Management of Inflammatory Bowel Disease in 2017

“The Story of Laura”

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Financial Disclosures

- Scientific Advisory Boards
  - Takeda
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“Laura”

- 19 year old female college student
- 3 months history of *diarrhea with a small amount of rectal bleeding*
- *Intermittent abdominal pain*
  - Generalized but worse in the Rt LQ
  - Worse about an hour after eating
- *20 lbs weight loss* since symptoms began
- Non-smoker
- No family history of IBD
Physical exam

Abdominal exam reveals mild Rt LQ tenderness. No mass.

Perianal exam is normal. No fistulae or abscess.

Rest of the physical exam is unremarkable

Laboratory findings include mild anemia (Hb 11, MCV 79). Albumin is 3.5 g/dL
You suspect underlying inflammatory bowel disease and recommend a colonoscopy.

Laura is reluctant.

Q: “Aren’t there tests that can diagnose Crohn’s without a colonoscopy?”
Diagnosis of IBD

A diagnosis of Crohn’s disease can be definitively made based on which of the following tests?

(a) Elevated C-reactive protein
(b) IBD serology suggesting “Crohn’s disease pattern”
(c) CT abdomen suggesting terminal ileal thickening
(d) None of the above
Diagnosis of IBD

Fecal markers

Calprotectin
- Cytosol protein in neutrophils
- Non-specific marker of intestinal inflammation
- Elevated calprotectin can trigger need for subsequent endoscopic evaluation

<table>
<thead>
<tr>
<th></th>
<th>Healthy</th>
<th>IBS</th>
<th>IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calprotectin (mcg/mL)</td>
<td>18.9</td>
<td>21.4</td>
<td>287.4</td>
</tr>
<tr>
<td>Lactoferrin (mcg/mL)</td>
<td>2.2</td>
<td>2.8</td>
<td>138.7</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>3.2</td>
<td>3.6</td>
<td>17.6</td>
</tr>
<tr>
<td>Blood leukocytes (G/L)</td>
<td>5.3</td>
<td>5.9</td>
<td>7.8</td>
</tr>
</tbody>
</table>

Diagnosis of IBD

Serologic markers

- Serologic markers in IBD are usually antimicrobial antibodies (Crohn’s disease) or pANCA (UC)

Higher ASCA in CD (p<0.001)  
Higher pANCA in UC (p<0.001)

Back to Laura

- Agrees to a colonoscopy
  - Deep ileal ulcerations
  - No narrowing visualized
  - Linear and serpiginous ulcers throughout the colon
  - Biopsy consistent with Crohn’s disease. No granuloma

- You decide to image her small bowel to rule out a more proximal obstruction
The **best modality** to image Laura’s small bowel to look for active inflammation or obstruction is

(a) CT abdomen with neutral contrast (CT enterography)
(b) MR enterography (MRE)
(c) Small bowel follow-through
(d) Ultrasound abdomen
(e) Plain X ray
CT enterography

- CT scan with IV contrast and large volumes of neutral oral contrast to achieve luminal distention
- Allows for better mucosal resolution (active inflammation), obstructive lesions (by distending lumen)
- Less useful for extra-luminal complications
CT enterography

- Active inflammation
  - Mural hyperenhancement
  - Mural stratification
    - Acute (water), chronic (fat)
  - Engorged vasa recta
  - Fat stranding

- Fistulas
Imaging in IBD
Radiation exposure

Single CT Scan: Lifetime Attributable Risk of Cancer Death By Age*

* Assumes linear-no threshold model of cancer risk

Estimated Lifetime Attributable Risk of Death from Cancer (%)

Age at Time of CT Study (yr)

Total
Digestive
Other
Leukemia

Imaging in IBD

MR enterography

- No radiation exposure
- Similar (or slightly superior) performance as CTE for assessment of active inflammation
Back to Laura

- MR enterography shows long-segment ileal inflammation

- No strictures or fistulæ noted

Q2: “Why did I get Crohn’s disease? No one else in my family has it”
Q3: Which of the following factors are **not associated** with risk of Crohn’s disease

(a) Genetics (family history)
(b) Smoking
(c) Stress
(d) Alcohol
(e) Diet
Pathogenesis of IBD
Genetics is important

