



Transplantation de microbiote fécal (TMF) pour le traitement des infections à *Clostridium difficile* (ICD) récidivantes

Docteur Rozenn HÉQUETTE-RUZ

JRPI

9 Octobre 2018

TMF : un peu d'histoire...

Premières descriptions

4^{ème} siècle en Chine

Médecine vétérinaire dès le 17^{ème} siècle « *transfaunation* »²

Premières publications

1958 : Eiseman *et al.* « Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis » Surgery.

Séries de cas jusqu'en 2013³⁻⁵

Premier essai randomisé en 2013 : Van Nood⁶

¹ Zhang *et al.*, Am J Gastroenterol. 2012

² Borody *et al.*, J Clin Gastroenterol. 2004

³ Bakken *et al.* Clin Gastroenterol Hepatol. 2011

⁴ Kassam *et al.* Am J Gastroenterol

Essai contrôlé randomisé

Inclus : au moins 1 récursive

Exclus :

- Immunosuppression
- ATB concomitants
- ICD compliquée

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Donor-Feces Infusion (N=16)	Vancomycin Only (N=13)	Vancomycin and Bowel Lavage (N=13)	P Value†
Age — yr	73±13	66±14	69±16	0.39
Body-mass index‡	22±3	22±4	24±4	0.41
Female sex — no. (%)	8 (50)	7 (54)	3 (23)	0.22
Karnofsky performance status§	50±18	50±17	56±21	0.62
Median Charlson comorbidity index (range) — score¶	3 (0–4)	1 (0–8)	1 (0–6)	0.53
Median recurrences of CDI (range) — no.	3 (1–5)	3 (1–4)	2 (1–9)	0.69
Previous failure of tapered vancomycin therapy — no. (%)	10 (62)	8 (62)	6 (46)	0.63
Reported antibiotic use before CDI — no. (%)	16 (100)	12 (92)	13 (100)	0.62
Hospital-acquired CDI infection — no. (%)	10 (62)	6 (46)	10 (77)	0.27
Admitted to a hospital at study inclusion — no. (%)	5 (31)	4 (31)	4 (31)	1.00
Days of antibiotic use for CDI since first diagnosis — no.	63±41	51±27	49±38	0.56
Use of proton-pump inhibitor — no. (%)	13 (81)	10 (77)	11 (85)	0.88
ICU admission in preceding month — no. (%)	1 (6)	0	1 (8)	1.00
Feeding tube present — no. (%)	3 (19)	2 (15)	2 (15)	0.96
Median stool frequency per 24 hr (range) — no.	5 (3–20)	5 (3–12)	5 (3–10)	0.72
Leukocyte count — per mm ³ **				
Median	8000	8100	6500	0.39
Range	4000–15,000	4000–23,000	3000–14,000	
Albumin — g/dl**	3.7±0.7	3.8±0.7	3.9±0.8	0.66
Median creatinine (range) — mg/dl**	1.3 (0.6–10.3)	1.0 (0.5–1.8)	0.9 (0.6–5.2)	0.26
Ribotype 027 in first sample — no. (%) ††	3 (23)	1 (11)	0	0.28

Compare 3 traitements :

- Vancomycine seule (500mg x 4/j 14 jours)
- Vancomycine + lavement (4L solution Macrogol)
- TMF (SNG) après cure courte Vancomycine (4j) + lavement



Compare 3 traitements :

- Vancomycine seule (500mg x 4/j 14 jours)
- Vancomycine + lavement (4L solution Macrogol)
- TMF (SNG) après cure courte Vancomycine (4j) + lavement

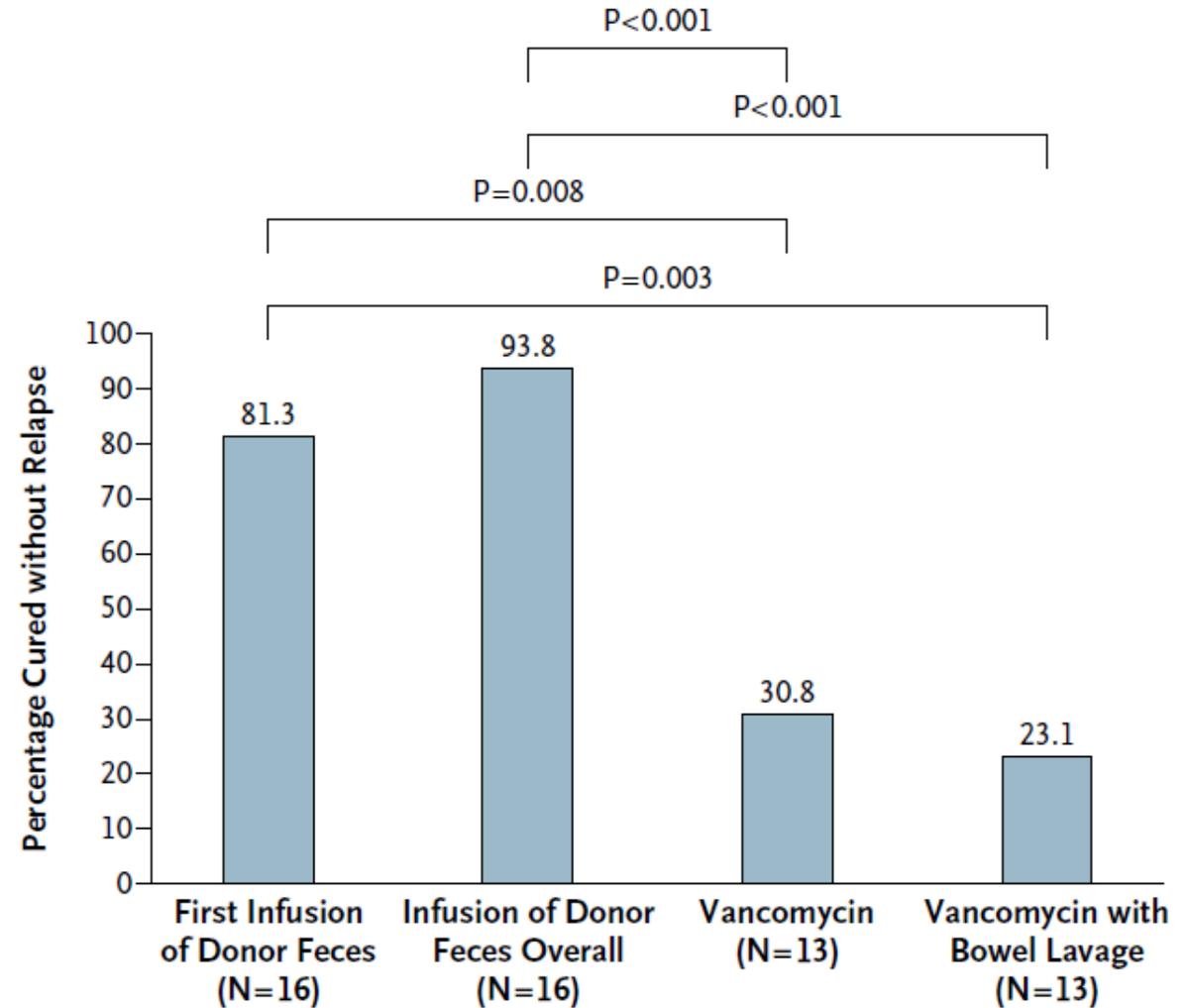


Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.

