The Effects of Synbiotic Therapy on Adult and Pediatric Ulcerative Colitis

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ANNU 696
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Outline

• Background on Ulcerative Colitis (UC)
• Synbiotic Therapy
• Research Findings
• Summary
• Conclusion
• Future Research Aims
Definition

Inflammatory bowel disease (IBD) characterized by intestinal inflammation with superficial ulcerations limited to the mucosa of the colon

- Age
- Gender

# Ulcerative Colitis vs. Crohn’s Disease

<table>
<thead>
<tr>
<th>Feature</th>
<th>UC</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Pain</td>
<td>Variable</td>
<td>Common</td>
</tr>
<tr>
<td>Depth of inflammation</td>
<td>Mucosal</td>
<td>Transmural</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Severe</td>
<td>Less severe</td>
</tr>
<tr>
<td>Distribution</td>
<td>• Diffuse</td>
<td>• Segmental</td>
</tr>
<tr>
<td></td>
<td>• Contiguous spread</td>
<td>• Noncontiguous spread</td>
</tr>
<tr>
<td></td>
<td>• Always involves rectum</td>
<td>• Rectal involvement</td>
</tr>
<tr>
<td></td>
<td>• Spares proximal GI tract</td>
<td>less common</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Occurs in entire GI tract</td>
</tr>
<tr>
<td>Fistula and sinus tracts</td>
<td>Rare</td>
<td>Common</td>
</tr>
</tbody>
</table>

Ulcerative Colitis vs. Crohn’s Disease

Crohn’s Disease

Ulcerative Colitis

UC is confined to the large colon
Symptoms

Intestinal
- Diarrhea
- Rectal bleeding
- Passage of mucus
- Tenesmus (rectal pain)
- Abdominal Pain
- Weight loss
- Lethargy
- Poor appetite

Non-intestinal
- Eye disorders
- Painful joins
- Skin conditions
- Liver abnormalities
- Blood clots
- Anemia

# Severity of UC

<table>
<thead>
<tr>
<th>Sign or symptom</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/dL)</td>
<td>Normal</td>
<td>3.0 to 3.5</td>
<td>&lt; 3.0</td>
</tr>
<tr>
<td>Body Temperature</td>
<td>Normal</td>
<td>99 to 100 °F</td>
<td>&gt; 100 °F</td>
</tr>
<tr>
<td>Bowel movements</td>
<td>&lt; 4 per day</td>
<td>4 to 6 per day</td>
<td>&gt; 6 per day</td>
</tr>
<tr>
<td>ESR (mm per hour)</td>
<td>&lt; 20</td>
<td>20 to 30</td>
<td>&gt; 30</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>Normal</td>
<td>30 to 40</td>
<td>&lt; 30</td>
</tr>
<tr>
<td>Pulse (beats per min)</td>
<td>&lt; 90</td>
<td>90 to 100</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>Weight loss (%)</td>
<td>None</td>
<td>1 to 10</td>
<td>&gt; 10</td>
</tr>
</tbody>
</table>

ESR = erythrocyte sedimentation rate

Epidemiology

• Affects 250,000 to 500,000 persons in the US

• Annual incidence of 2 to 7 per 100,000 persons

• Incidence has remained constant over the past 5 decades

• Financial cost is ~$500 million annually
  – 250,000 physician visits per year
  – 20,000 hospitalizations per year

Potential Mechanisms

↑ Pathogenic Bacteria

Inflammatory response in gut mucosa

Dysregulation of mucosal immune system

Triggered by commensal microflora in the gut

Clinical Diagnosis

• Clinical history used to differentiate between various etiologies of chronic diarrhea in suspected UC

• Physical examination for patient with established UC
  – Targets gastrointestinal, dermatologic and ocular systems
  – Arthritis and skin lesions provide information on severity
Diagnostic Testing

• Stool examinations for ova and parasites
• Stool culture
• Testing for Clostridium difficile
• Erythrocyte Sedimentation Rate
• C – reactive Protein
• Complete blood count
• Basic metabolic profile
• Colonoscopy or proctosigmoidoscopy and biopsy
Treatment Dependent on Severity of UC

