Infections à *Clostridium difficile*

Antibiotiques

et

Thérapeutiques basées sur le microbiote

DE LA DYSBIOSE A LA SYMBIOSE…DES OMBRES A LA LUMIERE

Dr Jérôme LARCHÉ
j.larche@oc-sante.fr

JOURNEE DES PRATICIENS EN HYGIENE D'OCCITANIE – Carcassonne 11 avril 2018

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CHRISTMAS 2012: RESEARCH

Using a dog's superior olfactory sensitivity to identify *Clostridium difficile* in stools and patients: proof of principle study

OPEN ACCESS

Marije K Bomers *consultant*[1], Michiel A van Agtmael *consultant*[1], Hotsche Luik *canine trainer and psychologist*[2], Merk C van Veen *resident*[3], Christina M J E Vandenbroucke-Grauls *professor*[4], Yvo M Smulders *professor*[1]

Je suis Cliff, le nouveau « Pet Scan » !! (Wouaff)

Cliff has been trained to sniff out the bacteria clostridium difficile

Results The dog's sensitivity and specificity for identifying *C difficile* in stool samples were both 100% (95% confidence interval 91% to 100%). During the detection rounds, the dog correctly identified 25 of the 30 cases (sensitivity 83%, 65% to 94%) and 265 of the 270 controls (specificity 98%, 95% to 99%).

Conclusion A trained dog was able to detect *C difficile* with high estimated sensitivity and specificity, both in stool samples and in hospital patients infected with *C difficile*.

Epidémiologie des infections à CDIF

POIDS DES ICD EN EUROPE ET AUX ETATS-UNIS

- **Etats-Unis**

- 453 000 ICD/an[1]

(IC 95% 397 100 – 508 500, HA et CO, HA ≥ 4 j, tous ES)

- 29 300 décès/an
- 1er agent responsable d'IAS (12,5%) [2]
- Menace urgente (CDC)

- **Europe**

- 124 000 ICD/an

(IC 95% 61 000 – 285 000, HA=CDI ≥ 3 j, ES court séjour)

- Mortalité attribuable: 3%

(3 700 décès attrib./an)

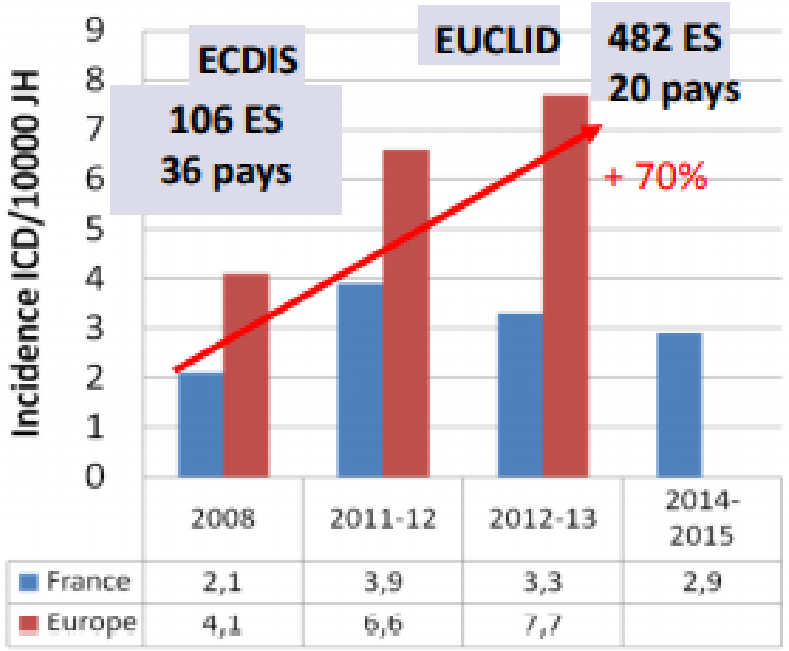
- 8ème agent responsable d'IAS (5,4%) [3]

[1]Lessa *et al*, NEJM 2015; [2] Magill *et al*, NEJM 2014

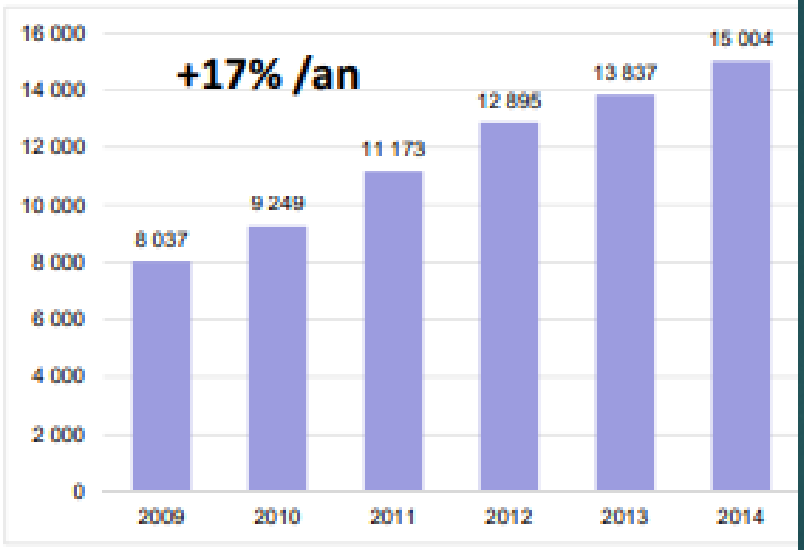
http://www.ecdc.europa.eu/en/publications/publications/healthcare-associated-infections-antimicrobial-use-pps.pdf

INCIDENCE DES ICD

- L'incidence continue d'augmenter en Europe [1–4, 6-7]
  - Amélioration des techniques diagnostiques
  - Sensibilisation croissante des cliniciens
  - Diffusion du clone NAP1/027/BI en Europe de l'Est



	2008	2011-12	2012-13	2014-2015
France	2,1	3,9	3,3	2,9
Europe	4,1	6,6	7,7	

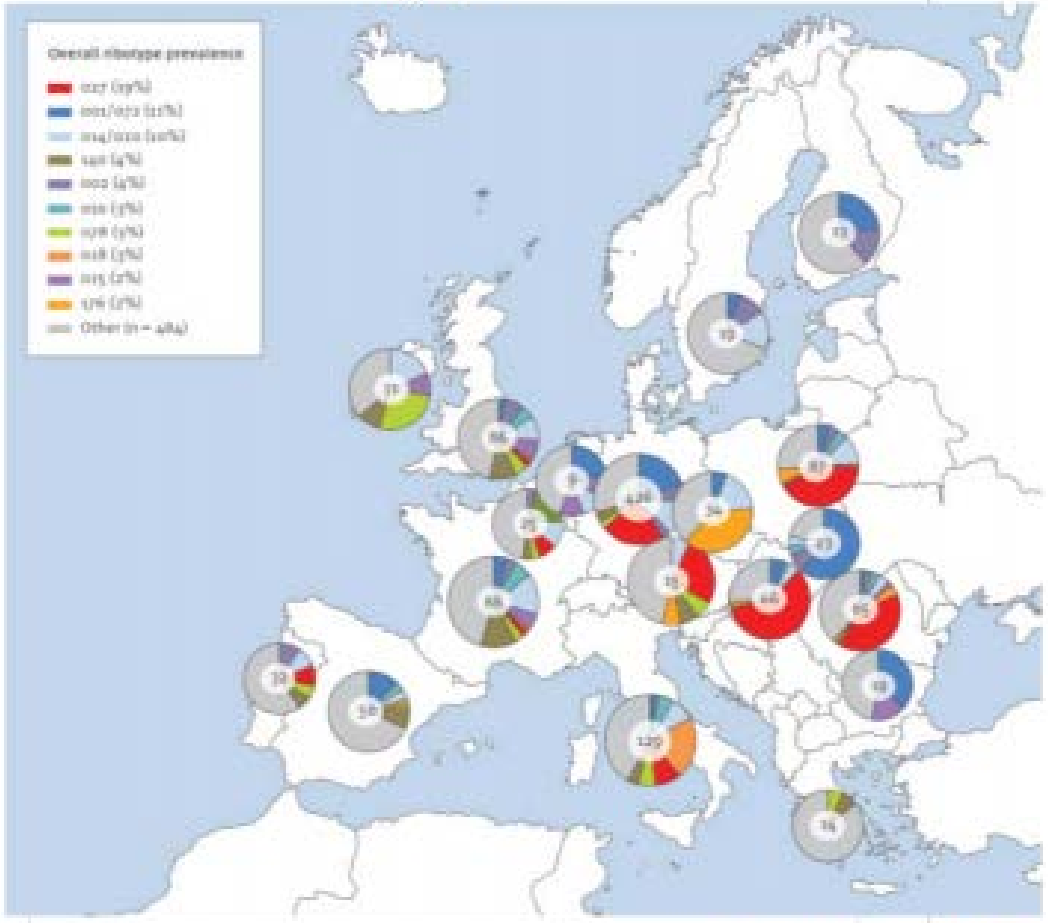


France, PMSI 2009 - 2014

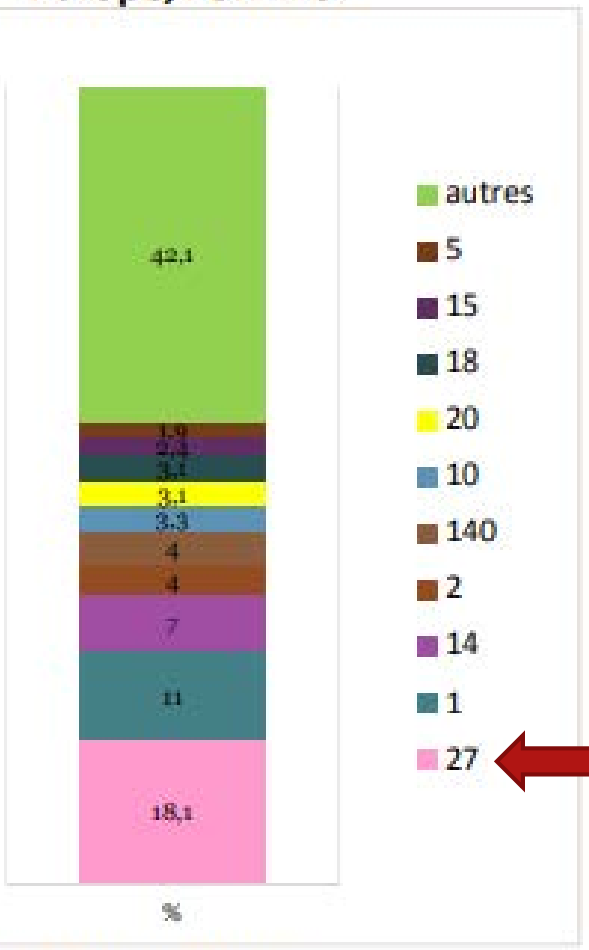
1. Bauer *et al* Lancet 2011
2. Davies *et al* Lancet 2014
3. Barbut *et al* Presse med 2015

EPIDÉMIOLOGIE MOLÉCULAIRE des ICD

US, 2011



Europe, 2012-13



Adapted from Davies KA, Lancet Infect Dis 2014;14: 1208–19
Davies KA, Eurosurv. 2016

TAUX DE MORTALITÉ et ICD

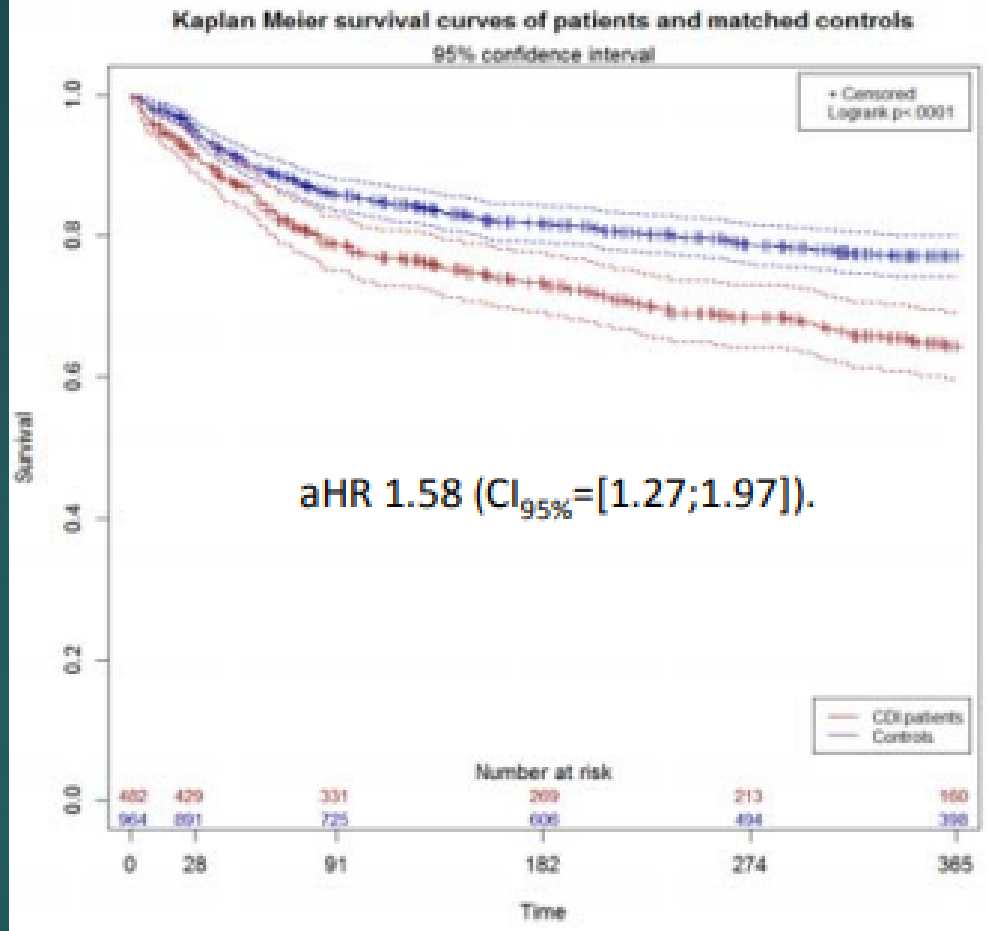
- Etude pan-Européenne hospitalière (2008):[1]
  - 22% des patients décèdent dans les **3 mois** suivant l'ICD (toutes causes confondes)
  - ~2% des patients décèdent directement de leur infection
  - 7% des cas : ICD cause contributive

