The Inflammatory Bowel Diseases: an Overview

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Conflicts

- Medical Advisory Board
  - Johnson and Johnson
- Educational Grants
  - J&J, Takeda, Pfizer, Celgene
Outline

- Epidemiology
- Pathogenesis
- Diagnosis
- Staging
- Management
- Cases
Epidemiology of IBD in North America

- Approximately 1.6 million people in US with IBD
- Most commonly presents in 20s but can present at any age
- Slight male predominance in UC
- Slight female predominance in CD

IBD Pathogenesis

- Genetic Predisposition
- Mucosal Immune System (Innate/Adaptive Immune Dysfunction)

IBD
IBD Pathogenesis

- Gut Colonization
- Genetic Predisposition
- Mucosal Immune System (Innate/Adaptive Immune Dysfunction)
IBD Pathogenesis

- Gut Colonization
- Genetic Predisposition
- Environmental Triggers
- Mucosal Immune System (Innate/Adaptive Immune Dysfunction)

IBD
Normal Intestine vs. Intestine with IBD

Environmental triggers (medications, infections, smoking, diet?)

Normally: inflammation is down-regulated

Normal bowel: controlled inflammation

IBD: Genetic Susceptibility failure to down-regulate inflammation

Inflamed bowel

Chronic uncontrolled inflammation = IBD

Diagnosis

History and Exam

Endoscopy/Histology

Laboratory Tests

Radiology

IBD
The Spectrum of IBD

IBD-Undefined

UC

CD
Clinical Symptoms

Crohn’s disease
- Nonbloody diarrhea
- Abdominal pain
- Fatigue
- Fever
- Weight loss
- Nausea/Vomiting
- Stunted growth (children)

Ulcerative colitis
- Bloody diarrhea
- Abdominal pain
- Urgency/Tenesmus
- Fever
- Loss of appetite
- Nausea/Vomiting
Clinical Symptoms

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Endoscopic Evaluation of Ulcerative Colitis

**Normal**
- Tan mucosa
- Normal vascular pattern

**Mild**
- Granular mucosa
- Edematous
- Loss of normal vascular pattern
- Friable

**Moderate**
- Coarsely granular
- Small ulcerations
- Friable

**Severe**
- Frank ulcerations
- Spontaneous hemorrhage

Normal Colon

- Tan mucosa
- Normal vascular pattern
Mild Colitis

- Granular mucosa
- Edematous
- Loss of normal vascular pattern
Moderate Colitis

- Coarsely granular
- Small ulcerations
- Friable
Severe Colitis

- Frank ulcerations
- Spontaneous hemorrhage
Histology of Patient Without Ulcerative Colitis

Non-IBD

• Aligned crypts
• No active inflammation

Images courtesy of John Hart, MD.
History of Ulcerative Colitis

**Non-IBD**
- Aligned crypts
- No active inflammation

**Active**
- Crypt distortion
- Inflammation infiltrates
- Crypt abscesses

Images courtesy of John Hart, MD.
Histology of Crohn’s Colitis

Crohn’s Colitis
(arrows indicate granulomas)

Images courtesy of John Hart, MD.
Case #1

- In the clinic, 67 M with BPH, gout, DJD, and ulcerative colitis in clinical remission for several years presents with abdominal pain and bloody diarrhea over three days
- Vs stable, PE with mild RLQ pain with no guarding/rebound, otherwise nl
- Meds: finasteride, acetaminophen, sulfasalazine, folate, MVN
- CBC 12.1/12/350, BMP nl, CRP 7
Case #1

- In the clinic, 67 M with BPH, gout, DJD, and ulcerative colitis in clinical remission for several years presents with abdominal pain and bloody diarrhea over three days.
- Vs stable, PE with mild RLQ pain with no guarding/rebound, otherwise nl.
- Meds: finasteride, acetaminophen, sulfasalazine, folate, MVN.
- CBC 12.1/12/350, BMP nl, CRP 7.
What is the immediate next best step?

