MALATTIE RESPIRATORIE E PATOLOGIE INFIAMMATORIE CRONICHE INTESTINALI
(M. di Crohn, Rettocolite ulcerosa e colite indifferenziata)

Paolo Giuffrida

Clinica Medica I, Fondazione IRCCS Policlinico San Matteo,
Università di Pavia, Pavia
Crohn's disease (CD): definition and diagnosis

**MEDICAL HISTORY**
- Smoking
- Non-steroidal anti-inflammatory drug use
- Appendicectomy status

**CLINICAL PRESENTATION**
- Subocclusive abdominal pain
- Diarrhoea & weight loss
- Fistulas

**LABORATORY TESTS**
- ↓ Hb, ↑ PLT, ↑ ESR, ↑ CRP, ↑ faecal calprotectin

**Terminal Ileum (45%)**
- Colon (32%)
- Ileocolon (19%)
- Upper GI tract (4%)

Baumgart DC & Sandborn WJ. Lancet 2012
CD: assessment of severity

CROHN’S DISEASE ACTIVITY INDEX (CDAI)
Number of liquid or very soft stools over the last 7 days
  Sum x 2
Daily abdominal pain over the last 7 days
  • None = 0
  • Mild = 1
  • Moderate = 2
  • Severe = 3
  Sum x 5
Daily general well being over the last 7 days
  • Well = 0
  • Slightly below par = 1
  • Poor = 2
  • Very poor = 3
  • Terrible = 4
  Sum x 7
Extraintestinal manifestations
  • Well = 0
  • Slightly below par = 1
  • Poor = 2
  • Very poor = 3
  • Terrible = 4
  Score x 20
Taking anti-diarrhoeals (i.e. lomotil)
  Value x 30
Abdominal mass
  • None = 0
  • Questionable = 2
  • Present = 5
  Value x 10
Haematocrit [(typical-current) x 6]
Weight {[(standard – current)/standard] x 100}

LEMANN SCORE

PREDICTORS OF DISABLING CD
  • Young age at diagnosis (< 40 years)
  • Immediate need for corticosteroids
  • Perianal disease

Best WR et al. Gastroenterology 1976
Beaugerie L et al. Gastroenterology 2006
Ulcerative colitis (UC): definition and diagnosis

MEDICAL HISTORY
• Non-steroidal anti-inflammatory drug use
• Appendicectomy status
• Smoking

CLINICAL PRESENTATION
• Bloody diarrhoea
• Urgency
• Abdominal pain

LABORATORY TESTS
↓ Hb, ↑ PLT, ↑ ESR, ↑ CRP, ↑ faecal calprotectin

Ordás I et al. Lancet 2012
### UC: assessment of severity

#### UC severity

**Severe**  
- Six or more motions a day with macroscopic blood in stools  
- Temperature $> 37.5 \, ^\circ\mathrm{C}$  
- Tachycardia  
- Severe anemia  
- ESR $> 30 \, \mathrm{mm/h}$

**Mild**  
Daily abdominal pain over the last 7 days  
- Four or less motions a day with no more than small amounts of macroscopic blood in stools  
- No fever  
- No tachycardia  
- Anemia not severe  
- ESR $\leq 30 \, \mathrm{mm/h}$

**Moderately severe**  
Intermediate between severe and mild

#### Mayo score

**Stool frequency**  
- 0 = normal number of stools for this patient  
- 1 = 1-2 stools more than normal  
- 2 = 3-4 stools more than normal  
- 3 = 5 or more stools more than normal

**Rectal bleeding**  
- 0 = no blood  
- 1 = streaks of blood with stool less than half of the time  
- 2 = obvious blood with stool most of the time  
- 3 = blood alone passed

**Physician’s global assessment**  
- 0 = normal  
- 1 = mild disease  
- 2 = moderate disease  
- 3 = severe disease

**Endoscopy component**  
- 0 = normal  
- 1 = mild disease (erythema, faded vascular pattern, mild friability)  
- 2 = moderate disease (marked erythema, absent vascular pattern, erosions, friability)  
- 3 = severe disease (spontaneous bleeding, ulcers)
Respiratory manifestations in IBD

