Inflammatory Bowel Disease: Clinics, Diagnosis, Differential Diagnosis

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Global map of IBD

Cosnes J et al, Gastroenterology, 2011
Crohn’s Disease

Ulcerative colitis

Benchimol et al Inflamm Bowel Dis, 2011
Gut microbiome, lifestyle and disease

Burkina Faso

Florence

C Filippo et al, PNAS 2010

DA Peterson et al, Cell Host Microbe 2008
Current concept on the pathogenesis of IBD

- Genetic predisposition
- Mucosal immune system (immunoregulatory defect)
- Environmental triggers (luminal bacteria, infection)

Other environmental factors → Microbes

Microbes → IBD

IBD

Barrier function

Host factors

Innate and adaptive immunity

Replicated Crohn’s disease loci
- NOD2
- IBD5
- IL23R
- ATG16L1
- Chr 5p13.1
- Chr 5q33.1 (IRGM)
- Chr 10q21.1

Additional replication required
- NCF4
- PHOX2B
- PTPN2
- TNFSF15
- Chr 16q24.1 (FAM92B)
João, 8 years old

- Anorexia
- Fatigue
- Anaemia
- ESR 54 mm

Colonoscopy:
Oedema, friability, ulcers, terminal ileitis
Francisco, 8 years old

- Fever
- Fatigue
- Loose stools
- CRP 71 mg/dl
Filipa, 11 years

- Weight loss
- Anaemia
- Thrombocytosis
Ricardo, 13 years

- Brought to medical care due to pain in both ankles
- For 8 months has had oral aphthae and occasional abdominal pain.
- Lost weight (2kg).
- Constipated.
- Recurrent anal fissures
- Family history irrelevant (no IBD)
Physical examination

• Weight 31kg (centile: <5); Height: 152cm (centile: 25-50); BMI 13.4kg/m$^2$ (centile: <3)
• Oedema on both ankles.
• Swelling of lower lip with large aphthous ulcers
• Abdomen soft though tender in lower right quadrant.
• Liver and spleen not palpable.
Which blood tests to order?

- Haemoglobin: 8.8 g/dL (=88 g/l)
- Mean Cell Volume: 85.6 fl
- Platelets: 482x10⁹/L
- Erythrocyte Sedimentation Rate: 49 mm/h
- C-Reactive Protein (CRP): 35 mg/L (normal <5)
Skin lesions in IBD
Signs and symptoms of IBD?

• Bloody diarrhoea ± weight loss
  – Acute intestinal infection
  – Ulcerative colitis
  – Crohn’s disease

• Anaemia, weight loss, abdominal pain, “appendicitis”
  – Crohn’s disease
  – Coeliac disease
  – Non intestinal disease

• But also...
  – Joint pain or swelling, pyoderma gangrenosum, recurrent aphtae, erythema nodosum
Screening tests for IBD

- Blood count, Platelets
- ESR
- Albumin
- Exclude coeliac disease
  - Anti-transglutaminase antibodies
  - Anti-endomysium antibodies
Abdominal ultrasound

• Important to evaluate terminal ileum (Crohn’s D)
  – Experience and motivation of radiologist!
  – Proper clinical information!
Simple tests if you think of IBD

• In patients with signs suggestive of IBD, existence of **anaemia** or **thrombocytosis** showed:

  • Diagnostic sensitivity: 90.8%
  • Specificity: 80%
  • Positive pred value: 90%
  • Negative pred value: 81%

J C Cabrera-Abreu, Arch Dis Child, 2004
Antibodies

• pANCA
  – Anti neutrophil perinuclear cytoplasm Ab’s
  – Against nuclear histone (distinct from vasculitic diseases)

• ASCA
  – Anti-

Crossed reaction with luminal bacteria?
<table>
<thead>
<tr>
<th></th>
<th>Crohn’s</th>
<th>Ulcerative Colitis</th>
<th>Not IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCA</td>
<td>50-70%</td>
<td>10-15%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>pANCA</td>
<td>30%</td>
<td>60-70%</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

**ASCA**

Crohn’s disease
- Risk of more severe disease
- Ileitis
- Higher risk of surgery
- Less frequent in children < 7 years

