Inflammatory Bowel Disease: Diagnosis, Treatment and Management
Faculty

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Disclosures

• Kimberly Carter, MS, PA-C has no financial relationships with commercial interests to disclose.

• Gerald W. Dryden, MD, MSPH, MSc, AGAF, FASGE serves on the speaker’s bureaus of Abbvie, Takeda, EnteraHealth and Salix. Dr. Dryden also conducts contracted research for Abbvie, Johnson & Johnson, Merck, Takeda, Pfizer, and Genetech.
Learning Objectives

After participating in the proposed educational activities, clinicians should be better able to:

1. Recognize patients with inflammatory bowel disease (IBD) who are at risk for complications, as determined by clinical indicators
2. Apply individualized treatment strategies to clinical IBD presentations to maximize outcomes while minimizing toxicity
3. Identify patients who are at high risk of complications from IBD specifically targeting new treatment goals including mucosal healing and deep remission
4. Implement treat to target therapy where appropriate to optimize benefits from IBD treatment options and facilitate adherence
PRE-TEST QUESTIONS
Pre-test ARS Question 1

On a scale of 1 to 5, please rate how confident you would be in evaluating and treating a patient with inflammatory bowel disease (IBD).

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
Pre-test ARS Question 2

Which clinical presentation of Crohn’s disease predicts an increased risk for progression to surgery?

1. 18 year old female who required surgery two years ago for small bowel fistula and intra-abdominal abscess. She now has recurrent symptoms of active Crohn’s.
2. 52 year old male who has taken mesalamine for 5 years to control occasional LLQ cramps, and intermittent diarrhea from colonic Crohn’s.
3. 33 year old male who required steroids at the time of initial diagnosis to control his severe abdominal pain and diarrhea from ileal Crohn’s. He smokes 2 packs of cigarettes per day.
4. 67 year old asymptomatic female who was found to have a few ileal ulcerations on screening colonoscopy.
5. 1 and 3
6. 2 and 4
Pre-test ARS Question 3

A 21 year old female presents with RLQ abdominal pain 6 months after resection of a strictured terminal ileum. A recent colonoscopy demonstrated multiple small bowel ulcerations despite ongoing infliximab therapy. Which action would most closely follow the “Treat to Target” strategy?

1. Continue with current dose of infliximab
2. Add oral mesalamine to her regimen
3. Order infliximab levels plus antibody to infliximab and decide to change dose or switch to different therapy
4. Repeat colonoscopy in 1 year to see if disease progresses
Pre-test ARS Question 4

A 38 year old male with long-standing pan-ulcerative colitis presents with an additional 2-3 bowel movements daily with occasional blood. You check for C. difficile and testing is negative. He wants to avoid the steroid side effects he’s had in the past. You recommend the following therapy:

1. Initiate infliximab induction dosing 5 mg/kg at 0, 2 and 6 weeks
2. Prescribe oral prednisone 60 mg daily
3. Initiate azathioprine 2.5 mg/kg daily
4. Begin colonic delivery of budesonide at 9 mg daily
5. All of the above
A 43 year old female with severe Crohn’s colitis has been well controlled on infliximab for years. She has recently experienced recurrent symptoms of RLQ abd pain and diarrhea. Colonoscopy demonstrated active ulcerations. Which diagnostic test can help you determine the cause of her flare?

1. Obtain stool sample for C. difficile testing
2. Send blood for CBC
3. Check infliximab levels and antibodies to infliximab
4. Order fecal calprotectin level
5. 1 and 3
6. 2 and 4
IBD: Clash of the host and environment

1. Defecative Adaptive Immunity
2. Innate Immune Response
3. Leaky TJ
4. "Leaky" epithelial barrier

Fava WJG 2011
IBD progression can be disabling
Efficacy of medical therapy dependent on degree of structural damage

Cosnes et al. Inflamm Bowel Dis 2002;8:244-50
Sx associated with IBD

- **DIARRHEA**: mucus or blood may be present in the stool; can occur at night; incontinence may occur.

