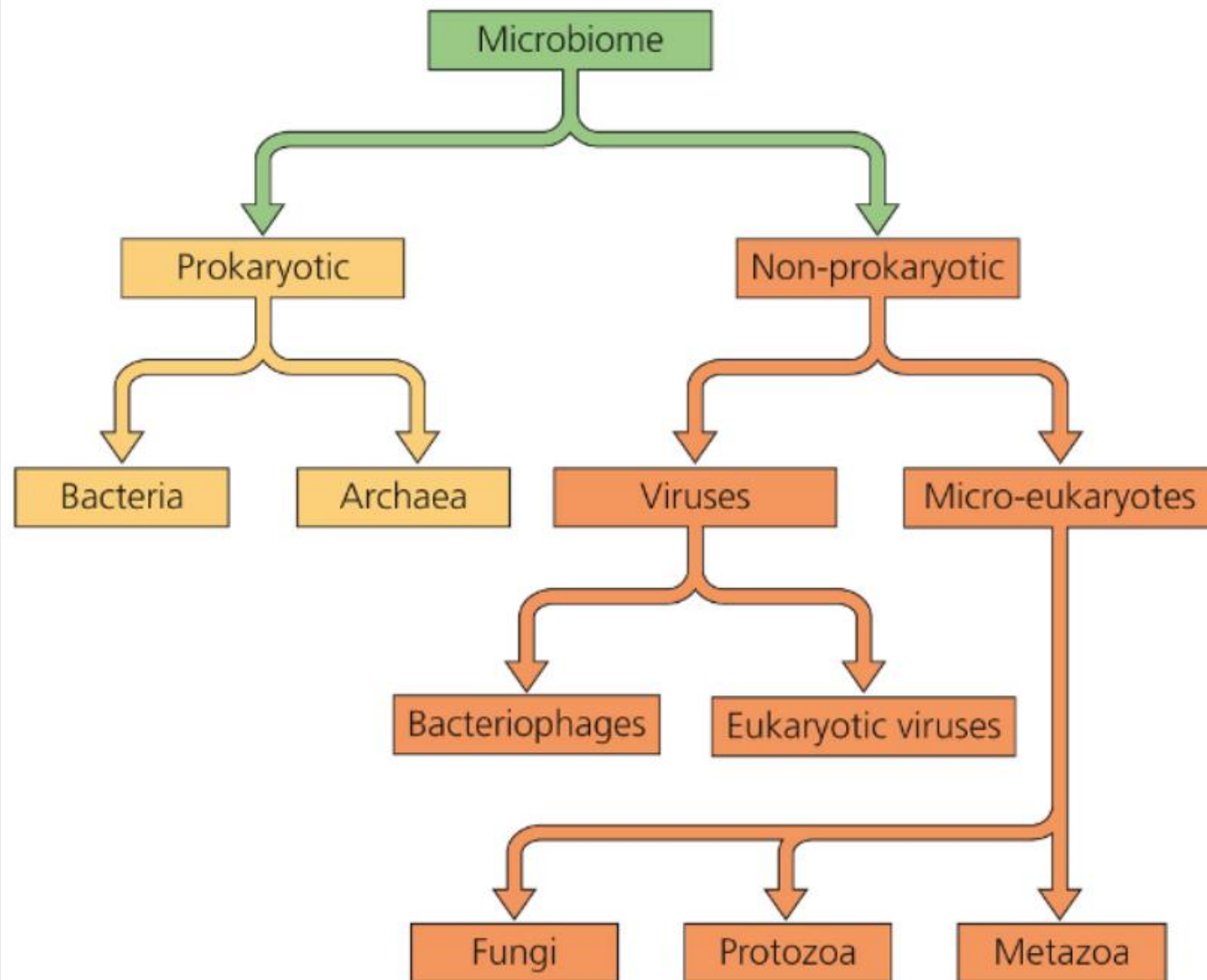


Microbiome Infections Greffes bactériennes

Actualités, perspectives – Rôle des médecins

Michel Moutschen
Herve – 21 janvier 2017

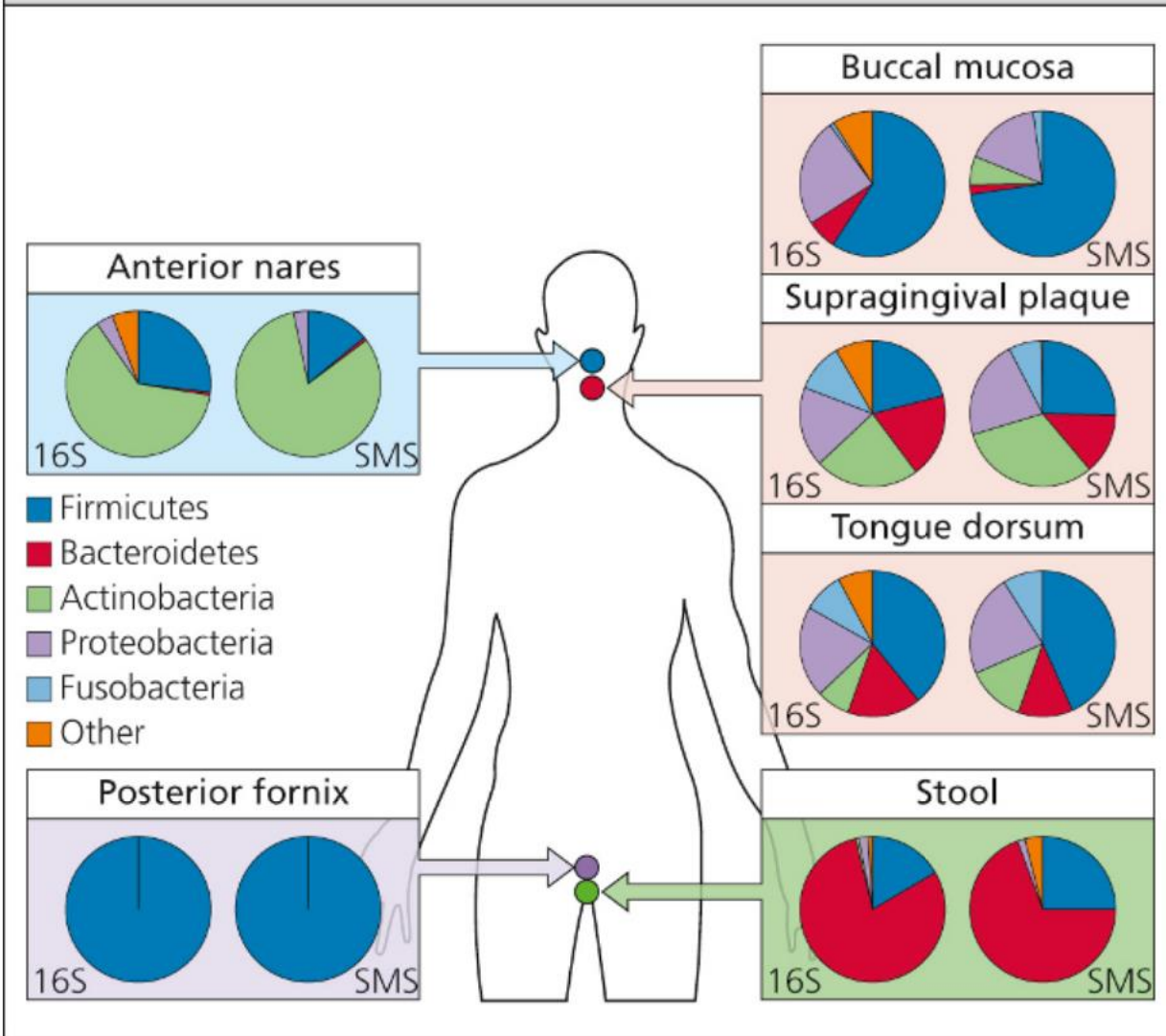
Micro-organisms represented in the human microbiome



Comment le microbiome peut-il être exploré?

