IBD: What Primary Care Providers Should Know

Amy Barto, M.D.
Center for Inflammatory Bowel Disease
Lahey Hospital and Medical Center
Disclosures

- I am a member of the speaker bureau for:
  - Abbvie

- I am currently involved in clinical trials with:
  - Celgene
IBD: What Primary Care Providers Should Know

**OBJECTIVES:**

1. Discuss the types of inflammatory bowel disease - review similarities and difference in terms of disease progression and treatment.

2. Present the diagnostic criteria and evaluation of these disorders.

3. Discuss the role of the primary care provider in managing/co-managing patients with inflammatory bowel disease.
Presentation Outline

- Background of inflammatory bowel disease
- What causes IBD?
- Crohn’s vs. ulcerative colitis
- Environmental triggers
- Extraintestinal manifestations
- Symptoms of IBD
- WHEN TO REFER FOR SUSPECTED IBD
- How to diagnose
- Treatment strategies
- Biologics for IBD
- Primary care management of IBD patients
Inflammatory Bowel Disease

- Total number of cases
  - Approx 1.4 million cases estimated in the United States
    - Ulcerative colitis (UC): ~50%
    - Crohn’s disease (CD): ~50%
- Males and females equally affected; mainly 15–35 yrs for CD (5–10 years later for UC)
- Genes, environment, race and ethnicity are factors
- Disease course
  - Chronic, lifelong disease without a medical cure
  - Surgical intervention in at least 2/3 of Crohn’s patients

1930-1960’s

Early Ideas: The Psychosomatic Hypothesis (UC)

- “Well-marked time relationship between ..emotional disturbance and symptoms.”

- UC patients “couldn’t cope, giving up.” “Diarrhea is substituted for real accomplishment.” “…childish, dependent personality”

- “Degree of difference so gross as to make a control group unnecessary.”
  -- Wittkower, BMJ, 1938
Current Theories of the Pathogenesis of IBD

Genetic Predisposition

Ulcerative Colitis

Crohn’s Disease

IBD

Immunologic Abnormalities

Environmental Factors

Genetic Advances

- **NOD2/CARD15** (products of 1st IBD gene)
- **Up to 39 genes identified**
  - In the (near) future, we will have a good understanding of how these genes lead to the development of IBD
  - Genes may help unlock why people with IBD present so differently
  - Gene therapy may become a reality
- **Currently there is no standard genetic testing for IBD**
How IBD Develops: A “Two Hit Hypothesis”

Genetic predisposition for IBD—Hit #1

The immune system reacts abnormally to the trigger--Hit #2
(when it should have just dealt with the insult and moved on)

Inflammatory cascade is activated and remains revved up

Inflammatory cells circulate through the body and attack the gut

The lining of the GI tract becomes swollen, with a visible rash on the surface

Development of abdominal pain, diarrhea, blood in the stools

Trigger--??Infection, true cause of IBD unknown
Globalization of IBD

IBD: Epidemiology

- High Incidence
- Moderate Incidence
- Unknown
Helminthic Ova in Active Crohn’s Disease

- 24 week open study
- 29 pts CDAI 220-450
- 2500 *T. suis* ova q 3 wks

**Response**
- >100 point drop in CDAI

**Remission**
- CDAI<150

Week 12 and Week 24 response and remission rates:

- Week 12: 68% Response, 70% Remission
- Week 24: 72% Response, 74% Remission
- Week 24: 76% Response, 78% Remission
Environmental Triggers

- Infections
- Antibiotics
- NSAIDs
- Diet
- Smoking
- Stress
Smoking and IBD

- Smoking makes Crohn’s worse
  - Worse prognosis, more aggressive
  - Higher risk of:
    - Need for immunosuppressive therapy
    - Surgery
    - Higher postoperative recurrence rates
  - Quitting smoking can be as powerful as adding a medication

- Smoking makes UC better (What?!)
  - Often first diagnosed within 5 yrs after quitting
  - ?Nicotine is key ingredient
  - Nicotine patches, enemas limited by side effects
  - Don’t get any ideas---smoking will still kill you
NSAIDs Can Flare IBD

