GUT MICROBIOME: IMPACT ON CLINICAL PRACTICE

AMERICAN COLLEGE OF PHYSICIANS

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UNIVERSITY OF MISSOURI - COLUMBIA

SEPTEMBER 15, 2017
BACKGROUND

RESEARCH ARTICLES ON MICROBIOME

![Graph showing the increase in citations of research articles on microbiome from 1980 to 2020. The x-axis represents the years from 1980 to 2020, and the y-axis represents the number of citations from 0 to 8000. There is a significant increase in citations from 2000 onwards.]
What is the microbiome?

• Microbiome:
  – Microbes and environment which they live
    • Includes microbiota, immune components, epithelium, and products of microbiota and host

• Microbiota:
  – Micro-organisms present in specific site
  – Gut has 1000-1200 bacterial species and at least $10^{14}$ bacteria
  – Most in the colon
What does the microbiota do?

CATABOLISM
BIOCONVERSION OF COMPLEX MOLECULES
SYNTHESIS OF COMPOUNDS
AUGMENT HOST PATHWAYS
DRUG METABOLISM (DIGOXIN, 5-ASA)
FERMENT RESISTENT POLYSACCHARIDES (NON-DIGESTABLE STARCH) TO SHORT CHAIN FATTY ACIDS

ENERGY SOURCE FOR COLONOCYTES
ANTI-INFLAMMATORY
ANTITUMOR

But wait, there’s more…
BILE ACIDS

CONJUGATED BILE ACIDS

↓

Microbially-mediated conversion

UNCONJUGATED BILE ACIDS
SECONDARY BILE ACIDS

FARNESOID X RECEPTORS (FXRs)
Nuclear hormone receptors

CHOLESTEROL AND LIPID METABOLISM
IMMUNE SYSTEM

• Increases development and activity of immune system
• Increase mucus and nutrient receptors in mucosal epithelium
• Alter antitumor responses to immunotherapies affecting cytotoxic T lymphocyte associated protein 4 or programmed cell death 1 (PD-1)
PROTECTION

• Colonization resistance to pathogenic organisms:
  – Direct competition for nutrients
  – Short chain fatty acid production
  – Immunologic effects on host
MICROBIOME IN SPECIFIC DISEASES
DEFINITIONS

PREBIOTIC
- NUTRIENT FAVORING THE GROWTH AND PREDOMINANCE OF BENEFICIAL MICROBES
- MOST ARE CARBOHYDRATES THAT HUMANS CANNOT BREAK DOWN BUT MICROBIOTA CAN

PROBIOTIC
- “LIVE MICRO-ORGANISMS” THAT INTEND TO HAVE A HEALTH BENEFIT TO THE HOST
- ORIGINALLY BASED ON FERMENTED FOOD PRODUCTS
- NOW, BASED MORE ON MICROBIOME OF HEALTHY PEOPLE
INFECTIOUS DISEASES
C. DIFFICILE PROBIOTICS

META-ANALYSIS
4 RCTs
n=336

TREATMENT OF INITIAL OR RECURRENT CDAD
ADULTS ON VANCOMYCIN/METRONIDAZOLE +
PROBIOTIC vs PLACEBO/NO PROBIOTIC

Comparison 1. S. boulardii versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Cessation of diarrhea</td>
<td>2</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotal only</td>
</tr>
<tr>
<td>1.1 Patients with initial or recurrent disease</td>
<td>1</td>
<td>124</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.33 [1.02, 1.74]</td>
</tr>
<tr>
<td>1.2 Patients with recurrent disease</td>
<td>1</td>
<td>32</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.67 [0.96, 2.93]</td>
</tr>
<tr>
<td>2 Recurrence of diarrhea</td>
<td>2</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotal only</td>
</tr>
<tr>
<td>2.1 Patients with initial or recurrent disease</td>
<td>1</td>
<td>124</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.59 [0.35, 0.98]</td>
</tr>
<tr>
<td>2.2 Patients with recurrent disease</td>
<td>1</td>
<td>32</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.33 [0.10, 1.00]</td>
</tr>
</tbody>
</table>

Comparison 2. L. plantarum versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Cessation of diarrhea</td>
<td>1</td>
<td>21</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.93 [0.79, 1.11]</td>
</tr>
<tr>
<td>2 Recurrence of diarrhea</td>
<td>1</td>
<td>20</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.55 [1.11, 1.89]</td>
</tr>
<tr>
<td>3 Bacteriological cure</td>
<td>1</td>
<td>21</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.75 [0.41, 1.38]</td>
</tr>
</tbody>
</table>