- Nouvelles techniques « omiques », sans culture : 20 à 60 % du microbiome n'est pas cultivable
- Techniques génomiques de nouvelle génération
 - Séquençage « ciblé » : 16S rRNA ou 18sRNA
 - Séquençage « gunshot »
- Même à l'aide de ces techniques une partie du microbiome reste non identifiée

Distribution of abundances per phyla based on targeted (16S: first pie) and shotgun metagenomic sequencing (SMS: second pie)



Haemophilus_influenzae	0,000%	Lachnospiraceae_GQ492888	0,132%	Knoellia_EU753661	0,044%	Betaproteobacteria_Nez_16S_OTU277	0,015%
Staphylococcus_aureus	65,797%	Anaerococcus_EU735709	0,117%	Lachnospiraceae_DQ456170	0,044%	Chloroplast_HQ119522	0,015%
Fusobacterium_EU776103	5,659%	Bacteroides_EU776065	0,117%	Neisseriaceae_HM327217	0,044%	Chryseobacterium_hominis	0,015%
Sutterella_EF404313	2,947%	Parabacteroides_merdae	0,117%	Parabacteroides_FJ369051	0,044%	Clostridium_sensu_stricto_7_FN868424	0,015%
Staphylococcus_epidermidis	1,847%	Propionibacterium_granulosum	0,117%	Planococcaceae_JF132289	0,044%	Corynebacterium_GQ085923	0,015%
Prevotella_GQ491301	2,096%	Bacteroides_FJ507209	0,103%	Prevotella_Nez_16S_OTU149	0,044%	Corynebacterium_JF098328	0,015%
Prevotella_FJ507997	1,935%	Lachnospiraceae_GQ492985	0,103%	Rothia_JQ453065	0,044%	Cyanobacteria_HM270452	0,015%
Enhydrobacter_HV550303	1,246%	Lactobacillus_AY959115	0,103%	Stenotrophomonas_HM371262	0,044%	Dialister_JX548469	0,015%
Faecalibacterium_EU771947	1,202%	Massilia_timonae	0,103%	Sutterella_Nez_16S_OTU136	0,044%	Erysipelotrichaceae_DQ794161	0,015%
Bacteroides_GQ448307	0,997%	Megamonas_HQ812183	0,103%	Veillonella_Nez_16S_OTU111	0,044%	Flavobacterium_Nez_16S_OTU267	0,015%
Prevotella_GQ448928	0,850%	Bacteroides_EF071154	0,088%	Actinobacteria_HQ750188	0,029%	Flavinifractor_EF399591	0,015%
Peptoniphilus_rhinitidis	0,616%	Bilophila_GQ492439	0,088%	Anaerococcus_HM300729	0,029%	Fusobacteriaceae_Nez_16S_OTU166	0,015%
Staphylococcus_Nez_16S_OTU32	0,557%	Lachnospiraceae_Nez_16S_OTU60	0,088%	Anaerostipes_butyraticus	0,029%	Fusobacterium_FJ978525	0,015%
Megamonas_EU778953	0,542%	Ruminococcaceae_DQ456384	0,088%	Bacteroides_Nez_16S_OTU179	0,029%	Gordonia_Nez_16S_OTU257	0,015%
Staphylococcus_JF162051	0,513%	S24-7_EU458461	0,088%	Blautia_Nez_16S_OTU137	0,029%	Haemophilus_parainfluenzae	0,015%
Anaerotruncus_DQ905645	0,454%	Staphylococcus_cohnii	0,088%	Brevibacterium_pityocampae	0,029%	Lachnospiraceae_DQ456379	0,015%
Ralstonia_JQ218560	0,425%	Acinetobacter_JQ923841	0,073%	Corynebacterium_JF217999	0,029%	Lachnospiraceae_Nez_16S_OTU192	0,015%
Anaerobiospirillum_Nez_16S_OTU20	0,396%	Acinetobacter_KC172007	0,073%	Dietzia_JF226207	0,029%	Lachnospiraceae_Nez_16S_OTU195	0,015%
Lachnospira_HQ783428	0,367%	Blautia_Nez_16S_OTU74	0,073%	Firmicutes_EU234148	0,029%	Lachnospiraceae_Nez_16S_OTU196	0,015%
Sutterella_HQ811912	0,367%	Defluvititaleaceae_HQ739932	0,073%	Kocuria_GQ157152	0,029%	Lactobacillus_EU464056	0,015%
Corynebacterium_pseudodiphtheriticum	0,000%	Lachnospiraceae_FJ366976	0,073%	Lachnospiraceae_DQ057421	0,029%	Lactobacillus_Nez_16S_OTU275	0,015%
Clostridium_sensu_stricto_1_EU773775	0,323%	Lachnospiraceae_FJ370495	0,073%	Lachnospiraceae_DQ057458	0,029%	Massilia_JX566630	0,015%
Pseudomonas_KC011157	0,323%	Lachnospiraceae_FJ370788	0,073%	Lachnospiraceae_EU771694	0,029%	Megamonas_Nez_16S_OTU233	0,015%
Catenibacterium_DQ809870	0,308%	Planococcaceae_JF129656	0,073%	Lachnospiraceae_GQ175509	0,029%	Microbacterium_EU468057	0,015%
Phascolarctobacterium_GQ493381	0,308%	Pseudomonas_EF157292	0,073%	Oxalobacteraceae_Nez_16S_OTU135	0,029%	Microbacterium_oxydans	0,015%
Bacteroides_EU531930	0,293%	Streptococcus_JQ465590	0,073%	Phascolarctobacterium_Nez_16S_OTU234	0,029%	Negativicoccus_HQ777147	0,015%
Haemophilus_Nez_16S_OTU34	0,000%	Variovorax_EU536101	0,073%	Planctomycetes_FJ543018	0,029%	Oscillospira_JN559553	0,015%
Helicobacter_canis	0,279%	Bacteria_Nez_16S_OTU85	0,059%	Prevotella_Nez_16S_OTU148	0,029%	Paracoccus_yeei	0,015%
Escherichia-Shigella_Escherichia_coli	0,264%	Bacteroides_EF401257	0,059%	Pseudomonas_EF205269	0,029%	Patulibacter_Nez_16S_OTU280	0,015%
Micrococcus_luteus	0,264%	Bacteroides_Nez_16S_OTU93	0,059%	Ruminococcaceae_FJ509257	0,029%	Peptoniphilus_Nez_16S_OTU209	0,015%
Bacteroides_EF403478	0,235%	Blautia_DQ795488	0,059%	Ruminococcaceae_GQ175425	0,029%	Peptostreptococcus_FJ557786	0,015%
Staphylococcus_JF006656	0,205%	Candidata_division_TM7_Nez_16S_OTU78	0,059%	Ruminococcaceae_Nez_16S_OTU126	0,029%	Phascolarctobacterium_DQ807939	0,015%
Haemophilus_Nez_16S_OTU79	0,000%	Lachnospiraceae_FJ506942	0,059%	Ruminococcaceae_Nez_16S_OTU131	0,029%	Photobacterium_JX016943	0,015%
Finegoldia_magna	0,191%	Lachnospiraceae_GQ492922	0,059%	Ruminococcaceae_Nez_16S_OTU137	0,029%	Prevotella_Nez_16S_OTU168	0,015%
Propionibacterium_GU940713	0,191%	Lachnospiraceae_Nez_16S_OTU109	0,059%	Ruminococcaceae_Nez_16S_OTU140	0,029%	Prevotella_Nez_16S_OTU171	0,015%
Staphylococcus_hominis	0,191%	Lachnospiraceae_Nez_16S_OTU88	0,059%	Streptococcus_DQ794879	0,029%	Prevotella_Nez_16S_OTU173	0,015%
Lachnospiraceae_DQ808185	0,176%	Lachnospiraceae_Nez_16S_OTU89	0,059%	Sutterella_Nez_16S_OTU159	0,029%	Prevotella_Nez_16S_OTU174	0,015%
Rothia_mucilaginosa	0,161%	Phascolarctobacterium_EF404208	0,059%	Staphylococcus_Nez_16S_OTU166	0,029%	Prevotella_Nez_16S_OTU176	0,015%
Blautia_EU465480	0,161%	Pseudomonas_JF178100	0,059%	Staphylococcus_Nez_16S_OTU212	0,029%	Prevotella_Nez_16S_OTU185	0,015%
Lachnospiraceae_KC245309	0,161%	Ruminococcaceae_DQ800238	0,059%	Staphylococcus_Nez_16S_OTU216	0,029%	Psychrobacter_JQ775371	0,015%
Micrococcaceae_terreus	0,161%	Ruminococcaceae_DQ800287	0,059%	Aerococcus_EF096525	0,015%	Rothia_JQ478041	0,015%
Odoribacter_GQ448681	0,161%	Staphylococcus_Nez_16S_OTU142	0,059%	Aeromonas_media	0,015%	Ruminococcaceae_DQ793259	0,015%
Streptococcus_JQ470312	0,161%	Succinivibrionaceae_Nez_16S_OTU82	0,059%	Anaerococcus_HM587319	0,015%	Ruminococcaceae_HM326891	0,015%
Anaerococcus_octavius	0,147%	vadinBB60_DQ456434	0,059%	Anaerococcus_JF177520	0,015%	Ruminococcaceae_HQ815119	0,015%
Ruminococcaceae_EF398999	0,147%	Anaerococcus_JF176641	0,044%	Arcobacter_GQ340204	0,015%	Ruminococcaceae_Nez_16S_OTU197	0,015%
Bacteroides_EU772886	0,132%	Blautia_Nez_16S_OTU113	0,044%	Atopostipes_AY005049	0,015%	Ruminococcaceae_Nez_16S_OTU208	0,015%
Lachnospiraceae_DQ794370	0,132%	Comamonadaceae_JF697501	0,044%	Bacteroides_Nez_16S_OTU167	0,015%	Ruminococcaceae_Nez_16S_OTU211	0,015%
		Corynebacterium_EU341180	0,044%	Bacteroidales_Nez_16S_OTU175	0,015%	Sporosarcina_KC286749	0,015%
		Escherichia-Shigella_Nez_16S_OTU106	0,044%	Bacteroides_HQ819387	0,015%	Sporosarcina_Nez_16S_OTU221	0,015%
		Granulicatella_JQ461559	0,044%	Bacteroides_KC245264	0,015%	Sporosarcina_Nez_16S_OTU223	0,015%
				Bacteroides_Nez_16S_OTU170	0,015%	Staphylococcus_JF194679	0,015%
				Bacteroides_Nez_16S_OTU178	0,015%	Staphylococcus_JF221361	0,015%
				Bacteroides_Nez_16S_OTU180	0,015%	Staphylococcus_Nez_16S_OTU187	0,015%
				Bacteroides_Nez_16S_OTU181	0,015%	Staphylococcus_Nez_16S_OTU189	0,015%
				Bacteroides_Nez_16S_OTU182	0,015%	Staphylococcus_Nez_16S_OTU205	0,015%
						Stenotrophomonas_Nez_16S_OTU227	0,015%
						Streptococcus_anginosus	0,015%
						Sutterella_DQ801079	0,015%
						Sutterella_Nez_16S_OTU163	0,015%
						Veillonella_JQ457856	0,015%
						Veillonella_Nez_16S_OTU236	0,015%
						Veillonella_pavula	0,015%
						Xanthomonadales_Nez_16S_OTU226	0,015%
						Zhihengliuella_AY289118	0,000%
						Corynebacterium_Nez_16S_OTU256	0,000%
						Haemophilus_Nez_16S_OTU229	0,000%
						Haemophilus_Nez_16S_OTU245	0,000%
						Lachnospira_HQ751709	0,000%
						Staphylococcus_warneri	0,000%

