INFLAMMATORY BOWEL DISEASE
Therapeutics 2
Spring 2004
Jennifer Kasiar, Pharm.D., BCPS

Required Reading:

Pathophysiology Content Questions:
1. Differentiate between ulcerative colitis and Crohn’s disease regarding the site involved, depth of involvement, hallmark signs, and pattern of inflammation.
2. Describe the role of aminosalicylates in patients with inflammatory bowel disease.
3. Differentiate between sulfasalazine and the newer 5-ASA products in the treatment of ulcerative colitis and Crohn’s disease with respect to dosing strategy and side effect profile.
6. Describe the mechanism and adverse effects of budesonide for the treatment of Crohn’s disease.
8. Differentiate the dosing regimens of infliximab in the different types of Crohn’s disease.
9. List adverse effects of infliximab.
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I. Background

Inflammatory Bowel Disease – a general term for a group of chronic inflammatory disorders of unknown cause involving the gastrointestinal tract. Chronic IBD is divided into two major categories:

1. Ulcerative colitis
2. Crohn’s Disease

II. Epidemiology

<table>
<thead>
<tr>
<th></th>
<th>Ulcerative Colitis</th>
<th>Crohn’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence (U.S.)</td>
<td>11 / 100,000</td>
<td>7 / 100,000</td>
</tr>
<tr>
<td>Age of Onset (yrs)</td>
<td>15-30 &amp; 60-80</td>
<td>Same as ulcerative colitis</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Jewish &gt; Non-Jewish Caucasian &gt; African American &gt; Hispanic &gt; Asian</td>
<td>Same as ulcerative colitis</td>
</tr>
<tr>
<td>Male:Female Ratio</td>
<td>1:1</td>
<td>1-2:1</td>
</tr>
<tr>
<td>Smoking</td>
<td>May prevent disease</td>
<td>May cause disease</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>No increased risk</td>
<td>Relative risk 1.9</td>
</tr>
<tr>
<td>Appendectomy</td>
<td>Not protective</td>
<td>Protective</td>
</tr>
<tr>
<td>Identical twins</td>
<td>8% concordance</td>
<td>67% concordance</td>
</tr>
<tr>
<td>Fraternal twins</td>
<td>0% concordance</td>
<td>20% concordance</td>
</tr>
</tbody>
</table>

Adapted from Harrison’s Principles of Internal Medicine. 15th ed. Table 287-1.

III. Anatomy of the Gastrointestinal Tract
IV. Etiology

The cause of Inflammatory Bowel Disease remains unknown.

A. Genetic Susceptibility
   • Family history
   • Defects in certain chromosomes (16, 12, 7, 3, 1) *(possible theory)*
   • Body’s normal bacterial flora

B. Host Factors
   • Intestinal epithelial cell barrier function
   • Vascular supply
   • Impaired autoimmunity

C. Environmental Factors
   • Smoking
   • Stress

V. Pathophysiology
Ulcerative colitis & Crohn’s disease differ in 2 general aspects;

1. Anatomic sites
   2. Depth of Involvement within the bowel wall

<table>
<thead>
<tr>
<th></th>
<th>Ulcerative colitis</th>
<th>Crohn’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Site involved</strong></td>
<td>colon/rectum</td>
<td>any part of the GI tract</td>
</tr>
<tr>
<td><strong>Depth of involvement</strong></td>
<td>mucosa/submucosa</td>
<td>mucosa/submucosa plus deep muscular layers, serosa, and regional lymph nodes</td>
</tr>
<tr>
<td><strong>Hallmark sign</strong></td>
<td>Bloody diarrhea</td>
<td>May present in many ways</td>
</tr>
<tr>
<td><strong>Cure</strong></td>
<td>Proctocolectomy</td>
<td>None</td>
</tr>
<tr>
<td><strong>Systemic involvement</strong></td>
<td>Unusual, but possible</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Pattern of Inflammation</strong></td>
<td>Uniform &amp; continuous</td>
<td>Discontinuous</td>
</tr>
<tr>
<td><strong>Involvement of rectum</strong></td>
<td>95% of cases</td>
<td>50% of cases</td>
</tr>
<tr>
<td><strong>Bowel wall features</strong></td>
<td>Severe disease: becomes extremely thin; risk of perforation high</td>
<td>Thickens &amp; lumen narrows; risk of perforation low</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Toxic Megacolon – a medical emergency</td>
<td>Risk of ulceration, fistula, &amp; fissures is common</td>
</tr>
</tbody>
</table>

