Clinical Challenges in Ulcerative Colitis 2012

David T. Rubin, MD, FACG
Professor of Medicine
Associate Section Chief for Education
Co-Director, Inflammatory Bowel Disease Center

What are the Clinical Challenges in UC?

• We don’t know the cause.
• We don’t have a (medical) cure.
• Patients live with active disease and symptoms.
• There is a high rate of primary non-response to medical therapy.
• There is a high rate of secondary loss of response to therapy after an initial response.
• Patients are afraid of side effects of their medications.
• Identifying the right timing for surgery (medically-refractory disease as well as with dysplasia).
• The IBD patient who is pregnant.
• Patient adherence to therapy.
• Misinformation about treatments abound on the internet.
Goals of Management for IBD

- Confirmation of diagnosis
- Induction of remission
- Maintenance of sustained, steroid-free remission
  - DEEP REMISSION
  - Healing the mucosa
- Prevention of hospitalization, surgery

What Prevents us from Accomplishing our Goals?

- Inaccurate classification system
  - Variations in phenotypes
  - Changing patterns over time
- Ineffective therapies
  - Mechanisms don’t work
  - Inter-patient variation
  - Wrong dosing
  - Lack of patient adherence
- Wrong goals for management (symptom-based vs. more objective)
- Focus on short-term management and not long-term goals
- Disconnect between patient and health care provider (lack of communication, misunderstanding, different expectations)
Patients’ concerns about ulcerative colitis

- 4034 completed questionnaires from 49,410 members of CCFA
  - Average age first symptoms experienced: 34 yrs
  - Average time to diagnosis: 2.47 yrs
  - ≥1 flare in preceding 12 months: 74%

<table>
<thead>
<tr>
<th>Primary concerns</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developing cancer</td>
<td>23</td>
</tr>
<tr>
<td>Uncertainty of disease progression</td>
<td>22</td>
</tr>
<tr>
<td>Losing bowel control</td>
<td>18</td>
</tr>
<tr>
<td>Energy level</td>
<td>12</td>
</tr>
<tr>
<td>Ostomy bag</td>
<td>8</td>
</tr>
<tr>
<td>Using steroids</td>
<td>7</td>
</tr>
<tr>
<td>Medication effects</td>
<td>5</td>
</tr>
<tr>
<td>Surgery</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment satisfaction</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine En-tabs</td>
<td>87</td>
</tr>
<tr>
<td>Dipentum</td>
<td>75</td>
</tr>
<tr>
<td>Canasa</td>
<td>74</td>
</tr>
<tr>
<td>Asacol</td>
<td>73</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>67</td>
</tr>
<tr>
<td>Rowasa</td>
<td>65</td>
</tr>
<tr>
<td>Pentasa</td>
<td>63</td>
</tr>
<tr>
<td>Colazal</td>
<td>62</td>
</tr>
</tbody>
</table>

Efficacy (97%) and lack of AE (74%) were the most important attributes

Loftus, Inflamm Bowel Dis 2006;12:1107–13

UC NORMAL Study

- Internet based US survey to assess how patients perceive the impact of their diseases.
  - UC: 451
  - RA: 309
  - Asthma: 305
  - Migraines: 305
- 300 gastroenterologists were also surveyed about their UC patients

Most patients see flare-ups of UC as “normal”

- Believe it is normal to have flare-ups: 74%
- Believe # of flare-ups they experience is normal: 81%
- Believe that even more flare-ups would be normal: 62%


Most UC patients report that living with UC is difficult and disruptive

<table>
<thead>
<tr>
<th></th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>UC is disruptive to their lives generally (% very or somewhat)</td>
<td>77%</td>
</tr>
<tr>
<td>To their emotional state (% very or somewhat)</td>
<td>82%</td>
</tr>
<tr>
<td>Having sexual relations (% very or somewhat)</td>
<td>75%</td>
</tr>
<tr>
<td>Their relationship with a spouse or partner (% very or somewhat)</td>
<td>64%</td>
</tr>
<tr>
<td>Relationship with other family/friends (% very or somewhat)</td>
<td>59%</td>
</tr>
<tr>
<td>UC makes it difficult to lead a normal life (% somewhat or strongly agree)</td>
<td>62%</td>
</tr>
<tr>
<td>Living with UC is a daily struggle (% somewhat or strongly agree)</td>
<td>61%</td>
</tr>
<tr>
<td>Having UC has wrecked important moments in their lives (% somewhat or strongly agree)</td>
<td>60%</td>
</tr>
<tr>
<td>Feel UC controls them, rather than them controlling UC (% somewhat or strongly agree)</td>
<td>53%</td>
</tr>
</tbody>
</table>