Le microbiome

- Co-évolution
- Réseau dense d'interactions bidirectionnelles avec tous les systèmes du corps humain
- Notre second génome

Comment le microbiome nous protège-t-il des infections?

- Compétition pour les nutriments et sites d'attachement
- Production de substances antimicrobiennes
- Education du système immunitaire, même à distance
- La première étape de beaucoup d'infections est la colonisation d'une niche (i.e. intestin, rhinopharynx, peau) par un pathogène
- La modification du microbiome qui en résulte est appelée dysbiose

Decreased Diversity of the Fecal Microbiome in Recurrent *Clostridium difficile*-Associated Diarrhea

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¹Department of Microbiology and Molecular Genetics, ²Medical Technology Program, ³Infectious Diseases Unit, Department of Internal Medicine, and ⁴National Food Safety and Toxicology Center, Michigan State University, East Lansing

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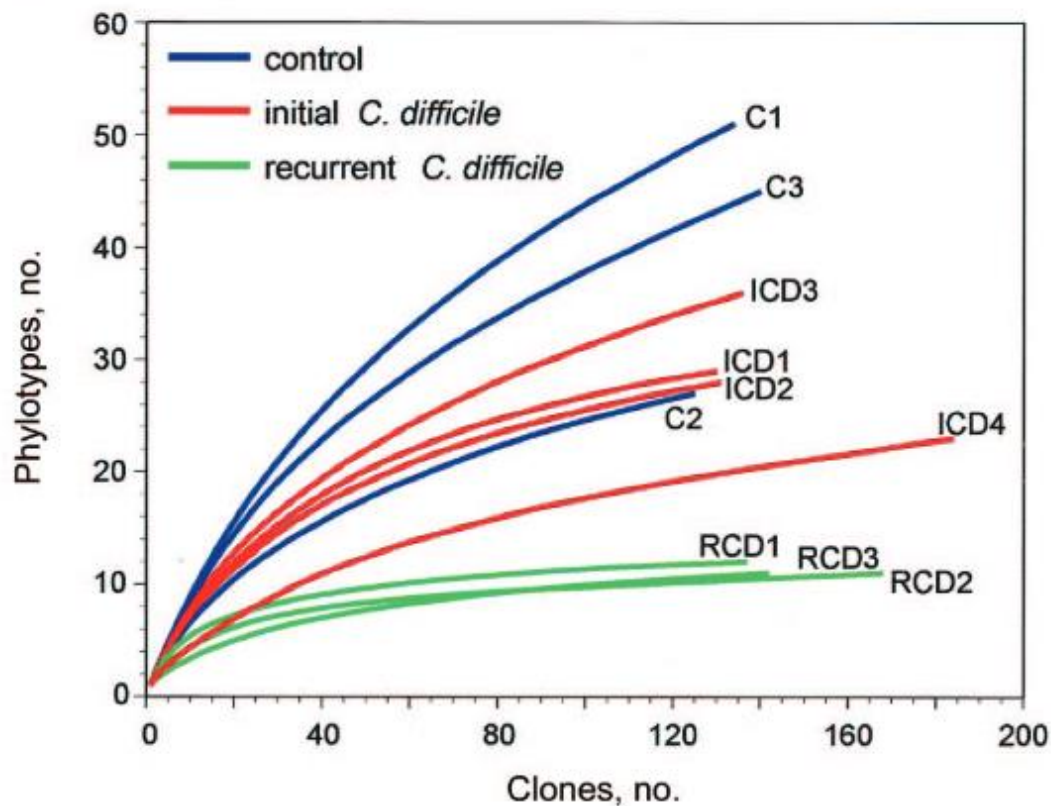