- Etude prospective française [3]
  - 1316 cas
  - 4% décèdent dans le **mois**
  - CDI est la cause attributable dans 1%

- Etude cas-témoins Canadienne (épidémie, 2004): [2]
  - ~7% des patients décèdent de leur ICD
  - L'ICD a contribué à la mortalité dans 8% des cas

1-Bauer *et al.*, Lancet 2011;377:63–73;
2-Eckert et al., MMI 2013, 43, 67-73
3- Loo V, *et al.*, N Engl J Med 2011, 365, 1693-703

L'ICD AUGMENTE LE RISQUE DE MORTALITÉ
Données françaises



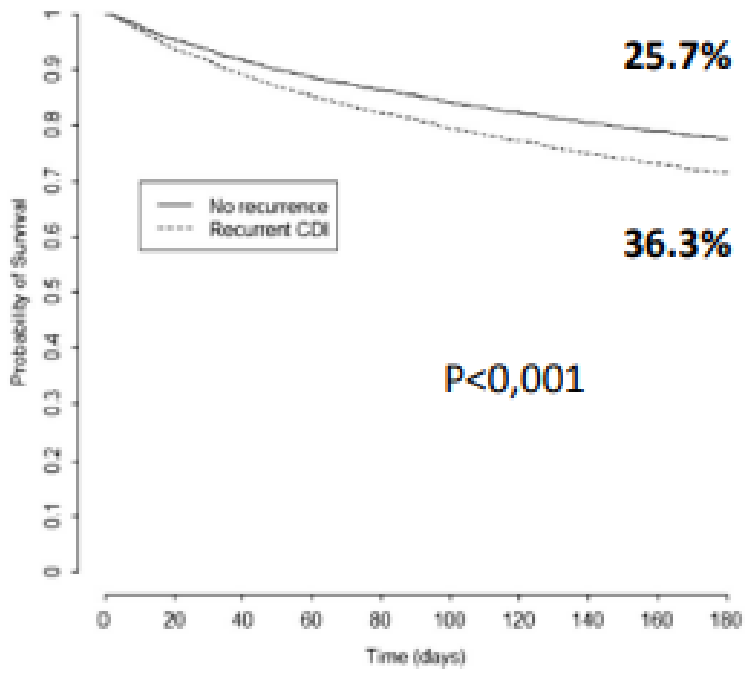
aHR 1.58 ($CI_{95\%}$=[1.27;1.97]).

- Base EGB (Echantillon Généraliste de Bénéficiaires)
- 482 patients avec ICD
- 964 témoins sans ICD appariés sur age, sexe, comorbidités et durée de séjour
- Analyse de survie de Kaplan Meier
- Modèle de régression multivariée de Cox est utilisé pour comparer le risque de décès après ajustement sur score de propension

Barbut F., J Hosp Infect. 2017 Jul 13

MORTALITÉ ET RÉCIDIVE d'ICD

- Etude rétrospective de cohorte dans un ES US, 2003-2009
- Donnés recueillies d'après le PMSI et la consultation des dossiers médicaux
- Analyse de Kaplan Meier comparant la mortalité à J180 selon la présence ou non de récidives
- Modèles de Cox pour identifier les facteurs de risque associés au décès (HR=1,33, 95% CI 1.12- 1.58) (p=0.001)



3958 patients, 421 avec récidives

Olsen MA, CMI 2015, 21, 164-180

Présentations cliniques des infections à CDIF

Tableau I. Facteurs de risque pour le développement d'infections à *Clostridium difficile*
(Adapté de réf.[4]).

- Utilisation d'antibiotiques (surtout céphalosporines de troisième génération, fluoroquinolones)
- Age ⩾ 60 ans
- Hospitalisation dans les 60 jours précédents et longue durée d'hospitalisation
- Utilisation d'antacides (inhibiteurs de la pompe à protons et antihistaminiques H2)
- Utilisation d'antidiarrhéiques
- Nutrition entérale
- Chirurgie viscérale récente
- Chimiothérapie
- Transplantation de cellules souches hématopoïétiques

Zanella et al. Revue Médicale Suisse – octobre 2013

Tableau 2. Formes cliniques des infections à *Clostridium difficile*
(Adapté de réf.[23]).

	Symptômes et signes cliniques	Examens complémentaires
Diarrhées à *C. difficile*	Diarrhées, douleurs abdominales, ± état fébrile	Coloscopie: sans particularité
Colite à *C. difficile*	Diarrhées, douleurs abdominales, état fébrile	Syndrome inflammatoire, coloscopie: lésions érythémateuses éparses ou diffuses sans pseudomembrane
Colite pseudomembraneuse	Diarrhées, douleurs abdominales, état fébrile	Syndrome inflammatoire, coloscopie: pseudomembranes (plaques jaunâtres 2-20 mm ± confluentes)
Colite fulminante	Diarrhées profuses ou iléus, douleurs abdominales, état fébrile, ± clinique de choc	Syndrome inflammatoire (parfois leucocytose >40 G/l), ± hyperlactatémie, sigmoïdoscopie: pseudomembranes, CT abdominal: mégacôlon, ± perforation colique

Zanella et al. Revue Médicale Suisse – octobre 2013
Bagder et al. J Parenter Enteral Nutr 2012;36

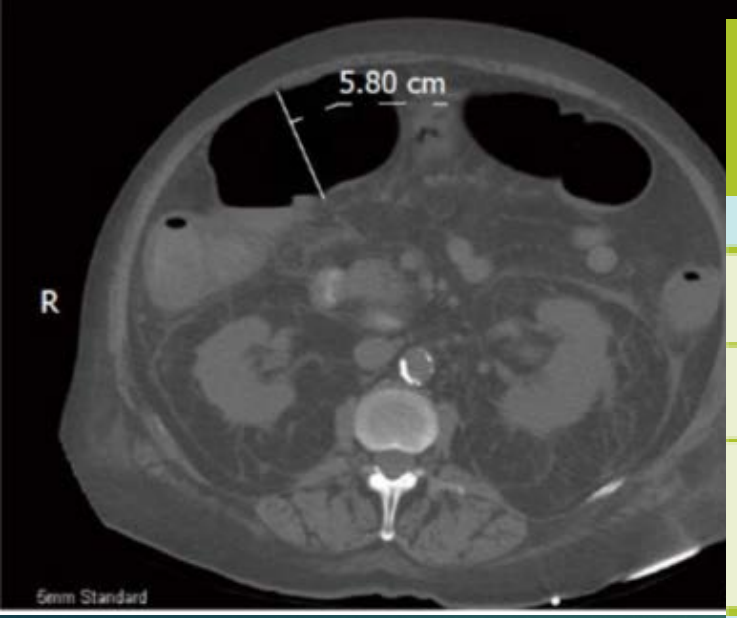
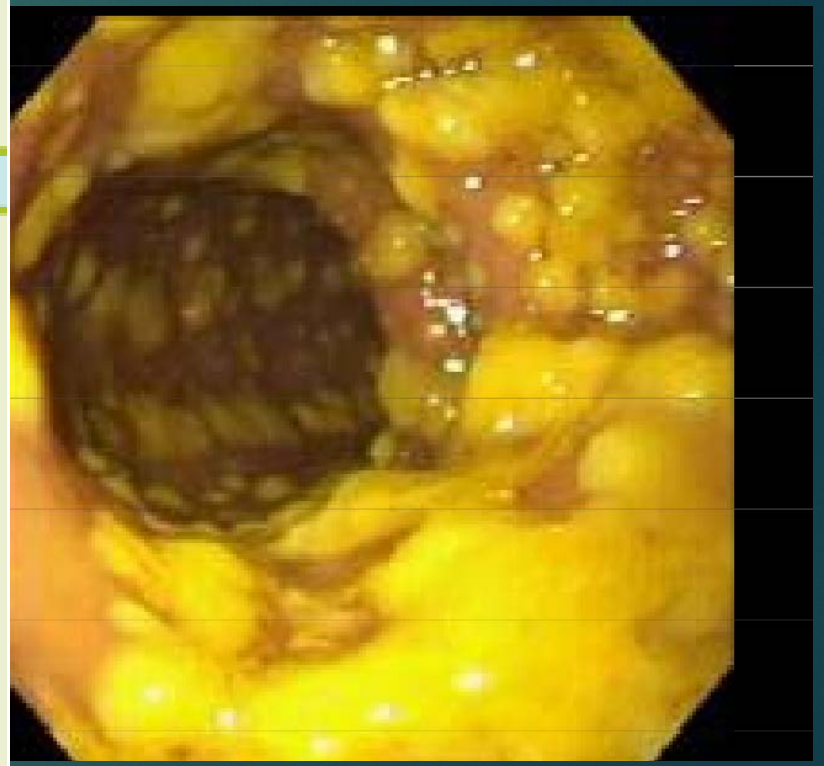


Tableau 3. Définition de la sévérité des infections à *Clostridium difficile*
(Adapté de réf.[1,5]).
ICD: infection à *Clostridium difficile*.

Critères de sévérité selon les experts américains	
ICD non sévère	Leucocytose < 15 G/l et créatininémie < 1,5 x valeur de base
ICD sévère	Leucocytose > 15 G/l ou créatininémie > 1,5 x valeur de base
ICD sévère compliquée	Hypotension ou choc ou iléus ou mégacôlon
Critères de sévérité selon les experts européens	
ICD sévère	Age > 65 ans ou comorbidités sévères ou patient aux soins intensifs ou immunodéficience ou Présence de ≥ 1 des critères suivants: Etat fébrile ≥ 38,5°C Frissons Instabilité hémodynamique (y compris choc septique) Signes de péritonite Signes d'iléus Leucocytose > 15 G/l Créatininémie > 1,5 x valeur de base Hyperlactatémie Colite pseudomembraneuse (endoscopie) Distension colique (CT-scan) Epaississement de la paroi colique (CT-scan) Densité de la graisse péricolique (CT-scan) Ascite sans autre cause



Zanella et al. Revue Médicale Suisse – octobre 2013
Cohen et al. Infect Control Hosp Epidemiol 2010;31

Prise en charge diagnostique des infections à CDIF

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European Society of Clinical Microbiology and Infectious Diseases: update of the diagnostic guidance document for *Clostridium difficile* infection

M.J.T. Crobach [1], T. Planche [4], C. Eckert [5], F. Barbut [5], E.M. Terveer [1], O.M. Dekkers [2,3], M.H. Wilcox [6], E.J. Kuijper [1,*]

[1] *Department of Medical Microbiology, Centre for Infectious Diseases, Leiden University Medical Center, Leiden, The Netherlands*
[2] *Departments of Clinical Epidemiology and Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands*
[3] *Department of Clinical Epidemiology, Aarhus University, Aarhus, Denmark*
[4] *Department of Medical Microbiology, St. George's Hospital, London, UK*
[5] *National Reference Laboratory for Clostridium difficile, Paris, France*
[6] *Department of Microbiology, Leeds Teaching Hospitals & University of Leeds, Leeds, UK*