Comparison 3. Lactobacillus rhamnosus GG versus placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Recurrent CDAD</td>
<td>1</td>
<td>15</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>2.03 [0.75, 5.43]</td>
</tr>
</tbody>
</table>

INSUFFICIENT EVIDENCE TO RECOMMEND PROBIOTIC THERAPY AS AN ADJUNCT TO ANTIBIOTIC THERAPY FOR C. DIFFICILE COLITIS

HARMFUL?
BACTEREMIA
FUNGEMIA
META-ANALYSIS
63 RCTs
n=11,811
INCIDENCE OF ANTIBIOTIC-ASSOCIATED DIARRHEA ADULTS & CHILDREN ON ANTIBIOTIC(S) + PROBIOTIC vs PLACEBO/NO PROBIOTIC

PREVENTION AND TREATMENT TOGETHER

C. DIFFICILE
PROBIOTICS

Hempel S, et al. JAMA 2012

META-ANALYSIS
63 RCTs
n=11,811
INCIDENCE OF ANTIBIOTIC-ASSOCIATED DIARRHEA ADULTS & CHILDREN ON ANTIBIOTIC(S) + PROBIOTIC vs PLACEBO/NO PROBIOTIC

PREVENTION AND TREATMENT TOGETHER

C. DIFFICILE
PROBIOTICS

Hempel S, et al. JAMA 2012
C. DIFFICILE PROBIOTICS

META-ANALYSIS

20 RCTS

n=3,818

INCIDENCE OF CDAD

ADULTS & CHILDREN ON ANTIBIOTIC(S) + PROBIOTIC vs PLACEBO/NO PROBIOTIC

**Figure 2.** Probiotics for the prevention of Clostridium difficile-associated diarrhea.

<table>
<thead>
<tr>
<th>Study, Year (References)</th>
<th>Experimental Group, n</th>
<th>Control Group, n</th>
<th>Weight, %</th>
<th>Relative Risk (95% CI) M-H Random</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arends et al. 2009 (82)</td>
<td>1 61</td>
<td>1 58</td>
<td>1.7</td>
<td>0.99 (0.66–1.50)</td>
</tr>
<tr>
<td>Boehnke et al. 2007 (33)</td>
<td>1 44</td>
<td>7 45</td>
<td>3.0</td>
<td>0.15 (0.02–1.14)</td>
</tr>
<tr>
<td>Brown et al. 2004 (36)</td>
<td>0 41</td>
<td>0 40</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Carl et al. 2006 (91)</td>
<td>0 73</td>
<td>2 78</td>
<td>1.4</td>
<td>0.21 (0.04–1.37)</td>
</tr>
<tr>
<td>Doman et al. 2009 (36)</td>
<td>0 140</td>
<td>1 180</td>
<td>1.2</td>
<td>0.31 (0.03–1.74)</td>
</tr>
<tr>
<td>Do et al. 2010 (37)</td>
<td>9 128</td>
<td>2 88</td>
<td>21.0</td>
<td>0.33 (0.11–0.96)</td>
</tr>
<tr>
<td>Hohlfeld et al. 2007 (38)</td>
<td>0 96</td>
<td>9 93</td>
<td>1.6</td>
<td>0.26 (0.09–0.78)</td>
</tr>
<tr>
<td>Kobayashi et al. 2005 (39)</td>
<td>3 110</td>
<td>10 137</td>
<td>7.9</td>
<td>0.32 (0.08–1.24)</td>
</tr>
<tr>
<td>Löwenstein et al. 2010 (40)</td>
<td>1 80</td>
<td>0 82</td>
<td>1.3</td>
<td>0.11 (0.07–0.15)</td>
</tr>
<tr>
<td>McFarland et al. 1995 (41)</td>
<td>3 97</td>
<td>4 96</td>
<td>5.9</td>
<td>0.71 (0.17–3.32)</td>
</tr>
<tr>
<td>Miller et al. 2006 (47)</td>
<td>4 99</td>
<td>7 94</td>
<td>8.9</td>
<td>0.87 (0.57–1.33)</td>
</tr>
<tr>
<td>Miller et al. 2008 (47)</td>
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<td>0 119</td>
<td>1.4</td>
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</tr>
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<td>Pfeiffer et al. 2004 (42)</td>
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<td>5 69</td>
<td>4.9</td>
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<tr>
<td>Pounds et al. 2010 (48)</td>
<td>1 212</td>
<td>4 231</td>
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<td>0.24 (0.09–0.72)</td>
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<td>Raffat et al. 2007 (49)</td>
<td>5 45</td>
<td>22 155</td>
<td>16.1</td>
<td>0.29 (0.09–0.87)</td>
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<tr>
<td>Ruberg et al. 2008 (50)</td>
<td>3 120</td>
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<td>0.43 (0.11–1.60)</td>
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<td>1 17</td>
<td>1.3</td>
<td>0.25 (0.05–1.39)</td>
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<td>Sellgren et al. 2010 (52)</td>
<td>0 42</td>
<td>0 42</td>
<td>Not estimable</td>
<td></td>
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<tr>
<td>Suttorp et al. 1999 (40)</td>
<td>2 176</td>
<td>5 64</td>
<td>6.5</td>
<td>0.33 (0.06–1.74)</td>
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<td>Thomas et al. 2005 (40)</td>
<td>3 123</td>
<td>2 114</td>
<td>6.0</td>
<td>0.47 (0.11–1.94)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1974</td>
<td>1844</td>
<td>100.0</td>
<td>0.34 (0.24–0.48)</td>
</tr>
</tbody>
</table>

