Management Principles of Ulcerative Colitis

Dr. Gerald Dryden
Ulcerative Colitis

- Chronic inflammatory process of the colonic mucosa
- Usually begins with gradual onset of rectal bleeding, urgency, diarrhea and abdominal discomfort
- Inflammation begins in rectum, extends proximally for variable extent
- Must be differentiated from infectious and other causes of mucosal inflammation
UC-Grading Severity

• Severity of disease can be determined by:
  – Truelove and Witt’s criteria
    • mild
    • moderate
    • Severe

• Easy to remember:
  – 2 historical points
  – 2 physical exam points
  – 2 laboratory values
# Truelove and Witt’s Criteria

<table>
<thead>
<tr>
<th></th>
<th>Mild Activity</th>
<th>Severe Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily bowel movements (no.)</td>
<td>&lt; or = to 5</td>
<td>&gt; 5</td>
</tr>
<tr>
<td>Hematochezia</td>
<td>Small amounts</td>
<td>Large amounts</td>
</tr>
<tr>
<td>Temperature</td>
<td>&lt; 37.5°C</td>
<td>&gt; or = to 37.5°C</td>
</tr>
<tr>
<td>Pulse</td>
<td>&lt; 90/min</td>
<td>&gt; or = 90/min</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>&lt; 30 mm/h</td>
<td>&gt; or = to 30 mm/h</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>&gt; 10 g/dl</td>
<td>&lt; or = to 10 g/dl</td>
</tr>
</tbody>
</table>

- Patients with fewer than all 6 of the above criteria for severe activity have moderately active disease
<table>
<thead>
<tr>
<th>Ulcerative Colitis Activity Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Stool frequency</td>
</tr>
<tr>
<td>0-3: normal</td>
</tr>
<tr>
<td>1-3: 1-2 stools daily &gt; normal</td>
</tr>
<tr>
<td>2-3: 3-4 stools</td>
</tr>
<tr>
<td>3-3: 4 stools</td>
</tr>
<tr>
<td>2. Rectal bleeding</td>
</tr>
<tr>
<td>0-3: None</td>
</tr>
<tr>
<td>1-3: Streaks of blood</td>
</tr>
<tr>
<td>2-3: Obvious blood</td>
</tr>
<tr>
<td>3-3: Mostly blood</td>
</tr>
<tr>
<td>3. Mucosal appearance</td>
</tr>
<tr>
<td>0-3: Normal</td>
</tr>
<tr>
<td>1-3: Mild friability</td>
</tr>
<tr>
<td>2-3: Moderate friability</td>
</tr>
<tr>
<td>3-3: Exudation, spontaneous bleeding</td>
</tr>
<tr>
<td>4. Physician's rating of disease activity</td>
</tr>
<tr>
<td>1-3: Normal</td>
</tr>
<tr>
<td>2-3: Mild</td>
</tr>
<tr>
<td>3-3: Moderate</td>
</tr>
<tr>
<td>4-3: Severe</td>
</tr>
<tr>
<td>Maximum score 3</td>
</tr>
<tr>
<td>13</td>
</tr>
</tbody>
</table>
# Endoscopic Appearance

<table>
<thead>
<tr>
<th>Feature</th>
<th>Ulcerative colitis</th>
<th>Crohn’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease distribution</td>
<td>Diffuse, continuous</td>
<td>Segmental</td>
</tr>
<tr>
<td>Rectal involvement</td>
<td>Always</td>
<td>Occasional</td>
</tr>
<tr>
<td>Disease severity distribution</td>
<td>Worse distally</td>
<td>Variable</td>
</tr>
<tr>
<td>Ileal involvement</td>
<td>Occasional backwash ileitis</td>
<td>Frequently</td>
</tr>
<tr>
<td>Feature</td>
<td>Ulcerative colitis</td>
<td>Crohn’s disease</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----------------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Disease location in bowel wall</td>
<td>Superficial, mucosal</td>
<td>Transmural</td>
</tr>
<tr>
<td>Lymphoid aggregates</td>
<td>Rare, underneath ulcers</td>
<td>Any location</td>
</tr>
<tr>
<td>Fissures</td>
<td>Occasionally superficial in fulminant colitis</td>
<td>Deep, any location</td>
</tr>
<tr>
<td>Sinuses and fistulas</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Granulomas</td>
<td>Related to ruptured crypts</td>
<td>Not related to crypts</td>
</tr>
</tbody>
</table>
Ulcerative Colitis

Endoscopic severity
Histologic Appearance

- Disrupted mucosal architecture
- Mixed inflammatory infiltrate
- Mucus depletion
- Crypt abscesses
UC Variants Resembling Crohn’s Disease