AIRWAY DISEASE
1) Upper airway disease
   - Subglottic stenosis
   - Diffuse tracheitis
2) Large airway disease
   - Bronchiectasis
   - Chronic bronchitis
3) Small airway disease
   - Bronchiolitis

PARENCHYMAL DISEASE
- Cryptogenic organizing pneumonia
- Eosinophilic pneumonia
- Cavitating nodules

PULMONARY VASCULATURE DISEASE
- Pulmonary embolism
- Wegener granulomatosis
- Churg-Strauss syndrome
- Microscopic polyangiitis

SEROSITIS
- Pleurisy
- Pericarditis

Camus P et al. Medicine 1993

Airway disease

**UPPER AIRWAY DISEASE**
Rare

Symptoms
- Hoarseness
- Stridor

Mucosa
- Cobblestone appearance

CT scan
- Circumferential tracheal wall thickening

Betancourt SL et al. AJR Am. J. Roentgenol 2011

**BRONCHIECTASIS**
66% of all airway manifestations

Symptoms
- Cough
- Copious amounts of sputum

CT scan
- Dilatated airways
- Bronchial wall thickening
- Branched opacities due to mucoid impaction

Betancourt SL et al. AJR Am. J. Roentgenol 2011

**BRONCHIOLITIS**
More frequent over the last years

Symptoms
- Bronchorrea
- Mild productive cough

Mucosa
- Bronchiole scarring
- Emphysematous changes

Chest radiograph
- Diffuse small irregular opacities

Pulmonary function test
- Airflow obstruction

Camus P et al. Medicine 1993
Cryptogenic organizing pneumonia

More commonly in UC

Symptoms: fever, cough, dyspnea, pleuritic chest pain

Chest radiograph
- Patchy focal opacities
- Diffuse infiltrates

CT scan
- Pleural opacities
- Air bronchograms
- Prominent nodular densities

Betancourt SL et al. AJR Am. J. Roentgenol 2011
Eosinophilic pneumonia

More commonly in patients taking sulfasalazine or mesalamine

Symptoms: fever, night sweats, malaise

Blood test: eosinophilia

Chest radiograph
- Bilateral peripheral airspace opacities

CT scan
- Peripheral consolidation

Histological features
- Airspace infiltrates of eosinophils
- Septal oedema
- Lymphatic dilatation

Cavitating nodules and serositis

CAVITATING NODULES
Infrequent

Symptoms: fever resistant to antibiotics

Associated with pyoderma gangrenosum

Pathological features
- Sterile lung abscesses (neutrophils + Fibrinous exudate) with central necrobiosis

Camus P et al. Medicine 1993

SEROSITIS
Uncommon
Young patients

Pleurisy
Nearly always unilateral involvement
Exudative

Pericarditis

A population-based database study on:
2857 Crohn’s Disease
2672 Ulcerative Colitis


<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Rate per 100,000</th>
<th>RR of comorbidity IBD versus non-IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IBD</td>
<td>Non-IBD</td>
</tr>
<tr>
<td>Younger than 50 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon cancer</td>
<td>188.14</td>
<td>90.36</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>152.51</td>
<td>69.62</td>
</tr>
<tr>
<td>Hodkin’s disease</td>
<td>17.82</td>
<td>86.74</td>
</tr>
<tr>
<td>Non Hodgkin’s lymphoma</td>
<td>19.95</td>
<td>67.92</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td><strong>302.16</strong></td>
<td><strong>180.60</strong></td>
</tr>
<tr>
<td>DVT</td>
<td>765.39</td>
<td>499.46</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 years and older</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon cancer</td>
<td>1055.17</td>
<td>1178.61</td>
</tr>
<tr>
<td>Rectal cancer</td>
<td>573.16</td>
<td>690.71</td>
</tr>
<tr>
<td>Hodkin’s disease</td>
<td>27.81</td>
<td>44.94</td>
</tr>
<tr>
<td>Non Hodgkin’s lymphoma</td>
<td>61.80</td>
<td>122.28</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td><strong>807.98</strong></td>
<td><strong>642.55</strong></td>
</tr>
<tr>
<td>DVT</td>
<td>2087.16</td>
<td>1579.44</td>
</tr>
</tbody>
</table>

