IBD 101, Therapies, and Safety Considerations

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The Children’s Hospital of Philadelphia
IBD Family Education Day
February 24, 2013
Objectives

- Discuss clinical presentation of Crohn’s disease and ulcerative colitis
- Review common diagnostic testing and monitoring
- Summarize medical and nutritional treatment
- 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

A proctitis

B left-sided colitis

C pancolitis

Colitis with Transition Zone

Pancolitis
Crohn Disease: Endoscopy

- Patchy Colitis, linear ulceration
- Crohn’s ileitis
- Small erosions (aphtae) in the colon
- Aphthous Ulcerations
Crohn disease -- Stricturing

Colonic Stricture

Ileal Stricture
Crohn disease – Fistulizing
<table>
<thead>
<tr>
<th>Crohn’s Disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any part of the GI tract</td>
<td>Colon only (± gastritis)</td>
</tr>
<tr>
<td>Discontinuous</td>
<td>Continuous</td>
</tr>
<tr>
<td>Ileum commonly involved</td>
<td>± backwash ileitis</td>
</tr>
<tr>
<td>Perianal disease</td>
<td>No perianal disease</td>
</tr>
<tr>
<td>Transmural inflammation</td>
<td>Mucosal inflammation</td>
</tr>
<tr>
<td>Fistulae and abscesses</td>
<td>Abscesses very rare</td>
</tr>
<tr>
<td>Granulomas</td>
<td>No granulomas</td>
</tr>
<tr>
<td>Strictures common</td>
<td>Strictures uncommon</td>
</tr>
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</table>
## IBD Presentation

<table>
<thead>
<tr>
<th>Symptoms/Signs</th>
<th>CD</th>
<th>UC</th>
</tr>
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<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

Aphthous ulcers
IBD – Ophthalmologic Findings

Episcleritis

Uveitis
IBD – Dermatologic Manifestations

Pyoderma gangrenosum

Erythema nodosum
Etiology of Growth Failure in IBD

MALNUTRITION

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

GROWTH FAILURE

- Inflammation
- Corticosteroids
- Pubertal Delay
Bone Monitoring

- Decreased bone density recognized in pediatric IBD

- DXA scan
  - Performed at diagnosis and repeated when clinically indicated

- Vitamin D

- Calcium

- Increased physical activity
Common Diagnostic Testing

- Labs
  - Hemoglobin
  - Albumin
  - ESR/CRP/platelets
  - Vitamin D

- Stool studies
  - Rule out infection
  - Calprotectin (marker of gut inflammation)

- Radiology

- Endoscopy/Colonoscopy
IBD – Radiology Testing

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

Recent trends
- MR enterography (pelvis/abdomen)
- High resolution ultrasound

Non-GI
- DXA
- Bone age
UGISBFT Compared to MR Enterography

Abnormal TI on SBFT with correlation on MRI before and after contrast
Ultrasound of the Bowel

NORMAL TI

ABNORMAL TI
Capsule Endoscopy

- Relatively easy to swallow
  - Endoscopically placed in younger patients
- Can visualize entire small bowel
- **MUST** rule out intestinal stricture prior to placement
- How much ulceration is normal?
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
Pediatric IBD “Step-Up” Algorithm

- Steroids
  - Severe: Prednisone
  - Moderate: Budesonide
  - Mild: Antibiotics

- Biologic therapy
  - 6-MP
  - Imuran
  - Methotrexate

- Surgery

- Enteral Nutrition

- Aminosalicylates
  - (Probiotics)
5-ASA Delivery Systems

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

Locations:
- JEJUNUM / ILEUM
- ASCENDING / DESCENDING / SIGMOID / RECTUM
- SMALL BOWEL
- COLON
Aminosalicylates (5-ASA)

- Locally reduce inflammation in the bowel
- First-line therapy for UC
  - Questionable efficacy for Crohn’s
- Chemoprotective effect?
- Well tolerated
  - Headaches, GI complaints most common
  - 3-5% with allergy to medicine
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

• Not proven effective for 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
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
Entocort (Budesonide)

- Special steroid formulation
  - Released in the terminal ileum
- Considerably less steroid side effects
- Effective for ileocolonic Crohn’s disease
- Not effective for UC, gastritis
- Role as maintenance therapy unclear
  - Evidence of some steroid side effects (growth suppression)
Uceris (Budesonide MMX)

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

FDA Approved 01/2013
Commercially Available 02/2013
Enteral Nutrition

- Improves nutrition for all IBD
- Effective therapy for pediatric Crohn’s
- UC → Not shown to be effective
- 100% of calories by formula
  - 80-90% as effective?
- Usually requires NG tube
- Proposed mechanism: Modulation of intestinal bacteria
Enteral Nutrition vs. Steroids for Active Crohn’s Disease

