Mucosal Healing in IBD

GIPS Forum, Vancouver, B. C.
March 17th, 2018

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Outline

• Natural history of IBD
• Evolving definition of mucosal healing
• Histological Indices
• Histological Prognostic Factors
• Conclusions
Natural History of IBD

• Thought to be progressive, complications increase over time
  – Up to 50% have surgery within 10 years of diagnosis
  – 70-80% have surgery within 20 years of diagnosis
• Post-surgical CD patients demonstrate the following
  – Inflammation in 1-2 weeks
  – Aphthous ulcers in 3 months
  – Clinical symptoms in 2-3 years
  – 30% will require additional surgery within 10 years
• Therefore, mucosal damage seems to precede clinical symptoms and complications

Goals of Treatment in IBD

• Improvement in quality of life
• Prevention of complications
• Reduction of hospitalization and surgery rates
• Induction and maintenance of remission

Mucosal Healing in IBD

- What is the definition of mucosal healing in IBD?

**Problems:**
- 1. The classical definition of mucosal healing has been based on the *endoscopic* appearance.
- 2. There is no universally accepted histological definition of remission.
- 3. There is no consensus on the optimal way to assess disease activity.

Measures of Disease Activity in IBD

• How do we assess disease activity?
  – Clinical – CDAI, SCCAI, HBI, Montreal, etc.
  – Endoscopic
    • Ulcerative colitis - Mayo, Baron, UCEIS, etc.
    • Crohn’s disease – SES-CD, CDEIS, Rutgeerts’, etc.
  – Histologic – ~30 indices for UC, several for CD

• How do we define remission?
  – No rectal bleeding/clinical symptoms
  – Mayo 0-1 to Mayo 0 (normal mucosa, inactive ulcerative colitis), CDEIS less than 6 to less than 3, SES-CD 0-2
  – Histologic – ?
Mucosal Healing in IBD

**Mayo 0**
- no friability, granularity, and intact vascular pattern

**Mayo 1**
- mild erythema or decreased vascular pattern

**Mayo 2**
- redness, no vascular pattern, friability, erosions

**Mayo 3**
- Spontaneous bleeding, ulcerations
### TABLE 1. Endoscopic Activity Indices for UC

<table>
<thead>
<tr>
<th>Index</th>
<th>Mucosal Features Assessed</th>
<th>Score Range</th>
<th>Remission Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Truelove and Witts Sigmoidoscopic Assessment(^{42})</td>
<td>Hyperemia, granularity, change in overall appearance</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Baron Score(^{43})</td>
<td>Vascularity, friability, bleeding</td>
<td>0-3</td>
<td>ND</td>
</tr>
<tr>
<td>Powell-Tuck Sigmoidoscopic Assessment(^{44})</td>
<td>Friability, bleeding</td>
<td>0-2</td>
<td>ND</td>
</tr>
<tr>
<td>Mayo Score Flexible Proctosigmoidoscopy Assessment(^{45})</td>
<td>Erythema, vascularity, friability, bleeding, ulceration</td>
<td>0-3</td>
<td>≤ 1</td>
</tr>
<tr>
<td>Sutherland Mucosal Appearance Assessment (UC-DAI)(^{46})</td>
<td>Edema, vascularity, granularity, friability, bleeding, ulceration</td>
<td>0-3</td>
<td>ND</td>
</tr>
<tr>
<td>Rachmilewitz Endoscopic Index(^{47})</td>
<td>Granularity, vascularity, mucosal vulnerability, mucus, fibrin, exudate, erosion, ulceration</td>
<td>0-12</td>
<td>≤ 4</td>
</tr>
<tr>
<td>Sigmoidoscopic Index(^{48})</td>
<td>Erythema, friability, granularity, ulceration, mucopus, vascularity</td>
<td>0-16</td>
<td>≤ 4</td>
</tr>
<tr>
<td>Sigmoidoscopic Inflammation Grade Score(^{49})</td>
<td>Edema, vascularity, granularity, friability, bleeding, ulceration</td>
<td>0-4</td>
<td>ND</td>
</tr>
<tr>
<td>Modified Baron Score(^{50})</td>
<td>Granularity, vascularity, friability, hyperemia, bleeding, ulceration</td>
<td>0-4</td>
<td>0</td>
</tr>
<tr>
<td>Ulcerative Colitis Endoscopic Index of Severity(^{51})</td>
<td>Vascularity, bleeding, erosions, ulceration</td>
<td>3-11</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND indicates not defined; UC, ulcerative colitis; UC-DAI, UC Disease Activity Index.
### Simple endoscopic score (SES-CD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of ulcers (cm)</td>
<td>None</td>
<td>Aphthous ulcers (diameter 0.1-0.5)</td>
<td>Large ulcers (diameter 0.5-2)</td>
<td>Very large ulcers (diameter &gt; 2)</td>
</tr>
<tr>
<td>Ulcerated surface</td>
<td>None</td>
<td>&lt; 10%</td>
<td>10-30%</td>
<td>&gt; 30%</td>
</tr>
<tr>
<td>Affected surface</td>
<td>Unaffected</td>
<td>&lt; 50%</td>
<td>50-75%</td>
<td>&gt; 75%</td>
</tr>
<tr>
<td>Presence of narrowings</td>
<td>None</td>
<td>Single, can be passed</td>
<td>Multiple, can be passed</td>
<td>Cannot be passed</td>
</tr>
</tbody>
</table>