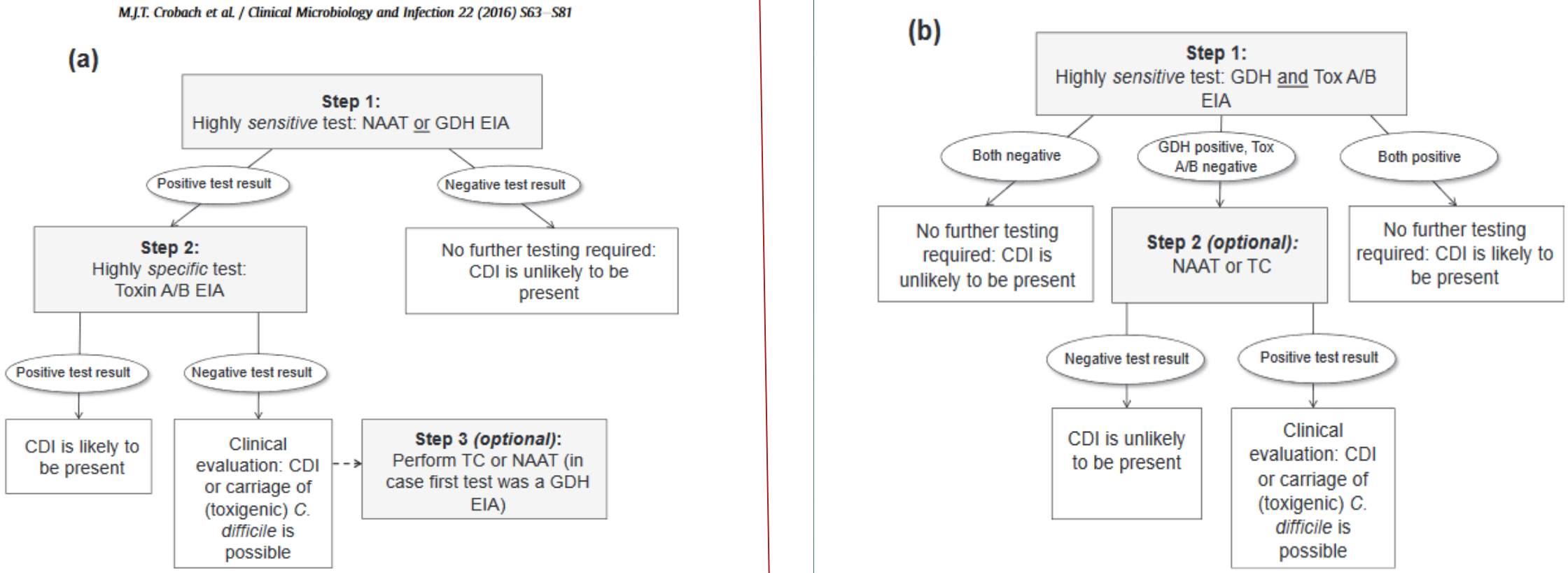

Fig. 3. Recommended algorithms for CDI testing. (a) GDH or NAAT–Tox A/B algorithm. (b) GDH and Tox A/B–NAAT/TC algorithm. CDI, *Clostridium difficile* infection; GDH, glutamate dehydrogenase; NAAT, nucleic acid amplification test; TC, toxigenic culture; Tox A/B, toxin A/B; EIA, enzyme immunoassay.

Prise en charge thérapeutique des infections à CDIF

Clinical Infectious Diseases

IDSA GUIDELINE

Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

L. Clifford McDonald,[1] Dale N. Gerding,[2] Stuart Johnson,[2,3] Johan S. Bakken,[4] Karen C. Carroll,[5] Susan E. Coffin,[6] Erik R. Dubberke,[7] Kevin W. Garey,[8] Carolyn V. Gould,[1] Ciaran Kelly,[9] Vivian Loo,[10] Julia Shaklee Sammons,[6] Thomas J. Sandora,[11] and Mark H. Wilcox[12]

[1]Centers for Disease Control and Prevention, Atlanta, Georgia; [2]Edward Hines Jr Veterans Administration Hospital, Hines, and [3]Loyola University Medical Center, Maywood, Illinois Hospital, Duluth, Minnesota; [5]Johns Hopkins University School of Medicine, Baltimore, Maryland; [6]Children's Hospital of Philadelphia, Pennsylvania; [7]Washington University Schoo St Louis, Missouri; [8]University of Houston College of Pharmacy, Texas; [9]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; [10]McGill University McGill University, Montréal, Québec, Canada; [11]Boston Children's Hospital, Massachusetts; and [12]Leeds Teaching Hospitals NHS Trust, United Kingdom

Clinical Microbiology and Infection

VOLUME 20, SUPPLEMENT 2, MARCH 2014

ORIGINAL ARTICLE 10.1111/1469-0691.12418

European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for *Clostridium difficile* infection

S. B. Debast[1], M. P. Bauer[2], E. J. Kuijper[3], on behalf of the Committee*

1) Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, Departments of 2) Infectious Diseases and 3) Medical Microbiology, Centre for Infectious Diseases, Leiden University Medical Centre, Leiden, the Netherlands

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A: Initial *Clostridium difficile* Infection: non-severe Disease

Non-antibiotic treatment

- In non-epidemic situations and with (non-severe) CDI clearly induced by the use of antibiotics, it may be acceptable to stop the inducing antibiotic and observe the clinical response for 48 h, but patients must be followed very closely for any signs of clinical deterioration and placed on therapy immediately if this occurs. (C-II).

Oral antibiotic treatment

- Metronidazole orally 500 mg three times daily for 10 days (A-I)
- Vancomycin orally 125 mg four times daily for 10 days (B-I)
- Fidaxomicin orally 200 mg twice daily for 10 days (B-I)

B: Severe *Clostridium difficile* Infection

Oral antibiotic treatment

- Vancomycin orally 125 mg four times daily for 10 days (A-I)
- Fidaxomicin orally 200 mg twice daily for 10 days (B-I)

Notes:

- It can be considered to increase the vancomycin dosage to 500 mg four times daily for 10 days (B-III)
- There is no evidence that supports the use of fidaxomicin in life-threatening CDI (D-III)

The use of oral metronidazole in severe CDI or life-threatening disease is strongly discouraged (D-I).

Surgical treatment

Total abdominal colectomy with ileostomy should be performed in case of:

- Perforation of the colon
- Systemic inflammation and deteriorating clinical condition not responding to antibiotic therapy; including toxic megacolon, an acute abdomen and severe ileus.

Surgical treatment should preferably be performed before colitis becomes very severe. Serum lactate may, *inter alia*, serve as a marker for severity (operate before lactate exceeds 5.0 mM).

A future alternative to colectomy may be diverting loop ileostomy and colonic lavage, combined with *antibiotic treatment* (intracolonic antegrade vancomycin and intravenous metronidazole).

C: First Recurrence or (Risk of) recurrent *Clostridium difficile* Infection

Oral antibiotic treatment

- Fidaxomicin orally 200 mg twice daily for 10 days (B-I)
- Vancomycin orally 125 mg four times daily for 10 days (B-I)
- Metronidazole orally 500 mg three times daily for 10 days (C-I)

Note: Fidaxomicin was not associated with fewer recurrences in CDI due to PCR ribotype 027 as opposed to non-027 ribotypes.

D: Multiple recurrent *Clostridium difficile* Infection

Oral antibiotic treatment

- Fidaxomicin orally 200 mg twice daily for 10 days (B-II)
- Vancomycin orally 125 mg four times daily for 10 days followed by pulse strategy (B-II)
- or
- Vancomycin orally 125 mg four times daily for 10 days followed by taper strategy (B-II)

Non-antibiotic treatment in combination with oral antibiotic treatment

For multiple recurrent CDI unresponsive to repeated antibiotic treatment, faecal transplantation in combination with oral antibiotic treatment is strongly recommended (A-I).

E: Treatment of *Clostridium difficile* Infection when oral Administration is not possible

Antibiotic treatment

Non-severe CDI: intravenous metronidazole 500 mg three times daily for 10 days (A-II).

Severe CDI: intravenous metronidazole 500 mg three times daily for 10 days (A-II) combined with vancomycin retention enema 500 mg in 100 mL normal saline four times daily intracolonic, or combined with vancomycin 500 mg four times daily by oral/nasogastric tube for 10 days (B-III).

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Table 6. Evidence for Resolution of Symptoms and Sustained Resolution ~1 Month (21–30 Days) After Treatment for Specific *Clostridium difficile* Treatment Agents

Outcomes	No. of Participants (No. of Studies)	Percentage Resolution	Relative Effect[a] (95% CI)	*P* Value	Quality of Evidence (GRADE)[b]	Reference, First Author
Direct comparisons of metronidazole and vancomycin						
Resolution of diarrhea at end of (10 days) treatment	RCTs prior to 2000: 156 (2)	95 (MTR) 98 (VAN)	RR, 0.97 (.91–1.03)	.4		Teasley [168] Wenisch [310]
	RCTs since 2000: 687[c] (3)	75 (MTR) 85 (VAN)	RR, 0.89 (.82–.96)	.002		Zar [188] Johnson [170]
	All RCTs: 843 (5)	78 (MTR) 87 (VAN)	RR, 0.89 (.85–.96)	.0008	⊕⊕⊕⊕ High	
Resolution of diarrhea at end of treatment without CDI recurrence ~1 month after treatment	RCTs prior to 2000: 156 (2)	85 (MTR) 84 (VAN)	RR, 1.0 (.90–1.2)	1.0		Teasley [168] Wenisch [310]
	RCTs since 2000: 687[c] (3)	59 (MTR) 70 (VAN)	RR, 0.84 (.74–.94)	.002		Zar [188] Johnson [170]
	All RCTs: 843 (5)	63 (MTR) 73 (VAN)	RR, 0.87 (.79–.96)	.003	⊕⊕⊕⊕ High	
Direct comparisons of fidaxomicin and vancomycin						
Resolution of diarrhea at end of (10 days) treatment	1105[d] (2)	88 (FDX) 86 (VAN)	RR, 1.0 (.98–1.1)	.36	⊕⊕⊕⊕ High	Louie [321] Cornely [324]
Resolution of diarrhea at end of treatment without CDI recurrence ~1 month after treatment	1105[d] (2)	71 (FDX) 57 (VAN)	RR, 1.2 (1.1–1.4)	<.0001	⊕⊕⊕⊕ High	Louie [321] Cornely [324]
Direct comparisons of FMT and vancomycin						
Resolution of diarrhea at end of treatment without CDI recurrence 56 days after treatment	29 (1)	81 (FMT) 31 (VAN[e])	RR, 2.6 (1.1, 6.2)	.01	⊕⊕⊕⊖ Moderate	van Nood [367]

Table 1. Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

Clinical Definition	Supportive Clinical Data	Recommended Treatment[a]	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	Leukocytosis with a white blood cell count of ≤15 000 cells/mL and a serum creatinine level <1.5 mg/dL	• VAN 125 mg given 4 times daily for 10 days, OR	Strong/High
		• FDX 200 mg given twice daily for 10 days	Strong/High
		• Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days	Weak/High
Initial episode, severe[b]	Leukocytosis with a white blood cell count of ≥15 000 cells/mL or a serum creatinine level >1.5 mg/dL	• VAN, 125 mg 4 times per day by mouth for 10 days, OR	Strong/High
		• FDX 200 mg given twice daily for 10 days	Strong/High
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	• VAN, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present.	Strong/Moderate (oral VAN); Weak/Low (rectal VAN); Strong/Moderate (intravenous metronidazole)
First recurrence	…	• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR	Weak/Low
		• Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode	Weak/Moderate
Second or subsequent recurrence	…	• VAN in a tapered and pulsed regimen, OR	Weak/Low
		• VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days, OR	Weak/Low
		• Fecal microbiota transplantation[c]	Strong/Moderate

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Initial episode, severe[b]	Leukocyto… blood c… cells/m… nine l…	• VAN, 125 mg 4 times per day by mouth for 10 days, OR • …200 mg given twice daily for 10 days	Strong/High Strong/High
Initial episode, fulminant	Hypoter… meg…	…nasogastric tube. If ileus, …ministered met-	Strong/Moderate (oral VAN); Weak/Low (rectal VAN); Strong/Moderate (intrave- …metronidazole)
First recurrence	…	the initi…	…ow
		• Use a prolonged tapered … imen was used for the initial episode … 10–14 days, 2 times per day for a week, once per … then every 2 or 3 days for 2–8 weeks), OR	…Low
		• FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode	Weak/Moderate
Second or subsequent recurrence	…	• VAN in a tapered and pulsed regimen, OR	Weak/Low
		• VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR	Weak/Low
		• FDX 200 mg given twice daily for 10 days, OR	Weak/Low
		• Fecal microbiota transplantation[c]	Strong/Moderate

- **Disparition du Metronidazole en 1ère intention dans les formes non sévères**
- **FMT fortement recommandée dès la seconde récurrence**