- **ABDOMINAL PAIN**: commonly present in RLQ in CD; periumbilically or LLQ in moderate to severe UC.

- **CONSTIPATION**: may be primary symptom in ulcerative colitis and inflammation limited to rectum; obstipation may occur and may proceed to bowel obstruction.

- **ABNORMAL BMs**: pain or rectal bleeding may be present, as well as severe urgency and tenesmus.

- **NAUSEA & VOMITING**: occurs more often in CD than UC.

Distinguishing IBD from IBS

• Differentiate purulent exudate from mucus
  – Presence of blood suggests pus associated with IBD

• Presence of blood in stool favors IBD
  – Bleeding more likely in UC than CD

• Scrutinize ROS for systemic sx, extraintestinal sx

• Specifically ask about prior history of peri-anal abscess, fistula, or fissure
  – May predate onset of IBD by years
Distinguishing IBD from IBS

• Alternating diarrhea and constipation more strongly suggestive of IBS than IBD

• Nocturnal diarrhea more common in IBD

• Functional symptoms remaining after bout of enteric infection may confuse the clinical diagnosis
  – Lingering abdominal pain, loose/urgent stools should prompt objective evaluation by endo/path
  – Post infectious IBS common but don’t want to miss IBD triggered by infection
Useful Laboratory Tests

• Blood work
  – CBC, TSH, ESR, c-RP

• Serologic markers
  – Anti-Saccharomyces cerevisiae Antibody (ASCA), Anti-neutrophil cytoplasmic antibody (ANCA), anti-OmpC, anti-CBir1

• Thiopurine metabolite levels
  – 6-methylmercaptopurine (MMPN) → liver toxicity
  – 6-thioguanine (TGN) → bone marrow toxicity

• Biologic drug levels (Infliximab, adalimumab)

• Antibodies to therapeutic agent
Confirming the diagnosis of IBD

• Clinical picture

• Endoscopic information/pathologic specimens

• Radiographic evidence

• Chronic course of symptoms
Endoscopic features of IBD

*Ulcereative colitis*

- Continuous inflammation extending from rectum proximally
- Variable mucosal changes from mild to severe
- Presence of ulcerations suggestive of fulminant colitis
- Evaluate for other causes of symptoms (infection, ischemia)
Endoscopic features of IBD

Crohn’s Disease

- Patchy edema, erythema
  - Discontinuous
- Apthous ulcerations
- Coalescing ulcerations
- Cobblestoning
CT/MR Enterography: Radiographic Eval of CD

- Non-invasive alternative to colonoscopy
- Detects mucosal ulcerations, fistulas and abscesses
- Can differentiate acute inflammation from fibrosis
- CT faster scan, radiation exposure
- MR longer scan, no radiation

Clinical scenario # 1

A 34 year old female diagnosed with Crohn’s disease presents with recurrent mild abdominal pain, diarrhea and bloating

She has a low grade fever on exam, with mild RLQ tenderness and a mildly elevated WBC

She has no gastroenterologist at this time, and has been in and out of the ER for abd pain

A colonoscopy from 3 months ago showed small apthous ulcers and recent stool studies were nl
Clinical scenario # 1

You would like to initiate therapy. What step do you take next?

1. Repeat colonoscopy
2. Order CT scan of the abdomen with contrast
3. MR enteroscopy
4. Evaluate disease severity to determine starting point for therapy
# Harvey Bradshaw Index of Severity

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. General well-being (0=very well, 1=slightly below par, 2=poor, 3=very poor, 4=terrible)</td>
<td></td>
</tr>
<tr>
<td>B. Abdominal pain (0=none, 1=mild, 2=moderate, 3=severe)</td>
<td></td>
</tr>
<tr>
<td>C. Number of liquid stools per day</td>
<td></td>
</tr>
<tr>
<td>D. Abdominal mass (0=none, 1=dubious, 2=definite, 3=definite and tender)</td>
<td></td>
</tr>
<tr>
<td>E. Complications (add 1 point per item present)</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td></td>
</tr>
<tr>
<td>Uveitis</td>
<td></td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td></td>
</tr>
<tr>
<td>Aphthous ulcers</td>
<td></td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
<td></td>
</tr>
<tr>
<td>Anal fissure</td>
<td></td>
</tr>
<tr>
<td>New fistula</td>
<td></td>
</tr>
<tr>
<td>Abscess</td>
<td></td>
</tr>
</tbody>
</table>

