Treatment of Inflammatory Bowel Disease

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What is IBD?

IBD is an immune-mediated chronic intestinal disorder, characterized by chronic or relapsing inflammation within the GI tract.
The two major forms are UC and CD;
Approximately 10-15% of patients present with an indeterminate colitis.

Ulcerative Colitis

- Inflammation and ulceration in the large intestine
- Affects mucosa and submucosa
- Continuous inflammation starts in the rectum and ascends up the colon
- Does not affect the small intestine

Crohn’s disease

- Can affect anywhere in the GI tract from mouth (oral ulceration) to anus (fistula).
- Transmural inflammation can extend from the mucosa through the submucosa and serosa and result in fistula to bowel or skin.
- Discontinuous “skip lesions.”
- May see granulomas on pathology.
IBD: Common and Progressive

- 1.4 million people in US have IBD (1)
- UC more prevalent than CD (1)
- Ranges from 26-246 cases per 100,000 people in North America
- Most common to diagnose between the ages of 20-39 (2)
- IBD has a progressive nature with potential of complications leading to surgery if not aggressively treated

(1) Loftus EV, Gastroenterology 2004;126(6):1504-17.
The Incidence and Prevalence of Immune-Mediated Inflammatory Disorders Is Increasing

- Multiple sclerosis
- Crohn’s disease (CD)
- Type 1 diabetes
- Asthma

Incidence of immune disorders (%)

IBD Signs and Symptoms

Crohn’s disease

- Chronic diarrhea +/- blood
- Rarely constipation
- Abdominal pain, often in right mid abdomen (mimics appendicitis)
- Unintended weight loss
- Fevers, anorexia, nausea; vomiting less common

Ulcerative Colitis

- Bloody diarrhea
- Mucus discharge
- Tenesmus
- Urgency of bowel movements
- Crampy abdominal pain
- Fevers, weight loss, constipation less common
### Symptoms
- Chronic diarrhea +/- bloody
- Rectal urgency for gas or small volume bloody or mucous stool
- Unintentional weight loss
- Fever

### Clinical Exam
- Abdominal tenderness, especially over McBurney’s point for CD
- Abdominal mass less likely
- Unintentional weight
- Iron deficiency anemia

### EIM’s
- Arthritis
- Uveitis
- Episcleritis
- Ankylosing Spondylitis
- Pyoderma gangrenosa
- Erythema Nodosum
Extraintestinal manifestations of IBD
Erythema nodosum
Pyoderma Gangrenosum
Episcleritis
Extraintestinal Manifestations of IBD

Activity parallels disease activity

- Erythema nodosum
- Episcleritis
- Peripheral arthritis (typically the knee or metacarpal phalangeal joints)

No correlation to disease activity

- Pyoderma gangrenosum
- Uveitis
- Spondyloarthropathy (axial arthritis)
## Signs and Symptoms of IBD and Other GI Conditions May Overlap

<table>
<thead>
<tr>
<th>Condition</th>
<th>Celiac Disease¹</th>
<th>IBS²</th>
<th>CD³</th>
<th>UC³</th>
<th>Small-Bowel Bacterial Overgrowth⁴</th>
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<tbody>
<tr>
<td>Abdominal pain</td>
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<td>Diarrhea</td>
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<td>Weight loss</td>
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<td>Bloating</td>
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<td>Anemia</td>
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<td>Constipation</td>
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<td>Mucus in stool</td>
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<td>Flatulence</td>
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<td>Blood in stool</td>
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<td>Anorexia</td>
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<td>Fever</td>
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<tr>
<td>Alternating diarrhea and constipation</td>
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Unlike IBD or celiac disease, IBS is not characterized by overt intestinal inflammation.
AGA Clinical Pathway for Crohn’s Disease: Assessing Inflammatory Status

Assess inflammatory status

Assess symptoms/signs
- Fever
- Abdominal pain
- GI bleeding
- Localized tenderness
- Weight loss
- Joint pain
- Cutaneous signs

Perform clinical lab testing
- CBC
- CRP
- CMP
- Fecal calprotectin
- ESR

Select imaging modalities (if indicated)
- Perform endoscopy
- Identify symptoms without inflammatory markers
- Identify symptoms with inflammatory markers*
- Perform CTE or MRE

Consider whether treatment decisions to be based on inflammatory markers vs confirming with colonoscopy. This may depend on whether there was historically good correlation between the biomarker selected and colonoscopy in the specific patient.

CMP, complete metabolic panel; CTE, computed tomography enterography; ESR, erythrocyte sedimentation rate; MRE, magnetic resonance enterography.

