Update in Inflammatory Bowel Disease (IBD)

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Disclosures

- NONE RELEVANT
Objectives

• Understand current insights into the pathophysiology that underlies IBD

• Become familiar with the risk:benefit ratio in treating IBD patients

• Be cognizant of the preventive care considerations for IBD patients

• Appreciate the potential for future therapies in IBD
Inflammatory Bowel Disease (IBD) vs. Irritable Bowel Syndrome (IBS)

- **IBD** = *Inflammatory Bowel Disease*
  - chronic intestinal *inflammation*
  - Crohn disease, ulcerative colitis

- **IBS** = *Irritable Bowel Syndrome*
  - no tissue abnormality (yet…)
  - change in bowel habits
    - diarrhea/constipation/alternating bowel patterns
    - pain relieved with defecation
    - increased sensitivity to intestinal motility/stimuli (visceral hyperalgesia)
Inflammatory Bowel Diseases

Ulcerative Colitis
Confined to the colon

Crohn Disease
Any portion of the GI tract

Frequency of Involvement
Most
Least
Etiologic Theory of Inflammatory Bowel Disease

Environment: triggers, microbiome, NSAIDs, ABx

Genetic Predisposition: SNPs, epigenetics

Mucosal Immune System: innate, adaptive
While IBD Genetics has made progress…

there is still a long way to go

how many more SNPs?
what about epigenetics?
what combinations are needed?
how do the resultant proteins lead to disease?

32 loci account for 20% of the heritability of Crohn disease

Genetics of IBD: 163 confirmed loci on meta-analysis of GWAS of CD and UC

- **CD genes**
  - 30 CD specific loci
  - *NOD2* specific loci

- **UC genes**
  - 23 UC specific loci

**110 IBD loci**

Common pathways:
- Leprosy
- Mycobacterial susceptibility
- Other immune-mediated disease

**Genes in common**

But not all genetics…

- Certainly familial
  - genetics vs epigenetics
- And monozygotic concordance > dizygotic
- But only about ½ of monozygotic twins of patients with Crohn disease will develop the disease too
  - almost all grew up together with similar but not identical environmental exposures
  - even lower for UC (~20%)

Environmental Triggers

HR 2.9 (1.9 if 1st year after infection excluded)

Table 2.

<table>
<thead>
<tr>
<th>Cesarean Number</th>
<th>Emergency Number</th>
<th>Elective Cesarean Number</th>
</tr>
</thead>
</table>

Cesarean Section Delivery Is Not a Risk Factor for Development of Inflammatory Bowel Disease: A Population-based Analysis

Charles N. Bernstein, Ankona Banerjee, Laura E. Targownik, Harinder Singh, Jean Eric Ghia, Charles Burchill, Dan Chateau, and Leslie L. Roos

Food Nutrition/Acculturation

Smoking
Hygiene Hypothesis

Not just hygiene

- Diet now has ABx-fed meat, processing, preservatives, and additives
- These by themselves can lead to changes (less mucus layer, closer distance of microbes to epithelium)
  - and they also change the microbiome with more mucolytic-producing bacteria

So…nature or nurture?

- Clearly there are racial/ethnic differences in IBD phenotype and presentation:
  - Age of diagnosis and IBD subtype different
  - More upper GI tract involvement of Crohn disease in non-Hispanic whites
  - Extraintestinal manifestations may be different (not seen in our study)
  - More surgeries and use of biologics and immunomodulators in non-Hispanic whites and American IBD phenotype?

Therapeutic Pyramid in IBD: changing in the era of personalized medicine

Induction of Remission
- Unapproved therapies
- Natalizumab/Vedolizumab
- Cyclosporine (UC)
- Anti-TNF
- Corticosteroids
- 6-MP/AZA
- 5-ASA

Maintenance of Remission
- Experimental/Natalizumab
- anti-TNF
- Methotrexate (CD)
- 6-MP/AZA
- 5-ASA
Medical Therapy in IBD

- Should we be aggressive?
  - Treat early or late?
  - Step-up or Top-down?
  - Mono- or dual therapy?

- Weighing risks and benefits
  - Risks of treatment
  - Benefits of treatment
  - Risks of NO treatment
    - worse disease, cancer
Treat Early or Late?

