Approach to the New Patient with Crohn’s Disease

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What is Crohn’s Disease?

- Inflammatory bowel disease involving the entire GI tract (mouth to anus)
- Disease is characterized in most patients by patchy inflammation which alternates between periods of active disease and periods of quiescence
- Inflammation is full-thickness
- Fistulas and strictures occur
- Symptoms depend on extent and severity of disease
A 19 year old woman presents to your office with 3 months of diarrhea and fatigue with abdominal pain.

- She has occasional nausea.
- Saw her primary care physician.
- Laboratory studies reveal stool positive for fecal leukocytes and CRP that is elevated as well as hemoglobin 9 g with low MCV.
- She is referred to you for help.
Approach to the New Patient with Crohn’s Disease

- Suspect the diagnosis
- Rule out infections
- Routine labs and stool cultures
- Early endoscopic assessment of colorectum and terminal ileum: clarify extent of disease macroscopically and microscopically
- Biopsy confirmation of the diagnosis
- Additional imaging studies as clinically indicated
- Assess clinical severity of disease
- Identify effective therapies to induce and maintain remission
- Prevention of long-term complications
Age-Specific Incidence of IBD*

*Per 100,000 population
Epidemiology of Crohn’s Disease Temporal Trends in Crohn’s Disease, Olmsted County, 1940-2004

- Prevalence: 100-250 cases per 100,000 ²⁻³
- ~600-800,000 cases in US ³

<table>
<thead>
<tr>
<th>Year of Diagnosis</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1940-49</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>1950-59</td>
<td>4</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>1960-69</td>
<td>6</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>1970-79</td>
<td>8</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>1980-89</td>
<td>10</td>
<td>12</td>
<td>22</td>
</tr>
<tr>
<td>1990-99</td>
<td>12</td>
<td>14</td>
<td>26</td>
</tr>
<tr>
<td>2001-04</td>
<td>14</td>
<td>16</td>
<td>30</td>
</tr>
</tbody>
</table>

Anatomic Distribution of Crohn’s Disease

Upper Gut 10%-15%

Small Bowel Alone 33%

Ileocolonic 45%

Colon Alone 20%
Clinical Presentation of Crohn’s disease

- Ileocecal disease: abd pain, diarrhea, fever
- Colonic disease: bloody diarrhea, weight loss, fever
- Perianal disease: pain, fistulae, edematous hemorrhoids, fissures
- Rectal-vaginal fistulae: 10% of women with rectal involvement
- Enterovesical fistulae: Recurrent UTI’s, pneumaturia

- 5% Gastroduodenitis
- 30% Ileitis/Jejunoileitis
- 25% Colitis
- 40% Ileocolitis
Most patients have chronic intermittent disease course and 10% have prolonged periods of remission.
Clinical Criteria for Crohn’s Disease Activity
(American College of Gastroenterology Practice Guidelines)

- **Mild-to-Moderate**: Ambulatory, no abdominal tenderness, painful mass, or obstruction

- **Moderate-to-Severe**: Unresponsive to treatment for mild-to-moderate stage or with prominent fever, weight loss, anemia, abdominal pain and tenderness, or intermittent nausea or vomiting

- **Severe-to-Fulminant**: Persistent symptoms on corticosteroids or with high fever, rebound tenderness, cachexia, or abscess

- **Remission**: Asymptomatic, no inflammatory sequelae, not requiring systemic corticosteroids

Hanauer et al., Am J Gastroenterol 2001; 96-635
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

Features that Help to Confirm a Diagnosis of Crohn’s Disease

- **History:**
  - Family history of Crohn’s disease
  - Smoking tobacco
  - “hemorrhoids”
  - Delayed growth or development

- **Physical exam:**
  - Low BMI
  - Abnormal perianal examination (skin tags, stricture, fistula, fissure)
  - Abnormal abdominal examination (inflammatory mass)
  - Extra-intestinal manifestations
## Distinguishing Ulcerative Colitis from Crohn’s Disease