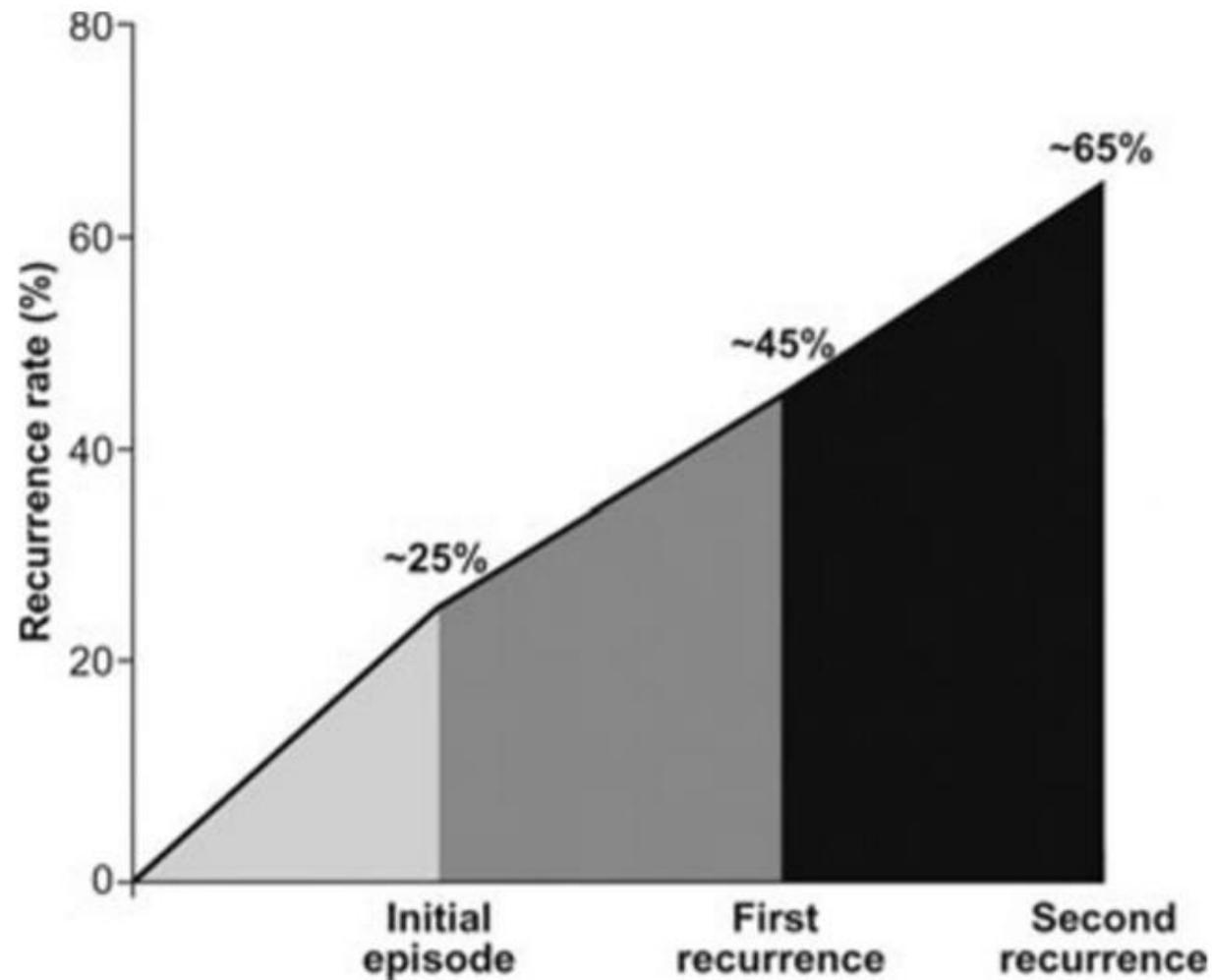
Shown are the proportions of patients who were cured by the infusion of donor feces (first infusion and overall results), by standard vancomycin therapy, and by standard vancomycin therapy plus bowel lavage.

TMF

- ❑ Quel rationnel ? *Pourquoi ?*
- ❑ Est-ce que ça marche ? *Efficace ?*
- ❑ En pratique, comment fait-on ? *Comment ?*

Rationnel

1. ICD récidivantes : traitements médicamenteux peu efficaces



1. ICD récidivantes : traitements médicamenteux peu efficaces

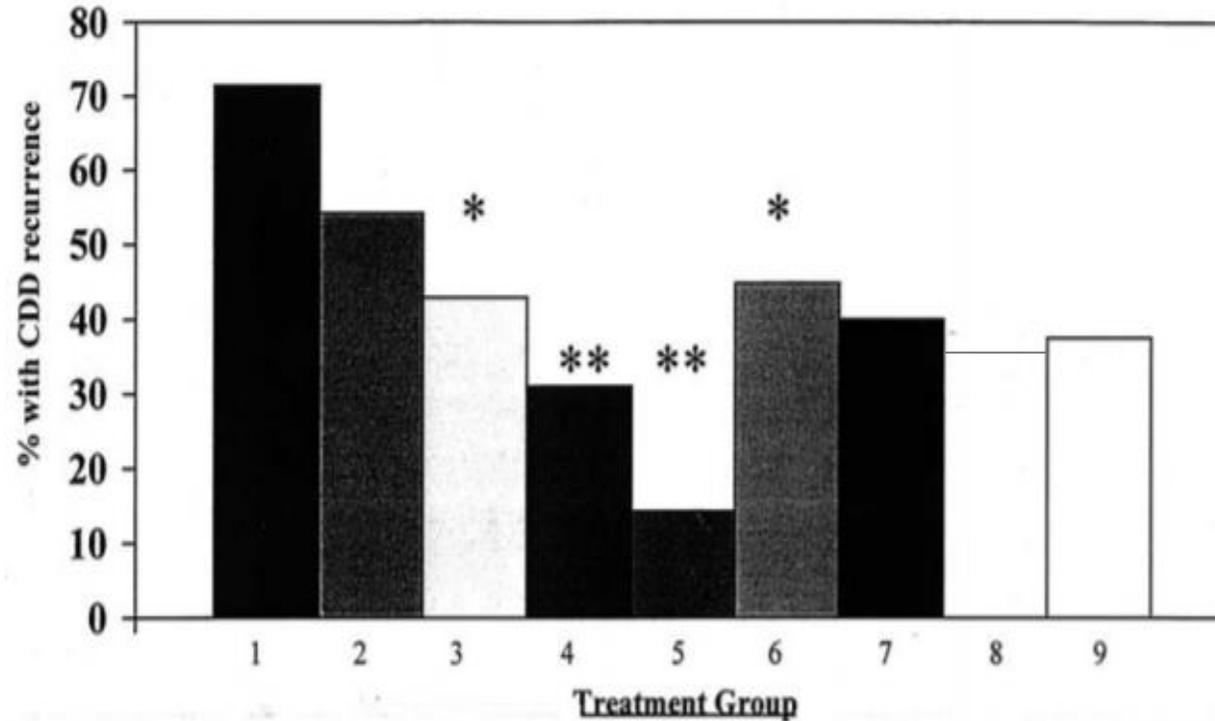
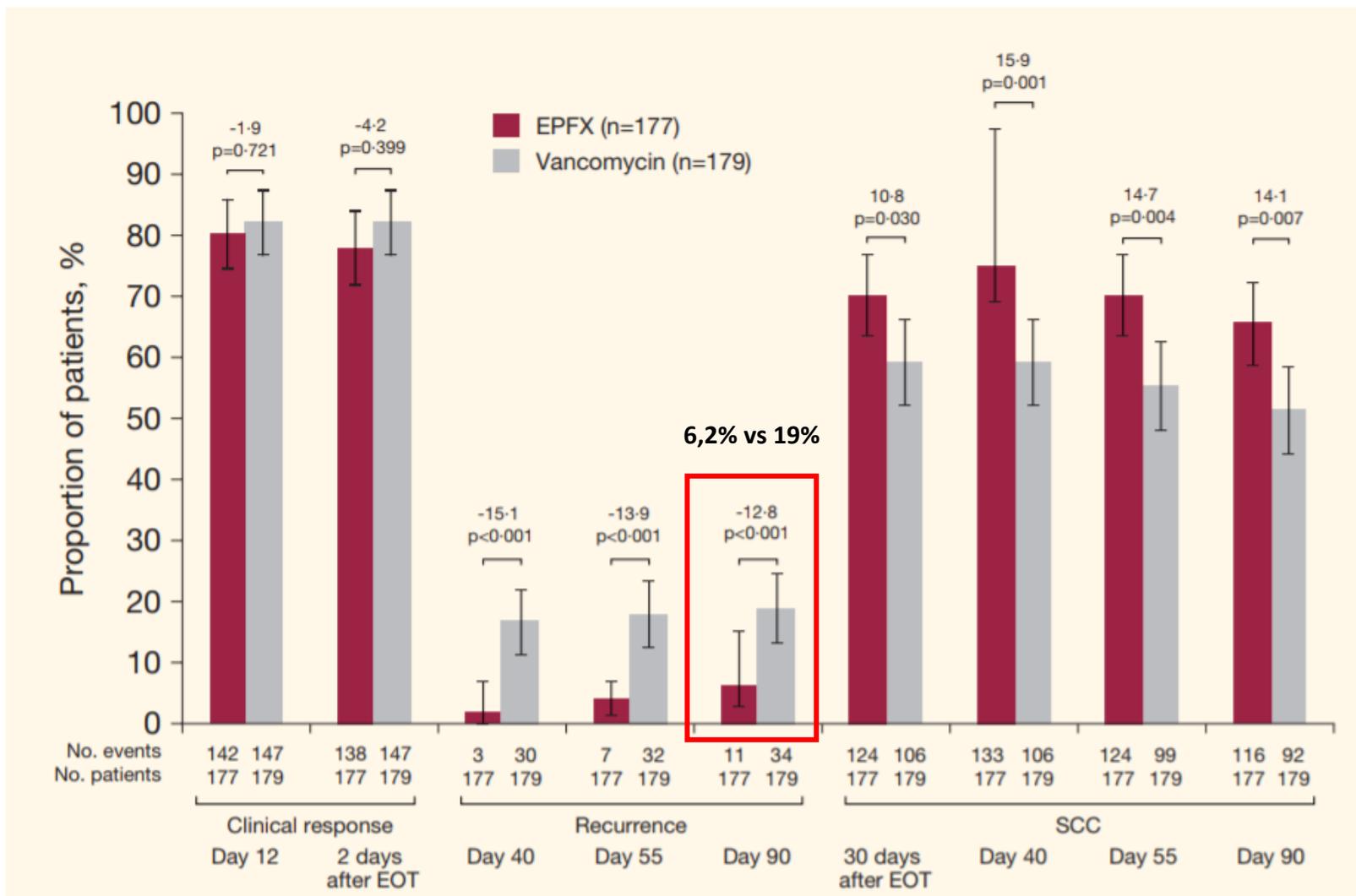


