Various forms of fecal microbiota transplantation for recurrent CDI
Potential Conflicts of Interest

**Research grants:** 3M, Astellas Pharma, DaVolterra, Evonik, Glycom, MaaT Pharma, Merck/MSD, Organobalance, Seres Therapeutics

**Speaker fees:** Astellas Pharma, Basilea, Falk, Gilead Sciences, Merck/MSD, Organobalance, Pfizer

**Consulting:** Alb Fils Kliniken GmbH, Astellas Pharma, DaVolterra, Ferring, MaaT Pharma, Merck/MSD
Overview

- Technical advances of classical FMT
  - Efficacy
  - Safety
  - Regulatory aspects

- FMT 2.0
  - Microbiota consortia
  - Prebiotics
  - Postbiotics
First randomized controlled trial

The study that "got the ball rolling"

Technical milestones

Frozen vs Fresh Fecal Microbiota Transplantation and Clinical Resolution of Diarrhea in Patients With Recurrent *Clostridium difficile* Infection
A Randomized Clinical Trial


Oral, Capsulized, Frozen Fecal Microbiota Transplantation for Relapsing *Clostridium difficile* Infection


First implementation of frozen, capsulized faecal microbiota transplantation for recurrent *Clostridium difficile* infection into clinical practice in Europe


Successful Resolution of Recurrent *Clostridium difficile* Infection using Freeze-Dried, Encapsulated Fecal Microbiota; Pragmatic Cohort Study

Efficacy in randomized trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Estimate (95% CI)</th>
<th>Cure/Treatment, No. of Patients</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Youngster et al [17] (2014)</td>
<td>0.700 (0.696 – 0.901)</td>
<td>14/20</td>
<td>6.58</td>
</tr>
<tr>
<td>Youngster et al [18] (2014)</td>
<td>0.700 (0.699 – 0.901)</td>
<td>14/20</td>
<td>6.58</td>
</tr>
<tr>
<td>Kao et al [25] (2015)</td>
<td>0.977 (0.932 – 1.000)</td>
<td>42/43</td>
<td>9.03</td>
</tr>
<tr>
<td>Khanna et al [27] (2016)</td>
<td>0.967 (0.902 – 1.000)</td>
<td>26/30</td>
<td>8.65</td>
</tr>
<tr>
<td>Orenstein et al [26] (2018)</td>
<td>0.871 (0.753 – 0.969)</td>
<td>27/31</td>
<td>8.09</td>
</tr>
<tr>
<td>Lee et al [19] (2016)</td>
<td>0.624 (0.552 – 0.695)</td>
<td>111/178</td>
<td>8.77</td>
</tr>
<tr>
<td>Jiang et al [20] (2017)</td>
<td>0.875 (0.759 – 0.951)</td>
<td>63/72</td>
<td>8.71</td>
</tr>
<tr>
<td>van Nood et al [21] (2013)</td>
<td>0.812 (0.621 – 1.000)</td>
<td>13/15</td>
<td>6.76</td>
</tr>
<tr>
<td>Cammarota et al [22] (2015)</td>
<td>0.650 (0.441 – 0.859)</td>
<td>13/20</td>
<td>6.43</td>
</tr>
<tr>
<td>Kelly et al [8] (2016)</td>
<td>0.909 (0.789 – 1.000)</td>
<td>20/22</td>
<td>8.06</td>
</tr>
<tr>
<td>SER-109 [24] (2016)</td>
<td>0.559 (0.433 – 0.686)</td>
<td>33/59</td>
<td>7.95</td>
</tr>
<tr>
<td>Dubberke et al [23] (2016)</td>
<td>0.639 (0.535 – 0.742)</td>
<td>53/83</td>
<td>8.33</td>
</tr>
<tr>
<td>Hota et al [9] (2017)</td>
<td>0.438 (0.194 – 0.881)</td>
<td>7/16</td>
<td>5.81</td>
</tr>
</tbody>
</table>