**Figure 3.** Risk for adverse effects with probiotics.

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<td>7 45</td>
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<td>Thomas et al. 2001 (46)</td>
<td>37 133</td>
<td>52 134</td>
<td>20.0</td>
<td>0.72 (0.51–1.01)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1791</td>
<td>1788</td>
<td>100.0</td>
<td>0.81 (0.63–1.00)</td>
</tr>
</tbody>
</table>

M-44 = Mantel-Haenszel.

* Miller and colleagues reported on 2 studies; the dosage of probiotic used was 3 times greater than in the study above.

M-44 = Mantel-Haenszel.

* Miller and colleagues reported on 2 studies; the dosage of probiotic used was 3 times greater than in the study above.
• BENEFITS:
  – Direct competition with \textit{C. difficile} for nutrients
  – Microbiota may convert conjugated bile salts secreted from liver to unconjugated primary bile acids or secondary bile acids
  • Some of these inhibit the growth of the vegetative form of \textit{C. difficile}
  – Remains stable for up to 24 weeks

\textbf{C. DIFFICILE Fecal Microbiota Transplant}
ORAL
UP TO 30 FROZEN FMT CAPSULES OF HEALTHY UNRELATED DONORS WITH MEAN FECAL MATTER PER CAPSULE 1.6g (1.0-2.05g)

ENEMA
RETENTION ENEMA OF 150g FRESH STOOL/300cc STERILE WATER

COLONOSCOPY
BOWEL PREP
200-300g DONOR STOOL (≤ 6 HOURS) IN 200-300cc STERILE SALINE

NASOENTERIC TUBE
25-30g DONOR STOOL IN 50cc STERILE SALINE (2 TO 3 MINUTES PER 50cc)

Youngster I, et al. JAMA 2014
Mattila E, et al. Gastroenterology 2012
van Nood E, et al. NEJM 2013
## C. DIFFICILE

### FMT

## DONOR SCREENING

<table>
<thead>
<tr>
<th>SAMPLE</th>
<th>INFECTIOUS AGENTS TO BE TESTED</th>
<th>LABORATORY TESTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool</td>
<td><em>C. difficile</em></td>
<td>Culture and toxin A/B test</td>
</tr>
<tr>
<td></td>
<td>Enteric bacterial pathogens</td>
<td>Selective media culture</td>
</tr>
<tr>
<td></td>
<td>Ova and parasites</td>
<td>Light microscopy</td>
</tr>
<tr>
<td></td>
<td><em>Treponema pallidum</em></td>
<td>HBV surface antigen</td>
</tr>
<tr>
<td>Serum</td>
<td>HBV</td>
<td>Anti-HCV antibodies by EIA</td>
</tr>
<tr>
<td></td>
<td>HCV</td>
<td>Anti-HIV antibodies by EIA</td>
</tr>
<tr>
<td></td>
<td>HIV 1 and HIV 2</td>
<td>Plasma reagin test</td>
</tr>
</tbody>
</table>
**C. DIFFICILE**

