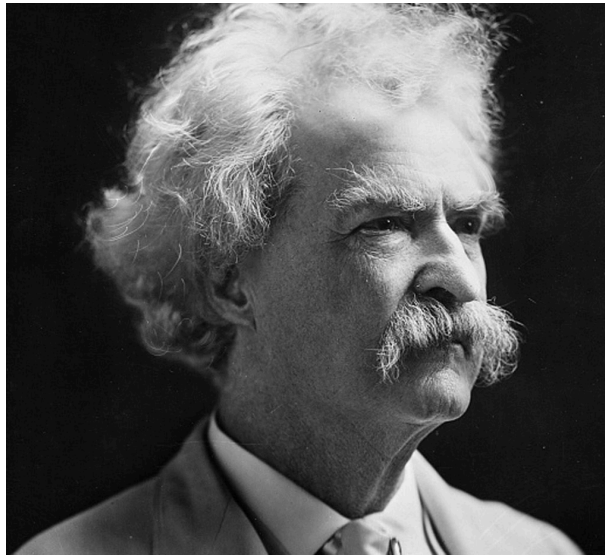
Nouvelles indications de la TMF ?

Etat de la recherche



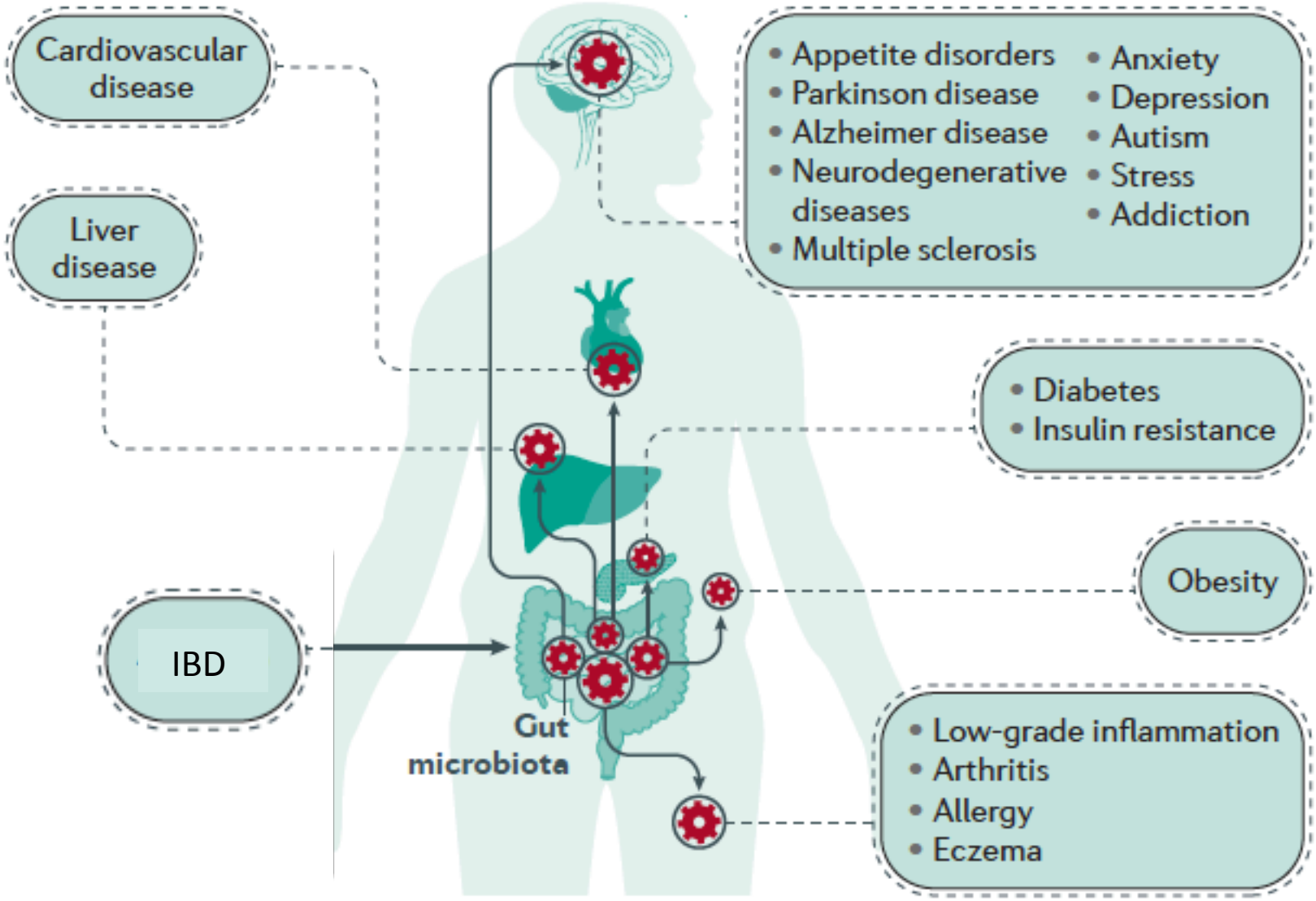
Dr Alexis Mosca
Hôpital Robert Debré (Paris)





" L'art de la prophétie est extrêmement difficile, surtout en ce qui concerne l'avenir. "

Mark Twain (1835-1910)



Patrice D. Cani, Nat Review, 2017

Le futur – voie d'administration



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

Christopher Staley, PhD[1,4], Matthew J. Hamilton, PhD[1,4], Byron P. Vaughn, MD[2], Carolyn T. Graiziger, BS[2], Krista M. Newman, MD[2], Amanda J. Kabage, MS[2], Michael J. Sadowsky, PhD[1,5] and Alexander Khoruts, MD[1,2,3,5]

The optimized lyophilized preparation satisfied all our preset goals for physicochemical properties, encapsulation ease, stability at different temperatures, and microbiota viability *in vitro* and *in vivo* (germ-free mice). The capsule treatment was administered to 49 patients. Overall, 43/49 (88%) of patients achieved a clinical success, defined as no recurrence of CDI over 2 months. Analysis of the fecal microbiome demonstrated near normalization of the fecal microbial community by 1 month following FMT treatment. The simplest protocol using the lowest dose ($2.1–2.5\times10^{11}$ bacteria in 2–3 capsules) without any colon purgative performed equally well in terms of clinical outcomes and microbiota engraftment.

Staley, Am J Gastroenterol, 2017

RCH: 3 essais cliniques randomisés

(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%) -

-> Effet donneur : 7/9 patients en rémission ont eu des selles d'un même donneur

(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%)

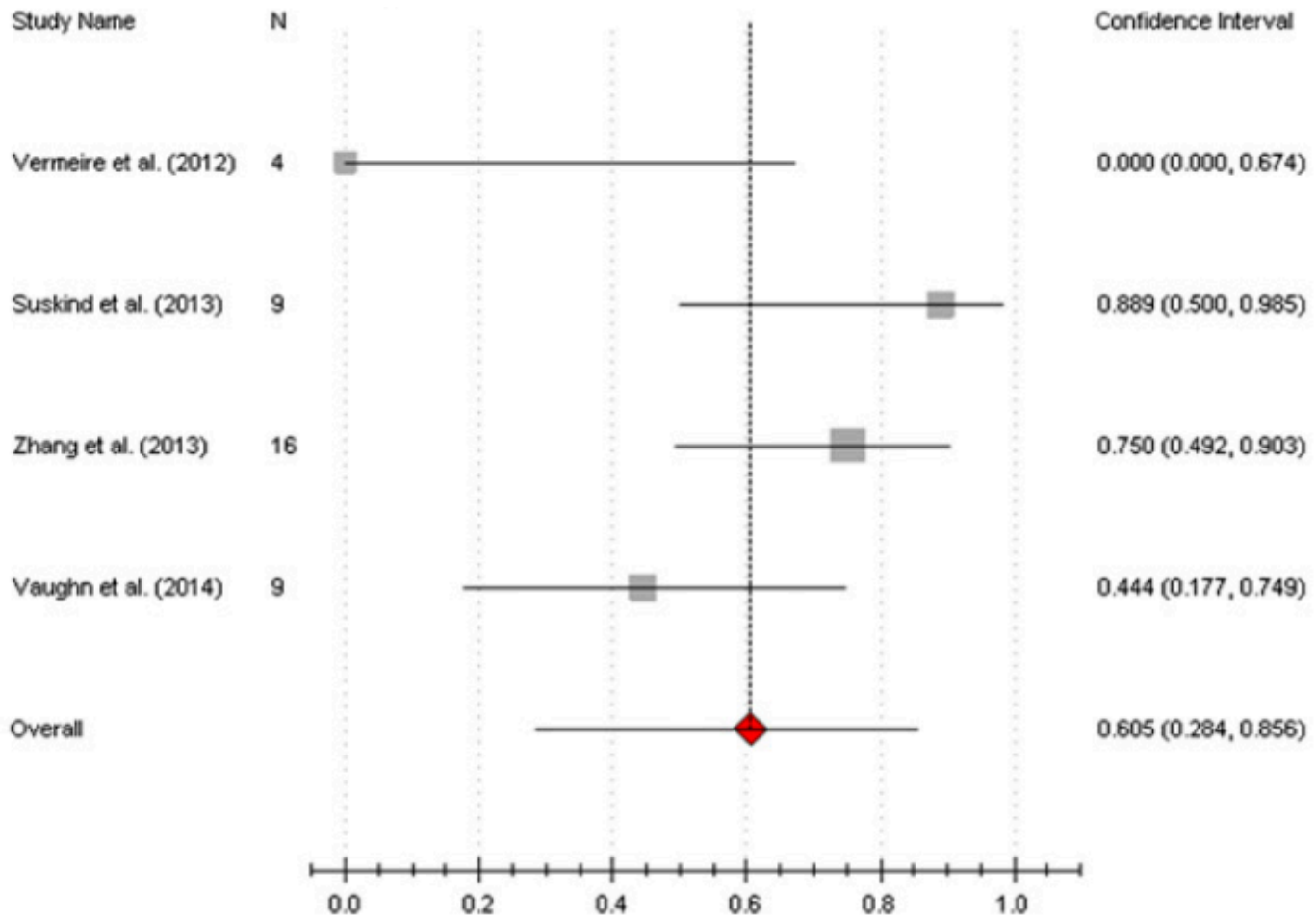
(3) 85 patients FMT (150 mL enema, blended stool from 3 to 7 unrelated donors) or placebo (150 mL enema) 5 days per week for 8 weeks

