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Faecal microbiota transplants and microbial ecosystem therapeutics as a treatment for recurrent *Clostridium difficile* infections

Background

Clostridium difficile infection (CDI) is one of the most common hospital-acquired infections. It is originated by a gram-positive strict anaerobic rod shaped bacteria, which can induce from watery diarrhoea to pseudomembranous colitis and toxic megacolon, becoming recurrent in most cases.

In the United States, during the 2011, caused about 500,000 infections and 15,000 deaths[1], achieving a higher mortality rate than the human immunodeficiency virus (HIV).[2]

His pathogenesis seems to be related to perturbations of the intestinal microbiota, caused mainly by broad spectrum antibiotics altering the balance of microbial populations, allowing the pathogen grow and infect.[3] It can be contracted by eating vegetative cells or spores. During the passage through the stomach most viable cells die, but spores persist, germinate in the small intestine, and multiply in the colon. The intestinal mucosa promotes the adhesion of *C. difficile* to the epithelium, where it produces enzymes and A and B toxins, responsible for causing severe inflammation, tissue degradation, watery diarrhoea and pseudomembranous colitis.[4]

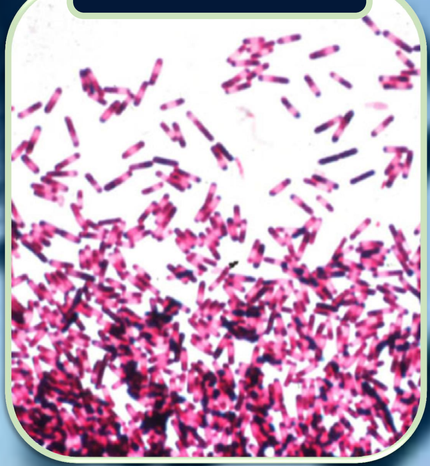
As it is difficult to treat and shows high failure rates for antibiotic therapy, there is an increasing interest in finding new promising therapies, as faecal microbiota Transplantation (FMT) and Microbial Ecosystem Therapeutics (MET), both aimed to restore the gut microbiota.

What are FMT and MET?

These are two techniques used to restore the normal intestinal microbiota composition, both aimed to remove *C. difficile* infection, especially in recurrence cases.

The FMT consists in donating stool from a healthy person to a sick one, they were implemented in 1958 as a clinical treatment addressed to humans. With the time, have evolved to MET, which are microbial communities synthesized in vitro, simulating faeces composition, making the practice more reproducible, simple and safe.[5]

C. difficile endospores[6]



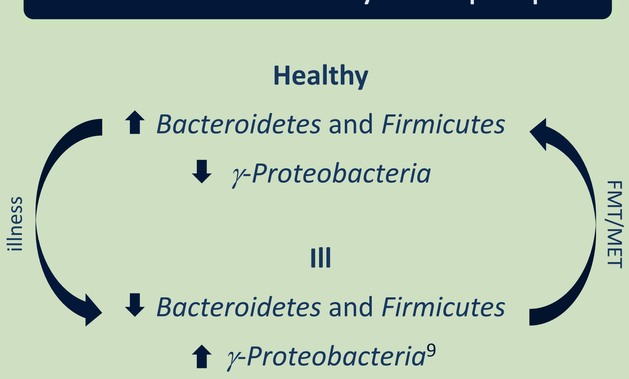
Why are FMT and MET useful?

They are useful because restore the normal microbiota, while antibiotics still cause more damage, promoting recurrent infections.

How does microbiota suppress *C. difficile*?[5]
-Competing for the same nutritional niche
-Producing molecules and bacteriocins with toxigenic activity
-Interacting indirectly with its lifecycle

It is a simple, safe and effective technique, normally without complications.[7] If it occurs, usually is due to the administration form and not because of the technique itself.[8]

Microbiota: healthy vs ill people



[9]

Obtaining the microbiota

Donor selection

Questionnaire in orther to see if candidates are qualify

⬇

If they are primising, undergo blood and faeces tests

⬇

Acceptation or denegation of stool

FMT: There is no need to be related with the patients because there is no problem of compatibility. Also there are faecal banks like Openbiome.[10]

MET: Only donor selection in the first phase of isolation. There are laboratories that produce MET like the probiotic RePOOPulate.[11]

Administration

- Lower gastrointestinal tract: colonoscopy or enema.
- Upper gastrointestinal tract: nasogastric tube, nasojejunal tube, esophagogastroduodenoscopy or pills.