<table>
<thead>
<tr>
<th></th>
<th>Ulcerative Colitis</th>
<th>Crohn’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Distribution</strong></td>
<td>Continuous, symmetric, and diffuse distribution</td>
<td>Distribution is often discontinuous and asymmetric with skipped segments and normal intervening mucosa</td>
</tr>
<tr>
<td><strong>Depth of Inflammation</strong></td>
<td>Mucosal/submucosal inflammation</td>
<td>Mucosal, submucosal, and/or transmural inflammation</td>
</tr>
<tr>
<td><strong>Site</strong></td>
<td>Colon affected exclusively</td>
<td>May affect any part of GI tract</td>
</tr>
<tr>
<td><strong>Rectal Involvement</strong></td>
<td>Almost always involves the rectum</td>
<td>Relative rectal sparing may be present</td>
</tr>
</tbody>
</table>

### IBD Specific Serologic Immune Markers

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Antigen</th>
<th>Non-IBD (%)</th>
<th>CD (%)</th>
<th>UC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pANCA</td>
<td>Histone H₁, bacterial antigen?</td>
<td>&lt;5%</td>
<td>10–25%</td>
<td>50–65%</td>
</tr>
<tr>
<td>ASCA</td>
<td>Anti-Saccharomyces cerevisiae antibody</td>
<td>5%</td>
<td>55–65%</td>
<td>5%</td>
</tr>
<tr>
<td>OmpC</td>
<td>E. Coli</td>
<td>&lt;5%</td>
<td>38–50%</td>
<td>2%</td>
</tr>
<tr>
<td>Anti-I2</td>
<td>Pseudomonas fluorescens</td>
<td>&lt;5%</td>
<td>54%</td>
<td>2%</td>
</tr>
<tr>
<td>Anti-Flagellin</td>
<td>CBir 1 Antigen</td>
<td>8-14%</td>
<td>50%</td>
<td>6%</td>
</tr>
</tbody>
</table>
Anti-CBir1 Helps Distinguish Between pANCA+ Patients

Anti-CBir1 (O.D.)

\[
P < 0.001 \text{ (level)}
\]

44%

11/25

4%

1/25

Crohn’s Disease

Image adapted from Frank Netter, MD in Netter's Anatomy
Fistula and Perianal Disease in Crohn’s Disease
Small Bowel Radiograph
CT Enterography Demonstrating Small Bowel Mucosal Hyperenhancement

58 HU

92 HU
CT Enterography: Crohn’s Colitis
MRI Enterography
Capsule Endoscopy and Small Bowel
Crohn’s Disease
IBD: Extra-intestinal Manifestations

- Skin
- Eye
- Bones and Joints
- Kidney
- Hepatobiliary
IBD: Dermatologic

- Pyoderma gangrenosum
- Erythema nodosum
IBD: Arthritis

- 20-25% of patients
- Axial skeleton (disease independent)
  - Ankylosing spondylitis
  - Sacroileitis
- Peripheral arthritis (related to disease activity)
  - Type 1: asymmetric, limited
  - Type 2: chronic, symmetric
Goals of Therapy

- Symptom management
- Induction and maintenance of asymptomatic remission
- Complete mucosal healing
- Maintenance of general well-being with as few side effects and long-term sequelae as possible
Current “Therapeutic Pyramid”

Crohn’s Disease

- Budesonide
- Antibiotics
- 5-ASA
- MTX
- AZA/6-MP
- Systemic Steroids
- Infliximab
- Surgery

Severity Levels:
- Mild
- Moderate
- Severe
Conventional approach to Induction Therapy: step-up

- Clinical approach to use “mildest” form of drug therapy to treat patients first
- Move to next step in non-responders
Treatment Options
Mild Crohn’s Disease

• Aminosalicylates
  — Sulfasalazine
  — Mesalamine
  — Balsalazide
• Antibiotics
  — Metronidazole
  — Ciprofloxacin
• Corticosteroids
  — Budesonide