-> clinical (steroid-free) and endoscopic remission at 8 weeks (27% vs. 8%)

(1) Moayyedi P, Gastroenterology 2015 (2) Rossen NG. Gastroenterology 2015 (3) Paramsothy S, Lancet 2017

Crohn: méta analyse d'essais ouvert

60% rémission



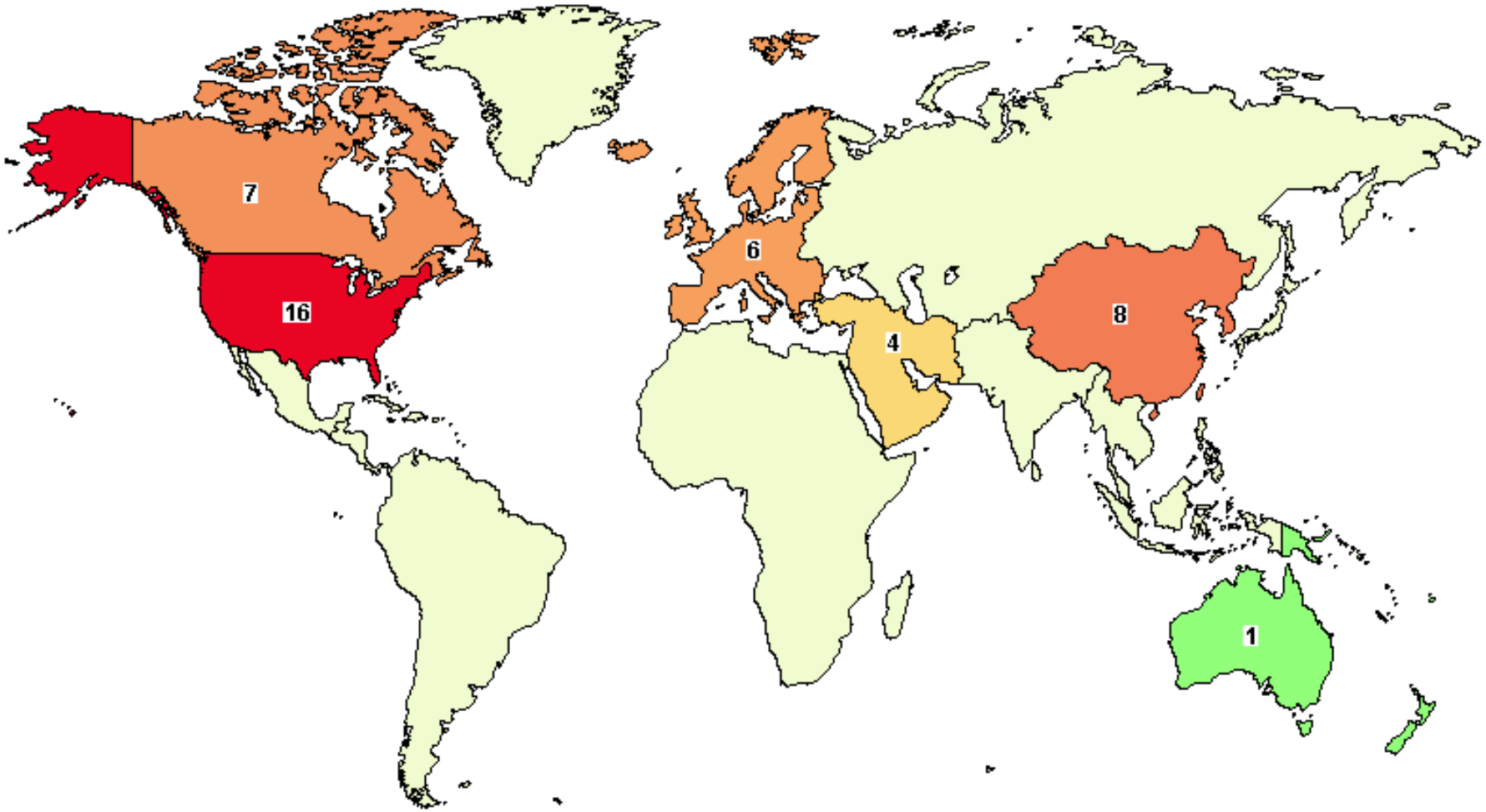
Colman, J. Crohns Colitis, 2014

Pouchite

Prospective controlled pilot study	2013	8	Chronic refractory pouchitis; nasogastric FMT	4 weeks	No improvement; 2 patients with ESBL-resistant coliform regained ciprofloxacin sensitivity
Case report	2016	1	Chronic pouchitis; FMT via sigmoidoscopy	3 months	Cure
Case series	2016	5	Chronic antibiotic-dependent pouchitis; FMT via upper endoscopy repeated at 3/4 week intervals	3 months	3 patients had sustained response
Prospective open-labeled pilot study	2016	9	Acute and chronic pouchitis; FMT at pouchoscopy	1 month (7 patients)	71% global symptom improvement

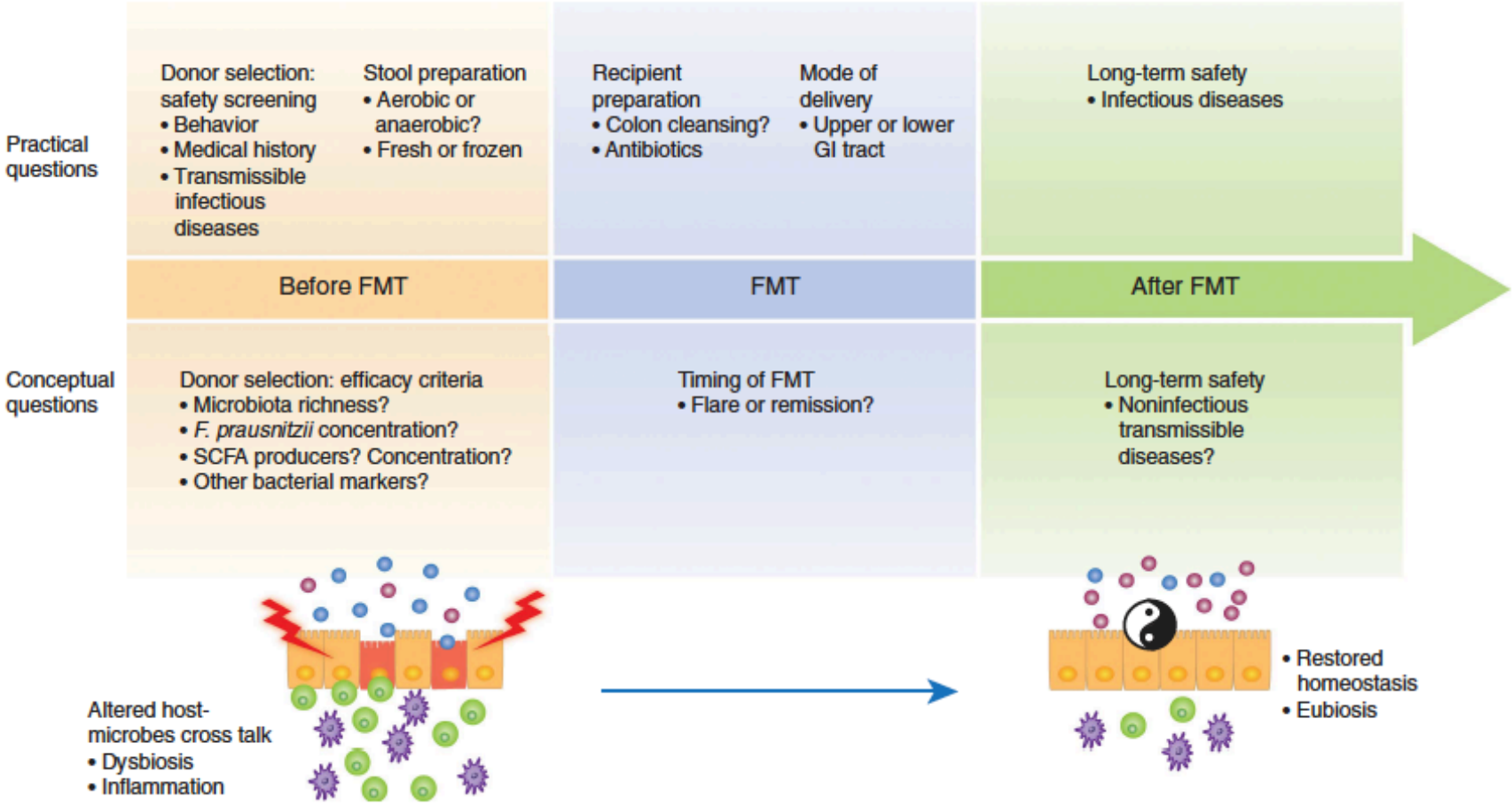
(1) Landy et al. Gut. 2013 (2) Fang et al. Int J Colorectal Dis. 2016 (3) Stallmach, Am J Gastroenterol. 2016
(4) El-Nachef Gastroenterology. 2016

