Approach to a New Patient with Ulcerative Colitis

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What is Ulcerative Colitis?

• Inflammatory bowel disease involving the large intestine (colon and rectum)
• Variable extent of large bowel involvement
  – Almost always starts in the rectum and may involve more bowel or progress proximally
  – Major symptoms usually come from the inflamed rectum
• Disease is characterized in most patients by active inflammation alternating with periods of quiescence (remission)
• Cause remains unknown, triggers of onset are usually not identifiable
Case

• A 23 year old woman presents to your office with 3 months of new onset rectal urgency and frequency.
• Sensation of incomplete evacuation and small amounts of bright red blood mixed with semi-formed stool.
• Saw her primary care physician who diagnosed it as irritable bowel and hemorrhoids.
• Because of ongoing problems, she sees you for help.
Approach to the New Patient

- 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
- 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

Symptoms depend on extent and severity of inflammation

- Bloody diarrhea
- Abdominal cramping
- Tenesmus - fecal urgency
- Systemic symptoms, fever, decreased stamina, weight loss
- Proctitis and Proctosigmoiditis
  - 50% of patients
  - Constipation in 25%
- Extraintestinal manifestations (1/3 patients)
Clinical Presentation of Ulcerative Colitis

- Urgency: 85%
- Increased Defecation: 83%
- Tenesmus: 63%
- Hard or Formed Stools: 47%

Natural History of UC

- Within 2 years of diagnosis
  - 17% experience colonic hemorrhage
  - 13% experience toxic colitis
- Disease progresses in 54% of patients within 5 years of diagnosis
- Complications highest among pancolitis patients
- 20 - 38% ultimately require proctocolectomy
- Increased risk of colon cancer

UC: Natural History*

*Percent of patients with disease activity, in remission, or having colectomy performed each year after diagnosis

## Severity of Ulcerative Colitis

*Modified Truelove and Witts Criteria*

<table>
<thead>
<tr>
<th>Sign/Symptom</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowel movements</td>
<td>&lt;4/d</td>
<td>4-6/d</td>
<td>&gt;6/d (mostly bloody)</td>
</tr>
<tr>
<td>Temperature (°F)</td>
<td>Normal</td>
<td>99-100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Weight loss (%)</td>
<td>None</td>
<td>1-10</td>
<td>&gt;10</td>
</tr>
<tr>
<td>Pulse (beats/minute)</td>
<td>&lt;90</td>
<td>90-100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>Normal</td>
<td>30-40</td>
<td>&lt;30</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>&lt;20</td>
<td>20-30</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>Normal</td>
<td>3.0-3.5</td>
<td>&lt;3.0</td>
</tr>
</tbody>
</table>

Determining Clinical Severity of Disease

**MILD**
- <4 stools/day ± blood
- Normal ESR
- No signs of toxicity

**MODERATE**
- ≥ 4 stools/day
- Minimal signs of toxicity

**SEVERE**
- >6 bloody stools/day +
  - Fever, tachycardia, anemia, or ↑ ESR

**FULMINANT**
- >10 stools/day, continuous bleeding, toxicity, abdominal tenderness/distension, transfusion requirement, colonic dilation on x-ray

Disease Severity in UC

- **Severe Activity (9%)**: Increasing activity from diagnosis, leading to colectomy or death within 1 year.
- **Moderate Activity (71%)**: >4 stools daily and/or daily presence of blood/pus and/or systemic symptoms.
- **Mild Activity (20%)**: ≤4 stools daily and/or presence of blood and/or pus in the stools less than daily; no systemic symptoms.

Adapted from Langholz E et al. Scand J Gastroenterol. 1991;26:1247-1256.
UC: Location and Extent

- 30% Extensive/Pancolitis
- 30% Proctitis
- 40% Distal/Left-sided colitis
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

Historical Features that Help to Confirm a Diagnosis of Ulcerative Colitis

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

Is it Clostridium difficile?

- 8-fold increase in the number of C. difficile cases in last 5 years
- 14-fold increase in the number of hospitalizations for C. difficile in IBD in last 5 years
- 5-fold increase in the number of colectomies in IBD patients who are C. difficile positive

Cases of C. difficile in IBD Patients*

*At IBD Center of the Medical College of Wisconsin, years 2003 to 2005.

