Diagnostic and Treatment Challenges in Inflammatory Bowel Disease

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  – Abbott Nutrition, Abbvie, Prometheus
OBJECTIVES

• Describe the available tools to establish an accurate diagnosis of inflammatory bowel disease (IBD)
• Review the therapeutic options from first line to biologic in IBD patients who continue to show symptoms
• Assess the efficacy, safety and future potential of key therapeutic advances for IBD
• Analyze the evolving roles and associated patient safety concerns of current and emerging therapies as novel targeted agents change standards of care

Key Point 1:

IBD is a Complex Disorder that May Require a Genetically Susceptible Host with an Appropriate Environmental Trigger(s)

Key Point 2:

IBD Results from an Exaggerated Mucosal Immune Response to Commensal Microorganisms

Pathogenesis of IBD

Incidence of IBD is Increasing Dramatically Worldwide

Summary: Inflammatory Bowel Diseases

- Chronic intestinal inflammation from a dysregulated immune response to the enteric microbiome in a genetically predisposed host
- Today we label them as Crohn’s disease and ulcerative colitis though we recognize a host of often overlapping phenotypes
- Presenting symptoms range from mild to severe and clinical course is often unpredictable ranging from easily controlled to fulminant disease

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The Five GI Symptoms

• Abdominal pain
• Nausea
• Vomiting
• Diarrhea
• Constipation

Clinical suspicion (acumen) is the key to diagnosing IBD
Crohn’s Disease (CD): Diagnosis

- Based on a composite of endoscopic, radiographic, and pathological findings
- Documentation of focal, asymmetric, transmural, or granulomatous features
- Sequence of testing based on presenting symptoms, physical findings, and basic laboratory abnormalities

ACG Guidelines

Crohn’s Disease: Diagnosis

- Genetic and serologic testing
  - not recommended at this time for diagnosis
- Endoscopy with biopsy—gold standard
  - Biopsy caveats (GI tract always has inflammatory cells)
  - EGD and colonoscopy (children)
- Small bowel imaging
  - Defines extent and transmural involvement
  - Small bowel series has very limited role
Crohn’s Disease

- Deep fissures
- Cobblestoning
- Segmental distribution
- Ileal involvement
- Granulomas on biopsy

Advances in Small Bowel Imaging

- MR Enterography (MRE)—transmural
  - No radiation
  - Time intensive (elective)
- CT Enterography (CTE)—transmural
  - Radiation
  - Rapid
- Ultrasonography (Europe)
- Video capsule endoscopy (VCE)—mucosal
  - ?monitoring
MRE: “Comb Sign”

MRE: Fistula and Psoas Abscess
Video Capsule Endoscopy

Diagnosis: Ulcerative Colitis (UC)

- Patient presenting with persistent bloody diarrhea, rectal urgency, or tenesmus
- Stool examinations exclude an infectious etiology
- Sigmoidoscopy or colonoscopy and biopsy should be performed to confirm presence of colitis
- Characteristic endoscopic and histologic findings with negative infectious evaluation will suggest the diagnosis of UC.

ACG Guidelines
Ulcerative Colitis

- Loss of vascular pattern
- Granularity
- Exudates
- Diffuse continuous disease

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**IBD: Management Goals**

- Address psychosocial issues
- Identify dysplasia and detect cancer
- Improve daily functioning
- Replenish nutritional deficits
- Relieve symptoms
- Treat inflammation
- Treat complications
- Minimize treatment toxicity
- Maintain remission

**IBD: Therapeutic Themes**

- Induction therapies
- Maintenance therapies
- “Step in” is better than “step up”
- Optimization of therapy
- Treat the whole patient
### Sequential Therapies for UC

**Disease Severity at Presentation**
- **Severe**
- **Moderate**
- **Mild**

**Therapy is stepped up according to severity at presentation or failure at prior step**

- **Aminosalicylate**
- **Corticosteroid**
- **Anti-TNF**
- **Cyclosporine**
- **Anti-TNF**
- **Cyclosporine**
- **Anti-TNF**
- **Thiopurine**
- **Induction**
- **Maintenance**
- **Colectomy**