**pANCA**

Ulcerative colitis
- in Crohn’s - colitis, with fewer complicaitons
Use of serologic markers

• In Diagnosis

  – Low individual value
  – May be useful, if prevalence is low
  – Useful in unspecific symptoms
  – Time to result?
  – DO NOT use in patients with typical symptoms
  – They DO NOT replace endoscopic and histologic diagnosis!
Use of serologic markers

• In differential diagnosis
  – In some cases of isolated colonic disease
  – In indeterminate colitis (10-15% of IBD)
Fecal Calprotectin

Fecal calprotectin in IBD

P Henderson et al Am J Gastroenterol 2012
Fecal calprotectin in Crohn’s Disease

R Shaoul et al, Inflamm Bowel Dis 2012
Fecal calprotectin in the diagnosis of Crohn’s disease

- N=60
- 6.6% had Normal F calpro
- There was no correlation between the level of F calpro and activity of the disease
- Isolated ileal disease was more often associated with high F calpro

R Shaoul et al, Inflamm Bowel Dis 2012
Fecal calprotectin in the diagnosis of Crohn’s disease

- N=60
- 6.6% had normal Fcalpro
- There was no correlation between the level of Fcalpro and activity of the disease
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R Shaoul et al, Inflamm Bowel Dis 2012

If you consider IBD, simple tests may help to identify patients for subsequent endoscopic diagnosis
Diagnosis of IBD

• Exclude infections
  – Standard culture
  – Clostridium difficile
  – CMV
Endoscopy

- Direct visualization of the mucosa.
- Possibility to obtain material for histology
Endoscopic features

Crohn’s disease
- Aphtoid ulcers
- Cobblesoning
- Stenosis
- Fistula
- Segmental distribution
- “Rectal sparing”

Ulcerative colitis
- Ulcers
- Erythema
- Loss of vascular pattern
- Granulous mucosa
- Friability
- Pseudopolyps
- Continuous lesion from the rectum

Colonoscopy and ileoscopy!
Benefit of Endoscopy

• Upper Endoscopy
  – Diagnostic benefit (granulomas) in 3%

• Ileoscopy
  – Isolated ileitis in 5.8%
  – Ileitis and granuloma in 13%

Cl de Bie et al, JPGN, 2012
Perform biopsies...

- Biopsy of all colonic segments
- Perform ileoscopy and ileal biopies
- In case of ileal disease sample tissue for diagnosis of CMV e TB infection
Visualization of small intestine

In Crohn’s and undetermined colitis

- Wireless capsule endoscopy
- Entero-CT
- Entero-MR
- Enteroclisis
Investigation of small Intestine in Eurokids

N=1404

Cl de Bie et al, JPGN, 2012
Histologic features

Crohn’s disease
- Submucosal or transmural involvement
- Ulcers, distortion of crypts
- Crypt Abscessos
- Granuloma
- Focal lesions

Ulcerative colitis
- Mucosal involvement
- Distortion of crypts
- Crypt abscesses
- Goblet cell depletion
- Mucin granuloma (rare)

Talk to your pathologist! Provide adequate clinical information and feedback
Assessment of IBD

• Confirm diagnosis with full work-up
• Evaluate extension
• Extra-intestinal signs or symptoms?
• Assess activity
• Check for immunization status
Crohn’s disease extension

Paris classification

L1 - Terminal ileal
L2 - Colonic
L3 - Ileocolonic
L4a - Gastro-duodenal
L4b - Jejunal/proximal ileal

Levine et al, Inflamm Bowel Dis, 2010
Other important items in Paris Classification

• Age of onset
  – A1a: 0-10 years
  – A1b: 10-17 years

• Growth
  – G_0: No growth delay
  – G_1: Growth delay
PCDAI
Pediatric Crohn’s Disease Activity