DVT, deep venous thrombosis

Bernstein CN et al. *Can J Gastroenterol* 2007
### Epidemiology of respiratory manifestations in IBD

#### Number of Patients (n=33)

<table>
<thead>
<tr>
<th>GENDER</th>
<th>SMOKING HISTORY</th>
<th>IBD TYPE</th>
<th>IBD ACTIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never Smokers</td>
<td></td>
<td>Ulcerative Colitis</td>
<td></td>
</tr>
<tr>
<td>Former Smokers</td>
<td></td>
<td>Crohn's Disease</td>
<td></td>
</tr>
<tr>
<td>Light Smokers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postcolectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Post-colectomy

9/33 patients (8 UC, 1 CD)

Patients presented with or had a recrudescence of respiratory manifestations within 1 year of colectomy (within 2 weeks in one case)
- bronchiectasis (n=5)
- chronic bronchitis (n=2)
- chronic bronchial suppuration (n=2)


3/7 patients (3 UC)

Patients presented with or had a recrudescence of respiratory manifestations within 1-4 months of colectomy
- bronchiectasis (n=2)
- chronic bronchitis (n=1)

Camus P et al. Medicine 1993

Colectomy may induce respiratory manifestations
Pathophysiological basis underlying gut-lung interplay

1) Common embryonic origin from the primitive foregut

2) Common histological features
   - Goblet cells
   - Submucosal mucus glands

3) Lympoid tissue

4) Colectomy

5) Recruitment of immune cells primed in the gut into effector site with the help of adhesion molecules or chemokines
## Prevalence of IBD in chronic respiratory disorders

<table>
<thead>
<tr>
<th>Airways disease</th>
<th>Patients seen in clinic</th>
<th>IBD cases (%)</th>
<th>Odds ratio 95% confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic bronchitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UC</td>
<td>66</td>
<td>1</td>
<td>6.39</td>
<td>0.85-47.98</td>
</tr>
<tr>
<td>CD</td>
<td></td>
<td>3</td>
<td>36.58</td>
<td>10.18-131.52</td>
</tr>
<tr>
<td>All IBD</td>
<td></td>
<td>4 (10)</td>
<td>16.04</td>
<td>3.92-65.76</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>215</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UC</td>
<td></td>
<td>4</td>
<td>7.88</td>
<td>2.71-22.91</td>
</tr>
<tr>
<td>CD</td>
<td></td>
<td>2</td>
<td>7.21</td>
<td>1.62-32.2</td>
</tr>
<tr>
<td>All IBD</td>
<td></td>
<td>7 (19)</td>
<td>8.38</td>
<td>2.43-28.89</td>
</tr>
<tr>
<td>Chronic cough</td>
<td>426</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UC</td>
<td></td>
<td>6</td>
<td>5.94</td>
<td>2.41-14.60</td>
</tr>
<tr>
<td>CD</td>
<td></td>
<td>2</td>
<td>3.62</td>
<td>0.82-16.11</td>
</tr>
<tr>
<td>All IBD</td>
<td></td>
<td>8 (22)</td>
<td>4.76</td>
<td>1.43-15.90</td>
</tr>
<tr>
<td>COPD</td>
<td>588</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UC</td>
<td></td>
<td>5</td>
<td>3.57</td>
<td>1.30-9.38</td>
</tr>
<tr>
<td>CD</td>
<td></td>
<td>4</td>
<td>5.26</td>
<td>1.71-16.19</td>
</tr>
<tr>
<td>All IBD</td>
<td></td>
<td>9 (24)</td>
<td>3.67</td>
<td>1.19-12.62</td>
</tr>
<tr>
<td>Asthma</td>
<td>893</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UC</td>
<td></td>
<td>6</td>
<td>2.81</td>
<td>1.15-6.9</td>
</tr>
<tr>
<td>CD</td>
<td></td>
<td>2</td>
<td>1.74</td>
<td>0.39-7.65</td>
</tr>
<tr>
<td>All IBD</td>
<td></td>
<td>9 (24)</td>
<td>2.54</td>
<td>0.78-8.26</td>
</tr>
<tr>
<td>Total</td>
<td>2192</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UC</td>
<td></td>
<td>22</td>
<td>4.21</td>
<td>1.71-10.41</td>
</tr>
<tr>
<td>CD</td>
<td></td>
<td>13</td>
<td>5.96</td>
<td>1.94-18.31</td>
</tr>
<tr>
<td>All IBD</td>
<td></td>
<td>37</td>
<td>4.26</td>
<td>1.48-11.71</td>
</tr>
</tbody>
</table>