42 essais en cours …



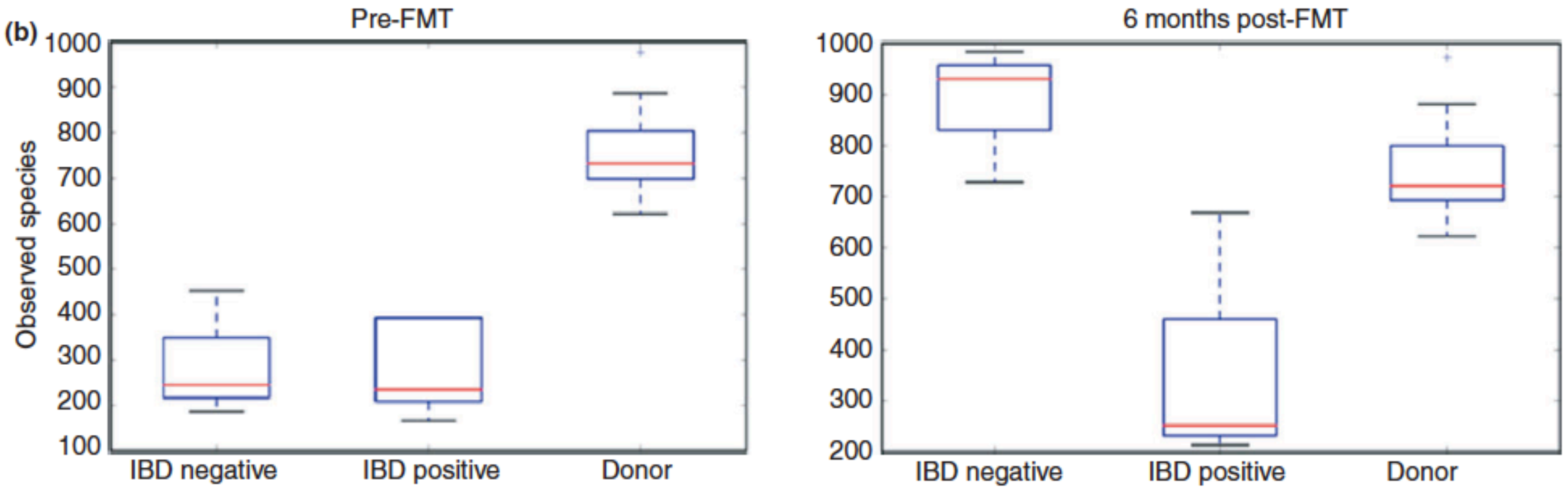
Source : https://ClinicalTrial.gov accès 15/06/2017

Nombreuses questions à résoudre …



Pigneur, Sokol. Mucosal Immunology, 2016

Un problème de diversité ?



Hourigan SK, al. Aliment Pharmacol Ther. 2015

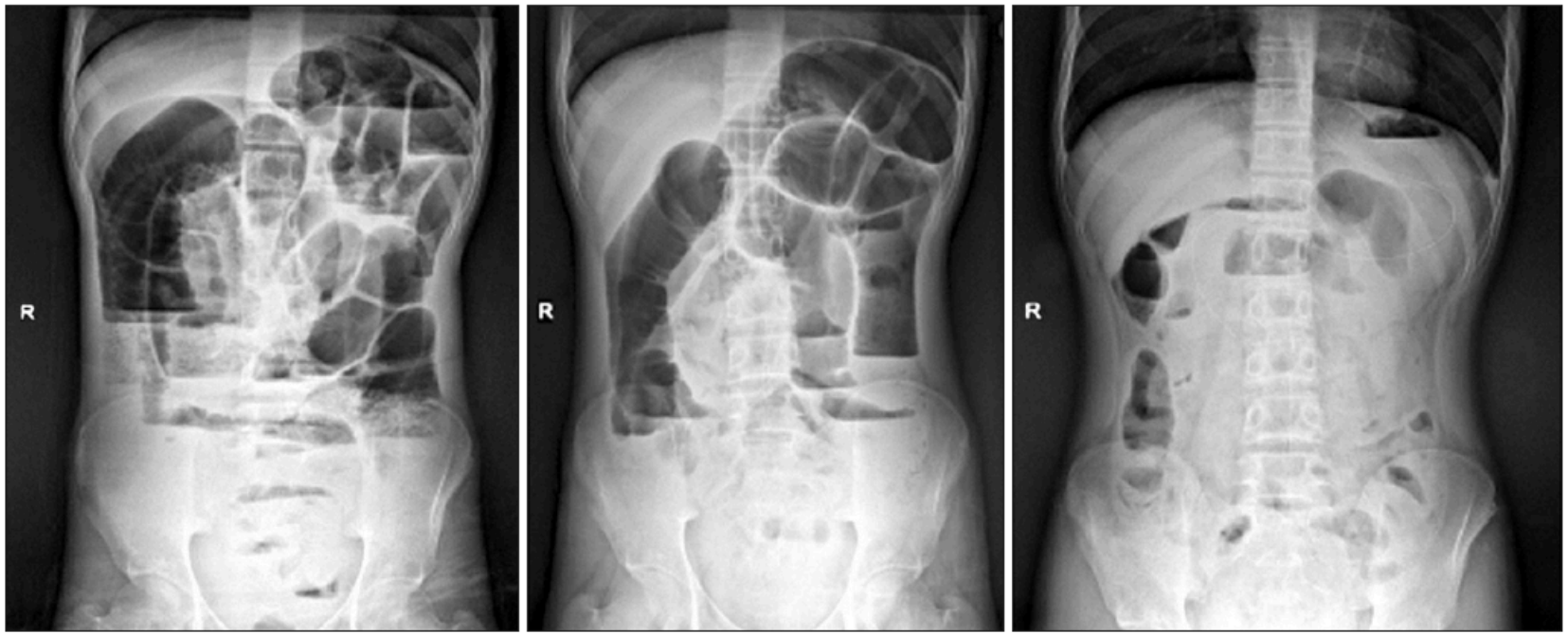
IBS : quelques séries

Case series	1989	55 (no mention of number of IBS patients)	IBS + IBD; retention enemas	1–12 months	36% cure of IBS; 16% symptom relief in IBS patients
Case report	1992	1	Chronic constipation; retention enemas	18 months	Long-term cure
Case series	1995	45	Chronic constipation treated with FMT	9–19 months	89% immediate improvement in constipation, bloating and abdominal pain; 60% response at follow-up
Case series	2001	6	UC and chronic constipation; single daily retention enemas for 5 days	8–28 months	All constipation patients with long-term restoration of normal bowel function
Follow-up study	2013	13	9 with IBS-D, 3 with IBS-C and 1 alternating IBS-D and IBS-C)	6–18 months	70% symptom resolution or improvement after FMT

(1) Borody, Med J Aust. 1989 (2) Andrews, Eur J Gastroeterol Hepatol. 1992 (3) Andrews, Gastroenterology 1995
(4) Borody, J Clin Gastroenterol. 2004 (5) Pinn, Am J Gastroenterol. 2014

Pseudo Obstruction Intestinale Chronique

- 9 patients (18-53 ans)
- FMT 1 fois/j pendant 6 jours (sonde NJ), issus de 4 donneurs anonymes
- Suivi 8 semaines après la fin du traitement