Figure 2. Analysis of 16S clone libraries of the fecal microbiota in patients with antibiotic-associated diarrhea due to *Clostridium difficile*. A, Relative abundance of members of predominant bacterial phyla, in fecal samples from healthy control subjects (C), patients with an initial episode of antibiotic-associated diarrhea due to *C. difficile* (ICD), and patients with recurrent antibiotic-associated diarrhea due to *C. difficile* (RCD). B, Rarefaction analysis of 16S clone libraries from each individual in the study. Phylotypes were based on an operational taxonomic-unit definition of 97% sequence identity.



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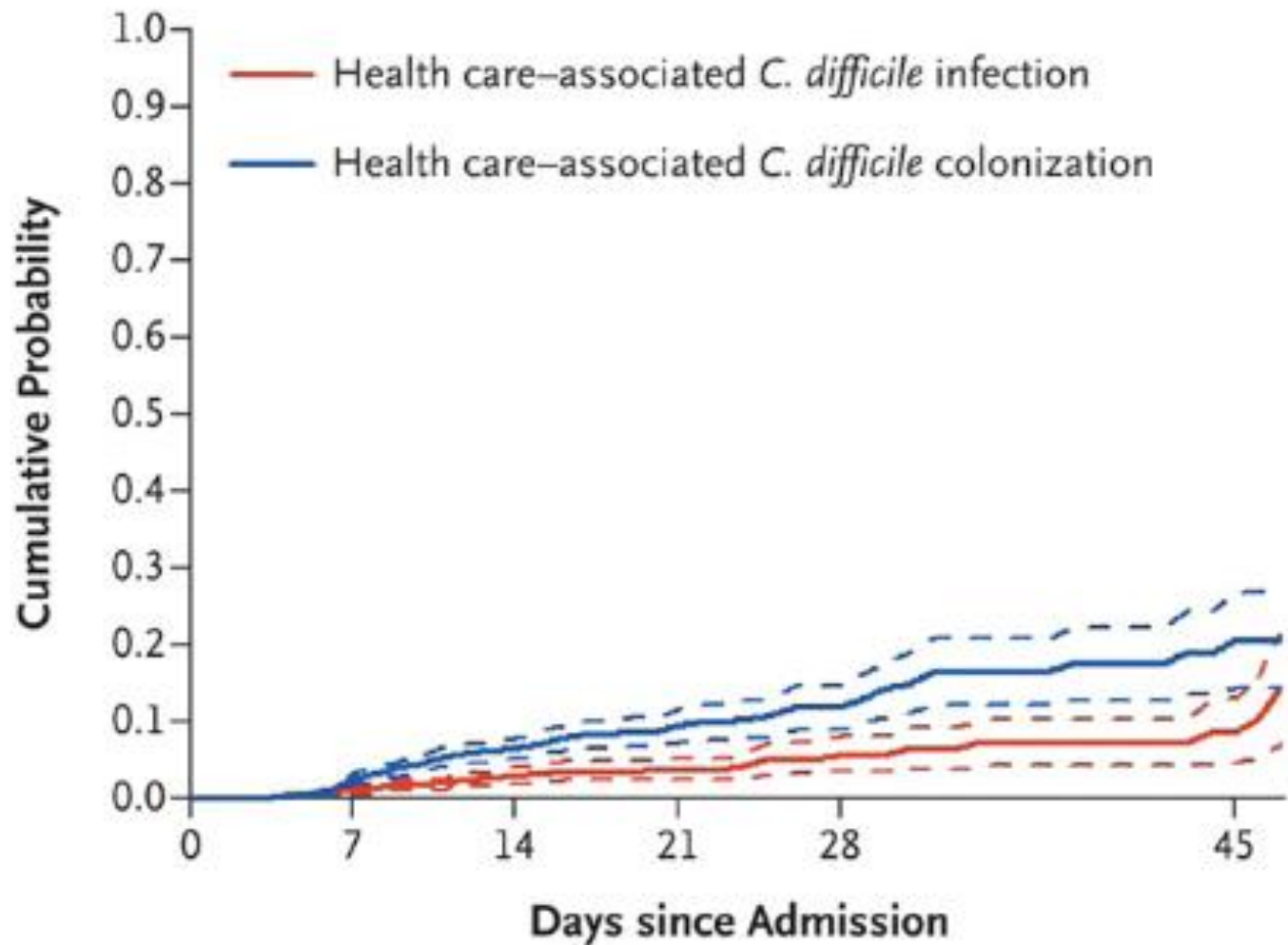
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ORIGINAL ARTICLE

Host and Pathogen Factors for *Clostridium difficile* Infection and Colonization

Vivian G. Loo, M.D., Anne-Marie Bourgault, M.D., Louise Poirier, M.D., François Lamothe, M.D., Sophie Michaud, M.D., M.P.H., Nathalie Turgeon, M.D., Baldwin Toye, M.D., Axelle Beaudoin, M.Sc., Eric H. Frost, Ph.D., Rodica Gilca, M.D., Ph.D., Paul Brassard, M.D., Nandini Dendukuri, Ph.D., Claire Béliveau, M.D., Matthew Oughton, M.D., Ivan Brukner, Ph.D., and Andre Dascal, M.D.

