echocardiogram without significant findings. As the patient presented a significant and progressive weakness, associated to an increase of ESR and a weight loss, a clinical suspect of polymyalgia rheumatica arised and a therapy with prednisone was started. A dramatic clinical improvement was observed, with the disappearance of the fever. Finally, a PET showed a significant uptake of the aortic arch and a definitive diagnosis of giant cell arteritis (or Horton arteritis) was established. Giant Cell Arteritis-It is a chronic, systemic vasculitis affecting large and medium vessels, with an histologic pattern of granulomatous inflammation. Patophysiologic findings in affected organs result from the ischemia related to inflammatory vessel disease. It involves predominantly the cranial branches of arteries arising from the...
arch of the aorta and its incidence varies between 7 and 29/100 000 in people aged >50 years in Europe; prevalence is higher in women. Temporal artery inflammation is frequent, especially in association to polymyalgia rheumatica and for this reason the disease is also known as temporal arteritis. The symptoms are often systemic (such as fever, weight loss, loss of appetite, weakness). Anemia and high ESR are common. In the case of temporal arteritis symptoms may include headache, jaw and tongue claudication, visual impairment, presence of tenderness of the artery, appearing thickened or nodular. Ischemic optic neuropathy is a threatening complication in untreated patients and sudden blindness may occur. Aortic imaging should be considered in suspected large-vessel disease as subclinical involvement is common and may progress to form aortic aneurysm or dissection. Diagnosis is often clinical, but biopsy of temporal artery is sometimes necessary. Positron-Emission Tomography (PET), as in the present case, has an important diagnostic role in arteritis involving arteries exceeding 4 mm in diameter, permitting to avoid the biopsy, but it is not able to detect the pathology when inflammation is limited only to temporal arteries. The treatment is based on glucocorticoids (usually starting with prednisone 40-60 mg/d), with the goal to reduce symptoms and prevent visual loss or vascular events.

Correlation between nail fold capillaroscopic parameters and frequency of anti-cyclic citrullinated peptide antibodies in psoriatic arthritis


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Background: Psoriasis is a chronic inflammatory skin disease involving various factors and autoimmune pattern. About 2-3% of the population is affected by this chronic inflammatory disease, a part of patients with longstanding psoriasis (about 25%) will develop psoriatic arthritis (PSA), sharing some characteristics of spondyloarthropathy. Psoriatic arthritis has been found to be associated with class I of the major histocompatibility complex and noted a number of commonalities with Rheumatoid Arthritis. The anti-cyclic citrullinated peptide antibodies (anti-CCP) were usually found in patients with Rheumatoid Arthritis (RA), and their presence is also associated with more destructive joint damage and aggressive course of the disease.

Objectives: the aim of the study was to determine the frequency of anti-CCP antibodies in patients with psoriatic arthritis and to evaluate their association with disease severity as well as to assess the Parvovirus B19 infection, and with capillaroscopic parameters.

Methods: The study included 46 pts (33 Females-13 Males, mean age 54.8 years, range 24-88 years) with PSA, we analyzed serum levels of anti-CCP antibodies by ELISA and we determined serum white blood cell count, erythrocyte sedimentation rate, C reactive protein and anti Parvovirus B19 antibodies. Patients underwent rheumatologic examination and symptoms were assessed using standardized questionnaires about psoriasis, smoking, drinking; and severity, frequency, distribution and number of articular symptoms was recorded. The disease severity was scoring using the PASI, and were recorded the number of involved joints, axial involvement with inflammatory lumbar pain, axial enthesopathy, spondiloarthropathies, and sacroiliitis graded between 2-3 according to New York criteria. Nail fold capillaroscopy was performed using a Videocap 3.0 (DS Medica) with magnification 200x. Sera from age and sex matched healthy volunteers (n=20) were used as controls.

Results: Detection of anti-CCP was possible in 38 pts with PSA (82, 6%) vs one (5%) healthy volunteer (p < 0.003). Moreover higher titration of anti-CCP was in 20 PSA pts with higher PASI vs PSA pts with intermediate PASI (p< 0.01). The prevalence of anti-B19 was 39, 1% (18 pts with PSA) vs 35% (7 healthy volunteers) p NS. The 20 PSA pts with higher PASI vs 18 PSA pts with intermediate PASI had higher ERS, higher CRP and a longer disease duration (>10 years). The 20 PSA pts with higher PASI and higher anti-CCP had stronger inflammation vs 18 PSA pts with intermediate PASI, had more aggressive muscular skeletal disease with osteonecrosis and HLA DR 7 positivity. In these 20 PSA pts by capillary microscopy were detected nailfold capillary abnormalities: micro hemorrhages, ectasias, microaneurysm, occurrence of dystrophic loops, arterio-venous sludge in 100% of pts vs 33, 3% of other group (18 pts). Micro hemorrhages tended to be associated with articular symptoms (p <0.05), with lower age at disease onset (p <0.01), with higher value of anti-CCP (p= 0.001).

Conclusion: our study shows a strong association among PSA and anti-CCP and could reflect a general chronic inflammation rather than joint inflammation. The high prevalence of anti B19 abs in pts with higher PASI suggests that Parvovirus B19 infection may play a role in psoriasis severity.