VI. Clinical Features/Laboratory Data

<table>
<thead>
<tr>
<th></th>
<th>Ulcerative colitis</th>
<th>Crohn’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bloody diarrhea</td>
<td></td>
<td>Diarrhea often without blood</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td>Fever</td>
</tr>
<tr>
<td>Weight Loss</td>
<td></td>
<td>Weight Loss</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td>Extraintestinal manifestations (See next table for list of extraintestinal manifestations)</td>
<td></td>
<td>Extraintestinal manifestations (See next table for list of extraintestinal manifestations)</td>
</tr>
<tr>
<td>Physical Exam (may see abdominal distention or tenderness)</td>
<td></td>
<td>Physical Exam (Right lower quadrant tenderness with associated mass or fullness)</td>
</tr>
<tr>
<td>Laboratory Data (↓ Hgb/Hct, ↑ WBC, hypokalemia reflective of the degree of diarrhea, hypoalbuminemia reflective of the protein loss through an ulcerated mucosa, elevated ESR, elevated LFTs)</td>
<td></td>
<td>Laboratory Data (mild ↓ Hgb/Hct, mild elevation in WBC, elevated ESR)</td>
</tr>
</tbody>
</table>

Extraintestinal Manifestations of IBD
## Dermatologic
**Erythema nodosum (EN)**
- Skin lesions characterized as hot, red, tender nodules measuring 1 to 5cm in diameter
- Usually found on anterior surface of lower legs, ankles, calves, thighs, & arms
- Therapy: Correct underlying bowel disease

**Pyoderma gangrenosum (PG)**
- More common in severe Ulcerative colitis than Crohn’s
- Skin lesions (or pustules) commonly found on bottom surface of feet and back of legs. (may also appear on the arms, chest, & face)
- Lesions may be single or multiple and may grow to as large as 30cm in diameter.
- Therapy: very difficult to treat; often requires IV antibiotics, IV steroids, IV cyclosporine, or dapsone

## Rhematologic
**Arthritis**
- Usually assymetric, polyarticular, and migratory
- Most often affects large joints of arms and legs
- Therapy: Correct underlying bowel disease

**Ankylosing spondylitis**
- More common in Crohn’s disease than ulcerative colitis
- Most often affects lower back and pelvis resulting in lower back pain, buttock pain, & morning stiffness
- Incidence does not correlate with IBD flares
- Therapy: Course of disease is continuous and progressive leading to permanent skeletal damage and deformity.

## Ocular
**Uveitis**
- Symptoms include ocular pain, photophobia, blurred vision, and headache
- Therapy: systemic steroids are usually required to prevent visual impairment

## Hepatobiliary
**Hepatomegaly**
- Hepatic steatosis – (note this is the first step in the process of developing cirrhosis)
  - Patients may have elevated LFTs
- Primary sclerosing cholangitis (PSC)
  - Characterized by bile duct inflammation and fibrosis, frequently leading to cirrhosis and hepatic failure
  - 1 to 5% of patients with IBD have PSC
  - Symptoms include fatigue, jaundice, abdominal pain, fever, anorexia, & malaise
  - Therapy: Patients with symptomatic PSC develop cirrhosis and hepatic failure over 5 to 10 years and eventually require liver transplantation.

