What is Mucosal Healing?

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Objectives

- Describe the strengths and weaknesses of various measures of mucosal healing in ulcerative colitis
- Identify the mucosal healing rates of key therapies and combinations of treatments for ulcerative colitis
- Describe the relative value of clinical end points vs mucosal healing in following patients with ulcerative colitis See comment on application addendum
Mucosal Healing in Ulcerative Colitis
How do you Measure Mucosal Healing in Ulcerative Colitis?

• Baron score
• Mayo/Sutherland ulcerative colitis disease activity index (UCDAI) composite instruments with endoscopy sub-score
• Ulcerative colitis endoscopic index of severity (UCEIS)
• Ulcerative colitis colonoscopic index of severity (UCCIS)

Thia KT, Sandborn WJ. Inflammatory Bowel Diseases 2011;17:1257-1254.
## Baron Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal: mat mucosal, ramifying vascular pattern clearly visible throughout, no spontaneous bleeding, no bleeding to light touch</td>
</tr>
<tr>
<td>1</td>
<td>Abnormal but not hemorrhagic: appearances between “0” and “2”</td>
</tr>
<tr>
<td>2</td>
<td>Moderately hemorrhagic: bleeding to light touch, but no spontaneous bleeding seen ahead of instrument on initial inspection</td>
</tr>
<tr>
<td>3</td>
<td>Severely hemorrhagic: spontaneous bleeding seen ahead of instrument at initial inspection, and bleeds to light touch</td>
</tr>
</tbody>
</table>

Mayo Scoring System for Assessment of UC Activity

- Four components
  - Stool frequency
  - Rectal bleeding
  - Findings of endoscopy
    - 0 = Normal or inactive disease
    - 1 = Mild disease (erythema, decreased vascular pattern, mild friability)
    - 2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
    - 3 = Severe disease (spontaneous bleeding, ulceration)
  - Physicians global assessment
- Used for FDA approval of Asacol and Remicade

Sutherland Index (UCDAI)

• 12 point index with 4 components
  • Stool frequency (0-3)
  • Rectal bleeding (0-3)
  • Mucosal appearance (0-3)*
    – 0 = Normal
    – 1 = Mild friability
    – 2 = Moderate friability
    – 3 = Exudation, spontaneous hemorrhage
  • Physicians global rating (0-3)
  • Used for FDA approval of Rowasa and Lialda

* Modified in Lialda trials so that friability is a score of $\geq 2$ points

Ulcerative Colitis Endoscopic Index of Severity (UCEIS)

- Validated instrument
- Developed from a library of flexible sigmoidoscopy videos using different combinations of descriptors predicting the overall assessment of severity using VAS
- Three descriptors
  - Vascular pattern (normal – 1, patchy obliteration – 2, obliterated – 3)
  - Bleeding (none – 1, mucosal – 2, luminal mild – 3, luminal moderate or severe – 4)
  - Erosions and ulcers (none – 1, erosions – 2, superficial ulcer – 3, deep ulcer – 4)
- The score from each of the descriptors are added to calculate the UCEIS score
- The UCEIS score accounts for 90% of the overall assessment of endoscopic severity as judged by VAS (pR2=0.90)

Ulcerative Colitis Colonoscopic Index of Severity (UCCIS)

• Validated instrument
• Developed from a library of colonoscopy videos (with 5 segments of colon scored) using different combinations of descriptors to predict the global or segmental assessment of endoscopic severity (GAES or SAES) or VAS
• Four descriptors
  – Vascular pattern (normal – 0, partially visible – 1, complete loss – 2)
  – Granularity (normal – 0, fine – 1, course - 2)
  – Ulceration (normal – 0, erosions – 1, shallow – 2, deep – 3, diffuse > 30% deep - 4)
  – Bleeding/friability (normal – 0, friable – 1, spontaneous bleeding – 2)
• The UCCIS score is 3.1 X vascular pattern + 3.6 X granularity + 3.5 X ulceration + 2.5 X bleeding/friability
• The UCCIS score accounts for 74-81% of the variance in the GAES score and 80-85% of the variance in the VAS score
• Results were similar for GAES and SAES

History of the Evolution of the Endpoint of Mucosal Healing in Ulcerative Colitis

- Improvement - change by 1 point on endoscopy subscore, remission = score of 0 points

- 2005 - Mucosal healing definition in infliximab trials –
  - Inclusion criteria
    - Endoscopic evidence of moderate or severe UC (endoscopy score ≥2) and total Mayo score of 6-12
    - Mucosal healing definition - endoscopy sub-score 0 or 1

- 2007 - Modified Sutherland (UCDAI) in MMX mesalamine trials
  - Mucosal appearance
    - 0 = Normal or inactive disease
    - 1 = Mild disease (erythema, decreased vascular pattern, minimal granularity)
    - 2 = Moderate disease (marked erythema, friability, granularity, absent vascular pattern, bleeding minimal trauma, no ulcerations)
    - 3 = Severe disease (ulcerations, spontaneous bleeding)

What are the Mucosal Healing Rates with Various Therapies in Ulcerative Colitis?