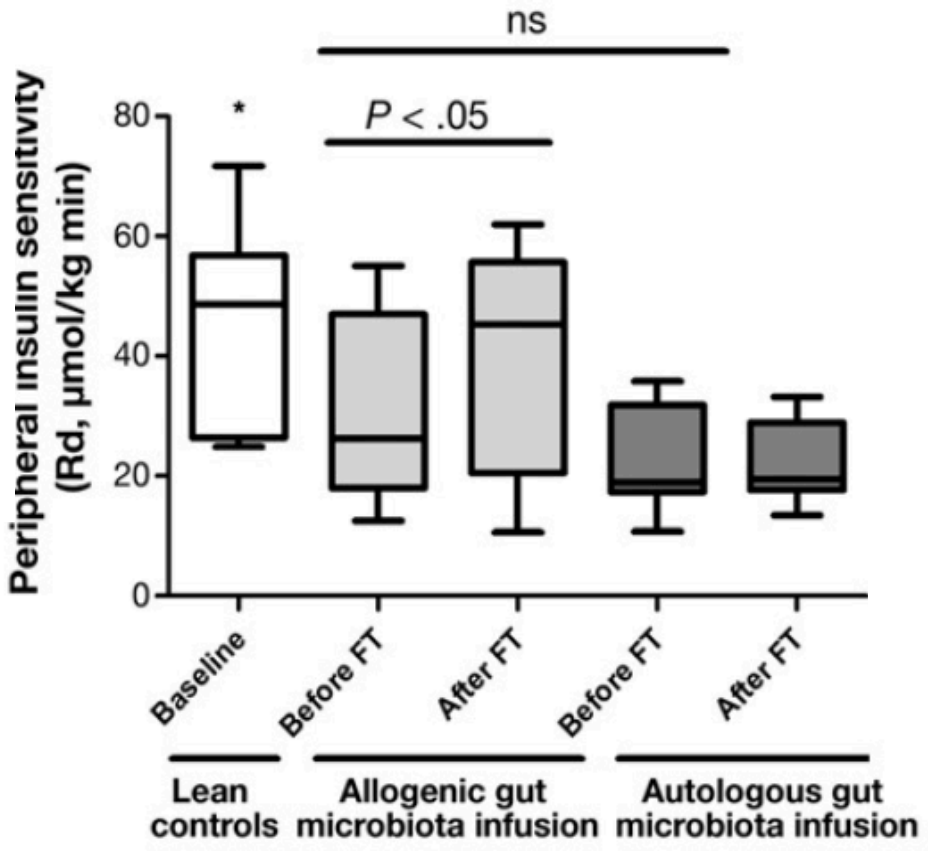


Before treatment | During treatment | After treatment

Résolution des symptômes chez 7/9 patients (71%)

Gu, J Neurogastroenterol Motil, 2017

Syndrome métabolique



Vrieze, Gastroenterology, 2012

Hépatologie

Chronic hepatitis B						
	Case-controlled, open-label pilot trial	2016	18	Patients with persistent hepatitis B e-antigen (HBeAg) positivity despite chronic antiviral therapy	unknown	5 patients treated with FMT. All showed reduced HBeAg titers and 2 had clearance of HBeAg

Ren, Hepatology. 2016

Hepatic encephalopathy						
	Case report	2015	1	Patient with cirrhosis and grade 1–2 hepatic encephalopathy received a series of weekly FMT for 5 weeks	7 weeks	Mental state returned to baseline with gut microbial composition similar to that of donor

Kao, Hepatology. 2016

Encéphalopathie hépatique : un essai randomisé

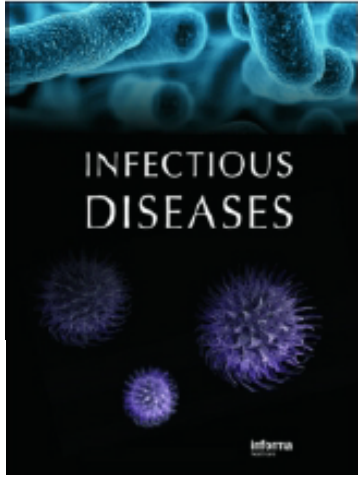
- 20 FMT-randomized patients received 5-days of broad-spectrum antibiotic pre-treatment then a single FMT enema from the same donor

- Using microbiome data from HE and healthy control participants, we performed a machine learning technique to identify a single donor who had the highest relative abundances of Lachnospiraceae and Ruminococcaceae among a universal stool donor bank

- Efficacité : 10/10 vs 5/10 (p=0.03).

Jasmohan, Hepathology, 2017

Eradication BHRe



REVIEW ARTICLE

Fecal microbiota transplantation for the intestinal decolonization of extensively antimicrobial-resistant opportunistic pathogens: a review

Amee R. Manges[a], Theodore S. Steiner[b] and Alissa J. Wright[b]

- 8 cas décrits dans la littérature
- 5 essais cliniques en cours

Amee R. et al (2016) Infectious Diseases

Short Report

Is faecal microbiota transplantation an option to eradicate highly drug-resistant enteric bacteria carriage?

B. Davido [a], R. Batista [b], H. Michelon [c], M. Lepainteur [d], F. Bouchand [c], R. Lepeule [e], J. Salomon [a], D. Vittecoq [f], C. Duran [a], L. Escaut [f], I. Sobhani [g], M. Paul [h], C. Lawrence [d], C. Perronne [a], F. Chast [b], A. Dinh [a,*]

[a] *Infectious Diseases Unit, Raymond Poincaré Teaching Hospital, APHP, Versailles Saint-Quentin University, Garches, France*
[b] *Pharmacy Department, Cochin Teaching Hospital, APHP, Paris Descartes University, Paris, France*
[c] *Pharmacy Department, Raymond Poincaré Teaching Hospital, APHP, Versailles Saint-Quentin University, Garches, France*
[d] *Microbiology Laboratory, Raymond Poincaré Teaching Hospital, APHP, Versailles Saint-Quentin University, Garches, France*
[e] *Antimicrobial Stewardship Unit, Henri Mondor Teaching Hospital, APHP, Paris-Est Créteil-Est University, Créteil, France*
[f] *Infectious Diseases Unit, Bicêtre Teaching Hospital, APHP, Paris-Sud University, Le Kremlin-Bicêtre, France*
[g] *Gastroenterology Department, Henri Mondor Teaching Hospital, APHP, Paris-Est Créteil-Est University, Créteil, France*
[h] *Pharmacy Department, Henri Mondor Teaching Hospital, APHP, Paris-Est Créteil-Est University, Créteil, France*

Eradication : 3/8

B. Davido et al. / Journal of Hospital Infection xxx (2017) 1-5

Hématologie

Immune thrombocytopenia	Case report	2011	1	Patient with UC and ITP treated with FMT	–	Prolonged reversal of thrombocytopenia

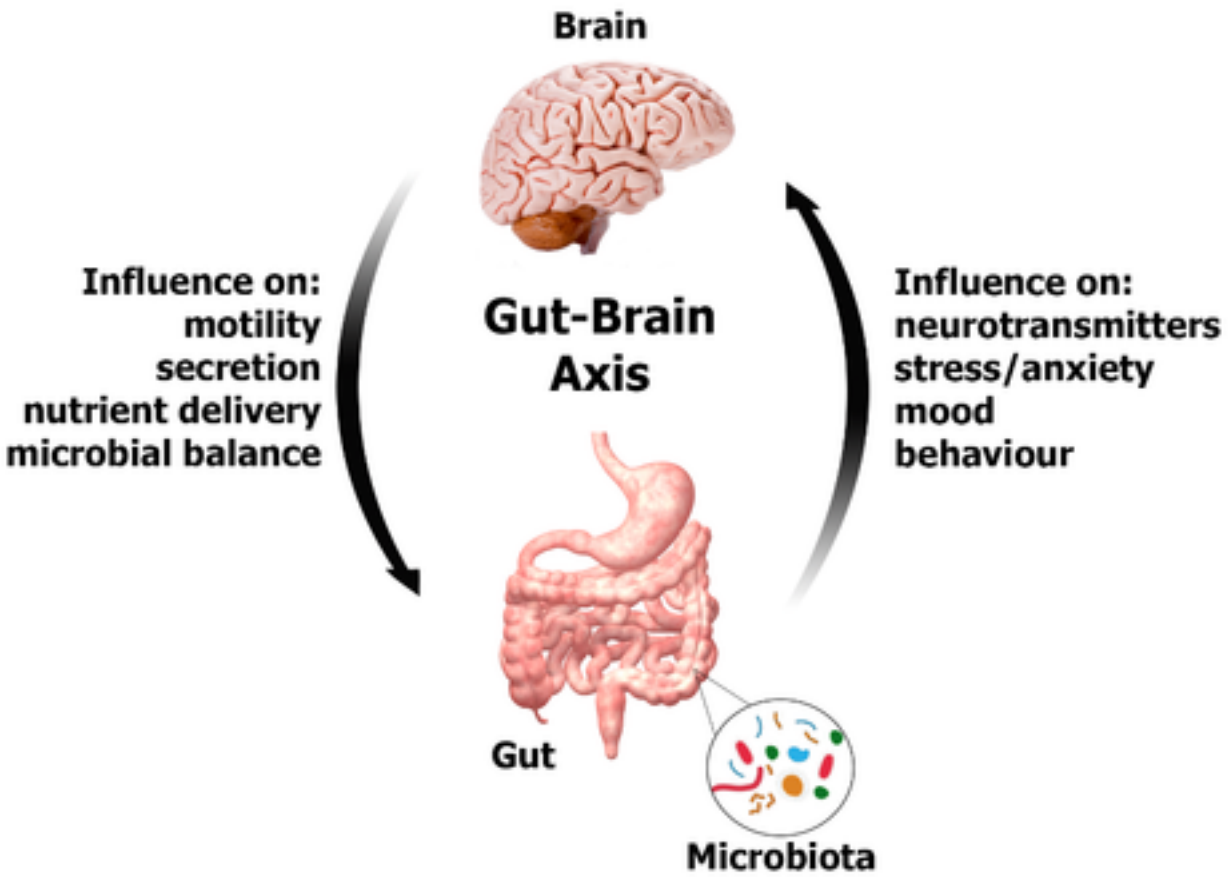
Borody, Am J Gastroenterol. 2011

Acute graft-versus-host disease	Case series	2016	4	Patients with AML and aGVHD post-allo-SCT were treated with FMT	–	3 patients with a complete response and 1 with partial response. Significant changes in gut microbiota composition post-FMT in responsive patients

Kakihana, Blood, 2016

Neurologie

The BRAIN-GUT Axis ?



