Inflammatory Bowel Disease

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Conflict of Interest

- No conflicts of interest

Road Map

- Background
- Differential diagnosis
- Presentation
- Medical Treatment
- Surgical Treatment
- Extraintestinal Manifestations
- Cancer Risk

Overview of Inflammatory Bowel Disease (IBD)

Ulcerative Colitis
- Incidence / 100,000
- Age-Specific Incidence of IBD*

Crohn’s Disease
- Incidence / 100,000

Scope of the Disorder (United States)

- 700,000 physician visits per year
- 100,000 hospitalizations per year
- Crohn’s disease accounts for two-thirds

*Per 100,000 population
**UC: Presenting Symptoms**

- Bloody diarrhea
- Abdominal cramping
- Tenesmus
- Weight loss
- Fevers
- Symptoms depend upon extent and severity of inflammation

**UC: Differential Diagnosis**

- Infectious
- Ischemic
- Malignant
- Diversion
- Radiation
- Solitary rectal ulcer syndrome
- Irritable bowel syndrome
- Crohn’s disease

**Endoscopic Spectrum of Severity**

UC – Spectrum of Disease

- Normal
- Mild
- Moderate
- Severe

**CD: Presentation**

- Diarrhea
- Chronic abdominal pain and tenderness
- Weight loss
- Fever
- Perianal disease
- Symptoms vary with location of disease

**CD: Clinical Features**

- Inflammation
- Obstruction
- Fistulization

- Abdominal pain
- Tenderness
- Diarrhea
- Weight loss
- Cramps
- Distention
- Vomiting
- Diarrhea
- Pain
- Air/feces in urine
- Types
  - Enteroenteric
  - Enterovesical
  - Retroperitoneal
  - Enterocutaneous

**CD: Differential Diagnosis**

- Lymphoma
- Yersinia
- TB or MAI
- CMV
- Herpes
- Ischemia
- UC
Risk for Developing CD

- **Offspr Both Parents:** 0%
- **MZ Twin Sib Ashkenazi Jewish Parent Offspring Jewish Ashkenazi:** 60%
- **DZ Twin Sib Non-Jewish Parent:** 50%
- **Homozygote NOD2:** 40%
- **Heterozygote NOD2:** 30%
- **General Population:** 10%
Epidemiologic Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>UC</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendectomy</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Smoking</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>OCP</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Breast feeding</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>High level of sanitation in childhood</td>
<td>?</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Chemical Structure of 5-Aminosalicylate (Mesalamine) and Its Prodrugs: Sulfasalazine, Balsalazide, and Olsalazine

Approved 5-ASA Formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Rectal Preparations</th>
<th>Azo-bonded Pro-drug</th>
<th>Moisture Dependent</th>
<th>Delayed Release</th>
<th>Delayed + Extended Release</th>
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<tbody>
<tr>
<td>Asacol®</td>
<td>Pentasa® (mesalamine)</td>
<td>Azulfidine® (sulfasalazine)</td>
<td>Pentasa® (mesalamine)</td>
<td>Asacol® (mesalamine)</td>
<td>APRISO® (mesalamine)</td>
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<tr>
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<td>Dipentum® (mesalamine)</td>
<td>Colazal® (balsalazide)</td>
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</table>

Rectal Corticosteroid Therapy

- Hydrocortisone Retention Enemas
  - 50% symptomatic response in distal colitis
- Hydrocortisone Foam Enemas
  - Reaches sigmoid colon
  - Less volume than enema preparation
- Hydrocortisone Suppositories
  - Useful in proctitis

Metronidazole in IBD

- Proven efficacy in perianal CD
- May be helpful in enteric CD
- No proven benefit in acute UC
- Potential neuropathy (parasthesias of distal extremities)
- Ciprofloxacin also effective
- Rifaximin may be effective

Meta-Analyses of Rectal 5-ASA in UC

Rectal 5-ASA vs Rectal Corticosteroids

- Improvement:
  - Symptomatic: 5-ASA better
  - Endoscopic: 5-ASA better
  - Histologic: 5-ASA better
- Remission:
  - Symptomatic: 5-ASA better
  - Endoscopic: 5-ASA better
  - Histologic: 5-ASA better