- A) MRI of the abd/pelvis
- B) Follow up with GI
- C) Start prednisone
- D) Send stool studies
- E) Transfuse 1 Unit PRBCs
Differential Diagnosis of IBD

- Infectious diarrhea
- Medication-induced injury
- Ischemic colitis
- Segmental colitis associated with diverticula (SCAD)
- Radiation injury
- Microscopic colitis
- Celiac disease
- Irritable bowel syndrome
Intestinal Infections Complicate IBD

- 10-13% of “flares” in IBD are secondary to stool infections
  - Stool infections are much more common in IBD than in non-IBD population

Intestinal Infections Complicate IBD

- The most common bacterial infections are:
  - 1) C. difficile
  - 2) C. jejuni
- All patients with IBD flare-like symptoms should undergo stool testing
- All IBD patients with C. diff should be treated with vancomycin

Radiology: early years

Barium Enema

Small Bowel Follow Through

“string sign”

http://emedicine.medscape.com/article/367666-overview#a2
CAT Scan: Comb sign

http://radiopaedia.org/articles/comb-sign
MRI: Active colonic inflammation
Case #2

- In clinic, a 22 y/o M with migraines, gastroparesis, and long-standing Crohn’s disease presents with diffuse abdominal pain and nausea.
- A colonoscopy the previous week showed no active disease. Has had a comprehensive evaluation of his symptoms with no cause found.
- Has had three other presentations in last 2 months with similar symptoms. Each time, a CT A/P has shown no causes.
- Vs: BP 128/72, HR 90; PE: moderate diffuse abd px with no rebound/guarding, BSs present, exam otherwise nl
- CBC 8/16/258, BMP nl, CRP nl
- Meds: Infliximab, Percocet
What is the next best step?

- A) Recommend a MRI instead
- B) Do a CT scan without contrast
- C) Start metronidazole and ciprofloxacin
- D) Consult GI
- E) Start prednisone
Reasons to Perform Imaging in IBD

- Crohn’s disease
  - Evaluate active small bowel inflammation
  - Stricture
  - Abscess
  - Perforation

- Ulcerative colitis
  - Toxic megacolon
  - Perforation
# Radiation Guide

<table>
<thead>
<tr>
<th>For this procedure:</th>
<th>Your effective radiation dose is:</th>
<th>Comparable to natural background radiation for:</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Computed Tomography (CT) - Abdomen and Pelvis</td>
<td>10 mSv</td>
<td>3 years</td>
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</tr>
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<td>Radiography - Spine</td>
<td>1.5 mSv</td>
<td>6 months</td>
</tr>
<tr>
<td>Radiography - Extremity</td>
<td>0.001 mSv</td>
<td>Less than 1 day</td>
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<tr>
<td>Computed Tomography (CT) - Head</td>
<td>2 mSv</td>
<td>8 months</td>
</tr>
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<td>Computed Tomography (CT) - Spine</td>
<td>6 mSv</td>
<td>2 years</td>
</tr>
<tr>
<td>Myelography</td>
<td>4 mSv</td>
<td>16 months</td>
</tr>
<tr>
<td>Computed Tomography (CT) - Chest</td>
<td>7 mSv</td>
<td>2 years</td>
</tr>
<tr>
<td>Radiographic Chest</td>
<td>0.1 mSv</td>
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<td>Bone Densitometry (DEXA)</td>
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Making the Decision to Perform a CT Scan or X-Ray

• Consider the risks and benefits of radiation exposure
• 50 mSv is association with increased risk of malignancy
  • 25% of IBD patients have undergone this degree of exposure
  • Most radiation exposure in IBD occurs in hospital

Prevalence of Irritable Bowel Syndrome (IBS) in Inflammatory Bowel Disease (IBD)

Staging of Disease after Diagnosis

- Extent and behavior
- Complications
- Extraintestinal manifestations
Staging of Disease after Diagnosis

- Extent and behavior
- Complications
- Extraintestinal manifestations
Anatomic Distribution of UC and CD

INFLAMMATORY BOWEL DISEASE

Ulcerative Colitis (UC)
- Mucosal Ulceration in Colon
  - Proctitis
  - Left-sided Colitis
  - Extensive Colitis

Crohn’s Disease (CD)
- Transmural Inflammation
  - Upper Gastrointestinal
  - Small Bowel
  - Colonic
  - Anorectal
CD - Distinguishing Features

- Granuloma
- Focal lesions
- Fistulization
- Strictures
- Asymmetric involvement

- Inflammatory
- Endoscopic features
- Skip lesions
- Small bowel involvement
- 20-30% without gross bleeding
- Rectal sparing
- Perineal disease

Courtesy of www.mcgillibd.ca
CD - Distinguishing Features

- Strictures
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Endoscopic features:
- Skip lesions
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Inflammatory features

Endoscopic features

Courtesy of www.mcgillibd.ca
Staging of Disease after Diagnosis

- Extent and behavior
- **Complications**
- Extraintestinal manifestations
Case #3

- 35 y/o F with hypothyroidism and ulcerative colitis presents with 5 days of abdominal pain, bloody diarrhea and severe urgency.
- CBC 14.1/9 (previously 12)/480, CRP 25, Stool studies neg
- T 99.8 otherwise Vs stable, PE: mild lower abd pain, otherwise nl
- CT A/P with diffuse colitis
- Meds: Lialda, Levothyroxine
You are entering the admission orders and start the patient on prednisone. What other medication do you ensure is ordered?