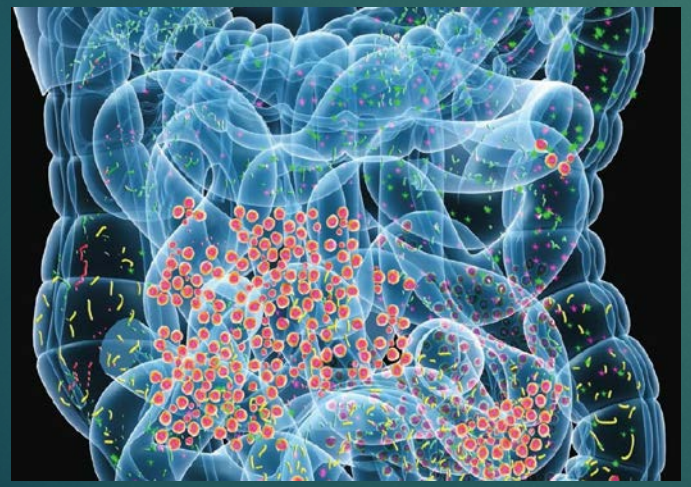
« Prévenir le *Clostridium*, c'est pas *Difficile…ou presque* »

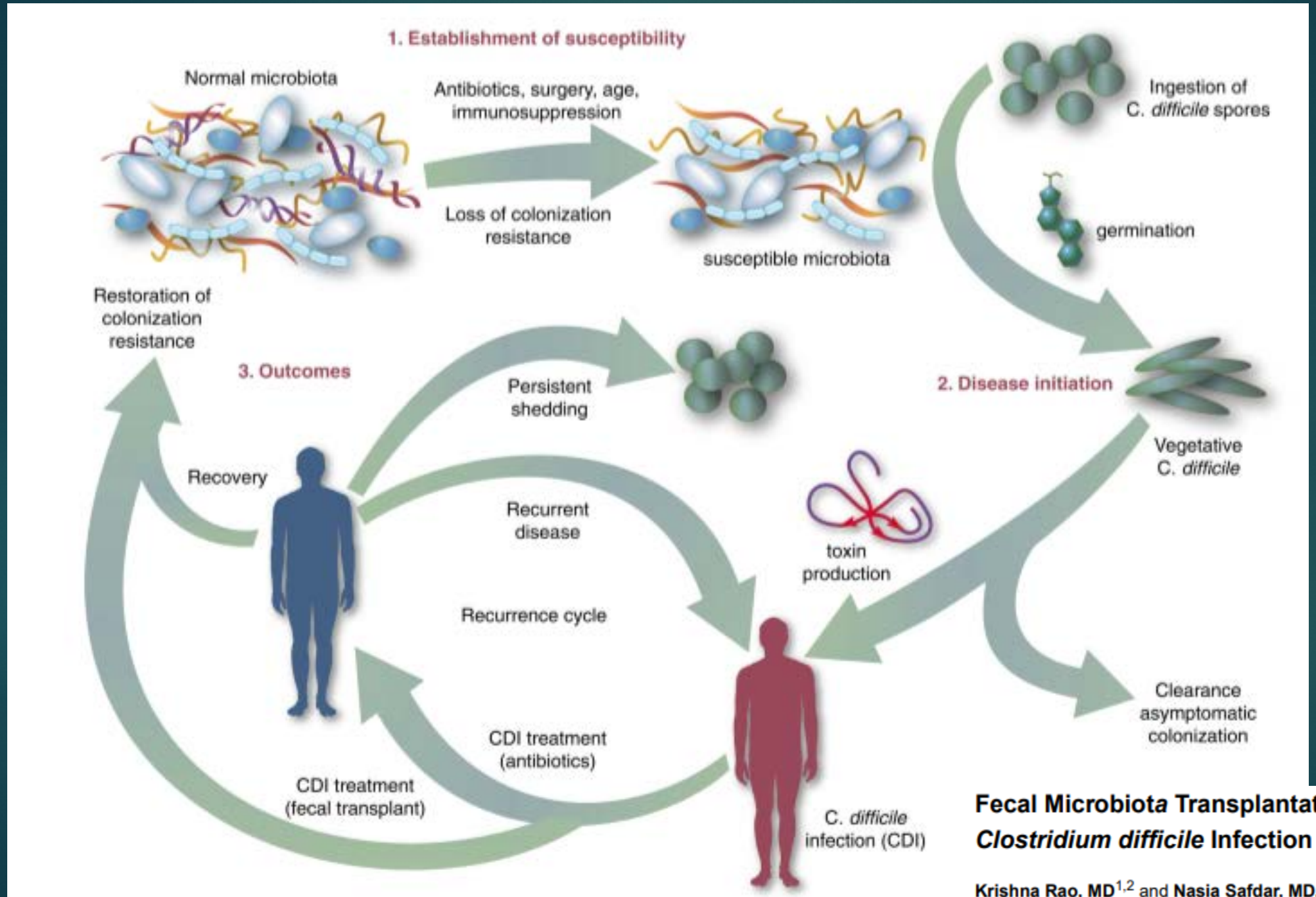
Table 5. Quasi-experimental Studies on the Association Between Antibiotic Stewardship Interventions and *Clostridium difficile* Infection

Year [Reference]	Area	Time Frame	Setting (Bed Size)	Dominant Strain	Stewardship Method	Target	Targeted Antibiotics Decrease	Global Change in Hospital Antibiotic Use	CDI Rate Method	Pre-intervention	Post-intervention	Reduction in CDI Rates
1994 [272]	US	1990–1992	Hospital (168)	J7	Restrictive use	Clindamycin	>90%	NR	[a]	15.8	1.9	88%
1997 [273]	UK	1994–1995	Hospital (NR)	NR	Restrictive use	Cefuroxime	>90%	NR	[b]	5.3	2.3	57%
1998 [274]	US	1992–1996	Hospital (703)	Clonal strain A	Restrictive use	Clindamycin	>90%	No change	[b]	11.5	3.3	71%
2003 [275]	UK	1995–2000	Hospital (800)	NR	Restrictive use	Ceftriaxone	>90%	NR	[c]	14.6	3.4	77%
2003 [276]	US	1991–1998	Hospital (159)	NR	Prospective audit and feedback	Third-generation cephalosporins and aztreonam	75%	Decreased	[c]	2.2	0.3	86%
2004 [277]	UK	1997–2002	Hospital (24 ward beds)	NR	Restrictive use	Cefotaxime	83%	No change	[a]	46	22	52%
2004 [278]	US	2001–2003	LTCF (100)	A	Restrictive use	Gatifloxacin	>90%	No change	[c]	1.32	0.51	61%
2007 [279]	Canada	2003–2006	Hospital (683)	027	Restrictive use	High-risk antibiotics	80%	Decreased	[c]	2.03	0.82	60%
2007 [280]	UK	1999–2003	Hospital (78 ward beds)	NR	Prospective audit and feedback	Cephalosporins and amoxicillin-clavulanate	50%–75%	No change	[b]	NR	NR	65%
2011 [281]	UK	2005–2007	Hospital (495)	027	Restrictive use	High-risk antibiotics	50%–75%	No change	[c]	2.22	0.45	80%
2012 [282]	Canada	2008–2010	Hospital (48 ICU beds)	NR	Prospective audit and feedback	High-risk antibiotics	20%	Decreased	[c]	1.12	0.71	37%
2013 [283]	UK	2008–2011	Hospital (215)	NR	Restrictive use	Ceftriaxone and ciprofloxacin	70%–90%	NR	[c]	2.398	1.2	50%
2011 [284]	Ireland	2004–2009	Hospital (665)	027	Restrictive use	Quinolones	>90%	NR	[c]	0.8	0.746	[d]
2012 [285]	Ireland	2004–2010	Hospital (233)	NR	Restrictive use	High-risk antibiotics	70%–90%	Decreased	[c]	0.8	0.7	[e]
2012 [286]	US	2007–2010	LTCF (160)	NR	Prospective audit and feedback	High-risk antibiotics	25%–50%	Decreased	[c]	NR	NR	[f]

Thérapeutiques basées sur le microbiote et infections à CDIF

- PROBIOTIQUES
- TRANSPLANTATION FECALE DE MICROBIOTE
- BACTERIOPHAGES





Fecal Microbiota Transplantation for the Treatment of *Clostridium difficile* Infection

J Hosp Med. 2016 January ; 11(1):

Krishna Rao, MD[1,2] and **Nasia Safdar, MD, PhD.**[3,*]

Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children (Review)

Goldenberg JZ, Yap C, Lytvyn L, Lo CKF, Beardsley J, Mertz D, Johnston BC

Probiotics compared to control for preventing *C. difficile* associated diarrhea

Patient or population: preventing *C. difficile* associated diarrhea
Setting: inpatient and outpatient
Intervention: probiotics
Comparison: control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with probiotics				
Incidence CDAD: complete case	Study population 40 per 1,000	16 per 1,000 (12 to 21)	RR 0.40 (0.30 to 0.52)	8672 (31 RCTs)	⊕⊕⊕◯ MODERATE [1]	Note: Risk with control calculated by pooled event rate across control groups
CDAD (baseline risk 0-2%)	Study population 11 per 1,000	8 per 1,000 (5 to 14)	RR 0.77 (0.45 to 1.32)	5845 (15 RCTs)	⊕⊕⊕◯ MODERATE [2]	
CDAD (baseline risk 3-5%)	Study population 38 per 1,000	20 per 1,000 (6 to 67)	RR 0.53 (0.16 to 1.77)	373 (3 RCTs)	⊕⊕◯◯ LOW [3,4]	
CDAD (baseline risk >5%)	Study population 116 per 1,000	35 per 1,000 (24 to 49)	RR 0.30 (0.21 to 0.42)	2454 (13 RCTs)	⊕⊕⊕◯ MODERATE [5]	
Incidence of *C. difficile* infection: complete case	Study population		RR 0.86 (0.67 to 1.10)	1214 (15 RCTs)	⊕⊕⊕◯ MODERATE [6]	

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	40 per 1,000	16 per 1,000 (12 to 21)				

This review includes 39 randomized trials with a total of 9955 participants. Thirty-one studies (8672 participants) assessed the effectiveness of probiotics for preventing CDAD among participants taking antibiotics. Our results suggest that when probiotics are given with antibiotics the risk of developing CDAD is reduced by 60% on average. Among trials enrolling participants at high risk of developing CDAD (> 5%), the potential benefit of probiotics is more pronounced with a 70% risk reduction on average. Side effects were assessed in 32 studies (8305 participants) and our results suggest that taking probiotics does not increase the risk of developing side effects. The most common side effects reported in these studies include abdominal cramping, nausea, fever, soft stools, flatulence, and taste disturbance. The short-term use of probiotics appears to be safe and effective when used along with antibiotics in patients who are not immunocompromised or severely debilitated. Despite the need for further research, hospitalized patients, particularly those at high risk of CDAD, should be informed of the potential benefits and harms of probiotics.

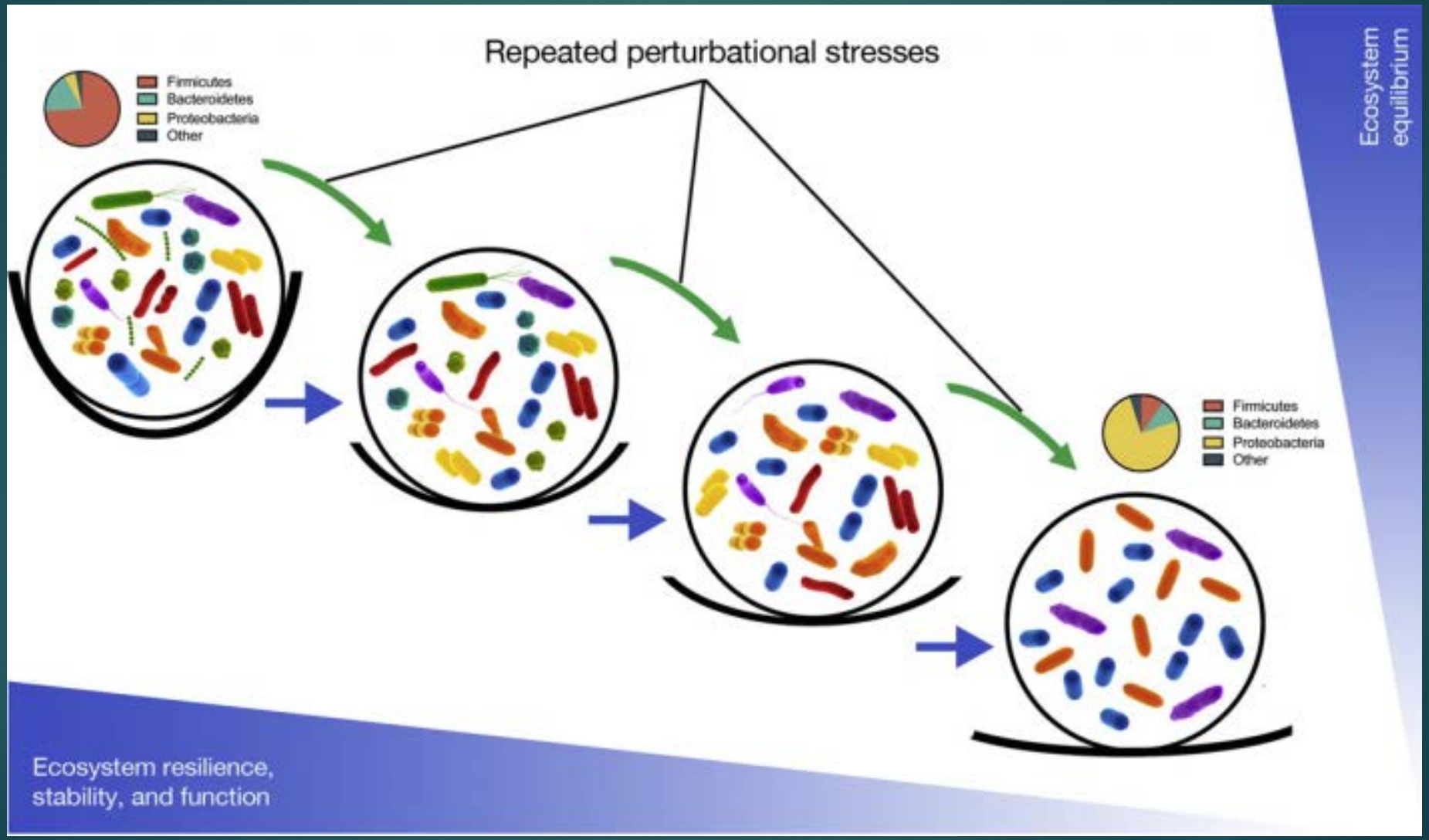
Incidence of *C. difficile* infection: complete case	Study population		RR 0.86 (0.67 to 1.10)	1214 (15 RCTs)	⊕⊕⊕◯ MODERATE [6]	

