Efficacy and Safety of Treatment for Pediatric IBD

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Objectives

- Discuss clinical presentation of Crohn disease and ulcerative colitis
- Review common diagnostic testing and monitoring
- Summarize medical therapies
- Overview of safety considerations

Etiology of IBD will be reviewed in later lectures
Normal Digestive Tract Anatomy

GI Tract

Colon (Large Intestine)
Normal Endoscopic Appearance

Colon

Terminal Ileum
Ulcerative Colitis

Colitis with Transition Zone

Pancolitis
Crohn Disease: Endoscopy

Patchy Colitis, linear ulceration

Small erosions (aphtae) in the colon

Aphthous Ulcerations

Crohn’s ileitis
Crohn disease -- Stricturing

Colonic Stricture

Ileal Stricture
Crohn disease – Fistulizing
# IBD Presentation

<table>
<thead>
<tr>
<th>Symptoms/Signs</th>
<th>CD</th>
<th>UC</th>
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</thead>
<tbody>
<tr>
<td>Rectal bleeding</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>Weight loss</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>Growth failure</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Perianal disease</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>++++</td>
<td>+++</td>
</tr>
<tr>
<td>Anemia</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Mouth ulcers</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Fevers/Arthritis</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>
IBD – HEENT exam

Photo courtesy of CDC - Sol Silverman, Jr., DDS

Aphthous ulcers
IBD – Ophthalmologic Findings

Episcleritis

Uveitis
IBD – Dermatologic Manifestations

Pyoderma gangrenosum

Erythema nodosum
Growth Failure in Pediatric IBD

- Increased needs
- Malabsorption
- Suboptimal intake
- Increased GI losses

MALNUTRITION

GROWTH FAILURE

- Pubertal Delay
- Corticosteroids
- Inflammation
Common Laboratory Testing

• CBC (complete blood count)
  – Hemoglobin (low: anemia)
  – WBC (high: infection, inflammation)
  – Platelets (high: inflammation, bleeding, anemia)

• CMP (complete metabolic panel)
  – Assess electrolytes, liver, kidney function
  – Albumin (low with intestinal inflammation)

• ESR/CRP
  – Markers of inflammation

• Vitamin D
Common Stool Testing

• Rule out enteric infections
  – Culture for bacteria
  – C. diff
  – Viral stool studies
  – Parasites

• Calprotectin
  – Sensitive marker of gut inflammation
IBD – Radiology Testing

Traditional Modalities
• Upper GI with Small Bowel Follow-Through
• Barium Enema
• CT scan

Recent trends
• MRI enterography (pelvis/abdomen)
• High resolution ultrasound
• CT enterography
Abnormal TI on SBFT with correlation on MRI before and after contrast
Ultrasound of the Bowel
Capsule Endoscopy

- Relatively easy to swallow
  - Endoscopically placed in younger patients
- Can visualize entire small bowel
- **MUST** rule out intestinal stricture prior to placement
Bone Monitoring

• Decreased bone density in pediatric IBD

• DXA scan
  – Performed at diagnosis and repeated when clinically indicated

• Vitamin D

• Calcium

• Increased physical activity
Treatment of Pediatric IBD Goals

- Improve growth and nutrition
- Improve quality of life
- Maximize therapeutic response
- Minimize toxicity
- Prevent disease complications
- Mucosal healing
- Promote psychological health
5-ASA Delivery Systems

- PENTASA
- ASACOL/DELZICOL/LIALDA/APRISO
- COLAZAL/AZULFIDINE/DIPENTUM
- ENEMA

Delivery Systems for:
- JEJUNUM / ILEUM / ASCENDING / DESCENDING / SIGMOID / RECTUM
- SMALL BOWEL
- COLON
Efficacy of 5-ASA’s

Ulcerative Colitis
• Oral therapy effective for induction and maintenance of remission
• Rectal, oral + rectal → More effective than just oral for distal disease

Crohn’s disease
• Efficacy unclear for induction or maintenance of remission
Antibiotics

• Decrease inflammation by changing or eliminating bacteria in GI tract

• Multiple indications for Crohn’s
  – Perianal disease
  – Abscess
  – Prevent post-operative recurrence
  – Treatment of mild or moderate disease

• Ulcerative colitis
  – Triple or quadruple antibiotics for refractory severe UC*

Probiotics

• Live microorganisms ➔ Alter flora of gut
• Promote more favorable bacteria
  – ↓ inflammation
• Many different preparations
• UC ➔ Effective, particularly for pouchitis
• Crohn’s ➔ Not proven effective
Systemic Corticosteroids

• Oral (prednisone), IV (Solumedrol), or rectal

• Suppress active inflammation

• Indication: Acute UC or Crohn’s flare

• Provide immediate symptomatic relief
  – Do not promote healing of GI tract

• **Not** indicated for maintenance therapy
  – Lose efficacy, side effects
Corticosteroids – Common Side Effects

