Inflammatory Bowel Disease

Crohn’s Disease and Ulcerative Colitis

Judith Collins, MD
Assoc Professor of Gastroenterology & Hepatology
Inflammatory Bowel Disease Program, OHSU
Today’s Objectives

• Define IBD, its potential causes and diagnosis
• Discuss management and treatment
• Discuss complementary and alternative medicine
• Mention the Pregnant Patient
• Review role of diet and nutrition in IBD
• Answer questions
What are Inflammatory Bowel Diseases?

- Inflammatory including Crohn’s disease and ulcerative colitis
  - 1.6 million Americans
  - 70,000 new cases each year
  - 1 in 200 people

- Symptoms, course of disease, and prognosis differ from one person to the next
Potential Factors to Consider
Spectrum of IBD

Crohn’s Disease
- Patchy, full-thickness inflammation
- Mouth to anus involvement
- Extra-intestinal manifestations

Ulcerative Colitis
- Continuous, superficial inflammation
- Colon and/or rectum
- Extra-intestinal manifestations

Indeterminate Colitis
10%-15%
Inflammatory Bowel Disease: Pathophysiology

- Idiopathic autoimmune diseases characterized by chronic inflammation of the bowel.

- While exact etiology is unknown, we are gaining understanding. Complex interaction of:
  - Genetic susceptibility
    (>100 Genes Associated w/IBD – UC/CD Overlap)
  - Environmental trigger(s)
    (? Infectious Trigger / Gut Microbiome)
  - Impaired immune regulation
    (Failure of immune tolerance)
Epidemiology of IBD

Prevalence: Influence by geography, ethnicity.

- ~500 cases/100,000 in the US population
- Divided equally between UC & Crohn’s
- Men and women affected equally

Incidence:

- Peak onset of disease is BIMODAL
  → Ages 15-25 and 55-65 years of age
Ulcerative Colitis

- Inflammation of the colon **ONLY**
- Does not involve the small intestine (Exception: “Backwash Ileitis”)
- Inflammation begins at the rectum and spreads proximally
- Inflammation is confluent and continuous
Ulcerative Colitis: Distribution

Rectum almost always involved
Clinical Presentation of UC

- Rectal bleeding - most common symptom
- Bloody diarrhea
- Abdominal cramping
- Tenesmus (persistent, ineffectual rectal spasm ~urgency)
- Fever / Sweats
- Symptoms depend on extent/severity of inflammation
UC: Differential Diagnosis

* Infectious diarrhea
* Ischemic colitis
* Irritable bowel syndrome
* Crohn’s disease
* Effect of Medications (NSAIDs, antibiotics)
* Diverticulitis
* GI malignancy
<table>
<thead>
<tr>
<th>UC - Spectrum of Disease</th>
<th>Normal</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<td><img src="image1" alt="Normal" /></td>
<td><img src="image2" alt="Mild" /></td>
<td><img src="image3" alt="Moderate" /></td>
<td><img src="image4" alt="Severe" /></td>
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<tr>
<td>Edema</td>
<td>Erythema</td>
<td>Friability</td>
<td>Granularity</td>
<td>Erosion</td>
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<td>denuded mucosa with pseudopolyps</td>
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Crohn’s Disease
(Regional Enteritis, Terminal ileitis, Granulomatous Colitis)

* Chronic, **TRANSMURAL** inflammation

* May involve **any portion** of the GI tract from the “mouth to the anus”

* Rectum **not** always involved – often spared

* Skip lesions common

* Perianal disease may occur
Crohn’s Disease: Sites of Involvement

- 40% Ileocolonic (ileum + colon)
- 30% Small bowel only –most often terminal ileum
- 25% Colon only
- 5% Gastroduodenal

TI is most commonly involved site in CD!
Crohn’s Disease: Clinical Presentation

• Diarrhea (usually non-bloody)

• Abdominal pain and tenderness (esp. RLQ)

• Weight loss

• Fever, nightsweats

• Iron deficiency anemia

• Obstructive symptoms → nausea/vomiting, postprandial pain
Crohn’s Disease: Differential Diagnosis

• Small bowel lymphoma
• Appendicitis
• Infection
• Celiac sprue
• Irritable bowel syndrome
• Ulcerative colitis
Endoscopic Findings

- Skip lesion
- Stellate ulcer
- Deep linear ulcers
- Cobblestoning
IBD: Diagnosis

• Clinical history
• Physical examination
• Endoscopic findings
• Pathology
• Radiographic findings
• Laboratory tests
• Stool studies (eval for infection)
IBD or infection?