Neurologie

Multiple sclerosis	Case series	2011	3	Multiple sclerosis patients treated with FMT for constipation	Up to 15 years	All patients experienced progressive improvement in neurological symptoms and regained the ability to walk; 2 patients had restoration of urinary function; 1 showed halting of disease progression for 15 years post-FMT
Myoclonus dystonia	Case report	2011	1	Female patient with myoclonic dystonia and chronic diarrhea	–	90% improvement in myoclonus dystonia symptoms; restoring her fine motor function, improving her ability to perform tasks that require dexterity, such as holding cups and fastening buttons

Borody, Am J Gastroenterol. 2011

Epilespie

World Journal of Gastroenterology

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

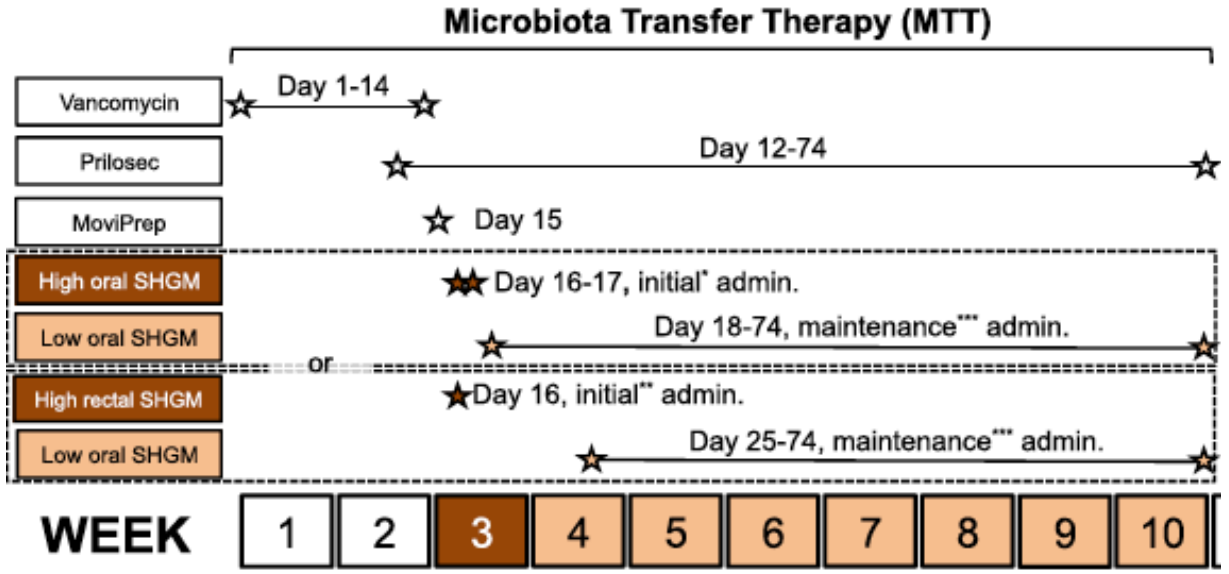
FMT x 3 (Trial: NCT01793831)

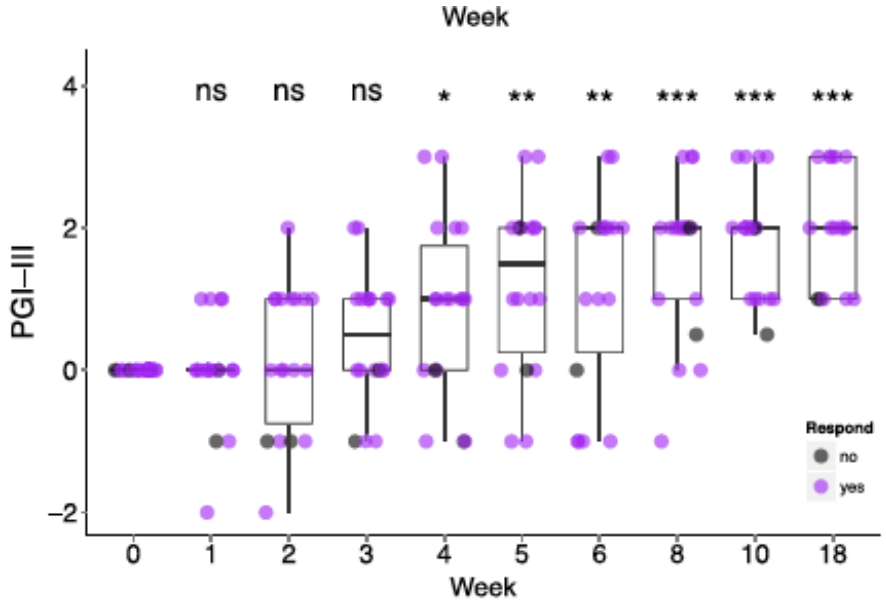
Donor = primary school girl

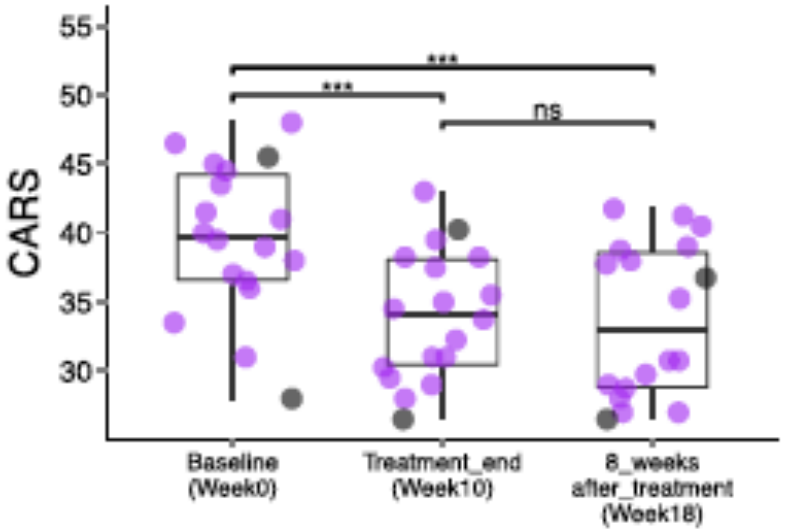
During the 20 mo of follow-up, FMT has proved its efficacy in preventing relapse of seizures after withdrawing the antiepileptic drugs

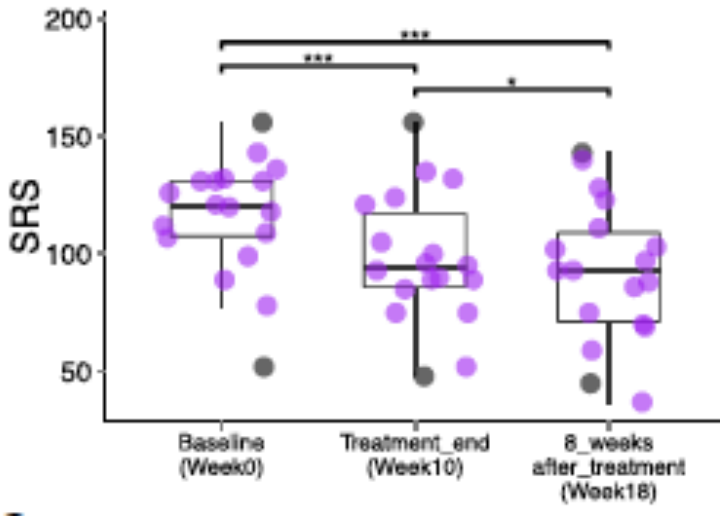
Autisme

18 enfants (7-16 ans)
Etude ouverte
Autisme + troubles digestifs
Traitement 10 semaines
Suivi 8 semaines après l'arrêt









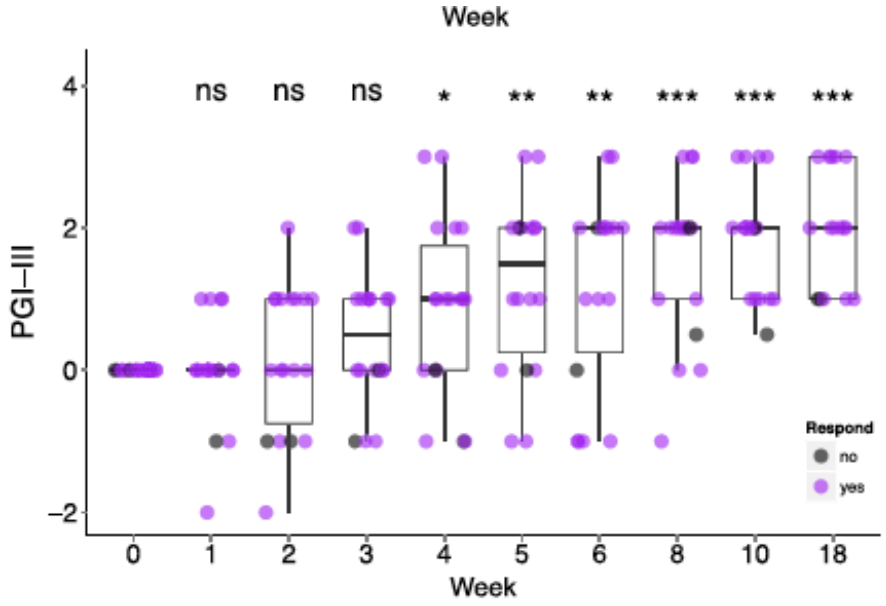
Kang et al. Microbiome (2017)

