Inflammatory Bowel Disease

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Assistant Professor of Medicine
Outline

• An Overview of Inflammatory Bowel Disease
• Genetics of Inflammatory Bowel Disease
  • What is the risk of IBD in the offspring of patients with IBD?
• Risk of Thrombosis in Inflammatory Bowel Disease
  • Should IBD patients admitted with bloody diarrhea receive DVT prophylaxis?
• Perioperative Medical Management of Inflammatory Bowel Disease
  • Is it safe to give anti-TNFs in the pre-operative period?
• Pretreatment Testing in Inflammatory Bowel Disease
  • What tests should be ordered prior to starting immunosuppressive medications?
• Health Maintenance in Inflammatory Bowel Disease
  • What vaccines should IBD patients receive?
Epidemiology

- Approximately 1.5 million pts in U.S.
  \( \approx \) Prevalence is 1 in 200

- Classically a disease of industrialized nations
  (N. America, NW Europe)

- 2 recent meta-analyses of global IBD trends
  Growing incidence in developing nations
  (Asia, S. America, Middle East)
  Also higher rates in immigrants to western
countries (Indian/African in Europe,
Latinos/Asians in U.S.)
Pattern: UC incidence increases 1\textsuperscript{st}, then CD
# Ulcerative Colitis

<table>
<thead>
<tr>
<th>Ulcerative rectocolitis – URC</th>
<th>Classification of Montreal</th>
</tr>
</thead>
<tbody>
<tr>
<td>E 1 – Proctitis</td>
<td>Limited to rectum (30%)</td>
</tr>
<tr>
<td>E 2 – Left Sided Colitis</td>
<td>Affects the rectum and left colon (distal to the splenic flexure) (30%)</td>
</tr>
<tr>
<td>E 3 – Pancolitis</td>
<td>Affects the rectum and colon proximal to the splenic angle (30%)</td>
</tr>
</tbody>
</table>
Crohn’s Disease

Summary of revised ‘Montreal classification’ of Crohn’s disease

<table>
<thead>
<tr>
<th>Age at diagnosis (A)</th>
<th>Location (L)</th>
<th>Upper GI modifier (L4)</th>
<th>Perianal disease modifier (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1 16 years or younger</td>
<td>L1 Terminal ileum</td>
<td>L1 + L4 Terminal ileum + Upper GI</td>
<td>B1* Nonstricturing, nonpenetrating + perianal</td>
</tr>
<tr>
<td>A2 17–40 years</td>
<td>L2 Colon</td>
<td>L2 + L4 Colon + Upper GI</td>
<td>B2p Stricturening + perianal</td>
</tr>
<tr>
<td>A3 Over 40 years</td>
<td>L3 Ileocolon</td>
<td>L3 + L4 Ileocolon + Upper GI</td>
<td>B3p Penetrating + perianal</td>
</tr>
<tr>
<td></td>
<td>L4 Upper GI</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*B1 category should be considered ‘interim’ until a prespecified time has elapsed from the time of diagnosis. Such a time period may vary from study to study (eg, 5–10 years is suggested) but should be defined in order for B1 behaviour to be considered ‘definitive’. Gi Gastrointestinal
## Clinical Presentation

<table>
<thead>
<tr>
<th>Ulcerative Colitis</th>
<th>Crohn’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal bleeding is the most common</td>
<td>Diarrhea (usually non-bloody)</td>
</tr>
<tr>
<td>Bloody diarrhea or mucous discharge</td>
<td>Chronic abdominal pain and tenderness (right lower quadrant)</td>
</tr>
<tr>
<td>Abdominal cramping</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Tenesmus (persistent spasm of the rectum)</td>
<td>“Obstructive symptoms”</td>
</tr>
<tr>
<td>Fever/Sweats</td>
<td>Nausea/vomiting, postprandial pain</td>
</tr>
<tr>
<td></td>
<td>Fever/Sweats</td>
</tr>
</tbody>
</table>
Extraintestinal Manifestations

- **Musculoskeletal (2-3%, CD)**
  - Peripheral arthritis*
  - Sacroilitis*
  - Ankylosing spondylitis (I)

- **Dermatologic (1-2%, CD)**
  - Erythema nodosum*
  - Pyoderma gangrenosum (I)

- **Ocular (1-2%, UC)**
  - Uveitis (I)
  - Scleritis*
  - Episcleritis*

- **Biliary (~3%, UC)**
  - Primary sclerosing cholangitis

- **Hematological**
  - DVT/PE*
  - Prophylaxis in all inpatients!

