Inflammatory Bowel Disease: Clinical Presentation, Diagnosis and Initial Treatment

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Disclosures

• Johnson and Johnson: Site PI Ustekinumab Trial (ended 8/31/2016)

Objectives

• Review IBD clinical presentations, differential diagnoses and evaluation choices to make the diagnosis
• Review initial IBD therapy
• Appreciate value of early biologic therapy initiation and use of combination therapy

- Due to time constraints: Emphasis on Crohn’s disease
  IBD health maintenance and alternative treatments not discussed

Case 1: Typical Crohn’s disease presentation

22 yo woman presents with five months of diarrhea, RLQ pain, and 10lb weight loss. Travel to the Caribbean 4 years ago.

What tests are routine?
What further testing is needed?
What are the management options?

Symptoms and signs of Crohn’s disease

• Diarrhea
  - Chronic, nocturnal, occasionally bloody (suggests more distal disease or deep ulceration)
• Abdominal pain
  - Especially right sided
• Fatigue
  - May have a greater need for sleep, lack of energy to exercise
• Weight loss and malnutrition
  - Mild, decreased appetite and intake, can be pain related, not always noticed
• Abdominal mass
  - Usually right side, often just greater fullness on palpation
• Fever
  - Suspicion for phlegmon, penetrating disease
• Growth delay (pediatric Crohn’s disease)

Diarrhea (suspected inflammatory)

• Stool for C. Difficile toxin
  - Vital as C. Diff is increased in IBD!
• Stool culture
  - Aeromonas
  - Pseudomonas
  - Yersinia (must ask for test)
• Stool Ova and Parasites (3 sets)
  - Giardia (antigen test)
• Stool calprotectin/lactoferrin
• Free T4
  - Hyperthyroid

Weight Loss/RLQ pain

• CBC and platelets
  - Anemia, leukocytosis or leukopenia (immunosuppression/HIV), thrombocytosis
• ESR and CRP
  - Inflammation, future monitoring
• CMP
  - Hypoalbuminemia, renal status, screen for co-existing liver disease
• Tuberculosis testing (especially at risk)
  - Unlikely to be helpful in non-immigrants, but useful in case of biologics therapy
Non-IBD Differential Diagnosis for Crohn’s Disease

- Medications – NSAIDs, mycophenylate
- Tubo-ovarian abscess, pelvic inflammatory disease
- Other intra-abdominal abscess (especially post-surgical)
- Diverticulitis (localized)
- Endometriosis
- Small bowel carcinoma
- Malignancy
  - Lymphoma, Cecal cancer; Metastatic
- Endocrine
  - Addison’s disease
- Infections
  - TB
  - Yersinia
  - Amebiasis
  - CMV
  - HIV (MAI, other opportunistic)
  - Chlamydia (LGV – perianal disease)
- Behcet’s disease
- Infiltrative disorders
  - Amyloidosis
  - Eosinophilic gastroenteritis
  - Ulcerative jejunoileitis
  - Autoimmune enteropathy
- Vasculitis
- Radiation enteritis

Differential Diagnosis: Crohn’s Disease: consider initially

- Medications – NSAIDs, mycophenylate
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Likely Crohn’s disease: Making the diagnosis

- Ileo-colonoscopy with biopsy
  - Vital for making diagnosis, especially of terminal ileal or colon disease
  - Biopsy terminal ileum, right and left colon, and rectum even with normal appearance!
    - Ileum may appear normal; determine disease extent; evaluate pathology!
- Imaging (MRE, CTE, SBFT)
  - 10% of patients have disease proximal to TI
  - 15% with penetrating disease at diagnosis
  - Get prior to colonoscopy with pain, fever, weight loss or obstruction symptoms
  - Determine extent of small bowel disease, narrowing, and complications
  - Expertise may be a factor

Ileo-colonoscopy with biopsy throughout

- Important for securing a diagnosis with histology
- Index colonoscopy most helpful in differentiating CD vs. UC
- Ruling out infection
- Risk stratification for determining medication plan
- Initial dysplasia screening

Histology

- In new IBD diagnosis, chronicity may still not be established
- Histology rarely can differentiate Crohn’s from UC unless epithelioid granulomas present
Crypt Distortion

Basal plasmacytosis

MRE vs. CTE in evaluating Crohn’s disease?