Fever and arthralgia: a couple to investigate

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A 23-year-old girl was seen in our internal medicine division because of fever, swelling and pain in the metacarpophalangeal, proximal and distal interphalangeal joints and knees. The patient had been in her usual health until approximately 20 days earlier. On examination, we didn’t find phlogosis signs in above-mentioned joints that, however, were aching at palpation. Laboratory-test results showed mild microcytic anemia (Hb 10.4 g/dL, MCV 73 fl) with sideropenia (17 mcg/dL, range 10-40) and hyperferritinemia (163 ng/mL, range 13-150), erythrocyte sedimentation rate at first hour of 28 mm and increased levels of c-reactive protein (4 mg/dL, range 0.0-0.5); rheumatoid factor and cyclic citrullinated peptides (CCP) were negative. We performed a therapy for 15 days with low-dose steroids as criterium exudativus obtaining considerable improvement. Two months later, the patient returned for relapse of symptoms accompanied by nonpuritic but painful urticarial lesions that persisted for about 72 hours, with left over cutaneous hyperpigmentation, ocular erythema and oral angioedema. On examination, the sclerae were injected and there were urticarial plaques with bilateral and symmetrical distribution on all body surface; the metacarpophalangeal, proximal and distal interphalangeal joints of the hands were swollen and tender. There wasn’t evidence of cutaneous or nail’s psoriasis. Laboratory-test results showed a worsening of anemia (Hb 9.7 g/dL); assays for antinuclear antibodies, Ro (SSA), La (SSB), Sm, RNP and ANCA were negative. However, we found low levels of complement proteins C3 (70 mg/dL, range 90-180) and C4 (7 mg/dL, range 10-40). The prominent cutaneous finding in this patient was urticaria. The lesions of simple urticaria are pruritic, edematous, evanescent plaques that last less than 24 hours. In contrast, the lesions of urticarial vasculitis tend to be painful or to burn rather than itch, generally last longer than 24 hours, and often heal with hyperpigmentation. Arthritis was another striking feature of this patient’s illness. She was unable to make a fist because of arthritis in his metacarpophalangeal, proximal and distal interphalangeal joints. This pattern is classic for an inflammatory arthritis. Radiographs of the hands showed no erosions. The deep purplish areas of the eyes suggested a diffuse scleritis. Among rheumatologic disorders that are associated with vasculitis, the most common causes of scleritis are rheumatoid arthritis, ANCA-associated vasculitides, particularly granulomatous polyangiitis, Henoch–Schoenlein purpura and hypocomplementemic urticarial vasculitis syndrome (HUVS). Several points argue against rheumatoid vasculitis as the diagnosis: it’s generally a complication of severe, long-standing, destructive rheumatoid arthritis, and
this patient had had joint symptoms for only a few weeks. The radiographs of the hands did not show the classic bone erosions. The patient had not clinical and laboratorial features of ANCA-associated vasculitis. Purpura is the sine qua non of Henoch–Schönlein purpura. We believe that the diffuse rash, the scleritis and the profound hypocomplementemia were consistent with HUVS. Hypocomplementemic urticarial vasculitis syndrome is characterized by urticarial vasculitis, possibly accompanied by fever, arthralgias, arthritis, scleritis and angioedema. Cardiovascular involvement is rare but can result in pericarditis: indeed an echocardiography showed a pericardial effusion with stimulated amount of fluid of about 200 cc. A biopsy specimen of a skin lesion revealed findings consistent with leukocytoclastic vasculitis and confirmed our diagnostic hypothesis. The administration of prednisone, 25 mg twice daily, and hydroxychloroquine 200 mg, once per day, was begun. At a follow-up appointment 21 days later, the patient reported absence of fever, urticaria and arthralgia with reduction of pericardial effusion.

**Circulating progenitor cells in rheumatoid arthritis**

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Circulating progenitors (CPCs) are multipotent precursors of different cell types of cardiovascular system, that participate in the turnover of healthy and damaged tissues, delaying atherogenesis and cardiovascular disease (CVD); an impairment of CPC number and function is reported in conditions of high CVD risk. Patients affected by rheumatoid arthritis (RA) present accelerated atherosclerosis and increased CVD; CV risk factors alone do not fully explain this difference. The inflammatory pathways in atherosclerosis and RA show striking similarities; in RA, the increased production of inflammatory mediators, including C-reactive protein (CRP), have detrimental effects on the endothelium leading to its dysfunction and lesions. Synovial neoangiogenesis is sustained by intraarticular CPC recruitment; it was suggested that while CPCs are recruited into the joints, cell depletion may occur in peripheral blood, impairing vascular repair. Excessive intracellular reactive oxygen species (ROS) is a common feature of CVD and RA. CPCs tolerate oxidative stress by enhancing antioxidant enzymes including superoxide-dismutase (MnSOD), catalase (CAT) and glutathione-peroxidase-type1 (GPx-1), which physiologically catalyze ROS inactivation: MnSOD partially inactivates ROS, generating free radicals that should be finally inactivated by cataleses and peroxidases. NADPH-oxidases (NOX) represent a source of ROS for CPCs. A slight increase of ROS promotes vascular repair and angiogenesis preventing tissue injury, while excessive ROS accumulation is toxic. Inflammation and oxidative stress affecting antioxidant system lead to CPC dysfunction, senescence and death, suggesting a key role of the redox balance in maintaining CPCs. In the present study we investigated the relationships between inflammation, CPCs, antioxidant enzymes and ROS in RA patients without additional risk factors for CVD; we also assessed arterial stiffness (AS) indices and carotid intima-media-thickness (cIMT), patterns of preclinical atherosclerosis. We recruited 33 patients (14 men and 19 women) and 33 healthy controls. Exclusion criteria were: diabetes mellitus, hypertension, dyslipidemia, thyroid, liver or kidney diseases, obesity, smoking habit, alcohol consumption, abnormal electrocardiographic or echocardiographic pattern, clinical history of CVD. No subject was taking any medication. Patients should not have been ever treated with immunosuppressive drugs, steroids, or DMARDs. Patients should not take NSAIDs for at least two weeks before inclusion. We evaluated fibrinogen, erythrocyte sedimentation rate (ESR), CRP, and Disease Activity Score (DAS). Fresh blood flow cytometry was used for cell identification. Cells that expressed the stem cells antigen CD34 were defined as progenitors, estimated and counted. The expression of MnSOD, GPx-1, CAT and NOX2 in CD34+ cells was evaluated by Real-Time PCR after the samples enrichment by immunomagnetic sorting (MiniMACS), and ROS levels by a fluorimetric method. cIMT and AS indices (Augmentation index: Aix, Pulse wave velocity: PWV) were measured by eTRACKING software implemented in Aloka ProSound Alpha10. Data distribution and sample size suggested to use a permutation test-based approach. The Non Parametric Combination test was used for comparisons. The correlations among the variables were assessed by Spearman’s test. The contribution of each variable on study variables was investigated by a multivariate regression analysis on whole study population; CPCs were tested for dependence from each potentially associated variable in RA patients by using univariate regression strategy. Age, BMI, gender, blood pressure, glucose and lipids were not different in patients and controls. Fibrinogen (345.5±74.6 mg/dl), CRP (6.89±4.5 mg/dl), ESR (34.1±14.6 mm/h), cIMT (1.16±0.2 vs 0.81±0.1 mm), PWV (7.87±2.9 m/s) and Aix (10.9±12.6%) were higher in RA patients (all p<0.001), while CPCs were reduced (1.89±0.59 vs 2.32±0.34 cells/µl, p<0.001) and displayed higher ROS levels than controls (107.3±73.3 vs 49.2±10.7 FU, p<0.001). In RA patients MnSOD was increased (1.62±0.65 n-fold, p<0.001), while GPx1 and CAT were reduced (0.88±0.26 n-fold, p<0.005; 0.85±0.51 vs n-fold, p<0.001). In whole study population we found a correlation between CRP and MnSOD, NOX2, ROS, PWV (all p<0.001) and Aix (p<0.005), while a negative correlation was found with CAT and GPx-1 (p<0.005 and p<0.01, respectively). CPCs were significantly correlated with CRP, ESR, PWV (all p<0.001), Aix (p<0.005), Fibrinogen and ROS (p<0.01). In RA patients CPCs correlated inversely with CRP (p<0.005), ESR (p<0.001), Fibrinogen, ROS, DAS (all p<0.01), PWV and Aix (both p<0.05). In controls the negative correlation between CPCs and CRP was confirmed (p<0.001), while ROS were positively correlated (p<0.005); no correlations with ESR, PWV or Aix. In RA patients Aix and PWV were not correlated with CRP, but with DAS (Aix: p<0.001; PWV: p<0.005) probably because in this model of chronic inflammation AS is a consequence of the inflammatory environment rather than the effect of a unique factor. Dependence analysis confirmed the negative association between Fibrinogen, CRP and ESR with CPCs. ROS appeared the main intracellular negative predictor for CPCs. ROS resulted to be associated with Fibrinogen and CRP plasma levels, and negatively associated with Aix. NOX2 and MnSOD were confirmed as main responsible of ROS accumulation. In RA patients, the univariate models for CPCs confirmed the negative association with CRP and ESR (both p<0.001), Fibrinogen (p<0.003), and DAS (p<0.01) among extracellular factors, and with ROS, NOX2 and MnSOD (negative), CAT and GPx-1 (positive) among intracellular factors (p value: <0.001, <0.001, =0.002, =0.007 and =0.016, respectively). DAS was significantly associated with Aix (p<0.01) and PWV (p<0.05). In conclusion, our data show that in RA patients, inflammation and oxidative stress are associated to the reduction of CPC number and to the impairment of their antioxidant system; this report suggest a perspective about the accelerated development of endothelial damage and atherosclerosis in RA.