Stool studies: C. Diff, C+S, O+P; biopsy stains + cultures

-VERY important - even in established IBD patient:
  -Clostridium difficile
    → Recent antibiotics predispose but not necessary in IBD
    → Test with flare of colitis symptoms

-Acute colitis: Shigella, Salmonella, Campylobacter, E. coli 0157:H7

-TB especially in endemic regions

-Other infectious mimics of IBD:
  -Amebiasis, Yersinia, CMV, HIV
  -Rectal STDs (HSV, N. gonorrhea)
## UC vs. CD: Pathologic Findings

<table>
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<tr>
<th>Ulcerative Colitis:</th>
<th>Crohn’s Disease:</th>
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<td>- Superficial inflammation (mucosa and submucosa)</td>
<td>- Granulomas present in ~20-40% (Pathognomonic, but not required)</td>
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<tr>
<td>- Inflammation is NOT transmural</td>
<td>-- Inflammation is transmural</td>
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Non-Caseating Granulomas in a Crohn’s disease patient:

- Ileal Granulomas (400x)
- Cecal Granulomas (400x)
Complications of IBD

- Colon cancer
- Toxic megacolon
- Strictures
- Fistulas
- Abscesses
Risk Factors for Colon Cancer in IBD

- Duration, Extent, and Severity of colonic disease
- Co-existing primary sclerosing cholangitis (PSC)
- Family history of colon cancer
- Dysplasia on biopsy

Risk Reduction:

- Tight control of inflammation
- Dysplasia surveillance colonoscopy with biopsies
IBD Complications: Toxic Megacolon

- Occurs in severe colitis (UC or CD – or C. diff)
- Often a dilated colon, but not always
- “Toxic” clinical picture resembles sepsis
- Associated with a fulminant clinical course

Treatment:
- Urgent surgical consultation
- IV antibiotics, fluid resuscitation
- Possible colectomy if no rapid improvement
CD - Clinical Patterns

- Pain
- Tenderness
- Diarrhea
- Low-grade fever
- Weight loss (anorexia)
Strictures:
- Narrowing of Bowel Lumen (common in Crohn’s)
- Inflammatory vs. fibrotic

Obstruction

- Post-prandial cramps
- Distention
- Borborygmi
- Vomiting
- Weight loss (food avoidance)
Fistulization

- **Enterocutaneous**
  Drainage via scar
- **Perianal**
  Pain, drainage
- **Rectovaginal**
  Drainage: feces and/or air
- **Enterointeric**
  May be asymptomatic
- **Enterovesical**
  Recurrent UTIs, pneumaturia
- **Retroperitoneal**
  Psoas abscess signs:
  back, hip, and thigh pain; limp
IBD Complications: Fistulas

• Seen in Crohn’s, not characteristic of UC

• May extend from any involved segment of bowel or colon to the:
  
  - Skin (enterocutaneous)
  
  - Vagina (rectovaginal)
  
  - Bladder (enterovesicular)
  
  - Adjacent loops of bowel
    (enterocolonic or enteroenteric)

→ Abscess can complicate penetrating (fistulizing) disease
Extraintestinal Manifestations

- Conditions outside the intestinal tract assoc w/ IBD

- May precede, accompany or follow IBD symptoms
  (Some are associated w/disease activity, some not)

**Rheumatologic**
- Peripheral arthropathy
- Sacroileitis
- Ankylosing spondylitis

**Skeletal**
- Osteoporosis
- Osteomalacia

**Dermatologic**
- Erythema nodosum
- Pyoderma gangrenosum

**Ophthalmological**
- Uveitis
- Episcleritis

**Renal**
- Nephrolithiasis
- Amyloidosis (uncommon)

**Hepatobiliary**
- Primary sclerosing cholangitis (PSC)
Extraintestinal Manifestations of IBD

Rheumatologic Manifestations
- Peripheral arthropathy
- Sacroileitis
- Ankylosing spondylitis

Sacroiliitis
- Can be asymptomatic and found incidentally on X-rays

Ankylosing spondylitis (AS)
- Insidious onset of low back pain, morning stiffness; progressive.
- HLA-B27 positive in 50%-75% of IBD patients with AS

Peripheral Arthritis
- Monoarticular
- Asymmetrical
- Large > small joint
- No synovial destruction
- No subcutaneous nodules
- Seronegative
Extraintestinal Manifestations of IBD

Dermatologic
- Erythema nodosum
- Pyoderma gangrenosum

Erythema Nodosum: ~5-10% of IBD
  - Raised, tender, red nodules
  - Commonly over anterior tibia.