N Engl J Med 2011; 365:1693-1703 | [November 3, 2011](#)



No. of Patients

3959

1723

592

274

148

45

Table 2. Odds Ratios for Health Care–Associated *Clostridium difficile* Infection and Colonization According to Various Patient and Pathogen Characteristics.*

Variable	Odds Ratio (95% CI)	
	Health Care–Associated <i>C. difficile</i> Infection	Health Care–Associated <i>C. difficile</i> Colonization
Age — per increase of 1 yr	1.02 (1.00–1.04)	1.00 (0.99–1.02)
Score on Charlson comorbidity index — per unit	1.01 (0.93–1.10)	1.02 (0.95–1.10)
Male sex vs. female sex	0.98 (0.64–1.49)	1.11 (0.75–1.64)
Hospitalization before current admission		
Never or >12 mo before	Reference	Reference
2–12 mo before	1.25 (0.76–2.07)	1.19 (0.74–1.90)
<2 mo before	1.61 (0.94–2.75)	2.18 (1.31–3.61)
Colonization with <i>C. difficile</i> ≤3 days before health care–associated infection	1.32 (0.57–3.02)	NA
Use of nasogastric tube†	1.28 (0.56–2.92)	0.81 (0.37–1.73)
Medication use†		
Antibiotic	5.25 (2.15–12.82)	1.04 (0.61–1.78)
Chemotherapy	1.33 (0.49–3.65)	2.37 (1.09–5.14)
Proton-pump inhibitor	2.64 (1.71–4.09)	1.71 (1.15–2.53)
H ₂ blocker	0.98 (0.55–1.73)	2.14 (1.24–3.70)
Glucocorticoid	0.97 (0.48–1.97)	1.33 (0.72–2.45)
NSAID	0.85 (0.55–1.30)	1.21 (0.79–1.84)
Serologic analysis		
Positive for antibody against toxin A vs. negative	0.72 (0.41–1.29)	1.02 (0.62–1.67)
Positive for antibody against toxin B vs. negative	1.27 (0.80–2.02)	1.75 (1.15–2.66)



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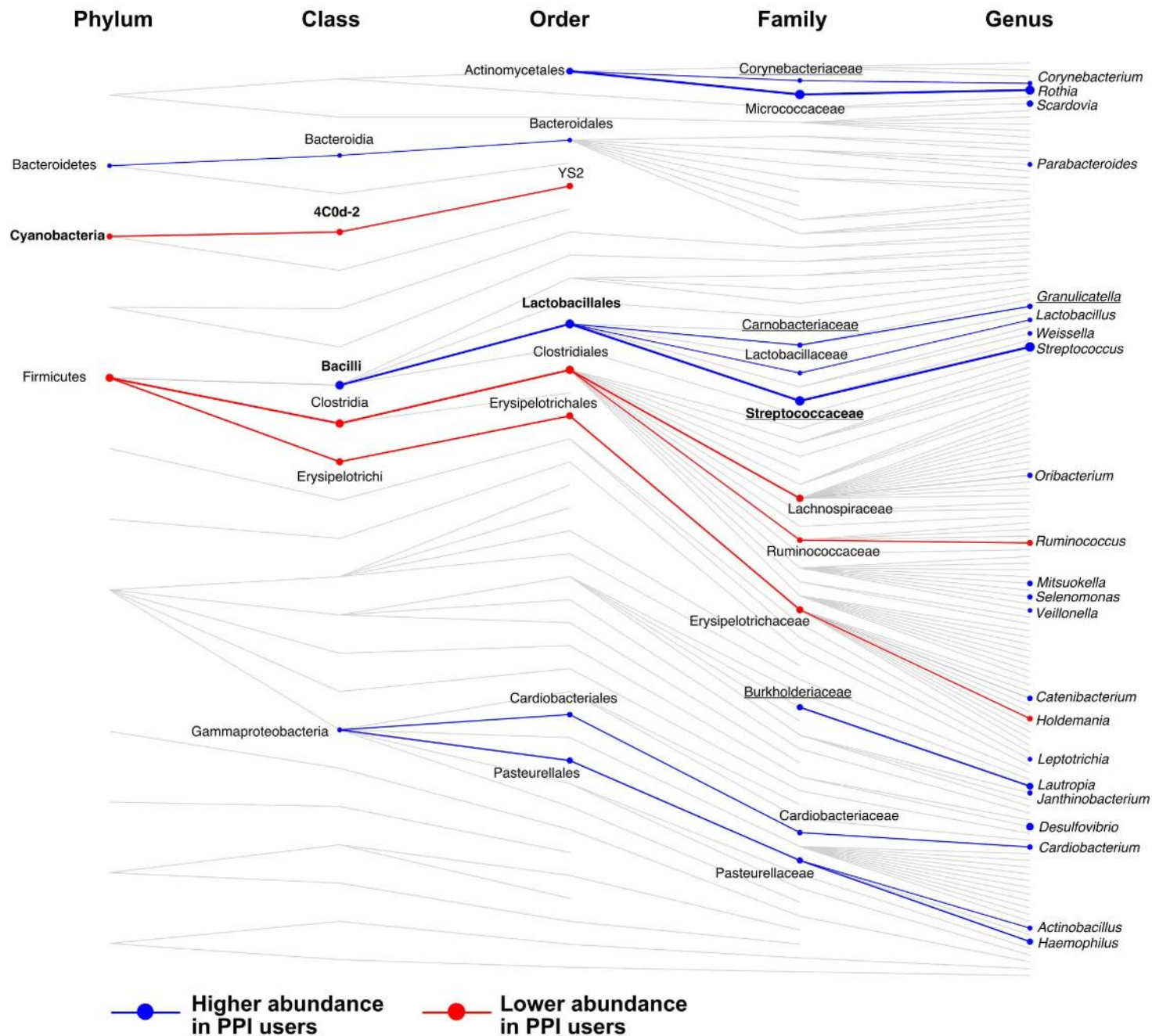
ORIGINAL ARTICLE

Proton pump inhibitors alter the composition of the gut microbiota

Matthew A Jackson,¹ Julia K Goodrich,^{2,3} Maria-Emanuela Maxan,⁴
Daniel E Freedberg,⁵ Julian A Abrams,⁵ Angela C Poole,^{2,3} Jessica L Sutter,^{2,3}
Daphne Welter,^{2,3} Ruth E Ley,^{2,3} Jordana T Bell,¹ Tim D Spector,¹ Claire J Steves¹

Jackson MA, *et al.* *Gut* 2016;**65**:749–756. doi:10.1136/gutjnl-2015-310861

Gut microbiota



Microbiome et infections virales

Table 1.**Summary of Expected Risks of Cell-Associated HIV Transmission as a Function of Vaginal Environment**

Vaginal Condition	Estimated Risk of Male-to-Female Transmission	Estimated Risk of Female-to-Male Transmission	Key Factors for Transmission by Cell-Associated HIV
Prepuberty	Highest	High	Cell-associated HIV survives likely trauma, thin epithelium, approximately neutral pH, little lubrication, cervical ectopy
Polymicrobial microbiota ± STIs	High	High	Cell-associated HIV survives, elevated pH, little lactic acid, inflammatory responses including cytokines that attract leukocytes, epithelial disruptions by STIs
Lactobacillus-dominated No STIs	Low	Lowest	Vaginally shed cell-associated HIV rapidly inactivated by lactic acid Cell-associated HIV in semen survives but postejaculation leukocytes rapidly immobilized by lactic acid acidity
Postmenopause	High	High	Cell-associated HIV survives, polymicrobial microbiota (CST IV-A, CST IV-B), elevated pH, thin epithelium, little lubrication



Approches thérapeutiques

Transplantation fécale et colite à Clostridium

- Colites à *C. difficile* : rechutes fréquentes
 - 10 à 20%
 - Après une première rechute : 40 à 60% de risque de nouvelle rechute
 - Traitements antibiotiques peu efficaces pour ces rechutes

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Duodenal Infusion of Donor Feces for Recurrent
Clostridium difficile

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D.,
Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D.,
Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D.,
Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

