Alternative Therapies for IBD

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Outline

• Background on the intestinal microbiota
• Fecal microbiota transplantation
• Diet as a treatment for IBD
• Probiotics
• Cannabinoids
• Andrographis panniculata
• Curcumin
• Boswellia serrata
Intestinal microbiota in health

• Communities of bacteria have co-evolved with humans to occupy specific anatomic niches and form complex ecosystems

• Colonization of microbiota begins at birth, and is influenced by method of delivery (vaginal vs cesarean) and lactation vs bottle-feeding.

• Microbial diversity peaks in adolescence and remains stable until older adulthood when diversity decreases

• Microbiota affected by diet and antibiotics

• Role of the microbiota in health:
  • Energy harvest from otherwise indigestible starches, regulation of metabolism, production of micronutrients and vitamins, gut epithelial cell renewal, immune system development, and protection from pathogenic organisms
Intestinal microbiota in health

- Intestinal microbiota comprised of $10^{14}$ cells (10x the # of human cells in the body!)
  - Only 30% are detectable by culture-based techniques
  - 3.3 million non-redundant microbial genes (150 times more than human genome)
- There are 500-2000 species present in any individual
Diseases in which an altered microbiome is implicated

**Gastrointestinal:**
- Irritable bowel syndrome (IBS)
- Inflammatory bowel disease (IBD)
- Constipation
- Colon cancer
- Recurrent *C. difficile* infection

**Metabolic:**
- Obesity
- Diabetes mellitus
- Metabolic syndrome

**Allergic/autoimmune:**
- Asthma
- Psoriasis
- Rheumatoid arthritis
- ITP

**Neuropsychiatric:**
- Autism
- Depression
- Multiple sclerosis
- Parkinson’s
Evidence to support a role for the microbiota in IBD

- IBD localized to segments of the bowel with highest bacterial concentrations
- Abnormal microbial composition in Crohn’s, UC and pouchitis
- Genetic polymorphisms associated with mucosal barrier function and intracellular bacterial recognition, processing and killing
- Some data to support the use of probiotics and antibiotics in IBD management
- Diversion of the fecal stream improves disease activity in Crohn’s disease
- All mouse models of IBD require presence of bacteria to induce inflammation
Microbiota in IBD

• Reduced diversity of bacteria in IBD
• Decrease in Firmicutes (bifidobacteria, lactobacillus, Faecalibacterium prausnitzii)
• Increase in mucosally-adherent bacteria
• Enhanced *E.coli* virulence in Crohn’s

Sartor RB, Gastroenterol 2008
Strategies to alter the intestinal microbiome

• Antibiotics
• Probiotics
• Prebiotics (diet)
• Fecal microbiota transplantation (stool transplant)
Fecal Microbiota Transplantation in IBD
Fecal microbiota transplantation

• First report of stool to treat human GI disease: 4th century China
  • Oral suspension of human feces ("yellow soup") to treat severe diarrhea
• First report in modern medical literature in 1958
  • 4 patients received fecal enema for pseudomembranous colitis

fmt.gastro.org

Zhang F, Am J Gastro 2012
Eiseman B, Surgery 1958
Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis

• 50 patients with mild to moderate active UC
• Randomized to FMT with donor stool or FMT with their own stool
• Given by nasoduodenal tube at day 0 and 3 wks later
• Primary outcome: clinical remission (SCCAI ≤2) plus endoscopic response (≥ 1 point drop in Mayo endoscopic score) at week 12
• Results:
  • 7/23 patients (30%) achieved remission with donor FMT
  • 5/25 patients (20%) achieved remission with placebo (self-FMT) \( P=0.51 \)
  • Patients who improved with donor FMT showed change in their microbiota

Rossen NG, Gastroenterol 2015
Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial

- 75 patients with active UC
- Randomized to receive FMT enema or water enema weekly x 6 wks
- Primary outcome: remission (total Mayo $\leq 2$, with endoscopic score 0) at week 7
- Trial stopped early for futility, but patients already enrolled were followed
- Results:

