Update On IBD Therapy

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Ohio State University Medical Center

Etiological Theories in Inflammatory Bowel Disease

IBD Epidemiology

• 1 in 250 of the general population in Europe and North America are affected
• 25% present during childhood and adolescence
• Incidence of UC is stable in the last 20-30 years
• Incidence of CD is increasing

Temporal Trends in Ulcerative Colitis

Olmsted County, Minnesota, 1940-2000

- Male
- Female
- Total

Year of Diagnosis

**IBD Epidemiology**

- 10-15% of IBD cases are familial
- Risk to individual family members 3-5%
  - Distributed across entire family
  - With both parents involved risk to children is 50%
- Familial clustering: CD vs. UC
  - 75%: concordant for disease type
  - 25%: “mixed”, having CV and UC within the same family
- Monozygotic twin concordance rates: provide an estimate of overall genetic penetrance
  - CD: 42-58%
  - UC: 6-17%

**Wireless Capsule Endoscopy**

**CT Enterography**

**Treatment Goals in Inflammatory Bowel Disease**

- Cure
- Maintained tissue healing
- GCS weaning
- Remission
- Improvement

GCS = glucocorticosteroid
Treatment of Inflammatory Bowel Disease: Stepwise Escalation

Future Therapy for CD: Inverting the Pyramid?

Model of Approximate Distribution of UC Severity at Presentation

Brand/Generic Conversion Chart

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesalamine delayed release</td>
<td>Asacol®</td>
</tr>
<tr>
<td>Mesalamine controlled release</td>
<td>Pentasa®</td>
</tr>
<tr>
<td>Mesalamine delayed release and extended release</td>
<td>Lialda®</td>
</tr>
<tr>
<td>Mesalamine enema</td>
<td>Rowasa®</td>
</tr>
<tr>
<td>Mesalamine suppository</td>
<td>Rowasa®</td>
</tr>
<tr>
<td>Mesalamine suppository</td>
<td>Canasa®</td>
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</table>
### Corticosteroid Therapy in UC

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Steroid dose</th>
<th>Steroid</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Truelove</td>
<td>Active</td>
<td>Cortisone</td>
<td>69</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 mg</td>
<td></td>
<td></td>
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<tr>
<td>Lennard-Jones</td>
<td>Maintenance</td>
<td>Prednisone</td>
<td>40</td>
<td>40</td>
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<tr>
<td></td>
<td></td>
<td>15 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Truelove</td>
<td>Severely</td>
<td>Prednisolone</td>
<td>73</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Active</td>
<td>60 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Lennard-Jones TP et al. Lancet 1985
Truelove TC et al. Gastroenterology 1990
Truelove TC et al. Lancet 1990a, 1990b

### Infliximab in Severe UC

- **Infliximab** vs **Placbeo**

- **Study**
  - Infliximab: 24
  - Placebo: 21

- **Time in days**
  - Infliximab: 17 17 17
  - Placebo: 7 7 7

- **Probability of response**

  - Infliximab: 0.9 0.8 0.7
  - Placebo: 0.6 0.5 0.4

  - **p = 0.0038 (logrank test)**

### Treatment of UC

- **Topical rx**
- **Sulfasalazine**
- **Mesalamine**
- **Corticosteroids**
- **Azathioprine/6-mp**
- **Infliximab**
- **Cyclosporine**

- **Surgery** — 25 - 30% of patients eventually require colectomy
Treatment of Crohn’s Disease: From Symptom Control to Disease Control

**Evidence-Based Use**

<table>
<thead>
<tr>
<th>Year</th>
<th>Sulfasalazine (T)</th>
<th>Antibiotics (T)</th>
<th>Corticosteroids (T)</th>
<th>5-ASA (T)</th>
<th>Budesonide</th>
<th>MTX</th>
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<tbody>
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<td>1979</td>
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<td>2005</td>
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Endoscopic Healing with Azathioprine

- **Immediate and Prolonged Outcomes of Corticosteroid Therapy in Crohn’s Disease**
  - Complete response: 58% (n = 43)
  - Partial response: 26% (n = 19)
  - None: 16% (n = 12)

1-Year Responses (n = 74)
- Steroid-dependent: 32% (n = 24)
- Prolonged response: 28% (n = 21)
- Surgery: 38% (n = 28) *One patient lost to follow-up*

Endoscopic Healing with Azathioprine
- Complete Healing: 70
- Near complete Healing: 10
- Partial Healing: 10
- No Healing: 0

- 28 patients with Crohn’s colitis or ileocolitis
  - In clinical remission while taking azathioprine for ≥ 9 months
  - No corticosteroids for ≥ 3 months
Rate of Surgery for CD and the Use of Immunosuppressives in Paris Over 3 Decades