- **Aminosalicylate**
- **Anti-TNF**
- **Thiopurine**

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### Treatment of Distal UC: Oral and Rectal Mesalamine Therapy

- **Oral (2.4 g/d)**
- **Rectal (4 g/d)**
- **Combined**

**Patients Reporting No Rectal Bleeding (%)**
- **1 Week**
- **2 Weeks**
- **3 Weeks**
- **6 Weeks**

- *P < .05 vs oral alone*

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*Slide Courtesy of the GI Health Foundation*
Predictors of Poor Response or Colectomy

- Serum albumin
- ESR >30 mm/h
- Bandemia
- Prolonged flare
- Active infection
- Hospitalization setting
- Severe endoscopic lesions
- Disease duration
- Stool frequency
- Percentage of bloody stools
- Body temperature >37.5° C
- Heart rate >90 bpm
- Increased CRP
- Toxic megacolon
- Low hemoglobin <10.5 g/dL

Suzuki Y et al. Dig Dis Sci. 2006;51:2031-2038
Cacheux W et al. Am J Gastroenterol 2008;103:637-642
Ananthakrishnan AN et al. Am J Gastroenterol. 2008;103:2789–2798

Course of UC

Disease Course One Year After Diagnosis

- Moderate-high activity (20%)
- Low activity (30%)
- No symptoms (50%)

CROHN’S DISEASE

IBD: Therapeutic Themes

- Induction therapies
- Maintenance therapies
- “Step in” is better than “step up”
- Optimization of therapy
- Treat the whole patient
GWAS Studies Have Identified over 180 Inflammatory Bowel Disease Susceptibility Loci

What causes IBD? Does it Vary with Age?
IBD patients may have unique signatures that predict complicated or treatment refractory disease

Clinical features: age, location, endoscopy, histology, etc.

Impact of Therapy Depends on Degree of Structural Damage and Velocity of Progression

Cosnes J et al. Inflamm Bowel Dis. 2002;8:244-250.
Progressive Bowel Damage in CD

Physical & Psychosocial Growth & Development

Early Surgery
Proactive Effective Medical Therapy
Reactive Maximal Medical Therapy
Surgery

FIGURE 1. Progression of digestive damage and inflammatory activity in a theoretical patient with CD.

Pariente et al. Inflamm Bowel Dis 2011

Evolving Classification
(Diabetes as the Model)

Ulcerative Colitis
- Mucosal
- Continuous

Crohn’s Disease
- Transmural
- Discontinuous
- Oral → Peri-anal

Indeterminate Colitis

IBD 1  IBD 2  IBD 3  IBD 4  IBD 5
Sequential Therapies for Crohn’s Disease

- **Disease Severity at Presentation**
  - Severe
  - Moderate
  - Mild

- **Induction**
  - Aminosalicylate
  - Budesonide

- **Maintenance**
  - Corticosteroid
  - Thiopurine/MTX

- **Anti-TNF**
  - Anti-TNF+/-
  - Thiopurine/MTX

- **Natalizumab**

Step-up according to severity at presentation or failure at prior step

Slide Courtesy of the GI Health Foundation
Predictors of Disabling Crohn’s

Referred cohort of 1128 CD patients

3 factors independently predictive disabling CD course within 5-year

- Initial requirement for steroids
  OR: 3.1 [95% CI: 2.2 – 4.4]

- Age at diagnosis below 40
  OR: 2.1 [95% CI: 1.3 – 3.6]

- Perianal disease at diagnosis
  OR: 1.8 [95% CI: 1.2 – 2.8]

Beaugerie L et al. Gastroenterology 2006;130:650-6

Consensus Predictors of Poor Outcome*

- Deep colonic ulcerations on endoscopy
- Persistent severe disease despite adequate induction therapy
- Extensive (pan-enteric) disease
- Marked growth retardation (> -2.5 height Z scores),
- Severe osteoporosis
- Strictureing or penetrating disease (B2 and/or B3 disease behavior) at onset
- Severe perianal disease