Diagnostic Considerations in Ulcerative Colitis

Diagnosis in IBD

Primary Dx of IBD
- Rule out imposters
- Obvious GI symptoms/signs and classic presentation
- Extra-intestinal symptoms/signs and findings
- Re-evaluation over time

Clarification of IBD Dx
- Ileocolonoscopy with biopsy
- Distinction between IBS and active inflammation
- Reliable expert pathology
- Evaluation of small bowel – WCE – CTE/MRE
- Exam under anesthesia, exploratory lap
- Use of other clues – family history – serologies – Non-GI specialists
Historical Features that Help to Confirm a Diagnosis of IBD

- Appendectomy protects against UC
- Ex-smokers may develop UC
- Smokers have CD
- Family history usually concordant

Early Appendectomy Protects Against UC

In patients with appendicitis.

Most Common “Imposters” in the Differential Diagnosis of IBD

- Infectious colitis (including Clostridium difficile)
- Ischemic colitis
- Drug-induced (NSAID) enterocolitis
- Solitary rectal ulcer syndrome
- Radiation enterocolitis

- Diversion colitis
- Endometriosis
- Malignancy
- Functional (IBS)
- Diverticular disease
- Acute self-limited colitis

Understanding Your Patient’s Disease Behavior Helps with Treatment and Discussions of Prognosis

Disease Behaviors of Ulcerative Colitis

Figure 1. Four predefined curves, depicting different courses of ulcerative colitis from diagnosis to 10 years’ follow-up. N = the number of non-operated patients (n = 379) reporting on each of them. Data were missing for six patients (1%).

### Disease Progression in Ulcerative Colitis

<table>
<thead>
<tr>
<th></th>
<th>Farmer¹</th>
<th>Stonnington²</th>
<th>Leijonmarck³</th>
<th>Langholz⁴</th>
<th>Sinclair⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>1116</td>
<td>182</td>
<td>1586</td>
<td>1161</td>
<td>537</td>
</tr>
<tr>
<td>Type of practice</td>
<td>Referral</td>
<td>Community</td>
<td>Community</td>
<td>Community</td>
<td>Community</td>
</tr>
<tr>
<td>Initial extent &lt; pancolitis</td>
<td>63%</td>
<td>~67%</td>
<td>63%</td>
<td>80%</td>
<td>89%</td>
</tr>
<tr>
<td>Extension From proctitis</td>
<td>46%</td>
<td>70%</td>
<td>29%</td>
<td>Not given</td>
<td>Not given</td>
</tr>
<tr>
<td>Extension From left-sided colitis</td>
<td>70%</td>
<td></td>
<td></td>
<td>Not given</td>
<td>30% at 10 years</td>
</tr>
</tbody>
</table>


### Distinguishing a Relapse from Something Else in a Patient with Ulcerative Colitis

- **History is key**
- Understanding the patient’s disease behavior and pattern helps
  - Is this a clinical relapse?
    - Lasts days (not A day)
    - Accompanied by bleeding
    - Extra-intestinal manifestations can be important clues
    - Antibiotic exposure or NSAID use?
- When in doubt, get objective evidence!
  - Labs
  - Endoscopic images
Knowing your Patient’s Prognosis Aids in Treatment Decisions

Definitions of Clinical Severity of Disease

- **FULMINANT**
  - >10 stools/day, continuous bleeding, toxicity, abdominal tenderness/distension, transfusion requirement, colonic dilation on x-ray
  - >6 bloody stools/day + Fever, tachycardia, anemia, or ↑ ESR

- **SEVERE**
  - ≥4 stools/day
  - Minimal signs of toxicity

- **MODERATE**
  - <4 stools/day ± blood
  - Normal ESR
  - No signs of toxicity

- **MILD**
  - ESR: Erythrocyte sedimentation rate.
Severity of Disease Correlates With Colectomy

**Severe Endoscopic Colitis** (n=46)  
- 93% underwent colectomy

**Moderate Endoscopic Colitis** (n=39)  
- 77% underwent colectomy

Predictors of Poor Response or Colectomy

- Serum albumin
- ESR >30 mm/h
- Bandemia
- Prolonged flare
- Active infection
- Hospitalization setting
- Severe endoscopic lesions
- Disease duration