**Overall (R² = 91.35%; P < .001)**

439/610

Clinical Resolution Rate

Figure 2. Analysis of all included studies. Forest plot shows weighted clinical resolution rates of fecal microbiota transplantation in patients with *Clostridium difficile* infection. Ev/Tt indicates number of patients with cure/number of patients treated. Abbreviation: CI, confidence interval.
### Efficacy - multiple administrations

<table>
<thead>
<tr>
<th>Study</th>
<th>Estimate (95% CI)</th>
<th>Cure/Treatment, No. of Patients</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Youngster et al [17] (2014)</td>
<td>0.900 (.769–1.000)</td>
<td>18/20</td>
<td>6.03</td>
</tr>
<tr>
<td>Youngster et al [18] (2014)</td>
<td>0.900 (.769–1.000)</td>
<td>18/20</td>
<td>6.03</td>
</tr>
<tr>
<td>Kao et al [25] (2015)</td>
<td>0.977 (.932–1.000)</td>
<td>42/43</td>
<td>10.80</td>
</tr>
<tr>
<td>Khanna et al [27] (2016)</td>
<td>0.967 (.902–1.000)</td>
<td>20/30</td>
<td>9.74</td>
</tr>
<tr>
<td>Orenstein et al [26] (2016)</td>
<td>0.935 (.849–1.000)</td>
<td>29/31</td>
<td>8.42</td>
</tr>
<tr>
<td>Lee et al [19] (2016)</td>
<td>0.961 (.932–.989)</td>
<td>171/178</td>
<td>11.52</td>
</tr>
<tr>
<td>Jiang et al [20] (2017)</td>
<td>0.903 (.834–.971)</td>
<td>55/72</td>
<td>9.49</td>
</tr>
<tr>
<td>van Nood et al [21] (2013)</td>
<td>0.938 (.819–1.000)</td>
<td>15/16</td>
<td>6.65</td>
</tr>
<tr>
<td>Camarota et (22) (2015)</td>
<td>0.900 (.769–1.000)</td>
<td>18/20</td>
<td>6.03</td>
</tr>
<tr>
<td>Kelly et al [8] (2016)</td>
<td>0.909 (.789–1.000)</td>
<td>20/22</td>
<td>6.57</td>
</tr>
<tr>
<td>SER-108 (24) (2016)</td>
<td>0.559 (.433–.686)</td>
<td>33/59</td>
<td>6.25</td>
</tr>
<tr>
<td>Dubberke et al (23) (2016)</td>
<td>0.882 (.825–.958)</td>
<td>74/83</td>
<td>9.58</td>
</tr>
<tr>
<td>Holm et al [3] (2017)</td>
<td>0.438 (.194–.681)</td>
<td>7/16</td>
<td>2.83</td>
</tr>
<tr>
<td><strong>Overall (P = .005; P &lt; .001)</strong></td>
<td><strong>0.890 (.841–.940)</strong></td>
<td><strong>539/610</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

**Figure 3.** Analysis of all studies including patients with *Clostridium difficile* infection (CDI) for whom the first fecal microbiota transplant (FMT) failed but who had clinical cure with >1 FMT. Forest plot shows weighted clinical resolution rates of FMT in patients with CDI. Ev/Ttr indicates number of patients with cure/number of patients treated. Abbreviation: CI, confidence interval.
### Efficacy by subgroups