Pyoderma Gangrenosum: <5% of IBD; legs, peristomal
  - Ulcerated, violaceous borders
  - Pathergy
Extraintestinal Manifestations of IBD

- Uveitis
- Episcleritis

Anterior Uveitis

Episcleritis
Hepatobiliary

- Primary sclerosing cholangitis (PSC)

**Extraintestinal Manifestations of IBD**

Chain of Lakes: Biliary strictures in PSC (seen by ERCP)
Thromboembolic Complications

Patients with active IBD are at high risk for thromboembolic events:

- Venous > arterial clotting may occur
- Can be serious / life threatening (DVT/PE or CNS)
- Correlates with active inflammatory burden, especially colonic.
- DVT Prophylaxis for all IBD inpatients!
IBD: Medical Therapy

Major Drug Categories:

- Aminosalicylates (5-ASA agents)
- Corticosteroids
- Immunomodulators
- Antibiotics
- Biologics
- “Combination Therapy”: Biologic + Immunomodulator
- Many novel agents in clinical trials!

Goals of Therapy:

- INDUCE remission
- MAINTAIN remission
- Enhance quality of life
- Avoid adverse events and toxicity
Aminosalicylates (5-ASA agents)

*(ie, mesalamine and its proprietary preparations)*

- Used in the treatment of UC & CD (better data in UC)
- Reduce intestinal inflammation
- Available in oral and topical preparations
- Monitor renal function q6-12 months

**Indications:**
- Induction therapy in mild to moderate IBD
- Maintenance therapy, esp in UC
IBD Therapy: Corticosteroids

(ie, prednisone, prednisolone, methylprednisolone)

- Used to treat both UC and CD
- Rapid onset anti-inflammatory
- **Indication**: Moderate to severe acute flares of UC/CD

**Warning:**

- Significant side effects, especially long-term use
- **NO** role in maintenance therapy of IBD
- Use “steroid-sparing” maintenance meds to prevent recurrent need for steroids
IBD Therapy: Antibiotics

*(ie, metronidazole, ciprofloxacin)*

- Used primarily in the treatment of CD
- Especially useful in perianal/perirectal CD and fistulizing CD
IBD Therapy: Immunomodulators
6-Mercaptopurine, Azathioprine, Methotrexate[+Folic Acid]

Mechanism of action: Suppress immune system

- Onset of action is delayed (generally 2-6 months)

Indications
- Maintenance of remission in UC/Crohn’s
- Steroid-sparing agent
- Fistulizing disease

- Associated with multiple toxicities, require monitoring of CBC, LFT’s long-term – but usually well-tolerated.

Risks Include: Infection, pancreatitis, lymphoma, skin cancer, leukopenia, LFT abnormalities
IBD Therapy: Biologics
*infliximab, adalimumab, certolizumab, golimumab*

- Target **specific** inflammatory pathways

- **Indications:**
  
  → Moderately to severely active CD (mucosal and fistulizing) and UC

**Risks Include:** Infection, lymphoma, skin cancer, infusion/injection reactions, loss of response/immunogenicity

→ TB, Hep B screening prior to therapy
IBD Therapy: anti-TNF Biologics

**infliximab, adalimumab, certolizumab, golimumab**

- Target specific inflammatory pathway

- **Indications:**
  - **Crohn’s (IFX, ADA, CER)**
    → Moderate to severely active mucosal and fistulizing disease
  - **UC (IFX, ASA, GLB)**
    → Moderate to severely active UC

  → Monitoring of levels and antibodies to drug
Anti-TNF Therapies in Crohn’s

**ACCENT I Infliximab**

- Wk 2 Response: 58
- Wk 30 Remission: 39 (P<.003)
- Wk 30 Remission Placebo: 21

**CHARM Adalimumab**

- Wk 4 Response: 58
- Wk 26 Remission: 40 (P<.001)
- Wk 26 Remission Placebo: 17

**Precise 2 Certolizumab**

- Wk 6 Response: 64
- Wk 26 Remission: 48 (P<.001)
- Wk 26 Remission Placebo: 29

Colombel et al Gastroenterology 2007; 132: 52-65
Schreiber et al NEJM 2007; 357: 239-50
Combination Therapy – Sonic Trial
Infliximab + Azathioprine

Concept:
Step Up
Top Down
Rapid Escalation

Combination Therapy (Sonic – Crohn’s):