- Stool frequency
- Percentage of bloody stools
- Body temperature >37.5
- Heart rate >90 bpm
- Increased CRP
- Toxic megacolon
- Low hemoglobin <10.5 g/dL

CRP=C-reactive protein.
**C. Difficile** is Rising in the IBD Population

![Graph showing annual incidence of C. difficile at Barnes-Jewish Hospital](graph.png)


**Impact of C. difficile in IBD**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Major findings</th>
</tr>
</thead>
</table>
| Issa et al. 2007¹ | Retrospective observational, single-center | • 76% acquired as outpatient  
• 50% hospitalized  
• 45% (2004) and 20% (2005) required colectomy (switched to vancomycin) |
| Ananthakrishnan et al. 2008² | Retrospective database | • Increased mortality, LOS, need for endoscopy and need for TPN  
• Decreased bowel surgery rate |
| Nguyen et al. 2008³ | Retrospective database | • Incidence nearly doubled (26.6 to 51.2 per 1000)  
• Increased mortality (OR 3.79) in UC  
• Increased LOS and hospital charges |

LOS=Length of stay; TPN=Total parenteral nutrition; OR=Odds ratio.

Hospitalized UC Patients with *C. difficile* Should be Treated with Vancomycin

- **Methods:** Retrospective, single center, 2005-10; IBD patients hospitalized with *C. difficile* (severe or not), followed for readmission, surgery, death
- **Results:** 67 UC, 58 CD patients:
  - Less re-admission and shorter hospitalization for UC patients treated with vancomycin versus metronidazole

Hospitalized UC patients with *C. difficile* should receive vancomycin regardless of severity score

Antibiotic Choice for Non-Severe CDI DOES Influence Outcomes in UC

- **Percent**
  - 12 Wk Readmit: MTZ, MTZ
  - 30 Day Readmit: MTZ, MTZ
  - Colectomy: MTZ, MTZ
  - Death: MTZ, MTZ

Upcoming ACG Guidelines:
Vancomycin is the therapy of choice for *C. difficile* in IBD patients

MTZ, metronidazole
VANC, vancomycin


What Are Considerations and Evolving Thoughts About Therapy in UC?
Treatment Options for UC

- 5-ASA
- Steroids
- Immune-modifiers
  - Thiopurine drugs, azathioprine, and 6-MP
- Biologic therapy – anti-TNF and anti-integrin
- Cyclosporine
- Surgery
- Alternative/integrative therapies?

5-ASA=5-aminosalicylic acid; 6-MP=6-mercaptopurine; TNF=Tumor necrosis factor.

Therapeutic Pyramid: Historical Approach to Ulcerative Colitis

- Traditional Approach
  - Patients have to “earn” therapy based on severity or failure of other approaches
  - Treatment is based on symptom resolution

- Evolving Approach
  - Assessment of prognosis
  - “Optimization” of azathioprine/6-MP (dose or metabolites)
  - Earlier adoption of biologic therapy
  - Distinction between cyclosporine and infliximab for severe/fulminant UC

- Future Approach
  - Individualized therapy based on genetics and physiology
  - Treatment to hard endpoints like mucosal healing or surrogates of it
  - Newer therapies with favorable safety and side effect profiles
  - Appreciation for the implications of a healed mucosa

Why do patients with IBD Not Respond to their Medications?

Primary Nonresponse
- Drug just doesn’t work
- Wrong diagnosis
  - Infection
  - Ischemia
  - Crohn’s disease
- Wrong dose
  - Not enough
  - Too much?
- Wrong delivery
  - Rationale
  - Allergy/intolerance

Secondary Nonresponse
- Change in dose (by you)
- Change in delivery
- Change in physiology
  - Does disease change over time?
- Intentional nonadherence
  - Episodic dosing strategy
  - Denial
  - Fear of therapy
- Unintentional nonadherence
  - Can’t afford medication
  - Inconvenient dosing regimen

5-ASA in Ulcerative Colitis
- Positioned as first-line therapy for mildly-to-moderately active UC
- Effective for induction and maintenance of remission
- Good safety profile
- Unclear: is there a dose response or delivery response?
- Mechanism of action incompletely understood
  - Presumably via an anti-inflammatory action
- Possible chemoprevention of colorectal dysplasia/cancer (but may not be clinically significant)