- Aspirin
- Ibuprofen
- Naproxen
- Celecoxib
- Rofecoxib
- Nabumetone
- Diclofenac
- Piroxicam
- Etodolac
- Ketoprofen
- Meloxicam
- Oxaprozin
- Sulindac
- Valdecoxib
- Indomethacin

- Aspirin
- Ibuprofen
- Motrin
- Advil
- Aleve
- Naprosyn

Tylenol (acetaminophen) is OK
Differences Between Crohn’s and Ulcerative Colitis
# Crohn’s vs. Ulcerative Colitis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Crohn’s Disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of involvement</td>
<td>Throughout the GI tract</td>
<td>Colon only</td>
</tr>
<tr>
<td>Pattern of involvement</td>
<td>Patchy disease</td>
<td>Continuous disease</td>
</tr>
<tr>
<td>Level of bowel involved</td>
<td>Full thickness of bowel wall</td>
<td>Mucosa (surface lining)</td>
</tr>
<tr>
<td>Granuloma cell</td>
<td>Present</td>
<td>Not present</td>
</tr>
<tr>
<td>Additional features</td>
<td>Stricture, abscess, fistula, perianal disease</td>
<td></td>
</tr>
</tbody>
</table>

Up to 2-5% of patients diagnosed with UC may have Crohn’s—This matters most when considering colectomy
Colonoscopy for Ulcerative Colitis

Mild-Moderate

Severe
Distribution of Ulcerative Colitis

and Proctosigmoiditis

46%

17%

37%

aka “pancolitis”
Distribution of Crohn’s Disease

- Colonic: 20%
- Ileal: 30%
- Ileocolic: 50%
Extraintestinal Manifestations

- Musculoskeletal
- Ophthalmologic
- Dermatologic
- Genitourinary/renal
- Hepatobiliary
- Cardiovascular
- Pulmonary
- Neurologic
When To Refer for IBD:

Act Quickly, Don’t Delay
Timing is Everything

By time of clinical symptoms (long before diagnosis), irreversible scarring/damage is already happening
Delay in Diagnosis of IBD

- Diagnosis can be delayed from more than 10 months to more than 2 years
- By that time, irreversible scarring has also started happening
- Patients with a prior diagnosis of IBS had more delay
- Can lead to:
  - Increased duration of symptoms
  - Progression of disease with complications
  - Delay in treatment/inappropriate treatment
Complications of IBD

- Crohn’s complications
  - Strictures
  - Abscess
  - Fistulas
  - Need for surgery

- UC complications
  - Toxic megacolon
  - Perforation
  - Hemorrhage
  - Need for surgery
Culling the (IBS) Herd for IBD

How to recognize alarm symptoms
Is it IBD or IBS?

- A 41 year old woman visits your office with complaints of abdominal pain, diarrhea and urgency on and off for 4 months. She has tried over the counter remedies and has seen a nutritionist but symptoms persist.

- Symptoms are worse when she drinks milk or when she is stressed out

- Probiotics have helped a little

- She is otherwise healthy
Upon further questioning, patient also states:

- Has had about a 10 lb unintentional weight loss
- Her joints are achy
- She has had low grade fevers
- Occasionally she wakes up at night to have diarrhea
- No blood in her stools
The Plot (not the stool) Thickens

- **Physical exam**
  - Tenderness to palpation RLQ

- **Labs**
  - Mild anemia
  - Elevated ESR and CRP

- **Imaging Studies**
  - CT scan shows thickening of the terminal ileum
Unlike IBD or celiac disease, IBS does **NOT** involve inflammation.