- Mesalamine
- Steroids
- Anti-TNF
  - Infliximab
  - Adalimumab
- Combination therapy
Delayed Release Oral Mesalamine:
Mild-to-Moderate Active Ulcerative Colitis

†Defined as “in remission” (complete resolution of all symptoms with all assessment scores = 0), OR “improved” (reduction in PGA score and ≥1 other component score and no score increased)
‡P=.03
§P=.003

Sigmoidoscopic Score of Zero at Week 8: MMX Delayed Release Mesalamine in Mild to Moderate UC

Delayed-Release Oral Mesalamine: Maintenance of Endoscopic Remission of UC

† "Maintenance of endoscopic remission at 6 months" (score of 0 out of 3 on sigmoidoscopic scale)
‡ P=.05; § P=.005.
Maintenance of endoscopic remission at 6 months in the per-protocol population and in the intent-to-treat population.

Oral Cortisone: Mild-to-Severe Active Ulcerative Colitis: Mucosal Healing at 6 Weeks

*Defined as normal or near normal (slight hyperemia or granularity) mucosa

Infliximab Induction and Maintenance Therapy in Patients with Ulcerative Colitis: Mucosal Healing

Mucosal healing = endoscopic subscore of 0 or 1

‡$P \leq .009$ vs placebo
‡$P < .001$ vs placebo

Mucosal Healing at Week 8

ACT 1 & ACT 2

Mucosal Healing at Week 30

ACT 1 & ACT 2

Adalimumab Induction and Maintenance of Mucosal Healing Response at Week 8 and 52 in Ulcerative Colitis

ITT analysis set: NRI
Mucosal healing: endoscopy subscore of 0 or 1

Infliximab, Azathioprine, or Infliximab + Azathioprine for Treatment of Moderate to Severe UC: UC SUCCESS Trial

Secondary End Point: Mucosal Healing at Week 16

Does the Achievement of Mucosal Healing in Patients with Ulcerative Colitis Alter Clinical Outcomes?

- Steroid free remission
- Colectomy
Mucosal Healing and Time to Colectomy in Infliximab-treated Patients: Endoscopy Subscore

## Association Between Week 8 Mayo Endoscopy Sub-score and Corticosteroid-Free Symptomatic Remission at Week 30 During Anti-TNF Antibody Therapy

<table>
<thead>
<tr>
<th>Week 8 Mayo endoscopy sub-score</th>
<th>Corticosteroid-free symptomatic remission, %</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>46</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6.5</td>
<td></td>
</tr>
</tbody>
</table>

Colombel JF. Gastroenterology 2011
Mucosal Healing After Treatment as Predictor of Subsequent Disease Course in Ulcerative Colitis

Mucosal Healing in Crohn’s Disease
How do you Measure Mucosal Healing in Crohn’s Disease?

• Crohn’s Disease Endoscopic Index of Severity (CDEIS)
• Simplified Endoscopic Score – Crohn’s Disease (SES-CD)
• Resolution of ulcers
• Rutgeert’s score
The Crohn’s Disease Endoscopic Index of Severity (CDEIS)

<table>
<thead>
<tr>
<th></th>
<th>Deep ulcerations 12 points</th>
<th>Superficial ulcerations 6 points</th>
<th>Surface of ulcerations (0–10 cm)</th>
<th>Surface of lesions (0–10 cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileum</td>
<td>0 or 12</td>
<td>0 or 6</td>
<td>0–10</td>
<td>0–10</td>
</tr>
<tr>
<td>Right colon</td>
<td>0 or 12</td>
<td>0 or 6</td>
<td>0–10</td>
<td>0–10</td>
</tr>
<tr>
<td>Transverse</td>
<td>0 or 12</td>
<td>0 or 6</td>
<td>0–10</td>
<td>0–10</td>
</tr>
<tr>
<td>Left colon</td>
<td>0 or 12</td>
<td>0 or 6</td>
<td>0–10</td>
<td>0–10</td>
</tr>
<tr>
<td>Rectum</td>
<td>0 or 12</td>
<td>0 or 6</td>
<td>0–10</td>
<td>0–10</td>
</tr>
</tbody>
</table>