<table>
<thead>
<tr>
<th></th>
<th>FMT (n=37)</th>
<th>Placebo (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission at wk 7</td>
<td>9 (24%)</td>
<td>2 (5%)</td>
</tr>
</tbody>
</table>

Moayyedi P, Gastroenterol 2015
• 7 of 9 patients who achieved remission had the same donor

• 3 of 4 patients with short disease duration (≤1 yr) achieved remission vs 6 of 34 patients with longer disease duration
OP017 Multi-donor intense faecal microbiota transplantation is an effective treatment for resistant ulcerative colitis: a randomised placebo-controlled trial

S. Paramsothy*1, M. Kamm2,3, A. Walsh4, J. van den Bogaerde5, D. Samuel6, R. Leong6, S. Connor7, W. Ng7, R. Paramsothy7, N. Kaakoush8, H. Mitchell8, W. Xuan9, E. Lin10, T. Borody10

- 81 patients with mild to moderate active UC
- Randomized to receive FMT-donor or placebo
- 1st dose given via colonoscopy, then enemas 5 days/wk for 8 weeks
- Each enema contained stool from 3-7 unrelated donors

<table>
<thead>
<tr>
<th>Outcome (at week 8)</th>
<th>Fecal Microbiota Group, % (n = 41)</th>
<th>Placebo Group, % (n = 40)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical remission</td>
<td>44</td>
<td>20</td>
<td>.02</td>
</tr>
<tr>
<td>Clinical response</td>
<td>54</td>
<td>23</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Endoscopic remission</td>
<td>17</td>
<td>8</td>
<td>.19</td>
</tr>
<tr>
<td>Endoscopic response</td>
<td>37</td>
<td>10</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Clinical remission plus endoscopic remission and response (1st outcome)</td>
<td>27</td>
<td>8</td>
<td>.02</td>
</tr>
</tbody>
</table>
Safety of FMT in IBD

• Generally safe, but lots of unknowns
• Several case reports of IBD exacerbation following FMT
• Risk of transmitting an infection from donor
• Risk of transmitting another disease from donor related to microbiota
  • Case of new-onset obesity following FMT for C diff

Watson, Gastronenterol 2012
Mellow M, Am J Gastro 2010
Angeberger S, Am J Gastro 2013
Alang N, Open Forum Infect Dis 2015
Unanswered Questions about FMT

• Recipient selection?
• Donor selection?
• Recipient Preparation:
  • antibiotics, bowel lavage
• Route of administration:
  • NGT, push enteroscopy, colonoscopy, enema
• Frequency of administration
• Post administration:
  • loperamide, lay supine
• Specific bacteria critical to the success of FMT?
Diet in IBD

Slides courtesy of David Suskind, MD
Western Diet and IBD

• High total fat, omega-6 fatty acids and animal proteins
  • Increased risk of CD and UC

• High fruits and fiber intake
  • Decreased risk of CD

• High in vegetables intake
  • Decreased risk of UC

Hou JK et al. Am J Gastroenterol. 2011
Asakura H et al. J. Gastro Hepatol. 2008
Effects of Modifying the Diet on Microbiome

Wu, G, Science 334, 105 (2011); 105-108
Exclusive enteral nutrition is equivalent to steroids for pediatric IBD

- Formula only for 8-12 weeks, no other oral intake allowed
- Equivalent remission rates with EEN vs steroids
- Exclusive enteral nutrition better than partial enteral nutrition

Dziechciarz P, Aliment Pharmacol Ther 2007
Cochrane Review of Enteral Nutrition in Adults with Crohn’s Disease

- Steroids are more effective than EN for induction in active Crohn’s
  - Meta analysis of 6 trials (192 patient on EN, 160 patient on steroids)
  - OR 0.33 for induction of remission with EN vs steroids
- No difference in elemental vs polymeric formulas
- Non-significant trend favoring a very low fat diet
Partial Enteral Nutrition with a Crohn’s Disease Exclusion Diet Is Effective for Induction of Remission in Children and Young Adults with Crohn’s Disease