Evolving Goals of Therapy for IBD: *Sustained Deep Remission*

**Goal**
- Response
- Remission
- Deep remission

**Clinical Parameters**
- Improved symptoms
- No symptoms
- Normal endoscopy

**Outcomes**
- Improved QoL
- Decreased hospitalisation
- Avoidance of surgery

**SUSTAINED**

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**SONIC: Steroid Free Remission**

All Randomized Patients (N=508)*

- AZA + placebo: 28.2% (48/170)
- IFX + placebo: 39.6% (67/169)
- IFX+ AZA: 55.6% (94/169)

Significance:
- p<0.001
- p=0.025
- p=0.002

Vedolizumab: Primary Maintenance Endpoint For Adult Crohn’s Disease

Patients % (95% CI)

- VDZ / Placebo (n=153)
- VDZ / VDZ Q8w (n=154)
- VDZ / VDZ Q4w (n=154)

Δ=15% p<0.01
Δ=17% p<0.001

Clinical Remission

LOSS OF RESPONSE TO ANTI-TNF THERAPIES

Ben-Horin, Aliment Pharmacol Ther 2011;33:987
Special Considerations: Biologics

- Mono vs. Combination therapy
- Dose optimization
- Immunogenicity

Strategies to Optimize Durable Biologic Response

- Regularly scheduled maintenance
- Concomitant immunomodulator
  - ?duration
- Monitoring drug/antibody levels
  - “treat to trough”
**Loss of Response After Immunomodulator Withdrawal**

- TL detectable & CRP <5 mg/L
- TL detectable & CRP >5 mg/L
- TL undetectable & CRP >5 mg/L

**IFX TROUGH LEVEL AND OUTCOME**

<table>
<thead>
<tr>
<th><strong>Crohn's disease</strong></th>
<th><strong>Ulcerative Colitis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trough level</strong></td>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>Detectable</td>
<td>Clinical remission, CRP, endoscopic remission(^1)</td>
</tr>
<tr>
<td>&gt; 3.5 ug/ml</td>
<td>Sustained response(^2)</td>
</tr>
<tr>
<td>&gt; 3 ug/ml</td>
<td>Sustained response(^3)</td>
</tr>
<tr>
<td>&gt; 5.6 mg/L</td>
<td>Lower CRP(^4)</td>
</tr>
<tr>
<td>Undetectable</td>
<td>Loss of response(^5)</td>
</tr>
</tbody>
</table>

\(^1\)Maser et al. Clin Gastroenterol and Hepatol 2006;4(10):1248-64
\(^2\)Cornillie et al. Gut 2014; 63:1721
\(^3\)Bontik et al. Journal of Crohn's and Colitis 2013;7(9):736-43
\(^4\)Lamblin et al. J Crohn's and Colitis 2012; 334
\(^5\)Drobe et al. Gastroenterology 2011; 279
\(^6\)Arias et al. Journal of Crohn's and Colitis 2012 OP10
\(^7\)Seow et al. Gut 2010; 59:49-54
Proactive Testing in Pediatric IBD: Week 14 IFX Levels and Outcomes

(n=58)

<table>
<thead>
<tr>
<th>Week 54 Outcome (Yes v. No)</th>
<th>Median IFX Level (ug/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent Remission</td>
<td>4.7 versus 2.6*</td>
</tr>
<tr>
<td>Clinical Remission</td>
<td>3.2 versus 2.2</td>
</tr>
<tr>
<td>Clinical &amp; Laboratory Remission</td>
<td>4.2 versus 3.0</td>
</tr>
<tr>
<td>Sustained Durable Remission Week 14 to 54</td>
<td>5.5 versus 3.1*</td>
</tr>
<tr>
<td>Sustained Durable Remission Week 22 to 54</td>
<td>5.1 versus 3.0*</td>
</tr>
</tbody>
</table>

* p<0.05  Singh et al. Inflammm Bowl Disease 2014;20:1708

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TREAT TO TARGET: WHAT DO WE MEAN?