**Systemic necrotizing vasculitis and myelodysplastic syndrome: a rare unfortunate association**

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A 58 year old male was referred to our unit for a clinical picture characterized by fever, profound fatigue, weight loss, painful subcutaneous nodules on the upper and lower limbs, numbness on the lower limbs, severe anemia and an
increase of inflammation markers present by several months. The research for infectious diseases was negative. The biopsy of a subcutaneous nodule had revealed a picture pathognomonic for vasculitis of medium-sized vessels (partially thrombosed vessels with the presence of dense inflammatory infiltrate in the absence of granulomas). The clinical and laboratory findings with the biopsy supported diagnosis of systemic polyarteritis nodosa (PAN). Therefore the patient was treated with high-dose steroid and methotrexate, but the clinical picture reappeared when steroid was tapered. It was decided to start intravenous cyclophosphamide infusion (750 mg/m² monthly) but was suspended after the third infusion for a severe infectious complications (pneumonia and gastrointestinal infection with acute abdomen). The patient was kept only in steroid therapy. Nevertheless, such was anemia to require periodic transfusions, and thrombocytopenia and leukopenia arose, too. When the patient came to our attention a relevant pancytopenia, apparently not related to immunosuppressive therapy, was evident. Therefore we decided to perform a osteoemedullary biopsy that showed a non specific picture. The bone marrow immunophenotyping demonstrated an aspecific increase proportion of immature cells and the cytogenetic analysis resulted normal. Because of persistent disease activity high-dose steroids were maintained, but the patient continued to be affected by many infectious complications. Few months later, persisting both the clinical picture despite steroid therapy and the pancytopenia, we decided to perform a second osteoemedullary biopsy which resulted suggestive for myelodysplasia. In the literature it was described the presence of systemic and/or immune manifestations in the course of myelodysplasia. In patients with myelodysplastic syndrome it was observed a difference in survival that was related to presence/absence of systemic vasculitis events (1,2). A clinical onset of myelodysplastic syndrome as panarteritis nodosa is not frequent. The pathophysiology of the vasculitis in the course of myelodysplastic syndrome is not well understood, some authors suggest the presence of an alteration of the phenomena of autoimmunity due to the basic hematologic disease (3,4). Therefore it seems suitable more early and aggressive therapeutic approach of myelodysplasia, consisting of recombinant human erythropoietin and growth factors (G-CSF and GM-CSF), to improve both the therapeutic approach of myelodysplasia, consisting of recombinant human erythropoietin and growth factors (G-CSF and GM-CSF), to improve both the

References:

Osteogenesis imperfecta: a complicated case report

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We describe the clinical case of a 52 year-old male, admitted in our Internal Medicine Department because of necessity to reevaluate the clinical condition of his Osteogenesis Imperfecta (OI) type I, that was diagnosed 5 years ago. In his medical history: hypercholesterolaemia since 2011, actually treated with statin; surgical intervention because a nasal septum deviation 20 years ago; bilateral otosclerosis since 2005; surgical intervention because a displaced distal radius fracture on February 2013; compound elbow fracture in 2007; acid acetylsalicylic allergy. On February 2013 he decided to stop smoking 10 cigarettes in a day. At physical examination: weight 88 Kg, height 173 cm, blue sclerae, blood pressure 125/90 mmHg, cardiac rate 60 bpm, a 4/6 grade murmur at cardiac apex, but not shorteness of breath at rest. At chest examination diffuse sour breathe, without pathological sounds; at abdominal examination no pathological evidences were found. The blood examinations showed hypercalcemia (22.1 mg%), Hemochrome, coagulation, liver and kidney functionality markers were normal. PTH, vitamin D, bone alkaline phosphatase, ESR and PCR were normal too. The electrogram showed a sinus bradycardia (CR 54 bpm) and the transthoracic echocardiography showed left ventricular and left atrial dilatation (LV 62 mm; LA 49 mm), mild tricuspid and aortic valve regurgitation and especially a severe mitralal insufficiency due to a severe flail-prolapse of the posterior leaflet, associated with a severe diastolic dysfunction. Because of the evidence, we immediately decided to transfer him to the nearest cardiosurgical ICU, where he was submitted to a cardiac plastic surgery of the mitral valve and following implant of a mitralic ring Edwards Physio II (32 mm). About 15 days later, he was submitted to a new cardiac surgery to implant a PM because an AV blockade. After a period of physical rehabilitation, we decided to submit the patient to DXA and audiometry, that revealed femoral osteoporosis (T-score: -2.83) and bilateral hypoacusis. So we confirmed the therapy with oral anticogulants, neridronate and calcium plus vitamin D3 supplementation. Actually he is in good clinical condition and he is submitting to a periodic ambulatorial follow up.