Section of thickened small bowel Crohn’s disease involvement in same patient

MRE vs. CTE in evaluating Crohn’s disease? Good Agreement

Counts of common imaging signs of Crohn’s disease among 42 patients for MRE and CTE as compared to MRE and CTE combined

MRE or CTE vs. Surgical Findings in Crohn’s disease

unexpected findings at surgery not infrequent

ITALIAN STUDY

- MRE accurately predicted surgical findings in 68 of 75 patients (80.7%)
- 7 patients surgical strategy or approach changed (9.3%)
- MRE highly sensitive for findings overall, less optimal for abscess

MRE or CTE vs. Surgical Findings in Crohn’s disease

unexpected findings at surgery not infrequent

CORNELL STUDY

- Higher than anticipated differences in 76 patients (43 MRE, 33 CTE)
- Surgical procedure modified in 20 (26%)
- Discordance rates 2 months before surgery: 25% MRE, 31% CTE

Likely Crohn’s disease: Making the diagnosis

Bottom line: At diagnosis recommend both ileocolonoscopy and either MRE or CTE (determine small bowel extent & complications)

- Ileo-colonoscopy with biopsy
  - vital for making diagnosis, especially of terminal ileal or colon disease
  - biopsy terminal ileum, right and left colon, and rectum

- Imaging (10% of patients have disease proximal to TI)
  - MRE Enterography (MRE: spares radiation, good sensitivity for findings)
  - CT Enterography (prefer if suspected abscess, rapid evaluation)
  - Small bowel series (best for careful evaluation of obstruction findings)
  - Ultrasound: studies look good, not done in the USA
Likely Crohn’s disease: Making the diagnosis

- Video Capsule Endoscopy (VCE)?
  - High sensitivity, however because of concern for Crohn’s stricture causing complication, I reserve for suspected small bowel Crohn’s disease when imaging and ileocolonoscopy are negative

- Serological studies (ASCA/ANCA)
  - Reasonable specificity (90%)
  - BUT poor sensitivity (~60%) (unless combined with calprotectin or lactoferrin)
  - Usually I reserve for special circumstances (e.g. contraindication to colonoscopy)

- Exploratory laparoscopy: “gold standard?” Rarely needed solely for diagnosis, usually for other purpose (e.g. rule out malignancy)

Video Capsule Endoscopy (VCE): niche is high NPV

- Symptomatic patients with negative colonoscopy and CTE/MRE findings
  - For diagnosis, evaluation of co-existing IBS in IBD, unexplained elevated calprotectin
  - Evaluate non-specific mucosal enhancement/thickening seen on imaging
  - Evaluate post-operative recurrence especially for more proximal CD
  - But use patency capsule first!
  - Evaluation of indeterminate colitis
  - Unexplained iron deficiency anemia in IBD
  - Promising evidence for colonic Crohn’s disease
    - Especially in children

Video Capsule Endoscopy (VCE) for small bowel CD?

- High sensitivity, yet due to concern for Crohn’s stricture causing complication, I reserve for suspected 3B Crohn’s disease when imaging and ileocolonoscopy are negative.
- Poor specificity found in a few studies (e.g. 53%, Solem, 2008)

Video Capsule Endoscopy (VCE):

Caveats in making diagnosis of Crohn’s disease

- Patients should be off of NSAIDs for >4 weeks
- Consider Crohn’s disease with >3 aphthous ulcers
  - BUT: 11% of volunteers with no NSAIDs have mucosal breaks 2 weeks after Diclofenac, 40% have mucosal breaks