Fecal Microbiota-based Therapeutics for Recurrent *Clostridium difficile* Infection, Ulcerative Colitis and Obesity

Christian Carlucci [a,*], Elaine O. Petrof [b], Emma Allen-Vercoe [a]

13 (2016) 37–45

[a] Department of Molecular and Cellular Biology, University of Guelph, 50 Stone Road East, Guelph, Ontario N1G 2W1, Canada
[b] Division of Infectious Diseases/GI Diseases Research Unit Wing, Department of Medicine, Kingston General Hospital, Queen's University, 76 Stuart Street, Kingston,



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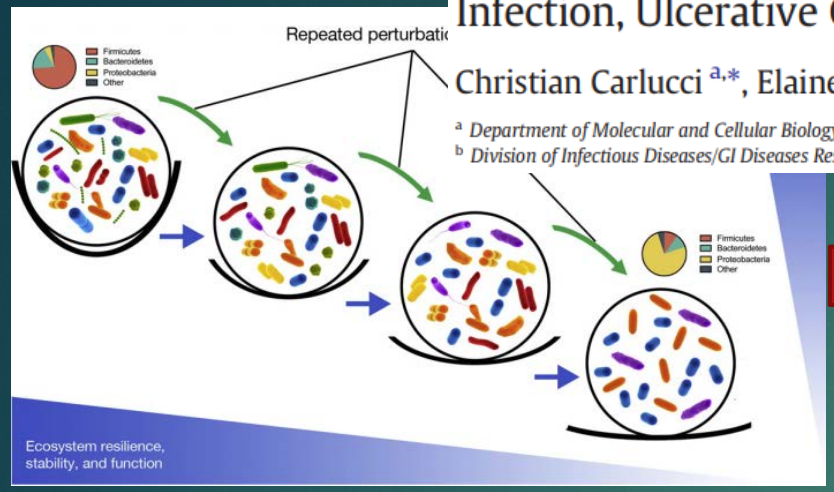


- **Diminution de la diversité microbienne**
- **Plus de Proteobacteria**
- **Moins de Bacteroidetes**
- **Moins de Firmicutes**

Microbial taxa positively correlated to select gut conditions in human subjects.

Condition	Study size/details	Microbial taxonomic changes associated with condition[a]	Reference
CDI	Fecal samples from n = 14 recurrent CDI patients (4 within this group given FMT)	↑ Proteobacteria, ↓ Bacteroidetes, ↓ Firmicutes	Weingarden et al., 2015
	Fecal samples from n = 94 CDI, and n = 89 non-CDI inpatients	↑ Proteobacteria, ↓ Firmicutes (except Enterococcus and Erysipelotrichia and some Lachnospiraceae)	Schubert et al., 2014
	Fecal samples from n = 9 recurrent CDI patients given FMT in van Nood et al. (2013) study	↑ Proteobacteria, ↑ Bacilli, ↓ Bacteroidetes, ↓ Firmicutes, ↓ overall microbial diversity compared to post-FMT and healthy donor samples	Fuentes et al., 2014
	Fecal samples from n = 22 *C. difficile* culture-positive elderly subjects, and n = 252 healthy elderly subjects	↑ Proteobacteria, Firmicutes (↓ Enterococcaceae and ↑ Lactobacillaceae), ↓ overall microbial diversity	Rea et al., 2012
	Fecal samples from n = 39 CDI patients, n = 36 *C. difficile*-negative nosocomial diarrhea patients, and n = 40 healthy control subjects	↓ Firmicutes, ↑ Proteobacteria, ↓ Microbial diversity in both diarrheal groups compared to healthy controls	Antharam et al., 2013
	Stool samples from n = 6 CDI patients given FMT	↑ Proteobacteria, ↓ Bacteroidetes, ↓ Firmicutes (specifically Lachnospiraceae, ↓ overall microbial diversity	Shahinas et al., 2012

Le 1er essai clinique randomisé évaluant la FMT dans les infections à CDIF

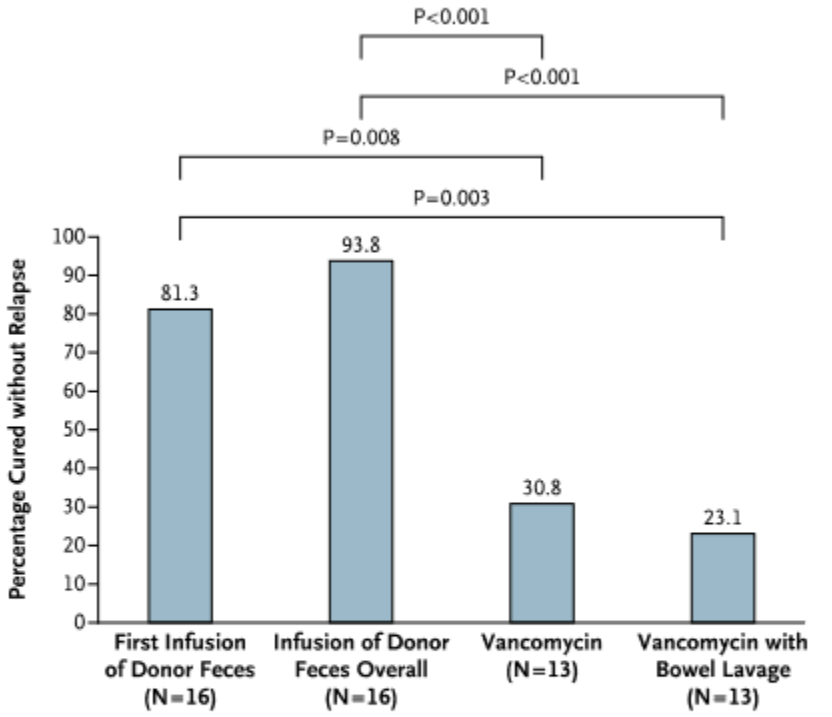


Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.

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.

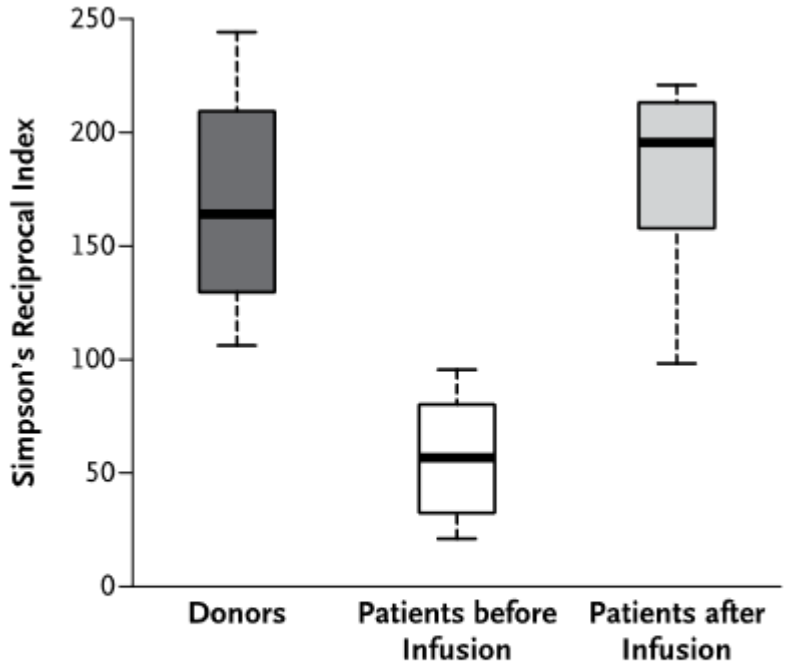


Figure 3. Microbiota Diversity in Patients before and after Infusion of Donor Feces, as Compared with Diversity in Healthy Donors.

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

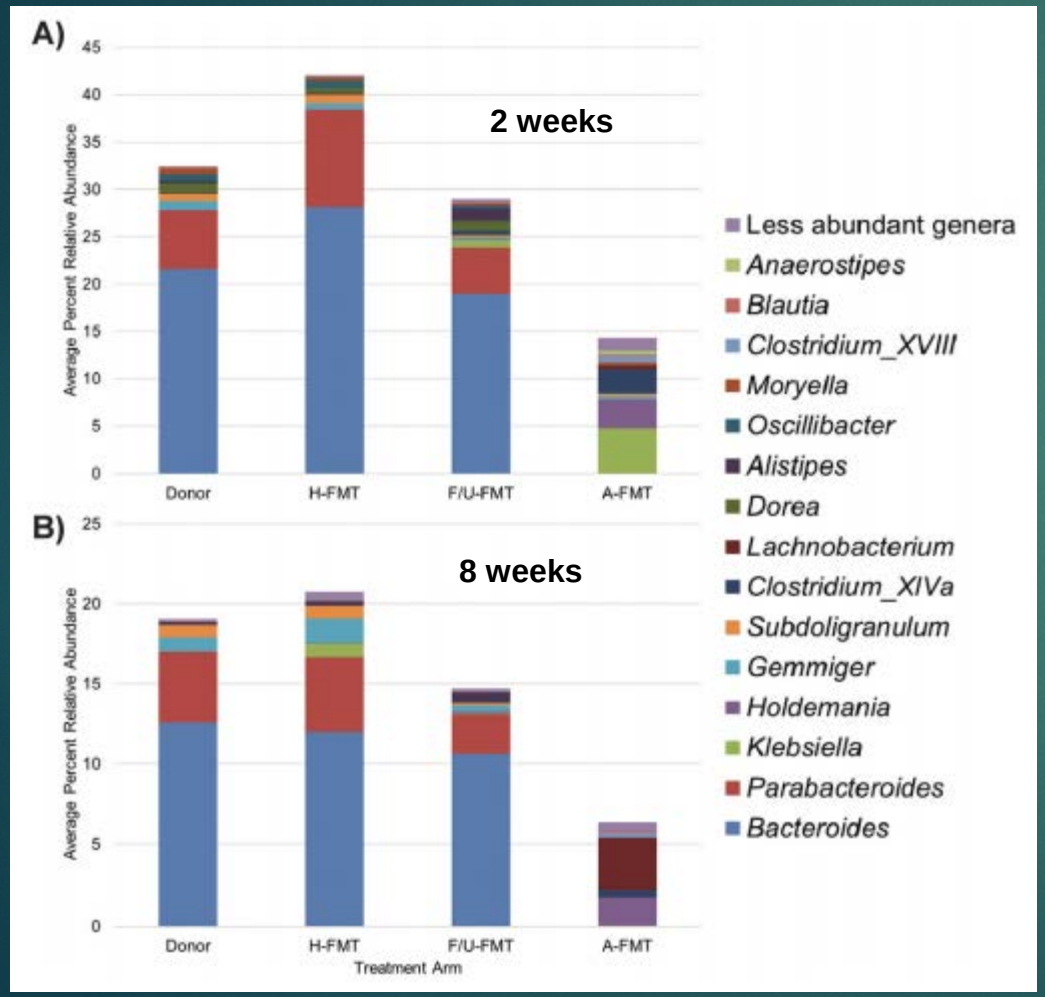
Adverse Event	On Day of Infusion of Donor Feces	During Follow-up
	no. of events	
Belching	3	0
Nausea	1	0
Vomiting	0	0
Abdominal cramps	5	0
Diarrhea	15	0
Constipation	0	3
Abdominal pain	2 (associated with cramping)	0
Infection	0	2†
Hospital admission	NA	1‡
Death	0	0
Other adverse event	1§	1‡