**TOTAL HARVEY BRADSHAW SCORE =**

**Activity Level**

- **<5** remission
- **5-7** mild disease
- **8-16** mod disease
- **>16** severe disease

Response = > 3pt drop
Determining activity/severity of CD

- Difficult task
  - Poor correlation between clinical score and colonoscopy

CDAI = Crohn’s Disease Activity Index  CDEIS = Chron’s Disease Endoscopic Index of Severity

2. Modigliani et al. Gastroenterology 1990;98;811-8
Biomarkers vs Colonoscopy

<table>
<thead>
<tr>
<th>N=140¹</th>
<th>SENS %</th>
<th>SPEC %</th>
<th>PPV %</th>
<th>NPV %</th>
<th>ACCU %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calprotectin &gt;70ug/g</td>
<td>89</td>
<td>72</td>
<td>88</td>
<td>76</td>
<td>87</td>
</tr>
<tr>
<td>CRP &gt; 5 mg/l</td>
<td>68</td>
<td>58</td>
<td>88</td>
<td>29</td>
<td>66</td>
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<tr>
<td>WBC &gt; 7.9 g/l</td>
<td>55</td>
<td>50</td>
<td>83</td>
<td>21</td>
<td>54</td>
</tr>
<tr>
<td>CDAI &gt; 150</td>
<td>33</td>
<td>68</td>
<td>80</td>
<td>20</td>
<td>40</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N = 164²</th>
<th>IL-6</th>
<th>Calprotectin</th>
<th>Lactoferrin</th>
<th>CDAI</th>
<th>SES-CD</th>
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</thead>
<tbody>
<tr>
<td>hs-CRP</td>
<td>0.65</td>
<td>0.47</td>
<td>0.52</td>
<td>0.16</td>
<td>0.46</td>
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<tr>
<td>IL-6</td>
<td></td>
<td>0.45</td>
<td>0.55</td>
<td>0.15</td>
<td>0.43</td>
</tr>
<tr>
<td>Calprotectin</td>
<td>0.76</td>
<td>0.23</td>
<td></td>
<td></td>
<td>0.45</td>
</tr>
<tr>
<td>Lactoferrin</td>
<td></td>
<td>0.19</td>
<td></td>
<td></td>
<td>0.48</td>
</tr>
<tr>
<td>CDAI</td>
<td></td>
<td></td>
<td></td>
<td>0.15</td>
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</table>

Current therapies for IBD

- **5-ASA (UC)**
  - Oral delayed release/sustained release formulations
  - Pro-drugs: Sulfasalazine, Olsalazine, Balsalazide
  - Once daily formulations: Apriso, Lialda

- **Immunomodulators (UC, CD)**
  - 6-mercaptopurine, azathioprine
  - Methotrexate

- **Biologics – Anti-TNF Ab**
  - Infliximab/Remicade (CD, UC)
  - Adalimumab/Humira (CD, UC)
  - Certolimumab/Cimzia (CD)
  - Golimumab/Simponi (UC)

- **Biologics – Anti-Integrin Ab**
  - Natalizumab/Tysabri (CD)
  - Vedolizumab/Entyvio (CD, UC)

- **Steroids (UC, CD)**
  - Prednisone
  - Methylprednisolone
  - Budesonide
  - Uceris (UC)
  - Enterocort (CD)
American College of Gastroenterology: Adult CD treatment guidelines

• Mild to moderate Crohn’s disease:
  – Use of oral mesalamine or sulfasalazine is:
    • Minimally effective compared to placebo (A)
    • Less effective than budesonide or prednisone (A)