Methods for assessing structural features in IBD

<table>
<thead>
<tr>
<th>Modality</th>
<th>Characteristics</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Histology | - Validated, easily possible | Sensitivity to structural changes limited to limited areas structures 
| - Prognostic value | | Incomplete resections 20% |
| SMI | - Widely available | Detection penetrating/structuring complications limited to limited areas structures 
| - Prognostic value | | Incomplete resections 20% |
| CTE | - Widely available, reproducible | Detection penetrating/structuring complications limited to limited areas structures 
| - Prognostic value | | Incomplete resections 20% |
| MRE | - High sensitivity & specificity | Detection penetrating/structuring complications limited to limited areas structures 
| - Prognostic value | | Incomplete resections 20% |
| IIE | - Detects more small bowel lesions than cross-sectional imaging | Sensitivity to structural changes limited to limited areas structures 
| - Prognostic value | | Incomplete resections 20% |

IBD Associated Serum Biomarkers

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Antigen</th>
<th>Non-IBD (%)</th>
<th>CD (%)</th>
<th>UC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCA</td>
<td>Saccharomyces cerevisiae</td>
<td>5%</td>
<td>55–65%</td>
<td>5–19%</td>
</tr>
<tr>
<td>pANCA – antineutrophil cytoplasmic antibody</td>
<td>Histone H1, bacterial antigen?</td>
<td>&lt;5%</td>
<td>2–25%</td>
<td>50–65%</td>
</tr>
<tr>
<td>Anti-cmpC</td>
<td>E. Coli</td>
<td>&lt;5%</td>
<td>40–60%</td>
<td>2%</td>
</tr>
<tr>
<td>Anti - G2</td>
<td>Pseudomonas fluorescense</td>
<td>5–10%</td>
<td>54%</td>
<td>10%</td>
</tr>
<tr>
<td>Anti-Flagellin</td>
<td>cBfR</td>
<td>8–10%</td>
<td>~50%</td>
<td>6%</td>
</tr>
</tbody>
</table>

1. Jensen et al, Inflamm Bowel Dis 2011
2. Goldstein et al, Gastroenterol Hepatol 2005
3. Malten L, J Gastroenterol, 2009
Accuracy of pANCA and ASCA to Distinguish Patients With IBD (n=554) From Controls (n=231)

Specificity is good (90 to 97%) - But inevitably a colonoscopy will be performed
Sensitivity is poor (50 – 60%), and therefore a negative test means little (NPV is low). So why test?

Main concern is IBD vs. IBS
- Poor negative predictive value (neg. test being true negative) with only ASCA and ANCA
- However, NPV over 90% if add Fecal Calprotectin (yet most IBD was active)

36 CD patients – CDAI 12 – 434; Avg 162
28 UC patients – All with Active Disease (Mayo 3 – 11; Avg 6)
30 IBS patients Schoepfer et al., Inflamm Bowel Dis, 2008

Fecal Calprotectin and Lactoferrin are Elevated in active IBD with mucosal inflammation (not sensitive enough to exclude IBD)

What additional testing is needed?
- Utility of screening EGD in adult-onset CD debated
  - Standard in pediatric IBD evaluations
  - Prioritize if dyspepsia, abdominal pain, vomiting
  - Upper GI tract disease found in 16% of patients irrespective of symptoms
  - Association between CD and H. pylori-negative focal gastritis
  - Rule out co-existing celiac disease?
    - IBD increased in celiac (up to 2%) but not vice-versa (0.5% celiac in IBD)
    - But when found can make a big difference in treating IBD
  - Test for vitamin B12, vitamin D deficiency and Iron saturation
    - Early B12 deficiency has identified in my practice Cronh's patients presenting as UC

Case 2: Typical UC presentation
35 yo man presents with two months of loose stools with rectal bleeding, cramping LLQ pain, mild anemia

DIFFERENTIAL DIAGNOSIS OF ULCERATIVE COLITIS:
- Crohn's disease
- NSAIDS
- Ischemia
- Malignancy (signet cell cancer)
- Radiation Colitis
- SLE
- Diverticular disease
- Infection
- Clostridium Difficile
- Amoebiasis
- CMV
- syphilis, HSV, chlamydia, gonorrhea
- Amyloidosis
SUSPICION OF INCORRECT DIAGNOSIS OF IBD?