Figure 1. Treatment response in 163 patients with RCDD. 1 = medium dose vancomycin; 2 = low dose vancomycin; 3 = high dose vancomycin; 4 = tapered vancomycin; 5 = pulsed vancomycin; 6 = low dose metronidazole; 7 = medium dose metronidazole; 8 = high dose metronidazole; 9 = miscellaneous. * $0.05 < p < 0.1$, compared to medium dose vancomycin (1 g/day); ** $p < 0.05$, compared to medium dose vancomycin (1 g/day).

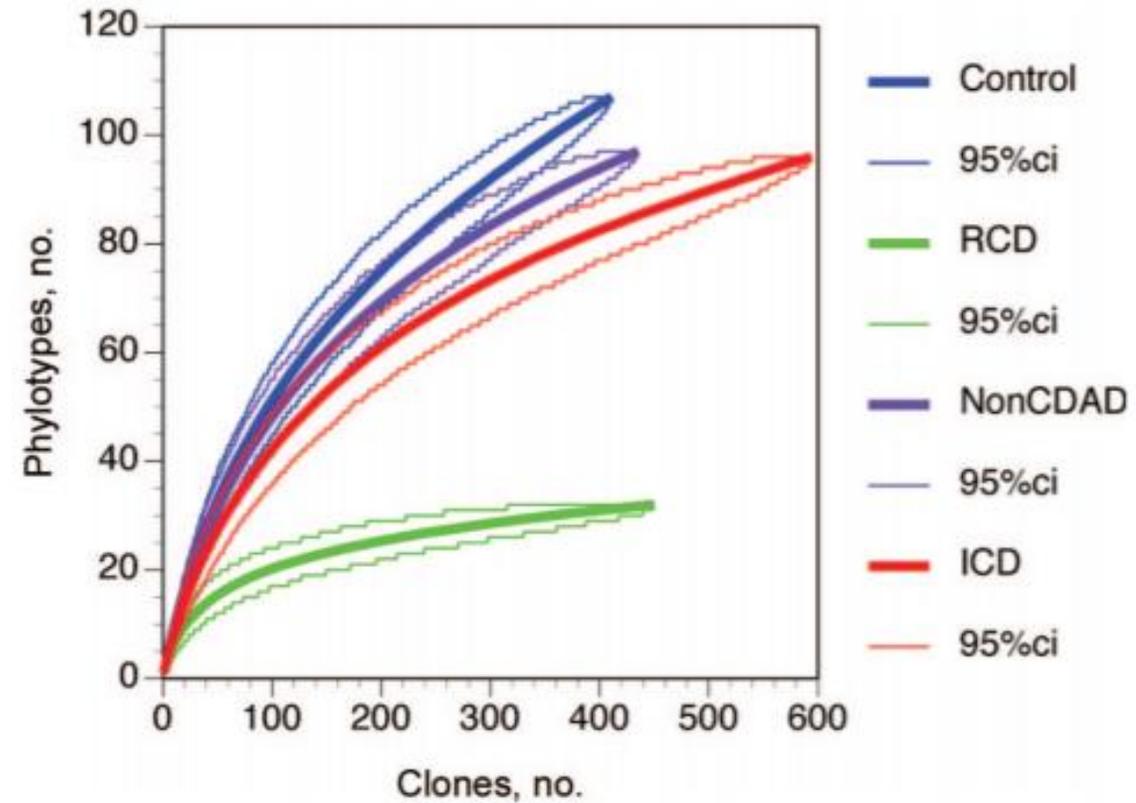
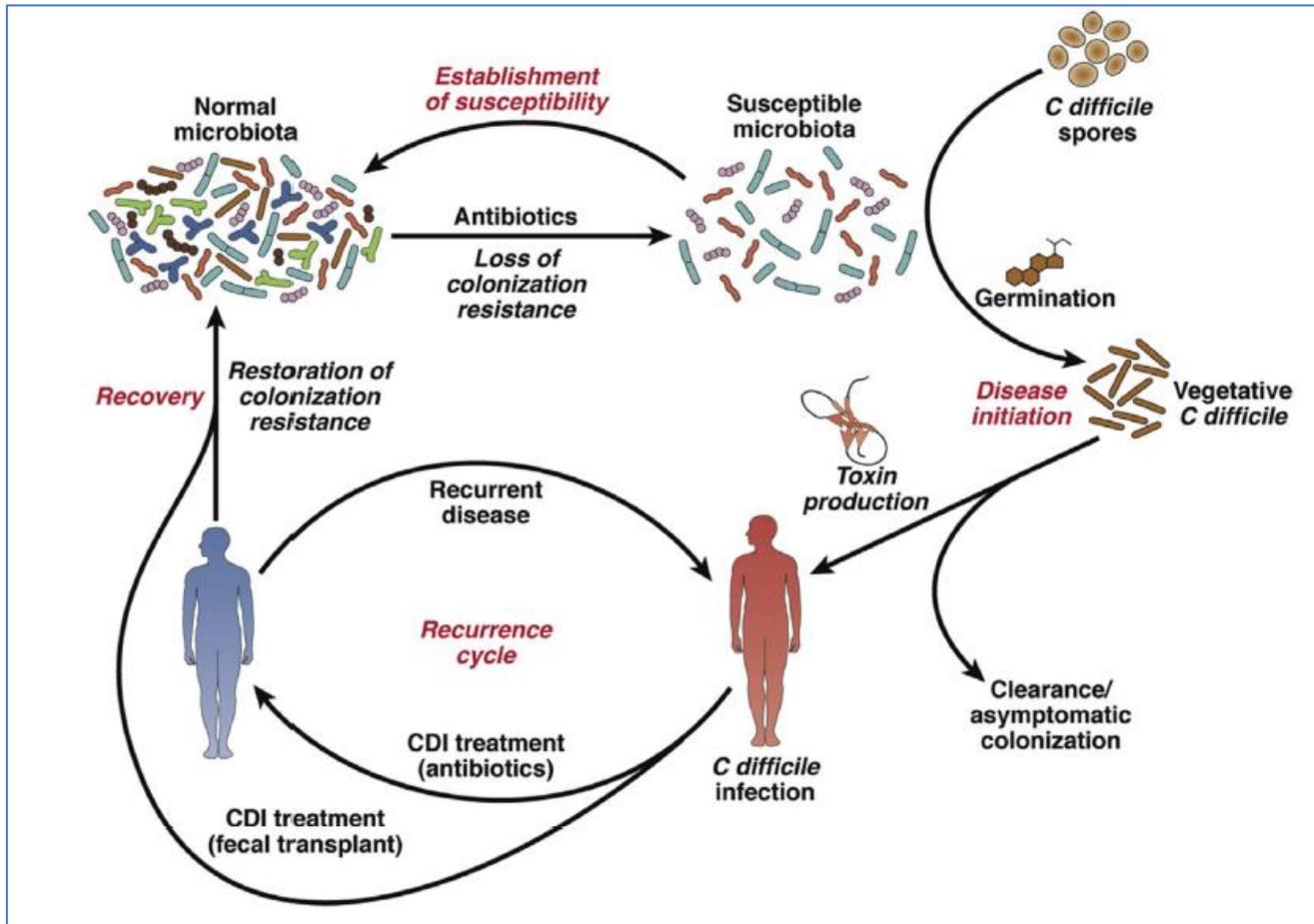
1. ICD récidivantes : traitements médicamenteux peu efficaces