Van Nood, NEJM 2013

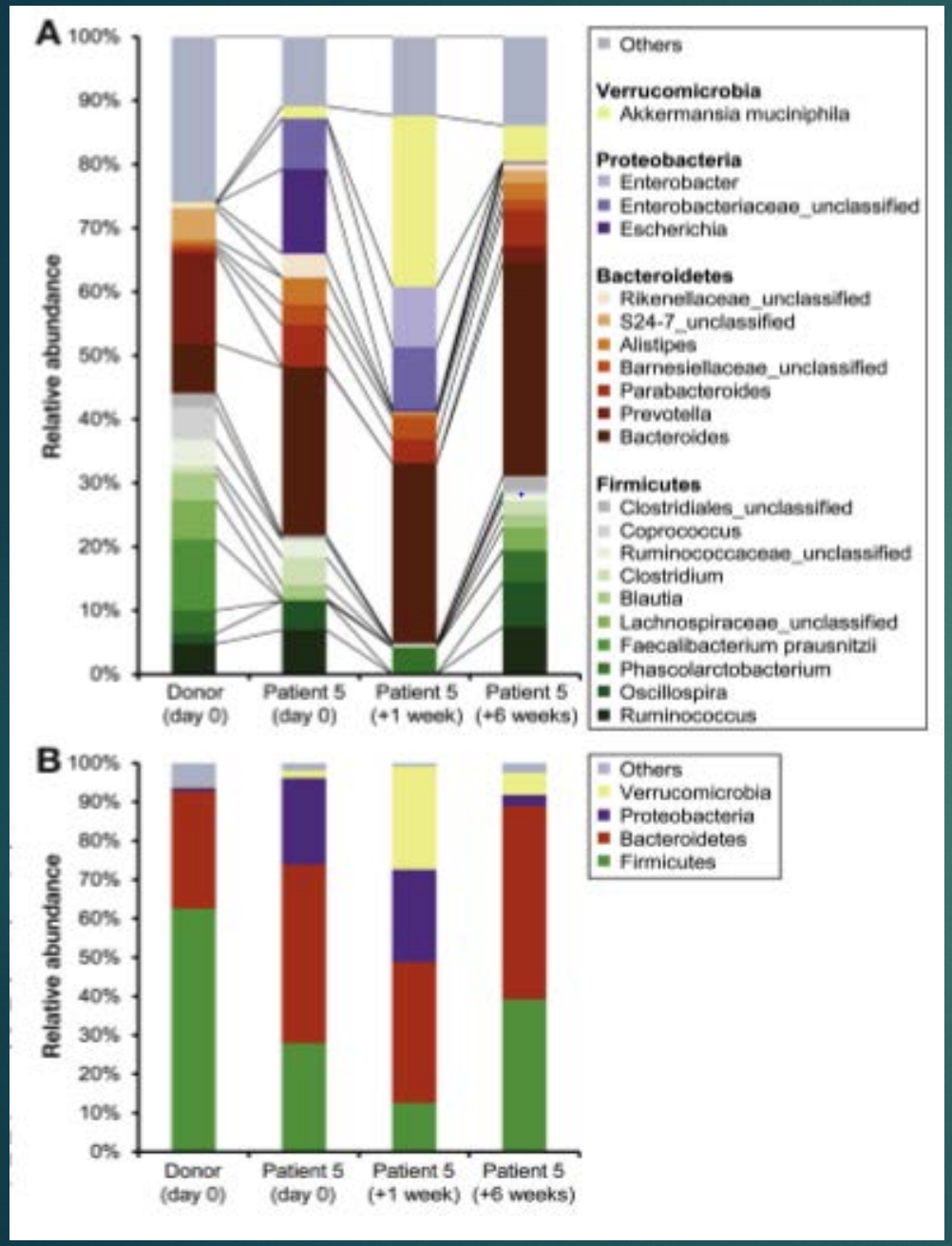
Complete Microbiota Engraftment Is Not Essential for Recovery from Recurrent *Clostridium difficile* Infection following Fecal Microbiota Transplantation

Christopher Staley,[a] Colleen R. Kelly,[b,c] Lawrence J. Brandt,[d] Alexander Khoruts,[a,e] Michael J. Sadowsky[a,f]

mBio® mbio.asm.org 2016 Volume 7 Issue 6



- **Greffe: FMT Hétérologue > Autologue**
- **Bénéfice des bactéries associées au métabolisme de l'acide biliaire ➔ Mécanisme pouvant renforcer la résistance aux infections**
- **Greffe « utile » plutôt que greffe « complète »?**

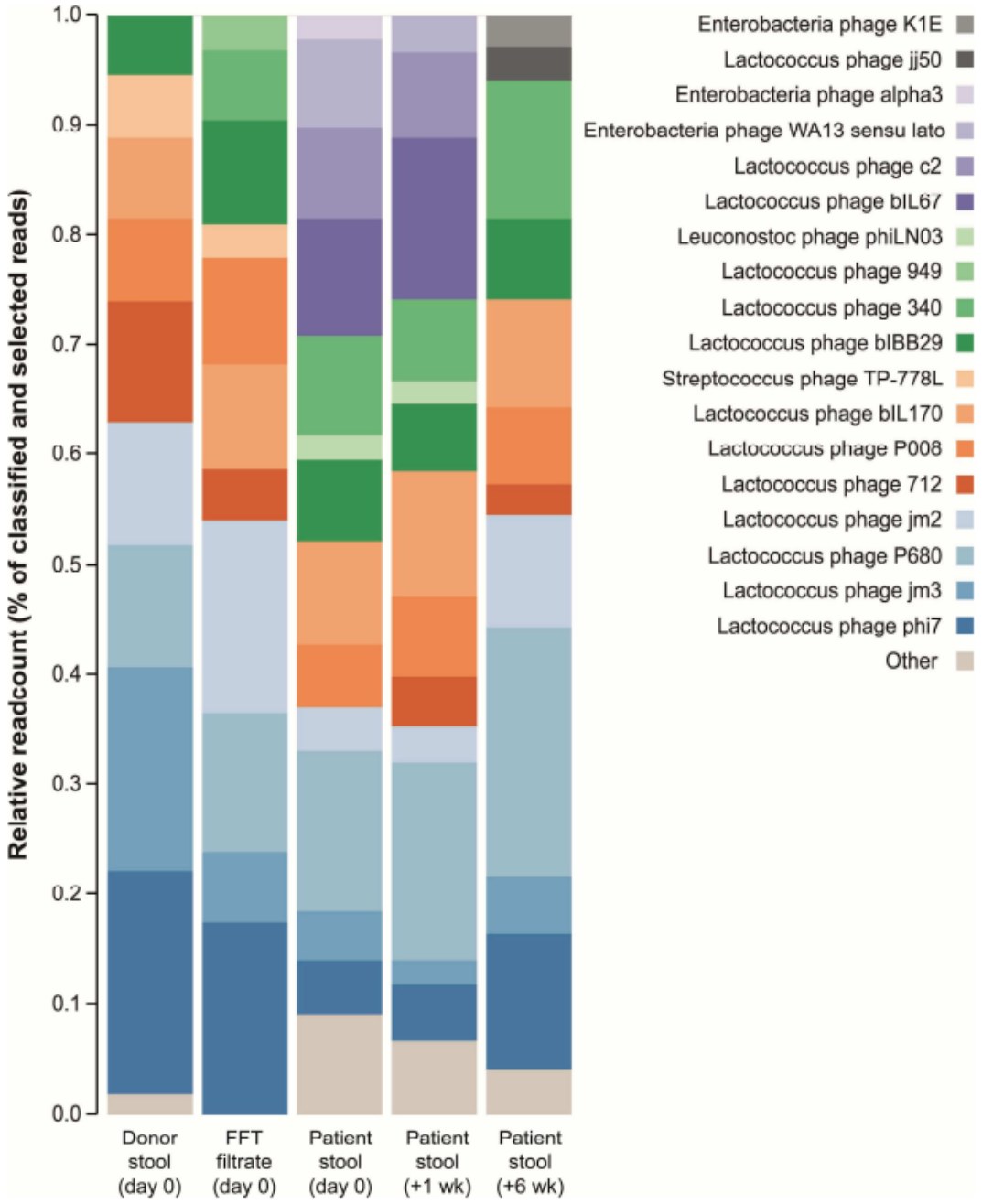


Efficacy of Sterile Fecal Filtrate Transfer for Treating Patients With *Clostridium difficile* Infection

Stephan J. Ott,[1,*] **Georg H. Waetzig**,[2,*] **Ateequr Rehman**,[3,*] Jacqueline Moltzau-Anderson,[3,4] Richa Bharti,[3] Juris A. Grasis,[5] Liam Cassidy,[6] Andreas Tholey,[6] Helmut Fickenscher,[7] Dirk Seegert,[2] Philip Rosenstiel,[3,§] and Stefan Schreiber[1,3,§]

Gastroenterology 2017;152:799–811

- **Restauration de la diversité du microbiote intestinal**
- **Diminution des Proteobacteria**
- **Augmentation des Firmicutes**



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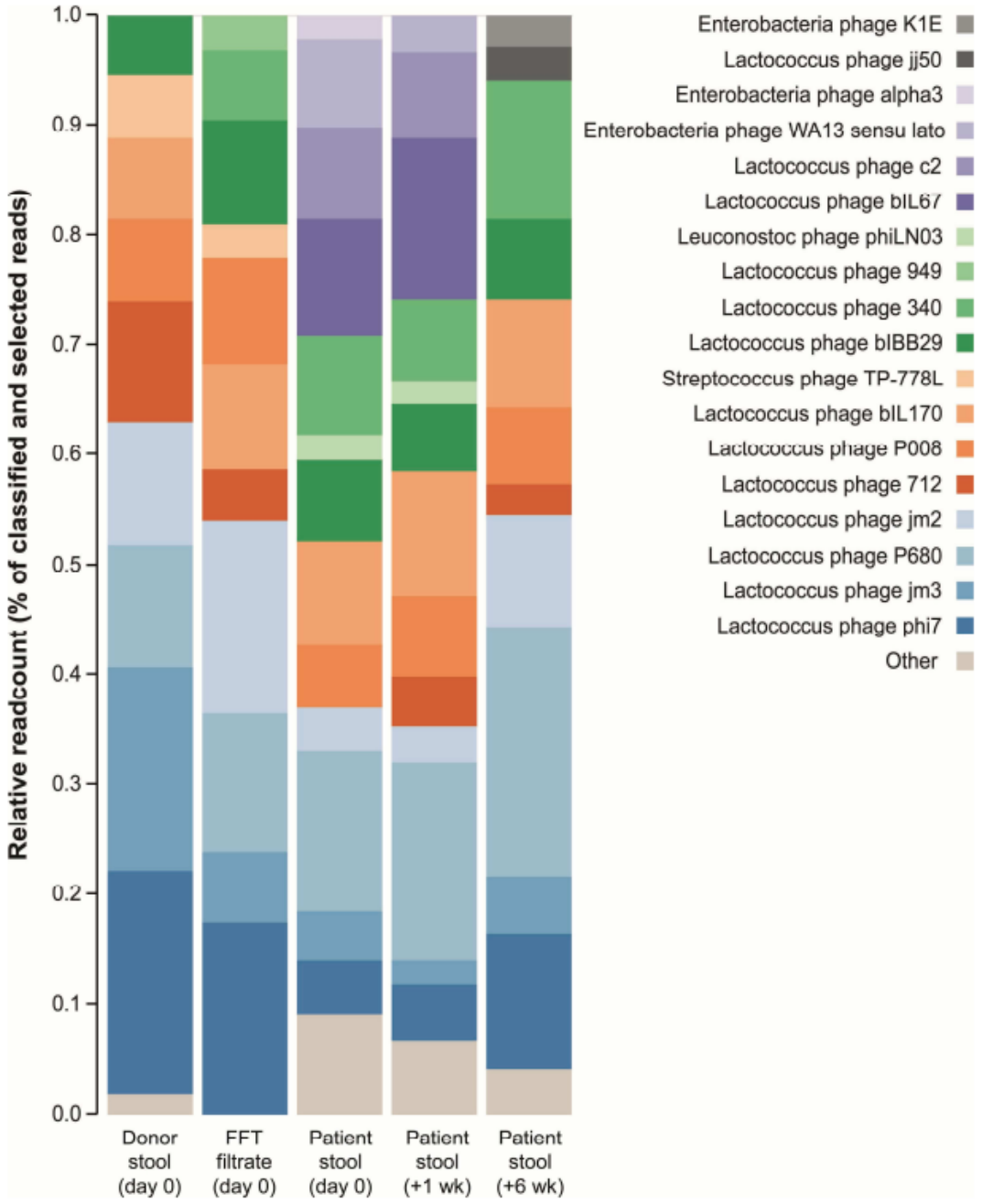
Gastroenterology 2017;152:799–811

- Restauration de la diversité du phageome intestinal
- Diminution des phages Enterobacteria
- Augmentation des phages Lactococcus



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Gastroenterology 2017;152:799–811

- Restauration de la diversité du phageome intestinal
- Diminution des phages Enterobacteria
- Augmentation des phages Lactococcus

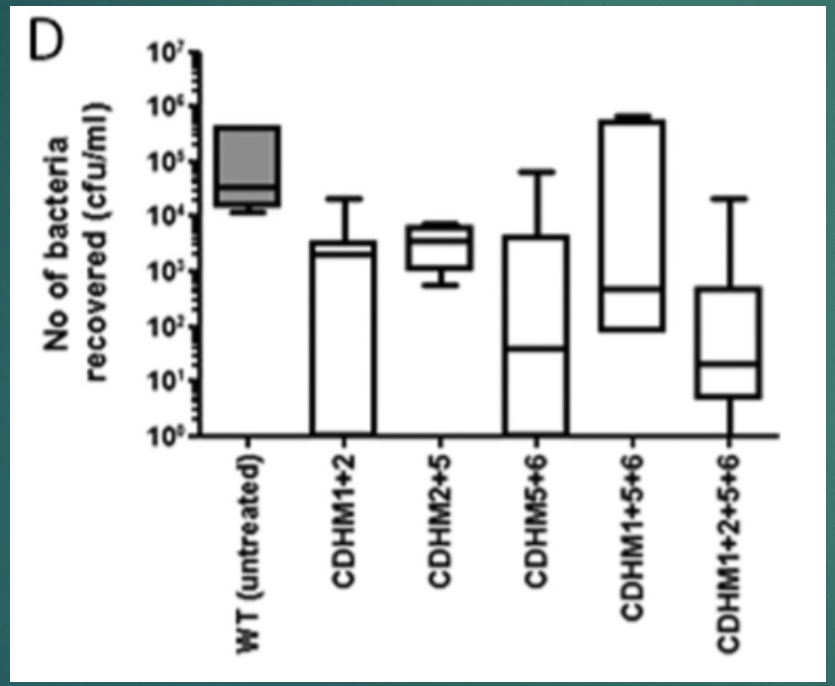
Action propre des phages sur CDIF ?

