When and How to use 5-ASAs, Antibiotics, and Steroids in IBD

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Disclosures

• **Speaker’s Bureau:**
  - Abbvie; Entera Health; Takeda

• **Consultant / Advisory/ Data Safety Monitoring/ Scientific Advisory Board:**
  - Abbvie; Celgene; Entera Health; Hospira; Janssen (Johnson & Johnson / Centocor); Sandoz Biopharmaceuticals; Takeda; UCB Pharma.
Note: CME Program

• “Brand names” of drugs typically not used, unless necessary.

• Necessary in this presentation:
  – Justification:
    • 5-ASA: Multiple agents with same generic name, but notably different delivery systems.
    • Budesonide: Two agents with same generic name, but notably different delivery system.
Aminosalicylates (“5-ASA”)

THE UNIVERSITY OF CHICAGO MEDICINE
Digestive Diseases Center
Aminosalicylates (“5-ASA”)

• Mesalamine (various formulations), balsalazide, olsalazine, sulfasalazine.

• FDA-approved for UC

• Commonly used “off-label” in Crohn’s

• Safe

• Effective in mild-moderate disease
Choosing the Right 5-ASA

• Release Location ➔ Location of disease
• Previous experience with 5-ASA
• Combination therapy (oral + topical)
• Adequate Dose
• Compliance
Choosing the Right 5-ASA

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5-ASA Release Sites:

- **Pentasa®**
  - Stomach
  - Small Intestine
  - Moisture

- **Apriso®**
  - Phosphatidylcholine
  - pH ≥ 6
  - Moisture

- **Asacol-HD®**
  - Large Intestine
  - pH ≥ 7
  - Moisture

- **Delzicol®**
  - Large Intestine
  - Azo-bond (orals)
  - Directly applied (topicals)

- **Lialda®**
  - Large Intestine
  - Phosphatidylcholine
  - pH ≥ 7
  - Moisture

- **Azulfidine®**
  - Large Intestine
  - Azo-bond (orals)
  - Directly applied (topicals)

- **Dipentum®**

- **Colazal®; Giazo®**

- **Rowasa®**

- **Canasa®**

* Lialda utilizes both.

Sources: FDA package inserts / company websites.
Choosing the Right 5-ASA

- Release Location ➔ Location of disease
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- Compliance
Previous 5-ASA Problems?

- Intolerance to specific 5-ASA?
- Intolerance to similar 5-ASA’s?
  - ie. same coating on Asacol, Asacol HD, and Lialda
- Intolerance to all 5-ASA’s?
- Even topicals?
Choosing the Right 5-ASA

- Release Location ➔ Location of disease
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Combination: 5-ASA oral + enema superior in active Left-sided UC

Percent of patients reporting no blood seen in stool

<table>
<thead>
<tr>
<th></th>
<th>Oral 5-ASA 2.4g</th>
<th>Enema 5-ASA 4g</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>14</td>
<td>33</td>
<td>40</td>
</tr>
<tr>
<td>Week 2</td>
<td>18</td>
<td>33</td>
<td>44</td>
</tr>
<tr>
<td>Week 3</td>
<td>27</td>
<td>44</td>
<td>70</td>
</tr>
<tr>
<td>Week 6</td>
<td>36</td>
<td>56</td>
<td>90</td>
</tr>
</tbody>
</table>

Combination: 5-ASA oral + enema superior in maintenance of Left-sided UC

72 patients with UC (greater than proctitis) in remission x 1 month, at least 2 relapses in past year

5-ASA oral (1.6 g/d) + 5-ASA enemas (4 g/d)

Double-blind randomized

5-ASA oral (1.6 g/d) + placebo enemas

Relapse rate 39% (p<0.05)

12 months

Relapse rate 72%

12 months

Choosing the Right 5-ASA

• Release Location → Location of disease
• Previous experience with 5-ASA
• Combination therapy (oral + topical)
• Adequate Dose
• Compliance
Little Evidence of 5-ASA Dose Response in Active UC Beyond 2.4 g/Day


pH-Released Mesalamine (6-Week Studies)
Little Evidence of 5-ASA Dose Response in Active UC Beyond 2.4 g/Day

Patients in Remission (%)

1.2g bid 4.8g qd Placebo

*P = 0.001; †P < 0.01; both comparisons vs placebo.

P ≤ 0.01 for all comparisons vs placebo.


pH-Released Multimatrix Mesalamine Studies
Probable Dose Response >2.4 g/Day in Moderately Severe Active UC

Patients with Overall Improvement* (%)

<table>
<thead>
<tr>
<th>Study</th>
<th>Mesalamine 2.4 g/day</th>
<th>Mesalamine 4.8 g/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCEND 1</td>
<td>57% (53/93)</td>
<td>72% (55/76)</td>
</tr>
<tr>
<td>ASCEND 2</td>
<td>59% (77/130)</td>
<td>72% (89/124)</td>
</tr>
<tr>
<td>ASCEND 3</td>
<td>66% (251/383)</td>
<td>70% (273/389)</td>
</tr>
</tbody>
</table>

*p = 0.0384, p = 0.036

Choosing the Right 5-ASA

- Release Location ➔ Location of disease
- Previous experience with 5-ASA
- Combination therapy (oral + topical)
- Adequate Dose

- Compliance
5-ASA: Compliance is Key…

Ulcerative Colitis: Maintenance of Remission

% patients remaining in remission

Adherent

Nonadherent

*P < .0001

Choosing the Right 5-ASA

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Emphasis: Simplify Dosing Regimens: ↑compliance; better outcomes
Antibiotics in IBD
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• Crohn’s Lumenal Disease
• Crohn’s Fistulas
• ? Ulcerative Colitis