356 patients
Age médian 75 ans

1^{er} épisode 78,9%
1^{ère} récurrence 15,4%
2^{ème} récurrence 5,6%

2. ICD récidivantes = dysbiose

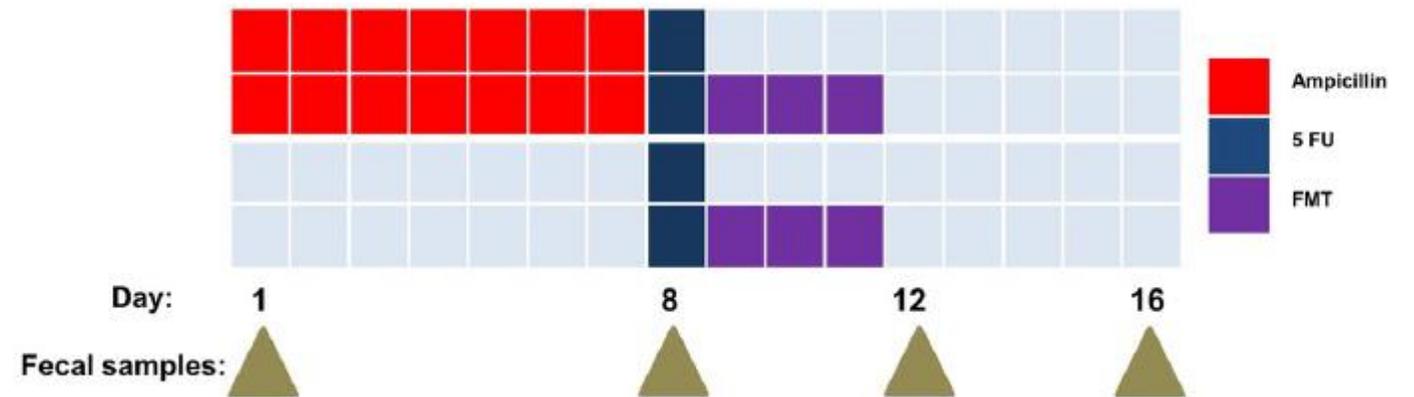


Rao & Young, Infect Dis Clin North Am. 2015

Chang *et al.*, JID 2008

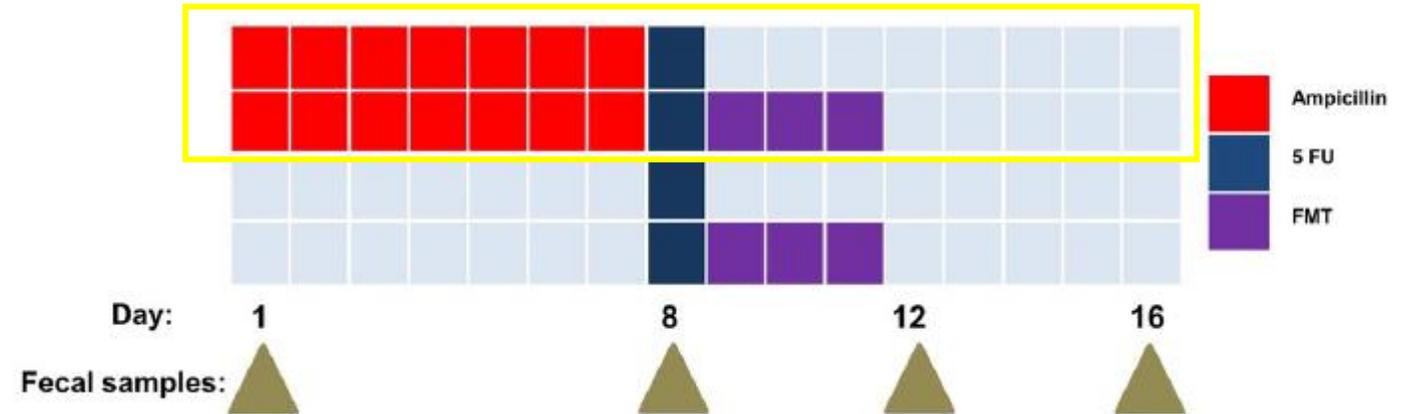
3. TMF : restauration du microbiote

Modèle murin



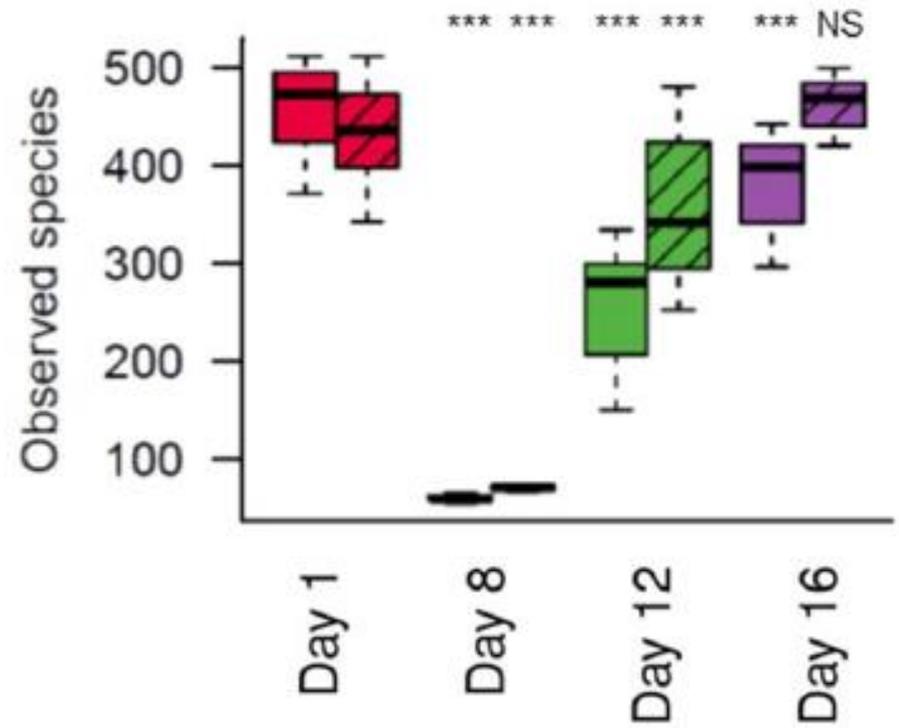