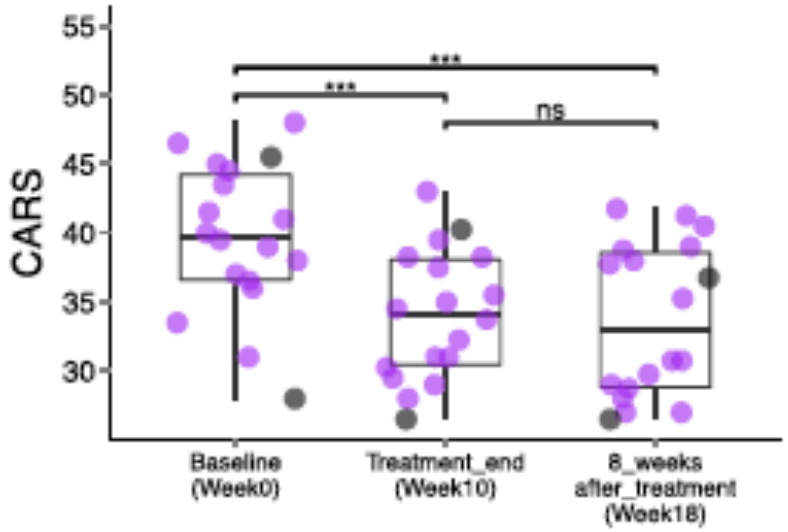
Autisme

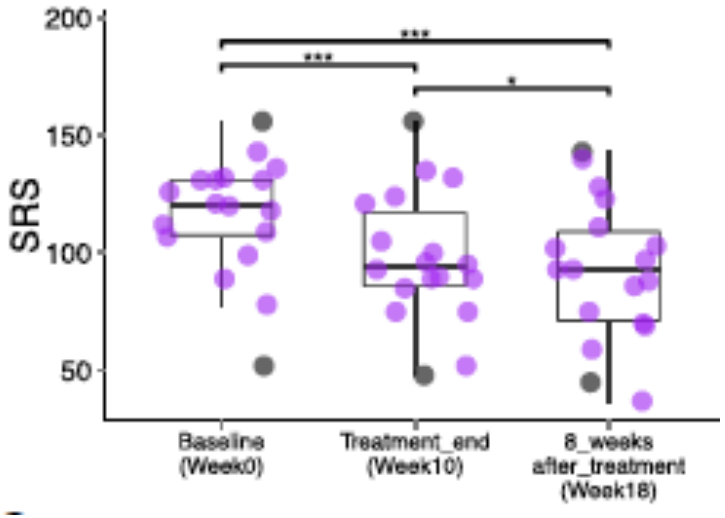
18 enfants (7-16 ans)
Etude ouverte
Autisme + troubles digestifs
Traitement 10 semaines
Suivi 8 semaines après l'arrêt

Effet de
- la Vancomycine ?
- la dose initiale ?
- la dose de maintenance ?
- les IPP ?

Effet placebo ?





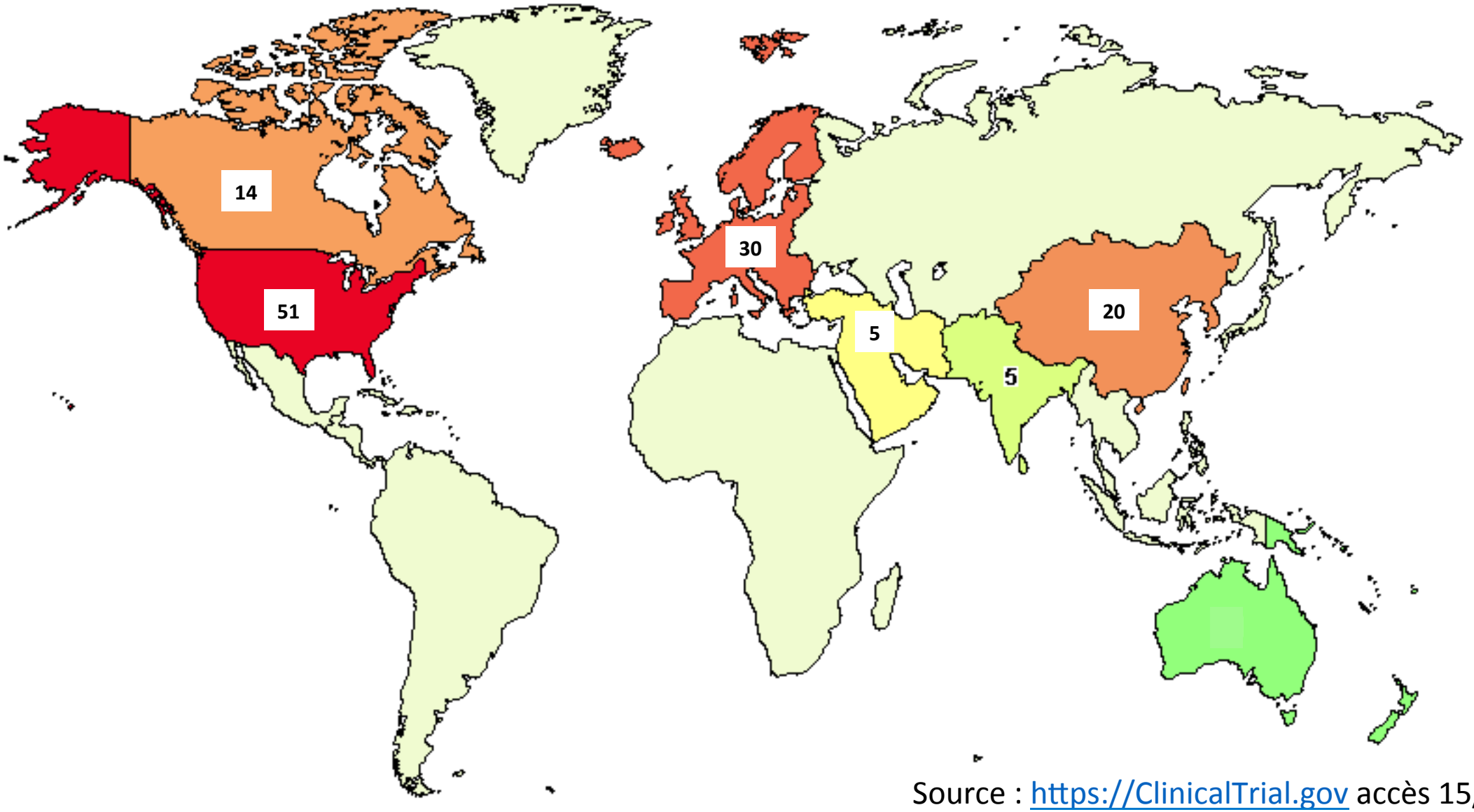


Kang et al. Microbiome (2017)

Essais cliniques en cours (hors IBD) aux USA …

Nonalcoholic steatohepatitis	Open-label interventional trial	5
Human I immunodeficiency virus (HIV)	Open-label interventional trial	12
Primary sclerosing cholangitis (PSC)	Open-label interventional trial	5
Irritable bowel syndrome	Randomized, double-blind interventional trial	16
	Multicenter, randomized, double-blind, placebo-controlled trial	110
Pancreatitis	Randomized, single blind interventional trial	60
Eradication of multidrug-resistant organism	Interventional open-label trial	20
	Interventional, multicenter open-label, randomized controlled trial	64
	Interventional open label	20
	Observational trial	50
Metabolic syndrome, obesity and diabetes	Placebo-controlled trial	20
	Randomized, controlled, double-blind trial	30