Osteogenesis Imperfecta (OI) or “brittle bone disease”, is a clinically heterogeneous heritable connective tissue disorder in which the causative defect is directly related to type I collagen, including abnormalities of collagen primary structure, insufficient quantity, abnormal post-translational modifications, folding, intracellular transport or matrix incorporation.1 The classification system of Sillence2 divides OI into four severity-based types, recently extended with OI types V–VII.3 The estimated incidence of OI is approximately 1 per 20,000 births.4 Most OI cases have autosomal dominant inheritance. Over 1500 dominant mutations in either COL1A1 or COL1A2, encoding the α1(1) and α2(2) of type I collagen, have been identified.5 These mutations alter the structure or quantity of type I collagen and cause a skeletal phenotype ranging from subclinical to lethal, commonly treated with oral and intravenous bisphosphonates in adults and children.6 Cardiovascular involvement is relatively rare in osteogenesis imperfecta and has a predilection for left-sided cardiac valves. Some OI patients develop mitral and aortic valve regurgitation and undergo valve replacement surgery.

Bibliography:
The examination revealed pitting edema of the dorsum of both hands, wrists, feet and pretibial area, signs of arthritis of the proximal interphalangeal joints of the hands, wrists, and joints of small joints of the hands, wrists and feet, associated with stiffness, especially on the right side. She noted the sudden onset of painful swelling on the second and fifth fingers of the right hand, swelling and tenderness of all flexor digitorum tendons, a limited range of motion, signs of diffuse arthrosis. There was onychopathy of the second finger bilaterally, 2nd and 4th of the left hand with pits on the nails, thickened and yellowish in color. Laboratory testing showed an increased level of CRP, VES, leukocyte count with prevalence of neutrophils and pro-BNP; there was mild anemia and hypoalectinemia; ANA and p-ANCA were positive. HLA B27, antistreptolysin O titer, screening for pneumonic agents (including Mycoplasma Pneumoniae) and sputum cultures were negative.

We report the case of a 73 year-old white woman with hypertrophic cardiomyopathy, hypertension, dyslipidemia, history of gastrointestinal bleeding (diverticular disease, angiodysplasia, hemorrhoids, gastritis and polyposis of the colon). She noted the sudden onset of painful swelling on the second and fifth fingers of the right hand, swelling and tenderness of all flexor digitorum tendons, a limited range of motion, signs of diffuse arthrosis. This condition also remitted spontaneously over several years; but to the best of our knowledge, symmetrical pitting edema has never been found in polymyalgia rheumatica and it involves predominantly proximal muscle as limb and shoulder girdle. Finally, there were already been reported in literature clinical findings of osteogenesis imperfecta and cardiovascular disease. Ann Thorac Surg 1995; 60:1439-1443. Review.

Objective: Magnetic resonance imaging (MRI) is considered the modality of choice for the diagnosis of spondyloarthropathy (SpA)-related spondylodiscitis, or discovertebral erosions (DE). Our aim was to analyze the prevalence and the clinical features of DE in patients with enteropathic SpA (EA) using MR

Methods: We evaluated 72 patients with EA and 43 controls for the study. All patients and controls underwent rheumatological and gastroenterological clinical examinations, and demographic features were recorded. For each patient, these factors were also recorded: duration of inflammatory bowel disease and arthritis from onset to enrollment, history of viral and bacterial infections, and occurrence of previous major trauma to the spine. These scores were taken: Bath Ankylosing Spondylitis Metrology Index (BASMI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Harvey-Bradshaw Index, and the Simple Clinical Colitis Activity Index. All subjects had MRI of the spine.

Results: On the basis of inclusion criteria, 43 patients with EA were included in the study. Twenty-three had axial EA (axEA) and 20 had axial and peripheral subset EA (overlap subset or peripheral type 3; axphEA). Twenty-two patients with EA (15/7 axEA/axphEA) showed DE (30.55%; p < 0.001). DE was significantly more prevalent in axEA subjects than in the overlap subset (p < 0.001). In axEA, DE had a significant direct correlation with arthritis duration (r = 0.546, p = 0.007). Patients with DE showed BASDAI, BASMI, and BASFI scores significantly higher than patients without DE (p < 0.001).

Conclusion: We found a high prevalence of DE among patients with EA (30.55%), confirming that DE is an important characteristic aspect of SpA. We found a high prevalence in patients in the axphEA subset (31.82%), suggesting that DE could be a characterizing feature of the overlap subset.

Arthritis, tenosynovitis and consolidative lung opacities with pleural effusion

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We report the case of a 73 year-old white woman with hypertrophic cardiomyopathy, hypertension, dyslipidemia, history of gastrointestinal bleeding (diverticular disease, angiodysplasia, hemorrhoids, gastritis and polyposis of the colon). She noted the sudden onset of painful swelling on the second and fifth fingers of the right hand, swelling and tenderness of all flexor digitorum tendons, a limited range of motion, signs of diffuse arthrosis. This condition also remitted spontaneously over several years; but to the best of our knowledge, symmetrical pitting edema has never been found in polymyalgia rheumatica and it involves predominantly proximal muscle as limb and shoulder girdle. Finally, there were already been reported in literature clinical findings of osteogenesis imperfecta and cardiovascular disease. Ann Thorac Surg 1995; 60:1439-1443. Review.

A hard therapy for a weak muscle

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Our case-report is about a 67 year-old white woman, ex smoker, with a history of hypertension, hypercholesterolaemia, osteoporosis, suffering from a chronic autoimmune thyroiditis and thyroidectomized for a follicular adenoma (cc. Hurtle), with a recent endoscopic polypectomy for two colic polyps with high-grade dysplasia. Her family history is positive for Systemic Lupus Erythematosus in two sisters.

She was admitted to our department due to transitory diplopia lasting 1-year, more severe during the evening, accompanied by the gradual onset of fatigue, dysphagia, dysphonias, marked weakness and loss of muscle mass (particularly in the shoulder and pelvic girdle), gait abnormality, arthralgias involving hands with morning stiffness, Raynaud’s phenomenon and clubbing fingers, weight loss and constipation. Laboratory testing showed anemia and increase in serum muscle enzymes (ALT, AST, CPK, myoglobin).