• Growth retardation
• Contribution to ↓ bone mineral density
• Excessive weight gain
• Cosmetic
  – Acne, moon facies, hirsutism
• Psychological
  – Sleep disturbance, mood instability
• Increased risk of infection
**UCERIS**
(budesonide)

UCERIS is not indicated for Crohn’s disease; it is indicated for the induction of remission in patients with active, mild to moderate UC

**TARGET:**
Full length of colon

**MMX® technology:**
Pill dissolves at pH ≥7.0, the approximate pH level near the entry to the colon

**Dosage:** 9-mg tablet QD

**Entocort® EC**
(budesonide)

Entocort® EC is not indicated for UC; it is indicated for the treatment of active, mild to moderate Crohn’s disease involving the ileum and/or ascending colon

**TARGET:**
Ileum/ascending colon

**Controlled ileal release:**
Pill dissolves at pH >5.5, the approximate pH level of the duodenum

**Dosage:** 3 mg x 3 capsules QD
Immunomodulators

• Suppress immune response that triggers intestinal damage in IBD

• Require longer period of time for efficacy

• Steroid sparing effects

• Used alone and in combination with biological therapies

Imuran (azathioprine)

Methotrexate

Purinethol (6-MP)

No live vaccines
6-MP/Imuran

- Oral medication administered every night
- Requires 3-4 months for maximal efficacy
- Effective for Crohn’s Disease and UC
  - Maintenance of remission
  - Decrease in steroid requirements
  - Perianal disease
  - ? Prevention/treatment of post-operative recurrence
Methotrexate

• Better studied in Crohn’s disease
  – May improve growth, perianal disease

• Administered once weekly
  – Subcutaneous injection vs. oral

• Laboratory monitoring required

• Requires 6-8 weeks for efficacy
  – Faster onset of action compared to 6-MP
  – Does not require monitoring of metabolites
**6-MP/AZA and MTX Adverse Effects**

### 6-MP/AZA
- Nausea
- ↓ white blood cell count
- Liver toxicity
- Pancreatitis
- Increased infection risk
- Increased skin cancer risk
- Slightly increased lymphoma risk

### Methotrexate
- Nausea
- ↓ white blood cell count
- Liver toxicity
- Poor appetite
- Increased infection risk
- Reaction at injection site
- No documented increased cancer risk
- Teratogenic
Enteral Nutritional Therapy

TO BE DISCUSSED LATER!
Biologic Therapies

- Pro-inflammatory cytokines contribute to inflammation in IBD
  - TNFα is elevated in IBD patients

- Biologics block and neutralize cytokines

- Used to treat moderate to severe Crohn’s disease and ulcerative colitis
Remicade (infliximab)
Humira (adalimumab)

• Moderate to severe Crohn’s disease
  – Decreases steroid requirement
  – Mucosal healing
  – Healing of perianal disease
  – Improvement of growth
  – Bone health
  – Prevention of post-operative recurrence

• Ulcerative colitis
  – Treatment of moderate to severe disease
  – Prevention of surgery
Improved Growth with Infliximab

Anti-TNF α Therapy

Remicade (infliximab)
- Intravenous infusion
- Loading dose
  - 0, 2, 6 weeks
- Maintenance dose
  - Every 8 weeks
- Can escalate if necessary

Humira (adalimumab)
- SQ injection
- Loading dose
  - Multiple injections wk 0,2
- Maintenance dose
  - Every 2 weeks
- Can escalate if necessary

Need to pre-screen for tuberculosis
No live vaccines
Anti-TNF Therapeutic Monitoring

• Measure trough level/antibodies against medicine

• “Sub-therapeutic drug level”
  – Less likely to be effective
  – Increase dose and/or decrease interval

• Antibodies against medication
  – Less likely to be effective
  – Can optimize dose
  – Might have to switch agents
  – Add immunomodulator
Vedolizumab (Entyvio)

• Gut specific anti-adhesion molecule

• 2014: Approved for adult Crohn and UC

• CHOP: ~30 patients have received

• Currently studying results
Remission (PCDAI $\leq 10$ or PUCAI $< 10$)
Traditional Pediatric IBD “Step-Up” Algorithm

- Steroids
- Aminosalicylates
- Antibiotics
- Severe
- Moderate
- Mild
- Budesonide
- Prednisone
- 6-MP/AZA
- Methotrexate
- Enteral Nutrition
- Surgery
- Infliximab/Adalimumab
- Probiotics
- Antibiotics
- Aminosalicylates
- Probiotics
- Enteral Nutrition
Does Early Use of Biological Therapy Improve Efficacy? Growth?