• Moderate to severe Crohn’s disease:
  – Use of oral prednisone 40-60mg daily is effective (A)
    • > 50% of treated patients become dependent/resistant
    • Elemental diets are less effective that prednisone, but can spare side effects (A)
    • AZA is effective at maintaining steroid induced remission (A)
    • MTX is effective at maintaining steroid induced remission (A)
    • Anti-TNF Ab are effective at inducing remission (A)
Predictors of rapid progression to surgery

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Current smoker</td>
<td>3.09 (1.47-6.51)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1.82 (1.05-3.18)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>2.07 (1.04-4.10)</td>
</tr>
<tr>
<td>Ileal localization only</td>
<td>2.22 (1.30-3.81)</td>
</tr>
<tr>
<td>Oral corticosteroid use in initial 6 months</td>
<td>3.79 (1.90-7.55)</td>
</tr>
</tbody>
</table>

OTHER PREDICTORS:
- Onset age < 40
- Presentation with fistulizing disease
- Need for operation early in disease course

Prognosis of CD patients with severe colonic ulcerations

- Retrospective cohort
- 102 pts with active CD
- Evaluated by colonoscopy for Severe endoscopic lesions (SEls - deep ulcerations >10% of mucosal area in at least one colonic segment)
- Need for colectomy increased over time when SEls present

Risk factors that identify patients likely to benefit from biologic therapy

• Complex fistula
• Deep ulcerations on endoscopy
• Young age
• Steroid resistance/dependence
• High risk anatomic locations (foregut disease, extensive disease, perianal disease)
• Severe disease activity (evidenced by wt loss, low albumin, anemia)
Considerations prior to anti-TNF therapy

• Preparation for therapy
  – Quantiferon Gold +/- TB skin test (ppd)
  – Chest X-ray
  – Hepatitis B - HepBsAg, HepBsAb, HepBcoreAb

• Contraindications:
  – History of CHF, MS/optic neuritis, active infection

• Ongoing therapy requires monitoring
  – Regular CBC, CMP testing
Month 6 Remission in CD with TNF Ab

(Patients Failing Aminosalicylates, Steroids, Immunosuppressants)

Certolizumab pegol – PRECISE 2
- Open-Label Induction Week 6: Pbo 64.1%, CzP 28.6%
- Week 26 Remission: Pbo 47.9%, CzP 30.7%
- Net Remission Week 26: Pbo 18.3%, CzP 29.5%

Infliximab – ACCENT I
- Open-Label Induction Week 2: Pbo 58.5%, IFX 21.0%
- Week 30 Remission: Pbo 39.0%, IFX 12.3%
- Net Remission Week 30: Pbo 22.8%

Certolizumab pegol – PRECISE 1
- Net Remission Week 26: Pbo 18.3%

Adalimumab – CHARM
- Open-Label Induction Week 4: Pbo 58.0%, ADA 17.0%
- Week 26 Remission: Pbo 40.0%, ADA 9.9%
- Net Remission Week 26: Pbo 23.2%

ADA=adalimumab; CZP=certolizumab pegol; IFX=infliximab
SONIC: Combination therapy for CD

- Subjects 21 years of older:
  - Moderate to severe CD (CDAI >220 and <450)
  - No prior exposure to biologics/immunomodulators
  - Normal TPMT

- Randomized to one of three arms:
  - Azathioprine 2.5mg/kg/day
  - Inflixamab 5mg/kg
  - Azathioprine + Inflixamab

- 1<sup>st</sup> endpoint: steroid-free remission at week 26
Steroid-free remission at week 26

Primary Endpoint

Mucosal healing at week 26

SONIC

Secondary Endpoint

Proportion of Patients (%)


Anti-Integrin Therapy for IBD
GEMINI II: Vedolizumab in CD
Efficacy at weeks 6 and 52

Placebo (N=148)
Vedolizumab (N=220)

Patients (%)

Response (Wk 6) 25.7 31.4 Δ 5.7
Remission 6.8 14.5 Δ 7.7
Response (Wk 52) 30.1 43.5 Δ 13.4
Remission 21.6 39 Δ 17.4
Steroid-free Remission 15.9 39 Δ 23.1

P=0.23
P=0.02
P=0.01
P<0.001
P=0.02

Clinical Scenario # 2

• You have assessed the patient from scenario #1 as having mild Crohn’s disease of the terminal ileum.