Each technique has got advantages and disadvantages in relation to the rate of success and the risk they pose to the patient. The best route should be evaluated in each case.[8]

Results and success of the techniques

Van Nood et al., 2013, evaluated efficacy of **FMT vs antibiotics.**[12]

- Vancomicin + bowel lavage: 23% resolution
- Vancomicin: 31% resolution
- Bowel lavge + FMT: 81% resolution

Brand et al., 2012, analysed the **response to FMT** of 77 patients with recurrent CDI.[7]

-The primary cure rate was 91% (resolution of symptoms ≤90 days after treatment)
-The secondary cure rate was 98% (after one further course of vancomycin with or without repeat FMT)

Petrof et al., 2013, develop a **MET** called RePOOPulate. Have been tested in two patients, both remained symptom-free after the treatment and restore the normal bowel pattern.[11]

Legislation

FMT and MET are considered by the Food and Drug Administration (FDA) as drugs with biological origin.

In July 2013 FDA accepted FMT as a treatment for patients those do not respond to the conventional procedure with antibiotics.

In other cases, if someone wants to apply those techniques, the responsible must request a new investigational drug application, in order to be accountable for the practice.[5]

Conclusions

- FMT and MET are promising techniques, but there is still a lot of work to do: understand how they exactly work, optimize the composition of the infusions, doses, routes of administration, study the long-term effects and define the legal issues.
- There is a tendency to prioritizing the investigation of the MET. Not only for treating CDI, but also other diseases. In the future it might be synthesized different MET aimed at specific groups of patients.[13]
- It's surprising how a natural technique with stool or derived stool products, could work even when antibiotics can't remove the infection.

References

1. CDC, *Clostridium difficile* infection. Page last updated, 2015. http://www.cdc.gov/HAI/organisms/cdiff/Cdiff_infect.html
2. LeBeau S, Khoruts A. 2014. Fecal Microbiota Transplantation: An Interview With Alexander Khoruts. Glob. Adv. Heal. Med. **3**:73–80.
3. Gough E, Shaikh H, Manges AR. 2011. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent clostridium difficile infection. Clin. Infect. Dis. **53**:994–1002.
4. To KB, Napolitano LM. 2014. Clostridium difficile Infection: Update on Diagnosis, Epidemiology, and Treatment Strategies. Surg. Infect. (Larchmt). **15**:490–502.
5. Petrof EO, Khoruts A. 2014. From stool transplants to next-generation microbiota therapeutics. Gastroenterology **146**:1573–1582.
6. Photography taken from: http://www.medicinageriatrica.com.br/2009/09/07/estudo-de-caso-infeccao-hospitalar-pelo-clostridium-difficile/
7. Brandt L. 2012. Fecal transplantation for the treatment of Clostridium difficile infection. Gastroenterol. Hepatol. (N. Y). **8**:191–194.
8. Boyle ML, Ruth-Sahd LA, Zhou Z. 2015. Fecal Microbiota Transplant to Treat Recurrent *Clostridium difficile* Infections. Critical Care Nurse **35(2)**:51-64.
9. Seekatz AM, Aas J, Gessert CE, Rubin T a., Saman DM, Bakken JS, Young VB. 2014. Recovery of the gut microbiome following fecal microbiota transplantation. MBio **5**:1–9.
10. http://www.openbiome.org/
11. Petrof EO, Gloor GB, Vanner SJ, Weese SJ, Carter D, Daigneault MC, Brown EM, Schroeter K, Allen-Vercoe E. 2013. Stool substitute transplant therapy for the eradication of Clostridium difficile infection: "RePOOPulating" the gut. Microbiome **1**:3.
12. Van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, Visser CE, Kuijper EJ, Bartelsman JFWM, Tijssen JGP, Speelman P, Dijkgraaf MGW, 13. Keller JJ. 2013. Duodenal infusion of donor feces for recurrent Clostridium difficile. N. Engl. J. Med. **368**:407–15.
14. Borody TJ, Campbell J. 2011. Fecal microbiota transplantation: current status and future directions. Expert Rev. Gastroenterol. Hepatol. **5**:653–655.
Background photography taken from: http://ndnr.com/gastrointestinal/chronic-diarrhea-after-%E2%80%A8c-difficile-eradication/