La transplantation de microbiote fécal

Passé, present, futur ...

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Journées Parisiennes de Pédiatrie, 6 octobre 2018, Paris
Cet intervenant :

- a déclaré ses liens d’intérêt
- estime qu’il ne peut pas influer sur cette présentation

Tous les orateurs ont reçu une déclaration de liens d’intérêt.
A bit of history..

- The indications for the fecal therapy included
  - food poisoning with the risk of death
  - high level of fever with neuropsychic symptoms
  - cold pathogenic febrile disease
  - seasonal febrile disease with high fever

Ge Hong
4th century

Chinese medical book
Zhou Hou Bei Ji Fang (Handy Therapy for Emergencies)
Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

The study was stopped after an interim analysis!
European Guidelines - 2014

European Society of Clinical Microbiology and Infectious Diseases: Update of the Treatment Guidance Document for Clostridium difficile Infection CLINICAL MICROBIOLOGY AND INFECTION VOLUME 20, SUPPLEMENT 2, MARCH 2014
Le principe: restaurer la diversité du microbiote intestinal

Autres mécanismes hypothétiques

- Compétition pour les éléments nutritifs

- Suppression directe par des peptides antimicrobiens

- Inhibition de la germination des spores médiée par les acides biliaires

- Activation de la résistance à la colonisation médiée par le système immunitaire


Indication

Récidive ou rechute d’ICD avec

• au moins *trois épisodes* de rechute

• et échec de 6-8 semaines de traitement par VANCOMYCINE « tappered » (et/ou Fidaxomycine)
6 mois plus tard ....
The BRAIN-GUT Axis?
## TMF pour *Clostridium difficile*

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>Age (years)</th>
<th>Number of children</th>
<th>Route FMT</th>
<th>Cure rate</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kronman <em>et al</em> (25)</td>
<td>2015</td>
<td>1-13</td>
<td>10</td>
<td>Nasogastric</td>
<td>90%</td>
<td>Transient vomiting and mucoid stool</td>
</tr>
<tr>
<td>Russell <em>et al</em> (26)</td>
<td>2014</td>
<td>1-19</td>
<td>10</td>
<td>Nasogastric (2) Colonoscopy (8)</td>
<td>90%</td>
<td>None</td>
</tr>
<tr>
<td>Pierog <em>et al</em> (27)</td>
<td>2014</td>
<td>1-21</td>
<td>6</td>
<td>Colonoscopy</td>
<td>100%</td>
<td>None</td>
</tr>
<tr>
<td>Walia <em>et al</em> (28)</td>
<td>2014</td>
<td>1-2</td>
<td>2</td>
<td>Colonoscopy</td>
<td>100%</td>
<td>None</td>
</tr>
<tr>
<td>Hourigan <em>et al</em> (29)</td>
<td>2015</td>
<td>6-17</td>
<td>8</td>
<td>Colonoscopy</td>
<td>100%</td>
<td>None</td>
</tr>
<tr>
<td>Kahn <em>et al</em> (30)</td>
<td>2012</td>
<td>1</td>
<td>1</td>
<td>Colonoscopy</td>
<td>100%</td>
<td>None</td>
</tr>
<tr>
<td>Wang <em>et al</em> (31)</td>
<td>2015</td>
<td>1</td>
<td>1</td>
<td>Nasojejunal</td>
<td>100%</td>
<td>None</td>
</tr>
<tr>
<td>Rubin <em>et al</em> (32)</td>
<td>2013</td>
<td>6-8</td>
<td>2 children with adult series</td>
<td>Upper tract (route nuclear)</td>
<td>50%</td>
<td>None</td>
</tr>
<tr>
<td>Kelly <em>et al</em> (33)</td>
<td>2014</td>
<td>6-16</td>
<td>5 immuno-comprised children with adult series</td>
<td>Not specified for children</td>
<td>89% (whole series)</td>
<td>No infectious complications</td>
</tr>
</tbody>
</table>
Gut dysbiosis is widespread in many conditions!
Ulcerative colitis: 3 RCT

(1) 75 patients FMT (50 mL enema, unrelated healthy donor) or placebo (50 mL water enema) once weekly for 6 weeks
- clinical and endoscopic remission at 7 weeks (24% vs. 5%)
- Donor effect: 7/9 patients in remission after FMT received fecal material from a single donor.