### 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

P<0.001 (level)

44%
11/25

4%
1/25

0.255

Ulcerative Colitis: Endoscopy
Ulcerative Colitis: Endoscopy
Peri-Appendiceal Red Patch
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
• Primary sclerosing cholangitis
  – Inflammation and fibrosis of biliary tree
  – 75%-80% of PSC patients have IBD (UC)
  – 5% of UC patients have PSC
  – Bowel disease independent, transplantation may be required
• Autoimmune hepatitis
  – More often with UC
• Gallstones
  – Cholesterol crystals and stones
  – Worse with colectomy
IBD: Ocular

- 1-13% of patients
- Anterior uveitis and scleritis (disease-related)
- Keratitis
- Steroid-associated
  - Cataracts (85% after 4 years of use)
  - glaucoma
Goals of Management of Ulcerative Colitis

• Confirm accurate diagnosis
• Induce remission
  – Defined as absence of inflammatory symptoms, feeling “well”
• Maintain remission
  – 95% of patients require maintenance therapies
  – Transition to maintenance occurs after successful induction
  – Need effective and safe long-term therapies
• Avoid surgery when possible, embrace it when necessary
• Enhance quality of life
• Avoid complications of
  – The disease
  – Therapy
Clinical Remission

- No urgency
- No bleeding
- No nocturnal symptoms
- Formed stools
- Able to distinguish flatus from stool
UC Treatment Pyramid: A “Step-up” Approach

Disease Severity

Severe

Moderate

Mild

5-ASAs = 5-aminosalicylate agents.

- 5-ASAs
- Corticosteroids
- Azathioprine/6-Mercaptopurine
- Infliximab
- Surgery
- Cyclosporine

Adapted from Isaacs KL et al. Inflamm Bowel Dis. 2005;11(suppl 1):S3-S12.
Ulcerative Colitis: Induction of Remission

- **Mild disease**
  - Aminosalicylate (5-ASA)
    - Topical therapy alone (distal disease)
    - Oral (extensive disease)
    - Or combination

- **Moderate disease**
  - Steroid taper
  - Infliximab

- **Severe disease**
  - IV steroids
  - Infliximab
  - Cyclosporine
Ulcerative Colitis: 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
5-ASA Delivery Systems

Bacterial Cleavage
- Sulfasalazine
- Olsalazine Dipentum™
- Balsalazide Colazal™
- Inert Carrier

pH Dependent Systems
- Asacol®
- Acrylic polymer coated mesalamine
- MMX™ mesalamine

Time Release System
- Lialda™
- Ethylcellulose-encapsulated mesalamine microspheres
- Pentasa®

MMX = multimatrix technology.
Location of 5-ASA Release

- **Stomach**
- **Jejunum**
- **Ileum**
- **Colon**

**Sulfasalazine prodrug; azo bond of 5-ASA + sulfapyridine**

**Dipentum® (olsalazine sodium) prodrug; azo bond of 2 5-ASA molecules**

**Colazal® (balsalazide disodium) prodrug; azo bond of 5-ASA + 4-ABA carrier**

**Asacol® (mesalamine) Delayed-Release Tablets**

**Lialda™ (mesalamine) Delayed Release Tablets**

**Pentasa® (mesalamine) Controlled-Release Capsules coated to release over time**

Approach to 5-ASA Use in IBD

- Choose drug and route of delivery to maximize dose at location of disease
- Consider disease and patient variables in customizing therapy
  - Be aware of interpatient variability
  - Encourage adherence to therapy
- Achieve remission before transitioning to maintenance therapy
  - No evidence to support dose reduction
  - Dose to achieve remission may be dose necessary for “durable” remission
- Encourage adherence to therapy
## Effective Dosages of Oral 5-ASAs for UC

<table>
<thead>
<tr>
<th>AGENT</th>
<th>INDUCTION (g/d) (note different MW)</th>
<th>MAINTENANCE (g/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfasalazine</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Olsalazine</td>
<td>1.5, 3</td>
<td>1</td>
</tr>
<tr>
<td>Delayed-release mesalamine</td>
<td>1.6, 2.4, 4.8</td>
<td>0.8, 1.6</td>
</tr>
<tr>
<td>Mesalamine microspheres</td>
<td>2, 4</td>
<td>2</td>
</tr>
<tr>
<td>Balsalazide</td>
<td>6.75</td>
<td>3, 6</td>
</tr>
</tbody>
</table>