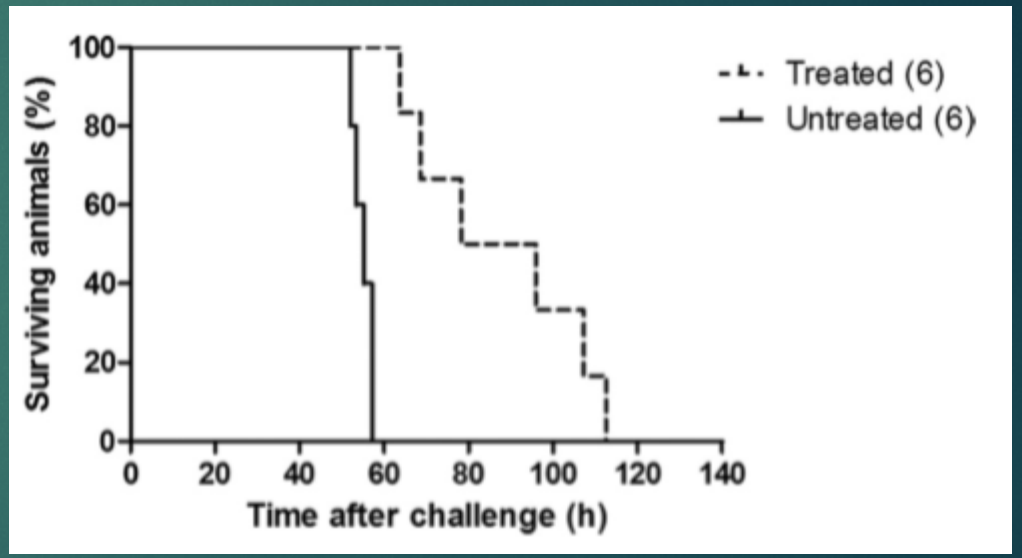
Bacteriophage Combinations Significantly Reduce *Clostridium difficile* Growth *In Vitro* and Proliferation *In Vivo*

Janet Y. Nale,[a] Janice Spencer,[b] Katherine R. Hargreaves,[a] Anthony M. Buckley,[b] Przemysław Trzepiński,[a] Gillian R. Douce,[b] Martha R. J. Clokie[a]

Department of Infection, Immunity and Inflammation, University of Leicester, Leicester, England, United Kingdom[a]; Institute of Infection, Immunity and Inflammation, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, Scotland, United Kingdom[b]

Antimicrobial Agents and Chemotherapy February 2016 Volume 60 Number 2





ORIGINAL ARTICLE

Bacteriophage transfer during faecal microbiota transplantation in *Clostridium difficile* infection is associated with treatment outcome

Zuo T, *et al*. *Gut* 2018;**67**:634–643.

What is already known on this subject?

- Faecal microbiota transplantation (FMT) is highly effective for the treatment of recurrent *Clostridium difficile* infection (CDI).
- Studies have shown bacterial colonisation after FMT, but data on viral alterations in CDI and the association between viral colonisation and treatment outcome are largely unknown.

Objective Faecal microbiota transplantation (FMT) is effective for the treatment of recurrent *Clostridium difficile* infection (CDI). Studies have shown bacterial colonisation after FMT, but data on viral alterations in CDI are scarce. We investigated enteric virome alterations in CDI and the association between viral transfer and clinical outcome in patients with CDI.
Design Ultra-deep metagenomic sequencing of virus-like particle preparations and bacterial 16S rRNA sequencing were performed on stool samples from 24 subjects with CDI and 20 healthy controls. We longitudinally assessed the virome and bacterial microbiome changes in nine CDI subjects treated with FMT and five treated with vancomycin. Enteric virome alterations were assessed in association with treatment response.

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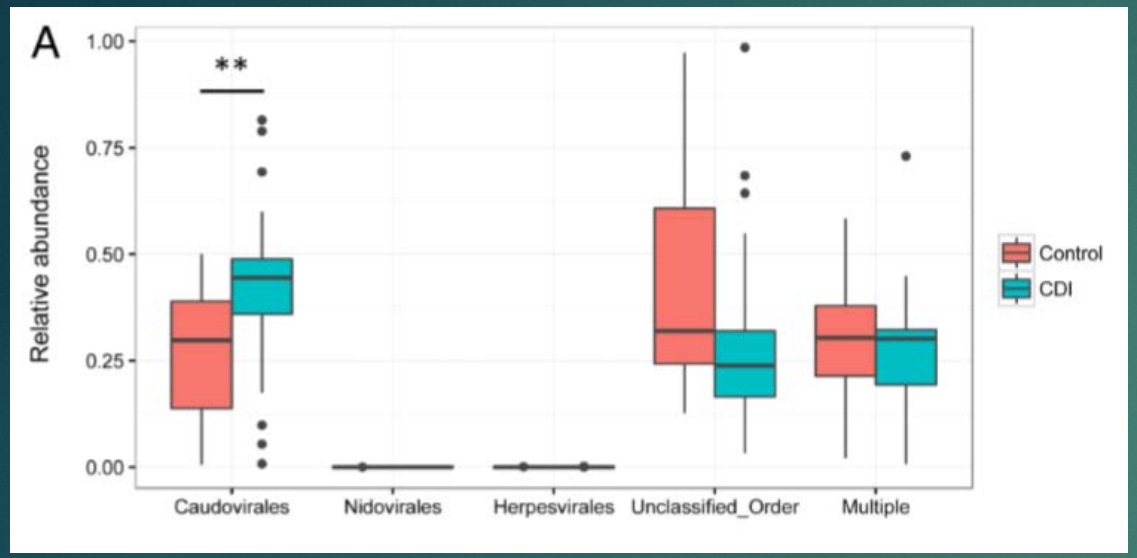

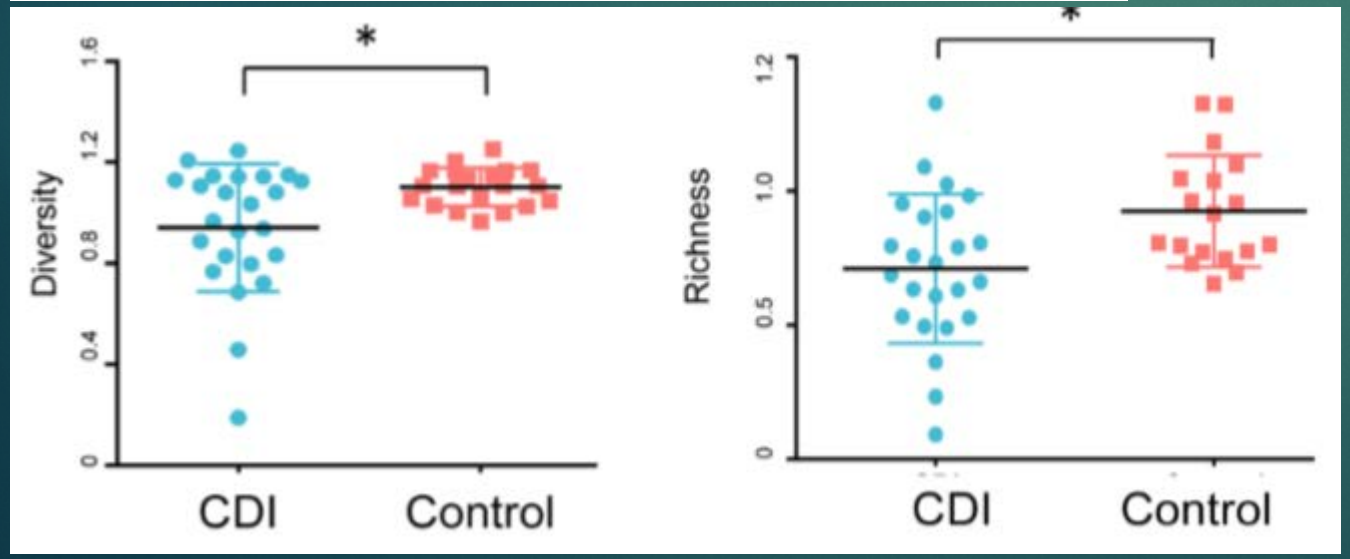

What are the new findings?

- CDI was characterised by a high abundance of *Caudovirales* bacteriophages and a low *Caudovirales* diversity, richness and evenness compared with healthy household controls.
- Donor-derived *Caudovirales* taxa occupied a significantly larger fraction of the enteric virome in CDI subjects who responded to FMT compared with those who did not.
- FMT was associated with alterations in the enteric virome and bacterial microbiome, while vancomycin treatment was associated with alterations of the bacterial microbiome only.
- Recipients infused with donor faeces consisting of a higher richness of *Caudovirales* than that of recipient were all cured with FMT. CDI subjects who had restoration of bacteria community only were found to have disease recurrence.

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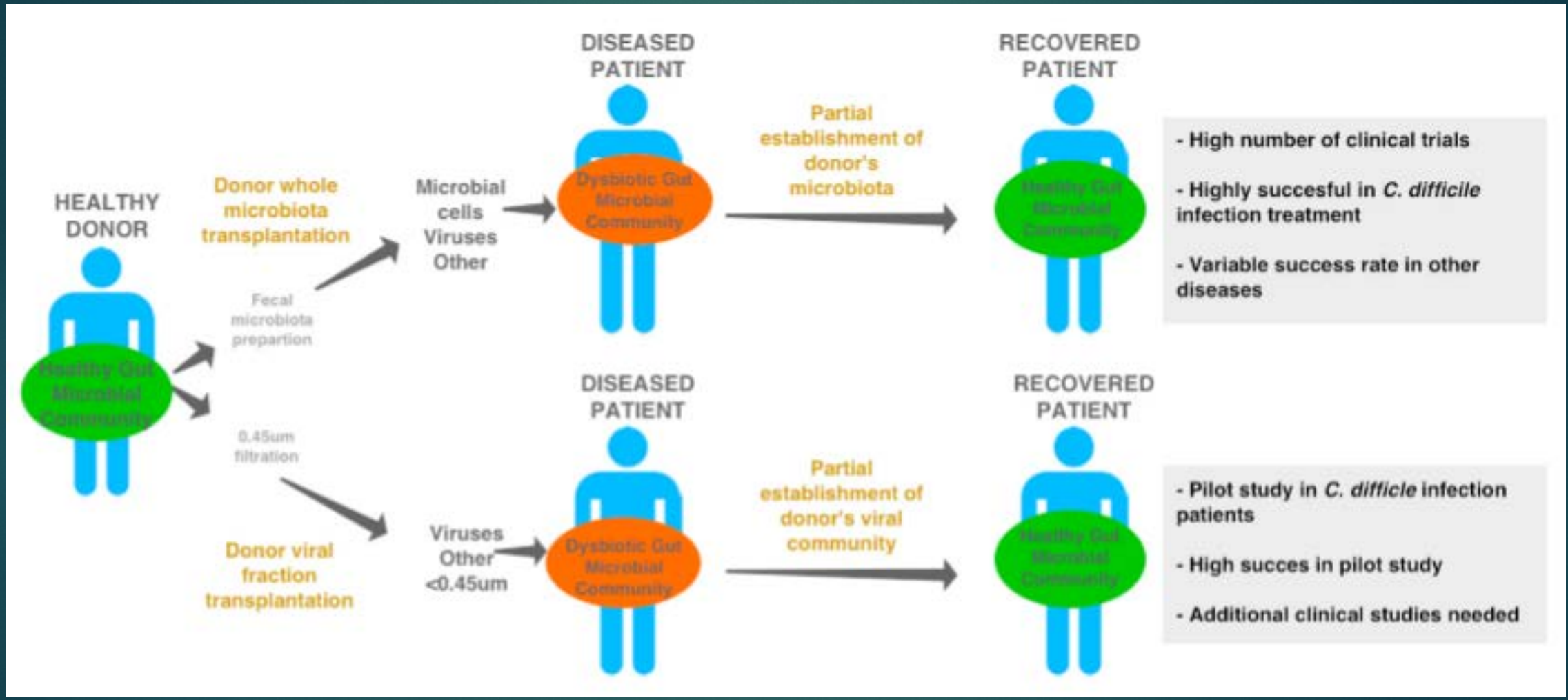
How might it impact on clinical practice in the foreseeable future?