Total (sum of all cases)  
N

Total/number of explored segments  
N/1-5

+ 3 if ulcerated stenosis  
0-3

+ 3 if nonulcerated stenosis  
0-3

CDEIS  
0 to 44
## Simplified Endoscopic Score – Crohn’s Disease (SES-CD)

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Presence and size of ulcers</strong></td>
<td>0.1 – 0.5 cm</td>
<td>0.5 – 2.0 cm</td>
<td>&gt; 2.0 cm</td>
<td></td>
</tr>
<tr>
<td><strong>Extent of ulcerated surface</strong></td>
<td>&lt; 10%</td>
<td>10% - 30%</td>
<td>&gt; 30%</td>
<td></td>
</tr>
<tr>
<td><strong>Extent of affected surface</strong></td>
<td>&lt; 50%</td>
<td>50% - 75%</td>
<td>&gt; 75%</td>
<td></td>
</tr>
<tr>
<td><strong>Presence and type of narrowing</strong></td>
<td>single</td>
<td>multiple</td>
<td>Endoscope doesn't pass</td>
<td></td>
</tr>
</tbody>
</table>

*The score should be evaluated for the 5 segments*

Daperno et al. Gastrointest Endosc 2004
Assessment of Post-Operative Disease Recurrence: Rutgeert’s Endoscopic Scoring System

<table>
<thead>
<tr>
<th>Grade</th>
<th>Endoscopic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No lesions in the distal ileum</td>
</tr>
<tr>
<td>1</td>
<td>≤ 5 aphthous lesions</td>
</tr>
<tr>
<td>2</td>
<td>&gt; 5 aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions or lesions confined to ileocolonic anastomosis (i.e. &lt; 1 cm in length)</td>
</tr>
<tr>
<td>3</td>
<td>Diffuse aphthous ileitis with diffusely inflamed mucosa</td>
</tr>
<tr>
<td>4</td>
<td>Diffuse inflammation with already larger ulcers, nodules, and/or narrowing</td>
</tr>
</tbody>
</table>
What are the Mucosal Healing Rates with Various Therapies in Crohn’s Disease?

- Steroids
- Azathioprine
- Anti-TNF
  - Infliximab
  - Adalimumab
  - Certolizumab pegol
- Combination therapy
Assessment Of Efficacy Of Medical Therapy: CDAI Versus CDEIS During Treatment With Infliximab

D’Haens Gastroenterology 1999
ACCENT 1 Infliximab in Active Crohn’s Disease (Naïve): Mucosal Healing at 10 and 54 Weeks in Week 2 Responders

Patients Demonstrating Mucosal Healing (%)

- Single Dose
- Combined dose group (5 mg/kg & 10 mg/kg infliximab maintenance)
- 5 mg/kg infliximab maintenance
- 10 mg/kg infliximab maintenance

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mucosal Healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Dose</td>
<td>10/32</td>
</tr>
<tr>
<td>Combined dose group</td>
<td>1/14 5/11 8/15</td>
</tr>
<tr>
<td>5 mg/kg infliximab maintenance</td>
<td></td>
</tr>
<tr>
<td>10 mg/kg infliximab maintenance</td>
<td></td>
</tr>
</tbody>
</table>

p = 0.010  
p = 0.007  
p = 0.026
Sonic: Mucosal Healing at Week 26

Proportion of Patients (%)

- AZA + placebo
- IFX + placebo
- IFX + AZA

Adalimumab in Crohn’s Disease Complete Mucosal Healing at Weeks 12 and 52 NRI Analysis*

ITT, intention to treat; NRI, nonresponder imputation.

*NRI for missing ulceration at Weeks 12 and 52 and for missing ulceration and ulceration assessment of switched patients at Week 52. Treatment displayed is original treatment at randomization. Analyzed using Cochran-Mantel-Haenszel test.

†Per protocol represents all ITT patients who did not have a significant protocol deviation.

Adalimumab in Crohn’s Disease CDEIS Remission at Weeks 12 and 52 (CDEIS Score ≤4): NRI Analysis*

* NRI for missing CDEIS values at visit; ITT=129 randomized patients irrespective of presence of mucosal ulceration at screening (as judged by review committee).
† From CMH test.
Adalimumab in Crohn’s Disease
Mean Change From Baseline in Total SES-CD

*From analysis of covariance (ANCOVA) with treatment, CR-70 status at Week 4, and baseline value as factors. Treatment displayed is original treatment at baseline.

SES-CD = Simplified endoscopic score-Crohn’s disease.

MUSIC: Certolizumab in Active Crohn’s Disease Endoscopic Response and Remission at Week 10, N=78

Endoscopic response*, CDEIS decrease > 5

Endoscopic remission*, CDEIS < 6

Complete endoscopic remission*, CDEIS < 3

% of patients

61.5

42.3

11.5

CDEIS = Crohn’s Disease Endoscopic Index of Severity Score.