- Regular assessment of disease activity using objective clinical and biologic outcome measures
- Adjust treatment if not accomplishing the goal
- Enables better outcomes in RA, hypertension, diabetes, hypercholesterolemia

Bouguen, Clin Gastroenterol Hepatol ePub 2013 Sep 10, PMID 24036054

TREAT TO TARGET: WHAT DO WE MEAN?

Predefined timeframe
Baseline Assessment
Assessment
Risk of progression
High
Low
Target
Therapy according to risk and target
Unreached Target
Avoidance of long-term bowel damage and disability
Control of intestinal inflammation
Continue therapy, target surveillance

Adapted from: Bouguen, Clin Gastroenterol Hepatol ePub 2013 Sep 10, PMID 24036054
**SUGGESTED ALGORITHM**

- Treatment
- Optimize ongoing drug switch to other class or add drugs
- 6 Months
- Target
  - No symptoms
  - No positive surrogate marker (CRP, +/- fecal marker)
  - No mucosal ulceration
- Yes
- Continue treatment for 1-2 years

Bouguen, Clin Gastroenterol Hepatol ePub 2013 Sep 10, PMID 24036054

**IS MUCOSAL HEALING ACHIEVABLE?**

Figure 1. Cumulative probability of achieving MH.

IS MUCOSAL HEALING ACHIEVABLE?

Figure 1. Cumulative probability of achieving MH.


HR 2.35 (95%CI 1.15-4.97)  
HR 4.28 (95%CI 1.9-11.5)

Weighing Risk: Partial Data

Risk of the disease

Risk of the therapy

Increased Incidence of Lymphoma with Thiopurines: Meta-Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis</td>
<td>1465</td>
</tr>
<tr>
<td>Korelitz</td>
<td>486</td>
</tr>
<tr>
<td>Kinlen</td>
<td>321</td>
</tr>
<tr>
<td>Fraser</td>
<td>626</td>
</tr>
<tr>
<td>Farrell</td>
<td>238</td>
</tr>
<tr>
<td>Connell</td>
<td>755</td>
</tr>
<tr>
<td>Pooled</td>
<td>3891</td>
</tr>
</tbody>
</table>

SIR (standardized incidence ratio)

Meta-analysis of Lymphomas Associated with anti-TNF agents

- 8905 patients representing 20,602 pt-years
- 13 Non-Hodgkin lymphomas

<table>
<thead>
<tr>
<th></th>
<th>NHL rate per 10,000</th>
<th>IRR</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>SEER all ages</td>
<td>1.9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IM alone</td>
<td>3.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anti-TNF vs SEER</td>
<td>6.3</td>
<td>3.32</td>
<td>1.5-7.1</td>
</tr>
<tr>
<td>Anti-TNF vs IM alone</td>
<td>6.3</td>
<td>1.7</td>
<td>0.5-7.3</td>
</tr>
</tbody>
</table>

Clin Gastroenterol Hepatol 2009; 7:874-81

Summary:
Inflammatory Bowel Diseases

- **Chronic** intestinal inflammation from a dysregulated immune response to the enteric microbiome in a genetically predisposed host
- A family of diseases currently simplified to two umbrella terms: Crohn’s disease and ulcerative colitis
- Accurate diagnosis and staging requires clinical suspicion and appropriate confirmatory testing.
Summary: Inflammatory Bowel Diseases

- Pyramid approach does not change the natural history and disabling outcomes of surgery, hospitalization, lowered QOL.
- Personalized approach of Risk stratification and “treat to target” are emerging as best practices.
- Therapeutic drug monitoring and optimization of therapy are critically important goals in the biologic era.
- Treatment of the whole patient will result in best overall outcomes.