Enteral Nutrition $\rightarrow$ As effective as steroids for improving symptoms, **more effective** for healing of GI inflammation

Enteral Nutrition

PROS

- No medication toxicity
- Promotes growth
- Improves nutritional deficits

CONS

- Usually requires NG tube placement
- Compliance difficult
Immunomodulators

- Suppress immune response that triggers intestinal damage in IBD
- Good maintenance medications
- Steroid-sparing effects
- Require longer period of time for efficacy
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
**Imuran (AZA) and 6-MP Metabolism**

- **AZA** → **6-MP** → **6-thiouric acid**
- **6-MP** → **6-MMP** → **6-TGN**
- **XO**
- **HPRT**
- **TPMT**

**TPMT**
- 89% have normal activity
- 11% have intermediate activity
- 0.3% have low activity
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
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)

- Crohn’s disease
  - Decreases steroid requirement
  - Healing of perianal disease
  - Prevention of post-operative recurrence
  - Joint disease
  - Improves linear growth
  - Improves bone density

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

Graph showing mean height velocity Z-score over time for different groups: All Patients, No Baseline Steroids, and Steroids at Baseline. The graph compares baseline and week 54 measurements.
Anti-TNF α Therapy

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

Humira (adalimumab)
- SQ injection
- Loading dose
  - Multiple injections wk 0,2
- Maintenance dose
  - Every 2 weeks
- Can escalate if necessary
  - Can not yet measure serum drug levels

Need to pre-screen for tuberculosis
Does Early Use of Biological Therapy Improve Efficacy? Growth?

- Biologic therapy
- 6-MP/AZA/Methotrexate
- Steroids
- Surgery
- 5-ASA, antibiotics

Early
Late

5-ASA
Antibiotics
Corticosteroid-Free Clinical Remission at Week 50

SONIC Trial

All Randomized Patients (N=508)*

* Patients who did not enter the Study Extension had Week 26 values carried forward

SONIC Trial

Mucosal Healing at Week 26

![Bar chart showing proportion of patients (%) with mucosal healing at Week 26 for different treatment groups: AZA + placebo (16.5, 18/109), IFX + placebo (30.1, 28/93), IFX + AZA (43.9, 47/107).]

Risk of Treating vs. Not Treating

Risk of Treatment

Risk of Disease
Long-Term Evolution of Crohn's Disease is Structural Damage

Cumulative Risk of Developing Colorectal Cancer in Ulcerative Colitis

Cumulative Probability (%) vs. Time From Diagnosis (y)

- Upper CL
- Cumulative risk of CRC
- Lower CL
- Rutter, et al. 2006

CL = confidence limit.


Infection

Lymphoma
Infections in IBD

- Most common adverse event associated with immunosuppression in IBD
  - More common in older patients
  - Often preventable with routine vaccines

- Steroids increase risk at higher doses

- 6-MP → Mostly viral infections

- Biologics → Serious opportunistic infections,
  - Rule out tuberculosis prior to initiating
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>
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</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

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

<table>
<thead>
<tr>
<th>Patient with Crohn’s disease receiving 6MP or Azathioprine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated annual risk = 4 per 10,000 treated patients</td>
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</tbody>
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Risk of Developing NHL – Immunomodulator & Anti-TNF

<table>
<thead>
<tr>
<th>Patient with Crohn’s disease receiving combination anti-TNF + Immunomodulator Therapy</th>
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</table>

Estimated annual risk = 6 per 10,000 treated patients
Hepatosplenic T-cell Lymphoma (HSTCL)

- Rare form of non-Hodgkins lymphoma
- Aggressive, usually fatal

- Signs/symptoms:
  - Enlarged liver and spleen
  - Fever, night sweats, weight loss
  - Abdominal pain

- Patients who developed HSTLC were:
  - Overwhelmingly male
  - Relatively young (median age 22, youngest 10)
HSTCL in IBD

- 36 reported cases of HSTCL in IBD patients
  - 20/36 had received infliximab and 6-MP/AZA
  - 16/36 had received 6-MP/AZA alone
  - Nearly all patients had taken 6-MP/AZA > 2 yrs

- > 1 million patients treated with infliximab
  - > 400,000 with IBD

- >99.99% of patients on monotherapy or combination therapy **will not** develop HSTCL
Key Points

- There are risks associated with IBD medications
- Serious complications are quite uncommon
- Risk of not treating IBD usually higher than risk of treatment
- Consider nutritional therapy when appropriate
- Immunomodulator, biologic therapy critical treatment for most patients
Thank you

Attending: Dr. Grossman / Dr. Tang Gel
Respiratory: Hilary - NP
Other Team Members: 

Notes: Dear doctor please save my brother's intestines. I will bring them in to show and tell. Thanks! Nick is awesome brother! Nick is awesome too!