Inflammatory Bowel Disease – What Every Clinician Needs to Know

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Conflict of Interest Disclosure

Adam S. Cheifetz

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<th>Company</th>
<th>Relationship</th>
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<td>Janssen</td>
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June 2016
Talk Overview

1. Brief review of Inflammatory Bowel Disease (IBD) including the epidemiology, pathophysiology, clinical features, and natural history

2. Discuss how the goals of care in IBD are evolving

3. Review the medical therapies available for IBD and the associated risks

4. Discuss the preventive care that is warranted in the patient with IBD
(Idiopathic) Inflammatory Bowel Disease

- Crohn’s Disease and Ulcerative Colitis

Indeterminate Colitis (IBD-u)

Other Colitides
- Microscopic colitis
- Collagenous
- Lymphocytic
- Diversion colitis
- Diverticular colitis
- Pouchitis

From the Johns Hopkins Digestive Disease Library
Epidemiology of IBD

- Approximately 1.6 million cases estimated in US
  - Divided equally between UC and Crohn’s disease
- Approximately 10,000 new cases diagnosed annually
- Onset at any age
- Peak incidence is in late adolescence and early adulthood
- Similar prevalence in males and females
Pathogenesis of IBD

Genetic Susceptibility

Altered Immune System

Environmental Triggers
Smoking in IBD

• Crohn’s disease
  – Increased risk in current smokers
  – Less responsive to treatment
  – More likely to develop recurrence

• Ulcerative Colitis
  – Smoking can protect against UC
  – Ex-smokers and non-smokers are more likely to develop UC
Nonselective NSAIDs Induce Clinical Relapse in IBD

- RCT of 209 IBD patients in clinical remission
- $\approx 20\% - 25\%$ relapse with nonspecific NSAIDs
  - Within 7 days
  - $1/3$ required steroids to induce remission
- Cox-2 specific NSAIDs and low dose ASA appear to be safe in the short term

<table>
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<tr>
<th>Disease Characteristics</th>
<th>Ulcerative Colitis</th>
<th>Crohn’s Disease</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Small intestine is NOT involved</td>
<td>“Mouth to anus”</td>
</tr>
<tr>
<td></td>
<td>Mucosal disease</td>
<td>Transmural</td>
</tr>
<tr>
<td></td>
<td>Rectal involvement</td>
<td>Rectal sparing</td>
</tr>
<tr>
<td></td>
<td>Continuous</td>
<td>Skip lesions</td>
</tr>
</tbody>
</table>

- **Proctitis**
- **Left-sided Colitis**
- **Pancolitis**

- **Upper GI**
- **Ileocolic**
- **Colon**

- **Small bowel**
- **Perianal**

- **5%**
- **50%**
- **20%**
- **30%**
- **33%**

**COPYRIGHT**
Progression of Crohn's Disease

Cumulative Probability (%)

Patients at risk:
N= 2002

Months
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192 204 216 228 240

Penetrating
Stricturing
Inflammatory

Up to 80% of CD Patients will Require Surgical Intervention and There Is a High Rate of Post-operative Recurrence


Clinical pearls

When to refer
• Rectal bleeding / iron deficiency anemia
• Night time symptoms
• Weight loss
• Strong family history of IBD or colon cancer

Patient with known IBD with GI symptoms
• Never assume symptoms are a flare of IBD
• Always rule out infection
• Assess for triggers of IBD
IBD Management Goals

Quality of Life

Endoscopic Remission

Induce Remission

Maintain Remission

Establish Diagnosis

Prevent Hospitalizations

Avoid Complications

Prevent Surgery

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Why Is Mucosal Healing Important Now?

- **In clinical trials**
  - Increasingly used as end point
  - More objective end point than clinical remission
- **In clinical practice**, mucosal healing can guide medical therapy
  - Assess disease activity
  - Growing evidence that mucosal healing is an important goal, because it appears to be associated with improved long-term outcomes
    - Decreased likelihood of a flare
    - Decreased progression to disease complications
    - Decreased need for surgery and hospitalization
- **Importance of mucosal healing still must be clarified**

Traditional Therapeutic Approach to IBD

- Surgery
- Anti-integrins
- Anti-TNF
- Prednisone
- 6-MP / AZA / MTX
- Budesonide
- Antibiotics (Crohn’s)
- Aminosalicylates
- Nutrition (Pediatric Crohn’s)
Sequential Approach to UC