PMID: 31294387
Endoscopic Appearance

Ulcerative Colitis
- Rectal involvement
- Continuous pattern

Crohn’s Disease
- Rectal sparing
- Patchy colitis
- Deep ulcers
- Ileal ulcers
- Cobblestoning
Fulminant Colitis / Toxic Megacolon

- **Toxic megacolon**
  
  Diagnostic criteria: Dilation of colon (total or segmental) \( \geq 6\text{cm} \)
  
  Any 3 of: Fever \( >101 \), HR \( >100 \), WBC \( >10 \), Anemia
  
  Any 1 of: dehydration, electrolyte abnormalities, hypotension, altered mental status

- **Poor Prognosis**
  
  47% underwent colectomy w/in 6 mo (38% urgent/emergent)
  
  20% mortality in 1970s \( \rightarrow \) 4-5% currently

- **Surgical Emergency**

Please involve gastroenterology and colorectal surgery early!
Goals of IBD Management

- Induce remission
- Maintain remission
- Minimize steroid exposure over lifetime
- Decrease short-term and long-term morbidity
- Decrease hospitalization rates
- Decrease surgical rates
- Decrease risk of cancer
Current Treatment Targets (STRIDE Guidelines)

Target for Ulcerative colitis
• Clinical remission and endoscopic remission
  • Resolution of bleeding and diarrhea
  • Mayo endoscopic subscore of 0-1

Target for Crohn’s Disease
• Clinical remission and endoscopic remission
  • Resolution of abdominal pain and diarrhea
  • Resolution of ulceration at ileocolonoscopy or resolution of findings on cross-sectional imaging

PMID: 26303131
Current Medical Treatments for Inflammatory Bowel Disease

**Antibiotics**
- Metronidazole
- Ciprofloxacin
- Vancomycin

**Corticosteroids**
- Prednisone
- Hydrocortisone
- Budesonide

**Immunomodulators**
- Thiopurines: 6-mercaptopurine, azathioprine
- Folic Acid Antagonists: methotrexate

**Aminosalicylates**
- Mesalazine
- Sulfasalazine
- Balsalazide
- Olsalazine

**IBD**
- Crohn's Disease
- Ulcerative Colitis

**Biologics**
- Infliximab
- Adalimumab
- Certolizumab
- Golimumab
- Vedolizumab
- Ustekinumab
- Tofacitinib
Ulcerative Colitis

- Mild: Mesalamine, SSZ
- Moderate: Steroids, 6MP/AZA
- Severe: Surgery, Biologic
Oral Aminosalicylates

- **Sulfasalazine**
  - Oldest, sulfa + SASA
  - Poorly tolerated

- **Asacol**
  - Eudragit coated
  - pH-dep release in TI/cecum

- **Pentasa**
  - Ethylcellulose-coated microgranules → timed release in small/large bowel

- **Colazol**
  - Newer azo-bonded formulation → release in colon

- **Lialda**
  - Multimatrix formulation touted for slower/more homogenous release in colon/rectum, higher dose / pill (1.2gm)
Crohn’s Disease

- Topical Steroids (Budesonide)
- Biologics 6MP/AZA
- Steroids Surgery

Early

Late
Targeted Therapies

Anti-TNF

Anti-InTEGRINS

Anti-IL-12, IL-23

Ustekinumab

SMALL MOLECULE
Tofacitinib = JAK2 kinase inhibitor
Case #1

- 23 year old Jewish woman with a history of ileocolonic Crohn’s disease diagnosed at age 18, complicated by small bowel strictures (Montreal A2L3B2). Patient was followed by a community physician who had been maintaining her on a combination of 6-mercaptopurine and oral mesalamine. She presents to the ED with post-prandial abdominal pain, nausea, and bloating. She reports 2-3 bowel movements with small amounts of blood per day. Her family history is significant for two uncles with Crohn’s disease and a cousin with ulcerative colitis. She does not smoke.

- Physical exam shows a woman in mild distress although vital signs are within normal limits. Abdominal exam demonstrates hyperactive and high pitched bowel sounds with tenderness in the RLQ.

- Labs are significant for a mild leukocytosis, but otherwise normal.