Raj AA et al. Respir Med 2008
Incidence of IBD in chronic respiratory disorders

IBD drug-induced respiratory manifestations

SULPHASALZINE OR MESALAMINE
- Eosinophilic pneumonia
- Interstitial disease
- Bronchiolitis obliterans

METHOTREXATE
- Hypersensitivity pneumonitis or pulmonary fibrosis

ANTI-TNF-α AGENTS
- Pulmonary tuberculosis
- Pericarditis
Sulphasalazine and mesalamine-induced eosinophilic pneumonia

Symptoms
- Dyspnea, chest pain, fever, cough (after 1-6 months of drug use)

Chest radiograph
- Bilateral infiltration

CT scan
- Bilateral non-segmental consolidations

Blood test
- Eosinophilia
- Mesalamine-induced lymphocyte stimulation test may be positive

Management
- Drug withdrawal ± systemic steroids

Follow-up
- Clinical and radiological improvement after 2 weeks of mesalamine cessation

Saltzkam K et al. AJR Am. J. Roentgenol 2001; Inoue M et al. Respir Investig 2014
**Methotrexate-induced hypersensitivity pneumonitis**

### Symptoms
- Dyspnea, fever, non-productive cough

### Pulmonary function test
- Restrictive with low CO diffusion capacity

### Pathological features
- Interstitial pneumonitis
- Granuloma
- Bronchiolitis

### BAL findings
- Lymphocytic alveolitis
- Increased eosinophils
- Reversed CD4/CD8 ratio

### Management
- Methotrexate withdrawal
- Supportive therapy

Anti-TNF-\(\alpha\) agent-induced tuberculosis (TB) - 1

25 cases of TB (12 IBD, 10 rheumatologic diseases, 3 psoriasis) in a cohort of 765 patients under anti-TNF-\(\alpha\) agents from 2001 to 2012:

- 16 under infliximab
- 6 under adalimumab
- 3 under etanercept

TB incidence:
- 1337/100,000 patient-years for patients on infliximab
- 792/100,000 patient-years for patients on adalimumab
- 405/100,000 patient-years for patients on etanercept

Combined immunosuppressive therapy (n=16):
- azathioprine (n=7)
- methotrexate and steroids (n=4)
- steroids (n=4)
- rituximab and steroids (n=1)

Latent TB (n=17):
- Negative tuberculin skin test and negative chest X-ray (n=13)
- Positive tuberculin test but negative IGRA (n=1) -> no chemotherapy -> disseminated TB 21 months after the beginning of infliximab
- Positive tuberculin test (n=3) -> isoniazid for 9 months -> active TB 8, 16 and 24 months after isoniazid treatment

ECCO Statement OI 6A
“Reactivation of latent TB in patients treated with anti-TNFs is increased and is more severe than in the background population [EL2]. Latent TB should be diagnosed by a combination of patient history, chest X-ray, tuberculin skin test and interferon-gamma release assay (IGRA) according to local prevalence and national recommendations.”