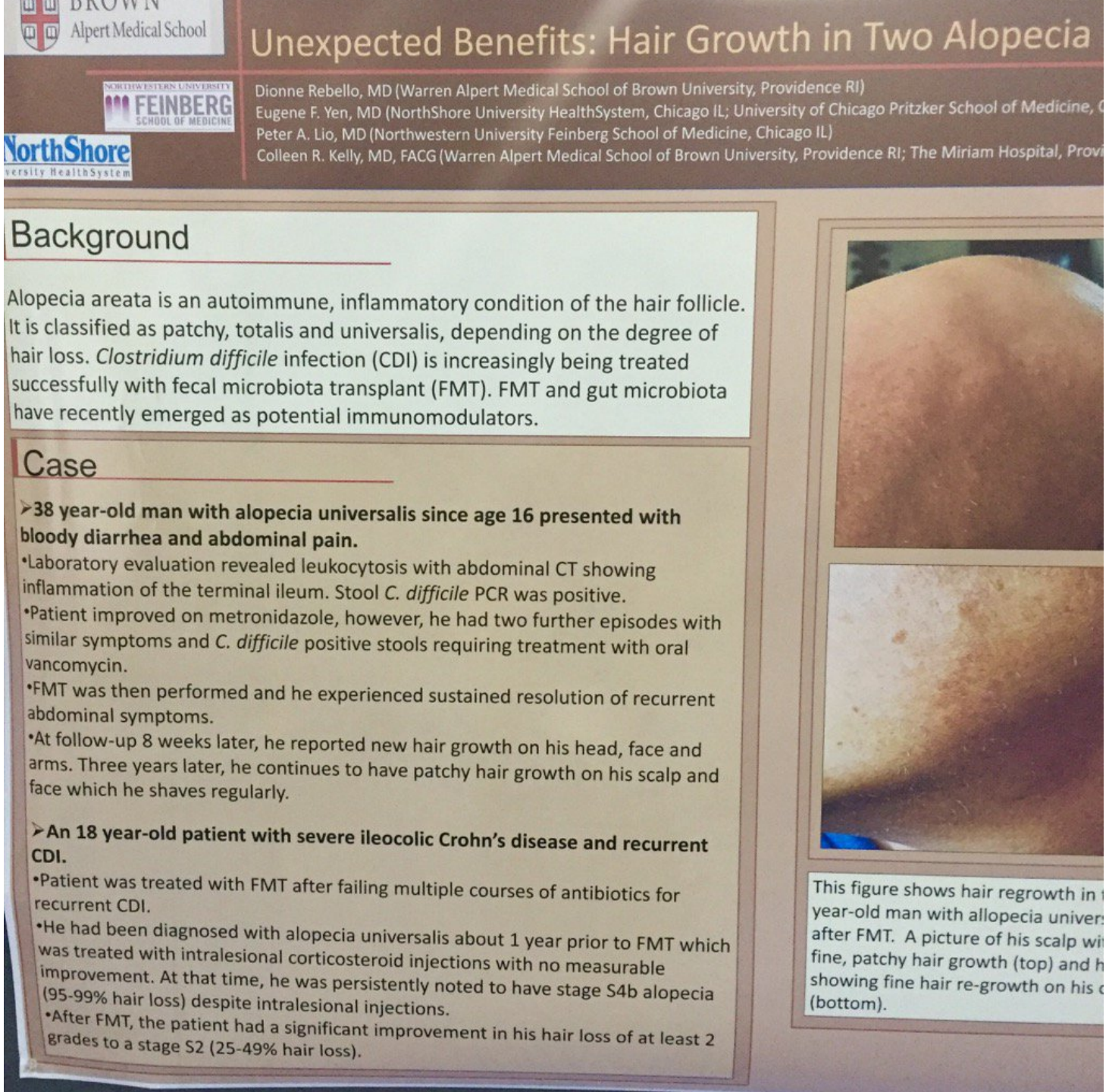
95 Essais cliniques en cours (hors IBD) …



Source : https://ClinicalTrial.gov accès 15/06/2017

Abdominal Obesity Metabolic Syndrome 3 studies
Acquired Immunodeficiency Syndrome 3 studies
Acute Graft Versus Host Disease 1 study
Acute Myeloid Leukemia 2 studies
Acute-On-Chronic Liver Failure 1 study
Alcohol-Related Disorders 2 studies
Arthritis, Infectious 1 study
Arthritis, Psoriatic 1 study
Autoimmune Diseases 2 studies
Bacterial Infections 2 studies
Basal Ganglia Diseases 1 study
Biliary Tract Diseases 1 study
Body Weight 4 studies
Bone Diseases 1 study
Central Nervous System Diseases 6 studies
Cholangitis, Sclerosing 1 study
Chronic Intestinal Pseudoobstruction 1 study
Confusion 1 study
DNA Virus Infections 1 study
Diabetes Mellitus 5 studies
Diabetes Mellitus, Type 2 3 studies
Dilatation, Pathologic 1 study
Disease Attributes 2 studies
End Stage Liver Disease 1 study
Endocrine System Diseases 5 studies
Enterocolitis 3 studies
Enterovirus Infections 1 study
Epilepsy 1 study
Fatty Liver 3 studies
Fecal Impaction 1 study
Fever 1 study
Fibrosis 6 studies
Food Hypersensitivity 1 study
Ganglion Cysts 1 study
Gastroenteritis 50 studies
Glucose Metabolism Disorders 7 studies
Graft vs Host Disease 3 studies
Gram-Positive Bacterial Infections 2 studies
HIV Infections 3 studies
Hepadnaviridae Infections 1 study
Hepatic Encephalopathy 4 studies
Hepatic Insufficiency 5 studies
Hepatitis A 3 studies
Hepatitis B 1 study
Homologous Wasting Disease 3 studies
Hypersensitivity 1 study
Idiopathic Thrombocytopenic Purpura 1 study
Ileitis 3 studies
Ileus 1 study
Immune System Diseases 7 studies
Immunologic Deficiency Syndromes 1 study
Insulin Resistance 4 studies
Irritable Bowel Syndrome 11 studies
Lentivirus Infections 1 study
Malnutrition 1 study
Metabolic Diseases 11 studies
Metabolic Syndrome X 3 studies
Movement Disorders 1 study
Multiple Sclerosis 1 study
Musculoskeletal Diseases 2 studies
Nasal Polyps 1 study
Neoplasms by Histologic Type 2 studies
Neurobehavioral Manifestations 1 study
Neurodegenerative Diseases 1 study
Non-alcoholic Fatty Liver Disease 3 studies
Nutrition Disorders 4 studies
Obesity 7 studies
Otorhinolaryngologic Diseases 1 study
Pancreatitis 3 studies
Parkinson Disease 1 study
Peanut Hypersensitivity 1 study
Peritonitis 1 study
Picornaviridae Infections 1 study
Primary Sclerosing Cholangitis 1 study
Pseudomonas Infections 1 study
Psoriasis 1 study
Respiratory Tract Infections 1 study
Retroviridae Infections 1 study
Severe Acute Malnutrition 1 study
Sexually Transmitted Diseases, Viral 1 study
Sinusitis 1 study
Skin Diseases, Papulosquamous 1 study
Spondylarthritis 1 study
Staphylococcal Infections 1 study
Substance-Related Disorders 2 studies
Synovial Cyst 1 study
Thrombotic Microangiopathies 1 study
Ulcer 30 studies
Urinary Tract Infections 1 study

Fantaisiste ?



Alpert Medical School

Unexpected Benefits: Hair Growth in Two Alopecia

Dionne Rebello, MD (Warren Alpert Medical School of Brown University, Providence RI)
Eugene F. Yen, MD (NorthShore University HealthSystem, Chicago IL; University of Chicago Pritzker School of Medicine,
Peter A. Lio, MD (Northwestern University Feinberg School of Medicine, Chicago IL)
Colleen R. Kelly, MD, FACG (Warren Alpert Medical School of Brown University, Providence RI; The Miriam Hospital, Provi

Background

Alopecia areata is an autoimmune, inflammatory condition of the hair follicle. It is classified as patchy, totalis and universalis, depending on the degree of hair loss. *Clostridium difficile* infection (CDI) is increasingly being treated successfully with fecal microbiota transplant (FMT). FMT and gut microbiota have recently emerged as potential immunomodulators.

Case

➢**38 year-old man with alopecia universalis since age 16 presented with bloody diarrhea and abdominal pain.**

- Laboratory evaluation revealed leukocytosis with abdominal CT showing inflammation of the terminal ileum. Stool *C. difficile* PCR was positive.
- Patient improved on metronidazole, however, he had two further episodes with similar symptoms and *C. difficile* positive stools requiring treatment with oral vancomycin.
- FMT was then performed and he experienced sustained resolution of recurrent abdominal symptoms.
- At follow-up 8 weeks later, he reported new hair growth on his head, face and arms. Three years later, he continues to have patchy hair growth on his scalp and face which he shaves regularly.

➢**An 18 year-old patient with severe ileocolic Crohn's disease and recurrent CDI.**

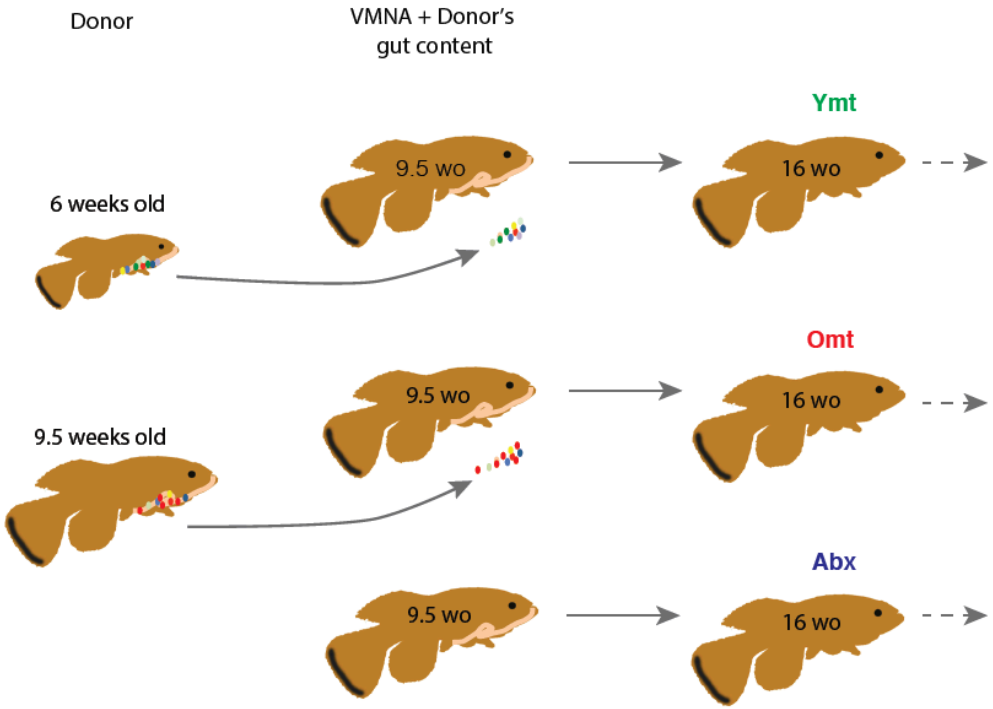
- Patient was treated with FMT after failing multiple courses of antibiotics for recurrent CDI.
- He had been diagnosed with alopecia universalis about 1 year prior to FMT which was treated with intralesional corticosteroid injections with no measurable improvement. At that time, he was persistently noted to have stage S4b alopecia (95-99% hair loss) despite intralesional injections.
- After FMT, the patient had a significant improvement in his hair loss of at least 2 grades to a stage S2 (25-49% hair loss).