Sequential Approach to UC

- Oral/Rectal Mesalamines
- Oral/Rectal Steroids
- AZA / 6-MP
- IV Steroids (hospitalized)
- IV Cyclosporine
- Anti-TNF
- Anti-TNF (non-hospitalized)
- Surgery
- Budesonide MMX

Vedolizumab (Entyvio)

- Selective adhesion molecule inhibitor (SAM-i)
- Monoclonal antibody to a4b7 integrin - intravenous
- Blocks inflammatory cells from getting to the intestines
- FDA approved summer 2014
- Appears effective
  - UC > Crohn’s
  - Maintenance > Induction
- Appears safe (as safe as anti-TNF, maybe safer)
- No cases of PML (progressive multifocal leukoencephalopathy)

# Medical Therapy of Crohn’s Disease

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- Safe and well tolerated
- Effective in UC, little to no data for CD
- Rare paradoxical response
- Rare interstitial nephritis
- Monitor renal function yearly
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- Few randomized controlled trials (small)
- Effective for perianal disease and suppurative complications
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- Ineffective for maintaining remission
- Side effects (increased serious infection and mortality)
- Budesonide is safer than prednisone, but only effective for ileal and right colonic disease
Corticosteroid Therapy for CD

Immediate Outcome* (n=74)

- Complete Remission 58% (n=43)
- Prolonged Response 32% (n=24)

1-Year Outcome (n=73†)

- Partial Remission 26% (n=19)
- Steroid Dependent 28% (n=21)
- No Response 16% (n=12)
- Surgery 38% (n=28)

* 30 D after initiating corticosteroid therapy
† 1 patient lost to follow-up

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Azathioprine (6MP) is Effective Treatment for Crohn’s Disease

Remission induced by prednisolone; tapered over 12 wk

- Takes up to 3 months to work
- Side effects:
  - Pancreatitis, Allergy
  - Bone marrow suppression
  - Hepatotoxicity
  - Infection
  - Increased risk of lymphoma (~4-5 fold over baseline)
  - Non-melanoma skin cancer
  - Abnormal PAP smears
  - Require frequent labs (CBC, LFTs)

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- 55% response rate
- **Contraindicated in pregnancy**
- Infection
- Monitor CBC and LFTs
- Bone marrow suppression
- Hepatitis
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Anti-TNFs for Crohn’s Disease

Monoclonal antibodies to tumor necrosis factor
Intravenous (IFX); Subcutaneous (ADA, CTP)
Similar efficacy < 40% of responders in remission at 1 year
Safety issues – infection, skin cancers, immunogenicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Placebo (n=170)</th>
<th>5mg/kg (n=172)</th>
<th>10mg/kg (n=157)</th>
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<tr>
<td><strong>Infliximab (Remicade)</strong></td>
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<tr>
<td>Remission at 26 weeks, %</td>
<td>17</td>
<td>40&lt;sup&gt;a&lt;/sup&gt;</td>
<td>47&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Remission at 56 weeks, %</td>
<td>12</td>
<td>36&lt;sup&gt;a&lt;/sup&gt;</td>
<td>41&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Adalimumab (Humira)</strong></td>
<td></td>
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<td></td>
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<td>Remission at 26 weeks, %</td>
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<td><strong>Certolizumab pegol (Cimzia)</strong></td>
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<tr>
<td>Remission at 26 weeks, %</td>
<td>26</td>
<td>42</td>
<td>.01</td>
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Safety Issues With Anti-TNF Therapy

- **Infection**
  - Serious and opportunistic (TB, fungal, bacterial, etc)
  - Ongoing infection is a contraindication
  - Need to be screened for TB and hepatitis B prior to initiation
- **Antigenicity** – antibodies to anti-TNF
- **Melanoma and non-melanoma skin cancers**
- **Psoriaform reactions**
- **Lymphoma?**
- **Demyelinating disorders, CHF, liver toxicity, autoimmunity (Lupus-like syndrome)**
SONIC:
Corticosteroid-free clinical remission at week 26

Primary Endpoint

Proportion of Patients (%)

AZA + placebo  IFX + placebo  IFX+ AZA

51/170  75/169  96/169

Columbel JF, et al NEJM. 2010
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Natalizumab (Tysabri): A Humanized, Monoclonal Ab Against α4 Integrins