Sigall-Boneh R, Inflamm Bowel Dis 2014
Partial Enteral Nutrition with a Crohn’s Disease Exclusion Diet Is Effective for Induction of Remission in Children and Young Adults with Crohn’s Disease

**TABLE 3.** Pairwise Comparisons of Parameters Between Weeks 0 and Week 12

<table>
<thead>
<tr>
<th>N = 36</th>
<th>Week 0</th>
<th>Week 12</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBI, mean</td>
<td>5.9 ± 2.7</td>
<td>0.75 ± 1.75</td>
<td>0.000</td>
</tr>
<tr>
<td>HBI, median (range)</td>
<td>6.0 (0–13)</td>
<td>0.0 (0–6)</td>
<td>0.000</td>
</tr>
<tr>
<td>PCDAI (n = 24)</td>
<td>25.7 ± 8.9</td>
<td>6.44 ± 8.07</td>
<td>0.000</td>
</tr>
<tr>
<td>CRP</td>
<td>2.3 ± 2.3</td>
<td>0.81 ± 0.64</td>
<td>0.002</td>
</tr>
<tr>
<td>ESR</td>
<td>25.7 ± 12.7</td>
<td>17 ± 8.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>12.0 ± 1.4</td>
<td>12.6 ± 1.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.8 ± 0.42</td>
<td>4.12 ± 0.39</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Pairwise comparisons only in subjects with parameters at both time points. Abnormally distributed variables are present as median values. HBI (used in all patients). PCDAI calculated only for children and adolescents through age 18 years. PCDAI, pediatric Crohn’s disease activity index.

Sigall-Boneh R, Inflamm Bowel Dis 2014
Specific Carbohydrate Diet (SCD)

• Removes
  • All grains (especially complex carbohydrates)
  • Milk products except for yogurt fermented > 24 hours
  • Sugars except honey
• Sidney Haas MD
  • Early 1930s used to treat celiac disease
• Popularized by Elaine Gottschall
  • Breaking the Vicious Cycle

Haas, S, Haas M, Am J Gastroenterol 1955 Apr;23(4):344-60
SCD at Seattle Children’s Hospital

• Retrospective study
  • 7 children with Crohn’s disease
  • Trialed dietary therapies as sole medical treatment for their Crohn’s disease
• Seattle Children’s Hospital
  • January 2005 to December 2012

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Prior to Diet Intervention</th>
<th>3 Months After</th>
<th>6 Months After</th>
<th>12 Months After</th>
<th>15 Months After</th>
<th>18 Months After</th>
</tr>
</thead>
<tbody>
<tr>
<td>One</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Four</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Five</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nine</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ten</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Specific Carbohydrate Diet

- Promising early evidence of benefit
- Unknowns/future directions:
  - Does SCD work better than placebo?
  - If SCD works, what is the mechanism:
    - Exclusion of a food antigen?
    - Diet-induced alteration of gene expression?
    - Alteration of the microbiota?
  - Can the SCD diet be relaxed a little bit and still be effective?
  - Is diet a therapy that will work for all IBD patients or only a subset?
  - Are there other diets that are effective?
Probiotics for IBD
Probiotics

• Definition:
  • Live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host

• Numerous products on the market
  • Wide variability in the bacterial species they contain
  • No good measure of dose for cross-comparison
  • Differing delivery mechanisms that impact viability of the microorganisms
  • Lack of regulation means potential inconsistency within a specific product

• Due to substantial heterogeneity, study results cannot be reliably pooled or extrapolated
Probiotics in Crohn’s disease

• Induction in active CD:
  • E. coli Nissle 1917, Bifidobacterium, Lactobacillus all ineffective

