Disease Assessment in Crohn’s Disease and Ulcerative Colitis

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Learning Objective

• Describe the clinical evaluation of IBD, including blood and stool biomarkers, endoscopic and radiographic imaging
### AGA Clinical Pathways for IBD (combined)

**Assess inflammatory status**

- **Assess symptoms/signs**
  - Diarrhea
  - Bleeding
  - Urgency/Tenesmus
  - Abdominal pain
  - Localized tenderness
  - Weight loss
  - Joint pain
  - Cutaneous signs

- **Perform clinical lab testing**
  - CBC
  - CRP
  - CMP
  - Fecal calprotectin
  - ESR

- **Select imaging modalities** (if indicated)
  - Perform endoscopy
  - Identify symptoms without inflammatory markers
  - Identify symptoms with inflammatory markers*
  - Perform CTE or MRE

Consider whether treatment decisions to be based on inflammatory markers vs confirming with colonoscopy. This may depend on whether there was historically good correlation between the biomarker selected and colonoscopy in the specific patient.

**Challenges to Current Clinical Endpoints in IBD**

- Symptoms may be non-specific
  - Do not correlate to endoscopic findings of “healing” in clinical trials
  - Do not delineate extent of disease
  - Patients live with active disease!

- Symptoms may lag behind the development of active inflammation

- Endoscopy has not been routinely included in goals

- Endoscopy is invasive and expensive
Mucosal Healing as a Surrogate for Longer Term Outcomes

Associated with:

- Better quality of life
- Fewer hospitalizations
- Fewer surgeries
- Longer time to clinical relapse
- Reduction in dysplasia/cancer (UC)

Sands, B. ACG-FDA Workshop 2012

Risk of Colectomy in Severe UC Patients with Severe Ulcerations

85 consecutive patients with active UC

Severe endoscopic lesions (SELS):

- Deep ulcers
- Well-like ulcers
- Large mucosal erosions
- Extensive loss of mucosal layer with or without residual mucosal areas

93%

No SEL

SEL

Colectomy 9/39 pts

Colectomy 43/46 pts

OR = 41 (95% CI 10.5-164)

Many Asymptomatic UC Patients Have Active Inflammation at Colonoscopy


Endoscopic Inflammation

<table>
<thead>
<tr>
<th>Grade of Endoscopic Inflammation</th>
<th>N=82 patients, 120 colonoscopies. Analysis represents mean values, per patient.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>17%</td>
</tr>
<tr>
<td>1</td>
<td>31%</td>
</tr>
<tr>
<td>2</td>
<td>12%</td>
</tr>
<tr>
<td>3</td>
<td>2%</td>
</tr>
</tbody>
</table>

Histologic Inflammation

<table>
<thead>
<tr>
<th>Grade of Histologic Inflammation</th>
<th>SES 0</th>
<th>SES 1–8</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>70.8%</td>
<td>27.3%</td>
</tr>
<tr>
<td>1</td>
<td>62.5%</td>
<td>18.2%</td>
</tr>
</tbody>
</table>

SES=Simple Endoscopic Score.

Mucosal Healing Reduces Risk for Colectomy in Crohn’s Disease

Risk of Colectomy According to Severe Endoscopic Lesions

<table>
<thead>
<tr>
<th>Year of follow-up</th>
<th>No severe endoscopic lesions</th>
<th>Severe endoscopic lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>43</td>
</tr>
<tr>
<td>8</td>
<td>31</td>
<td>62</td>
</tr>
</tbody>
</table>

Degree of Mucosal Healing and Risk of Major Abdominal Surgery

<table>
<thead>
<tr>
<th>Degree of mucosal healing</th>
<th>Patients undergoing MAS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>14.1</td>
</tr>
<tr>
<td>Partial</td>
<td>14</td>
</tr>
<tr>
<td>None</td>
<td>38.4</td>
</tr>
</tbody>
</table>

MAS=major abdominal surgery; SEL=severe endoscopic lesions (extensive and deep ulcerations on index colonoscopy)


Histological healing, the ultimate therapeutic goal in UC?

Histological remission and healing UC

- More likely symptom-free
- Reduced risk of relapse
- Reduced risk of surgery/hospitalization
- Reduced risk of colorectal cancer

- Long-term clinical, endoscopic, and histologic remission
- More favorable disease course

Histological remission associated with lower rate of hospitalization (OR 0.27; 95% CI, 0.07-0.95; P=0.048)

For every unit increase in cumulative mean histologic inflammation score, there was a 3-fold increase in advanced colorectal cancer.