Treatment with statin was interrupted in the suspect of drug-induced myopathy. She did a neurological consult that showed muscle fatigability, gait abnormality, waddling, wide-based gait with a hyperlordosis of the lumbar spine. Anti-ACh-R, Anti-MuSK and the repetitive nerve stimulation were negative. EMG revealed myopathic abnormalities probably related to hypothyroid myopathy but thyroid profile was normal. In the suspect of Multiple Sclerosis she did Brain-MRI that showed microvascular gliosis bilaterally in subcortical white matter on the frontal lobe and in periventricular white matter. For the occurrence of dyspnea, she had also performed cardio-pulmonary tests that showed low hypoxemia with normocapnia, normal spirometry and 6-minutes walking-test, without signs of cardiac involvement. HRCT showed interstitial lung disease with septal thickening and bronchiectasis. Considering her family history, she did autoantibodies screening and only TRAB, APCA and anti-nucleosome were positive. ACE test was negative and there were neither granulomas in the lungs nor mediastinal lymphadenopathies. Screening for acute viral or bacterial infections were negative. To exclude a paraneoplastic syndrome, the patient did a screening for malignancies, which was negative. In the meantime, the patient’s condition worsened dramatically to the point that she became bedridden. Then she did a quadriiceps muscle biopsy, which revealed an inflammatory myopathy.

In the hypothesis of polymyositis/overlap syndrome, the patient started a high-dose glucocorticoid therapy with Methylprednisolone at a dose of 60 mg/kg/die i.v. (continued with Prednisone 75 mg/die per os) and, ten days after, it was associated Azathioprine at dose of 50 mg/die (step-up to 100 mg/die few time later).

AZA was preferred to methotrexate because of the interstitial lung disease. The glucocorticoid-sparing agent was introduced also to reduce intermediate and long-term side effects. In particular, for history of severe osteoporosis, was given Teriparatide, considering the presence of severe esophageal dysfunction that contraindicates the use of bisphosphonates. The patient underwent ongoing assessment of the clinical response, with a rapid decline in serum enzyme levels but a very slow clinical improvement especially in muscle strength.

During the glucocorticoid tapering and the AZA step-up, within 40 days after the last hospitalization, the patient developed a disease flare with systemic flu-like symptoms, fever and increase of serum muscle enzymes, CRP and VES. The ECG showed left axial deviation with small voltage R-wave in precordial leads (not seen in the previous exams) with only a slight, not relevant, increase of troponin levels. So, she did TT and TE echocardiogram that revealed a slight diastolic dysfunction, thickening of left ventricular wall and a hypochogen irregular solid lesion in the septum, projecting into the ventricular lumen. It could be referred, first of all, to endomyocardial fibrosis due to polymiositis with cardiac involvement but also to malignancy, lymphoma, Loeﬄer’s disease and intraventricular thrombus. She started ASA and heparin. Cardiac-MRI described this area suggestive for intramyocardic fibrosis as a result of an inflammatory process.

Treatment with AZA was reduced to 50 mg/die and, in the setting of apparently resistant and progressive disease, she started therapy with IntraVenous ImmunoGlobulin at dose 0.6 mg/kg/die 5-day course once a month for 6 months. A specialized exercise therapy was started like a supplement treatment in order to enhance the quality of life.

During the first cycle of IVIG, while the patient was still receiving treatment with AZA, she presented an ingraavescent dyspnea with hypoxia. HRCT revealed consolidative parenchymal opacities with air bronchograms in the basal lobe bilaterally sized 50 mm in diameter maximum and others smaller areas with the same pattern, in the medium lobe and lingual; which were referable to inflammatory areas. She did bronchoscopy with bronco alveolar lavage that was negative, including P. Jiroveci. Treatment with AZA was interrupted and she started levofloxacin 500 mg bid i.v., with clinical and radiological resolution.

During the second cycle of IVG, she had fever, remitted after two days with levofloxacin. She presented also a self-limiting episode of melena probably due to increased adverse effect of simultaneous treatment with PANS, steroid, and heparin.

At the moment, the patient had just ended the sixth cycle and she is still tapering Prednisone. We are planning to continue IVIG for others six months, administered bimonthly. She had a gradually and significant improvement in scores of muscle strength, muscle-mass and neuromuscular symptoms since the fourth IVIG-cycle. Today she has returned to her normal daily activities without relapses or further complications.

**Steroid-induced osteonecrosis of the femoral head**

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A 67-Year-Old Ukrainian woman came to our observation for difficulty in walking and diffuse pain. She had no story of smoke or alcohol abuse. In 2012 a diagnosis of chronic ischemic inferior limbs disease and rheumatoid arthritis was made, for which she was started on prednisone 15mg/die without bone protection. In August 2012 she was in Italy and was hospitalized in our unit for systemic inflammatory disease (elevated ESR, RCP, thrombocytosis) with fever, splenomegaly and anemia. The diagnosis of rheumatoid arthritis made by Ukrainians colleagues was not confirmed in the absence of arthritis, negativity of rheumatoid factor and anti-CCP, and the absence of typical joint erosions on X-ray. Despite the probable chronic sialoadenitis showed by ultrasonographic study of submandibular salivary glands, Sjögren’s syndrome was excluded for the absence of xerophthalmia, xerostomia, suggestive eye signs and the negativity of anti-SSA and SSB. The radiological, endoscopic and nuclear medicine studies made it possible to rule out solid tumors (TC body, esophagastroduodenoscopy, colonoscopy, ultrasound and PET were negative). Microbiological tests on blood, urine and feces were negative for bacteria and parasites. The thyroid function, kidney and liver were normal; iron, vitamin B12 and folate were below the standard values and were therefore supplemented. In view of the thrombocytosis and modest splenomegaly, in the hypothesis of lymphmatic/myeloproliferative pathology, an evaluation of T and B lymphocyte peripheral subpopulations and a blood smear was made and was normal. Moreover the JAK2 gene mutation was absent. The steroid therapy was interrupted. One month later she was readmitted in the neurology unit for difficulty in walking, with diagnosis of severe pANCA- associated vasculitic axonal neuropathy and neurogenic bladder. She started therapy with steroids (methylprednisolone 1gr for 5 days and then prednisone 50mg/die po + cyclophosphamide 100m die po) and bone protection with bisphosphonate and vitamin D. The patient was transferred to a rehabilitation unit, and bone protection was unfortunately omitted.