(2) 48 patients FMT (via nasogastric tube, healthy donor) or placebo (autologous fecal microbiota) at 0 and 3 weeks
- No statistically significant difference in remission at 12 weeks (30% vs. 20%)

(3) 85 patients FMT (150 mL enema, blended stool from 3 to 7 unrelated donors) or placebo (150 mL enema) 5 days per week for 8 weeks
- clinical (steroid-free) and endoscopic remission at 8 weeks (27% vs. 8%)

Overall pooled estimate of clinical remission of 36.2% (95% CI 17.4%-60.4%)
51 ongoing clinical trials (FMT for IBD)...

Source: [https://ClinicalTrial.gov](https://ClinicalTrial.gov)
IBS

• 90 participants and randomly assigned them to active treatment (n=60) or placebo (i.e. patient own faeces: n=30)

• Response at 3 months after FMT:
  • 36 (65%) of 55 active treatment group vs 12 (43%) of 28 placebo group (p=0.049)

• Response at 12 months after FMT:
  • 31 (56%) of 55 active treatment group vs ten (36%) of 28 placebo group (p=0.075)

Johnsen, et al. The Lancet, 2017
Faecal microbiota transplantation alters gut microbiota in patients with irritable bowel syndrome: results from a randomised, double-blind placebo-controlled study

Sofie Ingdam Halkjær,1 Alice Højer Christensen,2 Bobby Zhao Sheng Lo,1 Patrick Denis Browne,3 Stig Günther,1 Lars Hestbjerg Hansen,3 Andreas Munk Petersen1

Halkjær SI, et al. Gut 2018
Decolonization after 3 months:
4/8 from CRE
7/8 from VRE
Fecal microbiota transplantation for patients with steroid-resistant acute graft-versus-host disease of the gut

Kazuhiko Kakihana,1,* Yuki Fujioka,2,3,* Wataru Suda,4,5,* Yuho Najima,1 Go Kuwata,6 Satoshi Sasajima,7 Iyo Mimura,8 Hidetoshi Morita,8 Daisuke Sugiyama,2 Hiroyoshi Nishikawa,2 Masahira Hattori,4,9 Yutaro Hino,1 Shuntaro Ikegawa,1 Keita Yamamoto,1 Takashi Toya,10 Noriko Doki,1 Koichi Koizumi,6 Kenya Honda,5,7,11 and Kazuteru Ohashi1

4 patients with steroid-resistant/dependent gut aGVHD received FMT

All patients responded to FMT, with 3 complete responses and 1 partial response

No severe adverse events attributed to FMT were observed.
Reconstitution of the gut microbiota of AB-treated patients by autologous FMT in HSCT

Taur et al., Sci. Transl, 2018
Autism: 1 open study

18 children (7-16 yrs)
Autism + GI symptoms

Treatment
10 weeks

Follow-up
8 weeks

Effect of
Vancomycin?
Initial dose?
Maintenance dose?
PPI?
Placebo effect?
Improvement of GI symptoms?

Kang et al. Microbiome (2017)
Fecal microbiota transplantation cured epilepsy in a case with Crohn’s disease: The first report

Zhi He, Bo-Ta Cui, Ting Zhang, Pan Li, Chu-Yan Long, Guo-Zhong Ji, Fa-Ming Zhang

22-year-old girl, with a 17-year history of epilepsy

FMT x 3 (Trial: NCT01793831)

Donor = primary school girl

During the 20 months of follow-up, FMT has proved its efficacy in preventing relapse of seizures after withdrawing the antiepileptic drugs.
Maladie coeliaque ?

Hair Growth in Two Alopecia Patients after Fecal Microbiota Transplant

Dionne Rebello, MD¹, Elaina Wang, BS¹, Eugene Yen, MD², Peter A. Lio, MD³, and Colleen R. Kelly, MD, FACG⁴
Many ongoing clinical trials

- IBD: 51
- IBS: 11
- Metabolic diseases: 8
- Obesity: 7
- Liver diseases: 7
- Brain diseases: 5
- ...

Source: https://ClinicalTrial.gov
The quest for the holy grail!!!!

Median lifespan was 41% longer
"Prediction is very difficult, especially if it's about the future."

Nils Bohr (1885-1962)
Nobel laureate in Physics
Many publications from the same group (Borody)

FMT beyond *C difficile*

- Multiple FMTs: capsules !!!

- Donor selection according to microbiome characteristics
  - Richness / diversity
  - Bacteria species / strains
  - Microbiota functions
  - SCFA
  - ...

- Donor matching: age? sex? microbiome characteristics?

- Recipient: colon cleansing? AB? Diet?

Staley, Am J Gastroenterol, 2017

PLoS Biol14(7): e1002503
TMF Koala