Inflammatory Bowel Disease: 2014
Update on Diagnosis and Management

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- Division of Gastroenterology

Objectives

- Evaluate efficacy and safety data of current and emerging therapeutic options for IBD
- Analyze new diagnostic methods into practice for IBD
- Describe the latest clinical findings surrounding the appropriate selection, clinical use, and monitoring of current barriers in the mgt of patients with IBD
- Assess effective strategies for managing IBD as well as the side effects, risks, and benefits of long-term combination therapies
Historical Background

- Early 19th century - Inflammation of the intestine as a noted cause of diarrhea - Francois-Joseph-Victor-Broussais

- 1859 – Sir Samuel Wilks uses “ulcerative colitis” to describe a condition similar to today’s UC.

- Sir William Hale White describes group of conditions known as “ulcerative colitis” that defied other known causes (growth, dysentery, tubercule, typhoid, and so forth)

- Modern Era begins with Truelove and Witt

- 2 surgeons and a medical doctor
  - Oppenheimer, Ginzberg, Crohn’s
**IBD: Overview**

- **Scope of the disorder (United States)**
  - 700,000 physician visits per year
  - 100,000 hospitalizations per year

- **Long-term outlook**
  - Chronic, lifelong disease without medical cures
  - Surgery for 50% to 80% of Crohn’s disease patients
  - Surgery for 20% of ulcerative colitis patients

- Most patients live normal, productive lives!

**Inflammatory Bowel Disease**

**Geographic Distribution**

- High Incidence
- Moderate Incidence
- Unknown

Ulcerative Colitis and Crohn’s Disease → same distribution
Bimodal distribution of age of onset

- **Young age** of onset
- **Chronic** inflammation of the bowel
- Remission and relapses
- Bowel surgery may be necessary
- Increased risk of depression or anxiety

Genetics of IBD: 163 confirmed loci

- 110 IBD loci
  - Common pathways:
    - Leprosy
    - Mycobacterial susceptibility
    - Other immune-mediated disease

- 30 CD specific loci
- 23 UC specific loci
- Genes in common

NOD2 Allelic Variants More Frequent in Fibrostenosing vs. Perforating Disease

While CD Genetics has made progress...

there is still a long way to go:

31 loci account for 20% of the heritability of Crohn's disease
Defining IBD: An Emerging Model

Adapted from Plevy S. J Clin Gastroenterol. 2004;38(suppl 1):S51-S56

Ulcerative Colitis Crohn’s Disease

NOD2

IBD2

IBDX

IBD3

IBD4

Anti-OmpC ASCA pANCA Anti-Cbir
Etiologic Theories in Inflammatory Bowel Disease

Genetic Predisposition

Mucosal Adaptive/Innate Immune System

Environmental Triggers (luminal bacteria, infection)

IBD

Environmental Factors

- Intestinal Microbiome
  - How diet affects disease?
  - How antibiotics affect disease?
- Smoking
  - (Negative risk factor) for UC development
  - Decreased response rate to therapy in both
- Clostridium difficile
  - Risk factor for
    - Development of disease
    - Colectomy in UC
Environmental Triggers

- Infections
- Antibiotics
- NSAIDs
- Diet (?)
- Smoking
- Stress (?)

IBD

1990 – what we used to diagnose

- Clinical presentation and physical exam
- Labs
  - Anemia
  - Inflammatory markers
- Radiographs
  - small bowel x-ray series
  - Exposure to radiation (lifetime risks for younger population)
What we can now look at in a new patient

- Assessing risk of a disease over time
- Genetic profiling
- Allowing for early decisions for aggressive management

Workup

- Blood
  - Serologic markers
- Stool – rarely used unless infectious (cdiff) considered. More often checked during a flare
- Endoscopy
- WCE
- Radiology
Serologic Testing

- pANCA
- ASCA
- anti-Omp C
- anti-CBir1
- anti-I2
- ALCA
- ACCA
- AMCA
- anti-L
- anti-C

Defining IBD: An Emerging Model

Adapted from Plevy S. J Clin Gastroenterol. 2004;38(suppl 1):S51-S56
Ulcerative Colitis
Endoscopic Appearance

Normal Colon

Mild-moderate UC

Severe UC

Medical Treatment – Before the modern era...