- **Proctitis**
  - Left-sided
  - **5-ASA suppositories**
    - Response?
      - Yes: Rectal 5-ASA maintenance
      - No: Oral 5-ASA maintenance

- **Mild to moderate**
  - Extensive
  - **Oral 5-ASA**
    - Response?
      - Yes: Oral 5-ASA maintenance
      - No: Urgent surgical consultation

- **Moderate to severe**
  - Complications
    - Perforation
    - Severe hemorrhage
    - Toxic megacolon

Long-Term Risks

• UC patients are at increased risk of developing colon cancer

• Severity and duration of disease affect the degree of risk

<table>
<thead>
<tr>
<th># of Years with UC</th>
<th>Colon Cancer Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>2%</td>
</tr>
<tr>
<td>20</td>
<td>8%</td>
</tr>
<tr>
<td>30</td>
<td>18%</td>
</tr>
</tbody>
</table>

• UC patients with proctitis or proctosigmoiditis are not considered to be at risk

Have researchers identified complementary treatments for UC in addition to medical therapy?

Yes; Synbiotic Therapy
**Synbiotics**

**Probiotics**
- Living microorganisms
- Improve intestinal microbial balance
- *Bifidobacteria*
- *Lactobacilli*

**Prebiotics**
- Non-digestible oligosaccharide
- Encourage growth of beneficial bacteria
- *Inulin*
- *FOS, GOS*

Synbiotic Therapy (ST)

• Mixture of prebiotics + probiotics

• Beneficially affects the host by:
  - Improving survival and implantation of live microbial dietary supplements in GI tract
  - Selectively stimulating growth and/or activating metabolism of one or more health-promoting bacteria

Is there research to support the use of ST in UC patients?
<table>
<thead>
<tr>
<th><strong>Sample size:</strong></th>
<th>N = 41, age NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 Control, 21 Synbiotic</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Duration of study:</strong></th>
<th>2 week trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year, Medical Center Hospital</td>
<td></td>
</tr>
</tbody>
</table>

| **Control treatment:** | Treated as usual on basis of medical background |

<table>
<thead>
<tr>
<th><strong>Synbiotic treatment:</strong></th>
<th>1 g freeze dried powder containing</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Probiotic 3x daily</td>
<td>$10^9$ CFU/g <em>Bifidobacterium breve</em></td>
</tr>
<tr>
<td>- Prebiotic 1x daily</td>
<td>strain <em>Yakult</em> (BbY) + 5.5 g of GOS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Outcome measure(s):</strong></th>
<th>Endoscopic Score - 1º</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Myeloperoxidase Analysis - 2º</td>
</tr>
<tr>
<td></td>
<td>Analysis of Fecal Organisms -2º</td>
</tr>
</tbody>
</table>

### Matt’s Classification

#### Endoscopic Score

<table>
<thead>
<tr>
<th>Grade 1:</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2:</td>
<td>Mild granularity of mucosa, with mild contact bleeding</td>
</tr>
<tr>
<td>Grade 3:</td>
<td>Marked granularity and edema of mucosa, contact bleeding, spontaneous bleeding</td>
</tr>
<tr>
<td>Grade 4:</td>
<td>Severe ulceration of mucosa with hemorrhage</td>
</tr>
</tbody>
</table>

↓ variability

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Comparison of Endoscopic Scores in Control vs. Synbiotic Treatment

Myeloperoxidase (MPO) Analysis

- MPO is secreted from neutrophils and macrophages accumulating in inflamed lesions
- Positively correlated with severity of IBD

Before trial, researchers confirmed MPO amounts in the LS of patients with Active UC were significantly higher

- Used the MPO amount in LS as a biological marker of active UC disease severity
Comparison of MPO:ALP levels in Control vs. Synbiotic Treatment