5-ASA Therapies

- Delivery systems:
  - Mesalamine with different delivery systems
    - Various pH-release mesalamines
    - Controlled-release mesalamine
    - Rectal preparations
  - Pro-drugs
    - Azo-bonded sulfasalazine, olsalazine, and balsalazide
- DELIVERY matters:
  - Consider Adherence!
  - In theory, switching delivery systems (or combining them) may improve response
  - Oral PLUS Topical (Rectal) therapy is better than either alone for induction of remission (distal and extensive)

5-ASA Safety Considerations

- Mesalamine intolerance: rare but important
- Pancreatitis
- Pneumonitis
- Renal insufficiency

![Risk of renal events with 5-ASA](image)

Adherence is Complex and Multifactorial

**Treatment-Related Factors**
- Dosage/dosing regimen
- Formulation
- Cost/reimbursement
- Adverse effects

**Illness-Related Factors**
- Severity, extent, duration of disease
- Frequency and intensity of flare-ups
- Complications

**Patient-Related Factors**
- Skills/knowledge to follow regimen
- Belief systems
- Psychiatric disorders
- Male gender, nonmarried status

---

**Outcome of Corticosteroids in IBD: Short and Long Term Efficacy**

### 1-Month Outcomes* (n=63)
- **Complete Remission**
  - 54% (n=34)
- **Partial Remission**
  - 30% (n=19)
- **No Response**
  - 16% (n=10)

### 1-Year Outcomes (n=63)
- **Prolonged Response**
  - 49% (n=31)
- **Steroid Dependent**
  - 22% (n=14)
- **Surgery**
  - 29% (n=18)

---

*30 days after initiating corticosteroid therapy

Risk of Surgical Resection in Patients with UC After Starting Corticosteroids*

- 185 patients in Olmsted County, MN diagnosed with UC from 1970 to 1993


Azathioprine vs 5-ASA for Steroid-Dependent UC

- Defined as clinical remission (Powell-Tuck Index Score of 0) and endoscopic remission (Baron Index Score ≤ 1) plus steroid discontinuation. Patients treated with concurrent tapering dose of steroids: 10.8 g at breakfast and lunch and 1.6 g at dinner.

**Infliximab in Ulcerative Colitis: ACT 1 and 2 Week 8 Results (Outpatients)**

**Clinical response**

<table>
<thead>
<tr>
<th>Proportion of Patients</th>
<th>Placebo</th>
<th>5 mg/kg</th>
<th>10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACT 2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Clinical remission**

<table>
<thead>
<tr>
<th>Proportion of Patients</th>
<th>Placebo</th>
<th>5 mg/kg</th>
<th>10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACT 2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


---

**Infliximab for Severe UC in the Hospital Setting**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Infliximab Dose</th>
<th>Outcome Measure</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sands 2001¹</td>
<td>11</td>
<td>5, 10, 20 mg/kg x 1</td>
<td>↓Lichtiger Score ≥5 to &lt;10 at 2 weeks</td>
<td>50% 0% ---</td>
</tr>
<tr>
<td>Armuzzi 2004²</td>
<td>20</td>
<td>5 mg/kg x 3</td>
<td>Sutherland score ≤2 at 2 weeks</td>
<td>100% --- 100%</td>
</tr>
<tr>
<td>Ochsenkühn 2004³</td>
<td>13</td>
<td>5 mg/kg x 3</td>
<td>↓Lichtiger Score ≥5 to &lt;10 at 3 and 13 weeks</td>
<td>83% --- 86%</td>
</tr>
<tr>
<td>Järnerot 2005⁴</td>
<td>45</td>
<td>5 mg/kg x 1</td>
<td>No colectomy at 90 days</td>
<td>67% 29% ---</td>
</tr>
</tbody>
</table>

UC SUCCESS: Azathioprine vs. Infliximab in Moderate to Severe UC
Primary Endpoint: Steroid-Free Remission at Week 16

![Graph showing the comparison between AZA, IFX, and IFX+AZA in the context of UC SUCCESS.]


Cyclosporine for Severe IV Steroid Refractory UC

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>CSA 4mg/kg</th>
<th>CSA + Steroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lichtiger (1994)</td>
<td>20 (stopped after interim analysis)</td>
<td>-</td>
<td>87%</td>
</tr>
<tr>
<td>D’Haens (2001)</td>
<td>30</td>
<td>64%</td>
<td>-</td>
</tr>
<tr>
<td>Svanoni (1998)</td>
<td>30</td>
<td>67%</td>
<td>93%</td>
</tr>
<tr>
<td>VanAssche (2003)</td>
<td>73</td>
<td>84%</td>
<td>-</td>
</tr>
</tbody>
</table>
CsA vs IFX in IV Steroid-Refractory UC: The CYSIF Study

First randomized, controlled study comparing CsA to IFX in IV steroid-refractory severe acute UC

- n=111: 55 received CsA, 56 received IFX
- Co-primary endpoints
  - Colectomy at day 7 in hospital
  - Colectomy at day 98

Laharie D et al. DDW 2011; May 9, 2011; Chicago, IL. Abstract 619.