- Medical therapy – many systemic side effects
  - Steroids
  - Sulfasalazine

- Surgery earlier in course of disease
  - Good for limited and easy to manage disease
  - Disease free state for good percentage of patients
  - High recurrence rate for many patients
  - Short bowel, nutritional deficiencies
Safety of early medical therapies

- We don’t have great data on early years
- Higher rates of small bowel malignancies in surgically bypassed bowel
- Higher rates of surgery overall

Corticosteroids in UC

- Immediate (30 days) response: 84%
- No response: 16%
- Prolonged response: 49%
- Steroid dependent: 22%
- Surgery: 29%

Mesalamines

- Used mainly in UC as most formulations are released in the colon
- Can be given in oral or rectally-administered forms
- Lots of pills
- Data debatable in crohn's

Purine analogues and MTX

- Used since 1950s for leukemia
- Mercaptopurine data
  - found to be 67% effective vs placebo
  - 83 total patients enrolled
  - Present, D et al NEJM 1989
- Have become very useful as adjunct therapy in recent times
Medical therapy – 2014
a new frontier of treatment options

- Goals (CMMS core measures)
  - Avoidance of steroids
  - Core measure – CMMS

- Early aggressive therapy
  - D’haen’s data

- Personalized management
  - Tpmt enzyme activity
  - Monitoring response to therapy and also therapeutic levels of drug

- Preventative medicine
  - Health maintenance

CMMS Core Measures – IBD

- **Measure 269**: Phenotype
- **Measure 270**: Corticosteroid sparing therapy
- **Measure 271**: Bone loss assessment
- **Measure 272**: Influenza vaccination
- **Measure 273**: Pneumococcal vaccination
- **Measure 274**: Testing for latent TB prior to initiation of anti-TNF therapy
- **Measure 275**: Testing for HBV prior to initiation of anti-TNF therapy
- **Measure 226**: Tobacco use and cessation screening
TPMT Phenotypic Distribution


Azathioprine/6-MP Toxicity in IBD

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<tbody>
<tr>
<td></td>
<td>Part I</td>
<td>Part II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>59</td>
<td>54</td>
<td>396</td>
<td>165</td>
<td>739</td>
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<tr>
<td>Allergy (%)</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pancreatitis (%)</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Myelotoxicity (%)</td>
<td>15</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Hepatotoxicity (%)</td>
<td>0.3</td>
<td>3</td>
<td></td>
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<tr>
<td>Infection (%)</td>
<td>5</td>
<td>17</td>
<td>7</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

*Includes increased LFTs only
The biologics

- 1997 – infliximab paper by steph schreiber – nejm
- Used to treat RA soon after
- 2008 – adalimumab approved
- 2009 – certalizumab pegol approved

Monoclonal Antibodies, Fusion Proteins and Fc-Free Fab’ Fragments Against TNF

- Chimeric monoclonal antibody
- Human monoclonal antibody
- Human recombinant receptor/Fc fusion protein
- Humanized Fc-Free Fab’ fragment

- Infliximab (Remicade®)
- Adalimumab (Humira®)
- Etanercept (Enbrel®)
- Certolizumabpegol (Cimzia®)
Cosnes et al., Inflamm Bowel Dis. 2002; 8: 244-250

Classifying disease at a point in time

- Assess long-term evolution of disease behavior
- Retrospective analysis of 2,002 pts
- 1995-2000
- Vienna Classification
  - Stricturing
  - Penetrating
  - Inflammatory

Impact of Therapy will Depend on Degree of Structural Damage & Velocity of Progression

Patients at risk:
N =
2002 552 229 95 37

Cosnes J et al. Inflamm Bowel Dis. 2002;8:244.
Impact of Therapy will Depend on Degree of Structural Damage & Velocity of Progression

Cosnes J et al. Inflamm Bowel Dis. 2002;8:244.

Impact of Therapy will Depend on Degree of Structural Damage & Velocity of Progression

Cosnes J et al. Inflamm Bowel Dis. 2002;8:244.
Why did biologics fail after 2 years?

- Long-term efficacy of infliximab - ACCENT I
  - 60% initial response
  - 30% maintenance of remission at 1 year
  - Scheduled dosing better than on-demand

- Why failure?
  - Immunogenicity
  - Do immunomodulators alter immunogenicity?

Immunogenicity

- Human anti-chimeric antibodies associated with:
  - Shorter duration of response
  - Higher rate of infusion reaction
    - Infliximab levels lower in those with infusion reactions
    - Duration of response lower in those with infusion reactions
  - Use of concomitant immunomodulators
    - Lower antibody titers
    - Higher infliximab trough levels

Step-up vs Top-down?