- Family history is the strongest risk factor
  - 10-fold increase incidence in family members
  - 20% of patients have a positive family history

- If a family member has CD or UC
  - Lifetime risk of IBD in first degree relatives:
    - 4.8 – 5.2% for Caucasians (non-Jewish)
    - 7.8% for Jewish patients

- Concordance is greater in identical > fraternal twins
Pathogenesis of IBD

...so is the environment

<table>
<thead>
<tr>
<th>Environmental factor</th>
<th>Disease onset</th>
<th>Disease course</th>
<th>Intervention Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD</td>
<td>++</td>
<td>++</td>
<td>✓</td>
</tr>
<tr>
<td>UC</td>
<td>-</td>
<td>-</td>
<td>✓</td>
</tr>
<tr>
<td>Appendectomy</td>
<td>-</td>
<td>? -</td>
<td></td>
</tr>
<tr>
<td>NSAIDS</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>? +</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fats</td>
<td>- ?+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fiber</td>
<td>? -</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stress</td>
<td>+</td>
<td>+</td>
<td>✓</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>-</td>
<td>-</td>
<td>✓</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>+</td>
<td>-</td>
<td>✓</td>
</tr>
<tr>
<td>Sleep</td>
<td>? +</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>
Pathogenesis of IBD
So What Happens?

You discuss the pathogenesis of Crohn’s disease with Laura and explain the expected natural history.

Q: Do I have severe Crohn’s disease?
Natural history of IBD
Progressive disease

- High potential
- Low potential

Cumulative probability

- Penetrating
- Stricturing
- Inflammatory
Natural history of IBD

Predictors of ‘severe disease’

- Need for steroids - 3.1 (95% CI 2.2 – 4.4)
- Age < 40 years - 2.1 (95% CI 1.3 – 3.6)
- Perianal disease - 1.8 (95% CI 1.2 – 2.8)

In ulcerative colitis:
- Weight loss
- Extensive colitis (UC)
Back to Laura

- Laura has no specific risk factors for severe disease which reassures his parents.

- You decide to start her on treatment

- But with what?
Which of the following therapies is appropriate for initial management of Laura’s Crohn’s disease?

(a) Ciprofloxacin and metronidazole
(b) Azathioprine or 6-Mercaptopurine
(c) Budesonide (Entocort®)
(d) Prednisone
Question #5

Management of IBD

Which of the following therapies are appropriate for long-term management of Laura’s Crohn’s disease?

(a) Prednisone or Budesonide®
(b) Anti-TNF biologic (infliximab, adalimumab, certolizumab)
(c) Mesalamine (Asacol®)
(d) Gluten-free diet
Management of IBD

Therapeutic Goals in IBD

- Normal bowel function and improved quality of life (QOL)
- Induce remission rapidly
- Maintain steroid-free remission over time (deep remission)
- Modify long-term outcomes of the disease
  - Avoid hospitalization and surgery
  - Eliminate disability
  - Minimize exposure to steroids
Management of IBD

Medical Therapies for IBD

- 5-Aminosalicylates
- Immunomodulators
- Anti-TNF
- Anti-Integrin
- Anti-IL-12/23
- Steroids
- Supportive therapy
- Antibiotics
- Sx
Management of IBD
5-Aminosalicylates

Pros
- Asacol HD® (mesalamine), Lialda®, Apriso®, sulfasalazine, balsalazide (colazal®)
  - Available in oral and topical formulations (enemas, suppositories) for local therapy
  - No systemic immunosuppression
  - Effective in mild-to-moderate ulcerative colitis

Cons
- High pill burden (less so with newer ER formulations)
- Questionable efficacy in Crohn’s disease
- May contain sulfa (sulfasalazine)
Management of IBD

Steroids, Immunomodulators

Steroids
- Very effective for induction of remission
- Also available as controlled-release formulations - budesonide (Entocort®)
- No role in maintenance of remission
- Associated with significant long-term consequences

Immunomodulators
- Azathioprine, 6-MP, methotrexate
- Effective for moderate severity disease
- Not effective for induction of remission (lag of 6-8 weeks of onset of action)
Management of IBD
Anti-TNF biologics