Histological Normalization in UC Is Associated with Lower Clinical Relapse Rates

- Complete Histological Remission
- Histological Quiescence
- Histological Inflammation

Clinical Relapse Free Survival vs Histological Healing


Defining Histological Remission

- No standardized definition
  - “Healing” vs. “Remission”
  - Multiple histological scoring systems
    - Residual inflammation with architectural distortion → Normalization
    - Absence of neutrophils is key
Limitations of Histological Assessments

- Lack of Validation or Standardization
  - Histological Reporting
  - Scoring
  - Definition of Remission
- Sampling Error & Transmural Assessments
- Invasive/Expensive Procedures (scope and pathologic interpretation)
  - Need for surrogate (e.g. super low calprotectin?)
- Will immunological and/or microbiological remission be required?

Is A Treat-to-Target Approach Feasible in IBD?

- Symptoms
  - QoL
- Labs
  - CRP
  - Calprotectin?
- Mucosal healing
  - Hospitalizations
  - Surgery
- Biologic
  - (Deep remission)
  - Histologic remission
  - Disease modification

ACG Southern Regional Postgraduate Course
December 3-4, 2016
Nashville, Tennessee
Working Definitions of Deep Remission

Deep remission implies resolution of inflammatory symptoms and objective signs of inflammation

No bowel damage or disability
- Resolution of symptoms
- Resolution of objective measures of inflammation (endoscopy, imaging, biomarkers)

Existing bowel damage or disability
- Improvement of symptoms
- Resolution of objective measures of inflammation (endoscopy, imaging, biomarkers)


Potential Role of Serologic and Genetic Testing

- Diagnosing Disease
- Predicting Development of Disease
- Predicting Course of Disease
ECCO Consensus on CD: Definitions and diagnosis

- Genetic factors and serological markers of immune reactivity, considered alone or in combination, have been so far unhelpful in predicting the future course of CD at diagnosis.
- No evidence-based recommendation can be made to implement the routine clinical use of molecular markers (genetic, serologic) for the classification of UC patients

Ideal Biomarkers

- Easy to measure
- Noninvasive
- Reproducible
- Inexpensive
- Responsive to change
- High PPV and NPV
### Overview of Biomarkers in IBD

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Description</th>
<th>Clinical Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calprotectin(^1,2)</td>
<td>Granulocyte cytosolic protein Stable in feces for days</td>
<td>• Elevated in NSAID enteropathy, cancer, celiac disease, microscopic colitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Sensitivity and specificity vary greatly based on cutoff value</td>
</tr>
<tr>
<td>Lactoferrin(^1,2)</td>
<td>Neutrophil granule protein Stable in feces</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein (CRP)(^1)</td>
<td>Acute-phase protein Produced in liver under influence of IL-6/TNF-α/IL-1β Short half-life (~19 hours)</td>
<td>• May be more elevated in CD than in UC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Elevated in other conditions (eg, infections, obesity, CAD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• May be low in ileal disease or those with low BMI, even in active disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Minimal or no CRP response in 10%–40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• May be influenced by genetic polymorphisms</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (ESR)(^1)</td>
<td>Rate RBCs settle in 1 hour</td>
<td>• Influenced by anemia, gender, pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Peaks less rapidly than CRP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Resolves more slowly than CRP</td>
</tr>
</tbody>
</table>

CAD=coronary artery disease; CRP=C-reactive protein; IL=interleukin; RBC=red blood cell

### Biomarkers Correlate Well With Endoscopic But Not Clinical Activity Indices

<table>
<thead>
<tr>
<th>IL-6</th>
<th>Calprotectin</th>
<th>Lactoferrin</th>
<th>CDAI</th>
<th>SES-CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsCRP</td>
<td>+</td>
<td>+</td>
<td>NS</td>
<td>+</td>
</tr>
<tr>
<td>IL-6</td>
<td>+</td>
<td>+</td>
<td>NS</td>
<td>+</td>
</tr>
<tr>
<td>Calprotectin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lactoferrin</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>CDAI</td>
<td>+</td>
<td>+</td>
<td></td>
<td>NS</td>
</tr>
</tbody>
</table>

+ indicates significant correlation coefficients (P<.05); NS, nonsignificant correlations.

When stratified by extent, correlation coefficients were highest for colonic disease.

CDAI=Crohn’s disease activity index; CRP=C-reactive protein; IL=interleukin; SES-CD=Simple Endoscopic Score-Crohn’s Disease.