Clinical Response and Remission in All Infliximab-Treated Patients

Healing of Colonic Ulceration with Infliximab

Infliximab Response
**ACCENT I: Mucosal Healing**

![Graph showing the effect of Infliximab on mucosal healing.](Image)

**ACCENT I: Hospitalizations**

![Bar graph showing hospitalizations.](Image)

**ACCENT I: Crohn’s Disease-Related Surgeries**

![Graph showing Crohn’s disease-related surgeries.](Image)
Serious Infections and Mortality in the TREAT Registry

<table>
<thead>
<tr>
<th>Serious Infections (Multivariate)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Current use of IFX</td>
<td>1.4</td>
<td>0.8–2.1</td>
</tr>
<tr>
<td>Current use of 6-MPI/AZA/MTX</td>
<td>0.9</td>
<td>0.6–1.3</td>
</tr>
<tr>
<td>Current use of corticosteroids</td>
<td>2.0</td>
<td>1.4–2.8*</td>
</tr>
<tr>
<td>Current use of narcotic analgesics</td>
<td>2.7</td>
<td>1.9–4.0*</td>
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*P < 0.001; **P < 0.001; ***P < 0.001.
IFX = infliximab; METX = methotrexate.

Indications for Surgery in Crohn’s Disease (CD)

- Failure of medical therapy
- Recurrent obstruction
- Perforation
- Fistula or abscess
- Hemorrhage
- Growth retardation (children)
- Carcinoma

Smoking and Clinical Recurrence

![Graph showing smoking history vs clinical recurrence rate](image)


Post Operative Recurrence Endoscopic Grade

![Endoscopic images](image)
Update on IBD Therapy, 2008

Wallace Crandall, M.D.
Director, The Center for Pediatric and Adolescent Inflammatory Bowel Disease

Overview

• Differences in pediatric and adult IBD
• Case discussion

Differences in Pediatric IBD

• Psychosocial issues
• Disease extent/distribution
• Aggressiveness of treatment
• Growth
• Sexual maturation
• Response to medications
Psychosocial Issues in Pediatric IBD

Differences in Pediatric IBD
- Psychosocial issues
- Disease extent/distribution
- Aggressiveness of treatment
- Growth
- Sexual maturation
- Response to medications

UC: Extent of Disease at Initial Diagnosis

<table>
<thead>
<tr>
<th>Age at Diagnosis</th>
<th>Proctitis</th>
<th>Left-sided Colitis</th>
<th>Pancolitis</th>
<th>Total No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15</td>
<td>41</td>
<td>44</td>
<td>84 (50%)</td>
<td>169</td>
</tr>
<tr>
<td>15-29</td>
<td>378</td>
<td>246</td>
<td>307 (30%)</td>
<td>931</td>
</tr>
<tr>
<td>30-39</td>
<td>240</td>
<td>121</td>
<td>101 (20%)</td>
<td>462</td>
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Pediatric patients had more extensive disease than adults at initial diagnosis

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<td>• 80% of pediatric patients with moderate to severe CD are treated with 6MP/Aza in first year of dx</td>
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<td>✓ 60% are treated with 6MP/Aza in first 3 months!</td>
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Case Presentation (Hybrid)

• 13 yom with a 2 month history of abdominal pain and diarrhea, recently with intermittent hematochezia

• Poor growth past 1-2 years
  ✓ Ht 10%ile (Expected 75%ile)
  ✓ Wt 3 %ile

Growth Impairment in CD

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<th>Growth Impairment</th>
<th>% of Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased height (%) at diagnosis</td>
<td>33–39</td>
</tr>
<tr>
<td>Decreased height (velocity) at diagnosis</td>
<td>88</td>
</tr>
<tr>
<td>Decreased height velocity in 46% of patients before symptom onset and 42% after symptom onset</td>
<td></td>
</tr>
<tr>
<td>Permanent stunting (&lt;5th%)</td>
<td>7–35</td>
</tr>
<tr>
<td>Do not achieve growth potential</td>
<td>25</td>
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Case Presentation (Hybrid)

• 13 yom with a 2 month history of abdominal pain and diarrhea, recently with intermittent hematochezia

• Poor growth past 1-2 years
  ✓ Ht 10%ile (Expected 75%ile)
  ✓ Wt 3 %ile

• Mild RLQ tenderness
• Nl perianal exam
The First Visit

- History and Physical “Red Flags”
  - Wt loss, growth failure, delayed puberty
  - Rectal bleeding
  - Fever, rash, arthritis, eye irritation
  - Atypical abdominal pain/diarrhea
  - History of significant infections
  - Positive family history
  - Perianal disease
  - Clubbing
  - Abdominal tenderness or mass