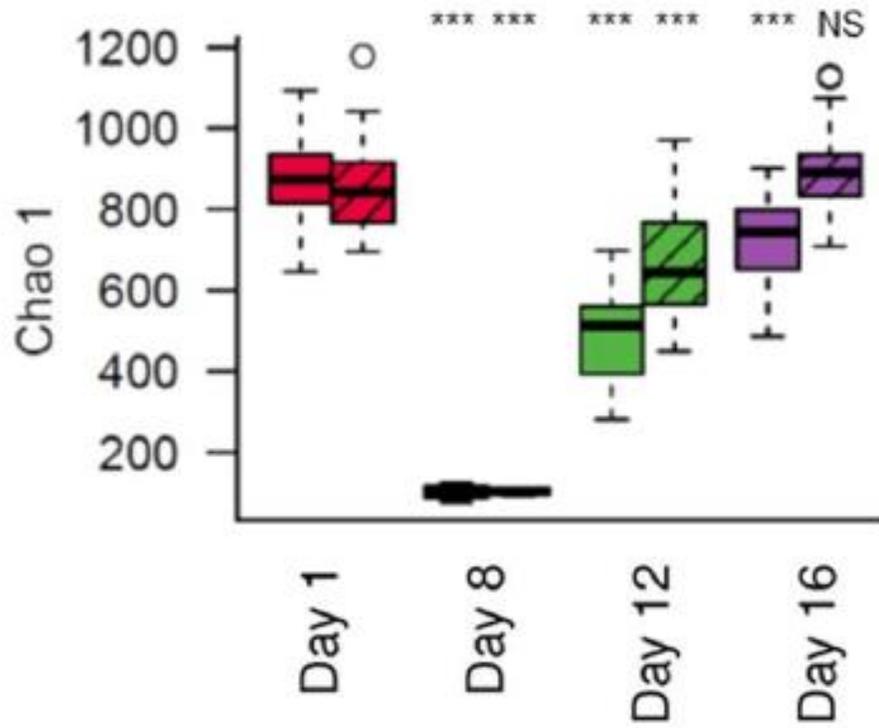
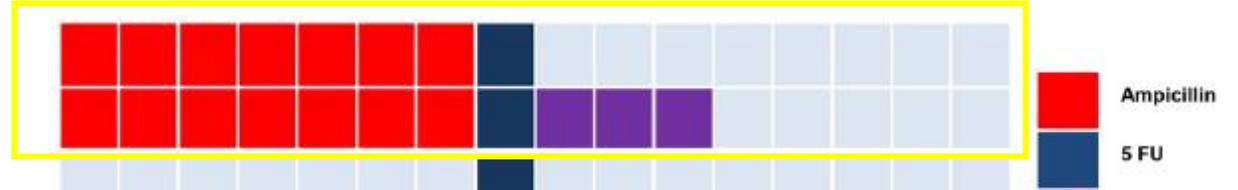
3. TMF : restauration du microbiote

Modèle murin



3. TMF : restauration du microbiote

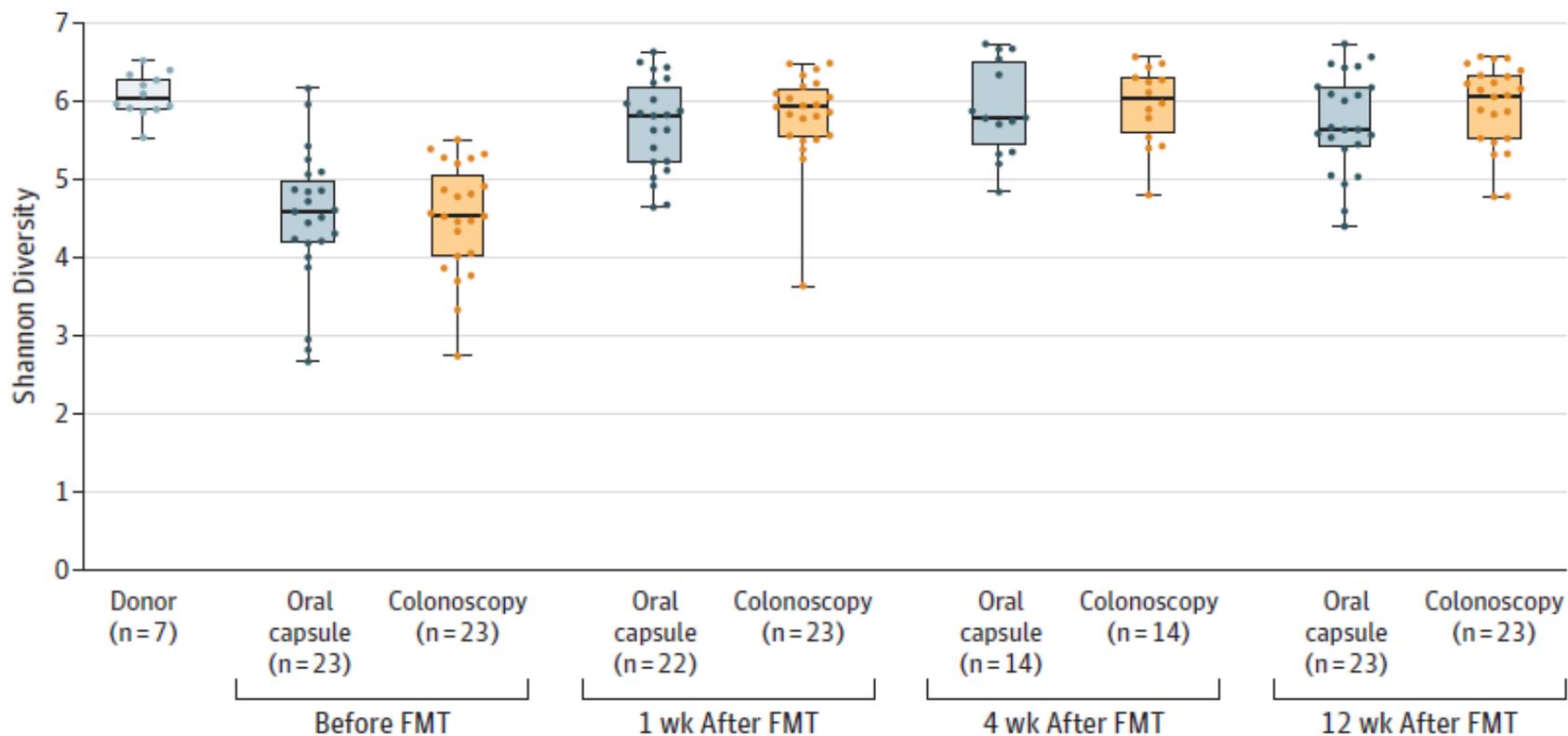
Modèle murin



3. TMF : restauration du microbiote

Chez l'homme

Figure 2. Shannon Diversity of Taxonomic Data From Patients With Recurrent *Clostridium difficile* Infection and Donors