Remission Rates

| Week 26          | 60% combined | 36% conventional |
| Week 52          | 62% combined | 42% conventional |

The best opportunity to induce mucosal healing is early in Crohn’s disease (EXTEND study)

- Adalimumab, induction-only (placebo)
- Adalimumab, every other week

p=0.039 for adalimumab vs placebo for disease duration <5 years vs. ≥5 years

All patients (n=135) received open-label adalimumab 160-/80-mg induction therapy at Weeks 0/2 and 129 patients were randomised at Week 4 to maintenance therapy with adalimumab 40 mg every other week or placebo

SO NIC

Clinical Remission Without Corticosteroids at Week 26

Primary Endpoint


Predicting response to anti-TNF therapy

<table>
<thead>
<tr>
<th>CLINICAL VARIABLE</th>
<th>NON RESPONSE</th>
<th>RESPONSE</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>UC vs. CD</td>
<td>14:8</td>
<td>6:66</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean age at diagnosis (years)</td>
<td>10.1</td>
<td>10.5</td>
<td>0.71</td>
</tr>
<tr>
<td>Gender M:F</td>
<td>8:14</td>
<td>40:32</td>
<td>0.12</td>
</tr>
<tr>
<td>Disease duration at start of IFX (months)</td>
<td>26</td>
<td>25</td>
<td>0.96</td>
</tr>
<tr>
<td>IMM use at start of IFX (%)</td>
<td>79%</td>
<td>92.8%</td>
<td>0.1</td>
</tr>
<tr>
<td>Duration of IMM at start of IFX (months)</td>
<td>12.7</td>
<td>15.3</td>
<td>0.57</td>
</tr>
<tr>
<td>pANCA +</td>
<td>76.2%</td>
<td>29%</td>
<td>0.0001</td>
</tr>
<tr>
<td>ASCA+</td>
<td>0%</td>
<td>46.9%</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

Guiding anti-TNF therapy

- Factors that increase or decrease the clearance of anti-TNF antibodies
  - Presence of anti-drug antibodies
  - Concomitant immunosuppressive therapy
  - High concentration of target antigen
  - Low serum albumin
  - High baseline CRP
  - BMI
  - Gender

- Severe UC (IV steroid refractory)

- Measuring antibody levels

Personalized medicine

- Monoclonal antibodies are susceptible to factors that affect their pharmacokinetics
  - Presence of anti-drug antibodies decrease the serum concentration of drug and can cause a 3-fold increase in drug clearance
  - Patients with detectable antibody have worse clinical outcomes than those without antibody

- Concomitant use of immunosuppressant therapy

- Pharmacokinetics to customize drug dosing for individual patients
Endpoints of therapy

- Clinical remission
- Endoscopic remission
  - Achievement of mucosal healing at week 8 led to significantly lower colectomy rate at 1 year.
  - Those patients also had significantly more steroid-free remission at one year

Goal now is Mucosal Healing
Safety: anti-TNFs

- Reactivation
- TB
- HBV
- Risk of infection
  - Intracellular pathogens: pneumocystis, atypical mycobacteria, listeriosis, legionella, coccidiomycosis, histoplasmosis, and aspergillus
- Lymphoma - unclear risk, ~6-7/10,000
- Demyelinating disorders
- Drug-induced lupus
- Arthralgias
- CHF

Risk: Benefit of Medications

- Need to consider risk of not going on medications

- Control inflammation
- Improve symptoms
- Improve quality of life
- Prevent relapse
- Reduce complications
- Reduce surgery
- Short-term side effects
- Long-term toxicity
- Cost

Potential Benefits
Potential Risks
Opportunistic Infections

Table 4. Association Between Use of Specific Medications and Odds for Opportunistic Infection

<table>
<thead>
<tr>
<th>Medication</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any medication¹</td>
<td>3.9 (2.2-6.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No medications</td>
<td>1.0 (reference)</td>
<td>.94</td>
</tr>
<tr>
<td>Mesalamine</td>
<td>1.0 (0.6-1.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No mesalamine</td>
<td>1.0 (reference)</td>
<td>.94</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>3.3 (1.8-6.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No corticosteroids</td>
<td>1.0 (reference)</td>
<td>.94</td>
</tr>
<tr>
<td>AZA/EMP</td>
<td>3.9 (2.0-7.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No AZA/EMP</td>
<td>1.0 (reference)</td>
<td>.94</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>4.0 (0.4-46)</td>
<td>.26</td>
</tr>
<tr>
<td>No methotrexate</td>
<td>1.0 (reference)</td>
<td>.94</td>
</tr>
<tr>
<td>Infliximab</td>
<td>4.4 (1.1-17)</td>
<td>.03</td>
</tr>
<tr>
<td>No infliximab</td>
<td>1.0 (reference)</td>
<td>.94</td>
</tr>
</tbody>
</table>

