Best Practices in the Diagnosis and Treatment of Inflammatory Bowel Disease

Talk outline

• Overview of IBD
• Review of benefits and risks of different medication classes
• Recent advances in IBD
• Quality improvement
IBD overview

- Chronic inflammatory condition of the GI tract – affects up to 1.4 million persons in the US
- Generally presents in patients in their teens or 20s
- Predisposing factors:
  - Genetics
  - Bacteria
  - Triggers – GI infections, NSAIDs, antibiotics

Global map of IBD incidence

IBD Incidence in North America

Incidence has increased dramatically¹
1940s: 2-3 cases per 100,000 person-years
1990s: 8-9 cases per 100,000 person-years

Newly diagnosed cases²
UC: 7000 to 46,000 per year
CD: 10,000 to 47,000 per year


Incidence of UC and CD over time in Olmsted County, Minnesota¹

Ulcerative colitis
Crohn’s disease

UC
Diffuse mucosal inflammation limited to colon
Affects rectum
May involve all or part of rest of colon

CD
Patchy transmural inflammation
May affect any part of GI tract
**Crohn’s disease**

- Chronic inflammatory disorder of the entire gastrointestinal tract
- Traditionally, up to 75% of patients will require at least 1 surgery
- There is no cure – patients generally need to stay on medication indefinitely


**Crohn’s disease distribution**

- Ileal Crohn’s disease
- Ileocolonic Crohn’s disease
- Colonic Crohn’s disease
- Upper GI Crohn’s disease
- Perianal Crohn’s disease
Distingushing Features of Crohn's Disease

Ulcerative Colitis

- Chronic inflammatory disorder of the colon and rectum
- Traditionally, 30-40% of UC patients eventually require colectomy


Diagnosis in IBD
Diagnosing IBD: Laboratory data

- Complete blood count (CBC)
  - Anemia, inflammation, infection
- ESR, C-reactive protein
  - Markers of inflammation
- Metabolic panel
  - Dehydration, electrolyte depletion, liver abnormalities
- Stool studies
  - Infection, inflammation

Diagnostic tools for IBD

- Ileocolonoscopy
- Small bowel imaging
  - Small bowel series
  - Computed tomography
  - Magnetic resonance imaging
  - Capsule endoscopy
- Serum biomarkers
- Fecal biomarkers
Diagnosing IBD: Endoscopy - CD

- Ulcers in Crohn's disease
- Strictures in Crohn's disease
- Anastomoses in Crohn's disease

Diagnosing IBD: Endoscopy - UC

0 = NORMAL  
1 = MILD  
2 = MODERATE  
3 = SEVERE

- No friability or granularity  
- Intact vascular pattern  
- Erythema  
- Decreased vascular pattern  
- Mild friability  
- Marked erythema  
- Absent vascular pattern  
- Friability  
- Erosions  
- Marked erythema  
- Absent vascular markings  
- Granularity  
- Friability  
- Spontaneous bleeding  
- Ulcerations


Slide courtesy of A. Kornbluth
### Methods for assessing structural features in IBD

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileocolonoscopy</td>
<td>Validated, widely available</td>
<td>Limited to luminal structures</td>
</tr>
<tr>
<td></td>
<td>Sensitive to changes</td>
<td>Incomplete examinations 20%</td>
</tr>
<tr>
<td></td>
<td>Prognostic value</td>
<td></td>
</tr>
<tr>
<td>- SBFT</td>
<td>Widely available</td>
<td>Patient tolerance</td>
</tr>
<tr>
<td></td>
<td>Detection penetrating/stricturing complications</td>
<td>Radiation exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bowel transit time</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No information about extraenteric disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>misses mild disease</td>
</tr>
<tr>
<td>- CT</td>
<td>Widely available, reproducible</td>
<td>Radiation exposure and overuse</td>
</tr>
<tr>
<td></td>
<td>Less interobserver variation</td>
<td>Misses mild disease</td>
</tr>
<tr>
<td></td>
<td>Fast study</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Extraenteric structures</td>
<td></td>
</tr>
<tr>
<td>- MRI</td>
<td>High sensitivity &amp; specificity</td>
<td>Limited availability</td>
</tr>
<tr>
<td></td>
<td>Reproducible over time</td>
<td>Heterogeneity in image acquisition and interpretation</td>
</tr>
<tr>
<td></td>
<td>Extraenteric structures</td>
<td>Have to lie still for appropriate breath-holding sequences</td>
</tr>
<tr>
<td></td>
<td>No radiation</td>
<td>Misses mild disease</td>
</tr>
<tr>
<td></td>
<td>Better for perianal disease</td>
<td></td>
</tr>
<tr>
<td>- WCE</td>
<td>Detects more small bowel lesions than cross-sectional imaging</td>
<td>Heterogeneity in interpretation</td>
</tr>
<tr>
<td></td>
<td>Widely available</td>
<td>Lower specificity for Crohn’s disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Capsule retention</td>
</tr>
</tbody>
</table>