**SES-CD** = sum of all variables for the 5 bowel segments. Values are given to each variable for every examined bowel segment.

Mucosal Healing in IBD

• Low observed correlation between clinical and endoscopic activity scores (r=0.13 to 0.39)

Low Correlation Clinic v. Endo

- Infection
- Irritable bowel syndrome
- Bacterial overgrowth
- Bile salt diarrhea
- Steatorrhea
- Depression
- Opioids, antibiotics, other drugs
Variable Correlation Endo v. Histo

• Disease activity in 131 UC patients
• Overall kappa=0.48
• Relatively high concordance in extreme cases (no endoscopic activity or severe disease)
• Diversity of results in endoscopically mild cases (Mayo 1)
  – 37% grade 0
  – 21% grade 1
  – 28% grade 2
  – 14% grade 4

Clinic v. Endo v. Histo

Endoscopic remission  \( n = 56/91 \) (62%)

\[ \kappa = 0.56, \text{ 95\% CI 0.36-0.77} \]

Clinical remission  \( n = 37/91 \) (41%)

\[ \kappa = 0.29, \text{ 95\% CI 0.10-0.49} \]

Histological remission  \( n = 47/91 \) (52%)

\[ \kappa = 0.47, \text{ 95\% CI 0.27-0.68} \]

<table>
<thead>
<tr>
<th>Measure of remission</th>
<th>Concordance with other measures of remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical (n=37)</td>
<td>Clinical: 100% (n=37)</td>
</tr>
<tr>
<td></td>
<td>Endoscopic: 81% (n=30)</td>
</tr>
<tr>
<td></td>
<td>Histological: 81% (n=30)</td>
</tr>
<tr>
<td>Endoscopic (n=56)</td>
<td>Clinical: 54% (n=30)</td>
</tr>
<tr>
<td></td>
<td>Endoscopic: 100% (n=56)</td>
</tr>
<tr>
<td></td>
<td>Histological: 75% (n=42)</td>
</tr>
<tr>
<td>Histological (n=47)</td>
<td>Clinical: 64% (n=30)</td>
</tr>
<tr>
<td></td>
<td>Endoscopic: 89% (n=42)</td>
</tr>
<tr>
<td></td>
<td>Histological: 100% (n=47)</td>
</tr>
</tbody>
</table>

Mucosal Healing – UC v. CD

• May be more meaningful as UC is predominately a mucosal disease
• Rectum involved in most cases of UC facilitating surveillance
• CD may require an advanced cross-sectional imaging component to help fully describe disease activity
  – mucosal disease may still be a good surrogate marker as ulcers correlate with rate of colectomy
  – 62% v. 18% @ 8 years in one study (Allez et al. Am J Gastroenterol. 2002; 97:947-53)
Emergence of Histological Indices

• Truelove and Richards Index (1956)
  – Simple system that categorized patients as having, 1) no inflammation, 2) mild-to-moderate, or 3) severe inflammation
  – >50% of patients in clinical remission had endoscopic or histologic evidence of disease activity
  – 37% of patients without endoscopic findings had histologic disease activity
  – There was fair agreement b/t clin & endo (k=0.27) and moderate agreement b/t clin & histo (k=0.58)

