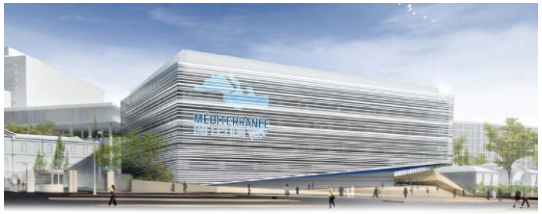
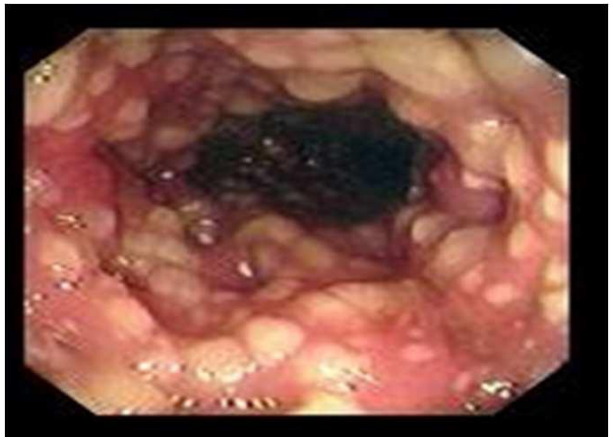
Transplantation fécale : techniques, indications, réglementation

Matthieu MILLION
IHU Méditerranée Infection, Marseille
13 juin 2019



Clostridium difficile



- Bacille à gram positif sporulé

-1er agent de diarrhée infectieuse nosocomiale

- Agent communautaire émergent

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journal homepage: http://www.elsevier.com/locate/ijantimicag

Clostridium difficile infections: do we know the real dimensions of the problem?

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Eur J Clin Microbiol Infect Dis (2012) 31:2263–2267
DOI 10.1007/s10096-012-1565-2

ARTICLE

***Clostridium difficile* O27 colitis: Hospital-onset but community-acquired**

S. Buffet-Bataillon · P. Tattevin · H. Sénéchal · M. Cormier · P. Vincent

Formes asymptomatiques :
5 à 7% des enfants

Traitement :
Metronidazole
Vancomycine
Fidaxomicine

MÉDITERRANÉE INFECTION

REVIEW 10.1111/1469-0691.12795

Faecal microbiota transplantation: from practice to legislation before considering industrialization

J.-C. Lagier[1,2]

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Reference	No. of patients	Patients with resolution, no. (%)[a]
Schwan et al [20]	1	1 (100.0)
Tvede et al [48]	2	1 (50.0)
Flotterod et al [49]	1	1 (100.0)
Paterson et al [50]	1	1 (100.0)
Paterson et al [50]	6	6 (100.0)
Lund-Tonnesen et al [18]	18	15 (83.3)
Persky et al [51]	1	1 (100.0)
Borody et al [452]	6	6 (100.0)
Aas et al [53]	18	15 (83.3)
Jorup- Ronstrom et al [54]	5	4 (80.0)
Wettstein et al [55]	16	15 (93.7)
Louie et al [56]	45	44 (97.7)
Nieuwdorp et al [57]	7	7 (100.0)
You et al [58]	1	1 (100.0)
Hellemans et al [59]	1	1 (100.0)
MacConnachie et al [60]	15	12 (80.0)
Khoruts et al [61]	1	1 (100.0)
Garborg et al [17]	40	33 (82.5)
Rohlke et al [62]	19	19 (100.0)
Russell et al [63]	1	1 (100.0)
Silverman et al [64]	7	7 (100.0)
Yoon et al [24]	12	12 (100.0)
T. Moore (unpublished)	65	64 (98.5)
Cutolo et al [65]	1	1 (100.0)
Eiseman et al [10]	4	4 (100.0)
Fenton et al [66]	1	1 (100.0)
Bowden et al [67]	16	13 (81.2)
Faust et al [68]	6	6 (100.0)

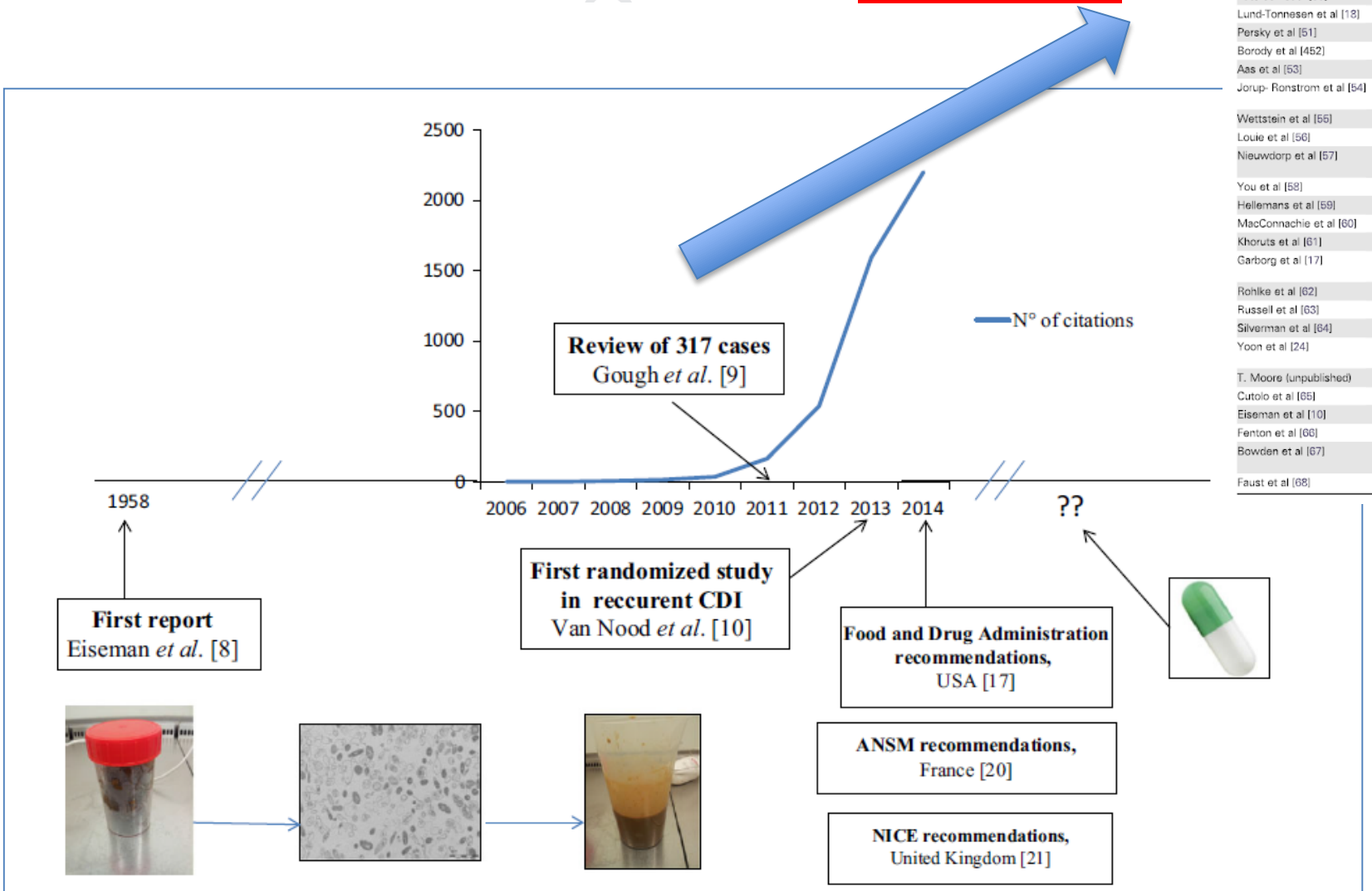
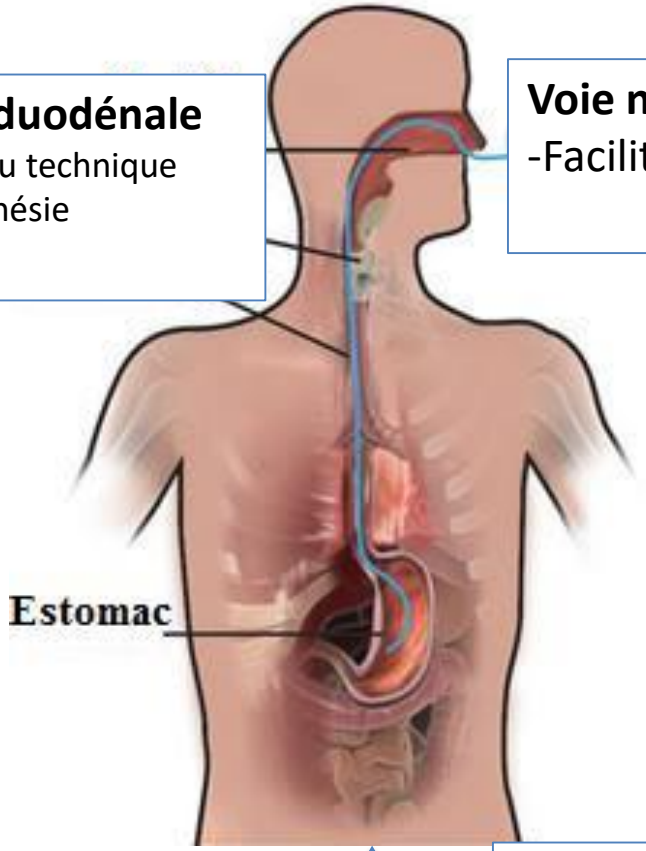


FIG. 1. Scientific and regulatory key events from 1858 to 2014 in faecal microbiota transplantation. We found an increasing number of citations by using the ISI web of knowledge and 'fecal microbiota transplantation' as the keyword. CDI, *Clostridium difficile* infection.

Voies d'administration

Voie duodénale
-Plateau technique
-Anesthésie

Voie naso-gastrique
-Facilité



Voie rectale
-Lavement
-Coloscopie
-Anesthésie / plateau technique

Formes récurrentes d'infections à CD

BACKGROUND

Recurrent *Clostridium difficile* infection is difficult to treat, and failure rates for antibiotic therapy are high. We studied the effect of duodenal infusion of donor feces in patients with recurrent *C. difficile* infection.

METHODS

We randomly assigned patients to receive one of three therapies: an initial vancomycin regimen (500 mg orally four times per day for 4 days), followed by bowel lavage and subsequent infusion of a solution of donor feces through a nasoduodenal tube; a standard vancomycin regimen (500 mg orally four times per day for 14 days); or a standard vancomycin regimen with bowel lavage. The primary end point was the resolution of diarrhea associated with *C. difficile* infection without relapse after 10 weeks.

RESULTS

The study was stopped after an interim analysis. Of 16 patients in the infusion group, 13 (81%) had resolution of *C. difficile*–associated diarrhea after the first infusion. The 3 remaining patients received a second infusion with feces from a different donor, with resolution in 2 patients. Resolution of *C. difficile* infection occurred in 4 of 13 patients (31%) receiving vancomycin alone and in 3 of 13 patients (23%) receiving vancomycin with bowel lavage ($P<0.001$ for both comparisons with the infusion group). No significant differences in adverse events among the three study groups were observed except for mild diarrhea and abdominal cramping in the infusion group on the infusion day. After donor-feces infusion, patients showed increased fecal bacterial diversity, similar to that in healthy donors, with an increase in Bacteroidetes species and clostridium clusters IV and XIVa and a decrease in Proteobacteria species.

CONCLUSIONS

The infusion of donor feces was significantly more effective for the treatment of recurrent *C. difficile* infection than the use of vancomycin. (Funded by the Netherlands Organization for Health Research and Development and the Netherlands Organization for Scientific Research; Netherlands Trial Register number, NTR1177.)