Likely diagnosis: Terminal Ileal Crohn’s
## Signs and Symptoms of IBD and Other GI Conditions May Overlap

<table>
<thead>
<tr>
<th></th>
<th>Celiac disease</th>
<th>IBS</th>
<th>CD</th>
<th>UC</th>
<th>Small bowel bacterial overgrowth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Weight loss</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Bloating</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Anemia</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Constipation</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucus in stool</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flatulence</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Blood in stool</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td></td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Alternating diarrhea/constipation</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Red Flags: Begin Consultation with a Gastroenterologist

Symptoms and History
- Chronic/bloody diarrhea
- Rectal urgency/bleeding
- Unintentional weight loss
- Fever
- Family history of IBD

Clinical Exam
- Anemia
- Abdominal tenderness/mass

EIMs
- Arthritis
- Uveitis
- Scleritis
- Pyoderma gangrenosum
- Erythema Nodosum
Diagnosis of IBD

- **Symptoms:**
  - **Location within the gut:**
    - Abdominal pain (RLQ for small bowel Crohn’s)
    - Nausea/vomiting (strictures with obstruction)
    - Diarrhea, often bloody in UC
  - **Systemic effects of more severe inflammation:**
    - Weight loss, malnutrition, anemia
    - Extraintestinal manifestations (joints, skin, etc)
    - Fatigue, malaise, depression
Diagnosis of IBD

- Laboratory findings:
  - Anemia, low albumin, elevated WBC
  - Elevated ESR, CRP (not always)

- Serologic testing for IBD:
  - Good concept in theory
  - Poor correlation with clinical picture
  - Perhaps will become a valuable **prognostic** tool
Diagnosis of IBD

- Radiologic testing:
  - Small bowel follow through
  - Barium enema
  - CT scan/CT enterography
  - MRI/MR enterography

- Endoscopic studies:
  - Upper endoscopy/colonoscopy
  - Small bowel capsule endoscopy (pill camera)
Treatment Options for IBD
Treatment Options for IBD

- Biologics
- Surgery
- Bowel Rest
- Systemic Corticosteroids
- Non-systemic Steroids
- Antibiotics
- Aminosalicylates
- AZA/6-MP/MTX

Levels:
- Severe
- Moderate
- Mild
Step-Up vs. Early Aggressive Therapy

Time Sensitive Approach

- Avoid prolonged use of steroids if not working or not able to taper
- Start with less potent therapies if able but move quickly if not responding
- Use stronger therapy earlier or as the first option for sicker patients
The Newest Frontier:
Biologic Therapy
Biologics in General

- Manufactured antibodies to specific proteins
- Biologics target individual steps in the inflammatory cascade
  - Steroids = nuclear bomb (hit the bad and the good)
  - Biologics = guided missile (more selective)
- Our first biologic was Remicade back in 1998
  - Truly a breakthrough in the treatment of Crohn’s
Finally — Choices!

Now currently available:

- Infliximab (Remicade) 1998
- Adalimumab (Humira) 2007
- Certolizumab pegol (Cimzia) 2008
- Natalizumab (Tysabri) 2008
- Golimumab (Simponi) 2013
- Vedolizumab (Entyvio) 2014
When to Use a Biologic?

- The patient is sick enough upon presentation to leap over other meds

- When conventional therapy has failed:
  - Patients who don’t respond to steroids or can’t taper off of them
  - Other immunomodulators have been tried
    - Azathioprine (Imuran, 6-MP)
    - Methotrexate
One Class of Biologics: Anti-TNF–α Therapy

- Tumor necrosis factor-α (TNF-α) is an important cytokine in the pathogenesis of Crohn’s disease
- It is elevated in the stool, mucosa, and blood of patients with Crohn’s disease
- Clinical trials have demonstrated that monoclonal antibodies against TNF-α are effective for both induction and maintenance of clinical remission in patients with moderate-to-severe Crohn’s disease

Anti-TNF alpha Biologics

75% human

Mouse Human

Infliximab (Remicade®)

Certolizumab pegol (Cimzia®:CDP870)

PEG: Polyethylene glycol

Adalimumab (Humira®:D2E7)

100% human

Mouse Human

CH1

VL 

VH
Vedolizumab (Entyvio)