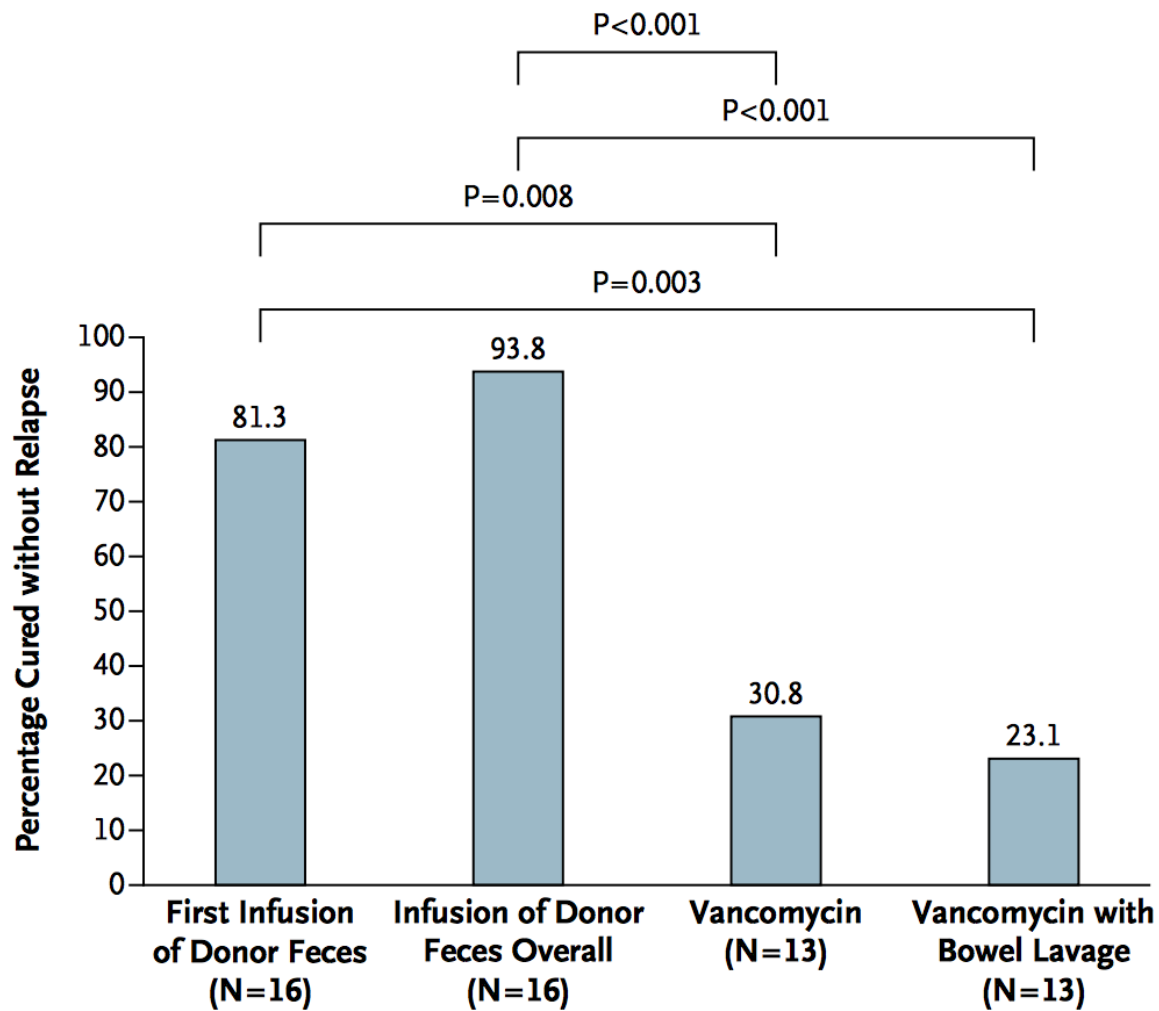


Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.

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
	<i>no. of events</i>	
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‡

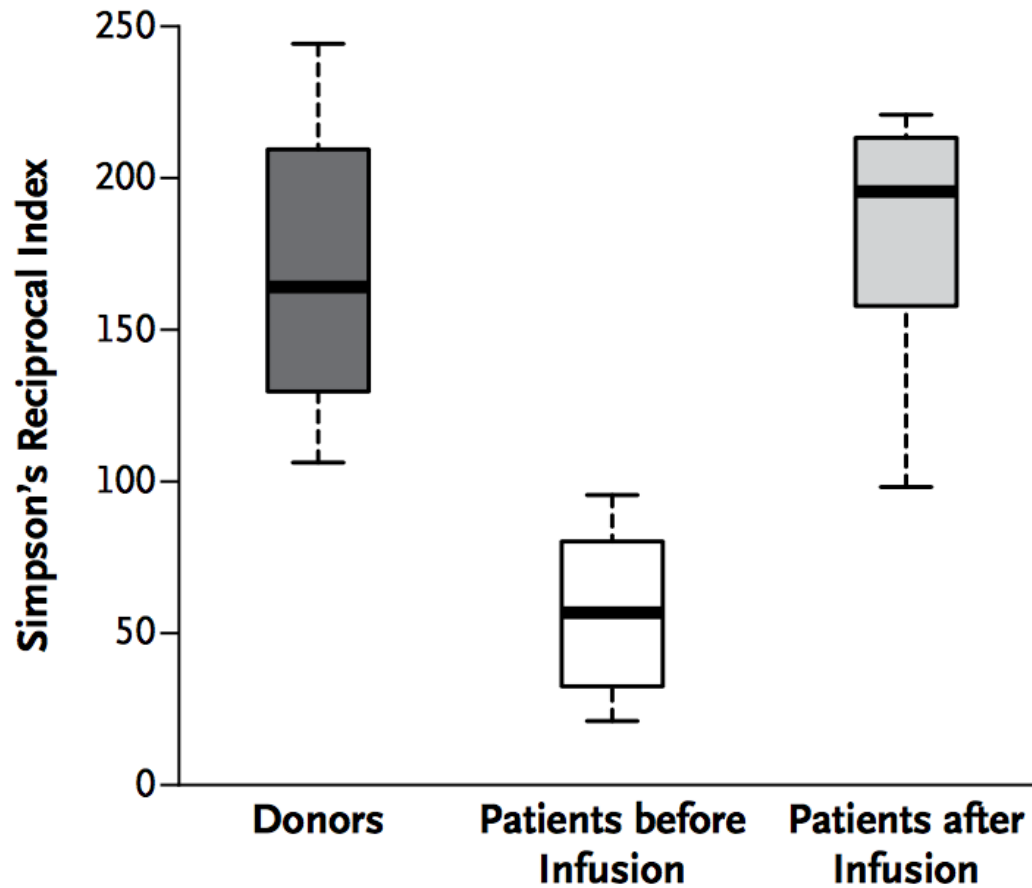


Figure 3. Microbiota Diversity in Patients before and after Infusion of Donor Feces, as Compared with Diversity in Healthy Donors.

Fecal Microbiota Transplantation for *Clostridium difficile* Infection

A Systematic Review

Dimitri Drekonja, MD, MS; Jon Reich, MD; Selome Gezahegn, MD; Nancy Greer, PhD; Aasma Shaukat, MD, MPH; Roderick MacDonald, MS; Indy Rutks, BS; and Timothy J. Wilt, MD, MPH

Background: The role of fecal microbiota transplantation (FMT) for *Clostridium difficile* infection (CDI) is not well-known.

Purpose: To assess the efficacy, comparative effectiveness, and harms of FMT for CDI.

Data Sources: MEDLINE (1980 to January 2015), Cochrane Library, and ClinicalTrials.gov, followed by hand-searching references from systematic reviews and identified studies.