**FMT**

**RCT FROM AMSTERDAM**

n=42

RESOLUTION OF RECURRENT CDAD AFTER 10 WEEKS

VANCOMYCIN (500 mg PO QID x 4 DAYS) + BOWEL LAVAGE + FMT VIA NASODUODENAL TUBE

vs

VANCOMYCIN (500 mg PO QID x 14 DAYS)

vs

VANCOMYCIN (500 mg PO QID x 14 DAYS) + BOWEL LAVAGE

---

- **FMT+VANCOMYCIN+LAVAGE**: 81%
  - 13/16
  - P<0.001

- **VANCOMYCIN**: 31%
  - 4/13

- **VANCOMYCIN+LAVAGE**: 23%
  - 3/13

---

C. DIFFICILE

FMT

META-ANALYSIS
11 OBSERVATIONAL STUDIES
n=273

TREATMENT OF RECURRENT OR REFRACTORY CDAD
ANTIBIOTICS + FMT

FMT ROUTE
COLONOSCOPY
ENEMA
NASOGASTRIC TUBE
NASOJEJUNAL TUBE
GASTROSTOMY

CLINICAL RESOLUTION
245/273 (89.7%)
C. DIFFICILE

FMT

REVIEW WITH POOLED ANALYSIS
12 STUDIES
n=182
TREATMENT OF SEVERE CDAD
FMT VIA COLONOSCOPY vs FMT VIA NASOGASTRIC TUBE

<table>
<thead>
<tr>
<th></th>
<th>CLINICAL CURE</th>
<th>RECURRENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMT – COLONOSCOPY</td>
<td>93.2%</td>
<td>5.4%</td>
</tr>
<tr>
<td>FMT - NGT</td>
<td>85.3%</td>
<td>5.9%</td>
</tr>
</tbody>
</table>

138/148         29/34

p=0.162

Postigo R, Kim JH. Infection 2012
• Allogeneic Stem Cell Transplantation:
  – Microbiota status is associated with risk of developing bacteremia

• Sepsis and ARDS:
  – Enrichment of GI microbes seem to influence pulmonary inflammatory response

• Surgical Intestinal Anastomoses:
  – Composition of GI microbes influence healing
INFLAMMATORY BOWEL DISEASE
INFLAMMATORY BOWEL DISEASE

Each disease had its own distinct microbiota.
INFLAMMATORY BOWEL DISEASE

• Intestinal microbiota distinctly different from non-IBD patients

• 2 issues:

CAUSATION?
HOST GENETIC SUSCEPTIBILITY

IBD ➔ ALTERED MICROBIOTA
OR
ALTERED MICROBIOTA ➔ IBD
IBD FMT

PILOT STUDY FROM CHINA
n=14
STEROID-DEPENDENT ULCERATIVE COLITIS
1 OR MORE FMT (STEP-UP FMT)

Clinical Response

<table>
<thead>
<tr>
<th></th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained Response at least 3 months</td>
<td>28</td>
</tr>
<tr>
<td>Clinical Response</td>
<td>57</td>
</tr>
</tbody>
</table>

8/14

4/14
RCT FROM AUSTRALIA
n=81
STEROID-FREE REMISSION WITH ENDOSCOPIC REMISSION IN CHRONIC ULCERATIVE COLITIS
INTENSIVE FMT
(COLONOSCOPY FMT → ENEMAS 5/WEEK x 8 WEEKS)
vs PLACEBO

IBD FMT

p=0.021

%
META-ANALYSIS
4 RCTs
n=277
REMISSION IN ACTIVE ULCERATIVE COLITIS
FMT vs PLACEBO

IBD
FMT

STILL DEBATING
FREQUENCY & PREPARATION

Costello SP, et al. Aliment Pharmacol Ther 2017
IBD PROBIOTICS

WHY?

HYPOTHESIZED INTERACTION
IBD PROBIOTICS

META-ANALYSIS

9 RCTs
n=651

INDUCING REMISSION IN ACTIVE UC
PROBIOTICS VS 5-ASA OR PLACEBO

4.1.1 Probiotics vs. 5-ASA

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Probiotics</th>
<th>Control</th>
<th>Risk ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rembacken (1999)</td>
<td>18</td>
<td>57</td>
<td>100.0%</td>
<td>1.24 [0.70, 2.22] 1999</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>57</td>
<td>59</td>
<td>100.0%</td>
<td>1.24 [0.70, 2.22]</td>
</tr>
<tr>
<td>Total events</td>
<td>18</td>
<td>15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable
Test for overall effect: Z=0.73 (P=0.46)