Seekatz *et al.*, mBio 2014

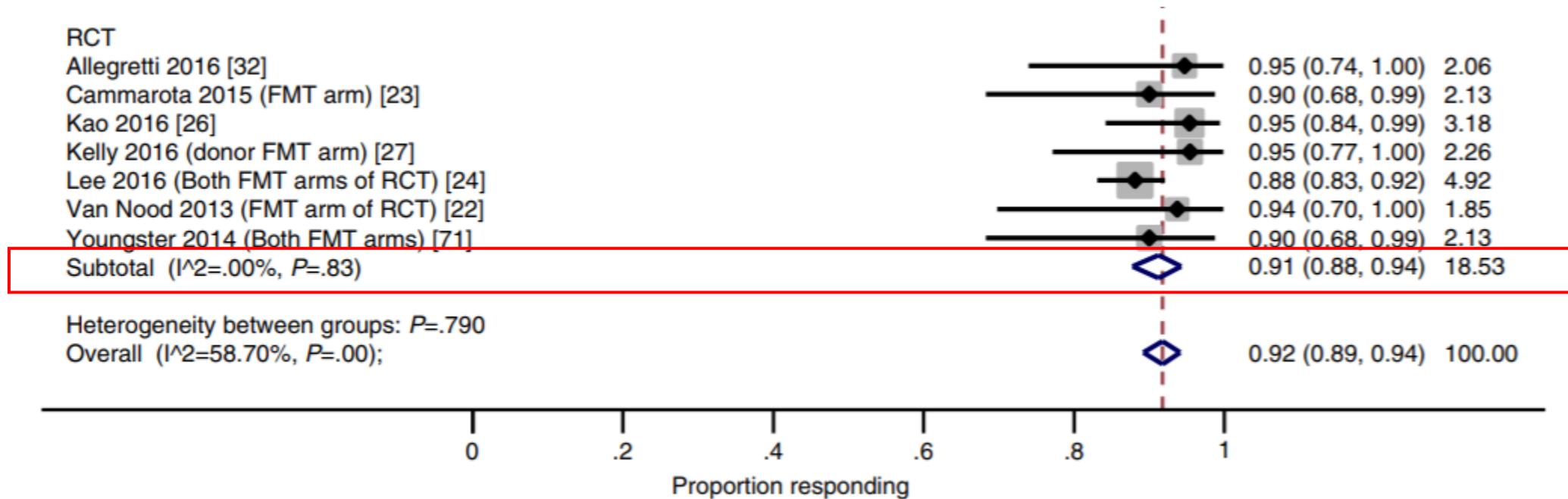
Kao *et al.*, JAMA 2017

Données cliniques - efficacité

1. Essais randomisés

Méta-analyse 2017

37 publications dont 7 RCTs



2. Formes graves et compliquées

Table 3. Summary of therapy outcome and number of fecal transplants needed to achieve resolution of symptoms in patients with severe and severe-complicated *Clostridium difficile* infection (CDI).

	Total (N = 57)	Severe CDI (N = 19)	Severe-complicated CDI (N = 38)	P Value
Number of FMT received, n (%)				0.261
1 FMT	33 (57.9%)	12 (63.1%)	21 (55.3%)	
2 FMTs	17 (29.8%)	4 (21%)	13 (34.2%)	
3 FMTs	5 (8.8%)	1 (5.3%)	4 (10.5%)	
4 FMTs	1 (1.7%)	1 (5.3%)	0 (0%)	
5 FMTs	1 (1.7%)	1 (5.3%)	0 (0%)	
Length of hospital stay (days), median (IQR; range)	11 (6 – 21; 2 – 97)	13 (6 – 17; 3 – 97)	9.5 (6 – 23; 2 – 72)	0.76
Overall success rate at 30 days, n (%)	52 (91.2%)	19 (100%)	33 (86.8%)	0.158

3. Selon le terrain : immunodépression

Méta-Analyse

44 publications (303 patients), pas d'essai randomisé

- Traitement immunosuppresseur (77,2%)
- Transplantés organe solide (18,2%)
- Cancer actif (16,2%)
- HSCT (2,5%)
- VIH (2,1%)

87% guérison après 1^{ère} TMF

93% après TMF multiples

4. Coût efficace

Table 2. Base case analysis of competing strategies for the management of second recurrence of community-onset *Clostridium difficile* infection.

Treatment	Cost (€)	QALY	ICER
Vancomycin pulse/taper	1235	0.1812	
Fidaxomicin	2464	0.1988	(Dominated)
FMT via duodenal infusion	1834	0.2013	(Dominated)
FMT via enema	1610	0.2019	18,092 ^a
FMT via colonoscopy	1816	0.2047	73,653 ^b

Abbreviations: FMT: fecal microbiota transplantation; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year. Costs values are reported as 2016 Euros.

^aICER calculated for FMT via enema relative to pulsed-tapered vancomycin.

^bICER calculated for FMT via colonoscopy relative to FMT via enema.

4. Coût efficace

Table 2. Base case analysis of competing strategies for the management of second recurrence of community-onset *Clostridium difficile* infection.

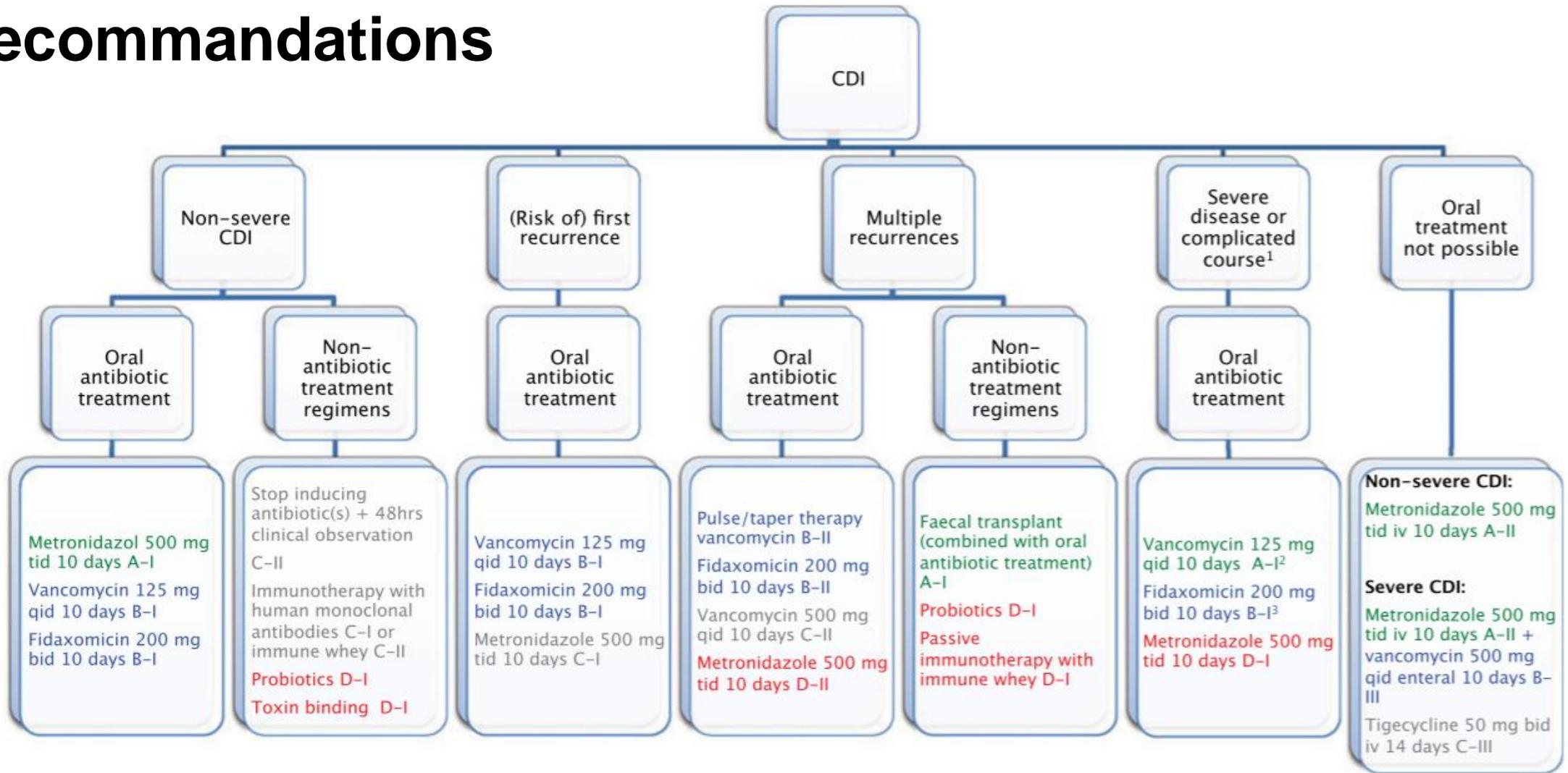
Treatment	Cost (€)	QALY	ICER
Vancomycin pulse/taper	1235	0.1812	
Fidaxomicin	2464	0.1988	(Dominated)
FMT via duodenal infusion	1834	0.2013	(Dominated)
FMT via enema	1610	0.2019	18,092 ^a
FMT via colonoscopy	1816	0.2047	73,653 ^b

Abbreviations: FMT: fecal microbiota transplantation; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year. Costs values are reported as 2016 Euros.