• She was started on antibiotics and mesalamine during her last ER visit. With her continued symptoms, she is asking you to help her control her symptoms.
Clinical Scenario #2

Based on the patient’s disease parameters and best treatment practices, which treatment would you recommend?

1. Tell her to hang in there, the medication should start working in the next few weeks.
2. Switch her to budesonide 9mg daily for 8 weeks
3. Consider the initiation of biologic therapy such as infliximab
4. All of the above
5. None of the above
Top-level recommendations for CD

- Objective evidence of the presence of inflammation should drive clinical decision making, not the presence of symptoms alone

- Combining antimetabolite therapy and a TNF-α-inhibitor results in optimal efficacy and protects the latter against sensitization

- Step-care is obsolete in CD

- Earlier intervention with combination therapy in high-risk patients will likely lead to improved results
Current therapies for IBD

- **5-ASA (UC)**
  - Oral delayed release/sustained release formulations
  - Pro-drugs: Sulfasalazine, Olsalazine, Balsalazide
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  - Prednisone
  - Methylprednisolone
  - Budesonide
  - Uceris (UC)
  - Enterocort (CD)
Starting Point for Mild-Mod Ulcerative Colitis

Therapy is stepped up according to severity at presentation or failure at prior step

- **Aminosalicylate**
- **Corticosteroid**
- **Infliximab**
- **Cyclosporine**

**Disease Severity at Presentation**

- **Severe**
  - 5-ASA: Once daily
  - 3x daily
  - 4x daily

- **Moderate**
  - Aminosalicylate
  - Corticosteroid

- **Mild**
  - Aminosalicylate

**Induction**

- Infliximab
- Cyclosporine

**Maintenance**

- Infliximab
- Thiopurine

**Colectomy**
Site of delivery
Based on 5-ASA Formulation

- Topical therapy’s ability to reduce inflammation directly linked to ability to reach site of inflammation

- 20% pancolitis
  - Oral
- 30-40% beyond sigmoid
  - Enema
- 40-50% rectosigmoid
  - Suppository
## Determining UC severity

### Truelove and Witt’s Mayo Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mild</th>
<th>Severe</th>
<th>Fulminant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stools</td>
<td>&lt;4</td>
<td>&gt;6</td>
<td>Continuous</td>
</tr>
<tr>
<td>Blood</td>
<td>Intermit</td>
<td>Freq</td>
<td>Continuous</td>
</tr>
<tr>
<td>Temp</td>
<td>NI</td>
<td>&gt;37.5</td>
<td>&gt;37.5</td>
</tr>
<tr>
<td>Pulse</td>
<td>NI</td>
<td>&gt;90</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Hgb</td>
<td>NI</td>
<td>&lt;75%</td>
<td>Transfusion</td>
</tr>
<tr>
<td>ESR</td>
<td>&lt;30mm</td>
<td>&gt;30</td>
<td>&gt;30</td>
</tr>
</tbody>
</table>

All mild parameters = mild severity
Fewer than all six severe = moderate
All 6 severe = severe

Stool frequency
0 = Normal
1 = 1-2 stools/day more than normal
2 = 3-4 stools/day more than normal
3 = > 5 more stools/day more than normal

Rectal bleeding
0 = None
1 = Visible blood with less than 50% of stools
2 = Visible blood with more than 50% of stools
3 = Passing blood alone

Mucosal appearance on endoscopy
0 = Normal or inactive disease
1 = Mild disease
2 = Moderate disease
3 = Severe disease

Physician rating of disease severity
0 = Normal
1 = Mild
2 = Moderate
3 = Severe

< 2 = remission
3-6 = moderate
6-12 = moderate to severe
Establishing UC Disease Activity: Clinical Grading vs Endoscopic Reality

Cohort study: Among 369 patients with UC undergoing colonoscopy, agreement between endoscopic findings and clinical grading correlated in only 56% of cases.