Van Nood, NEJM, 2013

Formes récurrentes d'infections à CD

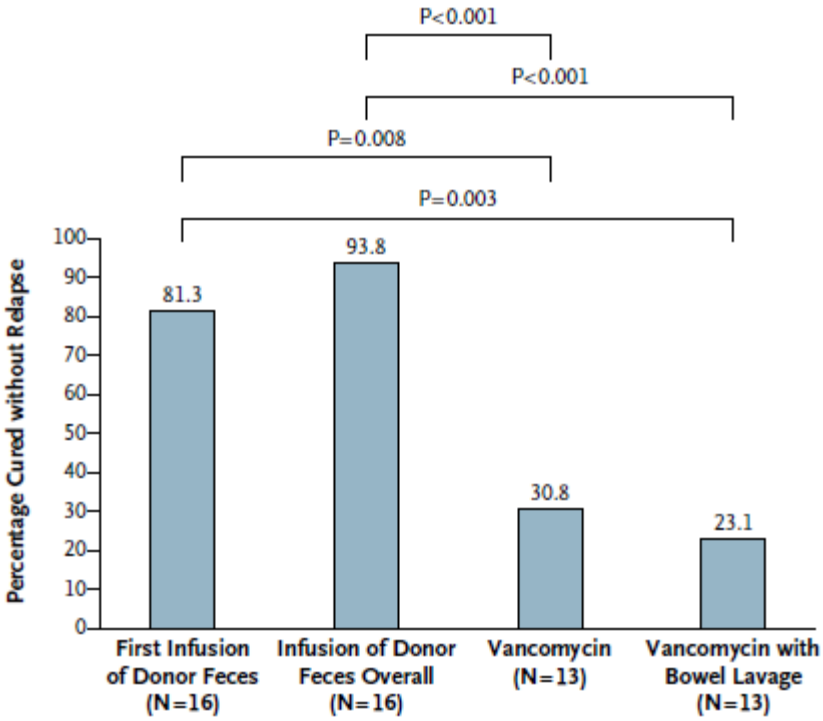


Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.

Shown are the proportions of patients who were cured by the infusion of donor feces (first infusion and overall results), by standard vancomycin therapy, and by standard vancomycin therapy plus bowel lavage.

Table 2. Adverse Events in 16 Patients in the Infusion Group.*

Adverse Event	On Day of Infusion of Donor Feces	During Follow-up
	no. of events	
Belching	3	0
Nausea	1	0
Vomiting	0	0
Abdominal cramps	5	0
Diarrhea	15	0
Constipation	0	3
Abdominal pain	2 (associated with cramping)	0
Infection	0	2†
Hospital admission	NA	1‡
Death	0	0
Other adverse event	1§	1‡

Van Nood, NEJM, 2013

Formes récurrentes d'infections à CD

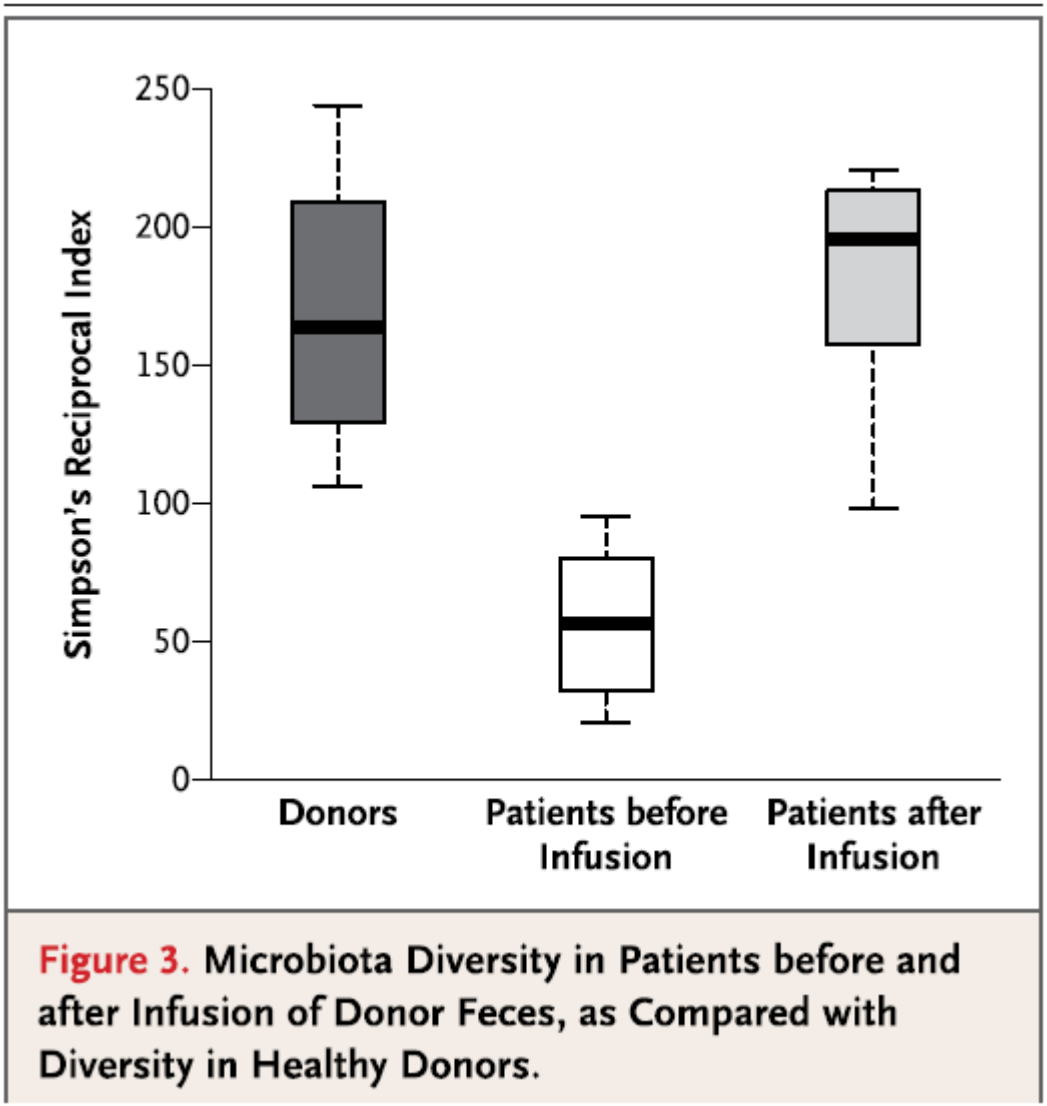


Figure 3. Microbiota Diversity in Patients before and after Infusion of Donor Feces, as Compared with Diversity in Healthy Donors.

Diminution de la diversité chez les patients

Restaurée 2 semaines après

Van Nood, NEJM, 2013

Formes récurrentes d'infections à CD

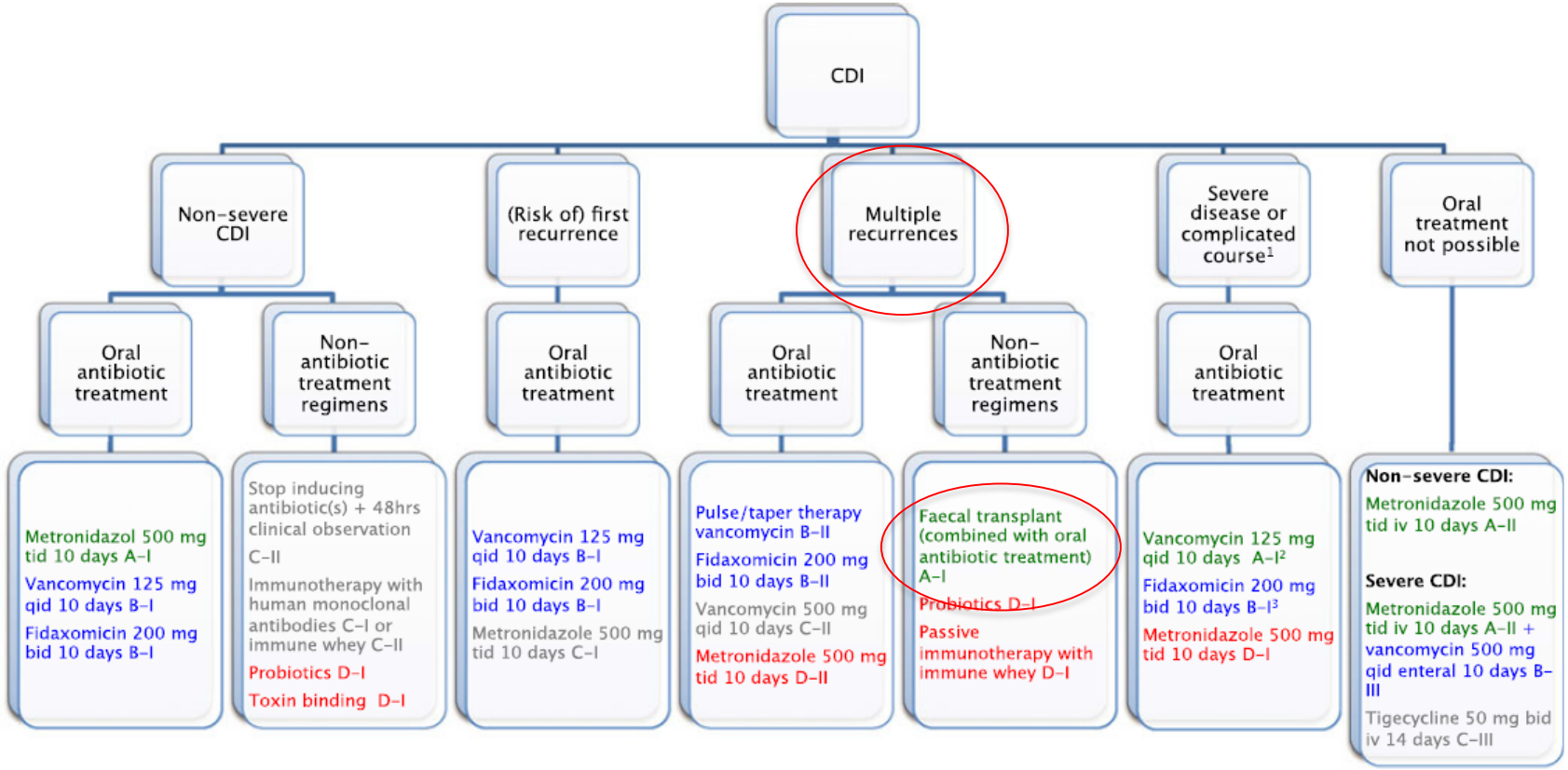
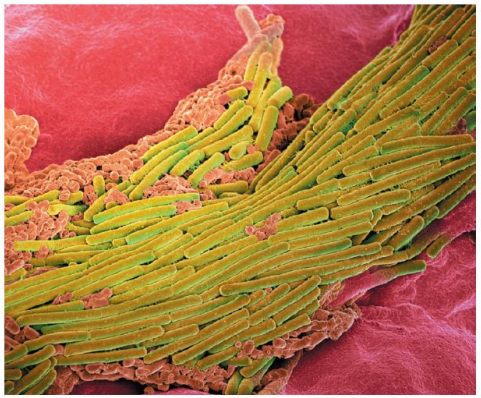


FIG. 1. Schematic overview of therapeutic regimens for *Clostridium difficile* infection (CDI). [1]Severe CDI or complicated course: surgical therapy not included in this overview; [2]It can be considered to increase the oral dosage of vancomycin to 500 mg four times daily for 10 days (B-III); [3]There is no evidence that supports the use of fidaxomicin in life-threatening CDI (D-III); Strength of Recommendation (SoR) A = green (Strongly supports a recommendation for use); SoR B = blue (Moderately supports a recommendation for use); SoR C = grey (Marginally supports a recommendation for use); SoR D=red (Recommendation against use).