- Discontinuous disease
- Backwash ileitis
- Upper GI tract involvement
- Granulomas
- Apthous ulcers
- Superficial ulcers
- Transmural inflammation
UC Variants Resembling Crohn’s Disease

• UC typically involves the colon diffusely and continuously

• Some UC cases may present with:
  – patchy or discontinuous disease
    • Tissue healing of topical medications
    • Quiescent phase of mild UC
  – Absolute or relative rectal sparing
    • Approximately 25% of pediatric UC patients present with rectal sparing
UC Variants Resembling Crohn’s Disease

• Other variant presentations of UC include:
  – Segmental sparing
    • UC patients with left sided disease can also have cecal or ascending colon involvement, but sparing of the transverse colon
      – This does not evolve into pancolitis or Crohn’s disease
    • Peri-appendiceal involvement as a “skip lesion” is common, occurring in up to 86% of cases

1. Matsumoto Gastrointest Endosc 2002
UC Variants Resembling Crohn’s Disease

- Inflammatory changes in the ileum
  - Severe colonic disease may lead to incompetence of the IC valve, which in turn allows retrograde flow of the fecal stream into the terminal ileum
  - A retrospective study of 200 consecutive UC patients demonstrated inflammation in the ileum in 17% of patients

UC Variants Resembling Crohn’s Disease

• 88% of cases involved mild inflammatory neutrophilic infiltrates
  – Inflammation occasionally associated with focal cryptitis, crypt abscesses, and superficial ulcerations.
  – A small number of cases involved skip lesions of the cecum or ICV, with patchy involvement of the terminal ileum

• “Backwash ileitis” can also be explained by infections, drug reactions, bowel prep effects or primary involvement of the terminal ileum
UC Variants Resembling Crohn’s Disease

- Inflammation of the ileum could be considered part of UC if the inflammatory changes are:
  - Mild, superficial and limited to the distal 2-3cm of the ileum
  - Occur in a patient who otherwise fulfills the diagnosis of UC
Granulomas in UC

- Approximately 30-40% of CD cases contain non-necrotic granulomas in the mucosa or bowel wall
- Epithelioid granulomas are NOT associated with UC
- However, granulomas associated with ruptured crypts or extravasated mucin occur commonly in UC and other forms of non-IBD colitis
Granulomas in UC

- Multiple tissue levels may demonstrate the relationship between the granuloma and crypt epithelium

- Rupture induced granulomas may contain a mixture of neutrophils and lymphocytes, which are not characteristic of CD granulomas
Apthous Ulcers in UC

- Apthous ulcers - mucosal erosion or superficial ulcer overlying a lymphoid aggregate
- These lesions are commonly seen in CD, in the terminal ileum and proximal colon
- However, a recent study demonstrated that 17% of colectomy specimens from UC patients contained apthous ulcerations (Yantis Am J Surg Pathol 2004)
UC-Treatment Principles

1. Determine extent/severity of disease
2. Determine most appropriate therapy
3. Achieve and maintain remission
4. Improve quality of life
UC-Treatment Principles
Selection of Treatment

- Nature of disease allow heavy reliance on surface active medications

- Treatment plan designed is based on
  - Severity
  - Extensive vs. distal
  - Presence of complications/extra-intestinal manifestations
  - Prior response to specific drugs

- Therapeutic decisions rarely based on histologic/endoscopic severity of inflammation
Site of Delivery

Based on 5-ASA Formulation

- Topical therapy’s ability to reduce inflammation directly linked to ability to reach site of inflammation

20% pancolitis

Oral

30-40% beyond sigmoid

Enema

40-50% rectosigmoid

Suppository
5-ASA Therapy

- Sulfasalazine
- Asacol (mesalamine)
- Pentasa (mesalamine)
- Dipentum (olsalazine)
- Colazal (balsalazine)

- Rowasa (mesalamine)
- Canasa (mesalamine)
5-ASA amounts per pill

Percent & Milligrams of 5-ASA per pill

<table>
<thead>
<tr>
<th>Medicine</th>
<th>% of 5-ASA per pill</th>
<th>Milligrams of 5-ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asacol 400mg tab</td>
<td>100%</td>
<td>267mg</td>
</tr>
<tr>
<td>Pentasa 500mg cap</td>
<td>100%</td>
<td>400mg</td>
</tr>
<tr>
<td>Colazal 750mg cap</td>
<td>36%</td>
<td>267mg</td>
</tr>
<tr>
<td>Sulfa 500mg tab</td>
<td>40%</td>
<td>200mg</td>
</tr>
</tbody>
</table>
Higher Dose Mesalamine More Effective in Moderately Active UC