Workup

- Stools for culture, Ova and Parasites, WBC, occult blood if non-bloody
- Labs: CBC, CMP, ESR, CRP, fecal calprotectin
- Celiac panel if non-bloody diarrhea and/or weight loss
- Imaging more helpful if predominately pain and not bleeding
- Next step is referral for colonoscopy
Treatment: depends on the clinical scenario

- Anatomic location of disease
- Disease severity and complications
- Goal of therapy
- Risk profile of treatment options: age, sex and disease duration
- Cost
- Compliance
- Disease: Crohn’s or UC
Disease location

- Rectum
- Left colon
- Entire colon
- Terminal ileum
- Proximal to mid small intestine
Definitions of Severity

- Asymptomatic remission
- Mild to moderate disease: ambulatory, absence of dehydration, toxicity, abdominal tenderness, mass, obstruction, or 10% weight loss
- Moderate to severe disease: Patients who have failed treatment for mild to moderate disease, or patients with abdominal pain, weight loss, nausea or vomiting, bleeding or anemia
- Severe, fulminant disease: Persistent symptoms despite conventional therapy or advanced therapy, or presenting with high fevers, obstruction, abscess, or cachexia
Goals of therapy

- Induction of remission
- Maintenance of remission
- Prevent recurrence
- Prevent complications
Early intervention is the key to prevent progression of disease

- Subclinical inflammation likely precedes onset of symptoms
- Most patients wait weeks to months before they present to PCP
- Treatment early on in the disease process may prevent more severe complications of fistula, abscess, and stricture formation
- Younger age of onset may predict more severe disease process
Common Therapies

- Oral 5-aminosalicylates (mesalamine)
- Antibiotics mainly for perianal disease or abscess
- Conventional glucocorticoids (prednisone)
- Non-systemic glucocorticoids (budesonide)
- Immunomodulators (azathioprine, 6-mercaptopurine, methotrexate)
- Biologic therapy (anti-TNF, Integrin antagonists, anti- Interleukins)
- Combination therapy
Risks of therapy

- Toxicity: myelosuppression, pancreatitis, hepatotoxicity
- Cancer risk: lymphoma, melanoma, nonmelanoma skin cancers
- Immunosuppression: infection, reactivation of TB or Hepatitis B
Algorithm for Treatment of Ulcerative Colitis

Mild disease
- Oral 5-ASA
- Budesonide-MMX
- Disease distribution dependent
  - Rectal 5-ASA
  - Maximize oral 5-ASA + rectal 5-ASA

Moderate disease
- Remission induction
  - Prednisone
  - Anti-TNF or - Anti-adhesion
  - Maintenance therapy
    - Thiopurine
    - Anti-TNF + thiopurine or methotrexate
    - Optimize anti-TNF dosing
    - Second anti-TNF + thiopurine or methotrexate

Severe disease
- Remission induction
  - Prednisone
  - Anti-TNF
  - Surgery
    - CyA when anti-TNF not option
  - Maintenance therapy
    - Thiopurine
    - Anti-TNF + thiopurine or methotrexate
    - Optimize anti-TNF dosing
    - Second anti-TNF + thiopurine or methotrexate
    - Anti-adhesion molecule
    - Surgery
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<th>Condition</th>
<th>Infliximab</th>
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<td>Moderate to Severe UC (Hospitalized)</td>
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Thiopurines in IBD

- Generally safe (avoid in males <30 or >50 on anti-TNF)
- Appropriate for UC failing 5ASA; steroid sparing
- Must optimize the dose after testing TPMT genetics for ability to metabolize the drug (1.5-2.5 mg/kg/day)
- Probably need higher doses in CD, in combination with biologic
- Combination therapy prevents immunogenicity and provides higher anti-TNF levels
- Combination therapy may be more effective, especially in naïve pts
- Increased risk of nonmelanoma skin cancers (risk twofold in meta-analysis)
Risk of Lymphoma using Thiopurines

- Post transplant-like lymphoma (EBV+) 1/1000 pt/yr
- Early post-mononucleosis lymphoma (<35 men) 3/1000 pt/yr
- Hepatosplenic T-cell lymphoma (<35 men on AZA/6MP) 0.1/1000 pt/yr

Beaugerie L et al Gastroenterology 2013
Issues With MTX

- Often used intramuscularly in Crohn’s Disease\(^1\)
- Common side effects:\(^1\)
  - Nausea/vomiting
  - Bone marrow suppression
  - Hepatic Fibrosis
- Liver biopsy is needed before and during MTX therapy in certain patients\(^1\)
- Requires continuous monitoring of CBC and LFTs\(^2\)
- Contraindicated if attempting pregnancy\(^2\)
  - Category X

GOT Walk of Shame
Dubrovnik, Croatia
The Iron Throne
Key Points

- Anti –TNF, Anti-Integrin, Anti-IL-12/23 therapies are the most effective therapies available to treat IBD
- Most beneficial to those with active inflammatory disease, ideally before onset of complications
- Must address identifiable safety risks and educate patients about signs and symptoms of adverse events
- Optimal and more durable response is obtained when combined with an immune modulator
- In the future I expect treatment to be determined by the patients inflammatory markers with combinations of biologic agents
Enjoy the Beach