Reguiero et al. Inflamm Bowel Dis 2011;17(4):1008-14
ACG practice guidelines: Adult ulcerative colitis

- UC suspected on clinical grounds should be confirmed by endoscopic and histologic data

- Left-sided UC can be treated with oral or topical 5-ASA or topical steroids (A)
  - Topical 5-ASA is more effective than oral (A)
  - Combination of oral and topical 5-ASA than either alone (A)
  - Pts refractory to oral may still respond to topical (A)
  - Pts refractory to above or systemically ill may respond to prednisone 40-60mg or anti-TNF (C)

ACG Practice Guidelines: Adult ulcerative colitis

- Mild to moderate extensive UC can be treated with 4-6g sulfasalazine or 4.8g mesalamine (A)

- Oral prednisone 40-60mg reserved for 5-ASA failures or those needing speedy relief (B)
  - AZA/6-MP effective for sx not completely relieved by steroids (A)
  - Infliximab is an effective strategy to steroid dependent patients (A)

- Pts with severe colitis not responding to oral therapy should be admitted for IV tx

Clinical Scenario # 3

• A 34 year old male was diagnosed with left-sided ulcerative colitis of mild severity. He initiated 5-ASA therapy dose on a TID basis.

• He responds well initially, but has a flare 6 months later. His gastroenterologist placed him on a 5-ASA suppository. Despite that, his diarrhea stools have increased by 1-2 more than usual per day. Less than half contain blood.
Clinical Scenario # 3

• You workup his diarrhea to rule out other causes and evaluate endoscopic appearance. There is no evidence of C diff or other infectious causes. Endoscopy reveals mild colitis.

Choose the most appropriate regimen to reduce steroid side effects.

1. Azathioprine 2.5mg/kg/day after TPMT testing
2. Once daily MMX budesonide (Uceris) 9mg x 8 wks
3. Inflixamab 5mg/kg 0, 2, 6 weeks then q8 weeks + Azathioprine 2.5mg/kg/day
4. None of the above
5. All of the above
MMX Budesonide (Uceris) for UC

- Budesonide: potent CS with high first-pass metabolism
- Widely used clinically
- Previously available in ileal release form for CD
- Alternative to systemic steroid therapy for mild to moderate UC
Oral MMX Budesonide

<table>
<thead>
<tr>
<th></th>
<th>Uceris 6 mg</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Overall CS side effect</td>
<td>14.5</td>
<td>11.5</td>
</tr>
<tr>
<td>Mood changes</td>
<td>6.5</td>
<td>3.3</td>
</tr>
<tr>
<td>Sleep changes</td>
<td>4.8</td>
<td>4.9</td>
</tr>
<tr>
<td>Acne</td>
<td>4.8</td>
<td>0</td>
</tr>
<tr>
<td>Moon face</td>
<td>4.8</td>
<td>4.9</td>
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<tr>
<td>Abnormal DEXA</td>
<td>14.3</td>
<td>12.8</td>
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</table>

Travis et al. Gastroenterology 2012;142(Suppl 1): S556
Budesonide MMX Foam

- RDBPC trial in mild to mod distal UC
- Budesonide MMX foam 2mg vs placebo foam
- Primary endpoint:
  - Clinical remission
- Secondary endpoints:
  - Endo score < 1
  - Bleeding = 0

### Adverse Rxn

<table>
<thead>
<tr>
<th></th>
<th>Budesonide</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Blood cortisol</td>
<td>17%</td>
<td>2%</td>
</tr>
<tr>
<td>Adrenal insuff</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Δ = 17.2
Δ = 16.0
Δ = 20.0
UC Remission Rates with TNF Ab
(Patients Failing Aminosaliyclates, Steroids, Immunosuppressants)