<table>
<thead>
<tr>
<th>Week 2/4 Response</th>
<th>Week 26/30 remission</th>
<th>Week 26/30 Overall remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>Adalimumab</td>
<td>Certolizumab pegol</td>
</tr>
<tr>
<td>58.5%</td>
<td>60%</td>
<td>64.1%</td>
</tr>
<tr>
<td>39%</td>
<td>40%</td>
<td>47.9%</td>
</tr>
<tr>
<td>22.8%</td>
<td>24%</td>
<td>30.7%</td>
</tr>
</tbody>
</table>
Management of IBD

New Therapeutic Paradigms

5-Aminosalicylates

Immunomodulators

Anti-TNF

Anti-integrin
Anti IL-12/23

Sx

Early effective treatment

Traditional "Step-up" approach
Management of ulcerative colitis

- How does management differ from Crohn’s disease?
  - Management of UC depends on (1) extent and (2) severity of disease
Management of ulcerative colitis

- **Proctitis**: Topical 5-ASA or CS

- **Extensive colitis**
  - **Mild**
    - Oral 5-ASA +/- CS
  - **Moderate**
    - Oral 5-ASA +/- CS
  - **Severe**
    - Steroids
    - Topical 5-ASA
    - Oral 5-ASA
    - AZA / 6-MP
    - Anti-TNF
    - Vedolizumab
    - Surgery
Her mom researches the drugs on the internet

Q: “I’ve heard these drugs are dangerous and can cause cancer”
The risk of which of the following is not increased in patients on immunosuppressive therapy for IBD?

(a) Reactivation of Tuberculosis
(b) Lymphoma
(c) Skin cancer
(d) Breast cancer
(e) All of the above are increased
Management of IBD

Complications of therapy

- Unpredictable side-effects
  - Drug hypersensitivity
  - Pancreatitis (Azathioprine / 6-MP)
  - Paradoxical flare (5-ASA)

- “More” predictable side-effects
  - Infections
  - Cancer
    - Lymphoma
    - Skin cancers, Cervical cancer
### Management of IBD

**Risk of Infections**

<table>
<thead>
<tr>
<th>Medication use</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>2.2</td>
<td>1.0 - 4.9</td>
</tr>
<tr>
<td>AZA/6MP alone</td>
<td>3.4</td>
<td>1.5 - 7.5</td>
</tr>
<tr>
<td>Infliximab</td>
<td>11.1</td>
<td>0.8 - 148</td>
</tr>
<tr>
<td>AZA/6MP + CS</td>
<td>17.5</td>
<td>4.5 - 68</td>
</tr>
<tr>
<td>AZA/6MP + IFX</td>
<td>1.6</td>
<td>0.1 - 19</td>
</tr>
<tr>
<td>AZA/6MP + IFX + CS</td>
<td>Infinite</td>
<td></td>
</tr>
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</table>

Management of IBD
Risk of Malignancy

Management of IBD
Risk of Malignancy
Solid organ tumors have not been associated with anti-TNF

Back to Laura

As her mother leaves the room first, Laura looks back at you and asks

Q: “Does this impact my ability to have children?”?
Question #7
Pregnancy and IBD

Which of the following is an appropriate response to Laura?

(a) You have a reduced likelihood of pregnancy
(b) You may have a higher risk of congenital anomalies
(c) There is a significant increase in risk of adverse pregnancy and fetal outcomes if you need to be on immunosuppression during pregnancy
(d) All the above
(e) None of the above
Pregnancy and IBD

- Crohn’s disease and ulcerative colitis are not associated with reduced fertility (except with J-pouch)

- Disease activity at conception is an important determinant of patient outcome during pregnancy

- Most medications are safe during pregnancy (except methotrexate; steroids may cause cleft lip / palate)

- Slight increase in LBW and SGA but otherwise comparable fetal outcomes
Summary

- Advances in diagnosis
  - Non-invasive markers of inflammation
  - Markers of prognosis
  - “Newer” imaging modalities

- Changing therapeutic paradigms
  - Recognition of new goals of treatment
  - New paradigms of treatment (“Early” / “Top-down”)

- “Comprehensive” IBD care