4.1.2 Probiotics vs. placebo

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Probiotics</th>
<th>Control</th>
<th>Risk ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kato (2004)</td>
<td>6</td>
<td>10</td>
<td>9.0%</td>
<td>0.86 [0.45, 1.64] 2004</td>
</tr>
<tr>
<td>Sood (2009)</td>
<td>44</td>
<td>77</td>
<td>24.4%</td>
<td>0.68 [0.56, 0.84] 2009</td>
</tr>
<tr>
<td>Ng (2010)</td>
<td>7</td>
<td>14</td>
<td>8.9%</td>
<td>0.78 [0.40, 1.49] 2010</td>
</tr>
<tr>
<td>Matthes (2010)</td>
<td>41</td>
<td>70</td>
<td>17.0%</td>
<td>0.90 [0.62, 1.31] 2010</td>
</tr>
<tr>
<td>Tursi (2010)</td>
<td>40</td>
<td>71</td>
<td>22.5%</td>
<td>0.82 [0.64, 1.06] 2010</td>
</tr>
<tr>
<td>Petersen (2014)</td>
<td>15</td>
<td>25</td>
<td>6.0%</td>
<td>3.00 [1.29, 7.00] 2014</td>
</tr>
<tr>
<td>Tamaki (2016)</td>
<td>13</td>
<td>28</td>
<td>12.3%</td>
<td>0.81 [0.49, 1.35] 2016</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>295</td>
<td>400</td>
<td>100.0%</td>
<td>0.86 [0.68, 1.08]</td>
</tr>
<tr>
<td>Test events</td>
<td>166</td>
<td>159</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2=04, \chi^2=12.66, df=6 (P=0.05), I^2=53\%$
Test for overall effect: $Z=1.29 (P=0.20)$

Test for subgroup differences: $\chi^2=1.34, df=1 (P=0.25), I^2=25.4\%$
IBD PROBIOTICS

RCT FROM GERMANY
n=11
PREVENTING CLINICAL RELAPSE IN CROHN’S DISEASE
PROBIOTIC VS PLACEBO x 6 MONTHS

SUSTAINED REMISSION (n)

<table>
<thead>
<tr>
<th></th>
<th>Lactobacillus</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

IBD PROBIOTICS

META-ANALYSIS

4 RCTs

n=333

PREVENTING CLINICAL OR ENDOSCOPIC RELAPSE AFTER SURGERY IN CROHN’S DISEASE

PROBIOTICS VS PLACEBO

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Probiotics</th>
<th>Placebo</th>
<th>Risk ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1.1 Clinical relapse of disease activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prantera (2002)</td>
<td>8 23</td>
<td>5 22</td>
<td>26.9%</td>
<td>1.53 [0.59, 3.97]</td>
</tr>
<tr>
<td>Marleau (2006)</td>
<td>9 48</td>
<td>6 50</td>
<td>26.6%</td>
<td>1.56 [0.60, 4.06]</td>
</tr>
<tr>
<td>Van Gossum (2007)</td>
<td>11 34</td>
<td>17 36</td>
<td>46.4%</td>
<td>0.69 [0.38, 1.24]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>105</td>
<td>108 100.0%</td>
<td>1.06 [0.59, 1.92]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>28</td>
<td>26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2=1.11, \chi^2=3.19, df=2 (P=0.20), I^2=37%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z=1.9 (P=0.55)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 3.1.2 Endoscopic relapse of disease activity (Rutgeerts score 1 or more) | | | | |
| Marleau (2006) | 39 48 | 41 50 | 30.7% | 0.99 [0.63, 1.51] | 2006 |
| Van Gossum (2007) | 26 34 | 28 36 | 24.6% | 0.68 [0.40, 1.12] | 2007 |
| Fedorak (2015) | 47 58 | 56 62 | 32.4% | 1.00 [0.64, 1.55] | 2015 |
| Subtotal (95% CI) | 163 | 170 100.0% | 1.09 [0.92, 1.29] | | |
| Total events | 134 | 130 | | |
| Heterogeneity: $\chi^2=0.22, \chi^2=6.32, df=3 (P=0.10), I^2=53\%$ | | | | |
| Test for overall effect: $Z=0.8 (P=0.35)$ | | | | |

| 3.1.3 Endoscopic relapse of disease activity (Rutgeerts score 2 or more) | | | | |
| Prantera (2002) | 17 23 | 11 22 | 18.0% | 1.21 [0.91, 1.39] | 2002 |
| Marleau (2006) | 26 48 | 33 50 | 30.7% | 1.32 [0.92, 1.51] | 2006 |
| Van Gossum (2007) | 19 34 | 17 36 | 20.8% | 0.86 [0.67, 1.10] | 2007 |
| Fedorak (2015) | 32 58 | 35 62 | 31.7% | 0.95 [0.71, 1.27] | 2015 |
| Subtotal (95% CI) | 163 | 170 100.0% | 1.04 [0.82, 1.31] | | |
| Total events | 94 | 96 | | |
| Heterogeneity: $\chi^2=0.02, \chi^2=4.43, df=3 (P=0.22), I^2=32\%$ | | | | |
| Test for overall effect: $Z=0.30 (P=0.77)$ | | | | |