• Effective for induction and maintenance of remission
  • Mod-Severe CD
  • TNF failures
• Progressive multifocal leukoencephalopathy (PML)
• FDA approved for mod-severe CD who failed anti-TNF
• Monotherapy only
• Closely monitored (TOUCH)
• 1:1000 Risk of PML

• JC antibody test available for risk stratification
Vedolizumab for Moderate to Severe Crohn’s Disease - Maintenance

- Week 52 endpoints

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (n=153)</th>
<th>Vedolizumab every 8 wks (n=154)</th>
<th>Vedolizumab every 4 wks (n=154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Remission, %</td>
<td>21.6</td>
<td>39*</td>
<td>36.4*</td>
</tr>
<tr>
<td>Clinical Response (CDAI 100)</td>
<td>30.1</td>
<td>43.5*</td>
<td>45.5*</td>
</tr>
<tr>
<td>Durable Clinical Remission at week 6 and 52, %</td>
<td>14.4</td>
<td>21.4</td>
<td>16.2</td>
</tr>
<tr>
<td>Steroid-free Remission</td>
<td>15.9</td>
<td>31.7*</td>
<td>28.8*</td>
</tr>
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</table>

Serious adverse events: 24.4% vs. 15.3%
Serious infections: 5.5% vs. 3%

Sandborn W. NEJM 2013
Surgical Indications

Ulcerative Colitis
- Complications
  - Perforation
  - Hemorrhage
  - Toxic megacolon
  - Cancer / Dysplasia
  - Symptomatic stricture
- Steroid dependence
- “Curative”
  - Permanent ileostomy
  - IPAA (ileal pouch anal anastomosis)

Crohn’s Disease
- Complications
  - Perforation
  - Abscess
  - Strictures
  - Fistulae
  - Malignancy / Dysplasia
  - Hemorrhage
  - Toxic megacolon
  - Perianal disease
- Steroid dependence
Is How We Treat IBD changing?

- Goals of care are evolving
  - Deep (clinical + endoscopic) remission
- Optimal treatment strategies still being defined
  - Individualized therapy (personalized medicine)
    - Concomitant immunomodulators?
    - Early aggressive therapy (top-down)?
    - Therapeutic drug concentration monitoring?
- Can we affect the natural history of IBD?
Personalized Medicine

Diagnosis

Risk stratification
- Clinical factors
- Serology/genetics
- Endoscopy

“High risk”
Early anti-TNF/combination therapy

“Low risk”
Budesonide or AZA

High-Risk Patients Should Be Considered for Early Anti-TNF or Combination Therapy

- Age at onset <40 years\(^1\)
- Smoker\(^2\)
- Perianal fistula\(^1\)
- Early steroid requirement\(^1,2\)
- Deep ulceration on endoscopy\(^3\)
- High-risk anatomy (foregut disease, extensive disease, rectal disease)\(^1,2\)

Anti-TNF combination with immunomodulator

• Improved outcomes at 1 year in biologic and immunomodulator naïve patients (SONIC and UC-SUCCESS)
  – Clinical and endoscopic remission
• Decreased antibody to anti-TNF formation
• Increased anti-TNF drug concentration

• However, risks of combination therapy
  – Hepatosplenic T-cell lymphoma
  – Opportunistic infections

Lichtenstein et al. Aliment Pharmacol Ther 2009;30:210-26
Rosh et al. Inflamm Bowel Dis 2007;13:1024-1030
Toruner et al. Gastroenterol 2008;134:929-36
Panaccione et al. Gastroenterol 2014;146:392-400
Early Treatment with anti-TNF

- Maintenance of remission
- Improved function and QOL
- Early promotion of mucosal healing to prevent complications and improve long-term outcomes

However,
- Majority of patients may not require more potent treatments initially
- Side effects of medications
- Cost

New Treatments

- Tofacitinib (JAK inhibitor)
- Ustekinumab (anti-IL-12/23)
- Ozanimod (S1P 1 and 5 receptor modulator)
- Mongerson (anti-SMAD7)
- Filgotinib (JAK inhibitor)
- Human mesenchymal stem cells

- Other approaches
  - *Trichuris suis*, fecal transplant, rifaximin
Vaccine Preventable Illnesses

- **Influenza** (injection – non-live; intranasal - live)
  - Yearly
  - Avoid intranasal (live) in immunosuppressed

- **Pneumococcus** (non-live)
  - Non-immunosuppressed: Consider PSV23 (Pneumovax) and PCV13 (Prevnar)
  - Immunosuppressed: PCV13 (Prevnar) followed ≥ 8 weeks later by PSV23 (Pneumovax). Booster PSV23 after 5 years.