- **ASCEND I and II trials**
  - Randomized, controlled phase III trials comparing 2.4gm/day with 4.8gm/day
  - Total of 687 patients randomized
  - Adverse events similar in both arms
  - Clinical remission
    - 4.8gm/day 72%
    - 2.4gm/day 58%

- Therapeutic dose response only seen in moderate disease activity, not in mild disease activity

Principles of Topical Therapy

- Directly delivers high concentrations of 5-ASA to rectal mucosa
- Best initial choice for active ulcerative proctitis/sigmoiditis
Topical Therapy Caveats

- Topical mesalamine agents are superior to topical steroids or oral 5-ASA alone for left sided disease.

- The combination of oral and topical aminosalicylates are more effective than either alone.

- In patients refractory to oral aminosalicylates or topical steroids, mesalamine enemas or suppositories may still be effective (not dose dependent).

Safdi AJG 1997 1867-71
Green Gastro 1998 15-22
Yang AJG 2001 S311-312
Summary of Topical Advantages

- Quicker response time
- Less frequent dosing
- Fewer side effects than oral

Safdi AJG 1997 1867-71
Green Gastro 1998 15-22
Yang AJG 2001 S311-312
Ulcerative Colitis

Moderate to Severe

• Moderate severity often responds to oral prednisone (40-60mg/day)

• More severe cases will need admission and IV steroids

• Careful monitoring for response if treating as an outpatient
Ulcerative Colitis

*Moderate to Severe*

- Begin steroid taper only after patient clinically “well” (2-4 weeks)
  - Decrease prednisone by 5mg/wk until reaching 20mg
  - Below 20mg, taper by 2.5mg to 5mg per week

- Flare during taper should prompt increase to lowest level prior to flare

- Inability to complete taper should prompt consideration of adding immuno-modulators
Moderate to Severe UC

*Immunomodulators*

- May require use of concomitant immunosuppression
- 6-mp/AZA have been shown to be helpful
- No role for methotrexate
UC Maintenance with Azathioprine
Controlled data: 1yr Remissions

Jewell (Gut 1974)
AZA 2.5 mg/kg (n=40)
PLCBO (n=40)

Hawthorne (BMJ, 1992)
AZA (x 100mg) (n=33)
PLCBO (n=34)
[withdrawal trial]
UC Maintenance Aza/6-MP
Uncontrolled Remission data

George (AmJGastro,96)
105 retrospective pts treated with 6-MP

Ardizzone (J.Clin.Gastro’97)
56 retrospective pts treated AZA 2mg/kg
Remission off steroids
Moderate to Severe UC

Anti-TNF Therapy

• If concomitant immuno-suppression ineffective, maximize therapy

• Consider Remicade for persistently active disease
  – 5mg/kg IV infusion 0, 2, 6 weeks, then q8 weeks
  – Same principles apply
Severe Ulcerative Colitis
General Treatment Guidelines

• Admit to hospital
  – 15% require at some point
• IV fluids/steroids
• GI consultation
• Surgical consultation
• Daily KUB
Severe Ulcerative Colitis

Steroid Therapy

- Steroids may be administered in continuous or split dose
  - ACTH 120 units/24 hours as continuous infusion
    • If no steroids within previous 30 days
  - Hydrocortisone 100mg q 8 hours
  - Methylprednisolone 16-20mg q 8 hours*
  - Prednisolone 30mg q 12 hours*
- Continue for 7-10 days, as long as improvement continues
  - If no improvement in 5-7 days, consider other therapy

*Less Na retention, K wasting
Severe Ulcerative Colitis

5-ASA Considerations

• No role for NPO (low residue diet)

• If already on 5-ASA products—STOP!!

• However, if not intolerant, concomitant administration of 5-ASA may improve short and long term response rates
  – 90% response rate when started early
  – 71% response without 5-ASA

Loftus AJG 2001 S299
Severe Ulcerative Colitis

*Pitfalls of Treatment*

- Prematurely withdraw acute therapy
- Wait too long to discard ineffective therapy
- Mistake steroid dependency for maintenance effect
- Withdraw patients from maintenance therapy
- Fail to educate patients on consequences of non-compliance
Severe Ulcerative Colitis

Predicting Need for Second-Line Therapy

• Much of the morbidity/mortality associated with severe UC comes from delayed surgery

• Need to select patients who will benefit from additional therapy early in course of disease