- Elderly (be sure it’s not ischemia or malignancy)?
- Atypical pathology
  - Especially mild findings: NSAIDs, diverticular disease, malignancy, amyloidosis
- Travel coinciding with onset?
- Extensive use of NSAIDs?
- Mucocutaneous aphthous lesions of mouth or genitals?
  - Consider Behcet’s disease
- Immunosuppression/HIV?
- Proctitis and history of unprotected receptive anal intercourse?
  . . . And always check for C. Diff!

IBD: Be sure to query/inspect for perianal disease and extra-intestinal manifestations of IBD

- Perianal disease
  - Diagnosis Crohn’s disease
  - Anal skin tags suggest Crohn’s
  - Consider anti-TNF early
  - All patients should see an ophthalmologist even without eye symptoms
  - Kidney stones are common
  - Need low oxalate diet
  - CT of liver with elevated Alk phos, bilirubin to r/o PSC

Perianal disease – diagnostic options

- 100% accuracy with any 2 modalities:
  - MRI pelvis
  - Rectal EUS
  - Exam under anesthesia

CD medical management: Stratify by risk

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Moderate/High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at initial diagnosis &gt; 30 years</td>
<td>Age at initial diagnosis &lt;30 years</td>
</tr>
<tr>
<td>Limited anatomic involvement</td>
<td>Extensive anatomic involvement</td>
</tr>
<tr>
<td>No perianal and/or severe rectal disease</td>
<td>Perianal and/or severe rectal disease</td>
</tr>
<tr>
<td>Superficial ulcers</td>
<td>Deep ulcers</td>
</tr>
<tr>
<td>No prior surgical resections</td>
<td>Prior surgical resection</td>
</tr>
<tr>
<td>No stricturing and/or penetrating disease</td>
<td>Stricturing and/or penetrating disease</td>
</tr>
</tbody>
</table>

Evidence for top down therapy

- Early pediatric evidence for azathioprine
- Top down versus step up trial – top down strategy yielded better rates of mucosal healing than step up
- Biologic more effective when given early in disease course
- Serologic predictors

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Is there a role for early thiopurine monotherapy in Crohn’s disease?

- There is further data that thiopurines play a limited role as a stand-alone agent early in diagnosis – AZTEC trial
  - 156 adults with recent CD diagnosis randomized to azathioprine at 2.5mg/kg/d vs. placebo – otherwise only steroids allowed
  - At 76 wks, rate of corticosteroid-free remission was 44.1% vs. 36.5%

Whom to choose for combination therapy

- Need to weigh a number of factors
  - Disease severity and extent
  - Men vs. women – HSTCL
  - Advanced age (overall risk vs. benefit reduced above age 65)*
  - Concerns with adherence
  - Ultimately if disease is severe, it’s important to be aggressive upfront, and then peel away medication after remission is achieved
    - Lymphoma risk with thiopurines mainly noticed after 1 year of use

2009 ACG guidelines: Treatment options guided by patient’s risk

- Low-risk
  - Ileum and/or proximal colon
  - Course of Budesonide 9 mg per day with or without AZA
  - Tapering course of prednisone with or without AZA
  - Diffuse or left colon
  - Tapering course of prednisone with or without AZA

- Moderate/High Risk
  - Anti-TNF+AZA > AZA monotherapy or anti-TNF monotherapy
  - Anti-TNF monotherapy > no therapy or AZA monotherapy
  - Consider MTX if thiopurine not tolerated

2016 ECCO guidelines

- Mild disease – oral budesonide
- Moderate disease
  - Budesonide or prednisone
  - Anti-TNFs in patients who are dependent, refractory or intolerant of steroids
  - Immunomodulator can be considered as an alternate to anti-TNF
- Severe disease
  - Systemic steroids
  - Anti-TNF with or without immunomodulator
  - Vedolizumab in patients refractory to steroids and/or anti-TNF

*Lewis, Schwartz, Lichtenstein Gastroenterology 2000, 1018-24

*Consider PPI therapy for upper tract disease
In my practice for Crohn’s disease...