In January 2013 for new symptoms (right hip pain), at hip x-ray was made and considered normal. One month later she was hospitalized for hip pain and difficulty to load on the inferior right limb, associated to lateral thigh mass. A ultrasonography exam showed in the right gluteal area a hypeo-
chogenic poorly evaluable mass. An MRI documented a fracture of the surgical neck of the right femur, with destruction of the femoral head, and slight decomposition and cranial-anterior dislocation of the distal stump. The residual articular portion of the femoral head was medial, around the round ligament. A needle biopsy was requested to evaluate some periarticular collections seen in MRI, but the results were inconclusive (focal macrophage infiltration and mild fibrosis). The patient underwent surgery for placement of hip prosthesis; the histological examination was negative for neoplastic cells or infection, and osteonecrosis was considered probable. The clinical case was immediately suggestive of osteonecrosis of the femoral head in steroid therapy, with rapid evolution of the clinical picture which has seen a real “explosion” of the femoral head with symptoms altogether resembling septic arthritis. We planned a gradual reduction of steroids, and reintroduction of bone-protective therapy; discharge took place without further complications, and the patient is doing well. This case underscores the importance of bisphosphonate therapy in every patient who starts steroid therapy, in order not only to protect him from osteoporosis, but also from avascular necrosis of the hip, as documented in the medical literature.

The multifaceted aspects of ‘ASIA syndrome’: experience of three cases

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Background: Several autoimmune syndromes have been described after different types of vaccines, and the mechanisms of autoimmunity induction in genetically susceptible individuals could be different: molecular mimicry, epitope spreading, formation of immune complexes, direct inflammatory damage. Recently, the role of adjuvants has been analysed as a possible trigger of autoimmunity. ‘ASIA’ syndrome is a new clinical entity described by Shoenfeld and Agmon-Levin that includes all post-vaccination phenomena related to a previous exposure to adjuvants.[1]

Patients and methods: We described three cases of patients who developed autoimmune syndrome after exposure to three different types of vaccines. Case n°1: A 18-year-old girl developed continue fever, generalized asthenia, polyarthritis and tenosynovitis and intra-articular effusion. Laboratory examinations showed positive ANA, anti-dsDNA at high titres. She was treated with prednisone (PDN) and hydroxychloroquine (HCQ) with gradual clinical and serological improvement. Case n°2: A 25-year old woman affected by familial Mediterranean fever (FMF) and multiple sclerosis (MS) underwent anti-human papilloma virus (HPV) vaccine and then developed a progression of demyelinating disease in course of therapy with interferon beta-1a. Autoantibody profile - which resulted negative in the past examinations – showed ANA and IgM anti-cardiolipin positivity. A brain and spinal cord MRI showed new bilateral periventricular brain and spinal lesions, occurred after the vaccine. She was treated with methylPDN boli and glatiramerol; colchicine therapy was maintained. At 2 years follow-up we observed no further FMF attacks as well as a persistently stable MS damage. Case n°3: A 17-year old female presented 6 weeks after the second dose of recombinant hepatitis B vaccine (Engerix-B O, SmithKline) complaining weakness, polyarthritis, fever, and myalgia. After few months, the patient presented Raynaud’s phenomenon, diffuse edema, especially at the face, arms, hands and legs. Laboratory findings showed an increase of muscle enzymes and ANA positivity (fine speckled pattern). A muscle biopsy showed ‘myopathic alterations with inflammation and cutaneous thickening as in a scleroderma process’. Cutaneous biopsy was also compatible with scleroderma. The patient started HCQ 600 mg/day and, after few months, we observed a progressive reduction of edema areas and normalization of serum markers of muscular damage.

Discussion: These patients had been exposed to different types of vaccines before the appearance of clinical manifestations. According to the criteria suggested by Shoenfeld and coll., they can have manifestations of ‘ASIA’ syndrome. As regards the role of HBV vaccination (HBV-v) in the development of autoimmunity, it has been extensively discussed in literature; HBV-v has been associated with immune and non-immune adverse events (AE) in post-marketing surveillance studies, as well as in case-series and case-reports. Although rare, it has been observed that AE may occur up to 3 years following immunization. Less is known about the possible effects of anti-HPV vaccine, but recent evidences have been linked it with the development of autoimmunity[2]. The role of immunostimulation of bacterial extracts – in course of estrogen and progestin treatment – to induce autoimmunity remains controversial and evidences are still lacking.

Conclusions: In order to identify genetic markers of individuals at high-risk to develop autoimmune phenomena/syndromes, and in order to avoid potential immunizations/reactivation of a latent disease, a systematic research of previous vaccination in patients with recent onset of autoimmune disease should be performed. Also, a strict observation of subjects at higher risk, such as females at a susceptible age and carriers of already known autoimmune markers should be made after the vaccine exposure.[3]

References:

Reactive arthritis associated with Hafnia alvei enteritis in a patient affected with familial mediterranean fever: which came first?

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Introduction: Familial Mediterranean fever (FMF) is a recessive, autosomal, autoinflammatory disorder characterised by brief, recurring, self-limiting episodes of fever and serositis resulting in abdominal, chest, joint and muscular pain; it is the most common of the periodic hereditary fevers and mostly affects Mediterranean populations. MEFV gene, which is mutated in FMF, encodes for pyrin, a protein with a pivotal role in the regulation of inflammation [1]. It has recently been observed that MEFV gene mutations, if present, can worsen the clinical course of several autoimmune rheumatic diseases [2].