### Fecal Flora and pH in UC patients Before and After Synbiotic Therapy

N = 20, randomly selected from ST

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bacteria</td>
<td>10.42 ± 0.36</td>
<td>10.28 ± 0.35</td>
</tr>
<tr>
<td>Bacteriodaceae</td>
<td>9.95 ± 0.47</td>
<td>9.46 ± 0.90 *</td>
</tr>
<tr>
<td>Bifidobacterium</td>
<td>9.85 ± 0.45</td>
<td>9.51 ± 1.12</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>7.25 ± 1.01</td>
<td>7.75 ± 0.73</td>
</tr>
<tr>
<td>Lactobacillus</td>
<td>7.18 ± 1.62</td>
<td>7.20 ± 1.50</td>
</tr>
<tr>
<td>B. Breve</td>
<td></td>
<td>5.75 ± 1.65</td>
</tr>
<tr>
<td>pH</td>
<td>6.42 ± 0.61</td>
<td>6.12 ± 0.53 *</td>
</tr>
</tbody>
</table>

Data for fecal flora are represented as $\log_{10}$ CFU/g wet weight

Feces ± SD, * p < 0.05

### Synbiotic Therapy (*Bifidobacterium longum*/Synergy 1) in Patients with Active Ulcerative Colitis

| Sample size: | N = 14, ages 24-67  
6 Placebo (5 full biopsy)  
8 Synbiotic (7 full biopsy) |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of study:</td>
<td>4 weeks, Gastroenterology Outpatient Clinic</td>
</tr>
<tr>
<td>Placebo treatment:</td>
<td>Potato starch capsule + 12 g/d maltodextrose</td>
</tr>
</tbody>
</table>
| **Synbiotic treatment:** | $2 \times 10^{11}$ CFU/d *Bifidobacterium longum*  
- 2x daily  
+ 6 g inulin-oligofructose |
| Outcome measure(s): | Clinical Activity Index (CAI)  
C-reactive Protein (CRP)  
Histology Scores of Rectal Biopsy |

Why *B. longum*?

- Researchers assessed 19 different Bifidobacteria isolates for:
  - Aerotolerance
  - Acid tolerance
  - Bile salt resistance
  - Adhesion to epithelial cells
  - Ability to utilize oligofructose as an energy source
  - Ability to survive freeze drying and long-term storage

<table>
<thead>
<tr>
<th></th>
<th>Synbiotic N = 8 (pre-trial)</th>
<th>Placebo N = 8 (pre-trial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>45 (25-66)</td>
<td>38 (26-59)</td>
</tr>
<tr>
<td>Duration of disease (y)*</td>
<td>10 (1-23)</td>
<td>7 (1-15)</td>
</tr>
<tr>
<td>Current drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>5-ASA</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Initial Clinical Activity Score (CAI)</td>
<td>5.6 (2-13)</td>
<td>4.7 (1-8)</td>
</tr>
<tr>
<td>Initial CRP (mg/l)</td>
<td>6.0 (0-16)</td>
<td>5.5 (0-17)</td>
</tr>
</tbody>
</table>

Values are mean (range) or number
* Disease extent unknown for one placebo patient
◆ UC related drugs only
CRP, C-reactive protein

### CAI (maximum score 19)

<table>
<thead>
<tr>
<th></th>
<th>Synbiotic N = 5</th>
<th>Placebo N = 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start of trial</td>
<td>5.6 ± 3.7</td>
<td>4.9 ± 3.2</td>
</tr>
<tr>
<td>End of trial</td>
<td>5.3 ± 3.4</td>
<td>3.1 ± 2.5</td>
</tr>
</tbody>
</table>

### CRP

<table>
<thead>
<tr>
<th></th>
<th>Synbiotic N = 5</th>
<th>Placebo N = 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start of trial</td>
<td>6.0 ± 6.5</td>
<td>1.6 ± 3.6</td>
</tr>
<tr>
<td>End of trial</td>
<td>1.8 ± 3.9</td>
<td>None ↑</td>
</tr>
</tbody>
</table>

A closer look…

• Certain probiotic strains (i.e. Lactobacillus, S. boulardii) should be used cautiously in patients taking:
  – Immunosuppressants
  – Chemotherapeutic agents

• Administering probiotics may cause an infection or pathogenic colonization in these patients