Mechanisms Unknown

Lack of Controlled Data
Antibiotics in IBD: Rationale

<table>
<thead>
<tr>
<th>Propose Antibiotic Action</th>
<th>IBD-Specific Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ↓ Luminal bacterial concentrations</td>
<td>• Overgrowth due to strictures, surgery, loss of IC valve</td>
</tr>
<tr>
<td>• Selectively eliminate bacterial subsets</td>
<td>• Subsets shown to cause differing severity of colitis</td>
</tr>
<tr>
<td>• ↓ Tissue invasion, microabscesses</td>
<td>• Crohn’s and severe UC can penetrate into deeper tissue layers</td>
</tr>
<tr>
<td>• ↓ Bacterial translocation, systemic dissemination</td>
<td>• Sequelae of penetrating disease</td>
</tr>
</tbody>
</table>
IBD Antibiotics

• Ciprofloxacin
  - Well tolerated
  - Side effects rare
  - Others (levofloxacin, moxifloxacin)

• Metronidazole
  - Cheap
  - Side effects – esp. neuropathy, taste eversion
  - Others: Tinidazole

• Rifaximin, others
Crohn’s Disease: Post-operative Delay in Relapse with Metronidazole

Crohn’s Disease: Post-operative Delay in Relapse with Ornidazole

Endoscopic

Clinical

**UC Antibiotics Clinical Trials**

### Ulcerative Colitis
- **Metronidazole**
  - Mixed data
- **Ciprofloxacin**
  - Mixed data
  - Benefits during steroid therapy
- **Rifaximin**
  - Uncontrolled data suggests potential efficacy


### Pouchitis
- **Ciprofloxacin**
  - Effective alone or in combination with other antibiotics.
- **Metronidazole / Tinidazole**
  - Effective alone or in combination with other antibiotics.
- **Rifaximin**
  - Effective alone or in combination with other antibiotics.

Shen B et al. Inflamm Bowel Dis 2001;7:301-5.
IBD: Corticosteroids
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Benefits

• Work very fast
• Work in patients who are very sick, usually quickly
• Usually works well if you’ve never had them, or only rarely

Drawbacks

• Many short-term side effects.
• “Laundry list of long-term side effects; some are irreversible
• Need to “wean” off slowly to allow your adrenal glands to start working
IBD: Corticosteroids

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Not A Long-Term Plan! Need to Get on Safer, More Effective Therapies!
IBD: Corticosteroids

- Oral, Parenteral, Topical (rectal)
- Effective in **INDUCING REMISSION**
- Ineffective in **MAINTAINING REMISSION**
- Prohibitive Side Effect Profile
Crohn’s Disease: Steroid Use

Response at 1 Month

Complete remission: 48%
Partial Remission: 32%
No Response: 20%

Response at 1 Year

Refractory

Steroid-Responsive

Steroid-Dependent

### Ulcerative Colitis: Steroid Use

#### Response at 1 Month
- Complete remission: 54%
- Partial Remission: 30%
- No Response: 16%

#### Response at 1 Year

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>29%</td>
</tr>
<tr>
<td>Steroid-Dependent</td>
<td>22%</td>
</tr>
<tr>
<td>Prolonged Response</td>
<td>49%</td>
</tr>
</tbody>
</table>

Corticosteroids

“Old School”

“Shotgun”: unfocused release:

- Prednisone, prednisolone, hydrocortisone (etc.)

“New School”

“Sniper”: focused release at sights of inflammation

- Budesonide
**Budesonide:**

- High Potency “Local” Corticosteroid

- Targeted Delivery To Bowel
  - Budesonide “CIR”
    - Small Bowel, Right Colon
  - Budesonide MMX:
    - Colon only

- Extensive Hepatic First-Pass Metabolism
  - Minimal systemic side-effects
Budesonide “CIR”: Crohn’s Disease

- **Budesonide-CIR (“Controlled Ileal Release”)** is currently available for Crohn’s Disease.
- Release starts at \( \text{pH} \approx 6 \).
  - Ideal for Small Bowel, Right Colon.
  - **NOT** ideal for ulcerative colitis, due to location of disease.

**Location of Absorption of Budesonide-CIR**

![Bar chart showing percentage of Budesonide absorbed in different parts of the bowel.](chart)

- Before Ileum: 0%
- Ileum: 40%
- Ascending Colon: 60%
- Rest of Colon: 10%

n=12


Budesonide “MMX”: Ulcerative Colitis

- **Budesonide-MMX** ("Multi-matrix") is currently available for Ulcerative Colitis.

- Release starts at **pH=7**.
  - Ideal for colonic release.
  - **NOT** ideal for small bowel Crohn’s disease due to location of disease.

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Budesonide “MMX”: Ulcerative Colitis

USA Study

- Placebo
- 5-ASA 2.4g
- Bud-MMX 6mg
- Bud-MMX 9mg

* p=0.0143

European Study

- Placebo
- Bud-CIR 9mg
- Bud-MMX 6mg
- Bud-MMX 9mg

* p=0.05; ** p=0.025 vs. placebo

Better Bone Mass Preservation

Corticosteroid-Naïve Crohn’s Disease Patients


![Graph showing T-Score Change over time with P-values for Budesonide CIR and Prednisolone.](image-url)
Summary

• 5-ASA:
  ▪ Match drug with disease location
  ▪ Combination therapy

• Antibiotics
  ▪ Crohns: Fistula, luminal, ? Post-op prevention
  ▪ UC: data lacking other than pouchitis

• Steroids:
  ▪ Budesonide whenever possible
  ▪ Check DEXA Bone Density

• Compliance is Key!
Lake Michigan!