• Two models predicted medical failure, need for early surgery:
  – Stool frequency >8/day, or 3-8/day with CRP>45mg/dL after 3 days steroid therapy: 85% require colectomy
  – #BM + 0.14 x CRP (mg/L)>8.0 as optimal cut-off to predict medical failure

Severe Ulcerative Colitis

*Risk Score for Early Detection*

- 167 patients with severe UC
  - Multiple logistic regression to analyze parameters within first 3 days of medical therapy
    - 67 (40%) failed to respond to medical tx

- Three factors identified by multiple logistic regression:
  - Mean stool frequency (<4=0, 4≤6=1, 6≤9=2, >9=4)
  - Colonic dilation within first three days (4)
  - Hypoalbuminemia <30g/L (1)

- Risk score formulated
  - >4 predicts non-response

Diagnostic Dilemma Scenarios
Fulminant Colitis

• Severe form of colitis with systemic toxicity

• Resected specimens often show extensive ulceration-right and transverse colon more severely affected than distal colon

• Ulcerations fissuring or knife-like defects extending into superficial muscularis propria

• Often associated with transmural lymphoid inflammation
  – Can confuse picture with Crohn’s disease
Diagnostic Dilemma Scenarios
Fulminant Colitis

• Yantiss found 27% had superficial fissuring ulcers in their colectomy\(^1\)
• No patients developed Crohn’s disease
• Swan found that 87% of fulminant colitis specimens could be accurately classified based on histological evaluation\(^2\)
  – The presence of granulomas and transmural inflammation in regions of intact mucosa predicted development of Crohn’s disease

\(^1\) Yantiss et al. Am J Surg Pathol 2005
\(^2\) Swan et al. Dis Colon Rectum 1998
Comorbid Diseases-CMV

- Presence of a superimposed “secondary disease” may alter interpretation of the underlying IBD

- Cytomegalovirus
  - May be associated with a flare of inflammation that is segmentally distributed in the right colon or ileum, and is more severe that the inflammation in the remainder of the colon
Diagnostic Dilemma Scenarios
Comorbid Diseases-C. diff

- Pseudomembranous colitis
  - C. difficile can spontaneously complicate IBD
  - Presence of characteristic pseudomembranes and necrotic crypts affecting areas uninvolved with IBD help establish diagnosis

- Chemical injury (NSAIDs)
Options for Severe Refractory UC

- Cyclosporine
- Infliximab
- Clinical trial
- Colectomy
Severe Ulcerative Colitis

*Cyclosporine*

- Severe UC failing to respond to IV steroids
  - Must weigh risks of infection, renal dz, HTN against colectomy
  - Short term response rates 70-80%

- Prior to initiating drug, check
  - Cholesterol (>120mg/dL)
  - Magnesium (>1.5mg/dL)

- 2mg/kg infused over 24 hours\(^1\)
  - target cya levels of 150-250 ng/mL whole blood

- Response in 3-5d on average, most within 7d

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Severe Ulcerative Colitis

Cyclosporine

- Responders transition to 5-6mg/kg/day Neoral
  - Target trough level at 100-200ng/mL
- Prophylaxis against *Pneumocystis carinii* while on triple immunotherapy
  - Bactrim tiw
- During first month after discharge, taper prednisone from 40-60mg/day to 20mg/day.
- After three to four months, cyclosporine can be discontinued.
- One week after cyclosporine discontinued, can begin to taper prednisone from 20mg/day to 0mg/day.
Severe Ulcerative Colitis

*Cyclosporine*

- Those who achieved remission on cyclosporine and were maintained on AZA, two thirds remain in remission at 5 years

- If the patient relapses during the drug taper, surgical resection warranted
Avoidance of Colectomy After CysA Induction

Cyclosporine

Monitoring Toxicity

- Check following at 0, 1, 2 weeks, then monthly
  - Blood pressure
  - CBC
  - Renal function
  - CsA concentration (100-200ng/mL)
Biologics in Severe UC
Fulminant Colitis

Patients Ineligible for Medical Therapy

- Medical emergency manifested by
  - high fever
  - abdominal tenderness
  - abdominal distension
  - hemorrhage

- May or may not have colonic distension

- Morbidity increased by delaying surgical therapy
UC-Indications for Surgery

• **Immediate**
  – Exsanguinating hemorrhage
  – Toxicity and/or perforation

• **Urgent**
  – Unresponsive severe colitis
  – Severe/acute complications of disease or therapy
    • Opportunistic infections
    • Steroid psychosis
    • Hemolytic anemia

• **Elective**
  – Suspected cancer
  – Dysplasia
  – Growth retardation
  – Osteonecrosis/compression fracture
  – Intractability
Ulcerative Colitis
Surgical Options