- CT enterography confirms the diagnosis of a high-grade ileal stricture with proximal dilation.

Montreal Classification

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<td></td>
<td>L4 Upper GI</td>
<td>-</td>
<td>-</td>
</tr>
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</table>
Is there a genetic basis for inflammatory bowel disease?
## Historical Perspectives

### Monozygotic Twin Concordance Rate
- **CD:** 20-55%
- **UC:** 6.3-17%

### Dizygotic Twin Concordance Rate
- **CD:** 0-3.6%
- **UC:** 0-6.3%

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**Table 2: Proband concordance rates and estimates of heritability of liability for ulcerative colitis (UC) and Crohn’s disease (CD)**

<table>
<thead>
<tr>
<th>Prevalence per 10⁶</th>
<th>Monozygotic twins</th>
<th>Dizygotic twins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prob* conc (%) r*</td>
<td>Prob* conc (%) r*</td>
</tr>
<tr>
<td>UC 78</td>
<td>6.3</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>(0.24–0.82)§</td>
<td></td>
</tr>
<tr>
<td>CD 54</td>
<td>58.3</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>(0.80–1.0)§</td>
<td></td>
</tr>
</tbody>
</table>

*proband concordance; †heritability of liability; ‡corrected r-value for common familial environmental factors; §95% confidence interval.

Tysk C et al. Gut 1988
Mapping the IBD Genetic Landscape

Gaya DR et al. Lancet 2006
Historical Perspectives

- **NOD2** - the first gene identified in Crohn’s Disease

- Bacterial sensor that recognizes muramyl-dipeptide, a building block of bacterial peptidoglycan

Ogura Y et al. Nature 2001
Predictive Genetic Biomarkers in Crohn’s Disease

- NOD2 polymorphisms were strongly correlated with ileal disease, early onset of disease, associated with more fibrostenotic vs. fistulizing disease

- Single center retrospective cohort analysis in 244 Caucasian patients in the UK

<table>
<thead>
<tr>
<th>Disease location</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileal</td>
<td>201</td>
<td>43</td>
</tr>
<tr>
<td>Colonic</td>
<td>150</td>
<td>94</td>
</tr>
<tr>
<td>Perianal</td>
<td>114</td>
<td>130</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease behavior</th>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileal</td>
<td>190</td>
<td>54</td>
</tr>
<tr>
<td>Colonic</td>
<td>158</td>
<td>84</td>
</tr>
<tr>
<td>Perianal</td>
<td>87</td>
<td>157</td>
</tr>
</tbody>
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Ahmad T et al. Gastroenterology 2002
What is the risk of transmitting IBD to offspring?

If the patient has UC, what is the risk of the offspring having CD or UC?

If the patient has CD, what is the risk of the offspring having CD or UC?

**Table 1.** Prevalence Proportion Ratio of Crohn’s Disease and Ulcerative Colitis Among Offspring of Patients With Ulcerative Colitis

<table>
<thead>
<tr>
<th>Number of Offspring</th>
<th>Offspring’s Disease</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crohn’s Disease</td>
<td>Ulcerative Colitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obs</td>
<td>Exp</td>
<td>PPR</td>
<td>Obs</td>
</tr>
<tr>
<td>11,022</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>4</td>
<td>1.9</td>
<td>2.1</td>
<td>26</td>
</tr>
<tr>
<td>Females</td>
<td>9</td>
<td>3.0</td>
<td>3.0</td>
<td>30</td>
</tr>
<tr>
<td>PPR = prevalence proportion ratio = the observed number of offspring with Crohn’s disease or ulcerative colitis divided by the expected numbers</td>
<td></td>
<td></td>
<td></td>
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**Table 2.** Prevalence Proportion Ratio of Crohn’s Disease and Ulcerative Colitis Among Offspring of Patients With Crohn’s Disease

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<td>Obs</td>
<td>Exp</td>
<td>PPR</td>
<td>Obs</td>
</tr>
<tr>
<td>3472</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>7</td>
<td>0.6</td>
<td>1.7</td>
<td>3</td>
</tr>
<tr>
<td>Females</td>
<td>12</td>
<td>0.9</td>
<td>13.6</td>
<td>10</td>
</tr>
<tr>
<td>PPR = prevalence proportion ratio = the observed number of offspring with Crohn’s disease or ulcerative colitis divided by the expected numbers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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</table>