^aICER calculated for FMT via enema relative to pulsed-tapered vancomycin.

^bICER calculated for FMT via colonoscopy relative to FMT via enema.

5. Recommendations



5. Recommendations

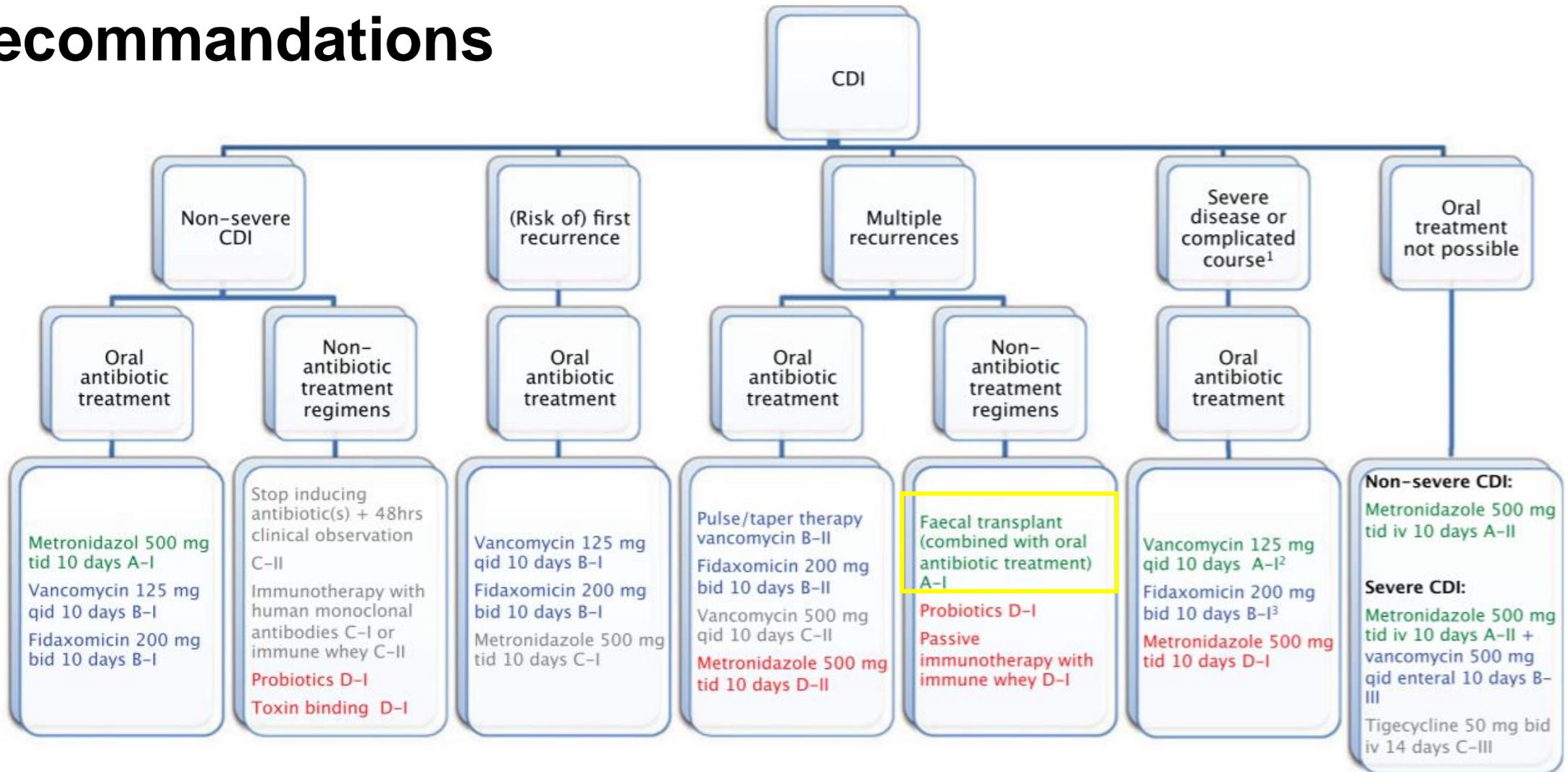


Table 1. Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

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 $\leq 15\,000$ cells/mL and a serum creatinine level < 1.5 mg/dL	<ul style="list-style-type: none"> • VAN 125 mg given 4 times daily for 10 days, OR • FDX 200 mg given twice daily for 10 days • Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days 	<p>Strong/High</p> <p>Strong/High</p> <p>Weak/High</p>
Initial episode, severe ^b	Leukocytosis with a white blood cell count of $\geq 15\,000$ cells/mL or a serum creatinine level > 1.5 mg/dL	<ul style="list-style-type: none"> • VAN, 125 mg 4 times per day by mouth for 10 days, OR • FDX 200 mg given twice daily for 10 days 	<p>Strong/High</p> <p>Strong/High</p>
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	<ul style="list-style-type: none"> • 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. 	<p>Strong/Moderate (oral VAN); Weak/Low (rectal VAN); Strong/Moderate (intravenous metronidazole)</p>
First recurrence	...	<ul style="list-style-type: none"> • VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR • 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 • FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode 	<p>Weak/Low</p> <p>Weak/Low</p> <p>Weak/Moderate</p>
Second or subsequent recurrence	...	<ul style="list-style-type: none"> • VAN in a tapered and pulsed regimen, OR • VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR • FDX 200 mg given twice daily for 10 days, OR • Fecal microbiota transplantation^c 	<p>Weak/Low</p> <p>Weak/Low</p> <p>Weak/Low</p> <p>Strong/Moderate</p>

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 $\leq 15\,000$ cells/mL and a serum creatinine level < 1.5 mg/dL	<ul style="list-style-type: none"> • VAN 125 mg given 4 times daily for 10 days, OR • FDX 200 mg given twice daily for 10 days • Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days 	<p>Strong/High</p> <p>Strong/High</p> <p>Weak/High</p>
Initial episode, severe ^b	Leukocytosis with a white blood cell count of $\geq 15\,000$ cells/mL or a serum creatinine level > 1.5 mg/dL	<ul style="list-style-type: none"> • VAN, 125 mg 4 times per day by mouth for 10 days, OR • FDX 200 mg given twice daily for 10 days 	<p>Strong/High</p> <p>Strong/High</p>
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	<ul style="list-style-type: none"> • 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. 	<p>Strong/Moderate (oral VAN); Weak/Low (rectal VAN); Strong/Moderate (intravenous metronidazole)</p>
First recurrence	...	<ul style="list-style-type: none"> • VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR • 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 • FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode 	<p>Weak/Low</p> <p>Weak/Low</p> <p>Weak/Moderate</p>
Second or subsequent recurrence	...	<ul style="list-style-type: none"> • VAN in a tapered and pulsed regimen, OR • VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR • FDX 200 mg given twice daily for 10 days, OR • Fecal microbiota transplantation^c 	<p>Weak/Low</p> <p>Weak/Low</p> <p>Weak/Low</p> <p>Strong/Moderate</p>

TMF en pratique

Recommandations pratiques TMF

- ❑ France : Groupe Français de transplantation fécale (GFTF) 2015 ¹
- ❑ Europe : European FMT Working group, 2017 ²

¹ Sokol *et al.*, HepatoGastro
2015

² Cammarota *et al.*, Gut 2017



Recommandations pratiques TMF

- ❑ France : Groupe Français de transplantation fécale (GFTF) 2015 ¹
- ❑ Europe : European FMT Working group, 2017 ²