Cumulative Probability (%)

Patients at risk:
N = 2002

Cosnes J et al. Inflamm Bowel Dis 2002;8:244-50.
Step up versus top down approach

CDAI >200, naïve to steroids, immunomodulators, and biologics

Mono- or dual therapy?

- CDAI 220-450, naïve to immunomodulators and biologics
- Similar findings in UC (SUCCESS trial)
- COMMIT (MTX) \(\rightarrow\) negative study but high response

Panaccione R. Gastroenterol 2014;146:392-400.
Medical Therapy in IBD

So the data suggest that we should:

◦ Treat early
◦ Treat aggressively
◦ Treat with combined therapy

Symptom remission

→ Steroid-free symptom remission
  → Mucosal healing
    → Deep (histologic) remission

Are we asking for problems?
What about the risk of NOT treating?

- Fewer CD surgeries in Hungary independently associated with earlier and greater AZA use.
What about the risks of NOT treating?

- Thiopurines reduce need for 1st resection in Crohn disease by 40%
  - Meta-analysis of 17 studies, >20,000 patients
  - HR: 0.59 (95% CI 0.48 – 0.73)

<table>
<thead>
<tr>
<th>Study population</th>
<th>Study name</th>
<th>Hazard ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
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</thead>
<tbody>
<tr>
<td>1.00</td>
<td>Vernier-Massouille</td>
<td>0.51</td>
<td>0.33</td>
<td>0.78</td>
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<tr>
<td>1.00</td>
<td>Ramadas</td>
<td>0.47</td>
<td>0.27</td>
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<tr>
<td>1.00</td>
<td>Schaefer</td>
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<td>1.29</td>
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<tr>
<td>1.00</td>
<td>Nguyen</td>
<td>1.18</td>
<td>0.90</td>
<td>1.55</td>
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<tr>
<td>1.00</td>
<td>Chatu</td>
<td>0.56</td>
<td>0.37</td>
<td>0.85</td>
</tr>
<tr>
<td>1.00</td>
<td>Pooled (population)</td>
<td>0.64</td>
<td>0.44</td>
<td>0.93</td>
</tr>
<tr>
<td>2.00</td>
<td>Picco</td>
<td>0.41</td>
<td>0.21</td>
<td>0.81</td>
</tr>
<tr>
<td>2.00</td>
<td>Peyrin-Birolet</td>
<td>0.50</td>
<td>0.30</td>
<td>0.83</td>
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<td>2.00</td>
<td>Gao</td>
<td>0.44</td>
<td>0.22</td>
<td>0.88</td>
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<tr>
<td>2.00</td>
<td>Camus</td>
<td>0.69</td>
<td>0.52</td>
<td>0.91</td>
</tr>
<tr>
<td>2.00</td>
<td>Pooled (hospital based)</td>
<td>0.57</td>
<td>0.45</td>
<td>0.73</td>
</tr>
<tr>
<td>Overall</td>
<td>Pooled (combined)</td>
<td>0.59</td>
<td>0.48</td>
<td>0.73</td>
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</tbody>
</table>

1= population-based study
2= hospital tertiary referral-based studies

What about the risk of NOT treating?

- Rate of IBD surgeries decreasing in last 6 decades
  - Meta-analysis of 30 studies
  - Due to better/more aggressive therapy?

What about the risk of NOT treating?

- Decreased cancer risk by aggressively treating IBD (ulcerative colitis)
  - Danish cohort
  - 178 million patient years
  - In recent years, relative risk of colorectal cancer in UC has disappeared
    - due to more aggressive therapy?

- This decrease not seen in Kaiser study
  - But probably selected for longer duration and greater severity

What about the risk of NOT treating?