- A) Metronidazole
- B) SQ Heparin
- C) Percocet
- D) Loperamide
- E) Ibuprofen
IBD Related Complications

Complications of Crohn’s Disease
- Fistulas
- Abscesses
- Intestinal blockage
- Malnutrition
- Gallstones
- Kidney stones
- Thrombosis
- Colon or rectal cancer
- Growth failure in children

Complications of Ulcerative Colitis
- Toxic megacolon
- Perforation
- Thrombosis
- Colon or rectal cancer
Colorectal Cancer Risk in IBD
Increased Risk of Venous Thromboembolism

Increased Risk of Venous Thromboembolism

3% of elderly UC admissions had VTE

Safety of DVT Prophylaxis

- 2007 Meta-analysis of 8 studies showed no increased risk of complications with the use of heparin in IBD inpatients

Opioid Use in IBD

Chi² for trend

- Any opiate - $P < .005$
- Codeine - $P = .008$
- Tramadol - $P < .005$
- Strong opiate - $P < .005$

**Increased premature mortality (HR >2)**

Chi² for trend

- Any opiate – $P < .005$
- Codeine – $P = .008$
- Tramadol – $P < .005$
- Strong opiate – $P < .005$

Staging of Disease after Diagnosis

- Extent and behavior
- Complications
- Extraintestinal manifestations
Extraintestinal Manifestations
Extraintestinal Manifestations

- Musculoskeletal
  - Peripheral arthritis*
  - Ankylosing spondylitis
- Skin
  - Erythema nodosum*
  - Pyoderma gangrenosum
- Ocular
  - Episcleritis*
  - Scleritis
  - Anterior uveitis
- Hepatobiliary
  - Primary sclerosing cholangitis

*Follows course of intestinal inflammatory disease
Two Main Management Strategies in IBD

- Medical
- Surgical
Two Main Management Strategies in IBD

- Medical
- Surgical
Goals of Medical Therapy in Moderate-Severe Crohn’s and UC

- Symptom resolution
Goals of Medical Therapy in Moderate-Severe Crohn’s and UC

- Symptom resolution
- Mucosal healing
Goals of Medical Therapy in Moderate-Severe Crohn’s and UC

- Symptom resolution
- Mucosal healing
- Minimizing complications of therapy
IBD Therapies in 1998

- **Antibiotics**
  - Ciprofloxacin
  - Metronidazole

- **Mesalamine**
  - Apriso
  - Asacol

- **Steroids**
  - Prednisone
  - Hydrocortisone enemas
  - Cortifoam

- **Immune Modulating Agents**
  - 6-Mercaptopurine
  - Azathioprine
  - Methotrexate

- **Surgery**
  - Ileal pouch-anal anastomosis
  - Small bowel resection
  - Stricturoplasty
IBD Therapies in 2019

- **Antibiotics**
  - Ciprofloxacin
  - Metronidazole

- **Mesalamine**
  - Apriso, Pentasa, Delzicol, Lialda, Rowasa, Canasa
  - Entocort
  - Prednisone
  - Hydrocortisone enemas
  - Cortifoam

- **Steroids**
  - Prednisone
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- **Immunomodulators**
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  - Methotrexate

- **Surgery**
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  - Small bowel resection
  - Stricturoplasty

- **Anti-TNF**
  - Infliximab
  - Adalimumab
  - Certolizumab
  - Golimumab

- **Anti-integrin**
  - Natalizumab
  - Vedolizumab

- **Anti-IL 12/23**
  - Ustekinumab

- **JAK Kinase Inhibitor**
  - Tofacitinib
Medical Therapy Alters the Natural History of IBD

- Induce and maintain gastrointestinal healing
- Prevent need for steroids
- Prevent strictures and penetrating complications
- Prevent extra-intestinal complications
- Decrease hospitalization/surgery
- Decrease long-term cost of care