### Small bowel series

![Small bowel series](image-url)
Small bowel series

MURAL HYPERENHANCEMENT
INCREASED MURAL THICKNESS

MURAL STRATIFICATION
(laminated appearance of thickened small bowel)
COMB SIGN – dilated vasa recta in the mesenteric vasculature

MR Small bowel CD

T1 Coronal plane. MRI       Endoscopy

Ordas I. DDW 2010. Abs # 546
Normal small bowel, good distention of bowel loops

Thickened terminal ileum

MR Small bowel CD

Gralnek, et al. APT 2008; 27: 146-154

Villous appearance (normal vs edematous), patchy or diffuse

Ulceration – number; extent; size, shape

Stricture – number, ulcerations, traversable

Capsule endoscopy in IBD

Gralnek, et al. APT 2008; 27: 146-154
Serum Biomarkers Associated with IBD

<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>5-15%</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-ompC</td>
<td>E. Coli</td>
<td>&lt;5%</td>
<td>40–50%</td>
<td>2%</td>
</tr>
<tr>
<td>Anti - I2</td>
<td>Pseudomonas fluorescens</td>
<td>5-10%</td>
<td>54%</td>
<td>10%</td>
</tr>
<tr>
<td>Anti-Flagellin</td>
<td>cBIR</td>
<td>8-10%</td>
<td>~50%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Complications increase with antibody sums

![Graph showing frequency of disease behavior (%) with OR values for number of immune responses.](image)

Dubinsky et al, Am J Gastroenterol 2006; 101: 360
**Fecal Calprotectin is Elevated with Increased Mucosal Inflammation in UC**

<table>
<thead>
<tr>
<th>Clinical activity index</th>
<th># of patients</th>
<th>Fecal calprotectin μg/ml</th>
<th>Endoscopic activity</th>
<th>Mean ± SD</th>
<th>Range</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission (0-4)</td>
<td>26</td>
<td>34 ± 29</td>
<td>9-132</td>
<td>1.9 ± 1.6</td>
<td>0-7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (5-10)</td>
<td>41</td>
<td>309 ± 287*</td>
<td>15-1148</td>
<td>6.4 ± 3.4*</td>
<td>1-12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate (11-17)</td>
<td>46</td>
<td>480 ± 309#</td>
<td>43-1436</td>
<td>8.8 ± 2.9#</td>
<td>3-12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe (≥ 18)</td>
<td>21</td>
<td>807 ± 232§</td>
<td>418-1371</td>
<td>11.3 ± 1.3§</td>
<td>8-12</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* P<0.01 btwn remission and mild; # P<0.01 btwn mild to moderate; § P<0.01 btwn moderate to severe

### Sensitivity (SENS), Specificity (SPEC), Positive Predictive Value (PPV), Negative Predictive Value (NPV), and Accuracy

<table>
<thead>
<tr>
<th></th>
<th>SENS (%)</th>
<th>SPEC (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calprotectin ≥ 50μg/g</td>
<td>93</td>
<td>71</td>
<td>91</td>
<td>81</td>
<td>89</td>
</tr>
<tr>
<td>Calprotectin ≥ 100μg/g</td>
<td>86</td>
<td>88</td>
<td>96</td>
<td>65</td>
<td>86</td>
</tr>
<tr>
<td>Clinical activity index ≥ 5</td>
<td>81</td>
<td>52</td>
<td>84</td>
<td>47</td>
<td>73</td>
</tr>
<tr>
<td>CRP ≥ 5mg/L</td>
<td>60</td>
<td>67</td>
<td>84</td>
<td>37</td>
<td>62</td>
</tr>
</tbody>
</table>

**Medical therapy for IBD**
Medical therapy in IBD

- Currently there is no cure for Crohn’s
- The only cure for ulcerative colitis is taking out the colon
- All but the patients with the mildest of disease will need to be on chronic lifelong therapy
- Goals of therapy –
  - Induce and maintain a clinical remission
  - Avoid complications of the disease
  - Achieve a good quality of life
  - Minimize short and long term toxicity