- Patients with moderate to severe disease and requiring any steroid (prednisone or budesonide) are started on immunosuppressive therapy.
- I rarely start thiopurines as monotherapy (mainly in those with greater TB risk – travel, job)
- I will combine with severe disease presentations and may withdraw after 1 year.
- Patients generally start infliximab or adalimumab
- But in women with future childbearing plans and milder disease I recommend certolizumab (does not cross placenta)
- Patients failing or are intolerant to anti-TNFs are started on ustekinumab
  - There may be a role for ustekinumab as first-line given safety profile
  - Lower efficacy of vedolizumab reserved for third-line agent
- Mild disease
  - budesonide at first; prednisone if distal colonic disease
  - early recurrence: prednisone and consider sulfasalazine* or AZA
- Avoid narcotics and get patients off of narcotics!

*only mesalamine with significant evidence for Crohn’s disease

With a grain of salt: comparative effectiveness of Infliximab (IFX) vs. Adalimumab (ADA) or Certolizumab-Pegol (CZP)

Drug management - UC

Low-risk disease

- Induction therapy
  - Oral 5-ASA and/or anti-TNF
  - Oral budesonide MMX slow-release and/or anti-TNF
  - Rectal steroids

- Maintenance
  - Maintenance with oral 5-ASA and/or rectal 5-ASA
  - Taper steroid over 60 days if remission or relapse - proceed to high-risk algorithm

High-risk disease (outpatient)

- Induction therapy
  - Steroids + initiation of thiopurine (oral steroids over 60 days)
  - Anti-TNF, with or without thiopurine
  - Vedolizumab +/- IMM

- Maintenance
  - Thiopurine alone
  - Anti-TNF, with or without thiopurine
  - Vedolizumab +/- IMM

Emerging change in practice: Adding vedolizumab as first-line agent in UC

- AGA guidelines give equal consideration to anti-TNF and vedolizumab
- Data support best efficacy of vedolizumab in treatment-naive patients
- No increased risk of any infection or serious infection
- 2830 patients, follow-up ~ 4811 patient-years
- Infusion reaction <1% patients
- <1% patients diagnosed with malignancy
- Consider in patients where avoidance of anti-TNF risks would be preferred (e.g. elderly patients, patients with history of TB, malignancy)
- Infliximab may still be most cost-effective first-line agent

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Important caveats:
- No direct comparisons
- Data represents all patients
- Not stratified by prior TNF exposure
- Not stratified by patients on IMM

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UC: Considering choice of biologic

CD: Considering choice of biologic

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8/23/2017
In my practice for UC . . .

**MILD:**
- Initiate with oral 5-ASA, use rectal therapy (5-ASA or topical steroids) if needed for better control of limited distal disease
- Consider sulfasalazine with joint/skin EIMs
- Maintenance with 5-ASA
- May add probiotics (VSL#3) or Curcumin (1.5 grams BID) if 5-ASA fails to maintain control

**MODERATE – SEVERE**
- Patients with severe disease are started on infliximab +/- thiopurine
- Patients hospitalized with severe disease may benefit from dosing at 10mg/kg
- Patients with more moderate disease azathioprine with steroid taper, vs. infliximab or adalimumab, vs. vedolizumab with a steroid taper
- Certain populations may benefit from vedolizumab as first line therapy
  - Elderly, recent or current malignancy, TB exposed