Régulation / Règlementation



Clostridium difficile (yellow cells) causes an intestinal infection that can be treated with processed stool.

How to regulate faecal transplants

For medical use, human stool should be considered a tissue, not a drug, argue **Mark B. Smith**, **Colleen Kelly** and **Eric J. Alm**.

Fecal transplants to follow FDA rules

US Food and Drug Administration (FDA) officials in April declared that fecal microbiota transplants (FMT) will be considered and regulated as biologic drugs. Anyone conducting such procedures is now required to file an investigational new drug application (IND). Although this regulatory change began taking shape two years ago, the April announcement brought forth critics and fans. The latter see this regulatory stance as perhaps enhancing prospects for companies developing products within this particular microbiota-related R&D space. But physicians currently evaluating FMT in patients express frustration as well as outright anger with FDA.

"FDA determined that fecal microbiota meets the definition of a drug and a biologic product and an IND is required to conduct studies in humans, even when [investigators] are not planning to develop a commercial product," says Jay Slater, director of the Division of Bacterial, Parasitic and Allergenic Products within the FDA Center for Biologics Evaluation and Research. "Defining the product is nontrivial, such as what are the active ingredients, potency, stability and consistency." FDA also says that, as it develops guidelines, it will exercise "enforcement discretion" when dealing with physicians who find the IND path burdensome so long as they obtain "adequate informed consent" from patients.

The first concern is safety, with a focus on identifying pathogens that might be present in donor samples for FMT, according to Phillip Tarr of Washington University School of Medicine in St. Louis. Another concern is that such material might carry antibiotic-resistance determinants. If not controlled, those or other risk factors could compound the clinical problems of patients with severe diarrhea caused by *Clostridium difficile*, the infection for which FMT is now being evaluated.

Several university-based investigators who are working with such patients say that, instead of INDs, they would prefer that federal officials establish a patient registry to track any adverse effects of FMT. David Berry, co-founder and chairman of Seres Health in Cambridge, Massachusetts. "A registry would be a step in the right direction, but would not give the same safety benefits to patients as an IND." The company, which is not pursuing FMT but is interested in microbiota and human health, sent more than half-a-dozen representatives to a workshop convened by FDA and National Institutes of Health officials on May 2 and 3, in Bethesda, Maryland.

For physicians, the prospect of agency oversight is daunting, says Colleen Kelly of Brown University Women's Medicine Collaborative, who holds two INDs for FMT clinical research. "When I was told I had to get these INDs, I had absolutely no idea where to start. FDA is used to dealing with companies and industry and regulatory experts, not people like us," she says. Kelly believes the way forward is standardized products, and this will probably happen through industry.

"We're creating an off-the-shelf product, [and] we are the first company to apply to the FDA for a microbiota restoration therapy product," says Lee Jones, who is CEO of Rebiotix in Roseville, a suburb of Minneapolis. "Our IND runs to 1,500 pages and it took more than one year and $2 million." The company's intellectual property position is "strong," she adds, and further helps to give it a "head start" over competitors.

Other companies have competing products to treat patients infected with *C. difficile*, whereas still others are developing

them. For instance, ViroPharma of Exton, Pennsylvania, markets an oral version of vancomycin, an antibiotic used for treating such patients but whose overuse can lead to such infections. The company's VP20621, a nontoxin-producing strain of that bacterium, which is in a phase 2 clinical trial, could be used much like FMT to recolonize the gastrointestinal tract and alleviate such infections. The company declined to comment on FDA's approach to regulating FMT.

Monarch Labs of Irvine, California, currently a supplier of FDA-approved maggots for medical use, in June announced plans to commercialize FMT products. "Monarch is seeking to be a controlled supplier of CGMP-processed FMT material," says its chairman James Kuo.

But companies commercializing FMT products will face a series of unknowns. "We deal with antibiotics and understand the regulatory process pretty well," says Barry Eisenstein of Cubist Pharmaceuticals in Lexington, Massachusetts. In 2011, FDA approved Dificid (fidaxomicin), a macrocyclic antibiotic jointly marketed by Cubist and Optimer Pharmaceuticals of San Diego, for treating *C. difficile* infections. For FMT, however, "There seems to be a continuum from the nonphysician home brew to the doctor's office to the more standardized medical centers to a product from industry to a mixture of well-defined components [bacterial cultures] that could be put together," he says. "Going from one end of the continuum to another, you're getting increasing standardization and opportunity to better study and understand potency, efficacy and safety—and, also, opportunities to commercialize. How [does FDA] regulate the individual at home who calls one of the gastroenterologists and tries to get some advice? I don't understand how that works."

FDA officials admit to confusion on that score, too.

Jeffrey L Fox

NATURE BIOTECHNOLOGY VOLUME 31 NUMBER 7 JULY 2013

La transplantation de microbiote fécal et son encadrement dans les essais cliniques

Mars 2014

Guidance for Industry

Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat *Clostridium difficile* Infection Not Responsive to Standard Therapies

Public Health England

Updated guidance on the management and treatment of *Clostridium difficile* infection

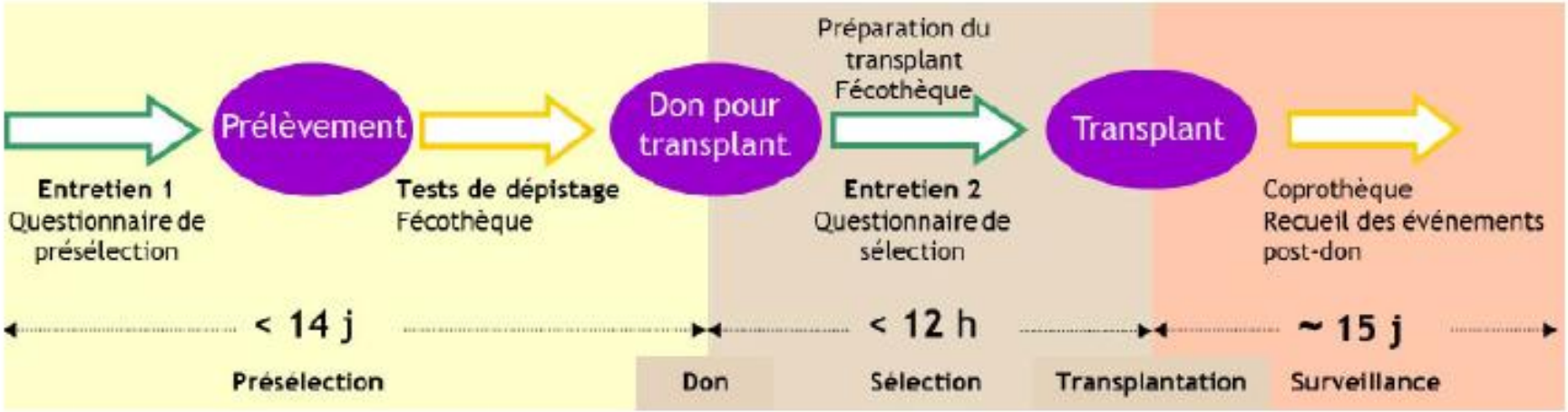
Régulation / Règlementation

En France

A ce jour, le Code de la Santé publique ne prévoit pas de statut particulier pour le microbiote fécal.

Toutefois, dans la mesure où le microbiote fécal est utilisé à visée curative à l'égard de maladies humaines, il doit être considéré comme un **médicament** conformément à l'article L. 5111-1 du Code de la Santé publique, qui définit un médicament comme « toute substance ou composition présentée comme possédant des propriétés curatives ou préventives à l'égard des maladies humaines ou animales, ainsi que toute substance ou composition pouvant être utilisée chez l'homme ou chez l'animal ou pouvant leur être administrée, en vue d'établir un diagnostic médical ou de restaurer, corriger ou modifier leurs fonctions physiologiques en exerçant une action pharmacologique, immunologique ou métabolique. *[...]* ».

Régulation / Règlementation



Régulation / Règlementation

Tableau 1 – Questionnaire de présélection (items spécifiques au don de selles)

INFORMATIONS	CRITERES DE NON INCLUSION ABSOLUE	CRITERES DE NON INCLUSION « RELATIVE » (à justifier)
Co-morbidités	▪ Donneur avec une **pathologie chronique connue** ▪ Antécédent de **fièvre typhoïde** ▪ Troubles digestifs (diarrhée aiguë ou chronique) dans les 3 mois précédant le don	Donneurs avec antécédents familiaux : - MICI (lien de parenté) - maladies auto-immunes (lien de parenté) - cancer colique (lien de parenté et âge d'apparition)
Traitement médicamenteux	Donneur suivant un **traitement curatif au long cours**	Donneur traité par anti-infectieux au cours des 3 mois précédant le don[3]
Voyages	▪ **Séjour en zone intertropicale** au cours des 3 mois précédant le don ▪ Résidence de plusieurs années en zone intertropicale ▪ **Hospitalisations à l'étranger** de plus de 24h dans les 12 derniers mois (y compris membres de l'entourage du donneur)[1]	/
Âge	Donneur mineur[2]	Donneur âgé (>65 ans)[4]
Statut pondéral	/	Donneur avec IMC>30[5]

Régulation / Règlementation

Tableau 2 – Questionnaire de sélection / Evènements depuis la visite de présélection

CRITERES DE NON INCLUSION	INCLUSION SUR LA BASE D'UNE APPRECIATION INDIVIDUELLE
▪ **Episode de diarrhée** (>3 selles molles à liquide /j) chez le donneur ou les membres de son entourage ▪ Situations à **risque de contamination :** - **Voyage à l'étranger** - **Contact avec du sang humain** (piercing, tatouage, piqûre, plaie, projection, soins dentaires…) - **Comportement sexuel à risque** - Présence de **lésions anales** (afin de limiter le risque de transmission du virus du papillome humain et des virus de l'herpès)	**Recherche des évènements suivants :** ▪ Consultation médicale (motif) ▪ Maladie contractée (laquelle, date et durée) ▪ Prise de médicaments (lesquels, date de la dernière prise)

Régulation / Règlementation

Pour résumer : profil « idéal » du donneur

- Age : 18-65 ans
- IMC<30
- Absence de pathologies chroniques
- Absence de traitement curatif au long cours
- Absence de prise d'antibiotiques dans les 3 mois précédant le don
- Absence de séjour à l'étranger dans les 3 mois précédant le don
- Absence de résidence de plusieurs années en zone intertropicale
- Absence d'hospitalisation à l'étranger dans les 12 mois précédant le don
- Absence de troubles digestifs à type de diarrhée aigüe ou chronique dans les 3 mois précédant le don
- Absence d'antécédents de fièvre typhoïde
- Aspect macroscopique normal des selles
- Dépistage négatif d'agents infectieux *(cf. liste proposée en annexe 1)*

Régulation / Règlementation

Conclusions

1. Le microbiote fécal répond à la définition d'un **médicament** dont la préparation relève de la responsabilité d'une **Pharmacie à Usage Intérieur**.

2. L'encadrement du risque pour un patient faisant l'objet d'une transplantation de microbiote fécal repose sur les éléments suivants :
a) **Utilisation dans le cadre d'essais cliniques** autorisés par l'ANSM
b) **Sélection rigoureuse et standardisée des donneurs :** questionnaire, entretien médical et dépistage d'agents infectieux dans le sang et les selles
c) **Traçabilité** du produit

Régulation / Règlementation

Annexe 1 – Liste des agents infectieux à dépister chez les donneurs

Toute dérogation à cette liste devra impérativement être justifiée.