<table>
<thead>
<tr>
<th>History (Recall, 1 week)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Pain</td>
<td></td>
</tr>
<tr>
<td>0 = None</td>
<td></td>
</tr>
<tr>
<td>5 = Mild: Brief, does not interfere with activities</td>
<td></td>
</tr>
<tr>
<td>10 = Moderate/Severe: Daily, longer lasting, affects activities, nocturnal</td>
<td></td>
</tr>
<tr>
<td>Patient Functioning, General Well-Being</td>
<td></td>
</tr>
<tr>
<td>0 = No limitation of activities, well</td>
<td></td>
</tr>
<tr>
<td>5 = Occasional difficulty in maintaining age-appropriate activities, below par</td>
<td></td>
</tr>
<tr>
<td>10 = Frequent limitation of activity, very poor</td>
<td></td>
</tr>
<tr>
<td>Stools (per day)</td>
<td></td>
</tr>
<tr>
<td>0 = 0-1 liquid stools, no blood</td>
<td></td>
</tr>
<tr>
<td>5 = Up to 2 semiformed with small blood, or 2-5 liquid</td>
<td></td>
</tr>
<tr>
<td>10 = Gross bleeding, or ≥ 6 liquid, or nocturnal diarrhea</td>
<td></td>
</tr>
</tbody>
</table>
## Laboratory

<table>
<thead>
<tr>
<th>HCT</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 years (Male and Female):</td>
<td>11-14 years (Male):</td>
</tr>
<tr>
<td>$0 = &gt; 33%$</td>
<td>$0 = \geq 35%$</td>
</tr>
<tr>
<td>$2.5 = 28%-32%$</td>
<td>$2.5 = 30%-34%$</td>
</tr>
<tr>
<td>$5 = &lt; 28%$</td>
<td>$5 = &lt; 30%$</td>
</tr>
<tr>
<td>11-19 years (Female):</td>
<td>15-19 years (Male):</td>
</tr>
<tr>
<td>$0 = \geq 34%$</td>
<td>$0 = \geq 37%$</td>
</tr>
<tr>
<td>$2.5 = 29%-33%$</td>
<td>$2.5 = 32%-36%$</td>
</tr>
<tr>
<td>$5 = &lt; 29%$</td>
<td>$5 = &lt; 32%$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ESR</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>$0 = &lt; 20 \text{ mm/hr}$</td>
<td>$2.5 = 20-50 \text{ mm/hr}$</td>
</tr>
<tr>
<td>$5 = &gt; 50 \text{ mm/hr}$</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Albumin</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>$0 = \geq 3.5 \text{ g/dL}$</td>
<td>$5 = 3.1-3.4 \text{ g/dL}$</td>
</tr>
<tr>
<td>$10 = \leq 3.0 \text{ g/dL}$</td>
<td></td>
</tr>
<tr>
<td>Examination</td>
<td>Score</td>
</tr>
<tr>
<td>-------------</td>
<td>-------</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td></td>
</tr>
<tr>
<td>0 = Weight gain or voluntary weight stable/loss</td>
<td>5 = Involuntary weight stable, weight loss 1%-9%</td>
</tr>
<tr>
<td><strong>Height at Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>0 = &lt; 1 channel decrease</td>
<td>5 = ≥ 1, &lt; 2 channel decrease</td>
</tr>
<tr>
<td><strong>Height at Follow-Up</strong></td>
<td></td>
</tr>
<tr>
<td>0 = Height velocity ≥ -1 SD</td>
<td>5 = Height velocity &lt; -1 SD, &gt; -2 SD</td>
</tr>
<tr>
<td><strong>Abdomen</strong></td>
<td></td>
</tr>
<tr>
<td>0 = No tenderness, no mass</td>
<td>5 = Tenderness or mass without tenderness</td>
</tr>
<tr>
<td><strong>Perirectal Disease</strong></td>
<td></td>
</tr>
<tr>
<td>0 = None, asymptomatic tags</td>
<td>5 = 1-2 indolent fistula, scant drainage, no tenderness</td>
</tr>
<tr>
<td><strong>Extraintestinal Manifestations</strong></td>
<td></td>
</tr>
<tr>
<td>(Fever ≥ 38.5°C for 3 days over past week, definite arthritis, uveitis, E. nodosum, P. gangrenosum)</td>
<td></td>
</tr>
<tr>
<td>0 = None</td>
<td>5 = 1</td>
</tr>
</tbody>
</table>