Study Selection: Any study of FMT to treat adult patients with CDI; case reports were only used to report harms.

Data Extraction: Data were extracted by 1 author and verified by another; 2 authors independently assessed risk of bias and strength of evidence.

Data Synthesis: Two randomized, controlled trials (RCTs); 28 case-series studies; and 5 case reports were included. Two RCTs and 21 case-series studies (516 patients receiving FMT) reported using FMT for patients with recurrent CDI. A high proportion of treated patients had symptom resolution; however, the role of previous antimicrobials is unclear. One RCT comparing FMT with 2 control groups ($n = 43$) reported resolution of symptoms in

81%, 31%, and 23% of the FMT, vancomycin, or vancomycin-plus-bowel lavage groups, respectively ($P < 0.001$ for both control groups vs. FMT). An RCT comparing FMT route ($n = 20$) reported no difference between groups (60% in the nasogastric tube group and 80% in the colonoscopy group; $P = 0.63$). Across all studies for recurrent CDI, symptom resolution was seen in 85% of cases. In 7 case-series studies of patients with refractory CDI, symptom resolution ranged from 0% to 100%. Among 7 patients treated with FMT for initial CDI, results were mixed.

Limitation: Most studies were uncontrolled case-series studies; only 2 RCTs were available for analysis.

Conclusion: Fecal microbiota transplantation may have a substantial effect with few short-term adverse events for recurrent CDI. Evidence is insufficient on FMT for refractory or initial CDI treatment and on whether effects vary by donor, preparation, or delivery method.

Primary Funding Source: U.S. Department of Veterans Affairs.

Ann Intern Med. 2015;162:630-638. doi:10.7326/M14-2693 www.annals.org
For author affiliations, see end of text.

Table 2. Summary Results for Reported Resolution of Symptoms After Initial FMT for Recurrent CDI, Overall and by FMT Method

FMT Method	Patients With Resolution of Symptoms Without Recurrence, %*	Studies/Total Studies Analyzed, n/N
Upper GI tract	77	7/187†
Colonoscopy	90	11/257†
Enema	78	5/45
Upper GI tract and colonoscopy	100	1/27
All methods	85	23/516‡

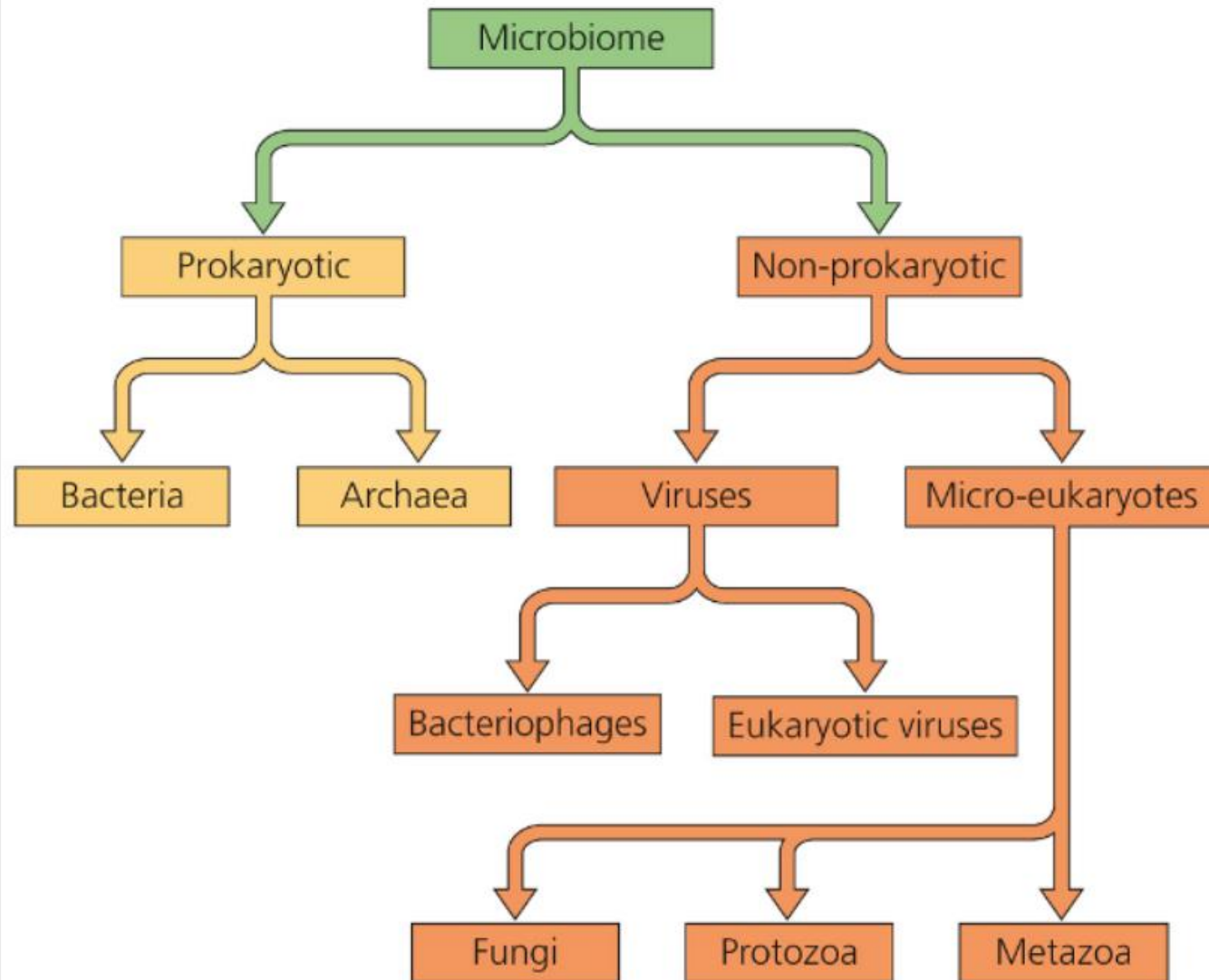
CDI = *Clostridium difficile* infection; FMT = fecal microbiota transplantation; GI = gastrointestinal.