- **TDaP** (non-live)
  - Every 10 years

Sands BE, et al. Inflamm Bowel Dis 2004
Vaccine Preventable Illnesses

- **HPV** (non-live)
  - Females and males age 9 – 26
- **Meningococcal** (non-live)
  - At risk (college, military)
- **Hepatitis B** (non-live)
  - Check immune status prior to anti-TNF therapy
  - Consider vaccination for all IBD patients
- **Hepatitis A** (non-live)
Vaccine Preventable Illnesses

- Varicella vaccine (*live*)
  - If no history of chicken pox and not immunocompromised
  - Can be considered in patients on “low dose immunosuppressants
    - Prednisone ≤ 20mg, azathioprine, 6-mp, methotrexate
  - *Avoid with anti-TNF*

- Zostavax (*live*)
  - Age > 50
  - Can be considered in patients on “low dose immunosuppressants
    - Prednisone ≤ 20mg, azathioprine, 6-mp, methotrexate
  - *Avoid with anti-TNF*
Bone Health:

Osteopenia & Osteoporosis is Common in IBD

- Osteopenia ≈ 50%; Osteoporosis ≈ 15%
- Fracture risk slightly increased

- Check Bone Density (DXA scan)
  - Steroids (> 3 months)
  - Post-menopausal women
  - Men > 65
  - Malnourished, very thin, ammenorrhic

- Treat and Follow closely
- Calcium and vitamin D for patients on corticosteroids
- Assess vitamin D level

Lichtenstein, IBD 2006
Cancer Prevention

- **Cervical cancer**
  - Yearly Pap if immunosuppressed

- **Skin cancer**
  - Yearly dermatology exam if immunosuppressed
  - Sun-exposure precautions

- **Colon cancer**
  - Risk is ≈ 2-3 times higher than general population
  - Occurs at younger age
  - Risk is same for UC and CD
  - Certain factors increase risk of colon cancer
    - Extent of disease (1/3), duration of disease (8-10 years), PSC, inflammation
  - Surveillance colonoscopies for patients with 1/3 colon involved
    - Every 1-3 years after 8-10 years of disease

_Farraye et al. Gastroenterology 2010_
Therapy related monitoring

- **Mesalamines**
  - Yearly renal function (also CBC, LFTs with sulfasalazine)
- **Thiopurines**
  - CBC, LFTs (every 3 months; more frequent at initiation)
- **Methotrexate**
  - CBC, LFTs (every 3 months; more frequent at initiation)
  - Periodic renal function
- **Anti-TNF**
  - TB screening prior to initiation; yearly assessment of risk factors
  - Hepatitis B screening prior to initiation
  - Periodic CBC, LFTs
- **Natalizumab**
  - JC virus prior to initiation and following on therapy
  - TOUCH program
  - CBC, LFTs
Summary

- UC: colon, mucosal, continuous
- Crohn’s: “mouth to anus”, transmural, skip lesions
- Avoid nonselective NSAIDs
- Smoking cessation in Crohn’s disease
- Major advances in treatment of IBD
- Goals of care are evolving—endoscopic healing, early aggressive therapy, combination therapy, therapeutic drug monitoring
- Remember to vaccinate patients
- Screen and treat for osteopenia / osteoporosis
- Cancer surveillance
  - Colon cancer, skin cancer (on IMM), and cervical cancer (on IMM)
- Monitor for complications of IBD medicines
Which of the following are characteristics of Crohn’s disease and not UC?

A. Small bowel involvement
B. Fistulas
C. Skip lesions
D. Perianal involvement
E. Rectal sparing
F. All of the above
Patients with IBD are at increased risk of which of the following?

A. Osteoporosis
B. Colon cancer
C. Ankylosing spondylitis
D. Venous thrombosis
E. All of the above
Side effects of IBD medications include?

A. Bone marrow suppression
B. Lymphoma
C. Pancreatitis
D. Infection
E. PML
F. All of the above