- Labs
  - CBC (microcytic anemia, thrombocytosis)
  - CRP/ESR (elevated in 90% of CD, 50% in UC)
  - Albumin (PLE, +/- nutrition)
  - LFTs/bili (autoimmune hepatitis, PSC, baseline)
  - Stool studies (Cx, C diff, possibly others)
  - Schedule EGD, colonoscopy, and SBFT

Adult Colonoscopy Prep May Be Inappropriate for Children

- History and Physical “Red Flags”
  - Wt loss, growth failure, delayed puberty
  - Rectal bleeding
  - Fever, rash, arthritis, eye irritation
  - Atypical abdominal pain/diarrhea
  - History of significant infections
  - Positive family history
  - Perianal disease
  - Clubbing
  - Abdominal tenderness or mass
Adult Colonoscopy Prep May Be Inappropriate for Children

Endoscopy Results

Endoscopic Findings in Colitis

Chronic Active Colitis

- Crypt branching
- Crypt distortion
- Crypt abscess
- Lamina propria infiltrate
Terminal Ileal Involvement in Crohn’s Disease

Summary of Evaluation

- Hb 11.6, ESR 45, nl albumin and liver enzymes
- Stool studies negative
- EGD, colonoscopy, SBFT showed ileal-colonic inflammation c/w Crohn’s

Treatment Goals

- Maximize therapeutic response
- Maximize adherence
- Minimize toxicity
- Improve quality of life
- Promote physical growth
- Promote psychological growth
- Prevent disease complications

Medications in IBD

<table>
<thead>
<tr>
<th></th>
<th>Crohn’s Induction</th>
<th>Crohn’s Remission</th>
<th>UC Induction</th>
<th>UC Remission</th>
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</thead>
<tbody>
<tr>
<td>5-ASA</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Abx</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Steroids</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>6MP/Aza</td>
<td>+/-</td>
<td>+</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>MTX</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Infliximab</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Others</td>
<td>?</td>
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### Medications in IBD

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<td>+</td>
</tr>
<tr>
<td>Others</td>
<td>?</td>
<td>?</td>
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### Initial Treatment

- Patient started on Prednisone 40 mg daily
- TPMT sent
  - Found to have normal alleles, and started on 6MP at 1.5 mg/kg/day

### Medications in IBD

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<tr>
<td>Others</td>
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### 6-MP Metabolism

- AZA → 6-MP → 6-TG → 6-MMP

- 6-TG: disease control, bone marrow suppression
- 6-MMP: hepatotoxicity
Case Presentation
• Patient in remission (steroids) in 2 weeks.
• Prednisone tapered by 5 mg per week starting at week 4.

Asymptomatic for 6 months, then mild, intermittent abd pain, occ loose stool
✓ NL growth velocity, but no “catch up” growth

Etiology of Growth Failure in CD
- Increased needs
- Suboptimal intake
- Malabsorption
- Increased GI losses

MALNUTRITION
GROWTH FAILURE
- Pubertal Delay
- Corticosteroids
- Inflammation

Case Presentation
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• ESR 29, Hb 12.2
Case Presentation

- Patient in remission (steroids) in 2 weeks.
- Prednisone tapered by 5 mg per week starting at week 4.
- Asymptomatic for 6 months, then mild, intermittent abd pain, occ loose stool
  ✓ NI growth velocity, but no “catch up” growth
- ESR 29, Hb 12.2
- Patient unwilling to consider additional evaluation or therapy (fear of steroids)

Case Presentation

- 6 months later
  ✓ Continued slow growth
  ✓ Minimal reported symptoms
- Repeat evaluation
  ✓ ESR 35, Hb 11.4
  ✓ 6MP metabolite levels “therapeutic”
  ✓ colonoscopy showed active ileitis (moderate) and mild colitis

Case Presentation

- 6 months later
  ✓ Continued slow growth
  ✓ Minimal reported symptoms
- Repeat evaluation
  ✓ ESR 35, Hb 11.4
  ✓ 6MP metabolite levels “therapeutic”
  ✓ colonoscopy showed active ileitis (moderate) and mild colitis
- Started on infliximab
Infliximab in Children with Crohn’s Disease: The REACH Trial (n=112)

Clinical Response at 10 weeks

- 100%
- 88%
- 67%

Remission at 54 weeks

- 100%
- 56%
- 24%

Induction = 5 mg/kg infusions at weeks 0, 2, 6
Responders at week 10 randomized to q8 vs q12 week maintenance

Hynes et al., J Pediatr Gastroenterol Nutr 2005; 41:539;
Hanauer et al., Lancet 2002; 359:1541-1549

Growth Curves