	SANG	SELLES
Bactéries	▪ *Treponema pallidum*	Coproculture standard et orientée: ▪ *Clostridium difficile* ▪ *Listeria monocytogenes* ▪ *Vibrio cholerae / Vibrio parahemolyticus* ▪ *Salmonella* ▪ *Shigella* ▪ Bactéries multirésistantes aux antibiotiques ▪ *Campylobacter sp*
Virus[1]	▪ Virus de l'immunodéficience humaine (HIV)[2] ▪ Virus T-lymphotropique humain (HTLV) ▪ Virus des hépatites B et C (HVB[2] HVC[2]) ▪ Cytomégalovirus (CMV) / Virus Epstein-Barr (EBV)[3]	▪ Adénovirus ▪ Astrovirus ▪ Calcivirus (norovirus, sapovirus) ▪ Picornavirus (entérovirus, Virus Aichi) ▪ Rotavirus ▪ Virus des hépatites A et E
Parasites	▪ *Strongyloïdes stercoralis* ▪ *Toxoplasma gondii*[3] ▪ *Trichinella sp.* ▪ Amibiase	▪ *Strongyloïdes stercoralis* ▪ *Cryptosporidium sp.* ▪ *Cyclospora sp.* ▪ *Entamoeba histolytica* ▪ *Giardia intestinalis* ▪ *Isospora sp.* ▪ *Microsporidies* ▪ *Blastocystis hominis* ▪ *Dientamoeba fragilis*

[1]Les virus sont recherchés dans les selles à l'aide de tests de biologie moléculaire par PCR
[2]Charge virale (PCR) en plus de la sérologie
[3]Uniquement pour vérifier l'absence de séro-discordance avec le receveur

La transplantation de microbiote fécal et son encadrement dans les essais cliniques

Novembre 2016 (Actualisation de la version de juin 2015)

Les mesures de sécurité décrites dans ce document correspondent aux exigences requises dans le cadre des essais cliniques portant sur la transplantation de microbiote fécal. Cette procédure peut également être utilisée en dehors des essais cliniques, par le biais de préparations magistrales sous la responsabilité d'une PUI (Pharmacie à usage intérieur). Dans ce cas, l'application rigoureuse des mesures définies ci-après est laissée à l'appréciation du médecin, au cas par cas, selon le caractère urgent de la situation et sur la base d'une évaluation du bénéfice escompté chez un patient donné eu égard aux risques liés à la transplantation de microbiote fécal. A ce jour, le traitement des infections récidivantes à Clostridium difficile représente la seule indication pour laquelle nous disposons de données relativement bien étayées concernant l'efficacité de la transplantation de microbiote fécal.

Dig Liver Dis. 2016 Mar;48(3):242-7. doi: 10.1016/j.dld.2015.08.017. Epub 2015 Sep 7.

Faecal microbiota transplantation in recurrent Clostridium difficile infection: Recommendations from the French Group of Faecal microbiota Transplantation.

Sokol H[1], Galperine T[2], Kapel N[3], Bourlioux P[4], Seksik P[5], Barbut F[6], Scanzi J[7], Chast F[8], Batista R[8], Joly F[9], Joly AC[10], Collignon A[11], Guery B[2], Beaugerie L[5]; French Group of Faecal microbiota Transplantation (FGFT).

⊕ Collaborators (54)

⊕ Author information

Abstract

Faecal microbiota transplantation is effective for treating recurrent forms of Clostridium difficile infection and its use in this indication is recommended in the most recent European and North American guidelines. In this context, faecal microbiota transplantation is beginning to be performed in France in clinical practice, while the rules governing this procedure have been defined in France only for clinical trials. To unify, secure, and evaluate practice in this field in France, the French Group of Faecal microbiota Transplantation (FGFT) was created in October 2014 with the support of the French National Society of Gastroenterology, the French Infectious Disease Society, and the National Academy of Pharmacy. We present here the deliberations of this group regarding the use of faecal microbiota transplantation for recurrent Clostridium difficile infection. The issues addressed are the indications, therapeutic sequence, delivery procedures, donor selection, methods and conditions of specimen preparation, and traceability.

KEYWORDS: Clostridium difficile; Faecal microbiota transplantation; Recommendations

Colites à CD 027

INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY DECEMBER 2013, VOL. 34, NO. 12

LETTER TO THE EDITOR

Clostridium difficile 027 Emerging Outbreak in Marseille, France

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Pierre-Edouard Fournier, MD, PhD;[1,3]
Philippe Colson, PharmD, PhD;[1,2]
Hervé Richet, MD, PhD;[1,2] Philippe Brouqui, MD, PhD;[1,2]
Didier Raoult, MD, PhD[1,2]

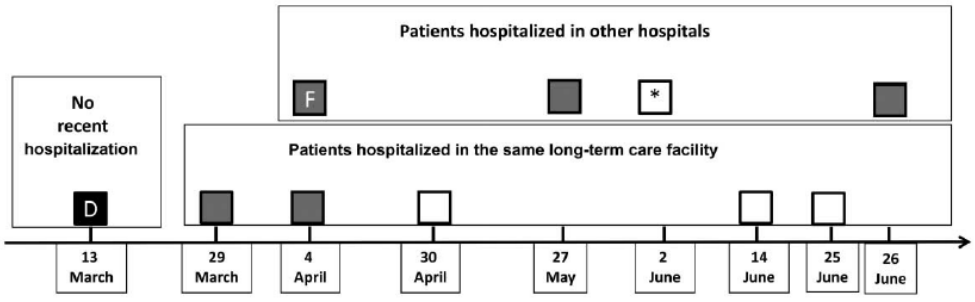


FIGURE 1. Schematic representation of the origin of the 10 cases (March 2013 through July 5, 2013).

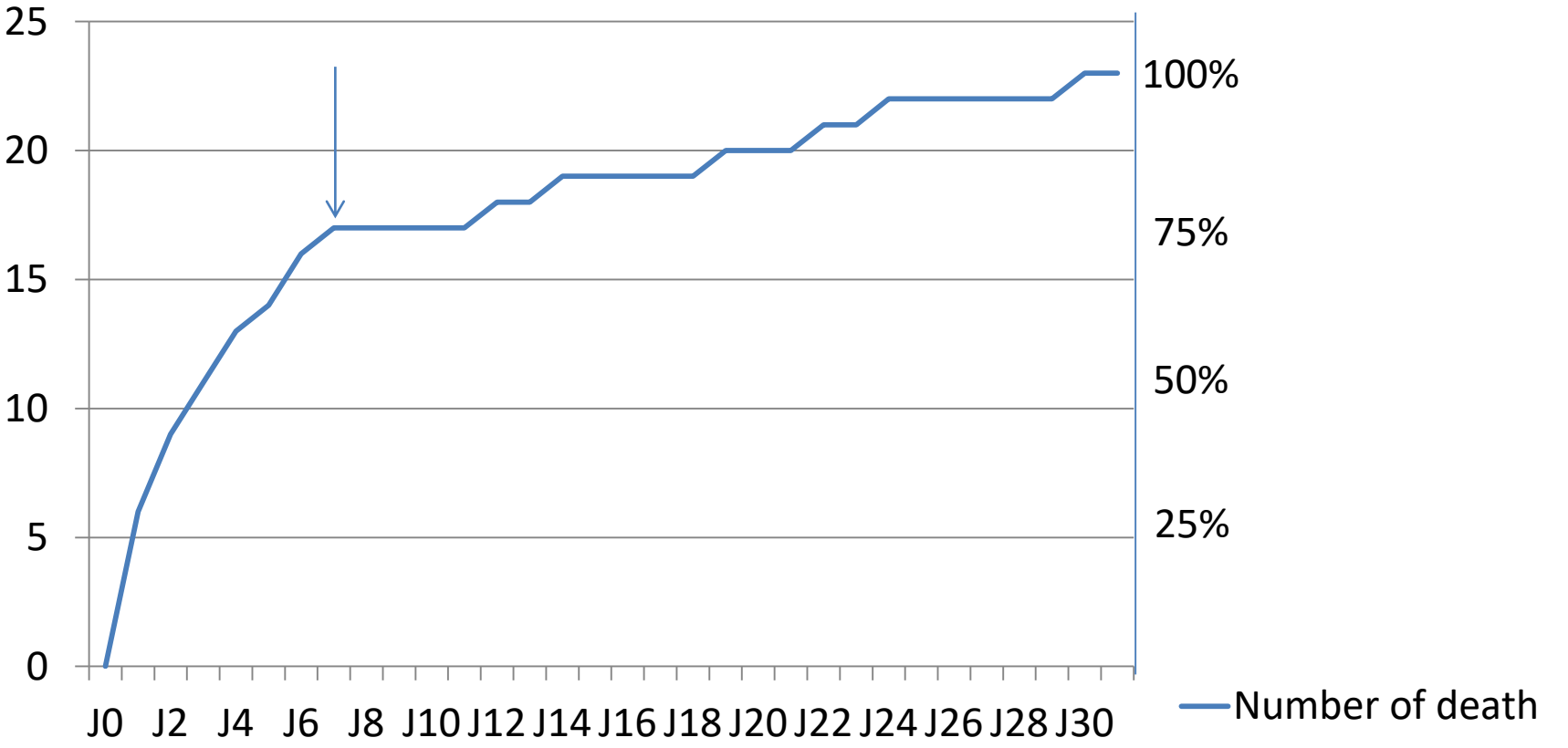
Eur J Clin Microbiol Infect Dis
DOI 10.1007/s10096-015-2394-x

ARTICLE

Dramatic reduction in *Clostridium difficile* ribotype 027-associated mortality with early fecal transplantation by the nasogastric route: a preliminary report

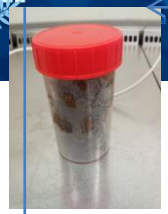
J.-C. Lagier[1,2] · M. Delord[2] · M. Million[1,2] · P. Parola[1,2] · A. Stein[1,3] · P. Brouqui[1,2] · D. Raoult[1]

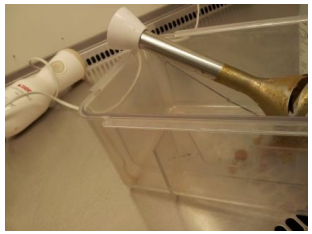
Number of death **Percentage of death**



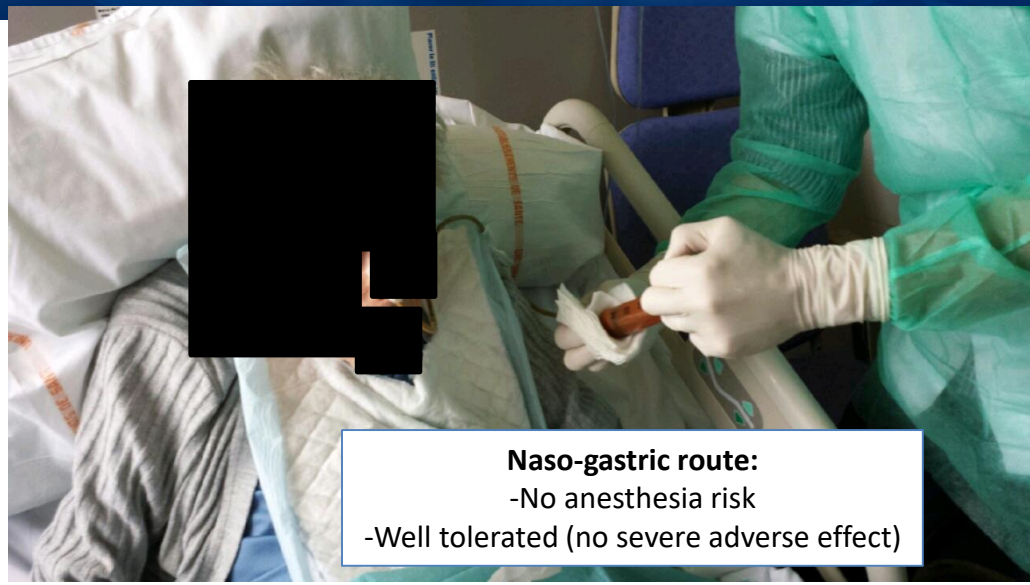
Fecal transplantation by naso-gastric route