A  Corticosteroid-free Clinical Remission at Wk 26

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients (%)</th>
<th>Statistic</th>
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<tr>
<td>Azathiopine Monotherapy</td>
<td>51/170</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Infliximab Monotherapy</td>
<td>75/169</td>
<td>P=0.006</td>
</tr>
<tr>
<td>Infliximab-Azathiopine</td>
<td>96/169</td>
<td>P=0.02</td>
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B  Mucosal Healing at Wk 26

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</thead>
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<tr>
<td>Azathiopine Monotherapy</td>
<td>18/109</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Infliximab Monotherapy</td>
<td>28/93</td>
<td>P=0.02</td>
</tr>
<tr>
<td>Infliximab-Azathiopine</td>
<td>47/107</td>
<td>P=0.06</td>
</tr>
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From Colombel et al., NEJM 2010, 326:15.
New Therapy in IBD: Vedolizumab

- Monoclonal antibody to the $\alpha_4\beta_7$ integrin.

- $\alpha_4\beta_7$ located on circulating B and T lymphocytes interacts with MAdCAM-1 on intestinal vascular endothelium.

- Blocks lymphocyte migration into intestinal tissue.

- Specific to the intestines unlike Natalizumab:
  - *Vedolizumab has NOT been associated with PML*

* FDA Approval granted May 2014 for UC and CD*
Vedolizumab in Ulcerative Colitis

Induction (6 weeks)

Primary Outcome

- PBO (n=149)
- VDZ (n=225)

Clinical Response

Patients, %

- PBO: 25.5%
- VDZ: 47.1%

\( p < 0.001 \)

Maintenance (52 weeks)

Glucocorticoid-Free Remission

- PBO: 13.9%
- VDZ: 45.2%

\( p < 0.001 \)

Mucosal Healing

- PBO: 19.8%
- VDZ: 56.0%

\( p < 0.001 \)

\( p < 0.01 \)

Feagan BF et al., NEJM 2013
Vedolizumab in Crohn’s

Induction (6 weeks)

- Clinical Remission:
  - PBO (n=148): 6.8%
  - VDZ (n=220): 14.5%
  - Mean Δ% (95% CI):
    - VDZ vs PBO: 7.3 (1.2, 14.3)
  - Statistical Significance: p < 0.001

- CDAI-100 Response:
  - PBO (n=148): 25.7%
  - VDZ (n=220): 31.4%
  - Mean Δ% (95% CI):
    - VDZ vs PBO: 5.7 (3.6, 15.6)
  - Statistical Significance: p < 0.03

Maintenance (52 weeks)

- Primary Outcome
  - Mean Δ% (95% CI):
    - VDZ/PBO vs VDZ: 21.6%
    - VDZ/Q8W vs VDZ: 30.0%
    - VDZ/Q4W vs VDZ: 28.8%
  - Statistical Significance:
    - VDZ/PBO vs VDZ: p = 0.01
    - VDZ/Q8W vs VDZ: p = 0.04
    - VDZ/Q4W vs VDZ: p = 0.02

- Secondary Outcomes
  - Mean Δ% (95% CI):
    - Clinical Remission:
      - VDZ/PBO vs VDZ: 14.4%
      - VDZ/Q8W vs VDZ: 15.4%
      - VDZ/Q4W vs VDZ: 13.4%
    - CDAI-100 Response:
      - VDZ/PBO vs VDZ: 13.4%
      - VDZ/Q8W vs VDZ: 15.3%
      - VDZ/Q4W vs VDZ: 16.9%
    - GC-Free Remission:
      - VDZ/PBO vs VDZ: 15.9%
      - VDZ/Q8W vs VDZ: 17.9%
      - VDZ/Q4W vs VDZ: 16.9%

Sandborn WJ et al, NEJM 2013
Vedolizumab - Conclusions

- Overall good efficacy, may be UC > CD (opposite of TNFs)
- Induction data limited by possible slow onset
- PML not reported / mechanistically unlikely
- Similar rate of adverse events vs. placebo in UC trial.
- Higher rate of adverse events vs. placebo in CD trial (serious infection (5.5% vs. 3.0%), malignancy (0.5% vs. 0.3%) and death (0.5% vs. 0.3%) – may be unrelated to drug (ie, intentional other drug overdose in 1 patient).