- Greater risk of hospitalizations and surgeries than lymphoma

Table 1. Comparing risk of lymphoma with immunomodulator therapy vs. risk of complications due to disease progression

<table>
<thead>
<tr>
<th>Number needed to treat to cause one additional lymphoma per year with therapy</th>
<th>Azathioprine/6-mercaptopurine</th>
<th>Anti-TNF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4,357 (age 20–29)</td>
<td>2380 (ref. 56)</td>
</tr>
<tr>
<td></td>
<td>355 (age &gt;65) (ref. 38)</td>
<td></td>
</tr>
</tbody>
</table>

| Number needed to cause one additional relapse per year by stopping therapy | 3 (ref. 58) |
| Number needed to cause one additional hospitalization per year with episodic therapy | 7 (ref. 59) |
| Number needed to cause one additional abdominal surgery per year with episodic therapy | 14 (ref. 59) |

TNF, tumor necrosis factor. Numbers adapted from referenced articles.

Risk vs reward

- IBD patients are willing to accept higher risks of lymphoma and infection in exchange for longer duration of disease remission

The risk of NOT treating...

- We live in a risk-averse/loss-averse society.
  - Better to have adverse event “playing it safe” than “going for it” even if defying mathematical odds.

- Sports
  - Baseball: taking the pitch on 3-0.
  - Basketball: coming out with 5 fouls.
  - Football: punting.
  - Hockey: not pulling the goalie.

- GI
  - Holding antiplatelets/anticoagulants at endoscopy/bleeding.

- Hippocratic oath “do no harm”
  - Has become “you don’t harm”.

Sins of Omission
Getting Too Little Medical Care May be the Greatest Threat to Patient Safety

CONCLUSIONS: While preventing iatrogenic injury resulting from medical errors is a critically important part of quality improvement, we found that the overwhelming majority of substantive medical errors identifiable from the medical record were related to people getting too little medical care, especially for those with chronic medical conditions.
Prevention in IBD

- **Vaccinations**
  - no LIVE vaccines if on an anti-TNF agent
    - intranasal influenza, MMR, yellow fever, zoster
  - otherwise routine vaccinations encouraged
    - influenza, pneumococcal, HPV
    - best uptake of vaccine BEFORE immunosuppression

- **Blood Pressure monitoring → general recs**
  - more so if on corticosteroids or cyclosporine

- **Tobacco cessation**
  - for all Crohn disease
  - for all UC once disease is controlled
    - cardiovascular and oncologic risks >> UC benefit
Prevention in IBD

- **Bone health**
  - vitamin D levels
  - bone densitometry (DEXA)
    - especially if prolonged corticosteroids

- **Vitamin B12 (+/- methylmalonic acid)**
  - especially if ileal disease/resection, small bowel dysmotility/overgrowth

- **Iron**
  - unless mild probably better to replace IV (hepcidin)

- **Eye Exams**
  - annually
  - closer attention if on corticosteroids or concern for episcleritis/uveitis (extraintestinal manifestations)
Prevention in IBD

- **Malignancy screening**
  - prostate and breast → same as general recs
  - non-melanoma skin → higher with thiopurine use
  - melanoma → higher with anti-TNF use
  - cervical and anal → increased risk
    - Pap smears, HPV, ?anal Pap smear
  - colon → depends on duration, extent, and control of disease
    - routine colonoscopies

- **Depression**
  - strong psychosocial effects of disease
Prevention in IBD

- Risks of immunosuppression
  - infection → **highest** with steroids
  - non-Hodgkin’s lymphoma → slight increased risk
    - very low risk of hepatosplenic T-cell lymphoma (mostly thiopurine + anti-TNF in teenage males)
  - bone marrow suppression
  - liver toxicity
  - reactivation of hepatitis B
  - reactivation of tuberculosis
  - liver, lung, marrow, fetus → methotrexate
  - progressive multifocal leukoencephalopathy (PML)
    - natalizumab risk based on JC virus status and duration of treatment
  - acne, mood swings, sleep disturbance, weight gain, cataracts, osteoporosis, diabetes, poor wound healing, etc → **MINIMIZE STEROIDS!!**
The future...is now

The diagram illustrates the interaction between lymphocytes and endothelial cells, with various molecules and proteins involved. The text below the diagram highlights the following:

- 
  - Vedolizumab: no PML
  - Ustekinumab: IL12/23
  - MAdCAM Ab: normal CNS immunosurveillance
  - Tofacitinib: small molecule

References:
- bionews-tx.com/wp-content/uploads/2013/12/vedolizumab.jpg