- Approved for Crohn’s and UC in May 2014
- Selective adhesion molecule
  - Inhibits leukocyte adhesion/migration from bloodstream into gut mucosa/tissue
  - Works ONLY on the gut
- Indication:
  - Induce and maintain clinical remission/response in patients with moderate-severe IBD unresponsive to conventional therapy
  - Do not have to have failed another biologic
- Favorable side effect profile
  - Thus far no increased risk of serious infection or malignancy
Vedolizumab

Inhibiting Diapedesis

leukocyte

blood vessel

integrins

adhesion molecule inhibitor

endothelial cell

gut mucosa
## Dosing/Administration: Induction

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Induction Dosing</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remicade</td>
<td>5 mg/kg week 0, 2, 6</td>
<td>IV</td>
</tr>
<tr>
<td>Humira</td>
<td>160 mg week 0</td>
<td>SQ</td>
</tr>
<tr>
<td></td>
<td>80 mg week 2</td>
<td></td>
</tr>
<tr>
<td>Cimzia</td>
<td>400 mg week 0, 2, 4</td>
<td>SQ</td>
</tr>
<tr>
<td>Simponi</td>
<td>200 mg week 0</td>
<td>SQ</td>
</tr>
<tr>
<td></td>
<td>200 mg week 2</td>
<td></td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>300 mg week 0, 2, 6</td>
<td>IV</td>
</tr>
</tbody>
</table>
# Maintenance Dosing

<table>
<thead>
<tr>
<th>Biologic</th>
<th>Maintenance Dosing</th>
<th>Escalation Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remicade</td>
<td>5 mg/kg q8wks</td>
<td>10 mg/kg q4wks</td>
</tr>
<tr>
<td>Humira</td>
<td>40 mg every other week</td>
<td>40 mg every week</td>
</tr>
<tr>
<td>Cimzia</td>
<td>400 mg q4wks</td>
<td>None</td>
</tr>
<tr>
<td>Simponi</td>
<td>100 mg q4wks</td>
<td>None</td>
</tr>
<tr>
<td>Entyvio</td>
<td>300 mg q8wks</td>
<td>300 mg q4wks</td>
</tr>
</tbody>
</table>
Options for Crohn’s vs. UC

**Crohn’s**
- anti-TNFs
  - Remicade
  - Humira
  - Cimzia
- Tysabri
- Entyvio
- Coming soon
  - Stelara
  - Mongersen
  - Fecal transplant

**UC**
- anti-TNFs
  - Remicade
  - Humira
  - Simponi
- Entyvio
- Coming soon
  - Amiselimod
  - Fecal transplant
<table>
<thead>
<tr>
<th>Medication</th>
<th>Category</th>
<th>Pregnancy</th>
<th>Breastfeeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-ASA</td>
<td>B</td>
<td>Safe</td>
<td>Safe</td>
</tr>
<tr>
<td>Flagyl</td>
<td>B</td>
<td>Safe(^1)</td>
<td>Safe</td>
</tr>
<tr>
<td>Infliximab</td>
<td>B</td>
<td>Safe</td>
<td>Safe</td>
</tr>
<tr>
<td>Cipro</td>
<td>C</td>
<td>Debated(^2)</td>
<td>Not Safe</td>
</tr>
<tr>
<td>Steroids</td>
<td>C</td>
<td>Safe</td>
<td>Safe</td>
</tr>
<tr>
<td>AZA/6MP</td>
<td>D</td>
<td>Safe</td>
<td>Not Safe</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>C</td>
<td>w/caution</td>
<td>Not safe</td>
</tr>
<tr>
<td>MTX</td>
<td>X</td>
<td>Not Safe</td>
<td>Not Safe</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>X</td>
<td>Not Safe</td>
<td>Not Safe</td>
</tr>
</tbody>
</table>

1. 2\(^{\text{nd}}\) and 3\(^{\text{rd}}\) trimester
2. Can affect cartilage development
Safety Is Key