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>WPR, % (95% CI)</th>
<th>Proportion Difference in WPR, % (95% CI)</th>
<th>PValue</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Delivery modality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>82.4 (79.7–95.2)</td>
<td>Colonoscopy vs enema: 21.1 (12.71–28.54);</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Enema</td>
<td>66.3 (52.7–79.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>81.5 (64.5–98.5)</td>
<td>Colonoscopy vs enema: 5.9 (–3.13 to 15.05)</td>
<td>.17</td>
</tr>
<tr>
<td><strong>Stool type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fresh</td>
<td>80.2 (63.3–97.1)</td>
<td></td>
<td>.40</td>
</tr>
<tr>
<td>Frozen</td>
<td>77.0 (65.3–88.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CDI type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent</td>
<td>79.0 (69.1–88.8)</td>
<td>15.1 (7.36–22.91)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Recurrent and refractory</td>
<td>63.9 (57.5–70.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Donor type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anonymous</td>
<td>76.9 (66.5–87.2)</td>
<td></td>
<td>.26</td>
</tr>
<tr>
<td>Known and anonymous</td>
<td>68.6 (22.4–114.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Type of CDI testing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EIA</td>
<td>78.6 (65.2–92)</td>
<td>2.11 (–7.55– to 0.58)</td>
<td>.65</td>
</tr>
<tr>
<td>Both EIA/PCR or PCR alone</td>
<td>76.5 (56.9–96.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CDI, *Clostridium difficile* infection; CI, confidence interval; EIA, enzyme immunoassay; PCR, polymerase chain reaction; WPR, weighted pooled rate.
### Response to treatment

<table>
<thead>
<tr>
<th>Route of application (%)</th>
<th>D30</th>
<th>D90</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All</strong></td>
<td>191/240 (79.6)</td>
<td>153/196 (78.1)</td>
</tr>
<tr>
<td>Upper GIT</td>
<td>79/104 (76.0)</td>
<td>68/93 (73.1)</td>
</tr>
<tr>
<td>Lower GIT</td>
<td>84/97 (86.6)</td>
<td>63/73 (86.3)</td>
</tr>
<tr>
<td>Oral Capsule</td>
<td>33/44 (75.0)</td>
<td>25/33 (75.8)</td>
</tr>
<tr>
<td>Combination*</td>
<td>4/4 (100.0)</td>
<td>2/2 (100.0)</td>
</tr>
</tbody>
</table>

*direct endoscopic jejunal and colonoscopic

Vehreschild et al. *United European Gastroenterol J.*, accepted.
### Dependent variable: Treatment failure at day 30

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate p-value</th>
<th>Multivariate (only remaining variables) p-value</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.001</td>
<td>0.001</td>
<td>1.060</td>
</tr>
<tr>
<td>Gender</td>
<td>0.527</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG status</td>
<td>0.154</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>0.149</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ribotype 027</td>
<td>0.739</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe CDI</td>
<td>0.397</td>
<td>0.096</td>
<td>0.332</td>
</tr>
<tr>
<td>Number of recurrences</td>
<td>0.050</td>
<td>0.069</td>
<td>1.508</td>
</tr>
<tr>
<td>Antibiotic induction</td>
<td>0.791</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
<td>0.100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimotility agent</td>
<td>0.907</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowel lavage</td>
<td>0.236</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frozen FMT preparation</td>
<td>0.409</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Route of application</td>
<td>0.176</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsules</td>
<td>0.194</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper gastrointestinal tract</td>
<td>0.995</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower gastrointestinal tract</td>
<td>0.154</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n=256
Context

- Risk factors for failure identified in other studies:
  - Use of enema as route of application
  - Female gender
  - Inadequate bowel preparation
  - Surgery prior to FMT
  - Inpatient status
  - Severity of CDI
  - Number of previous CDI recurrences

- My personal interpretation:
  - If six analyses yield different results, the impact of each risk factor may be minor (exception: use of enema)
  - Factors related to the composition of the FMT preparation may be more decisive

## Safety – Microtrans Registry

<table>
<thead>
<tr>
<th>Patients with adverse event (%)</th>
<th>19 (7.4)</th>
<th>n=256</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of adverse event – no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>3 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Belching</td>
<td>3 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Emesis</td>
<td>2 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Food intolerance</td>
<td>2 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td>2 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Others (retrosternal pressure, hemorrhage, pharyngeal pain, irritable bowel syndrome, loss of a tooth, polyneuropathy, weight gain, bloody diarrhea, hypertension, increased peristaltic activity)</td>
<td>Each 1 (0.4)</td>
<td></td>
</tr>
<tr>
<td>No adverse events</td>
<td>216 (84.4)</td>
<td></td>
</tr>
</tbody>
</table>
### Table 1. Baseline characteristics of the studies included