Medications in IBD – Benefits and Risks
**Medication Classes**

- 5-aminosalicylic acid agents
- Steroids
- Thiopurines
- Anti-TNF agents
- Natalizumab

**FDA approval table**

- Crohn’s disease –
  - Induction – mild to moderate
    - budesonide
  - Induction and maintenance – moderate to severe
    - infliximab, adalimumab, certolizumab pegol, natalizumab
- UC –
  - Induction – mild to moderate
    - budesonide MMX
  - Induction and maintenance – mild to mod
    - 5-aminosalicylic acid
  - Induction and maintenance - mod to severe
    - infliximab, adalimumab, simponi
**5-aminosalicylic acid (5-ASA) – benefits**

- Effective for induction and maintenance of remission of mild to moderate ulcerative colitis
- Comes in several forms – Azulfidine, Asacol, Lialda, Pentasa, Apriso
- Often combination therapy with rectal 5-ASA (Rowasa, Canasa) works better than oral alone
  - For proctitis, can treat with topical 5-ASA alone
- Probably a role for Pentasa with mild Crohn’s, but probably not more severe disease

**5-aminosalicylic acid - risks**

- Generally very safe and well tolerated
  - With some formulations need to take up to 12 pills a day
- A minority of patients will actually get worse on this class of medications
- Need to check kidney function (blood test) once a year
Corticosteroids - benefits

- Effective in the induction, but not maintenance of remission in both Crohn’s and UC
- Most common formulations are Prednisone and Entocort
- In UC, usually used with active flares when 5-ASAs are not working
  - Usually involves starting prednisone at 40mg a day, and taper over 8 – 10 weeks
- In Crohn’s involving the small intestines and right colon (most common locations), Entocort is preferred over prednisone

Corticosteroids - risks

- The long-term risks of steroids are significant:
  - Diabetes
  - High blood pressure
  - Increased risk of infection
  - Osteopenia and osteoporosis
  - Avascular necrosis of the hip
  - Water retention / weight gain
  - Cataracts
  - Skin thinning / bruising
  - Hormonal imbalance
  - Anger, anxiety or other psychiatric effects
Corticosteroids - risks

- Overall, 55% of patients on corticosteroids will have an adverse event and will have to discontinue therapy
- Historically, Crohn’s patients on corticosteroids have a high likelihood of becoming steroid dependent or requiring surgery
- **Long-term treatment with steroids is inappropriate !!!**

Thiopurines - benefits

- Steroid sparing oral agents
  - 2 medications – Imuran, 6-mercaptopurine
- Oral immunosuppressives – effective in maintaining remission in Crohn’s and UC in about 50% of patients
  - Usually started when 5-ASAs are not enough to control moderate to severe symptoms or for steroid dependence
  - No role for inducing a remission because it takes 2-4 months to become clinically active
    - Usually combined with a steroid taper when it is started
Thiopurines - risks

- Potential reactions / adverse events
  - Low white blood cell count
  - Increased risk for infection
  - Increased risk for lymphoma
    - About 4-5 times over the general population
  - Elevated liver function tests
  - Pancreatitis (3%)
  - Allergic reaction
  - Fatigue

- Need close blood monitoring
  - Especially important when medication is first started

- Overall, about 10% of patients will need to stop the medication because of a reaction or adverse event

Effectively communicating risk of lymphoma

(Siegel et al. APT 2011;33(1):23-32)
Anti-TNF agents - benefits

- Approved for induction and maintenance of remission for Crohn’s (infliximab, adalimumab, certolizumab pegol) and UC (infliximab, adalimumab, golimumab)
  - Usually started when 5-ASAs or thiopurines are not enough to control moderate to severe symptoms, or for steroid dependence
  - The most effective therapy available for perianal fistulizing disease
Anti-TNF agents - risks

- Potential reactions / adverse events
  - Immediate or delayed infusion or injection site reaction
  - Increased risk for infection
  - The risk of lymphoma is unknown
- Overall, about 10% of patients will have an adverse event, but only 1/250 events will be serious
  - Caution must be taken in combining these medications with steroids for an extended period
- Additionally, up to 50% of patients will lose response to an agent over time
  - Can switch to another anti-TNF, but usually not as effective as the first agent