Treatment Options
Moderate to Severe Crohn’s Disease

- Corticosteroids
  - Prednisone
- Immunomodulators
  - Azathioprine
  - 6-mercaptopurine
  - Methotrexate
  - Cyclosporine
- Biologics
  - Infliximab
  - Adalimumab
  - Certolizumab pegol
  - Natalizumab
- Surgical resection, diversion or bowel rest

Crohn’s disease: Maintenance of Remission

- Steroids ineffective
  - Steroid-dependent vs. maintenance
- Aminosalicylate dose-response
  - Topical therapy for distal disease
- Azathioprine/6-MP for steroid-dependence and after cyclosporine
- Infliximab, adalimumab, certolizumab pegol
- Natalizumabs
5-Aminosalicylic Acid Therapy in Crohn’s Disease

- 5-aminosalicylic acid (5ASA) is often the first pharmacologic therapy used in CD
- Less than 50% of patients in Olmsted County required corticosteroids to treat CD
- Two 5-ASA compounds are available:
  - Sulfasalazine
  - Mesalamine
    - different types of formulations available

Faubion et al., Gastroenterology 2001; 121:255
5-ASA in Crohn’s Disease

- Use is supported by both clinical experience and evidence
- Advocated in US and UK Guidelines
- Clinical utilities
  - Mild-moderate disease
  - Maintenance of remission after 5-ASA induction
  - ? Post-operative sub-groups?
- Not efficacious after corticosteroid-induction
- Long-term safety established
- Controversial by some experts due to absence of rigorous evidence or preponderance of negative studies
Meta-analysis of Mesalamine in Active Crohn’s Disease

Corticosteroids: Short- and Long-Term Efficacy in Crohn’s Disease

30-Day Responses (N=74)
- Complete: 58% (N=43)
- Partial: 26% (N=19)
- None: 16% (N=12)

1-Year Responses (N=74)*
- Prolonged Response: 28% (N=21)
- Steroid Dependent: 32% (N=24)
- Surgery: 38% (N=28)

*One patient lost to follow-up.
Summary: Steroids in the Treatment of Crohn’s Disease

- Only short-term efficacy
- No maintenance of response / remission
- Only deaths in controlled trials related to steroids and abscess
- Toxicity profile unacceptable for long-term use
- More recent evidence suggests that exposure to steroids may alter course of disease toward surgery or worse outcomes
  - This remains theoretical but steroid-sparing or steroid-avoiding strategies are favored and being studied
Evidence-based Treatment for Mild-to-Moderate Crohn’s Disease

- Mild-to-moderate Crohn’s disease
  - Left-sided disease restricted to colon
    - Sulfasalazine 16 weeks
      - Sulfa-allergic / failed treatment
  - Disease involving the ileum and/or ascending colon
    - Budesonide 8-16 weeks
      - Failed treatment

Conventional steroids

## Serious Potential Adverse Effects From Prolonged Corticosteroid Therapy

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Potential for developing adverse effect (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>20</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.23 relative risk for beginning insulin</td>
</tr>
<tr>
<td>Infection</td>
<td>13–20</td>
</tr>
<tr>
<td>Osteonecrosis</td>
<td>5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>?50</td>
</tr>
<tr>
<td>Myopathy</td>
<td>7</td>
</tr>
<tr>
<td>Cataracts</td>
<td>22 (dose-dependent)</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>? frequency (response genetically determined)</td>
</tr>
<tr>
<td>Psychosis</td>
<td>3–5</td>
</tr>
</tbody>
</table>

Sandborn WJ. *Can J Gastroenterol.* 2000;14(suppl C):17C-22C.
Maintenance of Remission with AZA