Orholm et al. AMG 1999
Genetics in IBD

• Multiple studies support a strong genetic basis for inflammatory bowel disease: Crohn’s disease > ulcerative colitis

• The first gene associated with inflammatory bowel disease, the bacterial sensor NOD2, is associated with more complicated ileal Crohn’s disease

• There is an increased risk that offspring of patients with IBD will develop IBD.
  • One parent with IBD: ~10%
  • Two parents with IBD: ~30%
Case #1

• 23 year old Jewish woman with a history of ileocolonic Crohn’s disease diagnosed at age 18, complicated by small bowel strictures (Montreal A2L3B2). Patient was followed by a community physician who had been maintaining her on a combination of 6-mercaptopurine and oral mesalamine. She presents to the ED with post-prandial abdominal pain, nausea, and bloating. She reports 2-3 bowel movements with small amounts of blood per day. Her family history is significant for two uncles with Crohn’s disease and a cousin with ulcerative colitis. She does not smoke.

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• CT enterography confirms the diagnosis of a high-grade ileal stricture with proximal dilation.
Should you give this patient VTE prophylaxis?
Thromboembolic Risk in IBD

• Several large cohort studies have demonstrated elevated thromboembolic risk in IBD patients, particularly in hospitalized patients. (PMID 11307809, 21339206, 23550660, 20211927, 20149425).

• Autopsy studies suggest the incidence of venous thromboembolic events in UC patients is up to 39%. (Graef et al Arch Intern Med 1966)

• Thromboembolic complications include CVA, mesenteric and portal vein thrombosis, Budd-Chiari, retinal vein occlusion, ischemic heart disease.
Mechanisms of hypercoagulability in IBD

- Venous stasis
  - ↑ blood viscosity
  - immobility
  - mechanical blockage

- Vascular injury
  - endothelial trauma
  - endothelial dysfunction

- Hypercoagulation
  - ↑ procoagulants
  - ↑ anticoagulants
  - ↑ platelet activity
  - ↓ fibrinolysis

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Fig 3. Effect of varying CRP concentrations (diluted in HBSS) on PBM TF PCA after 6 hours of incubation. Results represent average ± 1 SD of three experiments in duplicates on PBM (10⁶/mL) in RPMI 1640 + 1% FCS as measured by the one-stage clotting assay.

Cermak et al. Blood 1993
## Non-Hospitalized Patients

Meta-analysis: the risk of venous thromboembolism in patients with inflammatory bowel disease

<table>
<thead>
<tr>
<th>Study</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernstein 2001</td>
<td>3.47 (2.94, 4.09)</td>
<td>11.87</td>
</tr>
<tr>
<td>Miesler 2004</td>
<td>3.60 (1.68, 7.71)</td>
<td>4.01</td>
</tr>
<tr>
<td>Bernstein 2007</td>
<td>1.30 (1.23, 1.37)</td>
<td>12.99</td>
</tr>
<tr>
<td>Nguyen 2008</td>
<td>1.66 (1.33, 2.07)</td>
<td>11.03</td>
</tr>
<tr>
<td>Nguyen 2009</td>
<td>7.07 (4.07, 12.29)</td>
<td>5.98</td>
</tr>
<tr>
<td>Grainge 2010</td>
<td>3.40 (2.69, 4.29)</td>
<td>10.84</td>
</tr>
<tr>
<td>Rothberg 2011</td>
<td>3.11 (1.59, 6.08)</td>
<td>4.76</td>
</tr>
<tr>
<td>Kappelman 2011</td>
<td>1.50 (1.22, 1.84)</td>
<td>11.32</td>
</tr>
<tr>
<td>Merill 2011</td>
<td>2.03 (1.52, 2.71)</td>
<td>9.93</td>
</tr>
<tr>
<td>Saleh 2011</td>
<td>1.37 (1.36, 1.38)</td>
<td>13.14</td>
</tr>
<tr>
<td>Broms 2012</td>
<td>2.61 (1.24, 5.49)</td>
<td>4.15</td>
</tr>
<tr>
<td>Overall (I² = 95.9%, P = 0.000)</td>
<td>2.20 (1.83, 2.65)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis
### Hospitalized Patients