Pre-inclusion monitoring (blood and fecal samples tests)





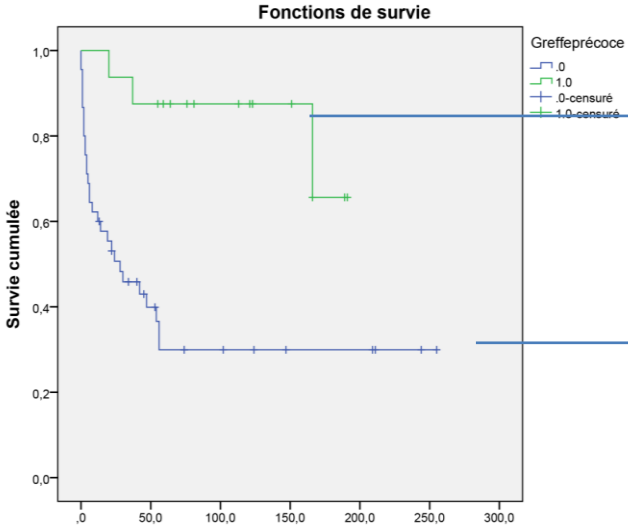
Dilution, blender, filtration



Naso-gastric route:
-No anesthesia risk
-Well tolerated (no severe adverse effect)

Early fecal Transplantation And C. difficile 027 infection

16 patients treated with early FMT and
42 patients treated by antibiotics :
1/16 died at day 31 in FMT group
23/42 died at day 31 in antibiotics group
P<0.001



Early FMT
And antibiotics

Only Antibiotics

2ème indication majeure de greffe de microbiote : colite à CD027 en première intention

Colite à CD graves

Eur J Gastroenterol Hepatol. 2013 Feb;25(2):255-7. doi: 10.1097/MEG.0b013e32835b2da9.

Faecal microbiota transplantation for severe Clostridium difficile infection in the intensive care unit.

Trubiano JA[1], Gardiner B, Kwong JC, Ward P, Testro AG, Charles PG.

⊕ Author information

Abstract

We describe a case of faecal microbiota transplantation (FMT) used for severe binary toxin-positive Clostridium difficile infection in an intensive care setting. The patient was admitted to the ICU of a tertiary hospital and failed traditional maximal pharmacological management. Adjunctive therapy with FMT given through gastroscopy resulted in resolution of the C. difficile-related symptoms. Although there is a growing experience with FMT for recurrent C. difficile infection, published evidence in severe disease is very limited. In a landscape of increasingly severe C. difficile infection, adjunctive FMT may be considered a useful early treatment option.

PMID: 23117471 [PubMed - indexed for MEDLINE]

Colite à CD graves

Letter to the Editor

Faecal microbiota transplantation as salvage therapy for fulminant *Clostridium difficile* infections

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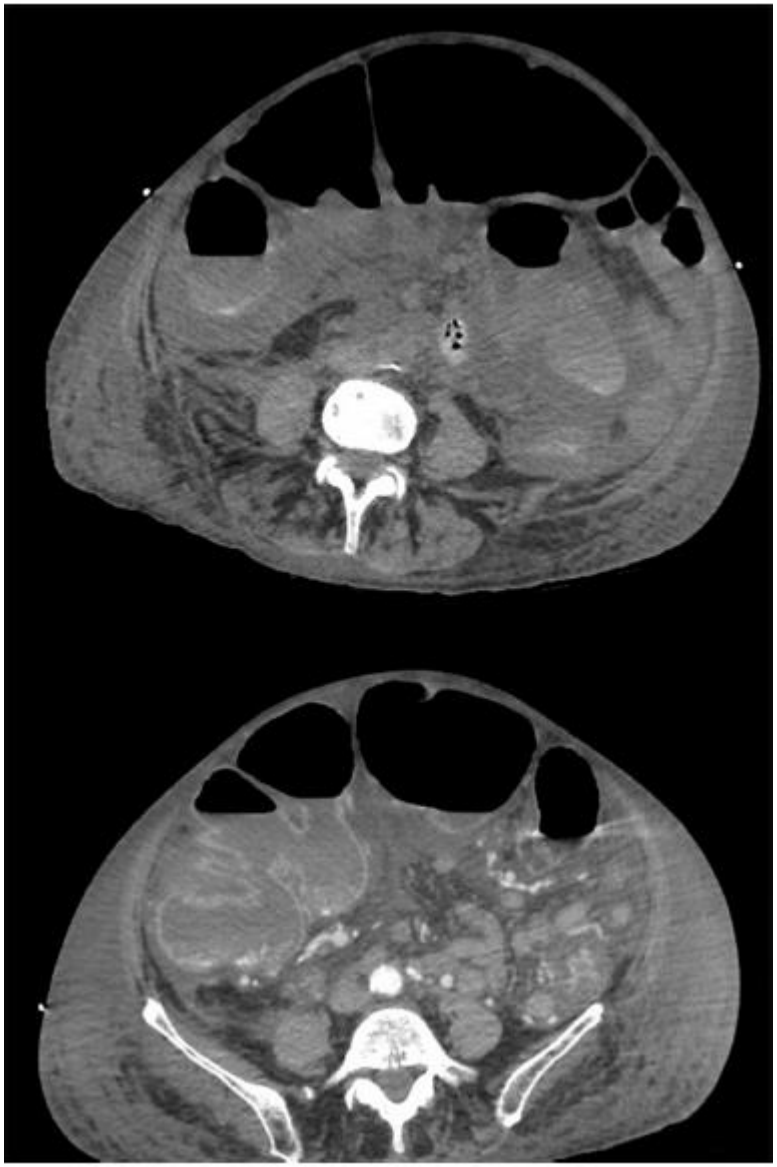
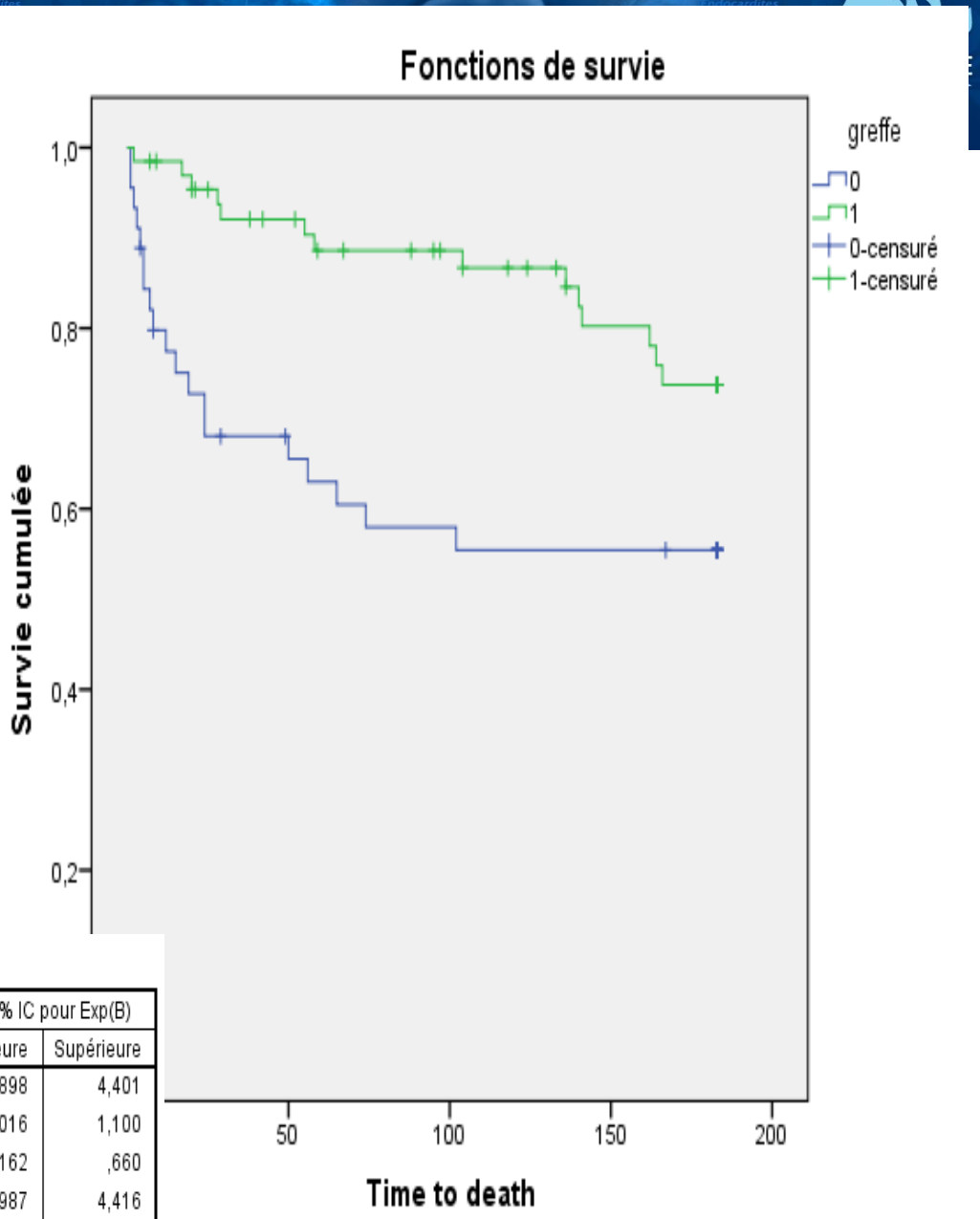


Au total

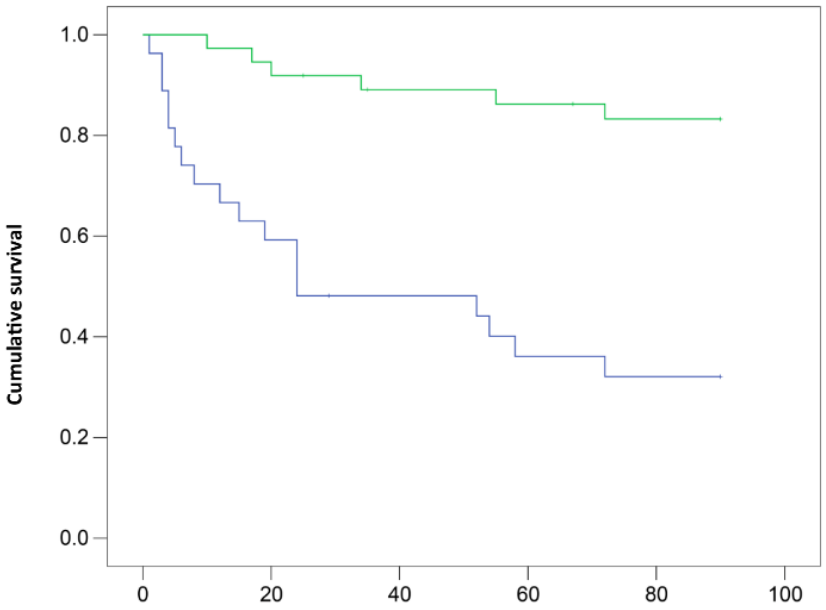
Divise le risque de mortalité par 3 indépendamment de l'âge, du sexe, du score de charlson score (co-morbidités) et de la détection du ribotype O27 hypervirulent



Variables dans l'équation

	B	E.S.	Wald	ddl	Signif.	Exp(B)	95,0% IC pour Exp(B)	
							Inférieure	Supérieure
sexe	,687	,405	2,873	1	,090	1,988	,898	4,401
âge	,055	,020	7,461	1	,006	1,057	1,016	1,100
greffe	-1,118	,358	9,731	1	,002	,327	,162	,660
O27	,736	,382	3,708	1	,054	2,088	,987	4,416
scorecharlson	,185	,079	5,524	1	,019	1,203	1,031	1,403

Microbiote humain
Greffe précoce – C. difficile- mortalité M3
CDI sévère



Number at risk						
FMT	37	34	31	30	28	28
No FMT	27	16	12	9	8	8

Chez les patients avec une infection sévère, la greffe améliore la survie

6/34 (17%) versus 18/26 (69%)
P < .0001

Multivariate OR 0.075
95%CI 0.01 – 0.34, P = .001

Nombre de patients sévères à traiter pour sauver une vie = 2

Traitement de première ligne des infections sévère à *C. difficile* ?