CYSIF: Primary Objective = Treatment Failure

Difference Cys vs. IFX failure rates:
-6.4% (95%CI: -24.8 to 12.0%)

Laharie D et al. DDW 2011; May 9, 2011; Chicago, IL. Abstract 619.
1. CSA vs Infliximab: Time to Colectomy

Colectomy rate

Cys: 18 ± 5%
IFX: 21 ± 5%
p = 0.66

Cys
IFX

Days since randomisation
% of patients

Days since randomisation
% of patients

α-Integrin Therapy for IBD

Mucosal and Inflammatory Zip Codes

Natalizumab blocks both α4β1 and α4β7 mediated trafficking, resulting in systemic effects.
Vedolizumab only targets α4β7 integrin, blocking lymphocytes trafficking to the gut.

Chemokines
VCAM-1
Leukocyte
MAdCAM-1
Vascular Endothelium
**GEMINI I – Vedolizumab for the Treatment of UC**

<table>
<thead>
<tr>
<th>Prior Anti-TNF Exposure</th>
<th>Placebo</th>
<th>Vedolizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Response 6 Weeks</td>
<td>20.5%</td>
<td>39.0%</td>
</tr>
<tr>
<td>Clinical Response 52 Weeks</td>
<td>24.0%</td>
<td>45.2%</td>
</tr>
</tbody>
</table>

*P< 0.005


**GEMINI I – Vedolizumab for the Maintenance of UC**

Primary and Secondary Outcomes Through 52 Weeks

Vedolizumab (VDZ) is more effective than placebo as induction and maintenance therapy in patients with moderate to severely active ulcerative colitis (anti-TNF exposed and naïve patients)

*P=0.05, **P=0.01, ***P=0.0001

GEMINI I – Safety of Vedolizumab for the Treatment of UC

<table>
<thead>
<tr>
<th></th>
<th>Maintenance ITT Population</th>
<th>Safety Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo N=126</td>
<td>VDZ Q8Wks N=122</td>
</tr>
<tr>
<td>Any Adverse Event (AE), %</td>
<td>84</td>
<td>82</td>
</tr>
<tr>
<td>Drug-related AE, %</td>
<td>32</td>
<td>30</td>
</tr>
<tr>
<td>AE resulting in discontinuation, %</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Serious AEs, %</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Serious infection AEs, %</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>


Mucosal Healing in Ulcerative Colitis: Endoscopic Remission

- **Current goal of treatment:** induction and maintenance of symptomatic improvement
  - Does not alter natural course of disease
  - Does not decrease lifetime risk for surgery
- **Clinical trials**
  - Mucosal healing endpoints only recently added to trials
  - Clinical endpoints lead to high placebo response, potentially diluting the effect of the therapy, even in large studies
  - “Hard” endpoint of mucosal healing reduces number needed to power study for treatment effect

Objective and Subjective Endoscopic Activity in UC

Role of Mucosal Healing in Disease and Management

- Inflammation predicts clinical relapse
- Severity of inflammation associated with greater risk of colectomy
- Severity of inflammation associated with greater risk of cancer
- Unknown: if achievement of mucosal healing improves treatment outcomes (presumably yes)

### Achieving Mucosal Healing With Therapy in Ulcerative Colitis

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Trial</th>
<th>Definition of mucosal healing</th>
<th>Evidence of mucosal healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-ASA</td>
<td>Multiple&lt;sup&gt;1-5&lt;/sup&gt;</td>
<td>No standard definition; generally a score of 0 or 1 on Mayo Score; some studies allowed friability</td>
<td>Yes</td>
</tr>
<tr>
<td>Steroids</td>
<td>Multiple&lt;sup&gt;6-8&lt;/sup&gt;</td>
<td>Endoscopic remission as 0 or 1 on Mayo score (as defined 30 years ago)</td>
<td>Yes</td>
</tr>
<tr>
<td>Azathioprine/6-MP</td>
<td>One study&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Score of 0 or 1 based on Baron scale</td>
<td>Yes?</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>ACT 1, 2 (infliximab)&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Mucosal healing was defined as an absolute subscore for endoscopy of 0 or 1</td>
<td>Yes</td>
</tr>
</tbody>
</table>