<table>
<thead>
<tr>
<th>Hospitalised periods</th>
<th>Events (n)</th>
<th>Person-years of follow-up</th>
<th>Risk per 1000 person-years (unadjusted)</th>
<th>Hazard ratio* (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>48</td>
<td>1907.5</td>
<td>25.2</td>
<td>2.1 (1.4–3.2)</td>
<td>0.0003</td>
</tr>
<tr>
<td>inflammatory bowel disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flare</td>
<td>12</td>
<td>320.3</td>
<td>37.5</td>
<td>3.2 (1.7–6.3)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Chronic activity</td>
<td>13</td>
<td>443.0</td>
<td>29.3</td>
<td>2.8 (1.5–5.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Remission</td>
<td>23</td>
<td>1102.2</td>
<td>20.9</td>
<td>1.7 (1.1–2.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Control</td>
<td>49</td>
<td>3532.2</td>
<td>13.9</td>
<td>1.0</td>
<td>..</td>
</tr>
</tbody>
</table>

*Grainge et al. Lancet 2010*
Society Guidelines

• Canadian Association of Gastroenterology Guidelines
  • LMWH, unfractionated heparin, or fondaparinux for hospitalized IBD patients without severe bleeding.
  • Anticoagulant thromboprophylaxis for IBD hospitalized for indication unrelated to their IBD.

• American College of Gastroenterology
  • In patients with acute severe ulcerative colitis, we recommend DVT prophylaxis to prevent VTE
  • No recommendation for Crohn’s disease, but the authors acknowledge an elevated risk of thromboembolism

• British Society of Gastroenterology
  • Recommends the use of subcutaneous heparin to reduce the risk of thromboembolism for acute severe ulcerative colitis
Case #1

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Treatment options?

• Medical Therapy

• Endoscopic Therapy

• Surgery
Prior to surgery, is it safe to give a patient an anti-TNF or steroids?
Steroid use increases the risk of post-operative infection and complications

Pre-operative steroid use defined as use of steroids for greater than 10 days within 30 days of surgery.

PMID: 25107847
<table>
<thead>
<tr>
<th></th>
<th>All IBD patients (N = 15,495)</th>
<th>Preoperative steroid use</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Crohn’s disease</td>
<td>Yes (N = 3033)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No (N = 4202)</td>
<td></td>
</tr>
<tr>
<td>30-day mortality</td>
<td>1.0%</td>
<td>0.7%</td>
<td>1.4%</td>
</tr>
<tr>
<td><strong>Infectious complications</strong></td>
<td>15.5%</td>
<td>15.2%</td>
<td>19.4%</td>
</tr>
<tr>
<td>Deep wound</td>
<td>1.9%</td>
<td>1.8%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>6.9%</td>
<td>7.9%</td>
<td>8.6%</td>
</tr>
<tr>
<td>Sepsis</td>
<td>6.4%</td>
<td>6.5%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Septic shock</td>
<td>1.6%</td>
<td>2.0%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2.0%</td>
<td>1.9%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3.5%</td>
<td>2.8%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>1.5%</td>
<td>1.8%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Bleeding requiring transfusion</td>
<td>6.8%</td>
<td>7.0%</td>
<td>9.8%</td>
</tr>
<tr>
<td>Cardiac complications</td>
<td>0.5%</td>
<td>0.4%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.2%</td>
<td>0.1%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>0.3%</td>
<td>0.3%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Neurological complications</td>
<td>0.3%</td>
<td>0.3%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>0.1%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Coma</td>
<td>0.1%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Peripheral nerve injury</td>
<td>0.1%</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Renal complications</td>
<td>1.1%</td>
<td>0.7%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>0.4%</td>
<td>0.3%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Progressive renal insufficiency</td>
<td>0.7%</td>
<td>0.4%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>2.5%</td>
<td>2.2%</td>
<td>5.4%</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>2.0%</td>
<td>1.8%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0.7%</td>
<td>0.7%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Return to operating room</td>
<td>7.1%</td>
<td>7.9%</td>
<td>9.1%</td>
</tr>
</tbody>
</table>

* P < 0.05.
Puccini Trial

- Determine whether exposure to TNF inhibitors was a risk factor for post-operative infection.
- 17 center prospective observational study
- 573 patients (mean age 43y, 46.8% female) with no TNF exposure, 382 (mean age 39y, 49.2% female) did have TNF exposure prior to surgery
- Frequency of any infection was 20.2% in the unexposed cohort and 19.4% in the exposed cohort (p=0.80). Surgical site infections were 12.3% vs. 12.7% (p=0.92).
- Rates of any post-operative complication was also similar.
Peri-operative management of IBD