2. Rutgeers et al. NEJM 2005;353:2462-76
SUCCESS: Combo therapy for UC

- Subjects 21 years of older:
  - Moderate to severe UC (Mayo score 6-12)
  - Naive to biologics or immunomodulators (or off for at least 3 months)
  - Normal TPMT

- Randomized to one of three arms:
  - Azathioprine 2.5mg/kg/day
  - Inflixamab 5mg/kg at 0, 2, 6 weeks then q8 weeks
  - Azathioprine + Inflixamab

- **1**° endpoint: steroid-free remission at week 16
Clinical remission without corticosteroids at week 16


\[
\Delta = 17.67; \ P = .017 \\
\Delta = 16.06; \ P = .032 \\
\Delta = -1.61; \ P = .813 \\
39.74
\]
Mucosal healing at week 16

Secondary Endpoint

GEMINI I: Vedolizumab in UC
Primary and secondary outcomes through 52 Weeks, maintenance ITT population

Treat to Target Strategy

- Shift from step-wise management to a proactive treat to target therapy in efforts to achieve new treatment goals of mucosal healing and deep remission.
- Use of objective clinical evidence and biological outcomes.
  - Laboratory, radiographic, endoscopic, histologic findings.
  - Therapeutic drug monitoring.
- Implement therapeutic adjustments/dose optimization where appropriate to optimize benefits from IBD treatment.

Implications of Dose Optimization

• Highest quartile generally has highest remission

• Higher trough levels enhance maintenance of remission, reduce immunogenicity

• Concomitant IMM reduces anti-drug Ab formation (in many, but not all, instances)

• Co-administration of IMM may help improve duration of response to therapy
Optimizing Therapy Via Drug Monitoring

- 82 pts with IBD flare on qow ADA → qw ADA
- Classified by ADA trough level (TRA), Ab to ADA (ATA)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Grp A</th>
<th>Grp B</th>
<th>Grp C</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRA&gt;4.9, ATA + (25%)</td>
<td>TRA&lt;4.9, ATA neg</td>
<td>TRA&lt;4.9, ATA&gt;10ng/ml</td>
<td></td>
</tr>
<tr>
<td>CR at 6 mos</td>
<td>29.2%</td>
<td>67%</td>
<td>12%</td>
</tr>
<tr>
<td>Time to relapse</td>
<td>5 (+/-2) mos</td>
<td>15 (+/-5) mos</td>
<td>4 (+/-3) mos</td>
</tr>
</tbody>
</table>

52 ADA failures at 6 mos induced with IFX

<table>
<thead>
<tr>
<th>Achieved CR</th>
<th>Grp A</th>
<th>Grp B</th>
<th>Grp C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>32%</td>
<td>50%</td>
<td>87%</td>
</tr>
<tr>
<td>CR at 6 mos</td>
<td>6.9%</td>
<td>25%</td>
<td>80%</td>
</tr>
<tr>
<td>Time to relapse</td>
<td>3 (+/-2) mos</td>
<td>5 (+/-3) mos</td>
<td>14 (+/-7) mos</td>
</tr>
<tr>
<td>CR at 12 mos</td>
<td>0%</td>
<td>0%</td>
<td>55%</td>
</tr>
</tbody>
</table>

Roblin et al. AJG 2014:109;1250-56
Clinical Decisions Based on Ab Status

<table>
<thead>
<tr>
<th>Dz Activity</th>
<th>Drug Trough Level</th>
<th>Ab to Drug</th>
<th>Clinical Decision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>No need to ✓</td>
<td>No need to ✓</td>
<td>Continue TX</td>
</tr>
<tr>
<td>Active dz, prior response</td>
<td>Trough level &gt; 5</td>
<td>Present or absent</td>
<td>Switch MOA</td>
</tr>
<tr>
<td>Active dz, prior response</td>
<td>Trough level &lt; 5</td>
<td>Absent</td>
<td>Dose Intensify</td>
</tr>
<tr>
<td>Active dz, prior response</td>
<td>Trough level &lt; 5</td>
<td>Present</td>
<td>Switch TNF</td>
</tr>
<tr>
<td>Active dz, no response</td>
<td>Trough level &lt; 5</td>
<td>Absent</td>
<td>Dose Intensify</td>
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<tr>
<td>Active dz, no response</td>
<td>Trough level &gt; 5</td>
<td>Present or absent</td>
<td>Switch MOA</td>
</tr>
</tbody>
</table>
Summary IBD