Comparison of Rectal Biopsies in Synbiotic vs. Placebo Treatment

Synbiotic Therapy

A = Patient with UC Pre-Synbiotic Therapy HS = 3

B = Placebo patient at start of study HS = 1.5

C = Patient with UC Post-Synbiotic Therapy HS = 1.5

D = Placebo patient at end of study HS = 2.5

Placebo

Histology Scoring

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No inflammation</td>
<td>Mild inflammation</td>
<td>Moderate Inflammation</td>
<td>Severe Inflammation</td>
</tr>
</tbody>
</table>

Summary

• The use of ST in UC patients has been shown to:
  – Improve endoscopic scores
  – Lower fecal pH
  – Decrease fecal counts of Bacteroides
  – Regenerate healthy epithelial tissue
  – Decrease histology scores

Is ST more effective than administering a pre- or probiotic?
Efficacy of Synbiotic vs. Probiotic or Prebiotic Treatment to Improve the QOL in Patients with Ulcerative Colitis

Sample size: N = 120 divided into 3 groups, age NA
- 40 Probiotic, 40 Prebiotic, 40 Synbiotic

Duration of study: 4 weeks, Hospital

Probiotic treatment: 2 x 10^9 CFU/capsule *Bifidobacterium longum*
- 1x daily

Prebiotic treatment: 4.0 g psyllium
- 2x daily

Synbiotic treatment: Probiotic + Prebiotic treatments

Outcome measure(s): Irritable Bowel Disease Questionnaire (IBDQ) - baseline, 2 weeks & 4 weeks
- C-reactive protein

IBDQ

- A disease-specific scale that evaluates health-related quality of life (QOL)\(^1\)

- QOL is significantly altered when the UC is active and in remission\(^2\)

- IBDQ scores represent how effectively remission is maintained in patients with UC\(^1\)

Comparison of IBDQ Scores in Probiotic, Prebiotic and Synbiotic Treatments

Comparison of CRP levels in Probiotic, Prebiotic and Synbiotic Treatments

<table>
<thead>
<tr>
<th></th>
<th>Probiotic</th>
<th>Prebiotic</th>
<th>Synbiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-treatment</strong></td>
<td>0.12 ± 0.11</td>
<td>0.26 ± 0.25</td>
<td>0.59 ± 1.1</td>
</tr>
<tr>
<td><strong>Post-treatment</strong></td>
<td>0.10 ± 0.01</td>
<td>0.17 ± 0.12</td>
<td>0.14 ± 0.14</td>
</tr>
</tbody>
</table>

Conclusion

• Administering a pre- and probiotic together as ST significantly improved IBDQ scores

• The prebiotic, probiotic and synbiotic treatments all decreased CRP levels
  – Significant decrease (p < 0.05) observed only in the ST group

  • CRP levels pre-ST

Is ST equally effective in Pediatric UC?
Case Report: Background

• 9 year old female

• Moderate to severe UC

• Chief complaints:
  – Abdominal pain
  – Weight loss
  – Loose stools

• 5 to 7 stools/d with presence of blood and mucous

• High doses of corticosteroids (40 mg/d) resolved symptoms

• Weaning corticosteroids unsuccessful

Case Report: Design

• Standard medical therapy
  – 1.5 g/d mesalazine
  – 40 mg/d steroids

• Synbiotic therapy
  – $2.0 \times 10^{10} \text{ CFU/d } Bifidobacterium longum R0175$
  – 15 g/d inulin

• Short Inflammatory Bowel Disease Questionnaire (SIBDQ)
  – Baseline
  – Every 2 months

• Patient kept daily record of symptoms
  – Stool consistency and frequency
  – Presence of blood and mucous
  – Presence of abdominal pain

Case Report: Outcomes

- Average SIBDQ score of 68.6 during synbiotic therapy
  - 10 = worst health
  - 70 = best health

- Study diary reported an absence of blood or mucous in stool and abdominal pain since initiation of synbiotic therapy

- Patient remained in clinical remission:
  - Absence of visible blood in the stools
  - No more than 2 bowel movements per day for 1 year

- No adverse effects reported

- Patient was able to be weaned from high doses of corticosteroids
## Synbiotic Therapy in Pediatric UC