• Good practice to involve your surgical colleagues early in the decision-making process

• If you think that surgery is a strong possibility for the patient within the next 30 days, avoid steroids

• Anti-TNFs do not have an increased risk of post-operative infections or complications and thus can be considered even in patients who will likely need surgery either as a method to try to avoid surgery or as a way to decrease inflammation
Case #1 Continued

• The patient undergoes an ileocolic resection with primary anastomosis is performed.
• The patient returns to your clinic one month post-op to discuss future medical management.
• In conjunction with the patient, you decide to start a combination of azathioprine and infliximab.
What laboratory tests should be ordered when starting azathioprine and infliximab?
Azathioprine & 6-mercaptopurine

- AGA recommends:
  - CBC every other week while dose adjusting and every 3 months thereafter
  - Periodic liver function tests
  - TPMT and NUDT15 genotype or phenotype before starting

- Tuberculosis screening: PPD or QuantGold; tx if positive

Anti-TNFs

- Tuberculosis screening: PPD or QuantGold; tx if positive
- Hepatitis B serologies, vaccination if negative, tx if positive

- Consider other vaccinations prior to initiation if possible.
  - Live virus vaccines: MMR, varicella zoster
Azathioprine $\rightarrow$ 6-mercaptopurine $\rightarrow$ Thiopurine Methyltransferase (TPMT) $\rightarrow$ 6-methylmercaptopurine

If low TPMT, much more goes towards 6-TGN leading to leukopenia

If low NUDT15, goes towards 6-TGN leading to leukopenia

6-thioguanine monophosphate

If low NUDT15, goes towards 6-TGN leading to leukopenia

6-thioguanine triphosphate

6-Thioguanine nucleotides

Rac1 inhibition, Apoptosis

DNA/RNA incorporation, Cytotoxicity

Hepatotoxicity

GST

MPK/DPK

Cellular Efflux, other

TPMT and NUDT15 available through ARUP laboratories as a send-out

PMID: 31342537
<table>
<thead>
<tr>
<th>Metabolizer Type</th>
<th>African (%)</th>
<th>Caucasian (%)</th>
<th>East Asian (%)</th>
<th>South Asian (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPMT Normal Metabolizer</td>
<td>80.2%</td>
<td>87.3%</td>
<td>95.8%</td>
<td>98.0%</td>
</tr>
<tr>
<td>TPMT Intermediate</td>
<td>9.7%</td>
<td>11.7%</td>
<td>3.39%</td>
<td>1.7%</td>
</tr>
<tr>
<td>TPMT Poor</td>
<td>0.29%</td>
<td>0.43%</td>
<td>0.030%</td>
<td>0.0076%</td>
</tr>
<tr>
<td>NUDT15 Normal Metabolizer</td>
<td>99.3%</td>
<td>98.6%</td>
<td>77.2%</td>
<td>86.4%</td>
</tr>
<tr>
<td>NUDT15 Intermediate</td>
<td>0.19%</td>
<td>0.39%</td>
<td>16.7%</td>
<td>12.4%</td>
</tr>
<tr>
<td>NUDT15 Poor</td>
<td>0.0001%</td>
<td>0.0004%</td>
<td>0.91%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

PMID: 30447069
Case #1 Continued

• Several visits later the patient returns with no complaints.
• Her last colonoscopy showed her disease was in remission.
• What healthcare maintenance recommendations should you make for this patient with IBD?
Preventative Care in IBD