• Clinical symptoms correlate poorly with endoscopic activity in IBD

• Patients must be evaluated with laboratory markers, advanced imaging or colonoscopy to determine active inflammation

• Steroids: effective short-term but use should be minimized by steroid-sparing agents

• Biologic therapy for IBD increasingly becoming treatment of choice, especially when risk factors present
Summary IBD

- 5-ASA has no role in the treatment of Crohn’s disease
- Pts with risk factors predicting poor outcome should be offered combination therapy
- Therapeutic drug monitoring and checking for anti-drug antibodies can improve outcomes
- Consider newer therapies such as vedolizumab for patients failing conventional therapy or anti-TNF/immunomodulators
POST-TEST QUESTIONS
Post-test ARS Question 1

Which clinical presentation of Crohn’s disease predicts an increased risk for progression to surgery?

1. 18 year old female who required surgery two years ago for small bowel fistula and intra-abdominal abscess. She now has recurrent symptoms of active Crohn’s.

2. 52 year old male who has taken mesalamine for 5 years to control occasional LLQ cramps, and intermittent diarrhea from colonic Crohn’s.

3. 33 year old male who required steroids at the time of initial diagnosis to control his severe abdominal pain and diarrhea from ileal Crohn’s. He smokes 2 packs of cigarettes per day.

4. 67 year old asymptomatic female who was found to have a few ileal ulcerations on screening colonoscopy.

5. 1 and 3

6. 2 and 4
Post-test ARS Question 2

A 21 year old female presents with RLQ abdominal pain 6 months after resection of a strictured terminal ileum. A recent colonoscopy demonstrated multiple small bowel ulcerations despite ongoing infliximab therapy. Which action would most closely follow the “Treat to Target” strategy?

1. Continue with current dose of infliximab
2. Add oral mesalamine to her regimen
3. Order infliximab levels plus antibody to infliximab and decide to change dose or switch to different therapy
4. Repeat colonoscopy in 1 year to see if disease progresses
A 38 year old male with long-standing pan-ulcerative colitis presents with an additional 2-3 bowel movements daily with occasional blood. You check for C. difficile and testing is negative. He wants to avoid the steroid side effects he’s had in the past. You recommend the following therapy:

1. Initiate infliximab induction dosing 5 mg/kg at 0, 2 and 6 weeks
2. Prescribe oral prednisone 60 mg daily
3. Initiate azathioprine 2.5 mg/kg daily
4. Begin colonic delivery of budesonide at 9 mg daily
5. All of the above
Post-test ARS Question 4

A 43 year old female with severe Crohn’s colitis has been well controlled on infliximab for years. She has recently experienced recurrent symptoms of RLQ abd pain and diarrhea. Colonoscopy demonstrated active ulcerations. Which diagnostic test can help you determine the cause of her flare?

1. Obtain stool sample for C. difficile testing
2. Send blood for CBC
3. Check infliximab levels and antibodies to infliximab
4. Order fecal calprotectin level
5. 1 and 3
6. 2 and 4
Post-test ARS Question 5

On a scale of 1 to 5, please rate how confident you would be in evaluating and treating a patient with inflammatory bowel disease (IBD).

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
Post-test ARS Question 6

Which of the statements below describes your treatment of patients with inflammatory bowel disease?

1. I do not treat inflammatory bowel disease, nor do I plan to this year.
2. I did not treat inflammatory bowel disease before this course, but as a result of attending this course I’m thinking of treating it now.
3. I do treat inflammatory bowel disease and this course helped me change my treatment methods.
4. I do treat inflammatory bowel disease and this course confirmed that I don’t need to change my treatment methods.