Side Effect Profiles of Biologics
Safety Information: Infections

- Risk of multiple infections:
  - Tuberculosis:
    - All patients have a PPD or Quantiferon gold blood test prior to start
    - High risk patients get a chest x-ray
    - Treat latent TB prior to start
  - Reactivation of hepatitis B (all patients get checked before starting)
  - Other fungal infections (coccidiomycosis, histoplasmosis)
  - Viruses/flu, shingles
  - Bacteria (pneumonia, cellulitis, sinusitis, etc)
  - Crohn’s related abscess
- Infections can lead to sepsis and death
Safety Information: Malignancy

- Increased risk of certain cancers:
  - Lymphoma
    - 3.5 fold higher risk than average population
    - Still rare: 4-6 out of 10,000 patients (baseline 2-4/10,000)
  - Non-melanoma skin cancers
    - Basal cell, squamous cell
    - Yearly dermatology checks, sunscreen

- No increased risk:
  - Solid organ tumors (breast, prostrate, etc)
  - Likely minimal to no risk of melanoma
Additional Safety Information

- Hypersensitivity reactions, including anaphylaxis:
  - Reactions can be delayed by days to weeks
  - Can include rashes, joint symptoms, fever

- 3.5 fold higher rate of lymphoma than expected in the general population—*still rare*

- Neurologic diseases (patients with MS can only get Tysabri or Entyvio, not the others)

- Pancytopenia, aplastic anemia

- Worsening of congestive heart failure
  - In some cases CHF was new-onset

- Rare autoimmune reactions including lupus-like syndrome

- Rare risk of liver toxicity
Protecting Patients on Biologics

- **Maintenance immunizations:**
  - Seasonal flu and H1N1 vaccines
  - Prevnar 13 every 5 years

- **Avoid live vaccines:**
  - Zostavax
  - Seasonal flu and H1N1 nasal mist
  - MMR

- **Coordinate vaccines for travel**
Case Study: Matt

The Diarrhea Comes Back to Haunt You…
Matt

- 25 year old software engineer
- Quit smoking a few years ago
- Took Advil pretty regularly for back pain
- Developed bloody diarrhea, diagnosed with UC
- Failed Asacol HD, required steroids
- Opted for Remicade which worked well
Matt

- Did great for over a year
- Now has diarrhea again
- Up to 10 stools a day with no blood
- No recent change in diet
- No other alarm symptoms
- His GI is on vacation
- So he is calling YOU
Matt: Differential Diagnosis

- Ulcerative colitis flare
- Infectious cause
- IBS
- Dietary indiscretion
  - Excessive fiber
  - Dairy
  - Artificial sweeteners
  - Increased caffeine
- Other unrecognized autoimmune disease
  - Celiac disease
Good Call

- No blood probably less likely a UC flare
- You order stool studies for infections
- C. diff is positive
- Treat with Flagyl and symptoms improve
Keep Your Differential Broad

- Consider that symptoms could be from many things
  - The disease activity itself
  - A complication of the disease
  - A complication of the medications used to treat the disease
  - Something else like IBS or a change in diet
Primary Care Follow Up of IBD

- Management of disease/medication complications
  - Immunizations
  - Steroid side effects
    - Yearly ophthalmology exams
    - Monitor for steroid-induced diabetes
    - Bone densities
  - Cancer prevention
    - Encourage regular colonoscopies for UC/Crohn’s colitis
    - Dermatology follow up
Primary Care Follow Up of IBD

- Encourage smoking cessation and NSAID avoidance
- Minimize radiation exposure (especially CT scans)
- Multidisciplinary approach
  - Work together as a team (patient, PCP, specialists)
  - Refer for nutritional, psychosocial support
  - Be open to alternative therapies

- Improve quality of life
Summary

- Crohn’s and UC are complex, lifelong diseases
- It is important to recognize signs of IBD and refer quickly
- Treatment options continue to expand
- Primary care providers play a vital role
  - Monitoring for disease/medication complications
  - Keeping patients safe through prevention
  - Understanding that these patients require ongoing multidisciplinary support
Thank You!