Pooled Odds Ratio

0.01 0.1 1 10 100

Corticosteroids better 5-ASA better

Oral/IV Corticosteroids

- **Role**
  - Induction of remission in UC and CD
- **Toxicity**
  - Metabolic
  - Musculoskeletal
    - Osteoporosis
    - Avascular necrosis
    - Arthralgias
  - Neuropsychiatric
  - Ocular
  - Immunologic
  - Growth Failure

**Remission Rate in Acute Crohn’s Studies With Budesonide CIR**


<table>
<thead>
<tr>
<th>Remission Rate at 8 Weeks (%)</th>
<th>Bud CIR 9 mg OD</th>
<th>Placebo</th>
<th>Pentasa 2 g BID</th>
<th>Prednisolone 40 mg</th>
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</thead>
<tbody>
<tr>
<td>80</td>
<td>50</td>
<td>40</td>
<td>30</td>
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<td>70</td>
<td>60</td>
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</tr>
<tr>
<td>40</td>
<td>30</td>
<td>20</td>
<td>10</td>
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</tbody>
</table>

**Oral Budesonide: Efficacy as Maintenance Therapy**


**Pharmacology of Thiopurines**

Azathioprine: 6-MP

2 : 1

2.5 – 3.0 mg/kg
100mg

1.0 – 1.5 mg/kg
50mg


Thiopurines are not indicated for IBD.

Effectiveness of Thiopurines

6-MP Response Rates in Crohn’s Disease

<table>
<thead>
<tr>
<th>% Patients</th>
<th>Placebo</th>
<th>6-MP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Improvement</td>
<td>8/39</td>
<td>67/2039</td>
</tr>
<tr>
<td>Steroid Discontinuation or Reduction†</td>
<td>15/28/64</td>
<td></td>
</tr>
</tbody>
</table>

P<.0001; *With clinical improvement maintained.

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6-MP: Toxicity

- Bone marrow suppression
- Pancreatitis
- Allergic reaction
- Liver toxicity
- Can now monitor metabolite levels to determine correct dosage

Thiopurines are not indicated for IBD.
Induction and Maintenance of Remission with Methotrexate

- **Induction**
  - Placebo
  - Methotrexate 25 mg IM Weekly

- **Maintenance**
  - 65% of 45% Responders = 30% Overall

- Methotrexate vs Placebo:
  - N=40
  - N=36

- *P* = 0.04

- Intravenous Cyclosporine in Severe, Refractory UC
  - Steroid-resistant patients
  - 4mg/kg/day
  - 82% response rate
  - Mean time to response: 7 days

Cyclosporine in IBD: Toxicity

- Renal insufficiency
- Seizures with low serum cholesterol
- Hair growth
- Hypertension
- Bone marrow suppression
- Liver toxicity

Infliximab in Moderate to Severe UC: The ACT 1 and 2 Trials

- Patients in Clinical Remission and Discontinuing Corticosteroids

- Placebo vs Infliximab 5 mg/kg vs Infliximab 10 mg/kg


Infliximab Maintenance of Remission in Crohn's Disease: ACCENT I

- Clinical Remission at Week 30*

- Placebo vs Infliximab 5 mg/kg vs Infliximab 10 mg/kg

- *P* = 0.003 vs placebo; † *P* = 0.0002 vs placebo


Fistula Response at Week 54 with Infliximab: ACCENT II*

![Graph showing Fistula Response at Week 54 with Infliximab]

*Randomized responders (secondary end point).
**P=0.001 vs placebo; †P=0.009 vs placebo.

SONIC Study Design

![Diagram of SONIC Study Design]

SONIC Clinical Remission Without Corticosteroids: Week 26

![Graph showing SONIC Clinical Remission Without Corticosteroids]

Anti-TNF Engineered Antibodies

![Diagram of Anti-TNF Engineered Antibodies]

Anchoring ACCENT I, CHARM, and PRECiSE 2 Results

![Graph showing Anchoring ACCENT I, CHARM, and PRECiSE 2 Results]

*Highly significant.
**Randomized trial with 80/40 mg induction dosing. Randomized responders = CR-70 at week 4.
Week 26 remission among randomized responders on 40 mg every other week dosing.
Can Early Highly Effective Therapy Alter CD Course?

- Induce and maintain gastrointestinal healing
- Prevent strictures and penetrating complications
- Prevent extraintestinal complications
- Decrease hospitalization and/or surgery
- Decrease long-term cost of care

Crohn’s Disease
Do We Treat Everyone with Early Combined TNF Antagonist Therapy?

No!