Directeur de Thèse - Marie HOCQUART

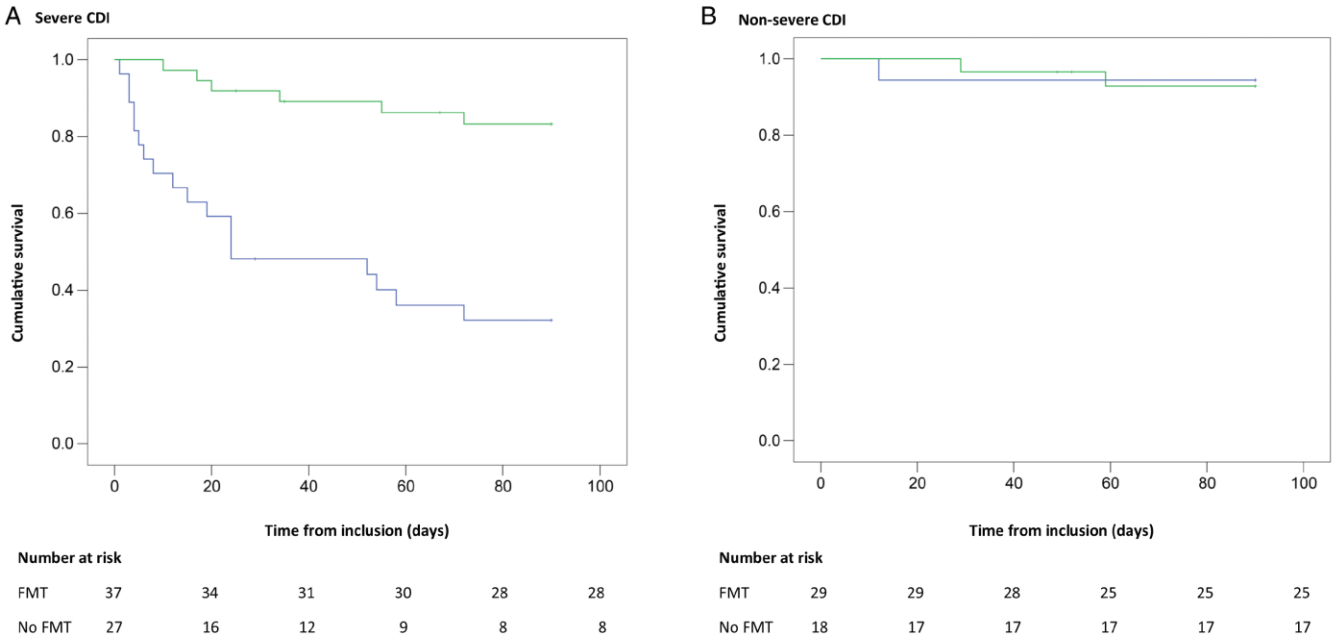


Figure 2. Effects of fecal microbiota transplantation (FMT) on *Clostridium difficile* infection (CDI) survival according to severity. Green line: FMT. Blue line: No FMT. *A*, Early FMT dramatically reduced mortality in patients with severe CDI (Kaplan-Meier curve, log-rank test, $P < .0001$). *B*, Early FMT did not reduce mortality in patients with nonsevere CDI (Kaplan-Meier curve, log-rank test, $P = .86$).

Aucun gain sur la mortalité chez les non-sévère
C'est donc les plus âgés et les plus graves qu'il faut transplanter !

0413732301 – jean-christophe.lagier@univ-amu.fr – Jeanchristophe.lagier@ap-hm.fr

Décolonisation de BHRe

Clin Microbiol Infect. 2014 May 20. doi: 10.1111/1469-0691.12683. [Epub ahead of print]

Donor feces infusion for eradication of Extended Spectrum beta-Lactamase producing Escherichia coli in a patient with end stage renal disease.

Singh R[1], van Nood E, Nieuwdorp M, van Dam B, Ten Berge IJ, Geerlings SE, Bemelman FJ.

Author information

A 60-year-old Caucasian male with end stage renal disease resulting from longstanding hypertension underwent his first post-mortal renal allo-transplantation in 2000, which was complicated by a steroid resistant acute rejection episode and subsequently resulted in transplantectomy within 3 months thereafter. In 2003, he underwent his second post-mortal renal allo-transplantation. From 2006 on he suffered from recurrent episodes of transplant pyelonephritis. In course of time his serum creatinine rose slowly and proteinuria developed. In 2008 a biopsy of the renal allograft showed chronic interstitial damage and tubulus atrophy compatible with chronic rejection and pyelonephritis. Between 2011 and 2012 he was admitted eight times for recurrent episodes of transplant pyelonephritis caused by an Extended Spectrum beta-Lactamase (ESBL) producing *Escherichia coli* (*E. coli*). Each

intestine. To study this hypothesis, a proof of principal study about the effectiveness of donor feces infusion against the large intestine colonisation by ESBL producing *Enterobacteriaceae* is currently being performed within our hospital.

REVIEW 10.1111/1469-0691.12799

The potential beneficial role of faecal microbiota transplantation in diseases other than *Clostridium difficile* infection

R. Singh[1], M. Nieuwdorp[2], I. J. M. ten Berge[1], F. J. Bemelman[1] and S. E. Geerlings[3]

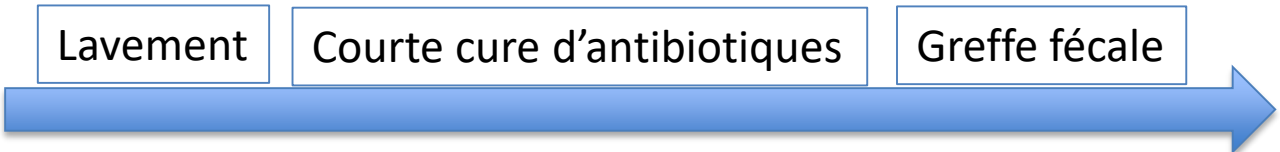
1) *Renal Transplant Unit, Division of Nephrology,* 2) *Division of Vascular Medicine and* 3) *Division of Infectious Diseases, Department of Internal Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands*

J Hosp Infect. 2015 Jun;90(2):173-4. doi: 10.1016/j.jhin.2015.02.013. Epub 2015 Mar 18.

Faecal microbiota transplantation for stool decolonization of OXA-48 carbapenemase-producing Klebsiella pneumoniae.

Lagier JC[1], Million M[1], Fournier PE[2], Brouqui P[1], Raoult D[3].

In December 2014, an 82-year-old female was admitted to the Infectious Diseases Department of Hopital Nord in Marseille, France, for asymptomatic stool carriage of an oxa-48 carbapenemase-producing *K. pneumoniae*. This digestive colonization, discovered in her rehabilitation center, had persisted for more than 1 month, as proven by recurrent positive cultures and PCR assays, and had contraindicated an hospitalization in long-term care facility. The patient and her family gave informed consent for the fecal microbiota transplantation, according to the French legislation. We used blood and feces samples of a healthy anonymous donor that were tested for the absence of pathogen, as previously recommended.[2] On the day prior to transplantation, the patient received a bowel lavage followed by four successive oral administrations of 2.5 MUI colimycine and 100 mg gentamicin over 24 hours. Then, we used a nasogastric tube toinoculate400 ml of an aseptically-prepared mixture made of 50 g of stool diluted in 0.9%.NaCl. No adverse event was observed. At days 7 and 14 after transplantation, the patient's feces were negative for carbapenemase-producing *K. pneumoniae*, and oxa-48-specific PCR was negative at day 7.



Infect Dis (Lond). 2016 Aug;48(8):587-92. doi: 10.1080/23744235.2016.1177199. Epub 2016 May 19.

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

Manges AR[1], Steiner TS[2], Wright AJ[2].

INFECTIOUS DISEASES, 2016
http://dx.doi.org/10.1080/23744235.2016.1177199

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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]

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ABSTRACT

Treatment options for multidrug-resistant (MDR) bacterial infections are limited and often less effective. Non-pharmacologic approaches to preventing or treating MDR infections are currently restricted to improved antimicrobial stewardship and infection control practices. Fecal microbiota transplantation (FMT), a highly effective treatment for recurrent *Clostridium difficile* infection, has emerged as a promising therapy for intestinal MDR bacterial decolonization. A total of eight case reports have been published showing FMT resulted in intestinal decolonization of extended spectrum β-lactamase (ESBL)-producing and carbapenemase-producing Enterobacteriaceae, vancomycin-resistant Enterococci, or methicillin-resistant *Staphylococcus aureus*. The procedure has been shown to work even in immunocompromised patients and those experiencing medical crises without any adverse events. Five trials are currently underway to further investigate the use of FMT for MDR bacterial decolonization. FMT is a completely novel way to eradicate drug-resistant bacteria from the intestinal reservoir and should be further investigated to address the global problem of difficult-to-treat, MDR bacterial infections.

ARTICLE HISTORY
Received 10 December 2015
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Published online 10 May 2016

KEYWORDS
Antimicrobial resistance; bacterial infections; bacteriotherapy; fecal microbiota transplantation; multidrug resistance

A 13-year-old girl with a history of recurrent otitis media and otomastoiditis, who subsequently developed hemophagocytic lymphohistiocytosis, sepsis and then osteomyelitis with a carbapenemase-producing *K. pneumoniae*,[32] which was resistant to standard antibiotic therapy, received FMT. The donor was the patient's

A 66-year-old male quadriplegic, who was ventilator-dependent and admitted to an intensive care unit (ICU), was heavily colonized with highly drug-resistant *A. baumannii*, carbapenemase-producing *P. aeruginosa* and vancomycin-resistant *E. faecalis*. He developed a UTI due to a carbapenemase-producing *K. pneumoniae* prior to ICU admission and *C. difficile* colitis within one week of admission, followed by multiple CDI recurrences.[34] In addition, over 15 weeks following admission, MDR bacterial infections occurred. The sister of the patient was screened and acted as the FMT donor. Vancomycin treatment was stopped one day prior to FMT and 480 mL of donor stool (preparation of stool not reported) was administered by colonoscope without complication. FMT successfully resolved recurrent CDI in the patient (negative *C. difficile* toxin tests over two years), and resulted in a reduction in post-FMT MDR infections.