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Odds Ratio</th>
<th>Weight (%)</th>
<th>Odds Ratio</th>
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</thead>
<tbody>
<tr>
<td>Azathioprine 2.5 mg/kg/day</td>
<td>Candy 1995</td>
<td>14/25</td>
<td>2/20</td>
<td>15.1</td>
<td>7.12 (2.11–23.99)</td>
</tr>
<tr>
<td></td>
<td>Summers 1979</td>
<td>16/19</td>
<td>15/20</td>
<td>9.4</td>
<td>1.73 (0.37–8.05)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>44</td>
<td>40</td>
<td></td>
<td>24.5</td>
<td>4.13 (1.59–10.71)</td>
</tr>
<tr>
<td>Azathioprine 2.0 mg/kg/day</td>
<td>O'Donoghue 1978</td>
<td>13/23</td>
<td>8/27</td>
<td>17.9</td>
<td>2.95 (0.97–9.00)</td>
</tr>
<tr>
<td></td>
<td>Rosenberg 1975</td>
<td>7/10</td>
<td>4/10</td>
<td>7.5</td>
<td>3.16 (0.57–17.62)</td>
</tr>
<tr>
<td></td>
<td>Willoughby 1971</td>
<td>4/5</td>
<td>2/5</td>
<td>3.9</td>
<td>4.48 (0.41–49.42)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>38</td>
<td>42</td>
<td></td>
<td>29.3</td>
<td>3.17 (1.33–7.59)</td>
</tr>
<tr>
<td>Azathioprine 1.0 mg/kg/day</td>
<td>Summers 1979</td>
<td>37/54</td>
<td>65/101</td>
<td>46.2</td>
<td>1.20 (0.60–2.41)</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>54</td>
<td>101</td>
<td></td>
<td>46.2</td>
<td>1.20 (0.60–2.41)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>136</td>
<td>183</td>
<td></td>
<td>100.0</td>
<td>2.16 (1.35–3.47)</td>
</tr>
</tbody>
</table>

AZA = azathioprine; CI = confidence interval.
Induction and Maintenance of Remission with Methotrexate

**Induction 1**

- Placebo
- Methotrexate 25 mg IM Weekly

**Maintenance 2**

- 65% of 45% Responders = 30% Overall
- *P* = 0.04

- Placebo: N=36
- Methotrexate 25 mg IM Weekly: N=40

*IM = intramuscular. *P* = 0.025 vs placebo.
Infliximab Maintenance of Remission: ACCENT I

Clinical Remission at Week 30*

* Week 2 responders (primary end point).
**P=0.003 vs placebo; †P=0.0002 vs placebo.
Fistula Response at Week 54 with Infliximab: ACCENT II*

*Randomized responders (secondary end point).

**P=0.001 vs placebo; †P=0.009 vs placebo.

Induction Therapy with Adalimumab: CLASSIC I
Clinical Remission at Week 4*28

* All randomized patients (primary end point).
**P=0.001 vs placebo.
Maintenance Therapy with Adalimumab: CHARM

Clinical Remission*

- Placebo
- Adalimumab 40 mg EOW
- Adalimumab 40 mg Weekly

_week 26:
- Placebo: 17%
- Adalimumab 40 mg EOW: 40%
- Adalimumab 40 mg Weekly: 47%

_week 56:
- Placebo: 12%
- Adalimumab 40 mg EOW: 36%
- Adalimumab 40 mg Weekly: 41%

* Randomized responders (primary end point).
**P<0.001 vs placebo.

EOW = every other week.
Adalimumab for Infliximab Failure: GAIN
Clinical Remission at Week 4*

- Placebo
- Adalimumab 160/80 mg

* All randomized patients (primary end point).

**P<0.001 vs placebo.

Maintenance Therapy with Certolizumab: PRECiSE 2

Clinical Remission at Week 26*

CRP = C-reactive protein.
* Week 6 responders (secondary end point).
** P<0.001 vs placebo.
† P=0.01 vs placebo.
Induction of Remission with Natalizumab: ENACT 1*

Week 10 Results: Subgroup Analysis

* All randomized patients (secondary end point).

Induction of Remission with Natalizumab: ENCORE*

* All randomized patients (secondary end point).