Approved: Infusion of 300mg at 0, 2, 6, then q8 weeks
IBD Pipeline: Ustekinumab in Crohn’s? IL-12/23 as Therapeutic Target (awaiting Phase III data)

From Benson et al; Nature Biotech 29(7), 2011
Biologics & Immunomodulators: Risks/Side Effects

Azathioprine/6-MP:
- Leukopenia, hepatotoxicity, pancreatitis (~3%), infection, lymphoma, skin CA
- Intolerance: Nausea, fatigue, flu-like illness, hypersensitivity rxn

Methotrexate:
- Teratogenic, infection, BM suppression, hepatotoxicity, pneumonitis
- Nausea, fatigue/malaise \rightarrow Folate Antagonist: Supplement Folic Acid

Anti-TNF:
- Infusion rxn, infection (incl TB), lymphoma, skin CA
- Lupus-like Rxn, demyelinating dz, hepatotoxicity, loss of response
\rightarrow TB, Hep B screening prior to therapy

Natalizumab: - Infection, PML; role for JC virus testing

Vedolizumab: - Infection, no PML
Pregnancy

- For most patients:
  - Risks of stopping therapy is higher than risk of continuing in pregnancy

- GI and high-risk OB should be involved

- Azathioprine/6MP, TNF agents, most 5-ASAs are commonly continued

- Corticosteroids may be used for flare

- 3rd Trimester TNFs generally avoided (except certolizumab)
  → Baby to avoid live vaccines first 6 months (ie, rotavirus)

- **Methotrexate Category X - Contraindicated**
Surgical Management of IBD

Ulcerative Colitis

- Proctocolectomy is a “cure” (with caveats)
- Indications:
  - Medically refractory disease
  - Cancer/dysplasia
  - Toxic megacolon/perforation

Crohn’s Disease: surgery is generally *palliative*

- Indications
  - Bowel obstruction (remove or open a stricture)
  - Toxic megacolon/fulminant colitis
  - Abscess drainage
  - Cancer/dysplasia
Comprehensive IBD Management

IBD Management Goals

- Minimize treatment toxicity
- Prevent/ Treat complications
- Reduce/ Eliminate inflammation
- Control symptoms
- Induce/ Maintain remission
- Prevent/ Treat complications
- Improve quality of life
- Ensure adequate nutrition
- Prevent cancer
- Provide emotional support

IBD Management Goals

An educational program for patients, families and caregivers living with Crohn’s disease and ulcerative colitis.
Understanding Treatment Options

- Prescription medications
- Over-the-counter agents
- Complementary and alternative therapies
- Surgery
Complementary and Alternative Medicine

• What is complementary and alternative medicine (CAM)?
  – Group of diverse medical and healthcare systems, practices and products not presently part of conventional medicine\textsuperscript{1}
  
  – Examples
    » Natural products (supplements, vitamins, probiotics
    » Mind and body medicine (meditation, acupuncture, yoga)
    » Massage
  
  – Lack strong scientific evidence on benefits in treating inflammatory bowel diseases
  – Not FDA-regulated
  – Important to seek out good data to minimize potential risk
  – Should complement, not replace, traditional therapies
  – Tell your doctor everything you are taking

\textsuperscript{1} NCCAM publication # D347.
Understanding the Importance of Diet & Nutrition in Managing IBD

• Causes of nutritional deficits
  – Decreased intake (no desire to eat)
  – Active disease
    • Protein and fluid loss
  – Decreased absorption of nutrients (when small intestine is affected by CD)
    • Fat
    • Vitamins
Understanding the Importance of Diet & Nutrition in Managing IBD

• Create a food journal
  – Eliminate problematic foods

• Strive for a well-balanced, healthy diet based on
  – Hydration
  – Electrolyte balance
  – Continual adequate nutrient intake
Summary

• CD and UC are distinct diseases – but inter-related

• SB disease, perianal disease, fistulas, strictures, skip lesions, and granulomas help distinguish CD.

• Both diseases are assoc with extraintestinal manifestations

• These are chronic diseases characterized by flares

• Treatment aims to control disease then maintain remission

• Treatment options overlap and will be expanding soon
CCFA Resources

- Irwin M. and Suzanne R. Rosenthal IBD Help Center
  M-F, 9:00 AM-5:00 PM ET
    - Phone: 1-888-694-8872
    - Email: info@ccfa.org

- Brochures and factsheets:
  online.ccfa.org/brochures

- Educational webcasts:
  www.ccfa.org/resources/webcasts.html
CCFA Resources

• Connect with other patients
  – CCFA Community website: www.ccfacommunity.org
  – Support groups and Power of Two (peer mentors): www.ccfa.org/chapters

• GI Buddy: online tracking tool and mobile app www.ccfa.org/gibuddy

• New Teen Website: www.justlikemeibd.org