The First Goal of Management in IBD: Obtain a Clear and Accurate Diagnosis

- A clear diagnosis should provide information that:
  - Explains the patient’s current symptoms and problems
  - Is accurate now and withstands the test of time
  - Provides prognostic information
  - Makes a distinction in the management decisions such that therapy chosen now impacts both short- and long-term outcomes.
  - May have implications for the care of others (ie family members).

- In 2011, should include disease extent and current severity and some element of longitudinal prognosis.
What is Disease Monitoring in IBD?

- Assessment of the status of disease activity over time.
- Performed in order to control disease and prevent symptomatic relapses or disability.
- Monitoring requires:
  - Understanding of the disease process
  - Acceptable methods of assessment
  - Interventions that are effective and tolerable (by the patient and by the MD)
- Examples:
  - Clinical follow-up
  - Routine laboratory testing for drug efficacy or safety
  - Measures of mucosal integrity or immune activity

Clinical Features of UC and CD

**Ulcerative Colitis**
- Continuous inflammation
- Colon only
- Superficial inflammation
- Variable extent
- Risk of cancer
- Extraintestinal manifestations

**Crohn’s Disease**
- Patchy inflammation
- Mouth to anus involvement
- Full-thickness inflammation
- Fistulas and strictures
- Risk of cancer
- Extraintestinal manifestations
### Montreal Classification

#### Crohn’s disease

<table>
<thead>
<tr>
<th>Location (L)</th>
<th></th>
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<tbody>
<tr>
<td>L1</td>
<td>Terminal ileum</td>
</tr>
<tr>
<td>L2</td>
<td>Colon</td>
</tr>
<tr>
<td>L3</td>
<td>Ileocolon</td>
</tr>
<tr>
<td>L4</td>
<td>Upper GI</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Behavior (B)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>Non-stricturing, non-penetrating</td>
</tr>
<tr>
<td>B2</td>
<td>Stricturing</td>
</tr>
<tr>
<td>B3</td>
<td>Penetrating</td>
</tr>
</tbody>
</table>

(p) modifier Perianal

#### ulcerative colitis

<table>
<thead>
<tr>
<th>Classification by Extent</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Ulcerative proctitis (E1)</td>
<td></td>
</tr>
<tr>
<td>Left-sided ulcerative colitis (E2)</td>
<td></td>
</tr>
<tr>
<td>Extensive ulcerative colitis (E3)</td>
<td></td>
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</table>
The Challenges to Diagnosis in IBD

- Lack of knowledge about the disease and its various manifestations (primary care?)
- Lag time of pre-symptomatic disease before presentation
- Inaccurate classification system
  - Overlap of phenotypes between UC and Crohn’s disease
  - Variations of existing disease presentations

The Spectrum of Utility in IBD

- Clinical Symptoms
- Predicting Behavior
- Rx Response
- Need for Surgery & Outcome
- Monitoring activity, response
- IBD Diagnoses
- Differentiation
- Monitoring activity, response
Diagnosis in IBD

**Primary Dx of IBD**
- Rule out imposters
- Obvious GI symptoms/signs and classic presentation
- Extra-intestinal symptoms/signs and findings
- Re-evaluation over time

**Clarification of IBD Dx**
- Ileocolonoscopy with biopsy
- Distinction between IBS and active inflammation
- Reliable expert pathology
- Evaluation of small bowel
  - WCE
  - CTE/MRE
- Exam under anesthesia, exploratory lap
- Use of other clues
  - family history
  - serologies
  - Non-GI specialists

Historical Features that Help to Confirm a Diagnosis of IBD

- Appendectomy protects against UC
- Ex-smokers may develop UC
- Smokers have CD
- Family history usually concordant

What about these phenotypes? Is this IBD?

- Oral facial granulomatous disease
- Isolated perianal disease
- Hydradenitis suppurativa
- Isolated pyoderma gangrenosum
- Peri-appendiceal red patch?
- Gastric inflammation in kids with UC?
- Rectal sparing in “UC”?
- “Incidental ileitis”
- Wireless capsule findings?
- Serologic markers?

Most Common “Imposters” in the Differential Diagnosis of IBD

- Infectious colitis (including Clostridium difficile)
- Ischemic colitis
- Drug-induced (NSAID) enterocolitis
- Solitary rectal ulcer syndrome
- Radiation enterocolitis
- Diversion colitis
- Endometriosis
- Malignancy
- Functional (IBS)
- Diverticular disease

Imaging in IBD

- Macroscopic vs Microscopic
- Diagnosis
  - explanation of symptoms or lab abnormalities
  - clarification of disease extent and severity
- Cancer screening and surveillance
- Prognosis, adjunctive to additional testing
- Choice of therapy (class or delivery system)
- Prevention of disease expression or complications?