~30 Histological Indices for UC

- Truelove and Richards (1956)
- Matts Score (1961)
- Watts Score (1966)
- Keren Score (1984)
- The Friedman Index (1985)
- Gomes Score (1986)
- Saverymuttu Index (1986)
- Floren Index (1987)
- Initial Riley Score (1988)
- Riley Score (1991)
- Hanauer Index (1993)
- Odze Index (1993)
- Sandborn Index (1993)
- Geboes Score (2000)
- Scheppach/D’Argenio Score (2001)
- Harpaz Index (2003)
- Modified Riley score (2005)
- Chicago/Rubin score (2007)
- Gramlich (2007)
- Baars (2012)
- Nishiyama (2014)
- Iacucci (2015)
- Wiernicka (2015)
- Theede (2015)
- Jauregui-Amezaga (2016)
- Marchal-Bressenot/Nancy (2017)
- Mosli/RHI (2017)
- etc...
Histological Indices for UC

• 11 of these 30 indices have been partially validated
• Arguably none have been fully validated
• Full validation requires...
  – Content validity – index is sufficient to measure UC (expert & literature support)
  – Criterion validity – index is adequate against a gold standard (no gold standard, usually a lab value)
  – Construct validity – index consistent with other measures of disease activity (clinical & endoscopy)
• An optimal histological index may not exist

Mucosal Healing in IBD

• What is the definition of mucosal healing in IBD?
  “Restoration of normal mucosal appearance by endoscopy of a previously inflamed region and the complete absence of ulceration and macroscopic and histological signs of inflammation.”

Histologic mucosal healing definition (IOIBD proposed):
• Induce absence of neutrophils (both in the crypts and lamina propria)
• Induce the absence of basal plasma cells and ideally reduce lamina propria plasma cells to normal; and
• Reduce lamina propria eosinophils to normal.

Clinical Predictors of Colectomy and Relapse in UC

- Mayo score $\geq 10$
- Mayo score $\geq 2$ after induction therapy
- Elevated CRP
- Prior anti-TNF treatment
- Other factors influence colectomy or relapse
  - Steroid dependency
  - Mayo $>2$ at baseline
  - No response, late response, or high CRP after induction
  - Others
• “...endoscopic remission is not always correlated with a histologically quiescent disease”

• Endoscopically quiescent, which will relapse first?

Histological Predictors of Relapse

Basal plasmacytosis and neutrophilic activity predicted relapse (37-50% had relapse)

Patients without basal plasmacytosis had only 14% relapse, while without activity had only a 9% relapse

Unclear if basal plasmacytosis is an independent predictor of relapse

Histological Predictors of Relapse

- 74 patients with endoscopically inactive UC were evaluated at baseline
- 27 of 74 patients relapsed in 12 mos (36%)
- Independent Predictors of Relapse
  - Younger age
  - Prior relapses in women
  - Basal plasmacytosis (hazard ratio 4.5)

Histological Predictors of Relapse

<table>
<thead>
<tr>
<th>Nonrelapsers (SD)</th>
<th>Relapsers&lt;sup&gt;a&lt;/sup&gt; (SD)</th>
<th>Hazard ratios (95% CI)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>&lt;sup&gt;b&lt;/sup&gt;P value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal plasmacytosis</td>
<td>29</td>
<td>4.35 (1.7–11.0)</td>
</tr>
<tr>
<td></td>
<td>Crypt atrophy</td>
<td>56</td>
<td>2.4 (1.1–5.3)</td>
</tr>
<tr>
<td></td>
<td>Crypt distortion</td>
<td>56</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>Paneth cell metaplasia</td>
<td>16</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Basal lymphoid aggregates</td>
<td>16</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>PMNs&lt;sup&gt;e&lt;/sup&gt;</td>
<td>24</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Cryptitis</td>
<td>24</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>Crypt abscesses</td>
<td>8</td>
<td>3.2</td>
</tr>
</tbody>
</table>

<sup>a</sup>Mean calculated using the value measured closest before a relapse.  
<sup>b</sup>Hazard ratios and <sup>b</sup>P values for univariate time-dependent Cox regression analysis.  
<sup>c</sup>No significant differences in white blood cell, hemoglobin, and albumin levels.  
<sup>d</sup>No erosions, ulcers, or granulomas detected; no significant difference in types and numbers of mononuclear cells in the upper two thirds of the lamina propria.  
<sup>e</sup>Polymorphonuclear leukocytes in the lamina propria.