Fecal Calprotectin Correlates With Disease Activity

- UC patients in remission on infliximab 5 mg/kg q8w (n=113)
  - Fecal calprotectin measured monthly for 1 year
  - Deep remission = normal endoscopy at baseline and week 52 + Mayo score <3
- 27% were in deep remission
- Fecal calprotectin levels highly correlate with disease activity
  - Fecal calprotectin <50 mg/kg at all time points in patients in deep remission
  - Median fecal calprotectin 477 mg/kg in patients with a flare
  - Two consecutive levels >300 mg/kg predicted a flare


Fecal Calprotectin Predicts Outcome After Induction Therapy With TNF Antagonists

- Patients
  - 60 IBD patients (CD, n=34; UC, n=26)
  - Treated with TNF antagonists
  - Documented FC level at baseline and after induction therapy
- Results
  - FC normalized (≤100 mcg/g) in 31 patients (52%)
  - At ~12 months, 84% of patients with normal FC after induction were in clinical remission vs 38% of those with elevated post-induction FC

*Remission defined as a Harvey-Bradshaw Index ≤4
Calprotectin best at discriminating inactive vs active CD

<table>
<thead>
<tr>
<th>Endoscopic activity</th>
<th>Inactive (0–3)</th>
<th>Mild (4–10)</th>
<th>Moderate (11–19)</th>
<th>High (≥20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>26</td>
<td>40</td>
<td>27</td>
<td>47</td>
</tr>
<tr>
<td>CDAI</td>
<td>79 ± 86 (13–281)</td>
<td>85 ± 70 (14–297)</td>
<td>116 ± 47 (44–323)</td>
<td>218 ± 75 (86–417)</td>
</tr>
<tr>
<td>P value</td>
<td>0.739</td>
<td>0.201</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Calprotectin (µg/g)</td>
<td>104 ± 138 (10–725)</td>
<td>234 ± 244 (12–1009)</td>
<td>295± 256 (68–912)</td>
<td>718 ± 320 (93–1327)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>0.008</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>12± 19 (3–94)</td>
<td>8± 10 (3–53)</td>
<td>23± 31 (3–172)</td>
<td>40± 28 (5–121)</td>
</tr>
<tr>
<td>P value</td>
<td>0.349</td>
<td>0.013</td>
<td>0.019</td>
<td></td>
</tr>
<tr>
<td>Leukocytes (g/L)</td>
<td>7.7± 3.1 (4–17.9)</td>
<td>7.6± 2.8 (3.7–13.6)</td>
<td>8.8± 3.1 (1.4–15.8)</td>
<td>11.1± 3.5 (2.9–18.6)</td>
</tr>
<tr>
<td>P value</td>
<td>0.903</td>
<td>0.117</td>
<td>0.004</td>
<td></td>
</tr>
</tbody>
</table>

Numbers are presented as mean ± SD and range


High Fecal Calprotectin is Associated with Risk of Relapse in IBD

43 CD — 25 (58%) relapsed over period of 12 months
37 UC — 19 (51%) relapsed over period of 12 months
In remission for 1-4 months

RR=relative risk.
“Routine Monitoring”

- Anemia
- Metabolic Profile
- CRP
- Vitamin D
- Vitamin B12
- Fecal Calprotectin

Causes of Anemia in Inflammatory Bowel Disease (IBD)

**Iron deficiency**
- Anemia of chronic disease

**Vitamin B_{12}** deficiency
- Folate deficiency
- Drug-induced (sulfasalazine, thiopurines)

**Hemolysis**

**Rare**
- Myelodysplastic syndrome
- Aplasia (often drug-induced)
- Innate hemoglobinopathies or disorders of erythropoiesis

Most common form of anemia in IBD\(^1,2\)
- Commonly caused by intestinal blood loss, malnutrition, and impaired iron uptake\(^1,2\)

2. Kulnigg S, Gasche C. Aliment Pharmacol Ther. 2006;24:1507-1523
Relationship between CDAI and CRP


Close monitoring of CRP and fecal calprotectin predicts clinical relapse after infliximab withdrawal

Working Definitions of Deep Remission

Deep remission implies resolution of inflammatory symptoms and objective signs of inflammation.

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UC: Stratify According to Colectomy Risk

Identify Patient at Low Risk for Colectomy
- Limited anatomic extent
- Mild endoscopic disease

Identify Patient at High Risk for Colectomy
- Extensive colitis
- Deep ulcers
- Age <40
- High CRP and ESR
- Steroid-requiring disease
- History of hospitalization
- C. difficile infection
- CMV infection

AGA Clinical Pathway for Crohn’s Disease: Characterizing Risk

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;30 years</td>
<td>&lt;30 years</td>
</tr>
<tr>
<td>Limited</td>
<td>Extensive</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Superficial Ulcers</td>
<td>Deep</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

• Current “Clinical Pathways” include assessment of laboratory, endoscopic and imaging assessments at diagnosis

• Clinical End-Points (Targets) include resolution of:
  • Clinical
  • Laboratory
  • Endoscopy

• Ongoing monitoring is critical to insure long-term outcomes

• Histologic and “deeper biologic” targets are likely to be clarified in future