• Maintenance of remission in CD:
  • S. Boulardii when added to mesalazine better than placebo
  • Lactobacillus GG ineffective

• Prevention of post-op recurrence in CD:
  • Lactobacillus GG and lactobacillus johnsonii ineffective

Malchow HA, J Clin Gastroenterol 1997
Guslandi M, Dig Dis Sci 2000
Prantera C, Gut 2002
Durchschein F, World J Gastroenterol 2016
Probiotics in Ulcerative Colitis

• Induction of active UC:
  • VSL#3 better than placebo
  • Bifido-fermented milk shows mild benefit

• Maintenance of remission in UC:
  • Lactobacillus GG similar to mesalazine
  • E. coli Nissle 1917 similar to mesalazine

• Pouchitis:
  • VSL#3 effective for maintenance of remission in antibiotic dependent pouchitis and for prevention of acute pouchitis
  • Lactobacillus GG effective for prevention of acute pouchitis

Jonkers D, Drugs 2012
Durchschein F, World J Gastroenterol 2016
Natural Therapies for IBD
Cannabinoids

• Cannabis sativa contains over 70 different cannabinoid compounds
• Δ9-tetrahydrocannabinol (THC) is the psychoactive compound
• THC enters the bloodstream rapidly and is then absorbed in fat tissue where it can be detected for > 4 wks
• THC can slowly re-enter the bloodstream from fat cells
• Effects:
  • Euphoria, relaxation, time distortion, sensory intensification, loss of inhibitions
  • Analgesic and anti-inflammatory properties (similar to aspirin)
  • Decreased gastric and colonic motility and secretion

Naftali T, Dig Dis 2014
Cannabis Induces a Clinical Response in Patients With Crohn’s Disease: A Prospective Placebo-Controlled Study

• 21 patients with CDAI score > 200, not responding to therapy
• Randomized to receive 8 weeks of:
  • Cannabis cigarettes (115mg THC) 2x/day
  • Placebo cannabis cigarettes (THC removed) 2x/day
• Results:
  • Symptom remission in 5/11 (45%) of THC group vs 1/10 (10%) placebo
  • Symptom response in 10/11 (90%) of THC group vs 4/10 (40%) placebo
  • No change in Hgb, WBC or CRP
• Conclusion:
  • THC improves symptoms but not inflammatory markers

Naftali T, Clin Gastroenterol Hepatol 2013
Cannabis Use Provides Symptom Relief in Patients with Inflammatory Bowel Disease but Is Associated with Worse Disease Prognosis in Patients with Crohn’s Disease

• Consecutive IBD patients (n=313) filled out a questionnaire on cannabis use

• Results:
  • 17.6% of respondents used cannabis for IBD symptoms (96% by inhalation)
  • Patients reported improvement in abd pain (84%), joint pain (48%), and diarrhea (28%)
  • Use of cannabis for >6 months was associated with a 5-fold increased odds of surgery

• Conclusion:
  • Cannabis use is common, it improves symptoms, but is associated with increased risk of surgery

Storr M, Inflamm Bowel Dis 2014
Curcumin Effective for Active UC

• 50 patients with mild-moderate active UC
• Randomized, double-blind, placebo-controlled design
• Curcumin (n=26) or placebo (n=24) added to mesalamine
• Results:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Curcumin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical remission wk 4</td>
<td>54%</td>
<td>0%</td>
</tr>
<tr>
<td>Clinical response</td>
<td>65%</td>
<td>12%</td>
</tr>
<tr>
<td>Endoscopic remission</td>
<td>38%</td>
<td>0%</td>
</tr>
</tbody>
</table>

• Conclusion:
  • Curcumin is better than placebo when added to mesalamine in active UC

Lang A, Clin Gastroenterol Hepatol 2015
Curcumin Effective for Maintenance of Remission in UC

Hanai H, Clin Gastroenterol Hepatol 2006
Andrographis Panniculata

• Randomized, double-blind placebo controlled trial
• Mild to moderate active UC (n=224)
• Placebo vs A. panniculata 1200mg or 1800g
• Results:

<table>
<thead>
<tr>
<th></th>
<th>A. Panniculata 1800mg</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response wk 8</td>
<td>60%</td>
<td>40%</td>
<td>P=0.04</td>
</tr>
<tr>
<td>Remission wk 8</td>
<td>38%</td>
<td>25%</td>
<td>P=0.25</td>
</tr>
<tr>
<td>Mucosal healing wk 8</td>
<td>50%</td>
<td>33%</td>
<td>P=0.04</td>
</tr>
</tbody>
</table>

• Phase 3 study terminated (interim futility analysis)
Boswellia Serrata

- AKA “Indian frankincense”
- Non-randomized, unblended study for 6 wks:
  - Boswellia resin 300mg 3 times/day (n=20)
  - Sulfasalazine 1g 3 times/day (n=10)
- Results:
  - Remission at week 6:
    - 14/20 (70%) in Boswellia group
    - 4/10 (40%) in sulfasalazine group

Gupta I, Planta Med 2001
Effects of Gum Resin of *Boswellia serrata* in Patients with Chronic Colitis

Inder Gupta¹, Ashok Parihar¹, Pawan Malhotra¹, Sanjay Gupta¹, Rainer Lüdtke², Hasan Safayhi³, Hermann P. T. Ammon³,*

Patients who presented with pain in lower abdomen, diarrhoea with or without blood and mucus were considered eligible and were included in the study after obtaining their voluntary consent. Exclusion criteria were: classical ulcerative colitis, colonic tuberculosis and malignancy, shigellosis as well as other infective pathologies. During the entire study period the subjects were put on standard diet and refrained from taking any other drug. Only patients with grade III disease were hospitalized. There was no iron substitution.

<table>
<thead>
<tr>
<th>Effect</th>
<th>Odds-ratio</th>
<th>95%-CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Boswellia</em> gum resin vs. sulfasalazine</td>
<td>2.01</td>
<td>0.15 – ∞</td>
<td>0.6142</td>
</tr>
<tr>
<td>grade III vs. grade II</td>
<td>27</td>
<td>0.03 – 2.73</td>
<td>0.3237</td>
</tr>
<tr>
<td>male vs. female</td>
<td>0.5</td>
<td>0.01 – 6.63</td>
<td>0.9391</td>
</tr>
<tr>
<td>1 kg weight extra</td>
<td>0.82</td>
<td>0.51 – 1.07</td>
<td>0.2051</td>
</tr>
<tr>
<td>1 year older</td>
<td>1.18</td>
<td>0.89 – 1.80</td>
<td>0.3478</td>
</tr>
</tbody>
</table>
Randomized, placebo-controlled, double-blind trial of Boswellia serrata in maintaining remission of Crohn's disease: Good safety profile but lack of efficacy.

- 82 patients with Crohn’s disease in remission randomized
  - Boswellia 1200mg 2x/day (n=42)
  - Placebo (n=40)
- Results:

<table>
<thead>
<tr>
<th></th>
<th>Boswellia</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 52 remission</td>
<td>60%</td>
<td>55%</td>
</tr>
<tr>
<td>Days until relapse</td>
<td>171</td>
<td>185</td>
</tr>
</tbody>
</table>
Summary

• Fecal microbiota transplantation is promising but remains investigational
  • Further studies needed to determine the optimal: recipients, donors, method of delivery, dose and duration
• Diet may have a role as a therapy
  • Encouraging preliminary data, but needs further study
• Probiotics have demonstrated some efficacy for specific products in limited situations (UC, pouchitis)
• Cannabinoids relieve symptoms but not inflammation
• Andrographis panniculata may (or may not) have benefit
• Curcumin is effective for **induction** and **maintenance** of remission in mild to moderate UC
• Boswellia serrata has not shown efficacy for UC or Crohn’s disease