## Hematologic
**Thromboembolic disease**
- Risk of clot formation, which may result in deep vein thrombosis (DVT), pulmonary embolism (PE), or stroke, increases when IBD becomes active

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VII. **Diagnosis**
Before making an accurate diagnosis of IBD, you must rule out other causes of diarrhea / colitis.
Differential diagnoses include:
Crohn’s disease
Ulcerative colitis
Infectious colitis
“Traveler’s” diarrhea
Non-specific colitis
Pseudomembranous colitis
Diverticulitis
Ischemic colitis
Bowel cancer
Radiation colitis
Ileoceleal tuberculosis

Clinical suspicion & one or more of the following procedures help make the diagnosis of IBD.
• Endoscopy and/or colonoscopy
• Sigmoidoscopy
• Radiography – administer barium enema rectally for radiographic review
• Biopsy

Severity Criteria for Ulcerative Colitis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowel movement frequency</td>
<td>&lt; 4 / day</td>
<td>&gt; 6 / day</td>
<td>&gt; 10 / day</td>
</tr>
<tr>
<td>Blood in stool</td>
<td>+/-</td>
<td>++</td>
<td>Continuous</td>
</tr>
<tr>
<td>Fever</td>
<td>Normal</td>
<td>&gt; 37.5°C (100.5°F)</td>
<td>&gt; 37.5°C (100.5°F)</td>
</tr>
<tr>
<td>Pulse</td>
<td>Normal</td>
<td>&gt; 90</td>
<td>&lt; 90</td>
</tr>
<tr>
<td>Hgb</td>
<td>Normal</td>
<td>&lt; 75% of Normal</td>
<td>Transfusion required</td>
</tr>
<tr>
<td>ESR</td>
<td>&lt; 30 mm/h</td>
<td>&gt; 30 mm/h</td>
<td>&gt; 30 mm/h</td>
</tr>
</tbody>
</table>

Crohn’s Disease Activity Index (CDAI)
• CDAI incorporates 8 Crohn’s disease-related variables:
  - number of liquid or very soft stools / day
  - abdominal pain & cramping
  - extraintestinal manifestations
  - abdominal mass
  - use of anti-diarrheal medications
  - hematocrit
  - body weight
  - any complications present
• CDAI score ranges from 0 to 600. Values are interpreted as follows:

<table>
<thead>
<tr>
<th>CDAI score</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 150</td>
<td>inactive disease</td>
</tr>
<tr>
<td>150-450</td>
<td>active disease</td>
</tr>
<tr>
<td>&gt; 450</td>
<td>extremely severe disease</td>
</tr>
</tbody>
</table>


VIII. Drug Therapy

*Goal of treatment is resolution of disease symptoms such that the patient can
carry on normal daily functions. None of these drugs are curative for IBD!

A. Treatment of Ulcerative colitis

1. Sulfasalazine (Azulfidine®)

   Mechanism of Action:

   Sulfasalazine
   \[\text{bacterial azoreductase (enzyme found in colon)}\]
   \[\text{Sulfa 5-acetylsalicylic acid (5-ASA)}\]

   • Active component is 5-ASA. It is thought that the sulfa moiety is responsible for adverse effects.
   • Exact mechanism of action is unknown. Sulfasalazine does inhibit \[\text{______}\] which is responsible for some anti-inflammatory effects, but is not the drug’s sole action.

   Dose: 4 – 8 grams / day

   Adverse Effects:
   • Dose-related.

Therapeutic Role: Sulfasalazine has been proven effective in the short-term (to achieve remission) & long-term (to maintain remission) treatment of mild or moderate disease.

2. Newer Acetylsalicylic Acid Preparations (Mesalamine, Olsalazine, Balsalazide)

   Mechanism of Action: These agents contain only the 5-aminosalicylic acid
(5-ASA) portion, unlike sulfasalazine which contains the sulfa moiety.
Therefore, these agents may be used as an alternative to patients
Intolerant to sulfasalazine. Like sulfasalazine, these agents work
primarily in the colon.

