Fecal Microbiota Transplantation for recurrent *Clostridium difficile* infection

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OVERVIEW

Clostridium difficile infection (CDI)[1]

- *Clostridium difficile* is an obligated anaerobic, gram positive spore-forming bacterium that belongs to *Firmicutes* group.
- Is the major causative agent for antibiotic-associated diarrhea, representing 2,3% within nosocomial infections with a high economic significance.
- Its pathology is through the production of toxin A (enterotoxin) and toxin B (cytotoxin). Furthermore, some strains (PCR ribotype 027) produces a binary toxin, which is related to increased severity.
- Current treatment based on antibiotics: Vancomycin, Metronidazol and Fidaxomicin

- Risk factors for *Clostridium difficile* infection are:
  - Elderly
  - prolonged length of hospital stay
  - antibiotic exposure
  - Immunosuppression
  - other disease (diabetes, cirrhosis,...)
  - Use of proton pump inhibitors
- Diverse spectrum of disease:
  - Diarrhea
  - Pseudomembranous and fulminant colitis

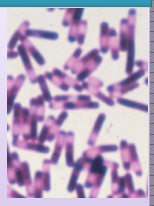

Figure 1: illustration of *Clostridium difficile from* anaerobe blood agar[2].

Fecal Microbiota Transplantation (FMT)

- Increased **interest** because of the **high incidence** and **severity** of **CDI** in the last 2 decades and the **high cure rates** that FMT shows.
- FDA classified FMT as an *unapproved new drug* (phase 1) which fits in a biological agent and drug definition.
- Little is known about how it work, but it's thought that gut microbes can:
  - Compete for **niche exclusion**
    - **Consumption of sialic acids**
  - Have a direct **toxigenic activity** (bactericines like thuricin)
  - Interfere with the lifecycle by the **metabolism of bile acids**

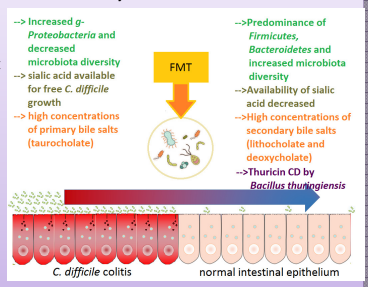

Figure 2: representation of post FMT effects on microbiota in patients. Based on[3-5]

MATERIALS AND METHODS

Criteria	Treatment
First recurrence	125mg oral Vancomycin for 14 d
Second recurrence	Pulsed Vancomycin: • 125mg oral Vancomycin for 7 wk
Three or more recurrences	Consider **fecal microbiota therapy**

Table 1: strategy for treatment recurrent CDI

Screening test to **donor** stool

- Blood analysis:
  - Total blood count
  - C-reactive protein
  - Creatinine
  - Liver enzyme levels
- Stool testing:
  - *C. difficile* toxin A/B and culture
  - Enteric pathogens
  - Parasites (e.g., *Giardia*)
  - HIV (1 and 2), HBV, HCV
- Other: illicit drugs, tattoos, other diseases (e.g., inflammatory bowel disease)

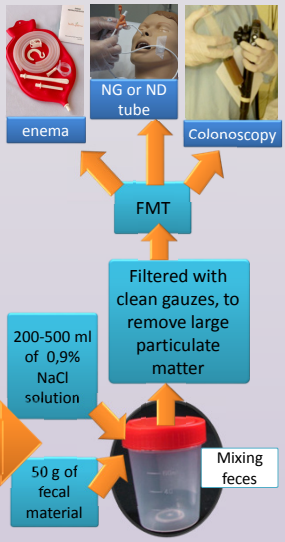

Figure 3: protocol of stool donor process[9]. NG (nasogastric), ND (nasoduodenal)

RESULTS

After Fecal Microbiota Transplantation:

- 90% of infection resolution, depending on the procedure characteristics of FMT:

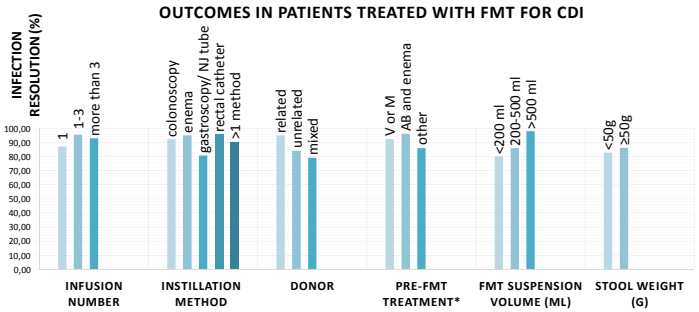

Figure 4: Outcomes in patients with FMT for CDI. * V (Vancomycin), M (Metronidazol), AB (antibiotics). Based on[6-8]

- Restoration of the normal diversity of microbiota and bile acids in gut.
- Few adverse effects (like mild transient fever, as a result of temporary systematic immune response to the applied bacteria)

DISCUSSION

Advantages of FMT	Disadvantages of FMT
• Inexpensive material (stool) • High reported cure rate (average of 80-90%) • Insignificant adverse effects • Fast response to the treatment (hours to days) • Antibiotic resistance avoided • Corrected imbalance of the microbiota in bowel	• Expensive screening for donors • Laborious and time consuming technique (laboratory technicians are required for the screening of donor material) • Invasive method of administration (nasoduodenal tube, colonoscopy, enemas,...) • Possible long term effects (autoimmune diseases, allergies and functional intestinal diseases) • Needing of standardized, licensed and ready to use method.

Table 2: list of advantages and disadvantages to compare for FMT extracted through different papers

FUTURE DIRECTIONS[10]

- Using **frozen stool** (adding glycerol as a cryoprotectant) instead fresh feces, because:
  - It shows the same success rate, with no significant side effects observed
  - It decreases the donation times per individual donor and can simplify some practical aspects
  - Investigation of **oral treatment**
- **Good manufacturing practice (GMP)** adapted for production of therapeutic fecal microbiota.
- **Synthetic communities of bacteria** (culture and administration of some strains) could be used in a not distant future.

Figure 5: Suspension of defined number of bacteria for therapeutic intestinal microbiota (GMP production by the University of Minnesota)[10]

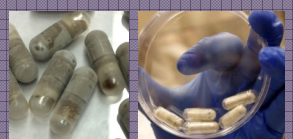

Figure 6: Fecal frozen capsules by Dr. Elizabeth Hohmann and Thomas Louie[11,12]

CONCLUSIONS

- *Clostridium difficile* is a current issue, with high mortality and very high costs
- Consequently to the analysis of advantages/ disadvantages and classification as a *unapproved new drug* by FDA, Fecal Microbiota Transplantation is systematically recommended only for recurrent cases of *Clostridium difficile* infection.
- Nevertheless, is a safety process with a high efficacy rates (80-90% depending on procedure characteristics)
- New generation FMT, like fecal pills or other methods, are under investigation for replacing the FMT available nowadays.

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