<table>
<thead>
<tr>
<th>References</th>
<th>Country</th>
<th>Baseline characteristic</th>
<th>Study design</th>
<th>Quality of study</th>
<th>Sample size (A)</th>
<th>Recurrences previous FMT</th>
<th>Stool volume</th>
<th>Donor characteristic</th>
<th>Follow-up period</th>
<th>Primary outcomes</th>
<th>Response after first treatment</th>
<th>Response after second treatment</th>
<th>Response after third treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Youngster et al. [23]</td>
<td>USA</td>
<td>Median age = 64.5 (11-89)</td>
<td>PGS</td>
<td>Good</td>
<td>20</td>
<td>≥3</td>
<td>48 g</td>
<td>Unrelated donors, age &lt; 50 years</td>
<td>8 weeks</td>
<td>Clinical resolution of diarrhea without relapse in 8 weeks</td>
<td>14/20</td>
<td>4/6</td>
<td>NR</td>
</tr>
<tr>
<td>Hirsch et al. [24]</td>
<td>USA</td>
<td>Median age = 61 (26-92)</td>
<td>PCS</td>
<td>Fair</td>
<td>19</td>
<td>≥2</td>
<td>2.3 g</td>
<td>Three healthy donors, BMI normal</td>
<td>90 days</td>
<td>Clinical resolution of diarrhea without relapse in 90 days</td>
<td>13/19</td>
<td>4/6</td>
<td>0/1</td>
</tr>
<tr>
<td>Youngster et al. [25]</td>
<td>USA</td>
<td>Median age = 64 (7-95)</td>
<td>RCS</td>
<td>Fair</td>
<td>180</td>
<td>≥3</td>
<td>48 g</td>
<td>Single healthy donor, BMI normal</td>
<td>8 weeks</td>
<td>Clinical resolution of diarrhea without relapse in 8 weeks</td>
<td>147/180</td>
<td>17/26</td>
<td>3/4</td>
</tr>
<tr>
<td>Hecker et al. [26]</td>
<td>Canada</td>
<td>Median age = 68 (36-89)</td>
<td>RCS</td>
<td>Fair</td>
<td>20</td>
<td>3</td>
<td>40 g</td>
<td>Two healthy male donors</td>
<td>12 weeks</td>
<td>Clinical resolution of diarrhea without relapse in 12 weeks</td>
<td>51/53</td>
<td>1/2</td>
<td>2/2</td>
</tr>
<tr>
<td>Kao et al. [27]</td>
<td>USA</td>
<td>Median age = 58.7 ± 18.5</td>
<td>PCS</td>
<td>Good</td>
<td>40</td>
<td>≥2</td>
<td>80-100 g</td>
<td>Seven healthy donors, BMI &gt; 30</td>
<td>2 months</td>
<td>Clinical resolution of diarrhea without relapse in 2 months</td>
<td>250-500 mg</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Stailey et al. [28]</td>
<td>USA</td>
<td>Median age = 62.3 ± 17.1</td>
<td>RCS</td>
<td>Good</td>
<td>49</td>
<td>≥3</td>
<td>40 g</td>
<td>Two healthy male donors</td>
<td>12 weeks</td>
<td>Clinical resolution of diarrhea without relapse in 8 weeks</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Adverse events:** Abdominal cramping and bloating, Abdominal pain, one hospitalization for severe AP, One transient high fever, two new diagnoses of UC, AP, diarrhea, nausea, fatigue, low-grade fever, No adverse events were reported, Nausea, vomiting, fever, abdominal discomfort, Flatulence, bloating and bowel movement irregularities.