| 3.1.4 Endoscopic relapse of disease activity (Rutgeerts score 3 or more) | | | | |
| Marleau (2006) | 14 48 | 15 56 | 23.8% | 0.97 [0.75, 1.27] | 2006 |
| Van Gossum (2007) | 12 34 | 13 36 | 22.5% | 0.98 [0.72, 1.32] | 2007 |
| Fedorak (2015) | 19 58 | 19 62 | 32.2% | 1.07 [0.83, 1.37] | 2015 |
| Subtotal (95% CI) | 163 | 170 100.0% | 1.13 [0.84, 1.52] | | |
| Total events | 59 | 55 | | |
| Heterogeneity: $\chi^2=0.00, \chi^2=2.92, df=3 (P=0.99), I^2=0\%$ | | | | |
| Test for overall effect: $Z=0.79 (P=0.43)$ | | | | |

Test for subgroup differences: $\chi^2=0.22, df=3 (P=0.97), I^2=0\%$
OBESITY
OBESITY

MICROBIOME INFLUENCES THE CALORIES THAT ARE ABSORBED

HUMANS CONVERT STARCHES INTO SIMPLE SUGARS THAT ARE ABSORBED EASILY

HUMANS CANNOT DIGEST MANY DIETARY POLYSACCHARIDES

MICROBIOTA ENZYMES CAN TURN THOSE DIETARY POLYSACCHARIDES INTO DIGESTIBLE SOURCES OF ENERGY

MICROBIOTA ↔ OBESITY

OBESE PEOPLE LOSE WEIGHT

*Bacteroidetes* increases relative to *Firmicutes*

OBESE PEOPLE RESUME PREVIOUS DIET

Proportion of *Firmicutes* increases
OBESITY

MICROBIOTA-PRODUCED SHORT CHAIN FATTY ACIDS & BILE ACIDS

GLUCAGON-LIKE PEPTIDE 1 & PEPTIDE YY
Association between obesity and intestinal microbiota in human and mouse models
Precise mechanism unknown
Meta-analysis shows direct association may be weaker than originally thought
EMERGING TREATMENTS
EMERGING TREATMENTS

ANTIBIOTICS

BACTERIOPHAGES

PROBIOTICS

PREBIOTICS/SYNBIOTICS

NUTRITIONAL THERAPY

MULTISPECIES COMMUNITIES
• Target specific group(s) of microbiota to allow for more desirable species
ANTIBIOTICS SIBO

META-ANALYSIS
4 STUDIES
BREATH TEST NORMALIZATION IN SIBO
ANTIBIOTIC vs PLACEBO

ANTIBIOTICS VS PLACEBO

<table>
<thead>
<tr>
<th>Study</th>
<th>Effectiveness ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collins (2011)</td>
<td>1.50 (0.47,5.38)</td>
<td>42.0</td>
</tr>
<tr>
<td>Biancone (2000)</td>
<td>3.50 (1.08,11.29)</td>
<td>21.4</td>
</tr>
<tr>
<td>Pimentel (2003)</td>
<td>8.39 (1.00,64.16)</td>
<td>10.5</td>
</tr>
<tr>
<td>Chang (2011)</td>
<td>0.97 (0.19,4.88)</td>
<td>26.2</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>2.55 (1.29,5.04)</td>
<td></td>
</tr>
</tbody>
</table>

RIFAXIMIN VS PLACEBO

<table>
<thead>
<tr>
<th>Study</th>
<th>Effectiveness ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collins (2011)</td>
<td>1.59 (0.47,5.38)</td>
<td>37.8</td>
</tr>
<tr>
<td>Biancone (2000)</td>
<td>3.50 (1.08,11.29)</td>
<td>40.8</td>
</tr>
<tr>
<td>Chang (2011)</td>
<td>0.97 (0.19,4.88)</td>
<td>21.4</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>1.97 (0.93,4.17)</td>
<td></td>
</tr>
</tbody>
</table>
ANTIBIOTICS
SIBO/IBS

RCT FROM INDIA
N=80
IBS PATIENTS ± GUT ASPIRATE CULTURE PROVEN SIBO
IBS-SIBO + NORFLOXACIN 800 mg/day x 10 days
VS
IBS-NO SIBO + PLACEBO