Natalizumab - benefits

- Effective in inducing and maintaining remission in Crohn’s disease
  - Also effective therapy in multiple sclerosis
- Administered as a once monthly infusion
- Usually started in patients who have failed an anti-TNF agent and for whom surgery is not a good option
- Patients must be off all immunosuppressants other than steroids
Natalizumab - risks

- Potential reactions / adverse events
  - Progressive multifocal leukoencephalopathy (PML)
    - 1:1000 risk, fatal or debilitating if acquired
    - Need close monitoring with neurologic exams – TOUCH program
    - Major risk factors – JC virus positive, prior immunosuppressives, use greater than 24 months
    - If it does not work in the first 3 months, it is stopped

CD - ACG guidelines (2009) – mild to moderate disease

- A
  - Sulfasalazine at 3-6g/d for colonic disease
  - Budesonide for ileal/right colon disease
  - Mesalamine less effective than steroids
- B
- C
  - Mesalamine at 3.2-4g daily
  - Metronidazole 10-20mg/kg/d in patients not responding to sulfasalazine
### CD – ACG guidelines (2009) - moderate to severe disease

#### A
- Prednisone for induction
- Azathioprine for maintenance of remission
- Anti-TNFs for patients with inadequate response with steroids, immunomodulators
  - Infliximab and infliximab/azathioprine more effective than azathioprine alone
- Natalizumab for patients with inadequate response to anti-TNF

#### B
- Methotrexate for steroid dependent and refractory patients
- Anti-TNF as alternative to steroid therapy in select patients

---

### UC – ACG guidelines (2010) - mild to moderate disease

#### A
- Sulfasalazine (4-6g/d) or 5-ASAs
- Thiopurines for patients who don’t respond to steroids
- Infliximab for patients steroid refractory or dependent who have failed thiopurine

#### B
- Oral steroids for patients resistant to combination oral/topical 5-ASAs

---

Lichtenstein et al. Am J Gastroenterol 2009;104:2208-20
UC – ACG guidelines (2010) - moderate to severe colitis

• A
  – 5-ASAs effective in reducing relapses
  – Thiopurines for maintenance of remission
  – Infliximab effective for induction and maintenance

• Recent advances in IBD
  – Top-down vs. step-up therapy
  – Mucosal healing as a goal of treatment
  – Using our medications smarter
  – When can immune based therapy be stopped
  – When is medical therapy futile
  – New and upcoming agents

I. Step-up vs. top-down therapy

Inflammatory Bowel Disease

Experimental Therapies
(IL-10/IV Azathioprine)
Infliximab
Cyclosporine
Methotrexate
6-Mercaptopurine/ Azathioprine
IV Corticosteroids
Oral Corticosteroids
Antibiotics
5-ASA/Sulfasalazine
Topical 5-ASA

Therapeutic pyramid
Top-down therapy

- Most applicable to Crohn’s disease
- Refers to starting anti-TNF agent (often with a thiopurine agent)
  - New data emerging that combination therapy may be most effective early in the course of disease
  - The hope is this will decrease complication, hospitalization and surgery rates
- Need to weigh the benefits and risks of combination therapy
  - Important to understand at diagnosis who will have an aggressive course with complications and need for early surgery
  - In the future, we will be able to better predict on the basis of clinical, genetic, and laboratory factors

II. Mucosal healing as a goal of therapy

- Clearly the chief goal of therapy is to induce and maintain a clinical remission
- There is evidence that patients in clinical remission who also achieve “mucosal healing” are less likely to flare over time
  - Mucosal healing does not always correlate well with clinical symptoms
- Currently our medications do an overall poor job at achieving mucosal healing
- There is no clear consensus as to how we should strive to achieve mucosal healing as a goal of therapy
III. Using our medications smarter

- Sometimes it is difficult to determine how well a medication is working
  - Everyone is different
- 6-MP/azathioprine – can check levels of the active metabolite
- Infliximab – can check levels of infliximab as well as antibody levels
  - Very expensive test, even with insurance
IV. When can anti-TNF or thiopurine therapy be safely stopped?