As part of an industry-sponsored trial investigating the use of an experimental microbiota suspension (RBX2660) for recurrent CDI treatment, investigators found that in

11 patients positive for VRE at baseline and receiving 1–2 doses of RBX2660, 8 (73%) were negative for VRE after one to six months following therapy. Of the remaining three patients, one died (unrelated to treatment), and two remained positive or re-tested positive at one or more of their follow-up visits. RBX2660 contains material from human stool and is designed to resemble whole stool used for FMT; it is administered in 50 mg/150 mL doses by enema.[36]

Five patients with underlying health conditions (e.g., Crohn's disease, pancreatic cancer) admitted to hospital for surgical procedures, and receiving pre- and post-operative antibiotics, developed severe MRSA enterocolitis shortly following their surgeries. Fully screened stool donors (three donors were closely to the FMT recipients) provided 60 grams of fresh stool, which was blended in 350 mL of sterile saline and filtered. All FMT recipients received 500 mg of vancomycin twice per day for three days until 12 h prior to FMT. Bowel lavage was not done prior to FMT. The stool filtrate was administered by naso-jejunal tube (volume of filtrate not reported) once a day for three days. FMT successfully resolved MRSA enterocolitis in these five patients; their stool cultures were negative for MRSA for three months post-FMT.[33]

A 33-year-old female cardiac and single kidney transplant patient was treated for multiple episodes of sepsis and UTI, including infections due to vancomycin-resistant Enterococcus, and experienced six episodes of recurrent *C. difficile* colitis. FMT was performed using the patient's spouse, after screening, as the donor. Donor stool (25–30 grams) was homogenized in 50–100 mL of saline and filtered, and administered by nasogastric tube. The patient's maintenance vancomycin treatment was terminated the night before FMT; use of bowel lavage was not reported. FMT successfully cleared *C. difficile* and multiple species of VRE [35] and the patient remained free from *C. difficile* and enterococcal infection after one year of follow-up. The authors acknowledge that termination of vancomycin therapy may also have contributed to VRE decolonization.

Décolonisation de BHRe

Diagnostic Microbiology and Infectious Disease 86 (2016) 470–471

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Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Gut eradication of VIM-1 producing ST9 *Klebsiella oxytoca* after fecal microbiota transplantation for diarrhea caused by a *Clostridium difficile* hypervirulent R027 strain

Sergio García-Fernández [a,b], María-Isabel Morosini [a,b], Marta Cobo [a,b], José Ramón Foruny [c], Antonio López-Sanromán [c], Javier Cobo [b,d], José Romero [a], Rafael Cantón [a,b], Rosa del Campo [a,b,*]

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Décolonisation de BHRe

Journal of Hospital Infection xxx (2017) 1–5

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevierhealth.com/journals/jhin

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,*]

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[e] Antimicrobial Stewardship Unit, Henri Mondor Teaching Hospital, APHP, Paris-Est Créteil-Est University, Créteil, France
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ARTICLE INFO

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Available online xxx

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Antimicrobials
Faecal microbiota transplantation
Multidrug-resistant organism

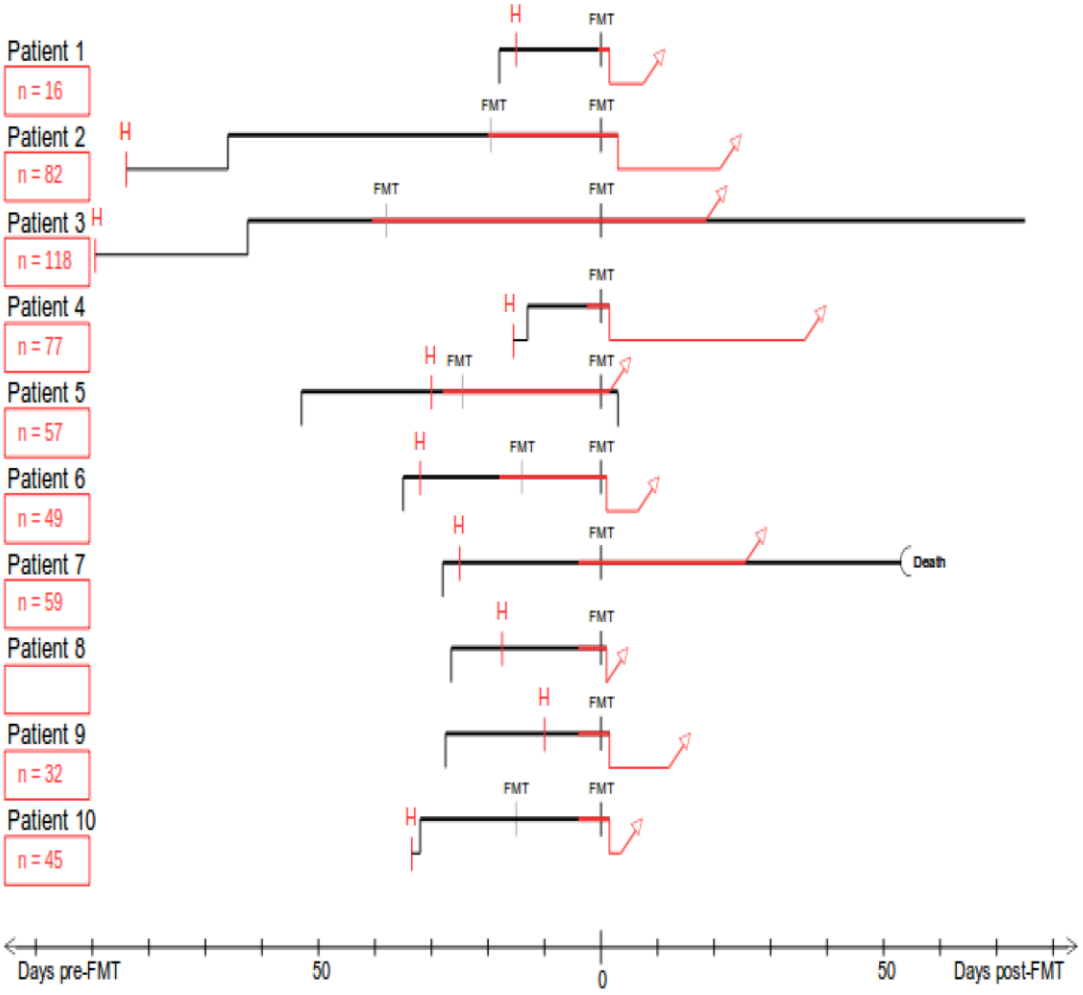
SUMMARY

Carbapenem-resistant Enterobacteriaceae (CRE) or vancomycin-resistant enterococci (VRE) carriage present a major public health challenge. Decolonization strategies are lacking. We aimed to evaluate the impact of faecal microbiota transplantation (FMT) on a cohort of patients with digestive tract colonization by CRE or VRE. Eight patients were included: six carrying CRE and two colonized by VRE. One month after FMT, two patients were free from CRE carriage, and another patient was free from VRE after three months. In our experience, this strategy is safe.

C	Colonization sites	Bacterial species	FMT (n)	Chlorhexidine pharyngeal decolonization	Post FMT colonization sites	FMT intestinal decolonization
82, F	R	Kp (oxa48)	1	0	-	Success
22, M	R, P	Kp (oxa48)	2	0	-	Success
41, M	R, P	Kp (oxa48)	2	1	R, P	Failure
41, M	R	Kp (NDM)	1	0	-	Success
88, M	R	Kp (oxa48)	2	0	-	Success
70, M	R, P	Eco, Kp (oxa48)	2	1	R, P	Failure
69, M	R	Kp, Eco, Ecl (oxa48)	1	1		Success
80,M	R, P	Kp (NDM)	1	1	-	Success

→ 75% d'efficacité

→ Courte cure d'antibiothérapie
Colimycine + aminosides per os



8/10 succès = 80%

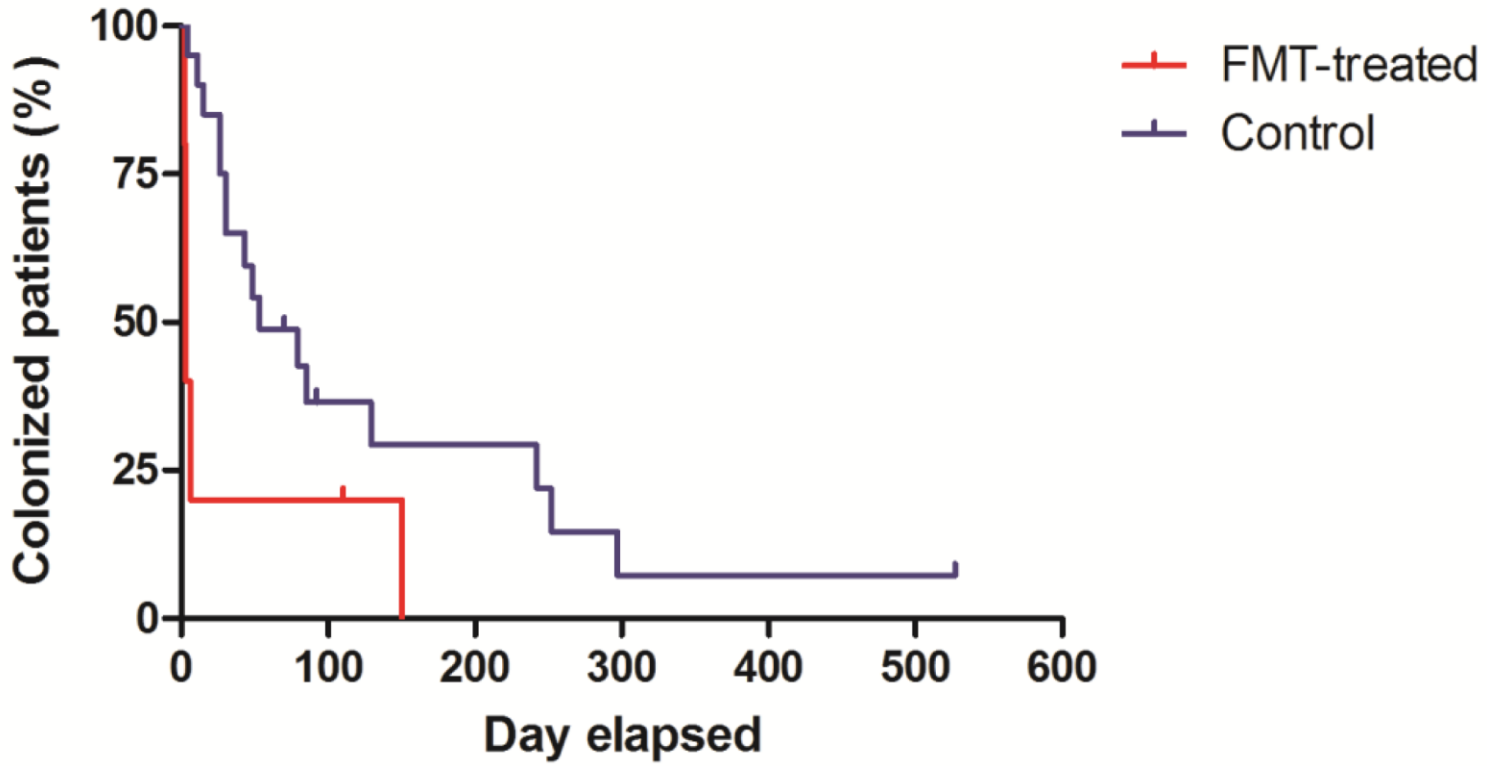
Dans les 8 succès, décolonisation effective dans les 10 jours qui suivent la FMT permettant le transfert – la réentrée dans le parcours de soin (rééducation, chimiothérapie,…)

Saidani, IJAA, 2018

Faecal microbiota transplantation shortens the colonisation period and allows re-entry of patients carrying carbapenamase-producing bacteria into medical care facilities.