**Total Score:** 0-100
Activity of Crohn’s using PCDAI

<table>
<thead>
<tr>
<th>Definition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission/Inactive</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Mild</td>
<td>10-30</td>
</tr>
<tr>
<td>Moderate to severe</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Response/Improvement</td>
<td>Drop of ≥ 12.5</td>
</tr>
</tbody>
</table>
UC Extension

Paris classification

E1  E2  E3  E4

Levine et al, Inflamm Bowel Dis, 2010
Montreal and Paris classifications

<table>
<thead>
<tr>
<th>Extent</th>
<th>Montreal</th>
<th>Paris</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1: ulcerative proctitis</td>
<td>E1: ulcerative proctitis</td>
<td>E2: Left-sided UC (distal to splenic flexure)</td>
</tr>
<tr>
<td>E2: left-sided UC (distal to splenic flexure)</td>
<td>E3: Extensive (hepatic flexure distally)</td>
<td></td>
</tr>
<tr>
<td>E3: extensive (proximal to splenic flexure)</td>
<td></td>
<td>E4: Pancolitis (proximal to hepatic flexure)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severity</th>
<th>Montreal</th>
<th>Paris</th>
</tr>
</thead>
<tbody>
<tr>
<td>S0: clinical remission</td>
<td></td>
<td>S0: never severe*</td>
</tr>
<tr>
<td>S1: mild UC</td>
<td></td>
<td>S1: ever severe*</td>
</tr>
<tr>
<td>S2: moderate UC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S3: severe UC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Severe defined by Pediatric Ulcerative Colitis Activity Index (PUCAI) ≥65.
<table>
<thead>
<tr>
<th>Item</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Abdominal pain</strong></td>
<td></td>
</tr>
<tr>
<td>No pain</td>
<td>0</td>
</tr>
<tr>
<td>Pain can be ignored</td>
<td>5</td>
</tr>
<tr>
<td>Pain cannot be ignored</td>
<td>10</td>
</tr>
<tr>
<td><strong>2. Rectal bleeding</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Small amount only, in &lt; 50% of stools</td>
<td>10</td>
</tr>
<tr>
<td>Small amount with most stools</td>
<td>20</td>
</tr>
<tr>
<td>Large amount (&gt; 50% of stool content)</td>
<td>30</td>
</tr>
<tr>
<td><strong>3. Stool consistency of most stools</strong></td>
<td></td>
</tr>
<tr>
<td>Formed</td>
<td>0</td>
</tr>
<tr>
<td>Partially formed</td>
<td>5</td>
</tr>
<tr>
<td>Completely unformed</td>
<td>10</td>
</tr>
<tr>
<td><strong>4. Number of stools per 24 hours</strong></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>0</td>
</tr>
<tr>
<td>3-5</td>
<td>5</td>
</tr>
<tr>
<td>6-8</td>
<td>10</td>
</tr>
<tr>
<td>&gt; 8</td>
<td>15</td>
</tr>
<tr>
<td><strong>5. Nocturnal stools (any episode causing wakening)</strong></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>10</td>
</tr>
<tr>
<td><strong>6. Activity level</strong></td>
<td></td>
</tr>
<tr>
<td>No limitation of activity</td>
<td>0</td>
</tr>
<tr>
<td>Occasional limitation of activity</td>
<td>5</td>
</tr>
<tr>
<td>Severe restricted activity</td>
<td>10</td>
</tr>
<tr>
<td><strong>TOTAL MAXIMUM SCORE</strong></td>
<td>85</td>
</tr>
</tbody>
</table>
### Activity of UC using PUCAI

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</tr>
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<td>10-34</td>
</tr>
<tr>
<td>Moderate</td>
<td>35-64</td>
</tr>
<tr>
<td>Severe</td>
<td>65-85</td>
</tr>
<tr>
<td>Significant response</td>
<td>Drop of ≥ 20</td>
</tr>
</tbody>
</table>
Conclusion

• IBD is increasing in childhood and adolescence
• Crohn’s disease may have subtle features
• Some simple tests may help select patients for further diagnostic work-up
• Firm diagnosis must rely on endoscopy and histology
• Exclude common infectious diseases
• Classify extent and severity of disease
• Talk to your radiologist and pathologist!