Histological Predictors of Relapse

- 179 patients with endoscopically inactive UC were evaluated at baseline
- Patients with neutrophilic activity (Geboes 3.1 or greater) had an increased risk of relapse (RR 3.5)
- Remission defined as Geboes 0 or 1 (structural changes and/or chronic inflammation, no neuts)
- Patients in clinical, endoscopic, and histological remission at baseline only had a 7% rate of relapse within the next 12 months

### Bryant et al. Gut 2016:65:408-14

<table>
<thead>
<tr>
<th>Variable</th>
<th>Corticosteroid requirement</th>
<th>Hospitalization for severe colitis</th>
<th>Colectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease extent</td>
<td>n.s.</td>
<td>3.21, p=0.02</td>
<td>4.06, p=0.02</td>
</tr>
<tr>
<td>Histologic remission</td>
<td>0.42, p=0.02</td>
<td>0.21, p=0.02</td>
<td>0.36, p=0.22</td>
</tr>
<tr>
<td>Endoscopic remission</td>
<td>0.86, p=0.65</td>
<td>0.83, p=0.74</td>
<td>0.71, p=0.64</td>
</tr>
<tr>
<td>Histo and Endo Remission</td>
<td>0.38, p=0.02</td>
<td>0.24, p=0.04</td>
<td>0.46, p=0.39</td>
</tr>
</tbody>
</table>
Normalization is better than just quiescence

Patients were categorized as...

1. **Histologic normalization**: completely normal mucosa with no features of chronicity present.
2. **Histologic quiescence**: features of chronicity including crypt atrophy or branching but no active inflammation, such as erosions, crypt abscesses, or focal neutrophil infiltration.
3. **Histologic activity**: presence of any epithelial infiltration by neutrophils, crypt abscesses, erosions or ulceration.

**Figure 1.** Kaplan-Meier analysis of effect of endoscopic mucosal and histologic activity on clinical relapse-free survival. (A) Clinical relapse-free survival versus histologic healing. (B) Clinical relapse-free survival versus endoscopic mucosal healing. (C) Clinical relapse-free survival versus histologic healing in patients with endoscopic mucosal healing.

Will the post-“mucosal healing”/post- biological agent era allow us to change the natural history of IBD?
Recent studies support the traditional common sense understanding...

- Active (acute, neutrophilic) inflammation is evidence of disease activity
- Basal lymphoplasmacytosis (or plasmacytosis) is evidence of residual ongoing disease
- Crypt architectural distortion and fibrosis are a form of ‘scarring’ of the mucosa (i.e. evidence of prior injury) and may persist without ongoing injury
Documentation of Activity in IBD

• Simple Clinical Diagnostic Approach
  – Colonic mucosa (CM) with crypt architectural distortion (CAD) = “quiescent” colitis
  – CM c CAD + basal plasmacytosis (BP) = chronic colitis
  – CM c CAD + BP + neutrophils = active chronic colitis (min, mild, moderate, severe)

• May no longer be sufficient, translation to various index scores may be necessary
Molecular signalling pathways involved in mucosal healing

Paneth cell
- Antimicrobial peptides
- Defensins, REG3γ
- Necroptosis
- RIP1/3

Intestinal epithelial cells
- TFF3
- PGE2
- TLR9
- NOD
- PKC
- Cox2
- MyD88
- TLR2
- TLR4
- TLR5
- EGFR
- NFκB
- IRF3
- Apical Junctional Complex
- Adherens Junction
- Tight junction
- Ras/Erk/MAPK
- PUMA
- Smad5
- NFκB
- STAT3/5
- NFκB
- CXCR4
- CXCL12

Goblet cell
- Trefoil factors
- Muc2

Conclusions and Future Directions

• Mucosal healing is best categorized as a lack of disease activity based on combined endoscopic and histological assessment, sometimes called “complete remission”

• A precise definition of histological remission has not been well established
  – more prospective studies are needed
  – common sense understanding may prevail

• Systematization of clinical treatment and surveillance algorithms will require systematization of pathologic evaluation
  – expect non-neoplastic synoptic “index” reporting for salient IBD activity features

• Incorporation of appropriate biomarkers/ancillary studies (protein, nucleic acid, etc.)

• Is histological mucosal healing a reasonable clinical goal for all patients?