High Risk Patients Should be Considered for Early Treatment with a TNF Antagonist

- Complex fistula
- Deep ulceration on endoscopy
- Young age (< 40)
- Steroid-dependence/resistance
- High risk anatomy (foregut disease, extensive disease, perianal disease)
- Severe disease activity (weight loss, low albumin and/or hemoglobin)

General TNF Class-Effect Adverse Events*

- Infection
  - Tuberculosis
  - Opportunistic infections
  - Serious infections
- Immunogenicity
  - Infusion reactions
  - Injection site reactions
  - Altered pharmacokinetics +/- loss of response
- Autoimmunity
- Demyelinating disease
- Congestive heart failure (very rare)
- Hepatotoxicity (very rare)
- Malignancy
  - Lymphoma
  - Death

*Sustained Clinical Remission with Natalizumab: ENACT-2*

P<0.001

UC Indications for Surgery

- Exsanguinating hemorrhage
- Toxicity and/or perforation
- Dysplasia/ Cancer
- Growth retardation
- Systemic complications
- Intractable disease
Crohn’s Disease:
Indications for Surgery
• Failure to respond to medical therapy
• Management of complications
  – Dysplasia/ Cancer
  – Strictures
  – Perforation
  – Fistulae
  – Perianal disease

EIMs of IBD:
Epidemiology and Etiology
• 1+ EIM occurs in >6% of patients
• Clinical activity may follow bowel activity
• More common with colonic involvement
• More common in women than in men
• Herald relapse

IBD: Systemic Complications

Kidney stones
Arthritis and joint pains
Eye inflammation
Liver and bile duct inflammation
Gallstones
Skin lesions
Lower bone density
Growth failure in children
Subfertility
Eye inflammation
Liver stones
Ovaries
Uterus
Arthritis and joint pains

Erythema Nodosum in IBD

*Higher incidence in women.
Musculoskeletal Disorders in IBD

- Peripheral arthritis
- Sacroiliitis
- Ankylosing spondylitis


Bone Disease in Inflammatory Bowel Disease

- Prevalence of osteoporosis (T ≤ -2.5) using DXA: 5 - 40%
- Prevalence of osteopenia (T –1.0 to -2.49): 16 - 77%
- Corticosteroid use is strongly associated with osteoporosis

AGA medical position statement. Gastroenterology 2003

AGA Recommendations for Managing Osteoporosis

IBD patient:
- Any of:
  - Prolonged steroid use (>3mo consec or recurrent courses)
  - Low trauma, fragility fracture
  - Postmenopausal or male age >50
  - Hypogonadism

T score ≥ 1
- Basic Prevention:
  - Ca/Vit D
  - Exercise
  - Smoking cessation
  - Avoid alcohol
  - Minimize corticosteroids
  - Treat hypogonadism

T score -2.5 to -1
- DXA
- Prevention and:
  - Repeat DXA 2 years
  - Prolonged CS consider BP and DXA 1 year

T score < -2.5
- Vert Fracture Regardless of DXA
- Prevention and:
  - Screen other causes low BMD
  - Bisphosphonate therapy or
  - Refer to bone specialist

Relative Risk of Colon Cancer Based on Extent of UC

Risk of Colon Cancer in Crohn’s Colitis

• The same as UC given equal extent and duration of disease
• ASGE and AGA recommend screening and surveillance colonoscopy as in UC

Risk Factors for Colon Cancer in IBD

• Strictures that cannot be passed
• Extensive colitis
• Long duration of disease
• Young age at diagnosis
• Primary sclerosing cholangitis
• Family history of colon CA

Take Home Messages

• IBD is a chronic disease
• IBD requires life-long medical therapy
• Most IBD medications have side effects
• Most IBD patients have a normal life expectancy
• Complications of IBD include extraintestinal manifestations and an increased risk of colon cancer.

Who should have a DEXA scan to assess bone density?

A. Men 50 and above with IBD
B. Women under 50 with Crohn’s disease who have never been on steroids
C. IBD patients who have been on steroids ≥ 3 months
D. IBD patients who had a fragility fracture
E. A, C, and D

In which Crohn’s patient should combination anti-TNF/immunomodulator therapy be considered?

• 45 year woman with mild ileitis
• 16 year old teen with Crohn’s colitis responding to 6-MP
• 38 year old woman with complex perianal fistulizing disease
• 24 year old man with ileocolitis responding well to entocort
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