AP, abdominal pain; ITT, intention to treat; NA, not applicable; NR, not reported; PCS, prospective case series; RCS, retrospective case series; RCT, randomized-controlled trial; UC, ulcerative colitis.

# Safety – Immunocompromised patients

## Table 2. Adverse events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Number of patients sustaining this AE</th>
<th>Reason for Immunocompromise</th>
<th>Day post-FMT event occurred</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deaths</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1</td>
<td>SOT</td>
<td>13</td>
</tr>
<tr>
<td>Aspiration</td>
<td>1</td>
<td>SOT and esophageal cancer</td>
<td>1</td>
</tr>
<tr>
<td><strong>Hospitalizations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever, diarrhea, encephalopathy and pancytopenia</td>
<td>1</td>
<td>Cirrhosis and non-Hodgkin’s lymphoma</td>
<td>4</td>
</tr>
<tr>
<td>Abdominal pain post FMT colonoscopy</td>
<td>1</td>
<td>SOT</td>
<td>0</td>
</tr>
<tr>
<td>IBD flare; Crohn’s (2), UC (1)</td>
<td>3</td>
<td>IBD</td>
<td>&lt;84</td>
</tr>
<tr>
<td>Cerebrovascular accident; nausea and vomiting</td>
<td>1</td>
<td>ESRD and panhypopituitarism</td>
<td>21</td>
</tr>
<tr>
<td>Colectomy</td>
<td>1</td>
<td>IBD</td>
<td>&lt;28</td>
</tr>
</tbody>
</table>

### Fall and sustained hip fracture
- 1 End-stage COPD
- 84

### Influenza B and diarrhea (non-CDI)
- 1 SOT
- 3

### Catheter infection
- 1 Cancer
- 14

### Other adverse events
- Self-limited diarrheal illness
  - 3 ESRD; Sjogren’s; SOT
  - ≤84
- Fever
  - 1 SOT
  - 1
- Bloating and abdominal discomfort immediately post FMT
  - 3 HIV; ESRD; IBD
  - 1–2
- Hip pain
  - 1 IBD
  - ≤84
- Crohn’s flare
  - 1 IBD
  - ≤84
- Pertussis
  - 1 IBD
  - ≤30
- Nausea
  - 1 IBD
  - 30
- Minor mucosal tear during colonoscopy used to administer FMT
  - 1 SOT
  - 0

AE, adverse event; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; FMT, fecal microbiota transplantation; IBD, inflammatory bowel disease; SOT, solid organ transplant; UC, ulcerative colitis.

*Serious Adverse Events: death, hospitalization, or life-threatening event.

US Regulation of FMT

- FDA classification: drug
- Does not require an Investigational New Drug Application (IND) for physicians performing the procedure and stool banks providing fecal matter for individuals with Clostridium difficile infection (CDI) not responding to standard therapies.
- IND required for other indications
German Regulation of FMT

- FMT is considered a currently non-registered drug
- § 13 Abs. 2b AMG and § 20d AMG (Medicines Act)
- Physicians can administer a non-registered drug as a treatment of last resort, if they manufactured it themselves
- For clinical trials, a good manufacturing practice (GMP) facility is required
Good manufacturing practice facility

Definition: System for ensuring that products are consistently produced and controlled according to quality standards
Other procedural considerations

- Location of donation – home vs. facility
- Extent of donor screening
- Use of quarantine during manufacture
- Integration of quality control into manufacture
- etc…
FMT 2.0?

-80°C storage
Lyophilization

Capsules

Classical FMT

Optimization of administration

© by author
FMT 2.0?