Mesalamine for Mild to Moderate UC

Efficacy of Oral Mesalamine in Treatment of Active UC

N = 87 (6 weeks)

Patients (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo (n = 38)</th>
<th>1.6 g/day (n = 11)</th>
<th>4.8 g/day (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Remission</td>
<td>5%</td>
<td>9%</td>
<td>24%</td>
</tr>
<tr>
<td>Partial Response</td>
<td>13%</td>
<td>18%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Oral vs Rectal Mesalamine vs Combination Therapy in Active Distal UC

*% of Patients With Cessation of Bleeding

*< .05 vs oral mesalamine

N=60, 6 weeks

Assessing the Safety and Clinical Efficacy of a New Dose of Asacol (800 mg) ASCEND I+II

Treatment Success at Week 6
Pooled Population

% of Patients Improved

- Moderate Population: 58% (p=0.0034)
- Mild+Moderate Population: 53% (p=NS)
- Mild Population: 41% (p=NS)

# Multi Matrix System Mesalamine

Gastro-resistant, pH dependent coating  
Lipophilic and hydrophilic matrices

<table>
<thead>
<tr>
<th></th>
<th>% in clinical and endoscopic remission at 8 weeks</th>
<th>Kamm et al.$^1$</th>
<th>Lichtenstein et al.$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMX 2.4 QD</td>
<td>40.5*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMX 4.8 BID</td>
<td>-</td>
<td></td>
<td>34.1*</td>
</tr>
<tr>
<td>MMX 4.8 QD</td>
<td>41.2*</td>
<td></td>
<td>29.2*</td>
</tr>
<tr>
<td>Asacol 2.4 TID</td>
<td>32.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>22.1</td>
<td>12.9</td>
<td></td>
</tr>
</tbody>
</table>

*p<.01 vs. placebo

1Kamm MA et al Gastroenterol. 2007;132:66-75  
• 41.2% patients nonadherent
  – 81% of these “unintentional”
• Predicted by
  – Disease activity
    (OR, 0.55; \( P = 0.002 \))
  – New patient status
    (OR, 2.14; \( P = 0.04 \))
  – Disease duration
    (OR, 0.5; \( P = 0.0001 \))

Corticosteroids: Dependency—Short- and Long-term Efficacy

<table>
<thead>
<tr>
<th>1-Month Outcomes* (n=63)</th>
<th>1-Year Outcomes (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete Remission</strong></td>
<td><strong>Prolonged Response</strong></td>
</tr>
<tr>
<td>54% (n=34)</td>
<td>49% (n=31)</td>
</tr>
<tr>
<td><strong>Partial Remission</strong></td>
<td><strong>Steroid Dependent</strong></td>
</tr>
<tr>
<td>30% (n=19)</td>
<td>22% (n=14)</td>
</tr>
<tr>
<td><strong>No Response</strong></td>
<td><strong>Surgery</strong></td>
</tr>
<tr>
<td>16% (n=10)</td>
<td>29% (n=18)</td>
</tr>
</tbody>
</table>

*30 days after initiating 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.
Risk of Surgical Resection in Patients with UC After Starting Corticosteroids*

185 patients in Olmsted County, MN diagnosed with UC from 1970 to 1993.
AZA vs 5-ASA for Steroid-Dependent, Active UC

N=72

*Defined as clinical remission (Powell-Tuck Index Score of 0) and endoscopic remission (Baron Index Score ≤ 1) plus steroid discontinuation. Patients treated with concurrent tapering dose of steroids. †0.8 g at breakfast and lunch and 1.6 g at dinner.

6-Mercaptopurine as Maintenance Therapy for Ulcerative Colitis

UC – Maintenance Therapy n=83

Probability of Remission

Continued 6-MP

Stopped 6-MP

Months

0.0 0.2 0.4 0.6 0.8 1.0

0 20 40 60

Infliximab for Ulcerative Colitis: ACT1 and ACT2

Clinical response

Clinical remission

Proportion of patients

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 colitis?
  - 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
Summary: The New Patient with UC

- Early and accurate diagnosis
- Assessment of extent and severity of disease
- Choice of induction therapy determines your maintenance therapy
- Discuss the importance of maintenance therapy
- Ongoing monitoring and follow-up