Dose:

<table>
<thead>
<tr>
<th>Product</th>
<th>Trade Name(s)</th>
<th>Formulation</th>
<th>Dose/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesalamine</td>
<td>Rowasa, Salofalk,</td>
<td>Enema</td>
<td>1-4 grams</td>
</tr>
<tr>
<td></td>
<td>Claversal, Pentasa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rowasa</td>
<td>Suppository</td>
<td></td>
<td>1-4 grams</td>
</tr>
<tr>
<td>Asacol</td>
<td>5-ASA coated with Eudragit-S</td>
<td></td>
<td>1 grams</td>
</tr>
<tr>
<td>Claversal (Salofalk)</td>
<td>5-ASA coated with Eudragit-L</td>
<td></td>
<td>2.4 grams</td>
</tr>
<tr>
<td>Pentasa</td>
<td>5-ASA encapsulated in ethylcellulose microgranules (oral tablet)</td>
<td></td>
<td>1-4 grams</td>
</tr>
<tr>
<td>Olsalazine</td>
<td>Dipentum</td>
<td>Dimer of 5-ASA oral capsule</td>
<td>1-3 grams</td>
</tr>
<tr>
<td>Balsalazide</td>
<td>Colazide</td>
<td>Capsule</td>
<td>2.16 grams</td>
</tr>
</tbody>
</table>

Adverse Effects: Minimal.

Olsalazine is associated with ________________________________ in 15-25% of patients necessitating discontinuation of the drug.

Therapeutic Role: Generally reserved for patients who cannot tolerate sulfasalazine. Oral & rectal preparations are good for **mild to moderate distal colitis** and **remission of distal colitis**. Oral preparations have also been shown effective in the treatment of **mild to moderate extensive colitis** and **remission of extensive colitis**.
3. Glucocorticoids

Mechanism of Action:

Dose:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>Suppository Enema IV</td>
<td>1 PR bid 1 PR qhs 100mg q6-8h</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Oral</td>
<td>40-60mg/day then taper</td>
</tr>
<tr>
<td>Methyprednisolone</td>
<td>IV</td>
<td>20-40mg q6h</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Enema</td>
<td>2 – 3 mg</td>
</tr>
</tbody>
</table>

Adverse Effects:

<table>
<thead>
<tr>
<th>Short-term</th>
<th>Long-Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Fluid retention</td>
<td>Cataracts</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>HPA axis suppression</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Hypokalemia</td>
</tr>
<tr>
<td>Increased WBC count</td>
<td>Decreased wound healing</td>
</tr>
<tr>
<td>Myopathies</td>
<td>“Cushingoid” appearance</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td></td>
</tr>
</tbody>
</table>

Therapeutic Role: Most efficacious agents used in **active UC** but are not useful as maintenance therapy. Specifically rectal corticosteroid preparations are useful in **mild to moderate disease** and oral corticosteroids are useful in **severe distal and extensive colitis**. Parenteral corticosteroids are generally reserved for **extremely severe disease**.
5. Immunomodulatory Drugs (Azathioprine and 6-mercaptopurine)

Mechanism of Action:

AZT:

6-MP:

Adverse Effects:

At onset of administration: pancreatitis, hepatitis, fever, rash
Long-term complications: neutropenia, thrombocytopenia, neoplasias

Therapeutic Role: Typically used for steroid-sparing effect. In UC, these agents are reserved to induce & maintain remission of distal and extensive colitis for patients who are steroid-dependent and those with refractory disease.

6. Cyclosporine

Mechanism of Action:

Dose:

Adverse Effects:

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasthesias</td>
<td>26%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11%</td>
</tr>
<tr>
<td>Tremor</td>
<td>7%</td>
</tr>
<tr>
<td>Nausea / Vomiting</td>
<td>6%</td>
</tr>
<tr>
<td>Renal Insufficiency</td>
<td>6%</td>
</tr>
<tr>
<td>Headache</td>
<td>5%</td>
</tr>
</tbody>
</table>

Therapeutic Role: Resolve extremely severe extensive colitis refractory to conventional parenteral corticosteroids.
Figure 1: Treatment approaches for ulcerative colitis.