-80°C storage
Lyophilization

Capsules

Classical FMT

Modified ecosystem

Defined ecosystem

Optimization of administration

Development of probiotics

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Regulation through Microbiota

Normal microflora (or treatment with FMT)

- Primary bile salts → Secondary bile salts
- Inhibition vegetative growth
- Germination: C. difficile (spore) → C. difficile (vegetative)

- No toxin production

Normal colonic epithelium

Antibiotic-perturbed intestinal microflora

- Primary bile salts → Secondary bile salts
- Inhibition vegetative growth
- Germination: C. difficile (spore) → C. difficile (vegetative)

- Toxin production

C. difficile colitis

Modified Bacterial Ecosystem

• **SER-109: A Phase 3 Study (ECOSPOR III)** to evaluate the safety and efficacy of SER-109 versus placebo. ECOSPOR III incorporates learnings from prior SER-109 development efforts. The study is expected to enroll approximately 320 patients with multiply recurrent *C. difficile* infection, randomized 1:1 to either SER-109 or placebo. The study is sized to contribute to an adequate safety database that may support product approval. ECOSPOR III will utilize more than 100 clinical sites across the U.S. and Canada. The study’s primary endpoint will compare the reduction of *C. difficile* recurrence rates in subjects who receive SER-109 verses placebo at up to eight weeks after dosing. *(SER-109-012 Study)*
RePOOPulate – defined Microbial Ecosystem Therapeutic (MET-1)

- 33 strains cultivated under anaerobe conditions
- Composition based on analysis of microbiota of healthy donors

FMT 2.0?

Development of prebiotics

Synthetic prebiotics

Classical FMT

Modified ecosystem

Defined ecosystem

Optimization of administration

-80°C storage
Lyophilization

Capsules

Development of probiotics

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Prebiotics - HMOs

- Human milk oligosaccharides (HMOs)
- Important component of human milk
- Function not fully elucidated – prebiotic properties suspected
Prebiotics - HMOs

Baseline

Antibiotic - z’FL

Week 1 - z’FL

Week 3 - z’FL

Antibiotic - control

Week 1 - control

Week 3 - control
FMT 2.0?

Development of prebiotics

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Bacterial metabolites

Synthetic metabolites

Synthetic prebiotics

Synthetic metabolites

Bacterial metabolites

Development of postbiotics

Development of probiotics
Regulation through Microbiota

Normal microflora (or treatment with FMT)

- Primary bile salts
  - Germination
    - C. difficile (spore)
  - Vegetative growth
    - C. difficile (vegetative)

- Secondary bile salts
  - Inhibition vegetative growth

Antibiotic-perturbed intestinal microflora

- Primary bile salts
  - Germination
    - No toxin production
  - Vegetative growth
    - Toxin production

- Secondary bile salts

Normal colonic epithelium

C. difficile colitis

Primary and secondary bile acids (BA) after FMT.
Modification of secondary bile acids

ABSTRACT: Standard antibiotic-based strategies for the treatment of Clostridium difficile infections disrupt indigenous microbiota and commonly fail to eradicate bacterial spores, two key factors that allow recurrence of infection. As an alternative approach to controlling C. difficile infection, a series of bile acid derivatives have been prepared that inhibit taurocholate-induced spore germination. These analogues have been evaluated in a highly virulent NAP1 strain using optical density and phase-contrast microscopy assays. Heterocycle substitutions at C24 were well-tolerated and several tetrazole-containing derivatives were highly potent inhibitors in both assays, with complete inhibition of spore germination observed at 10–25 μM. To limit intestinal absorption, C7-sulfated analogues designed to avoid active and passive transport pathways were prepared. One of these derivatives, compound 21b, was found to be a potent inhibitor of C. difficile spore germination and poorly permeable in a Caco-2 model of intestinal epithelial absorption, suggesting that it is likely to be gut-restricted.
Summary

- Routes of application and storage are evolving
  - Encapsulation
  - Frozen/freeze dried preparations
- Enemas are less effective than other routes of application
- Serious adverse events are rare, but often related to endoscopy
- Capsules are most likely the safest and most practical route of application
- The likelihood of longterm side-effects remains largely unknown
- Regulatory requirements differ substantially between countries
- Future developments include microbiota consortia, prebiotics and postbiotics

FMT capsule
Clinical Microbiome Research Group

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