Case report A 29-year-old healthy woman experienced an episode of diarrhoea lasting 6 days and followed by low-grade fever (with a maximum temperature of 37.3°C), arthritis of wrists and knees, occasional cervical pain and left eye conjunctivitis. She was hospitalized in another Hospital and clinical examination revealed pain and swelling of the metacarpophalangeal joints (2° and 3°, bilaterally), of the wrists and knees, with MRI signs of tenosynovitis and intra-articular effusion. Laboratory examinations showed increase of acute phase reactants (ESR 60 mm/h, CRP 30 mg/l), while the
autoimmunity screening profile was negative. An echocardiogram, performed on suspicion of a connective tissue disease, revealed a minimal pericardial effusion. She received a preliminary diagnosis of ‘undefined arthritis’ and came to our attention for further clinical investigations. An accurate clinical history allowed to know that since her adolescence patient had experienced perimenstrual abdominal pain attacks with fever, diagnosed as ‘premenstrual syndrome’, lasting few days. She denied oral/genital aphthosis, and family history of autoimmune diseases. Her father was a heterozygous carrier of MEFV gene mutations (M680I) and recently he had received a diagnosis of FMF. Because of the clinical suspicion of FMF, patient began colchicine therapy (1 mg/day), with disappearance of abdominal pain attacks. Given the favourable response to colchicine, the presence of recurrent febrile episodes with abdominal pain and the diagnosis of FMF in a first degree relative, according to the Tel Hashomer criteria we made the diagnosis of FMF. However, daily slight fever persisted as well as joint pain. A further diagnostic work-up was made: urethral and vaginal swabs were negative for usual and atypical germs, as well as bacterial culture of urine, blood and pharyngeal mucosa. Given the previous history of transient diarrhoea, stool culture was performed, and it revealed heavy growth of Hafnia alvei, a Gram negative pathogen belonging to Enterobacteriaceae family. HLA class I analysis was negative for locus B27 while MEFV gene analysis confirmed the M680I heterozygous mutation. She received a definitive diagnosis of ‘reactive arthritis due to gastrointestinal bacterial infection in course of FMF’ and she was treated with antibiotic therapy, while colchicine therapy was maintained. We observed a complete disappearance of fever, joint pain and conjunctivitis and a normalisation of acute phase reactants values, including serum amyloid A ones.

Discussion and conclusions: Hafnia alvei is a rare human pathogen and it may be responsible for serious community-acquired and nosocomial infections. A literature survey performed without any date limitations found only one case of reactive arthritis caused by H. alvei. It has been documented that the Gram negative bacteria can independently activate the inflammasomes [3], contributing to exacerbate the inflammatory response in predisposed individuals. On the other hand, it has been observed that MEFV mutations could be an adjunctive aggravating factor for the severity of rheumatoid arthritis, systemic lupus erythematosus, as well as a further predisposing factor for the development of ankylosing spondylitis and spondyloarthritids [2,4]. In our case we could speculate that a chronic infectious stimulus in a patient with MEFV gene mutation could have predisposed to a more aggressive inflammatory response. Further genome-wide association studies are needed in order to investigate the role of MEFV gene mutations as modifier factors in other inflammatory or rheumatic autoimmune diseases.

References:

ANCA associated vasculitis following influenza vaccination: a ‘complicated’ case
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Introduction: ANCA associated vasculitis (AAV) are a heterogeneous group of disorders that includes granulomatosis with polyangiitis (GPA, or Wegener’s granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA, or ChurgStrauss syndrome). GPA is characterized by necrotizing granulomatous vasculitis that most commonly involves the upper respiratory tract, lungs, and kidneys. The presence of two or more abnormal urinary sediment (red cell casts), oral ulcers or nasal discharge, haemoptysis or granulomatous inflammation on biopsy, are considered as features to distinguish GPA from other vasculitides. Genetic, environmental and infectious factors may contribute to the AAV pathogenesis. Immunization with influenza vaccine (Inf-V) has been previously related with the onset (or relapse) of several autoimmune phenomena and diseases, including primary vasculitides.

Case report: A 53-year-old Caucasian healthy man was admitted to our Department because of persistent fever, pain and signs of inflammation (i.e. rubor, tumor, calor) of both wrists and ankles, and insonorous dyspnea. An accurate clinical history revealed that the patient underwent influenza vaccination 6 weeks before the onset of the symptoms and he progressively developed rhinosinusitis symptoms with occasional nasal discharge. His family and past history were unremarkable. On admission, he was pyrexic (T max 39°C), blood pressure was 170/80 mmHg, and a muculo-papular skin rash of the trunk was present; on lung auscultation, vesicular murmur was absent on the right base. Hemogasanalysis showed a moderate hypoxemia (PaO2 62 mmHg). A chest CT scan was performed, showing moderate right pleural effusion, without evidence of further abnormalities. Laboratory tests revealed a mild normocytic anaemia (Hb 11.4 gr/dL), elevation of erythrocyte sedimentation rate (ESR 84 mm/h) and C-reactive protein (CRP 5 mg/dL, with normal value till 0.5). Multiple urinalyses revealed persistent dysmorphic microhematuria with red cell casts; also, proteinuria was present in a nonnephrotic range (1747 mg/24h), while creatinine was 1.4 mg/dL. Immunological screening was otherwise negative, except for the presence of c-ANCA antibodies, tested by means of indirect immunofluorescence, with a value of 90 units per milliliter (normal value < 6.9), also confirmed by enzyme-linked immunosorbent assay (ELISA) for proteinase-3. Microbiological tests (serologies for EBV, CMV, HIV, HCV, HBV, Adenovirus, Echovirus, Coxackie, Mycoplasma pneumoniae, Quantiferon TB Gold test) were also negative. To confirm the hypothesis of AAV with renal involvement a renal biopsy was performed, revealing focal necrotizing glomerulonephritis with crescents and glomerular sclerosis; diffuse and granular deposition of C3 was present on immunofluorescence staining. He was treated with steroids (methylprednisolone 1 mg/Kg/day, progressively tapered) and cyclophosphamide (IV CyP, 15 mg/Kg/3 weeks) for 6 months; 2 months later c-ANCA and acute phase reactants were negative, and microhematuria disappeared. 5 months after the beginning of maintenance therapy with steroids and azathioprine he developed pain, edema and erythema involving the superior right eyelid, with macroscopic evidence of granulomatous and purulent lesions. Orbital MRI was performed, showing several micro-abscessual areas at right conjunctival eyelid and at orbital wall level. PCR for M. tuberculosis, as well as bacterial and fungal cultures were negative. Laboratory examinations showed mild increase of ESR, while cANCA were negative. A conjunctival biopsy showed granulomatous vasculitis process with histiocites, neutrophils and multinucleated giant cells, consistent with a granulomatosis with polyangiitis (GPA) diagnosis complicated with orbital involvement. Rituximab therapy was then begun (1000 mg twice with an interval of 14 days between the infusions, according to scientific evidences). After the first infusion we observed a progressive reduction of the edema and erythema at eyelid level.