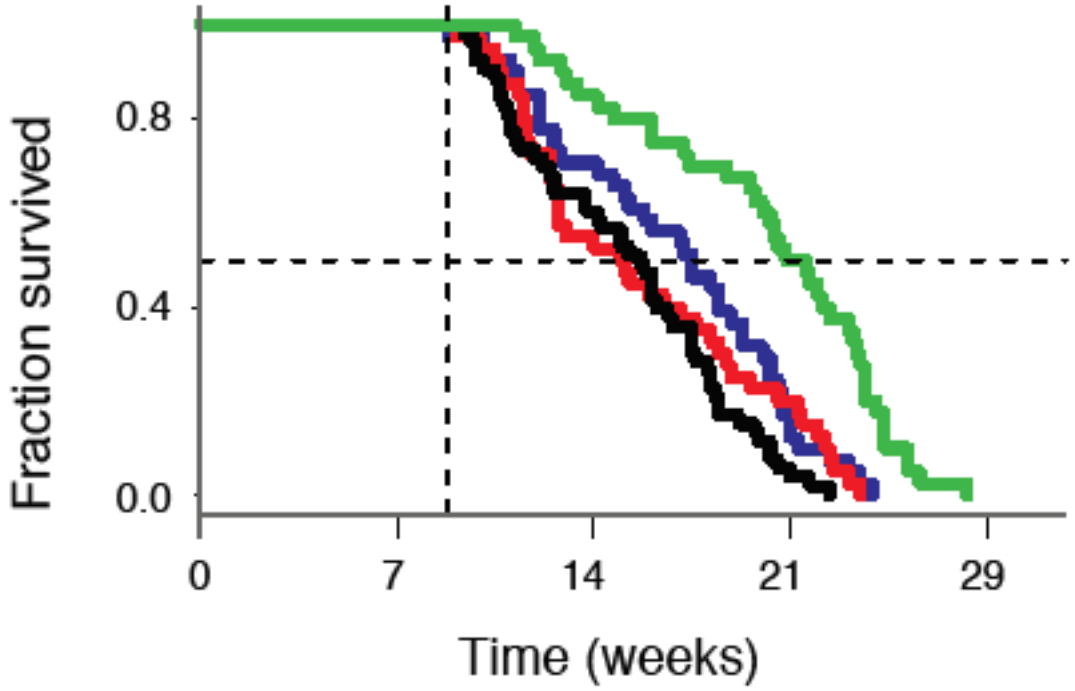
This figure shows hair regrowth in
year-old man with allopecia univers
after FMT. A picture of his scalp wi
fine, patchy hair growth (top) and h
showing fine hair re-growth on his
(bottom).

Le graal !!!!

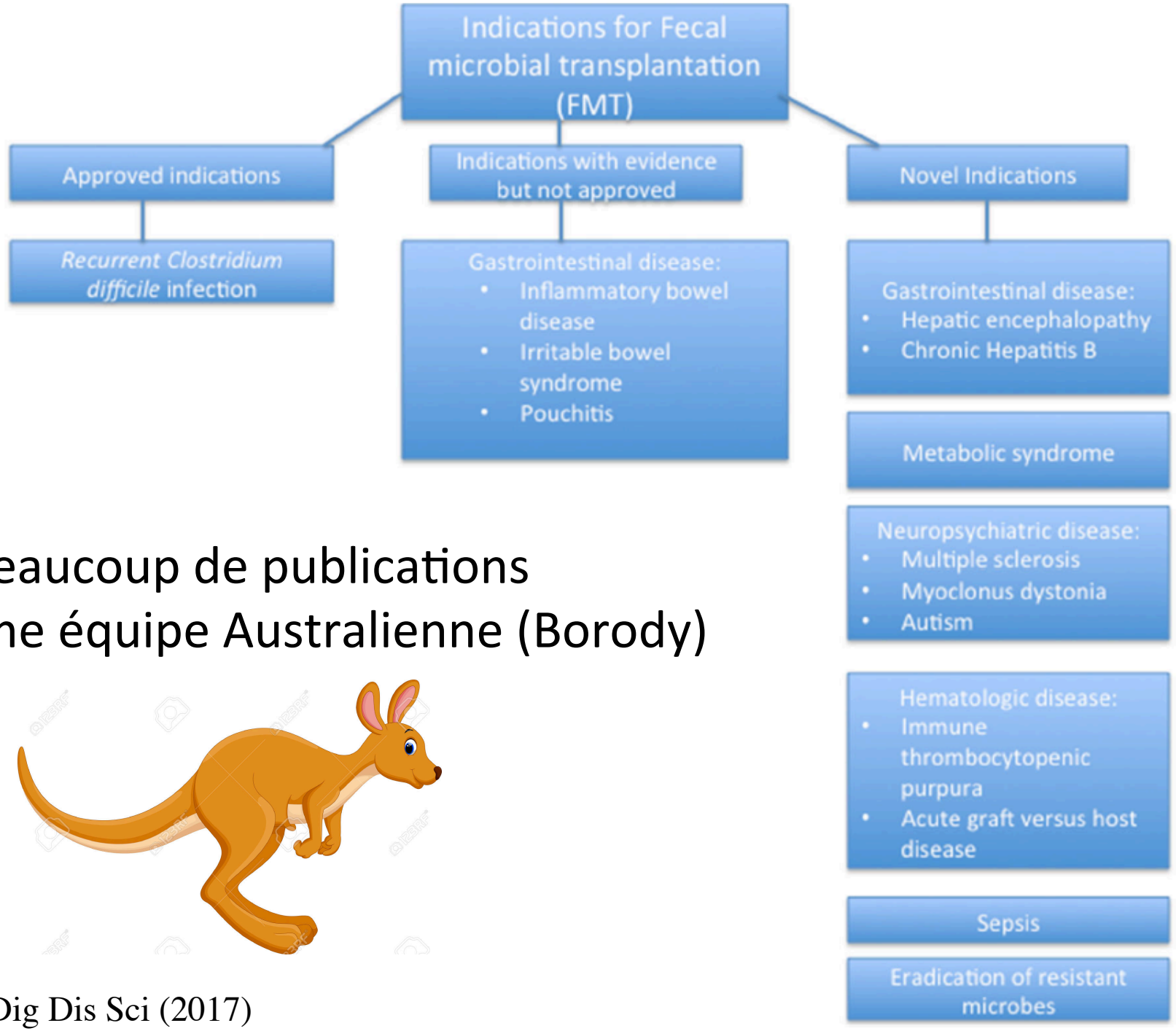








Median lifespan was 41% longer



Beaucoup de publications
de la même équipe Australienne (Borody)

Cohen, Maharshak. Dig Dis Sci (2017)

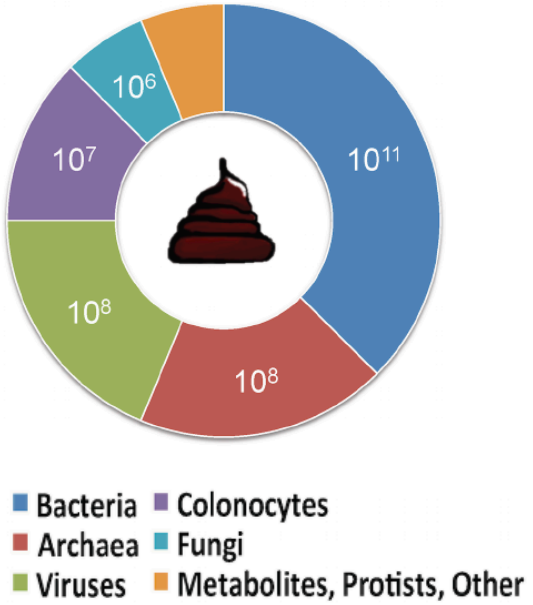
La FMT hors *C difficile*

- Multiples FMT : intérêt des capsules !!!

- Choix du donneur en fonction des caractéristiques de son microbiote
  - Richesse/diversité
  - Espèces bactériennes
  - Fonctions microbiennes
  - Acides gras chaîne courte
  - …

- Donneur enfant ?

- Receveur : préparation ? Match avec donneur ?



PLoS Biol14(7): e1002503

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LA MICRONUTRITION

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