**P≤0.001 vs placebo.

Indications for Surgery: Crohn’s Disease

- **Absolute indications**
  - Free perforation
  - Massive hemorrhage
  - Cancer/dysplasia
  - High-grade bowel obstruction

- **Relative indications**
  - Intractability
  - Complex fistula/abscess
  - Perianal complication
  - Growth retardation

Crohn’s Disease
Postoperative Recurrence Rates

Disease-Free Survival (%)

Years

Reoperation

Clinical Symptoms

Endoscopic Lesions

Potential Benefits of Accurate Diagnosis in IBD

- Health
- Subclinical Inflammation
- Symptomatic Inflammation
- Complications
- Disability

- Disease Prevention
- Prevention of Symptomatic Disease
- Prevention of Complications
- Prevention of Relapse
Predictors of Disabling Crohn’s Disease

- Factors significantly associated with disabling Crohn’s disease within 5 years of diagnosis
  - Initial requirement for steroid use: OR 3.1; 95% CI, 2.2-4.4
  - Age below 40 years: OR 2.1; 95% CI, 1.3-3.6
  - Presence of perianal disease: OR 1.8; 95% CI, 1.2-2.8

- Positive predictive value
  - 0 factors: 61%
  - 1 factor: 67%
  - 2 factors: 91%
  - 3 factors: 93%

Cl = confidence interval; OR = odds ratio.
Beaugerie et al. Gastroenterology. 2006;130:650-656.
## Risk of Complicated Disease Behavior

### Clinical Features And Serologies

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Development of Strictures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileum involved at diagnosis</td>
<td>1.83 (1.18-2.83)</td>
<td>0.007</td>
</tr>
<tr>
<td>ASCA positivity</td>
<td>1.47 (1.02-2.11)</td>
<td>0.04</td>
</tr>
<tr>
<td>Follow-up duration</td>
<td>1.07 (1.05-1.09)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Development of Fistulae</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anal involvement at diagnosis</td>
<td>4.35 (2.73-6.93)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ASCA positivity</td>
<td>1.76 (1.23-2.52)</td>
<td>0.002</td>
</tr>
<tr>
<td>Follow-up duration</td>
<td>1.04 (1.02-1.06)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Need for IBD-Related Surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileal involvement at diagnosis</td>
<td>3.14 (1.59-6.19)</td>
<td>0.0009</td>
</tr>
<tr>
<td>Development of fistulae</td>
<td>6.95 (3.80-12.69)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Development of strictures</td>
<td>6.92 (3.91-12.26)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Duration of follow-up</td>
<td>1.09 (1.05-1.13)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CI = confidence interval; *multivariate.

Complications Increase with Number of Positive Serologies
ASCA, CBir1, I2, OmpC

* Numbers represent odds ratios.


P=0.002 (for trend)
Step-Up vs Top-Down Approach

Conventional Management vs Early Combined Immunosuppression

**Step-Up (N=64)**
- + Infliximab
- + Azathioprine/Methotrexate
- Steroids

**Top-Down (N=65)**
- Infliximab (3 doses) + Azathioprine
- Continue Azathioprine
- + Episodic Infliximab
- Steroids

Top-Down vs Step-Up: Results

Steroid-Free Remission Without Surgery

Proportion of Patients on Immunosuppressants

Weeks

Patients (%)

Weeks

Patients (%)

*P<0.01.

**P<0.05.

Top-Down vs Step-Up Endoscopic Results

*P=0.0028.
Summary: The New Patient with CD

- Early and accurate diagnosis
- Assessment of extent and severity of disease
- Identify predictors of complicated disease
- Choice of induction therapy determines your maintenance therapy
- Choose effective induction and maintenance therapies, including surgery when needed
  - “Step-up” therapy remains the usual approach
  - Earlier immunosuppressive therapy may be better in some populations of more severe or complicated patients
- Discuss the importance of maintenance therapy
- Ongoing monitoring and follow-up
Communicating with your Patient

- Emphasize that this is a treatable condition
- Remind the patient about the importance of adherence to therapy and maintenance of remission
- Anticipate their questions about the disease:
  - Does stress cause relapses?
  - What role does diet play in causing or controlling the disease?
  - Are there “natural remedies” or alternative therapies?
- Provide additional educational resources
  - www.ccfa.org
- Plan healthy follow-up visits