Years

Natural course

Disease complications
Medical Treatment of Refractory CD in the Age of Biologics

Pretreatment

Medical Treatment of Refractory CD in the Age of Biologics

UC Medical Management

Mild-Moderate UC

Induction and Maintenance

5-Aminosalicylic Acids, Topical Steroid

Moderate-Severe UC

Induction

Steroids, Anti-TNF-α Agents, Anti-Integrin, JAK inhibitors

Maintenance

Thiopurines, Anti-TNF-α Agent, Anti-Integrin, JAK inhibitors
CD Medical Management

Mild-Moderate CD
- Induction and Maintenance
  - Enterocort, Antibiotics

Moderate-Severe CD
- Induction
  - Steroids, Anti-TNF-α Agents, Anti-Integrins, Anti-Interleukin 12/23

- Maintenance
  - Thiopurines, Anti-TNF-α Agents, Anti-Integrins, Anti-Interleukin 12/23
Diet and IBD

- Multiple diets have been described for use in IBD including the Paleo diet, FODMAP, and Specific Carbohydrate Diet (SCD)
- No data that any particular diet plays a role in gut inflammation in IBD
- In patients with active inflammation, best to avoid high fiber foods
- Food journal
Fecal Transplant and IBD

- UC: 4 RCTs with 277 patients followed up to 12 weeks
  - Clinical Response: 49 vs 28%*
  - Clinical Remission: 28 vs 9%*
  - Endoscopic Remission: 14 vs 5%*

Fecal Transplant and IBD

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  - Clinical Response: 49 vs 28%*
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*p < 0.05
Fecal Transplant and IBD

- UC: 4 RCTs with 277 patients followed up to 12 weeks
  - Clinical Response: 49 vs 28%*
  - Clinical Remission: 28 vs 9%*
  - Endoscopic Remission: 14 vs 5%*
- CD: 5 uncontrolled cohort studies with 71 patients followed up to 15 months
  - Clinical Response: 63%
  - Clinical Remission: 52%
  - Endoscopic Remission: 0% (6 patients)
- Safety: generally well tolerated but LT effects unclear

Health Care Maintenance Issues

- Vaccines
- Skin cancer screening
- Bone Health/Osteoporosis
- Psychosocial issues
Vaccines in IBD

• IBD itself should not impact vaccine response
• Generally lives vaccines contraindicated in the immunosuppressed
  • Include Rubella, Varicella, Yellow fever, Zoster
• Annual influenza vaccine
• Pneumococcal vaccine

Melmel GY. Inflamm bowel dis 2009.
Human Papilloma Virus (HPV)

- HPV linked with cervical and anal cancers
- Women with IBD have an increased risk for cervical dysplasia
  - Increased risk with >6 months immune modulator use
- HPV vaccine available and safe in immunosuppression, but no specific guidelines for IBD
- Recommended for women and men ages 9 to 26

www.cdc.gov
Herpes Zoster Vaccines

- IBD patients are at higher risk of developing shingles, particularly on immune suppression
- Zostavax: live-attenuated zoster vaccine
- Shingrix: inactivated zoster vaccine
  - Approved in 2017 and given in 2 doses: 2nd dose is given 2-6 months after first dose
  - Approved for ≥50 years old
  - Can be given to patients on low levels of immune suppression (prednisone ≤20 mg, methotrexate, azathioprine, 6-MP)
  - Safety with biologics and tofacitinib under study
Skin Cancer

- Increased risk of nonmelanoma skin cancer in patients on azathioprine or 6-MP
- Possible increased risk of melanoma in patients on anti-TNF agents
- Patients on immunosuppression should have a full body skin exam at least once per year
Osteoporosis

- Risk Factors in general population:
  - Previous history of osteoporotic related fractures
  - Advanced age
  - Family history of osteoporosis
  - Lack of exercise
  - Smoking
  - Hypogonadal state

Osteoporosis

- **Risk Factors in general population:**
  - Previous history of osteoporotic related fractures
  - Advanced age
  - Family history of osteoporosis
  - Lack of exercise
  - Smoking
  - Hypogonadal state

- **Risk factors specific to IBD patients:**
  - Chronic inflammatory activity
  - Chronic or recurrent corticosteroid use
  - Malnutrition
  - Low body weight
  - Low intake or absorption of Ca & Vit D