<table>
<thead>
<tr>
<th>Society</th>
<th>Surveillance intervals</th>
<th>Annual surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGA 2010</td>
<td>Every 1–2 years. Extensive or left-sided colitis. After two negative exams, further examinations can be performed every 1–3 years</td>
<td>More frequent surveillance. Family history CRC in FDR, OR Ongoing endoscopic or histologic inflammation, OR Anatomic abnormality (foreshortened colon, stricture, or inflammatory pseudopolyps)</td>
</tr>
<tr>
<td>ASGE 2015</td>
<td>Interval can be lengthened beyond every 1–3 years. If mucosa is endoscopically and histologically normal on two or more surveillance colonoscopies</td>
<td>Every 1–3 years. If no risk factors requiring annual surveillance. Active inflammation. OR History of dysplasia. OR Anatomic abnormality (stricture, multiple pseudopolyps). OR Family history CRC in FDR. OR PSC.</td>
</tr>
<tr>
<td>BSG 2010</td>
<td>Lower risk. Every 5 years. Extensive colitis with no active endoscopic or histologic inflammation. OR Left-sided colitis. OR Crohn’s colitis with ≤50% involvement</td>
<td>Intermediate risk. Every 3 years. Extensive colitis with mild active endoscopic or histologic inflammation. OR post-inflammation polyps. OR Family history CRC in FDR &gt; 50</td>
</tr>
<tr>
<td>ECCO 2017</td>
<td>Every 5 years. Neither intermediate nor high risk features</td>
<td>Intermediate risk. Every 2-3 years. Extensive colitis with mild or moderate active inflammation. OR postinflammatory polyps. OR Family history CRC in FDR &gt; 50 year/old</td>
</tr>
<tr>
<td>NICE 2011</td>
<td>Low risk. Every 5 years. Extensive but quiescent ulcerative colitis or Crohn’s colitis. OR Left-sided ulcerative colitis or Crohn’s colitis</td>
<td>Intermediate risk. Every 5 years. Extensive ulcerative colitis or Crohn’s colitis with mild active inflammation. OR Post-inflammation polyps. OR Family history CRC in FDR &gt; 50 year/old</td>
</tr>
</tbody>
</table>

In patients with at least left-sided colitis begin surveillance 8 years after diagnosis. Screen every 1-2 years.

IBD patients with PSC begin screening upon diagnosis of PSC. Screen every year.
Preventative Care in IBD

Please try to vaccinate your patients prior to starting any immunosuppression

PMID: 28071656
Preventative Care in IBD

Live virus vaccines are contraindicated in patients on high level immunosuppression

<table>
<thead>
<tr>
<th>Table 3. Live vaccine recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infectious agent</strong></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Measles Mumps Rubella</td>
</tr>
<tr>
<td>Varicella</td>
</tr>
<tr>
<td>Herpes zoster</td>
</tr>
</tbody>
</table>

IBD, inflammatory bowel disease.
*See text for details.

High Level Immunosuppression (IDSA): daily corticosteroids >=20mg/day for >=14 days, or within 3 months of stopping, current treatment with anti-TNFs, ustekinumab, or tofacitinib.

Low Level Immunosuppression: Treatment with lower doses of corticosteroids, methotrexate, azathioprine, 6-MP, or vedolizumab.

PMID: 28071656
Preventative Care in IBD

Melanoma and non-melanoma skin cancers

• Patients with IBD (both UC and CD) should undergo screening for melanoma independent of the use of biologic therapy. Strong recommendation with low level of evidence.

• IBD patients on immunomodulators (6-mercaptopurine or azathioprine) should undergo screening for non-melanoma squamous cell cancer (NMSC) while using these agents, particularly over the age of 50. Strong recommendation with low level of evidence.

Cervical cancer screening

• Female IBD patients particularly on thiopurines should undergo annual cervical cancer screening.

PMID: 28071656
Preventative Care in IBD

Bone Density Scan

• Patients with conventional risk factors for abnormal bone mineral density with UC and CD should undergo screening for osteoporosis with bone mineral density testing at the time of diagnosis and periodically after diagnosis. Conditional recommendation with very low level evidence.

Smoking cessation is a must!
Outline

• Genetics of Inflammatory Bowel Disease
  • Genetic basis for IBD CD>>UC
  • Increased risk for IBD in offspring of IBD patients
  • One parent with IBD: ~10%, two parents with IBD: ~30%

• Risk of Thrombosis in Inflammatory Bowel Disease
  • Increased risk of thrombosis in both hospitalized and non-hospitalized IBD patients
  • Guidelines recommend standard prophylaxis for hospitalized patients w/o severe bleeding

• Perioperative Medical Management of Inflammatory Bowel Disease
  • If possible, avoid steroids within 30 days prior to surgery
  • Peri-operative anti-TNFs do not have increased post-surgical complications

• Optimizing therapy in Inflammatory Bowel Disease
  • Check TB and HepB status before starting immunomodulators and biologics

• Health Maintenance in Inflammatory Bowel Disease
  • Please vaccinate your IBD patients with inactivated vaccines!
  • Cancer screening
  • Bone Density Scan
  • Smoking Cessation