SYMPTOM RESOLUTION AT 1 MONTH

IBS-SIBO VS PLACEBO
IBS-NO SIBO VS PLACEBO

ANTIBIOTICS
HEPATIC ENCEPHALOPATHY

INHIBITORY NEUROTRANSMISSION THROUGH GAMMA-AMINOBUTYRIC ACID (GABA) RECEPTORS IN THE CENTRAL NERVOUS SYSTEM AND CHANGES IN CENTRAL NEUROTRANSMITTERS AND CIRCULATING AMINO ACIDS
META-ANALYSIS
10 RCTs
n=547
FULL RESOLUTION OF HE
RIFAXIMIN
VS
PLACEBO/
NON-ABSORBABLE
DISACCHARIDES/
OTHER ANTIBIOTIC
ANTIBIOTICS
POUCHITIS

- Inflammatory condition of the ileal pouch reservoir of an ileal pouch-anal anastomosis
- Hypothesized to result from an abnormal immune response to altered luminal and/or mucosal bacteria in genetically susceptible hosts
- Acute & Chronic Pouchitis → Antibiotics
- Chronic Relapsing Pouchitis?
POUCHITIS
PROBIOTICS

RCT FROM ITALY
n=40
CHRONIC POUCHITIS RELAPSE
PROBIOTIC (VSL#3 6 g/day) vs PLACEBO x 9 MONTHS AFTER REMISSION INDUCED BY CIPROFLOXACIN + RIFAXIMIN

RELAPSE OF POUCHITIS (%)

VSL#3

Placebo

BACTERIOPHAGES

• Uses naturally occurring bacteriotropic viruses to target specific members of disruptive or pathogenic microbiota
• Possible phage resistance due to bacteria altered surface structure
• More research needed before common in practice

PROBIOTICS

“Live micro-organisms” which, when administered in adequate amounts, confer a health benefit on the host”

- WORLD HEALTH ORGANIZATION
PROBIOTICS

POTENTIAL MECHANISMS

1. Suppress growth of epithelial binding/invasion by pathogenic bacteria
2. Improve intestinal barrier function
3. Modulate immune system:
   - Increase protective cytokines (IL-10 & TGF-beta)
   - Suppress proinflammatory cytokines (TNF)
4. Modulate pain perception:
   - Induce expression of micro-opioid and cannabinoid receptors in intestinal epithelial cells

PROBIOTICS

TYPES COMMONLY USED

LACTIC ACID BACILLI
LACTOBACILLUS AND BIFIDOBACTERIUM

ESCHERICHIA COLI (NON-PATHOGENIC)
E. COLI NISSLE 1917

CLOSTRIDIUM BUTYRICUM

STREPTOCOCCUS SALIVARIUS

SACCHAROMYCES BOULARDII
NONPATHOGENIC STRAIN OF YEAST

Kruis W. Dig Dis 2013
Shen J, et al. Inflamm Bowel Dis 2014
PROBIOTICS

COMMON PRODUCTS

**VSL#3**
(Bifidobacterium breve, B. longum, B. infantis, Lactobacillus acidophilus, L. plantarum, L. paracasei, L. bulgaricus, Streptococcus thermophiles)

**ALIGN**
(B. infantis)

**CULTURELLE**
(L. rhamnosus GG)

**DANACTIVE**
(L. casei)

**MUTAFLOR**
(E. coli Nissle 1917)

**FLORASTOR**
(S. boulardii)

**WHAT ABOUT YOGURT?**
PROBIOTICS

YOGURT

NOT ALL LIVE CULTURES SURVIVE STOMACH ACID
NOT ALL LIVE CULTURES COLONIZE MICROBIOTA EFFICIENTLY
SOME ARE PASTEURIZED IN U.S. → KILLING BACTERIA
LACTOSE MAY INCREASE SYMPTOMS

PROBIOTICS

POTENTIAL TREATABLE DISEASES

C. DIFFICILE COLITIS
ULCERATIVE COLITIS (NOT CROHN’S DZ)
POUCHITIS
IRRITABLE BOWEL SYNDROME/SIBO
HEPATIC ENCEPHALOPATHY
CELIAC DISEASE
PROBIOTICS

POTENTIAL ISSUES

SCIENCE LACKING ON MECHANISMS
ENTHUSIASM >>> EVIDENCE
BASED ON MICROBIOTA OF HEALTHY ADULTS
FDA ALLOWS MANY TO FALL UNDER
DIETARY SUPPLEMENTS
MANY PROBIOTICS ON MARKET DO NOT
MEET WHO DEFINITION
“ADEQUATE AMOUNTS” NOT FULLY DEFINED
# Probiotics Summary