# Psycho-Social Issues

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<tr>
<th>Variable</th>
<th>Depression</th>
<th>Anxiety Disorder</th>
<th>Bipolar Disorder</th>
<th>Schizophrenia</th>
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<tr>
<td><strong>Cohort</strong></td>
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<tr>
<td>IBD</td>
<td>1.42 (1.32–1.52)</td>
<td>1.24 (1.17–1.31)</td>
<td>1.45 (1.19–1.77)</td>
<td>1.11 (0.76–1.60)</td>
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<tr>
<td><strong>Sex</strong></td>
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<td>Male</td>
<td>1.0</td>
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<tr>
<td>Female</td>
<td>1.76 (1.64–1.90)</td>
<td>1.54 (1.48–1.62)</td>
<td>1.58 (1.34–1.87)</td>
<td>0.75 (0.55–1.02)</td>
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<td><strong>Age, y</strong></td>
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<td>18–24</td>
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<td>25–44</td>
<td>1.95 (1.66–2.30)</td>
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<td>1.74 (1.18–2.57)</td>
<td>0.96 (0.57–1.62)</td>
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<td>45–64</td>
<td>2.34 (1.98–2.76)</td>
<td>2.15 (1.87–2.47)</td>
<td>2.06 (1.38–3.08)</td>
<td>1.51 (0.89–2.58)</td>
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<td>≥65</td>
<td>1.99 (1.68–2.36)</td>
<td>2.05 (1.78–2.37)</td>
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<td>0.97 (0.56–1.67)</td>
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Management of IBD Requires Multidisciplinary Approach

- Gastroenterology
- Colorectal surgery
- Radiology
- Pathology
- Nutrition
- Social work
- Nursing
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- Gastroenterology
- Colorectal surgery
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- Nursing
- Primary Care Provider
Conclusions

- CD and UC tends to occur in younger adults
- Pathogenesis results from a combination of genetics, environmental factors, gut microbiota, and an aberrant immune system
- Diagnosis of IBD is based on history and exam, labs, radiographic imaging, and endoscopy and histology
Conclusions

• IBD is a systemic disease with multiple complications
• New therapies have improved patient outcomes
• Health care maintenance issues in IBD are key
Case #1

- In the clinic, 67 M with BPH, gout, DJD, and ulcerative colitis in clinical remission for several years presents with abdominal pain and bloody diarrhea over three days
- Vs stable, PE with with mild RLQ pain with no guarding/rebound, otherwise nl
- Meds: finasteride, acetaminophen, sulfasalazine, folate, MVN
- CBC 12.1/12/350, BMP nl, CRP 7
What is the immediate next best step?

- A) MRI of the abd/pelvis
- B) Call a GI consult
- C) Start prednisone
- D) Send stool studies
- E) Transfuse 1 Unit PRBCs
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Case #2

- In clinic, a 22 y/o M with migraines, gastroparesis, and long-standing Crohn’s disease presents with diffuse abdominal pain and nausea.

- A colonoscopy the previous week showed no active disease.

- Has had three other presentations in last 2 months with similar symptoms. Each time, a CT A/P has shown no causes.

- Vs: BP 128/72, HR 90; PE: moderate diffuse abd px with no rebound/guarding, BSs present, exam otherwise nl

- CBC 8/16/258, BMP nl, CRP nl

- Meds: Infliximab, Percocet
What is the next best step?

- A) Recommend a MRI instead
- B) Do a CT scan without contrast
- C) Start metronidazole and ciprofloxacin
- D) Consult GI
- E) Start prednisone
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Case #3

- 35 y/o F with hypothyroidism and ulcerative colitis presents with 5 days of abdominal pain, bloody diarrhea and severe urgency.
- CBC 14.1/9 (previously 12)/480, CRP 25, Stool studies neg
- T 99.8 otherwise Vs stable, PE: mild lower abd pain, otherwise nl
- CT A/P with diffuse colitis
- Meds: Lialda, Levothyroxine
You are entering the admission orders and start the patient on prednisone. What other medication do you ensure is ordered?

- A) Metronidazole
- B) SQ Heparin
- C) Percocet
- D) Loperamide
- E) Ibuprofen
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Cases: Major takeaways

- IBD patients with diarrhea should undergo stool studies
- Use of appropriate imaging can prevent unnecessary radiation exposure
- In IBD inpatients, the benefits of DVT prophylaxis almost always outweigh the risks
- Narcotics in IBD are associated with increased mortality
CD and UC Patient Support Groups:
ccfa.org
crohnsforum.com

Sasha Taleban, MD
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(206)992-8114 (cell)