What’s Wrong with Using Clinical Endpoints Rather Than Mucosal Healing?

• Clinical endpoints don’t correlate with endoscopic findings
Crohn’s Disease Symptoms (CDAI) versus Crohn’s Disease Endoscopic Findings (CDEIS) During Treatment with Prednisolone

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

Correlations Between hsCRP, IL-6, Fecal Markers, CDAI, and Endoscopic Activity in Crohn’s Disease (N=164)

<table>
<thead>
<tr>
<th></th>
<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>0.65</td>
<td>0.47</td>
<td>0.52</td>
<td>0.16</td>
<td>0.46</td>
</tr>
<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></td>
<td></td>
<td>0.76</td>
<td>0.23</td>
<td>0.45</td>
</tr>
<tr>
<td>Lactoferrin</td>
<td></td>
<td></td>
<td></td>
<td>0.19</td>
<td>0.48</td>
</tr>
<tr>
<td>CDAI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.15</td>
</tr>
</tbody>
</table>

Correlation coefficients highlighted in red were significant (\(P<0.05\)).
When stratified by extent, correlation coefficients were highest for colonic disease.

CDAI, Crohn’s Disease Activity Index; SES-CD, Simple Endoscopic Score for Crohn’s Disease

Corticosteroid-Free Clinical Remission at Week 26 by Baseline Endoscopy Status
Assessment Of Post-Operative Disease Recurrence: Rutgeert’s Endoscopic Scoring System
6-Mercaptopurine and Mesalamine for Prevention of Post-Operative Recurrence of Crohn’s Disease
Does the Achievement of Mucosal Healing in Patients with Crohn’s Disease Alter Clinical Outcomes?

- Hospitalization
- Steroid free remission
- Surgery
ACCENT 1: Infliximab – Hospitalization and Surgery Rate by Mucosal Healing Status

*Endoscopic assessment at weeks 0, 10 and 54; mucosal healing was defined as the absence of mucosal ulceration

Steroid Avoidance Had More Endoscopic Healing at 2 Years: Secondary Endpoint of the Top-down/Step-up Trial


% of Patients

% of Patients in Remission

...and these patients did better in the next 2 yrs!
EXTEND: Deep Remission* Rates with Adalimumab at 1 Year

*Deep remission defined as clinical remission (CDAI <150) and complete mucosal healing in EXTEND
All patients (n=135) received adalimumab 160/80 mg induction therapy, before randomisation (n=129) to adalimumab 40 mg eow or to placebo. Deep remission was assessed in those who had ulceration at baseline (n=123).
CDAI: Crohn’s disease activity index; eow: every other week

EXTEND: Patients who Achieved Deep Remission* with Adalimumab at Week 12 And Hospitalization Rates

All-cause hospitalization through Week 52

<table>
<thead>
<tr>
<th>Remission Status</th>
<th>All Hospitalization (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep remission*</td>
<td>0/11</td>
</tr>
<tr>
<td>Non-deep remission*</td>
<td>9/53</td>
</tr>
</tbody>
</table>

CD-related hospitalization through Week 52

<table>
<thead>
<tr>
<th>Remission Status</th>
<th>Hospitalization (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep remission*</td>
<td>0/11</td>
</tr>
<tr>
<td>Non-deep remission*</td>
<td>5/53</td>
</tr>
</tbody>
</table>

*Deep remission defined as clinical remission (CDAI <150) and complete mucosal healing in EXTEND CD: Crohn’s disease; CDAI: Crohn’s disease activity index

Mucosal Healing After Treatment as Predictor of Subsequent Disease Course in Crohn’s Disease

MH = mucosal healing.

Mucosal Healing Predicts Long-term Outcome of Maintenance Therapy with Infliximab in CD

Sustained clinical benefit long-term with respect to mucosal healing during IFX treatment

Proportion of patients with sustained clinical benefit (%)

Follow-up since first IFX (months)

At risk: 75 67 52 41 26 19 15 10 4 2

Mucosal healing (N=75)

No mucosal healing (N=27)

Need for major abdominal surgeries by degree of mucosal healing (median 22.3 months follow-up)

Patients needing surgery (%)

Complete mucosal healing (N=85) 14.1% 12/85

Partial mucosal healing (N=43) 14% 6/43

No mucosal healing (N=86) 38.4% 33/86

Breslow: P=.239
LogRank: P=.058

Conclusions

- Mucosal healing
  - Is measurable
  - Is achievable
  - May
    - Increase steroid free remission
    - Reduce hospitalization
    - Reduce surgery