- Early
  - Biologic therapy
    - 6-MP/AZA/Methotrexate
    - Steroids
    - Surgery

- Late
Corticosteroid-Free Clinical Remission at Week 50

SONIC Trial

Early Anti-TNF Therapy in Pediatric Crohn Disease

• Observational cohort of pediatric CD patients (inflammatory)

• Propensity score analysis matched patients on baseline characteristics in 68 triads
  – Early anti-TNF (<3 mo)
  – Early immunomodulator
  – Neither

• Early anti-TNF
  – Higher remission rate
  – Improved height z-score

Steroid-free Remission* at 1 Year

*Remission: PCDAI≤10, steroid free, no surgery

Walters TD et al. Gastroenterology 2014; 146:383-91
Risk of Treating vs. Not Treating

Risk of Treatment

Risk of Disease
Long-Term Evolution of Pediatric Crohn Disease is Structural Damage

![Graph showing the evolution of inflammatory, stricturing, and penetrating forms of Crohn disease over time.](image-url)
What we (parents, patients and physicians) are most concerned about:

Infection

Lymphoma
Pediatric IBD Risk of Serious Infection: A Systematic Review

Serious Infections per 10,000 Patient-Years

Vaccination

• Ensure that vaccines are up to date at time of diagnosis

• All non-live vaccines should be given
  – Annual flu shot
  – HPV vaccine

• Avoid live vaccines if immunosuppressed
  – MMR, Varicella, intranasal flu, others
  – Try to confirm Varicella immunity prior
  – Consider pneumococcal vaccine
## Risk versus Benefit of Biologics and Immune Suppressants in IBD

<table>
<thead>
<tr>
<th>Event</th>
<th>Estimated Frequency (annual, pt-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hodgkin Lymphoma (baseline)</td>
<td>2/10,000</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma (on IM)</td>
<td>4/10,000</td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma (on anti-TNF)</td>
<td>6/10,000</td>
</tr>
<tr>
<td>Hepatosplenic T-cell Lymphoma</td>
<td>Unknown</td>
</tr>
<tr>
<td>Death from sepsis</td>
<td>4/1000</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>5/10,000</td>
</tr>
</tbody>
</table>

Adapted from Siegel CA. Comprehensive approach to patient risk. Risk versus benefit of biologics and immune suppressants. In: Targan S, Shanahan F, Karp L, eds. Inflammatory Bowel Disease: Translating basic science into clinical practice
Risk of Developing NHL – No immune suppression

Patient with Crohn’s disease (without immune suppression)

Estimated annual risk = 2 per 10,000 treated patients
Risk of Developing NHL -- Immunomodulator

Patient with Crohn’s disease receiving 6MP or Azathioprine

Estimated annual risk = 4 per 10,000 treated patients
Risk of Developing NHL – Immunomodulator & Anti-TNF

Patient with Crohn’s disease receiving combination anti-TNF + Immunomodulator Therapy

Estimated annual risk = 6 per 10,000 treated patients
Less Risk of Malignancy with Biologic Monotherapy?

Drug Therapies and the Risk of Malignancy in Crohn’s Disease: Results From the TREAT™ Registry

Gary R. Lichtenstein, MD¹, Brian G. Feagan, MD, FRCPC², Russell D. Cohen, MD³, Bruce A. Salzberg, MD⁴, Robert H. Diamond, MD⁵, Wayne Langhoff, PhD⁶, Anil Londhe, PhD⁶ and William J. Sandborn, MD⁷

OBJECTIVES: We assessed potential associations between malignancy and antitumor necrosis factor therapy in patients with Crohn’s disease (CD), as this relationship is currently poorly defined.

METHODS: Utilizing data from the Crohn’s Therapy, Resource, Evaluation, and Assessment Tool (TREAT™) Registry, a prospective cohort study examining long-term outcomes of CD treatments in community and academic settings, influences of baseline patient/disease characteristics and medications were assessed by survival analysis and multivariate models. Standardized incidence ratios and exact 95% confidence intervals were determined as the ratio of events observed (TREAT) vs. expected (general population of USA).

RESULTS: As of 23 February 2010, 6,273 CD patients (infliximab during registry = 3,420 (during or within 1 year before registry = 3,764); other-treatments-only: 2,509), were enrolled and, on average, had been followed for 5.2/7.5 years, respectively, for all/currently active patients. Crude cancer incidences were similar between infliximab- and other-treatments-only-exposed patients. Multivariate Cox regression analysis demonstrated that baseline age (hazard ratio (HR) = 1.59/10 years; P < 0.001), disease duration (HR = 1.64/10 years; P = 0.012), and smoking (HR = 1.38; P = 0.045) but neither immunosuppressive therapy alone (HR = 1.43; P = 0.11), infliximab therapy alone (HR = 0.59; P = 0.16), nor their combination (HR = 1.22, P = 0.34) were independently associated with the risk of malignancy. When compared with the general population, no significant increase in incidence was observed in any malignancy category. In an exposure-based analysis, use of immunosuppressants alone (odds ratio = 4.19) or in combination with infliximab (3.33) seemed to be associated with a numerically, but not significantly, greater risk of malignancy than did treatment with infliximab alone (1.96) relative to treatment with neither.

CONCLUSIONS: In the TREAT Registry, age, disease duration, and smoking were independently associated with increased risk of malignancy. Although results for immunosuppressant use were equivocal, no significant association between malignancy and infliximab was observed.
Risk of Disease Often Greater than Risk of Treatment
Thank you...