- The restoration of virome community is as important as that of bacterial microbiome in FMT.
- Donor selection based on virome characteristics should be considered in FMT practice.

The Human Gut Phage Community and Its Implications for Health and Disease

Pilar Manrique [1], Michael Dills [1] and Mark J. Young [2,*] *Viruses* 2017, *9*, 141;

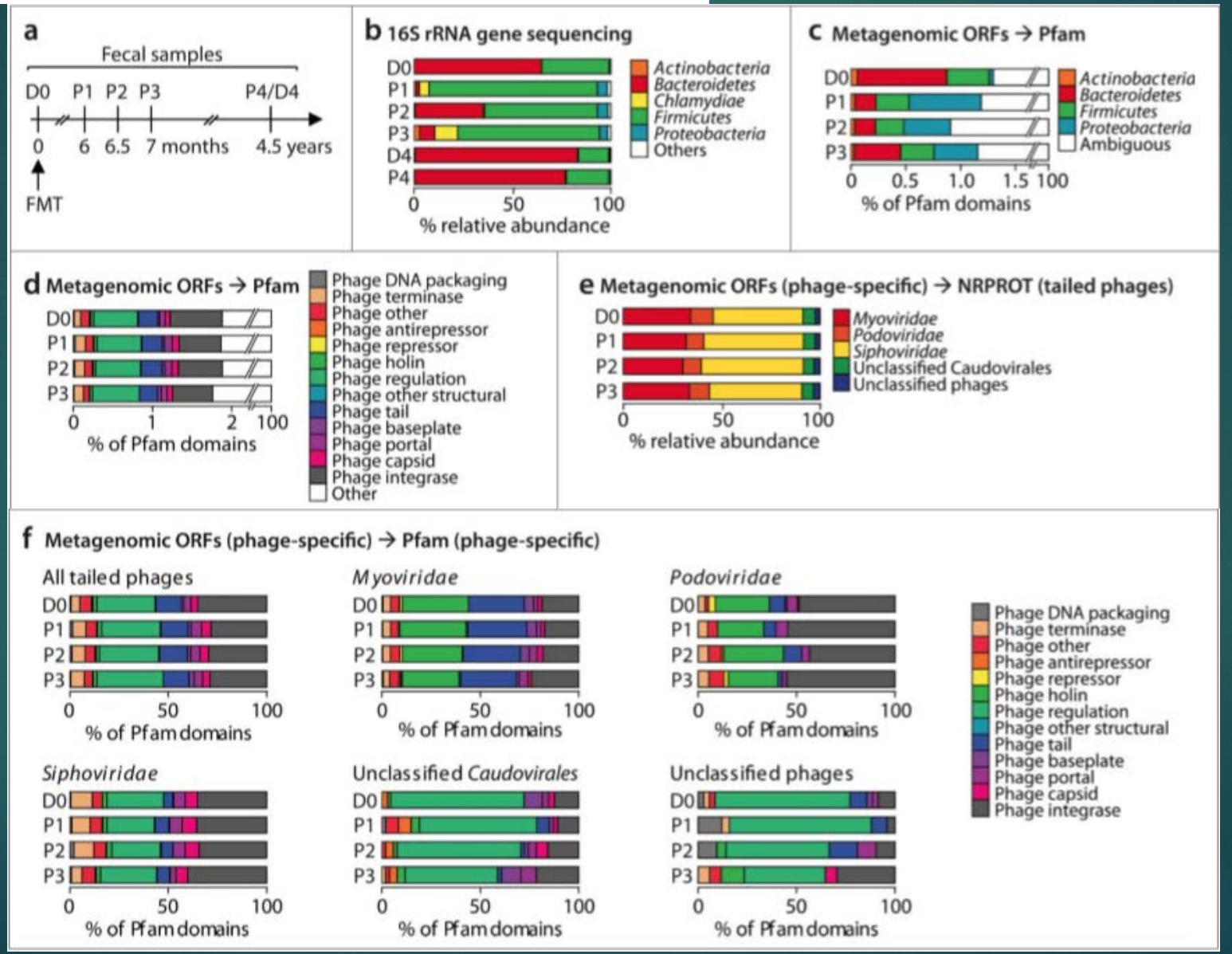


Stable core virome despite variable microbiome after fecal transfer

Felix Broecker[a,b,c,#], Giancarlo Russo[d,#], Jochen Klumpp[e], and Karin Moelling[a,b]

[a]Institute of Medical Microbiology, University of Zurich, Zurich, Switzerland; [b]Max Planck Institute for Molecular Genetics, Berlin, Germany; [c]Present address: Department of Microbiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [d]Functional Genomics Center Zurich, University of Zurich and ETH Zurich, Zurich, Switzerland; [e]Institute of Food, Nutrition and Health, ETH Zurich, Zurich, Switzerland

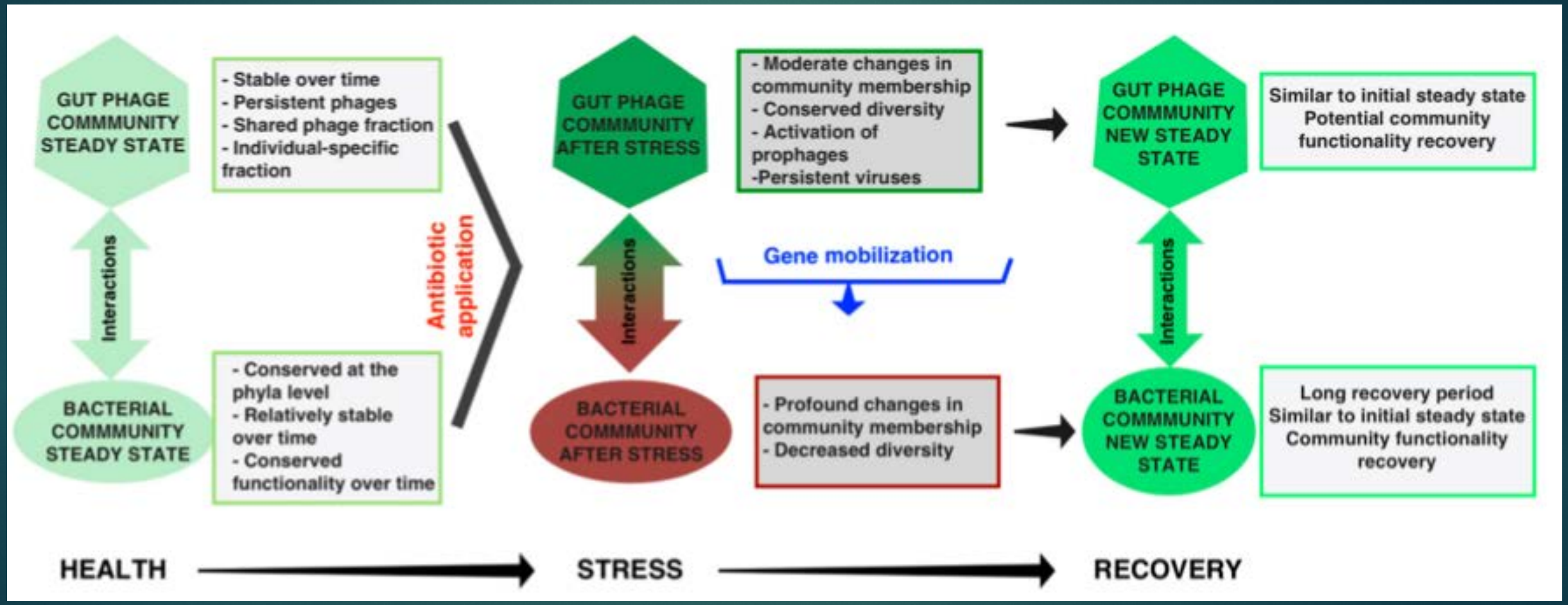
GUT MICROBES
2017, VOL. 8, NO. 3, 214–220



The Human Gut Phage Community and Its Implications for Health and Disease

Pilar Manrique [1], Michael Dills [1] and Mark J. Young [2,*] *Viruses* 2017, *9*, 141;

Des capacités de résilience différentes entre phageome et microbiome



The human gut microbiota and virome: Potential therapeutic implications

Emidio Scarpellini[a], Gianluca Ianiro[b], Fabia Attili[c], Chiara Bassanelli[d], Adriano De Santis[d], Antonio Gasbarrini[b,*]

POTENTIAL THERAPEUTIC APPLICATIONS OF BACTERIOPHAGES

ANTIMICROBIAL PURPOSES

A)

Pure lytic phages

Mono-phagic administration

- Clonal selection
- Phage preparation alteration

Rapid development of resistance to phages

B)

Antibiotics + lytic phages

Multi-phagic administration

Synergistic action

Less resistance to phages

MICROBIOTA MODULATION

C)

Phages + healthy gut microbes

- Nutrients biosynthesis
- Nutrients degradation

Host/microbiome benefit

High microbiota stability

/ Digestive and Liver Disease 47 (2015) 1007–1012

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

ansm
Agence nationale de sécurité du médicament et des produits de santé

Novembre 2016 (Actualisation de la version de juin 2015)

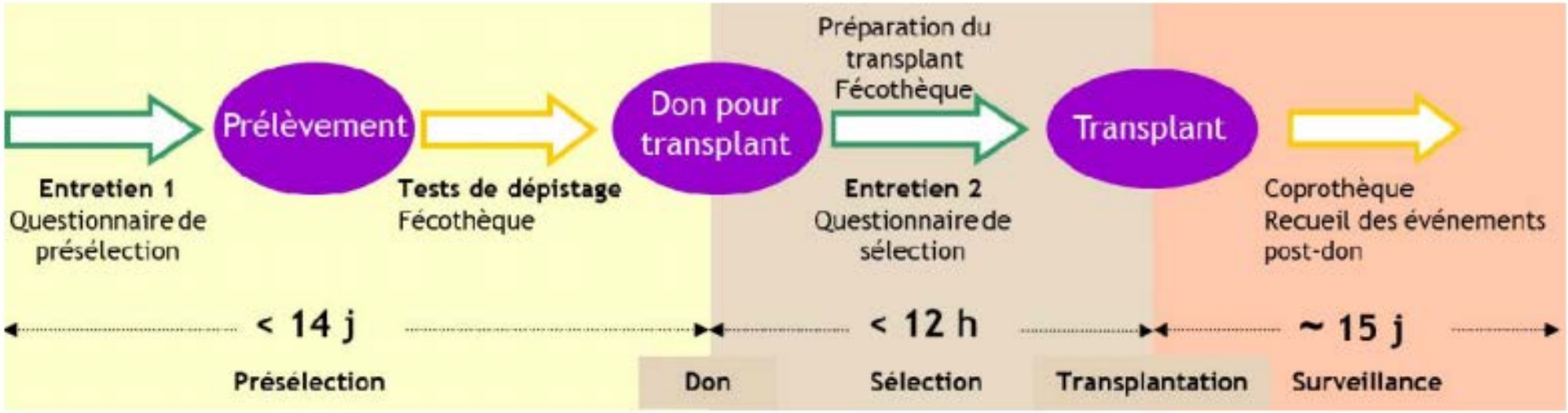
En France

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. *[…]* ».

A ce stade précoce de développement de ce produit et en l'absence d'autorisation de mise sur le marché, celui-ci peut être utilisé dans le cadre législatif et réglementaire applicable aux préparations magistrales et hospitalières (article L. 5121-1 du Code de la Santé publique), ou aux médicaments expérimentaux destinés à un essai clinique (article L. 5121-1-1 du même code).

Chronologie (versant « donneur ») de la transplantation fécale (en l'absence de congélation)



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)*

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

« …dans ces transmutations, dans ces métamorphoses, le vivant est toujours autre que la matière qui le compose, l'humain est autre que le vivant dont il émerge, et la vie intérieure, la conscience, la mémoire et les rêves vivent de leur propre existence dans et hors de ce corps qui les a fait naître et qu'ils animent. »