Abreu C et al. J Crohns Colitis 2013
ECCO Statement OI 6B
“Patients diagnosed with latent TB prior to anti-TNF should be treated with a complete therapeutic regimen for latent TB [EL1]. In other situation, specialist advice should be sought. Chemotherapy for latent TB may vary according to geographic area or the patient’s epidemiological background [EL5]. When there is latent TB and active IBD, anti-TNF therapy should be delayed for at least 3 weeks after starting chemotherapy, except in case of greater clinical urgency and with specialist advice.”


ECCO Statement OI 6C
“When active TB is diagnosed, anti-TB therapy must be started, and anti-TNF therapy must be stopped but can be resumed after two months if needed [EL4].”

28-yr-old female,

Medical history:
- Non-stricturing/non-penetrating Crohn’s ileocolitis, erythema nodosum, past azathioprine-related leukopenia. Due to the onset of peripheral arthritis and CD relapse, adalimumab treatment was started.
- Autoimmune thyroiditis

After 7 administrations of adalimumab, patients was hospitalized for chest pain and fever

Transesophageal echocardiography: large pericardial effusion with mild thickening of pericardium

Blood tests: negativity for Quantiferon, Borrelia, Parvovirus B19, EBV, CMV, Toxoplasma, ANA, ENA, anticardiolipin antibody, c3/c4

Two episodes of heart palpitation -> 12-lead EKG -> parossistic atrial fibrillation

Pericarditis management: iv aspirin and oral steroids, adalimumab withdrawal.

4 weeks later: resolution of pericardial effusion, mild thickening of pericardium
66-yr-old female, hospitalized for dyspnea and cough

3 yrs before: Crohn’s ileocolitis + pyoderma gangrenosum and polyarthritis. Adverse reaction to steroids

Chest x-ray: multiple nodules in the left lung base

Lung biopsy: cryptogenic organizing pneumonia, granuloma

Infliximab: 5mg/kg/IV

4 weeks later: resolution of symptoms and nodules

Management of respiratory manifestations in IBD patients

Drug-induced lung disease

- Yes
  - Drug discharge
    - Respiratory manifestations
      - Resolved
        - IBD management with other drug(s)
      - Present
        - Po or iv steroids

- No
  - Inhaled, po or iv steroids
    - Respiratory manifestations
      - Resolved
        - Follow-up
      - Present
        - Immunosuppressants
    - After steroid tapering

Conclusions

RESPIRATORY MANIFESTATIONS IN IBD

- More frequent in UC than in CD
- Unrelated to disease activity in the bowel
- More frequently airway disease
- A high degree of suspicion is necessary to detect the lung involvement
- Early detection is important as the respiratory involvement often respond well to steroid treatment
- In case of drug-induced manifestations, drug withdrawal is recommended
Acknowledgements

Prof. Leonardo M. Fabbri
Prof. Raffaele Antonelli Incalzi
Prof. Francesco Perticone
Prof. Gino Roberto Corazza

Giovani Internisti SIMI

Dott. Agostino Buonauro
Dott. Carmelo Buttà
Dott. William Capeci
Dott. Sebastiano Cicco
Dott. Alfredo De Giorgi
Dott. Andrea Denegri
Dott. Paolo Di Giosia
Dott.ssa Alessandra Forgione

Dott. Lorenzo Falsetti
Dott. Alessandro Grembiale
Dott. Giusi Lorusso
Dott. Alberto Maria Marra
Dott.ssa Maristella Masala
Dott.ssa Caterina Mengoli
Dott.ssa Gloria Montanari
Dott. Lorenzo Nobili

Dott.ssa Serena Pignataro
Dott.ssa Miriam Pinna
Dott.ssa Valeria Raparelli
Dott.ssa Sara Roversi
Dott.ssa Isabella Savore
Dott.ssa Diana Spinelli
Dott. Eliezer Joseph Tassone
Dott.ssa Giovanna Viticchi