Discussion and conclusions: Orbital inflammation is considered a rare and serious complication in course of GPA. We describe a case of refractory GPA complicated with orbital involvement in a previously healthy man who underwent Inf-V 6 weeks before the onset of his symptoms. A literature survey focused on AAV following Inf-V yielded 6 similar cases; 4 patients out of 6 developed the symptoms 2 to 4 weeks since the immunization and re-
ceived a GPA diagnosis. In our case the latency period between Inf-V administration and symptoms onset could suggest a causal relationship between the two events. Molecular mimicry, bystander activation, direct or immune complex-mediated vascular damage could be some of the mechanisms involved in mediating the autoimmune response following Inf-V. Furthermore, as Inf-V licensed in Europe may contain adjuvants, a possible role of Inf-V immune adjuvant in the development of post-vaccination phenomena could not be excluded. The identification of genetic markers of high-risk individuals through vaccine genomic studies could be useful in a next future, in order to avoid potential immunization or reactivation of a latent disease.

**Antiphospholipid syndrome: primary or secondary to Systemic Erythematous Lupus? Description of a clinical case with avitaminosis D in premenopausal women**

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**Introduction:** Low levels of vitamin D have been described in the obese individuals and in some autoimmune diseases (multiple sclerosis, rheumatoid arthritis, SLE, undifferentiated connective tissue disease, autoimmune thyroid diseases, type 1 diabetes mellitus, idiopathic inflammatory myopathies). In SLE we demonstrated an association between low level of vitamin D and disease activity (1). A vitamin D deficiency is common in antiphospholipid syndrome (APS): in premenopausal women with primary APS (pAPS) more than 50% have hypovitaminosis D (2-4); levels <15 ng/ml were significantly associated with thrombotic events (5).

**Clinical case:** A 45 year old woman was admitted for DVT femoropopliteal dx complicated by pulmonary embolism. Former smoker, 1 preterm birth for bicornuate uterus, non abortions. Thrombocytopenia observed at age 27 during pregnancy (PLT 57,000-48,000). At age 31 she was hospitalized for pancycopenia in the course of infection by viruses: thrombocytopenia was confirmed. At 38 years laparoscopic hysterectomy for uterine fibromatosis, subsequent onset of hypertension and iron deficiency anemia. In the same year admitted to a critical lower limb ischemia by occlusion of the tibial and dorsal artery of the foot, regraded with medical therapy (ASA) and smoking cessation; persistence of thrombocytopenia, PTT 44 sec (28-40), positive lupus anticoagulant, IgG aCL 80 GPL (nv 0-13), normal PCR and rheumatoid factor, ANA 1:160 (homogeneous pattern), anti-dsDNA and anti-ENA negative, C3 and C4 normal, AT III normal. At 42 years detection of mammary fibroadenomas and subclinical hyperthyroidism (TSH 0.05 µU/ml nv: 0.35-5.5), normal FT4 and FT3, anti-TPO and anti-thyroglobulin negative, total cholesterol 234 mg/dl. The following year she was hit by renal colic: abdominal ultrasound showed distal ureteral lithiasis. At the time she was obese (up to 108 Kg, h 164 cm). Two weeks before the current admission, the patient fell to the ground and had a trauma at right hemithorax with fracture of the VII rib. For two weeks she was immobilized. She noted progressive edema in the right leg and the day of admission important dyspnea at rest. The venous Doppler ultrasound of the lower limb showed right axis femoropopliteal thrombosis. CT pulmonary angiography: multiple intraluminal filling defects such as thrombosis are present in both the left and right branch of the pulmonary artery and in both segmental and sub-segmental branches bilaterally. Laboratory tests have confirmed the thrombocytopenia (85,000-52,000), the pattern immunological and coagulative known (IgG aCL 123 GPL:nv<15, IgM aCL normal, IgG anti-fβ2GPI 125 SGG:nv<20, IgM anti-fβ2GPI normal-ELISA Quanta Lite, INOVA Diagnostic Inc, San Diego,USA), for the first time positive anti-dsDNA (1:40, nv<1:10). In addition, ANA 1:320 (immunofluorescence on HEp-2 cells), homogeneous pattern, negative neoplastic markers and hepatitis B and C, hyperuricemia, hypercholesterolemia, hypertriglyceridemia, increase of γGT and alkaline phosphatase, AMA and ASMA negative, TSH lower limits, normal FT3 and FT4. Intercurrent urinary infection by Enterobacter aerogenes. Dosage of serum 25-hydroxyvitamin D (25 OHD): <4 µg/L (LIAISON Clia), calceinemia 9.3 mg/dl (nv 8.8-10.6), normal phosphorus, PTH 164 ng/L (nv 9-55), FSH (7.6 U/L) and LH (2.7 U/L) normal. The patient reported normal exposure to sunlight. For the detection of increased cortisol evening, ACTH (76 ng/L: nv 10-50) and cortisoloria we performed the dexamethasone test with negative result. Shortly relevant data of abdominal CT are mild splenomegaly, arterial calcification and hypodense formation of 13 mm in right ovary not confirmed by a subsequent transvaginal ultrasound. Hepatosteatosis at abdominal ultrasound. A mammography showed multiple bilateral nodules with characteristics of kindness, compatible with fibroadenomas. Thyroid ultrasound: slightly irregular glandular profiles, heterogeneous echogeneity due to the presence of small areolas hypoechoic confluent between them and tiny cysts. The patient was immediately treated with fondaparinux associated with warfarin getting anticoagulation effective in a sixth day. Therapy with ramipril, furosemide, clonidine, amlodipine, allopurinol, simvastatin, cholecalciferol was administered too. At discharge INR 2.47. Subsequent monitoring of the INR results are hightly variable. A check of the lower limb venous Doppler, performed after one month, showed partial recanalization of the femoropoplitea axis.

**Conclusion:** We have described the clinical case of a young woman obese and hypertensive, affected by DVT associated with pulmonary embolism after rib fracture. 7 years before the diagnosis had been made of APS "primary" after the detection of thrombocytopenia (present at a young age) and arterial ischemia of a lower limb. For seven years shi was treated with ASA without complications. We found a triple aPL positivity and very low vitamin D levels. Issues for consideration:-The marked deficiency of vitamin D is secondary to obesity or the APS?-The actual detection of high-titer ANA positivity with anti-dsDNA antibodies is indicative of progression to SLE? Is indicated preventive therapy with hydroxylchloroquine? - Considered the cardiovascular risk factors (hypertension, obesity, dyslipidemia, hyperuricemia, fatty liver, avitaminosis D) and the triple aPL positivity a regimen of anticoagulation with INR between 3.0 and 4.0 is indicated? - How long anticoagulant therapy? Indefinitely?

**References:**