### Unanswered Questions in UC Management

**5-ASA**

- Is there benefit to dose reduction for maintenance after induction of remission?
- Can steroid induction be followed by successful 5-ASA maintenance?
- Should 5-ASA be continued when thiopurine or biologic therapy is used?
  - Is there an additive benefit?
  - Are there other reasons to consider this?
    - In whom?
- Is there a dose response with 5-ASA’s?
Unanswered Questions in UC Management (cont’d)

- What role do TPMT and 6-TG/6-MMP testing play in the use of thiopurine therapies?
- Where should infliximab be positioned in UC?
  - Earlier?
  - After failure of some therapies?
  - For steroid sparing?
  - Can cyclosporine be given after infliximab fails? When?
- Should we be using cyclosporine more often? In whom?
  - Can infliximab be given after cyclosporine fails?
- When should surgery occur when patients are on immunosuppressives?
- Does methotrexate work in UC?
- Is there a role for additive probiotic therapy in UC maintenance?
- Should we be treating to achieve mucosal healing?

TPMT=Thiopurine S-methyltransferase; 6-TG=6-thioguine; 6-MMP=6-methyl-mercaptopurine.

Not all Dysplasia is Created Equal
Which is potentially worse?

- GRADE:
  - IND vs. LGD vs. HGD
- MORPHOLOGY:
  - Flat vs. Polypoid
  - “Invisible” vs. raised
- FIELD EFFECT/SYNCHRONICITY:
  - Unifocal vs. multifocal
- LONGITUDINAL FOLLOW-UP?
  - Dysplasia on a single exam vs.
    metachronous lesions on serial exams
Not all Dysplasia is Created Equal
Which is potentially worse?

- **GRADE:**
  - IND vs. LGD vs. HGD
  - HGD

- **MORPHOLOGY:**
  - Flat vs. Polypoid
  - “Invisible” vs. raised

- **FIELD EFFECT/SYNCHRONICITY:**
  - Unifocal vs. multifocal

- **LONGITUDINAL FOLLOW-UP?**
  - Dysplasia on a single exam vs. metachronous lesions on serial exams

---

Which Patients with Dysplasia Should NOT be followed?

**HIGHER RISK**
- Unresectable lesion
- PSC
- Uncontrolled inflammation in addition to dysplasia
- Multifocal dysplasia
- Pseudopolyposis
- Males?
- Left sided lesions?

**THE PATIENT WHO WON’T LET YOU**
- Poor prep
- Non-compliant
- No follow-up
High Fecal Calprotectin Is Associated With Risk of Relapse in IBD

- 43 CD, 25 (58%) relapse over period of 12 months
- 37 UC, 19 (51%) relapsed over period of 12 months

In remission for 1–4 months

- UC calprotectin <50 mg/L
- UC calprotectin >50 mg/L
- CD calprotectin <50 mg/L
- CD calprotectin >50 mg/L

RR 10.6 (CD)
RR 13.4 (UC)

Improving Care of UC Patients: Emphasis on Communication

- Clarify definitions and expectations
  - “Expect remission, which means…..”
- Anticipate concerns
  - “I want to address a common concern about patients and empower you to feel in control…”
  - Discuss the known rare rate of cancer and the importance of prevention programs
- Expect non-adherence
  - “It’s often hard for patients to take medications every day. Here are some strategies that might help…”
  - Schedule healthy visits to emphasize maintenance.
- Have a plan and be available!
  - “Despite our efforts, you may have a relapse. Here’s some suggestions about what to do, including calling me.”
  - Customize treatment in anticipation of times when relapse may occur.
Summary: Clinical Challenges in UC

- Improving the care of UC patients should involve expanding discussions and open lines of communication to emphasize definitions and encourage adherence.
- Patients’ major fears remain cancer and surgery.
  - The cancer risks are lower than previously estimated.
  - Adherence to therapy and stable maintenance reduces relapse rates.
- Understand your patient’s disease behavior and prognosis and then individualize your treatment plans.
- Steroid-free durable remission is the preferred endpoint and is achieved more reliably when the mucosa is healed.
- Some dysplasia in colitis can be safely followed with more intensive surveillance strategies.
- New evidence for treatment of UC includes combination immunosuppressive therapy and also novel treatment mechanisms.