<table>
<thead>
<tr>
<th>Disease</th>
<th>Recommended</th>
<th>Background</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pouchitis</td>
<td>YES</td>
<td>VSL#3 in addition to standard medical therapy</td>
</tr>
<tr>
<td>Ulcerative Colitis</td>
<td>LIKELY</td>
<td>Helps maintain remission in addition to therapy</td>
</tr>
<tr>
<td>Crohn’s Disease</td>
<td>NO</td>
<td>Remains unproven</td>
</tr>
<tr>
<td>C. Difficile Diarrhea</td>
<td>YES</td>
<td>Prevention only</td>
</tr>
<tr>
<td>IBS</td>
<td>NO</td>
<td>More research needed</td>
</tr>
<tr>
<td>Hepatic Encephalopathy</td>
<td>NO</td>
<td>No benefit</td>
</tr>
<tr>
<td>Celiac Disease</td>
<td>NO</td>
<td>No benefit</td>
</tr>
</tbody>
</table>
**PREBIOTICS**

- Non-digestible carbohydrates that are meant to be metabolized by specific microbes to foster their growth
- **Examples:**
  - Inulin
  - Resistant Starches
- **May be diet modification:**
  - Enteral feeding in children with Crohn’s disease
  - Low FODMAP diet in IBS
NUTRITIONAL THERAPIES

- Using diets to promote beneficial microbiota

- Low FODMAP Diet in IBS

- Enteral Feeding in Children with Crohn’s DZ

- Enteral Feeding in Adults with Crohn’s DZ
INDUCING REMISSION IN CHILDREN WITH CROHN’S DISEASE
Enteral Nutrition vs Steroids

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>RR (random) 95% CI</th>
<th>RR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borrelli</td>
<td>15/19</td>
<td>12/18</td>
<td>1.18 [0.79, 1.77]</td>
<td></td>
</tr>
<tr>
<td>Seidman 1991</td>
<td>6/10</td>
<td>9/9</td>
<td>0.60 [0.36, 1.00]</td>
<td></td>
</tr>
<tr>
<td>Terrin</td>
<td>9/10</td>
<td>5/10</td>
<td>1.80 [0.94, 3.46]</td>
<td></td>
</tr>
<tr>
<td>Seidman 1993</td>
<td>26/34</td>
<td>31/34</td>
<td>0.84 [0.68, 1.04]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>73</td>
<td>71</td>
<td>0.97 [0.68, 1.40]</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: Chi² = 9.40, df = 3 (P = 0.02), I² = 68.1%
Test for overall effect: Z = 0.15 (P = 0.88)
NUTRITIONAL IMPACT

IBD

META-ANALYSIS

7 RCTS

N=352

INDUCING REMISSION IN CROHN’S DISEASE

Enteral Nutrition vs Steroids

ADULTS

OR 0.33 (95% CI: 0.21 – 0.53)

Winner = Steroids

NUTRITIONAL IMPACT

META-ANALYSIS

5 RCTS

n=403

INDUCING AND SUSTAINING REMISSION IN CROHN’S DISEASE

**ENTERAL NUTRITION THERAPY WITH INFLEXIMAB**
(Elemental or Polymeric Formula, With or Without Low-Fat Diet Restriction)

**VS**

**INFLIXIMAB ALONE WITH NO DIETARY MANIPULATION**

**INDUCTION OF REMISSION**

**REMISSION > 1 YEAR**
MULTISPECIES COMMUNITIES

• Restoring deficient microbiota by harvesting normal microbiota from healthy individual and give it to another individual

FECAL MICROBIOTA TRANSPLANT
"Microbiota centered" precision medicine
- Microbiota composition
- Microbiota function

"Host centered" precision medicine
- DNA/RNA
- Metabolites
- Immune function

Microbiota assessment
- Identify deleterious organisms
- Identify deficient microbiota functions

Host assessment
- Genomic susceptibility
- Predict drug response
- Predict adverse reactions

Data analysis

Microbiota modulation

CUSTOMIZED THERAPY
SUMMARY

MICROBIOME IS COMPLEX

MICROBIOME PLAYS A SIGNIFICANT ROLE IN MANY DISEASES

MICROBIOME MANIPULATION MAY HELP IN CERTAIN DISEASES

FUTURE IS BRIGHT IN RESEARCH WITH MICROBIOME AS DISEASE MODIFIERS