Saïdani N, Lagier JC, Cassir N, **Million M**, Baron S, Dubourg G, Eldin C, Kerbaj J, Valles C, Raoult D Brouqui P.

Int J Antimicrob Agents. 2018 Nov 23. pii: S0924-8579(18)30339-X. doi: 10.1016/j.ijantimicag.2018.11.014. [Epub ahead of print]



Fecal Microbiota Transplant for Relapsing *Clostridium difficile* Infection Using a Frozen Inoculum From Unrelated Donors: A Randomized, Open-Label, Controlled Pilot Study

Ilan Youngster,[1,2,3] Jenny Sauk,[2,4] Christina Pindar,[1] Robin G. Wilson,[4] Jess L. Kaplan,[2,5] Mark B. Smith,[6] Eric J. Alm,[6] Dirk Gevers,[7] George H. Russell,[2,5] and Elizabeth L. Hohmann[1,2]

[1]Division of Infectious Diseases, Massachusetts General Hospital, [2]Harvard Medical School, [3]Division of Infectious Diseases, Boston Children's Hospital, [4]Division of Gastroenterology, Massachusetts General Hospital, and [5]Department of Pediatric Gastroenterology and Nutrition, Massachusetts General Hospital for Children, Boston; and [6]Department of Biological Engineering, and [7]Broad Institute, Massachusetts Institute of Technology, Cambridge, Massachusetts

Background. Recurrent *Clostridium difficile* infection (CDI) with poor response to standard antimicrobial therapy is a growing medical concern. We aimed to investigate the outcomes of fecal microbiota transplant (FMT) for relapsing CDI using a frozen suspension from unrelated donors, comparing colonoscopic and nasogastric tube (NGT) administration.

Methods. Healthy volunteer donors were screened and a frozen fecal suspension was generated. Patients with relapsing/refractory CDI were randomized to receive an infusion of donor stools by colonoscopy or NGT. The primary endpoint was clinical resolution of diarrhea without relapse after 8 weeks. The secondary endpoint was self-reported health score using standardized questionnaires.

Results. A total of 20 patients were enrolled, 10 in each treatment arm. Patients had a median of 4 (range, 2–16) relapses prior to study enrollment, with 5 (range, 3–15) antibiotic treatment failures. Resolution of diarrhea was achieved in 14 patients (70%) after a single FMT (8 of 10 in the colonoscopy group and 6 of 10 in the NGT group). Five patients were retreated, with 4 obtaining cure, resulting in an overall cure rate of 90%. Daily number of bowel movements changed from a median of 7 (interquartile range [IQR], 5–10) the day prior to FMT to 2 (IQR, 1–2) after the infusion. Self-ranked health score improved significantly, from a median of 4 (IQR, 2–6) before transplant to 8 (IQR, 5–9) after transplant. No serious or unexpected adverse events occurred.

Conclusions. In our initial feasibility study, FMT using a frozen inoculum from unrelated donors is effective in treating relapsing CDI. NGT administration appears to be as effective as colonoscopic administration.

Clinical Trials Registration. NCT01704937.

Conservation du microbiote fécal

Research

Preliminary Communication

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

Ilan Youngster, MD, MMSc; George H. Russell, MD, MSc; Christina Pindar, BA; Tomer Ziv-Baran, PhD; Jenny Sauk, MD; Elizabeth L. Hohmann, MD

IMPORTANCE Fecal microbiota transplantation (FMT) has been shown to be effective in treating relapsing or refractory *Clostridium difficile* infection, but practical barriers and safety concerns have prevented its widespread use.

OBJECTIVE To evaluate the safety and rate of resolution of diarrhea following administration of frozen FMT capsules from prescreened unrelated donors to patients with recurrent *C difficile* infection.

DESIGN, SETTING, AND PARTICIPANTS Open-label, single-group, preliminary feasibility study conducted from August 2013 through June 2014 at Massachusetts General Hospital, Boston. Twenty patients (median age, 64.5 years; range, 11-89 years) with at least 3 episodes of mild to moderate *C difficile* infection and failure of a 6- to 8-week taper with vancomycin or at least 2 episodes of severe *C difficile* infection requiring hospitalization were enrolled.

INTERVENTIONS Healthy volunteers were screened as potential donors and FMT capsules were generated and stored at −80°C (−112°F). Patients received 15 capsules on 2 consecutive days and were followed up for symptom resolution and adverse events for up to 6 months.

MAIN OUTCOMES AND MEASURES The primary end points were safety, assessed by adverse events of grade 2 or above, and clinical resolution of diarrhea with no relapse at 8 weeks. Secondary end points included improvement in subjective well-being per standardized questionnaires and daily number of bowel movements.

RESULTS No serious adverse events attributed to FMT were observed. Resolution of diarrhea was achieved in 14 patients (70%; 95% CI, 47%-85%) after a single capsule-based FMT. All 6 nonresponders were re-treated; 4 had resolution of diarrhea, resulting in an overall 90% (95% CI, 68%-98%) rate of clinical resolution of diarrhea (18/20). Daily number of bowel movements decreased from a median of 5 (interquartile range [IQR], 3-6) the day prior to administration to 2 (IQR, 1-3) at day 3 ($P = .001$) and 1 (IQR, 1-2) at 8 weeks ($P < .001$). Self-ranked health scores improved significantly on a scale of 1 to 10 from a median of 5 (IQR, 5-7) for overall health and 4.5 (IQR, 3-7) for gastrointestinal-specific health on the day prior to FMT to 8 (IQR, 7-9) after FMT administration for both overall and gastrointestinal health ($P = .001$). Patients needing a second treatment to obtain resolution of diarrhea had lower pretreatment health scores (median, 6.5 [IQR, 5-7.3] vs 5 [IQR, 2.8-5]; $P = .02$).

CONCLUSIONS AND RELEVANCE This preliminary study among patients with relapsing *C difficile* infection provides data on adverse events and rates of resolution of diarrhea following administration of FMT using frozen encapsulated inoculum from unrelated donors. Larger studies are needed to confirm these results and to evaluate long-term safety and effectiveness.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01914731

Supplemental content at jama.com

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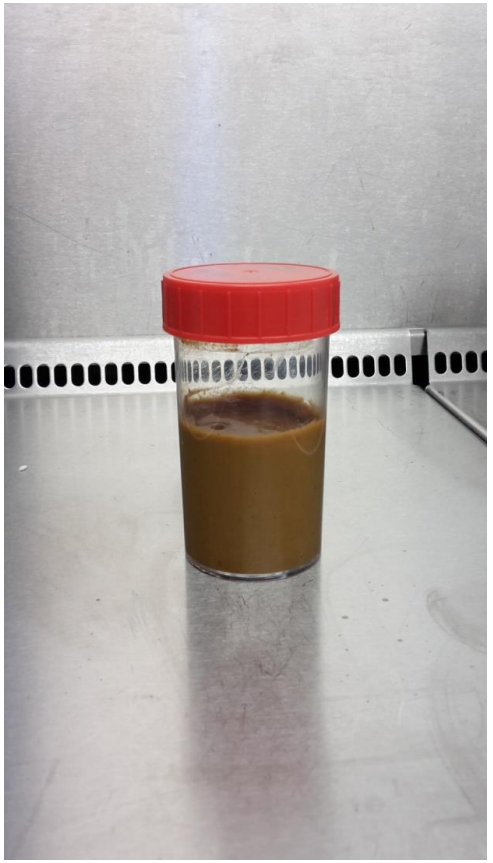
Conservation du microbiote fécal

Gélules lyophilisées

Selle 50g
Sérum physiologique
150mL

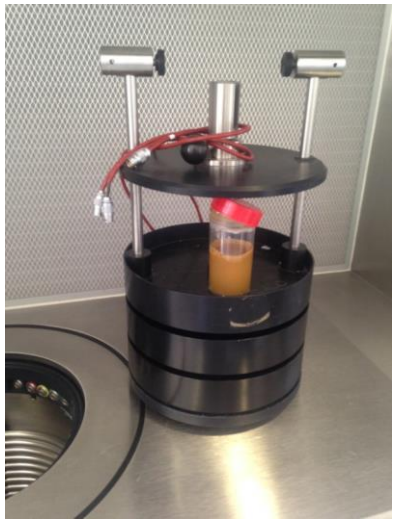
Conservation du microbiote fécal

Filtration



-80°C
12h

Conservation du microbiote fécal



12-16h

Conservation du microbiote fécal

J Clin Gastroenterol. 2015 Jul;49(6):537-8. doi: 10.1097/MCG.0000000000000330.

Freeze-dried, Capsulized Fecal Microbiota Transplantation for Relapsing Clostridium difficile Infection.

Tian H[1], Ding C, Gong J, Wei Y, McFarland LV, Li N.

Author information

Open Forum Infect Dis. 2016 May 5;3(2):ofw091. eCollection 2016.

Fecal Microbiota Transplantation by Freeze-Dried Oral Capsules for Recurrent Clostridium difficile Infection.

Hecker MT[1], Obrenovich ME[2], Cadnum JL[2], Jencson AL[2], Jain AK[3], Ho E[4], Donskey CJ[5].

Conservation du microbiote fécal

COLON/SMALL BOWEL

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]

OBJECTIVES: **Fecal microbiota transplantation (FMT) is increasingly being used for treatment of recurrent *Clostridium difficile* infection (R-CDI) that cannot be cured with antibiotics alone. In addition, FMT is being investigated for a variety of indications where restoration or restructuring of the gut microbial community is hypothesized to be beneficial. We sought to develop a stable, freeze-dried encapsulated preparation of standardized fecal microbiota that can be used for FMT with ease and convenience in clinical practice and research.**

METHODS: **We systematically developed a lyophilization protocol that preserved the viability of bacteria across the taxonomic spectrum found in fecal microbiota and yielded physicochemical properties that enabled consistent encapsulation. We also treated a cohort of R-CDI patients with a range of doses of encapsulated microbiota and analyzed the associated changes in the fecal microbiome of the recipients.**

RESULTS: **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.**

CONCLUSIONS: **A single administration of encapsulated, freeze-dried fecal microbiota from a healthy donor was highly successful in treating antibiotic-refractory R-CDI syndrome.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

Am J Gastroenterol advance online publication 14 February 2017; doi:10.1038/ajg.2017.6

En conclusion

Clinical Infectious Diseases

Article Contents

Comments (0)

Fecal Microbiota Transplantation: Do We Need Harmonization?

Tatiana Galpérine; Harry Sokol; Benoît Guery

Clin Infect Dis cix092. **DOI:** https://doi.org/10.1093/cid/cix092
Published: 03 February 2017

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To the Editor—We read with great interest the study published by Hota et al [1]. In their single-center, open-label, randomized, controlled trial, the authors compared the effectiveness of 14 days of oral vancomycin followed by a single fecal microbiota transplantation (FMT) by enema to a 6-week taper of oral vancomycin in patients experiencing acute episodes of recurrent *Clostridium difficile* infection. For the first time and in contrast to 5 clinical, randomized trials [2–6], this study concluded that FMT was not significantly more effective than vancomycin taper, and the study was stopped after an interim analysis. Although there is no single universally accepted FMT protocol, these findings are challenging, and several factors may have contributed to the suboptimal outcome.

En conclusion

Applications pratiques

- Au-delà de CD et BHRe
  - Microbiote et rectocolite hémorragique
  - Microbiote et diarrhée chronique
  - Microbiote et cancer (autogreffe pré-post chimio)
  - Microbiote et obésité
  - Microbiote et malnutrition
  - …….

Merci de votre attention

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