Small Intestinal Crohn’s Disease as Seen by Wireless Capsule Endoscopy
Promise and Problems of CE in IBD

**PROMISE**
- Exquisite imaging of small bowel mucosa
- Less invasive diagnostics (?)
- Emerging information about significance of findings, etc
- Recent FDA indication for monitoring of CD

**PROBLEMS**
- Observer-dependent interpretation
  - training required
  - inter/intra observer variability
- Uncertain significance of many findings- what’s “normal”?  
  - Short-term  
  - Long-term  
  - Need blinded comparator studies
- Heterogeneous data quality of studies
- Capsule retention

Are All Small Bowel Lesions CD?
Diagnostic Yield of Wireless Capsule Endoscopy in Suspected or Known Crohn’s

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Indication</th>
<th>Diagnostic Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costamagna</td>
<td>3</td>
<td>Suspected CD or recurrence</td>
<td>67% CD</td>
</tr>
<tr>
<td>Scapa</td>
<td>13</td>
<td>Suspected CD</td>
<td>46% CD</td>
</tr>
<tr>
<td>Eliakim</td>
<td>20</td>
<td>Suspected CD</td>
<td>60% CD</td>
</tr>
<tr>
<td>Fireman</td>
<td>17</td>
<td>Suspected CD</td>
<td>71% CD</td>
</tr>
<tr>
<td>Liangpunsakul</td>
<td>3</td>
<td>Abdominal pain, ↓ Fe anemia</td>
<td>100% CD</td>
</tr>
<tr>
<td>Herrera</td>
<td>21</td>
<td>Suspected CD</td>
<td>43% CD</td>
</tr>
<tr>
<td>Mow</td>
<td>50</td>
<td>Known or suspected CD</td>
<td>60% CD</td>
</tr>
</tbody>
</table>

How Often do Lesions Occur in Normal Volunteers?

- Findings from a study of COX-2 selective NSAIDs, and SB injury in *normal volunteers*
  - 14% on no NSAIDS had “mucosal breaks” at baseline

- CE studies in osteoarthritis patients without GI symptoms and on no NSAIDS
  - 17% on acetaminophen and no NSAIDS, had SB lesions at baseline

Goldstein et al. CGH 2005  Graham, et al CGH 2005

The Problem of Strictures
**Capsule Retention**

![Radiographic image and clinical scenario image]

**Capsule Retention Rate in CD Depends on Clinical Scenario**

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients (n)</th>
<th>Capsule retention (%)</th>
<th>CD?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herrerias</td>
<td>21</td>
<td>0</td>
<td>Suspected</td>
</tr>
<tr>
<td>Fireman</td>
<td>17</td>
<td>0</td>
<td>Suspected</td>
</tr>
<tr>
<td>Eliakim</td>
<td>20</td>
<td>0</td>
<td>Suspected</td>
</tr>
<tr>
<td>Sant’Anna</td>
<td>20</td>
<td>5</td>
<td>Susp (hi prob)</td>
</tr>
<tr>
<td>Mow</td>
<td>50</td>
<td>4</td>
<td>Known</td>
</tr>
<tr>
<td>Buchman</td>
<td>30</td>
<td>6</td>
<td>Known</td>
</tr>
<tr>
<td>Cheifetz</td>
<td>38</td>
<td>13</td>
<td>Known</td>
</tr>
<tr>
<td>Cheifetz</td>
<td>64</td>
<td>10</td>
<td>Suspected strictures</td>
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</table>
Small bowel radiographs: is it time to retire?

CT Enterography

- Combines high-resolution CT scanning with some of the concepts of barium radiography
- Ingestion of large volume of a *negative* contrast agent (either PO or via NJT) to distend loops
  - Water or diluted PEG
- Intravenous contrast, scan after 70 seconds (venous phase)
- Thin slices on helical CT
- Signs of inflammation
Homogeneous Mural Enhancement of Small Bowel

Perienteric Fat Stranding
Fistulas

- Tracts
- Usually enhancing (unless perianal)
- +/- fluid/air

Effective Doses of Radiation

- CXR: 0.1 mSv
- Round trip airflight, NYC-London, 0.1 mSv
- Mammogram: 0.7 mSv
- SBFT: 2-6 mSv
- Average annual background radiation, 2.4 mSv
- Standard CTE (single phase): 8-12 mSv
- Radiation worker exposure annual limit: 20 mSV
- Bleed protocol CTE (triple phase): 30-40 mSv
- International Space Station, annual: 170 mSv
MR Enterography

A. Enteroclysis
B. MRI Enterography

Ileal Inflammation

Accuracy of MRE versus Ileocolonoscopy (IC)

- 22 pediatric subjects underwent MRE and IC for newly diagnosed Crohn's disease
- 98 subjects with established Crohn's disease

<table>
<thead>
<tr>
<th>TI/Anastomosis</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>72% (53% - 86%)</td>
<td>85% (74 – 92%)</td>
</tr>
<tr>
<td>Colorectum</td>
<td>59% (42% - 74%)</td>
<td>90% (80% - 96%)</td>
</tr>
</tbody>
</table>