- **Mild**
  - Colitis
    - Sulfasalazine 4-6g/d or Oral mesalamine 3-6g/d
  - Reduce sulfasalazine or mesalamine dose to 2g/d

- **Moderate**
  - Proctitis
    - As above or mesalamine enema or corticosteroid enema
  - As above or Mesalamine enema 1g/d or 1g/qod

- **Severe**
  - Colitis (continued)
    - Sulfasalazine 4-8g/d or Oral mesalamine 3-6g/d PLUS Prednisone 5-60mg/d
  - Taper prednisone then after 1-2 months reduce sulfasalazine or mesalamine dose to those listed above
  - Add azathioprine or 6-MP

- **Fulminant**
  - Hydrocortisone IV 100mg q6-8hr
  - Change to PO prednisone
  - Cyclosporine 4mg/kg/d
  - Add sulfasalazine or mesalamine and attempt to withdraw steroids after 1-2 months
  - Maintenance dose of sulfasalazine or mesalamine
B. Treatment of Crohn’s Disease

1. Sulfasalazine (Azulfidine)
   
   Dose:
   
   Therapeutic Role: Oral aminosalicylates are effective for the short- & long-term treatment of mild or moderate colonic disease.

2. Other 5-Aminosalicylates
   
   Therapeutic Role: Same as sulfasalazine

3. Metronidazole
   
   Dose: Metronidazole 500mg po BID
   
   Therapeutic Role: Use in conjunction with oral aminosalicylates in treatment of mild active disease.

4. Glucocorticoids
   
   Dose: Refer to chart in Ulcerative colitis section
   
   Therapeutic Role: *Central role in therapy. Effective in active disease, but not recommended to maintain remission due to adverse effects. Generally reserved for moderate to severe active disease.

5. Budesonide
   
   Mechanism of Action:
   
   Adverse Effects:
   
   Dose: 9mg capsule (equals ~40mg of oral prednisone)
   
   Therapeutic Role: Most benefit has been seen in mild to moderate disease restricted to the colon. Remains questionable if useful in maintaining remission.

6. Immunomodulatory Agents (Azathioprine and 6-mercaptopurine)
Dose: Azathioprine 1,800mg IV LD
     50mg/hr IV for 36 hours
     1mg/kg/day po

6-mercaptopurine 1.5mg/kg/day po

Therapeutic Role: **Moderate to severe active disease** and **remission** in patients who are steroid-dependent.

7. Cyclosporine

Dose:

Therapeutic Role: **Severe refractory disease**. Remains questionable if cyclosporine is effective in Crohn’s disease.

8. Infliximab (Remicade®)

Mechanism of Action:

Indications:
- Crohn’s disease (moderate to severe)—shown to ↓ signs / symptoms when there has been an inadequate response to conventional therapy.
- Crohn’s disease (fistulizing)—shown to ↓ number of draining enterocutaneous fistulas
- Crohn’s disease (maintenance) –

Dose:
- Crohn’s (mod-severe)

- Crohn’s (fistulizing)

- Crohn’s (maintenance)

Adverse Effects:

Figure 2: Treatment approaches for Crohn’s disease.
Mild

**Ileocolonic or Colonic**
- Sulfasalazine 3-6g/d
- or oral mesalamine 3-4g/d

Moderate

- As above PLUS Prednisone 40-60mg/d
- Refractory & fistulizing disease Add infliximab

Severe

- Hydrocortisone IV 100mg q6-8hr
- Taper prednisone then after 2-3 weeks
- Add azathioprine, 6-MP or methotrexate

Fulminant

**Small Bowel**
- Oral mesalamine 3-4g/d
- or metronidazole

**Perianal**
- Sulfasalazine or oral mesalamine and/or metronidazole 10-20mg/kg/d

**Small Bowel**
- Oral mesalamine 3-4g/d
- or metronidazole

**Small Bowel**
- Refractory & fistulizing disease
  - Add infliximab
  - Add azathioprine, 6-MP or methotrexate

**Small Bowel**
- Cyclosporin IV 4mg/kg/d