• In most cases, therapy cannot be safely stopped without a significant risk of relapse
• In patients on an anti-TNF agent in combination with a thiopurine agent, a subset of patients probably can stop one the medications
  – In order to achieve this, patients should have clinical and endoscopic remission as well as have no elevated markers of inflammation
  – We are only now learning which factors predict the ability to come off medication

V. When is medical therapy futile in IBD

• Sometimes medical therapy is inappropriate. Examples include:
  – A scarred down stricture that is best approached with surgery
  – Extensive fistulizing disease or abscess within the abdomen which needs surgery (followed by medical therapy)
  – Patients with no detectable active disease
VI. New agents available

- Ulcerative colitis –
  - Budesonide MMX for induction of mild to moderate ulcerative colitis
  - Adalimumab for induction and maintenance of moderate to severe disease
  - Golimumab for induction and maintenance of moderate to severe disease
- Crohn’s – nothing recent

VI. New agents: in development

- Ulcerative colitis –
  - Vedolizumab – cousin of natalizumab
    - Does not affect the CNS
  - Tofacitinib – oral agent – beginning Phase III study
- Crohn’s disease –
  - Ustekinumab – Phase III, finished enrolling
  - Vedolizumab
Cost effectiveness

- There is a growing push to use more biologic agents such as infliximab and adalimumab
- These medications are expensive!
- In order to sustain this, they have to show that they are cost-effective

Direct medical costs for CD: 18K per patient per year
- IBD patients are more likely to have emergency room visits, hospitalizations and surgeries than patients without IBD
- Inpatient costs make up a significant costs of an IBD patient
• Biologics – very expensive
  – Infliximab – weight based – 2-4K per infusion, minimum of 6 infusions per year
  – Adalimumab – 2K per month
• Biologics have been shown to decrease the rate of hospitalization and surgery

• Recent systematic review in Crohn’s disease
• Infliximab and adalimumab were found to be cost effective when given induction therapy followed by episodic therapy for 5 years
• Unclear if still cost effective when maintenance therapy administered

• Often need to raise dose in non-responders
  – Checking drug levels can be helpful
    • Current tests prohibitively expensive
• In UC, surgery – colectomy with J-pouch procedure may be cost-effective
  – Versus continued surveillance strategies

Quality improvement
How is the AGA helping improve quality of care in IBD?

Develop measures

AGA Task Force on Quality
Members of AGA, CCFA, Research Community, Physician Consortium for Performance Improvement (PCPI), Surgeon, Internist, Payor, patient

National Quality Forum (NQF)
National consensus organization for quality measures

Approve measures

Centers for Medicare and Medicaid Services (CMS)
Voluntary individual reporting program to provide an incentive payment for those who satisfactorily report data on quality measures

Physician Quality Reporting System (PQRS)

AGA IBD QI Measures 2012 PQRS

1. Document disease activity and severity
2. Recommend steroid-sparing therapy after 60 days
3. Assess bone health if steroid-exposed
4. Recommend influenza vaccine
5. Recommend pneumococcal vaccine
6. Document recommendation for cessation of smoking
7. Assess for HBV status pre-anti-TNF
8. Assess for latent TB pre-anti-TNF

www.gastro.org/practice/quality-intiatives
CCFA Quality Program – Step 1

- Developing a set of “Quality Indicators” (QIs)
- QIs are measureable elements of practice performance for which there is evidence or consensus that can be used to assess the quality of care provided and hence change it.
- Quality Indicators are minimally acceptable care (i.e. necessary care)


Developing “Process” QIs

- 500 + Potential QIs from Practice Guidelines
- Top 100 List
- 35 Candidate QIs
- Final Top 10 QIs

Electronic voting + in-person RAND panel

2nd RAND panel December 2010

QI subcommittee

>2000 articles with 21 reviewers

Literature review & electronic voting
CCFA Process Measures
“Highlights”

- Test for TB before anti-TNFα therapy
- Test for *C. difficile* in flares
- Flex sig. for CMV in steroid-refractory hospitalized UC
- Check TPMT before starting thiopurines
- Recommend steroid-sparing agents if >4m steroids
- Recommend colectomy or close surveillance for low-grade dysplasia in colitis
- Recommend smoking cessation if smoker with CD
- Educate patients regarding vaccinations


Developing “Outcome” Measures

- 73 Potential Outcome QIs from
  (a) Committee Suggestions
  (b) “Because” Statements
  (c) Improve Care Now
  (d) Committee Chairs

- Electronic voting + in-person RAND panel (DDW 2011)

- Top 40 List

- Final Top 10 Outcome QIs
CCFA Outcome Measures

- Steroid-free clinical remission
- Days lost from work/school
- Days hospitalized
- ED visits
- Malnutrition
- Anemia
- Normal health related QOL
- Narcotic use
- Nighttime BMs or leakage
- Incontinence


Conclusions

- IBD is a complex, heterogeneous condition that affects patients for many decades
- Significant morbidity and associated costs to society
- Effective medications are available, but very expensive