- 4/10 false negative MRE’s were due to radiologic interpretation errors
- MRE has modest sensitivity for terminal ileal Crohn’s disease, utility in the colon is lower
- Radiologists interpreting MRE should be well-trained

MRE had good sensitivity for ileal lesions, but sensitivity for colonic lesions was limited

Ability of MRI to Evaluate Therapeutic Response in Crohn’s Disease

- Magnetic resonance enterography (MRE) to evaluate response to Crohn’s therapy
- 27 subjects received adalimumab or corticosteroids for induction of remission
- Novel index (MaRIA) quantified severity of MR findings
- MaRIA correlated with CDEIS (r=0.70 at week 12)
- MaRIA score >40 predicted endoscopic remission (sensitivity 0.82, specificity 0.85)
- MRE can accurately evaluate response to Crohn’s therapy
- MR enteroclysis to evaluate effects of infliximab on transmural Crohn’s
- MR enteroclysis score of severity in ileal Crohn’s disease (MICD) calculated
- Primary endpoint: proportion of subjects with >2 points and >50% decrease in MICD at 26 weeks
- 15 subjects in final analyses
- 32% met primary endpoint
- Results were not compared with endoscopic or histological findings
- MR enteroclysis can monitor effects of infliximab in Crohn’s disease
- What should be done for patients who have evidence of active disease on MRI but are in clinical remission?
US to predict Crohn’s Disease Course

Clinical recurrence-free survival by US recurrence

Clinical recurrence-free survival by endoscopic recurrence

- Small bowel US (SB-US) to predict repeat resection after ileocolonectomy among 107 Crohn’s patients
- Median follow-up 3.3 years
- ≥12 recurrence in 86%
- SB-US predicted need for surgery as well as IC
- SB-US could be an alternative to IC to assess course after ileocolonic resection for Crohn’s

Daperno et al. DDW 2011; abstract no. Su1187.

Microbial Marker Antibodies in Crohn’s Disease (n = 303)

- 79.9% of Patients

Serology as Initial Test?

- No prospectively supported data
- Diagnostic algorithms not published
- ↓ prevalence: ↑ false positives
- ↑ in autoimmune disorders
  - ASCA: celiac, Behcet's, PBC, hepatitis
  - ANCA: eosinophilic & collagenous colitis
  - OMP-C & I2: infection, diverticulitis
- Cost


Serologies in IBD: What is State of the Art in 2011?

- Diagnosis vs. Prognosis

  The accurate integration of serology testing is a function of the pre-test probability of IBD
  - i.e. If pre-test probability is low, positive serologies are likely to be false positives
  - i.e. If pre-test probability is high, negative serologies are likely to be false negatives

- Serologies therefore are of diagnostic value in patients with intermediate likelihood of IBD
**Predictors of Disabling Disease:**

5-year clinical course after diagnosis

- **Age at onset**
  - <40 years vs ≥40 years; p=0.0004

- **Location of disease**
  - small bowel + colon vs small bowel only; p=0.002

- **Smoking status**
  - smoker vs ex- or non-smoker; p=0.09

- **Perianal lesion at diagnosis**
  - yes vs no; p=0.01

- **Required steroids for first flare**
  - yes vs no; p=0.0001

Beaugerie et al, Gastroenterology 2006; 130: 650

**Serum Immune Responses Predict Rapid Disease Progression in Children with CD**

Serologic markers: ASCA, anti-OmpC, anti-I2, anti-CBir1

The Risk of Chronic Pouchitis is Significantly Increased With Pre-Op High Level pANCA

![Graph showing cumulative incidence of chronic pouchitis over time.]


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Should we be treating to achieve mucosal healing?

**YES!!**
- The inflamed and injured bowel is the hallmark of active disease.
- A healed bowel is the sign of disease control or resolution.
- Many of our therapies can achieve it.
- Existing strategies are not effective at longer term management control.

**WAIT - NOT YET!**
- We can't get there in most patients with existing therapies.
- How is this defined???
  - Partial?
  - Complete?
  - Histology?
  - Endoscopy?
  - Radiographic??
- Cost
- Convenience
**Fecal Calprotectin Levels in IBD Patients with Active Disease and “Mucosal Healing”**

![Graph showing fecal calprotectin levels in IBD patients with active disease and mucosal healing.](image)

- Crohn's disease active / remission
- Ulcerative colitis active / remission

* p < 0.0001

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**IBD Diagnosis and Management: The Near Future**

- **First Visit:**
  - **Phenotype:** Location, EIM, Behavior
  - IBD Panel
    - Serology
    - Genetics
    - Proteomics

- **IBD Subtype**

- **Disease Prognosis**
- **Patient-specific treatment plan**
- **Disease Monitoring for Efficacy and Safety**
- **Targeted-specific therapy**