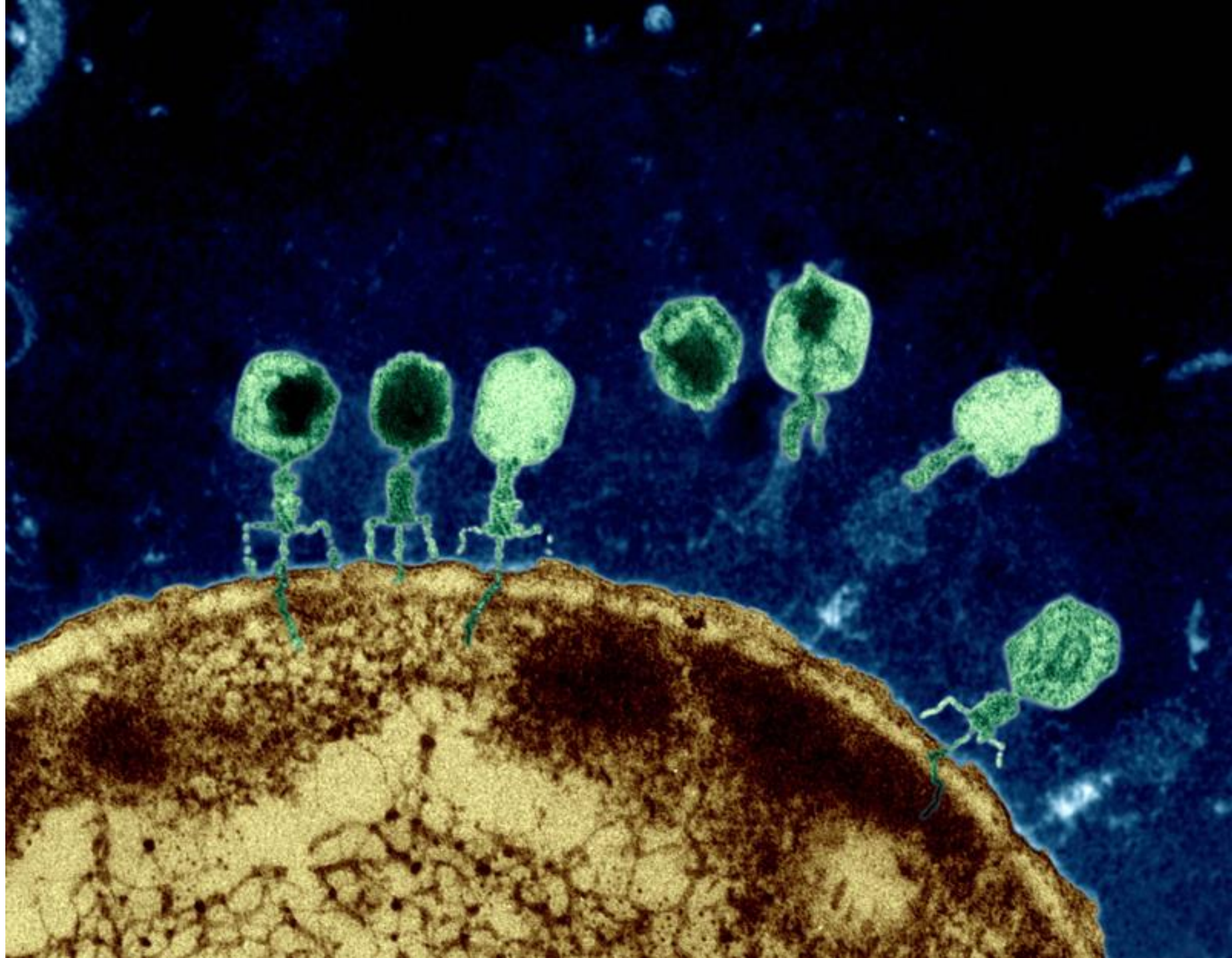
* Because of small sample sizes and the abundance of data from case-series studies, 95% CIs were considered to be unreliable and were not calculated.

† Includes 10 patients from reference 18.

‡ Total number of studies is 1 less than the sum of individual rows.

Micro-organisms represented in the human microbiome





J Antimicrob Chemother 2014; **69**: 2326–2336
doi:10.1093/jac/dku173 Advance Access publication 28 May 2014

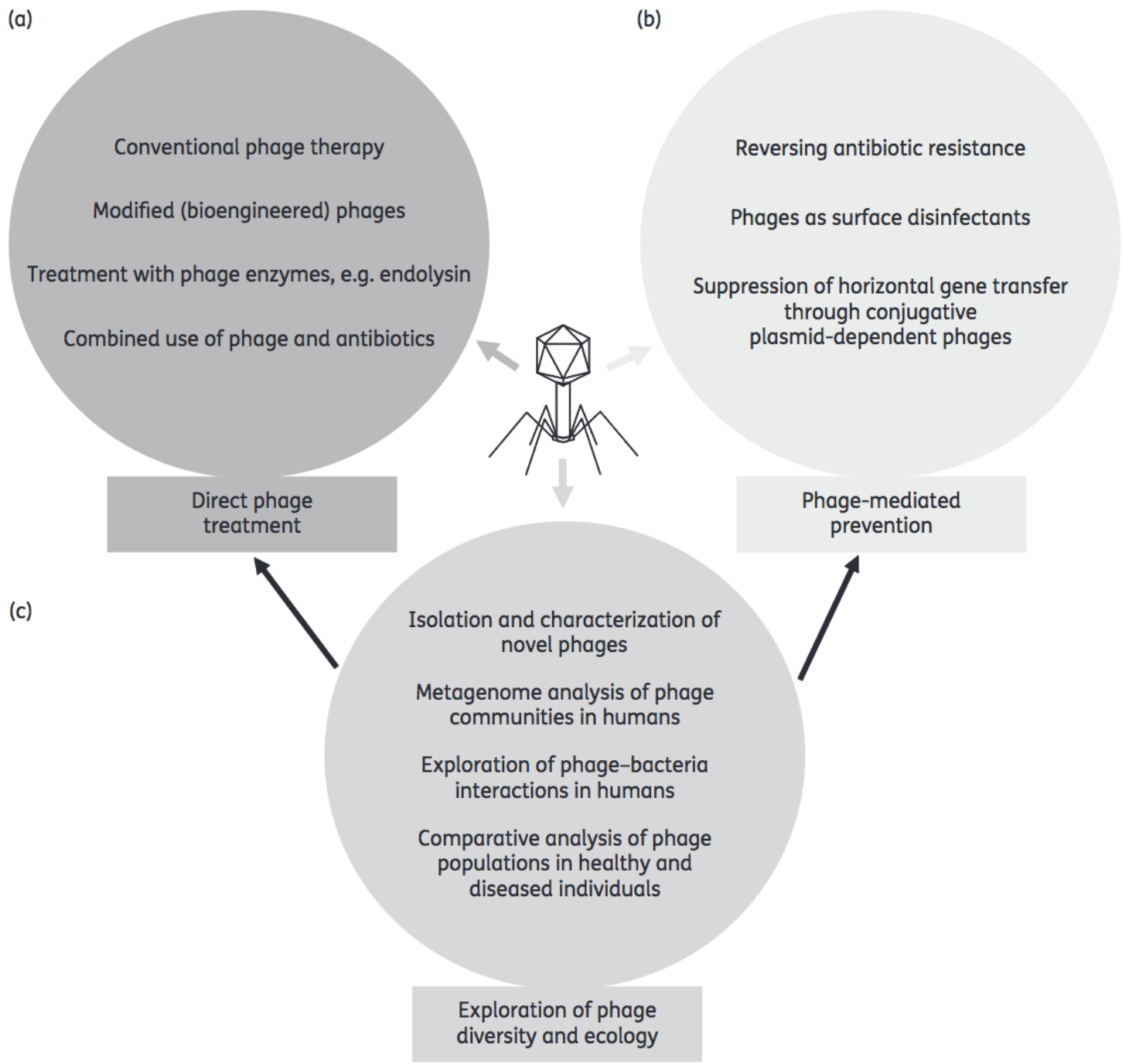
**Journal of
Antimicrobial
Chemotherapy**

Viruses versus bacteria—novel approaches to phage therapy as a tool against multidrug-resistant pathogens

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Le rôle des médecins

- Respecter et favoriser la diversité du microbiome
 - Aspects quantitatifs et qualitatifs du régime alimentaire
 - Exercice physique
 - Vitamine D
 - Pas d'interventions médicamenteuses en dehors des indications formelles
 - IPP
 - Antibiotiques
 - Probiotiques?
 - Analyse « écologique » de l'impact des vaccins futurs?

Le style de vie aurait-il plus d'impact sur notre microbiome que sur « nous-mêmes? »