<table>
<thead>
<tr>
<th>Sample size:</th>
<th>N = 9, ages 8 to 18</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 Placebo, 4 Synbiotic</td>
</tr>
<tr>
<td>Duration of study:</td>
<td>10 months or until relapse</td>
</tr>
<tr>
<td>Placebo treatment:</td>
<td>15 g/d non-resistant maltodextrin and a capsule of maltodextrin + ascorbic acid</td>
</tr>
<tr>
<td>Synbiotic treatment:</td>
<td>$2.0 \times 10^{10}$ CFU/d <em>Bifidobacterium longum</em> R0175 + 15 g/d inulin</td>
</tr>
<tr>
<td>Outcome measure:</td>
<td>SIBDQ (baseline, every 2 months)</td>
</tr>
<tr>
<td></td>
<td>Study diary (stool frequency, blood or mucous, abdominal pain and overall feeling)</td>
</tr>
</tbody>
</table>

Synbiotic Therapy in Pediatric UC

- 60% (3 out of 5) receiving placebo experienced relapse
- 75% (3 out of 4) receiving synbiotic in remission at 10 months

SIBDQ Score
70 = Highest
10 = Lowest

![Bar chart showing SIBDQ scores at Study Entry and at time of relapse or 10 months for placebo and synbiotic groups.](chart.png)

## Synbiotic Therapy in Pediatric UC

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>ST</th>
<th>Placebo</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool frequency, number/d</td>
<td>1.5 ± 0.4</td>
<td>2.2 ± 2.4</td>
<td>.624</td>
</tr>
<tr>
<td>Days with formed stool, %</td>
<td>61.4 ± 46.5</td>
<td>61.3 ± 38.0</td>
<td>.806</td>
</tr>
<tr>
<td>Days without abdominal pain, %</td>
<td>97.3 ± 4.9</td>
<td>89.1 ± 14.9</td>
<td>.213</td>
</tr>
<tr>
<td>Days without blood or mucous in the stool, %</td>
<td>100 ± 0</td>
<td>71.6 ± 41.9</td>
<td>.032</td>
</tr>
<tr>
<td>Days feeling well, %</td>
<td>99.3 ± 0.9</td>
<td>63.4 ± 34.4</td>
<td>.014</td>
</tr>
</tbody>
</table>

mean ± SD

Summary

• Synbiotic Therapy in Pediatric UC has been shown to:
  – Increase SIBDQ scores\textsuperscript{1,2}
  – Reduce severity of symptoms
    • Absence of blood and mucous in stools\textsuperscript{1}
    • Decreased abdominal pain\textsuperscript{1}
    • Decreased # of bowel movements\textsuperscript{1}
  – Reduce relapse rate
    • 3 out of 4 in ST group were in remission at 10 months\textsuperscript{2}

Are there contraindications to the implementation of ST?
Contraindications

• Caution needs to be exercised when using probiotics in severely immuno-compromised individuals\textsuperscript{1,2}

• As of March 2010, no reports of bifidobacterial sepsis had been reported \textarrow{low pathogenicity}\textsuperscript{2}

• Probiotics should be consumed at least two hours from the administration of antibiotics\textsuperscript{2}

• Probiotics should not be used in\textsuperscript{1,2}:
  – Critically ill
  – Severely immunosuppressed
  – Indwelling central catheters

Summary

• The use of ST in Adult UC:
  – Improved QOL
  – Improved markers of inflammation
  – Improved endoscopic/histologic scores
  – Reduced severity of symptoms

• The use of ST in Pediatric UC:
  – Improved QOL
  – Reduced severity of symptoms
  – Maintained remission
Future Research Aims

• Larger sample size
• DBRCT
• Longitudinal studies
  – 1 month to 1 year
• Severity/Status
  – Mild, Moderate or Severe
  – Active vs. Inactive

• Include objective measures
  – Diagnostic tests
• Compare efficacy of different synbiotic mixtures
  – Prebiotic
  – Probiotic
Conclusion

I would suggest the use of ST for:

- Adult and pediatric patients suffering from mild to moderate UC that are not immuno-suppressed or critically ill along with standard medical treatment (if tolerated)

- No adverse effects reported
- Improve QOL
- Decrease severity of symptoms
- Alternative to steroids
Questions?

A HAPPYcolon IS A HEALTHY colon