¹ORs and 95% CIs as assessed by multiple variable conditional logistic regression adjusting for age at first Mayo Clinic visit for IBD.
²P value using conditional logistic regression.
³Mesalamine, corticosteroids, AZA/EMP, methotrexate, infliximab, cyclophosphamide, or tazosimus.

Toruner et al. Gastroenterology April 2008

Opportunistic Infections

Table 5. Association of Immunosuppressive Medication* Combinations With Opportunistic Infection

<table>
<thead>
<tr>
<th>Combination</th>
<th>Cases (n = 100)</th>
<th>Controls (n = 200)</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>38 (38%)</td>
<td>129 (64%)</td>
<td>5.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>36 (38%)</td>
<td>99 (29%)</td>
<td>2.9 (1.5-5.3)</td>
<td>&lt;.001³</td>
</tr>
<tr>
<td>2 or 3</td>
<td>24 (24%)</td>
<td>12 (6%)</td>
<td>14.5 (4.9-43)</td>
<td>&lt;.001³</td>
</tr>
<tr>
<td>Age at first Mayo Clinic visit for IBD</td>
<td></td>
<td></td>
<td>1.1 (1.0-1.2)</td>
<td>.02</td>
</tr>
<tr>
<td>Specific combinations²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No medications</td>
<td>39 (29%)</td>
<td>129 (65%)</td>
<td>5.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids alone</td>
<td>16 (10%)</td>
<td>27 (14%)</td>
<td>2.3 (1.0-4.9)</td>
<td>.04</td>
</tr>
<tr>
<td>AZA/EMP alone</td>
<td>20 (20%)</td>
<td>31 (15%)</td>
<td>3.4 (1.5-7.5)</td>
<td>.002²</td>
</tr>
<tr>
<td>Infliximab alone</td>
<td>3 (3%)</td>
<td>2 (1%)</td>
<td>11.1 (0.8-148)</td>
<td>.07</td>
</tr>
<tr>
<td>AZA/EMP + corticosteroids</td>
<td>10 (10%)</td>
<td>6 (3%)</td>
<td>17.5 (4.5-64)</td>
<td>&lt;.001¹</td>
</tr>
<tr>
<td>AZA/EMP + infliximab</td>
<td>1 (1%)</td>
<td>5 (2%)</td>
<td>5.6 (0.1-19)</td>
<td>.72</td>
</tr>
<tr>
<td>AZA/EMP + infliximab + corticosteroids</td>
<td>5 (5%)</td>
<td>0 (0%)</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td>Age at first Mayo Clinic visit for IBD</td>
<td></td>
<td></td>
<td>1.1 (1.0-1.2)</td>
<td>.01</td>
</tr>
</tbody>
</table>

²P value using conditional logistic regression.
³P value using conditional logistic regression.

Toruner et al. Gastroenterology April 2008
Risk of Developing NH Lymphoma

Patient receiving anti-TNF + Immunomodulator Therapy for 1 year


Surgery in IBD

Ulcerative Colitis
- Remove entire colon/rectum
- Refractory disease
- Colon cancer
- Options
  - Total proctocolectomy (TPC) with ileostomy
  - TPC and ileal pouch-anal anastomosis (IPAA) → 2 vs 3 stage

Crohn's Disease
- Surgery does not cure
- Disease recurs after resection
- Less after an “ostomy”
- Resection of inflamed segments to treat complications (stricture, abscess, fistula) or refractory disease
Biosimilars

- Approved in Europe
- Success has yet to be determined
- Gives an excellent lower-cost option to those that do well
- Likely just as good for patients naïve to biologics

Other therapies on the horizon

- Stem cell
  - Local
  - Systemic
- Parasite therapy – natural immunomodulator
- Other biologic therapy
  - Microbial transplants (human donors vs cultured bacteria mention rePOOPulate trial)
Balancing the risks and benefits

Thank you!!

Questions...