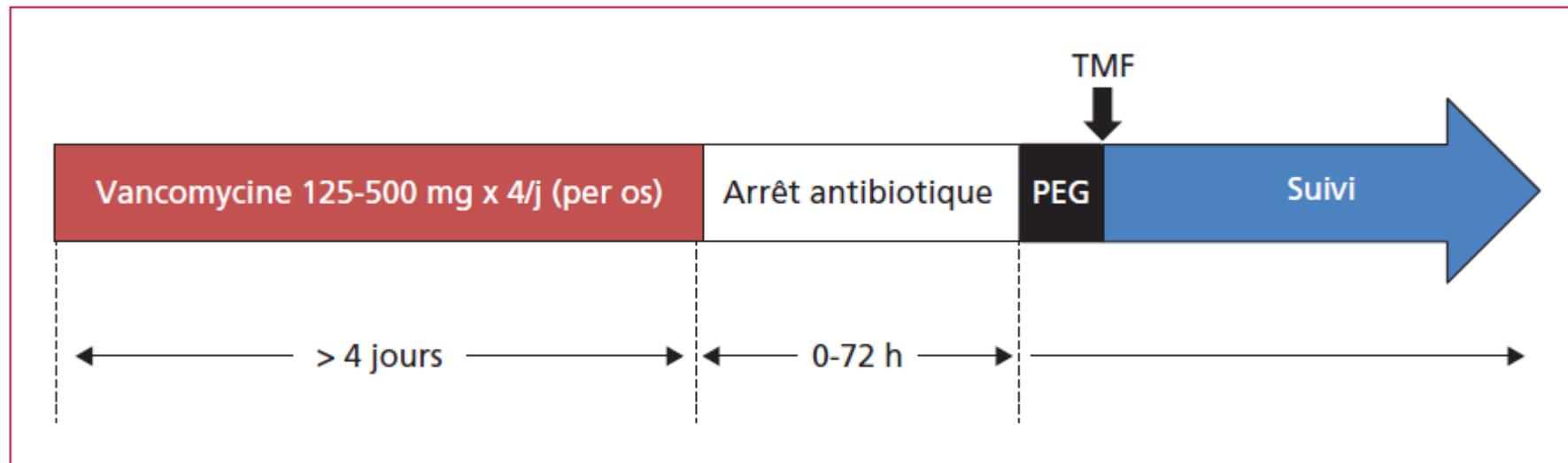


Figure 1. Transplantation de microbiote fécal : séquence thérapeutique.

¹ Sokol *et al.*, HepatoGastro 2015

² Cammarota *et al.*, Gut 2017

1. Sélection des donneurs

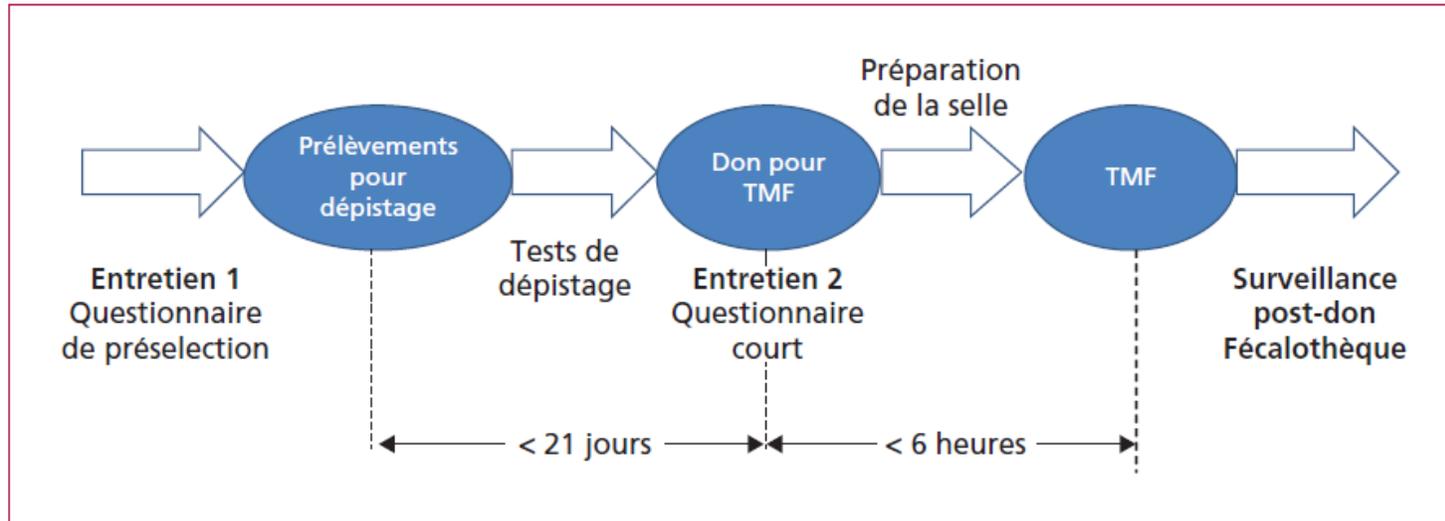


Figure 2. Chronologie (versant « donneur ») de la transplantation de microbiote fécal (TMF).

1. Sélection des donneurs

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

Informations	Critères d'exclusion au don	Critères de sélection avec appréciation individuelle
Co-morbidités	<ul style="list-style-type: none"> ■ Troubles digestifs (diarrhée aiguë ou chronique) dans les 3 mois précédant le don ■ Pathologie chronique connue ■ Antécédent de fièvre typhoïde 	Donneurs avec antécédents familiaux : <ul style="list-style-type: none"> – MICI (lien de parenté) – maladies auto-immunes (lien de parenté) – cancer colique (lien de parenté et âge d'apparition) Donneurs avec antécédents personnels d'hypertension artérielle ou hypercholestérolémie non compliquée
Traitement médicamenteux	Donneur suivant un traitement au long cours ¹ Prises d'antibiotiques dans les 3 mois ¹	Traitement de l'hypertension artérielle ou de l'hypercholestérolémie non compliquée
Voyages	<ul style="list-style-type: none"> ■ 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 24 h dans les 12 derniers mois (y compris membres de l'entourage du donneur)² 	Consommation de gibier (doit faire rechercher une trichinose dans le bilan de dépistage)
Âge	Donneur mineur ³	Donneur âgé (> 65 ans) ⁴
Statut pondéral	Non limitant	Donneur avec IMC > 30 ⁵

1. Sélection des donneurs

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

Informations	Critères d'exclusion au don	Critères de sélection avec appréciation individuelle
Co-morbidités	<ul style="list-style-type: none"> ■ Troubles digestifs (diarrhée aiguë ou chronique) dans les 3 mois précédant le don ■ Pathologie chronique connue ■ Antécédent de fièvre typhoïde 	Donneurs avec antécédents familiaux : <ul style="list-style-type: none"> – MICI (lien de parenté) – maladies auto-immunes (lien de parenté) – cancer colique (lien de parenté) Donneurs avec antécédents d'hypertension artérielle ou hypercholestérolémie non compliquée
Traitement médicamenteux	Donneur suivant un traitement au long cours ¹ Prises d'antibiotiques dans les 3 mois ¹	Traitement de l'hypertension de l'hypercholestérolémie non compliquée
Voyages	<ul style="list-style-type: none"> ■ 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 24 h dans les 12 derniers mois (y compris membres de l'entourage du donneur)² 	Consommation de gibier (doigté) ou de viande crue dans le bilan de santé
Âge	Donneur mineur ³	Donneur âgé (> 65 ans) ⁴
Statut pondéral	Non limitant	Donneur avec IMC > 30 ⁵

Profil « idéal » du donneur :

Âge : 18-65 ans

IMC < 30

Absence de pathologie chronique

Absence de traitement curatif au long cours

Absence de séjour à l'étranger (dans un pays à risque infectieux*) dans les 3 mois précédant le don

Absence d'hospitalisation à l'étranger (dans un pays à risque infectieux*) dans les 12 mois précédant le don

Aspect macroscopique normal des selles

Dépistage négatif d'agents infectieux (cf. liste proposée en annexe 1)

Tableau 2. Liste des agents infectieux à dépister chez les donneurs

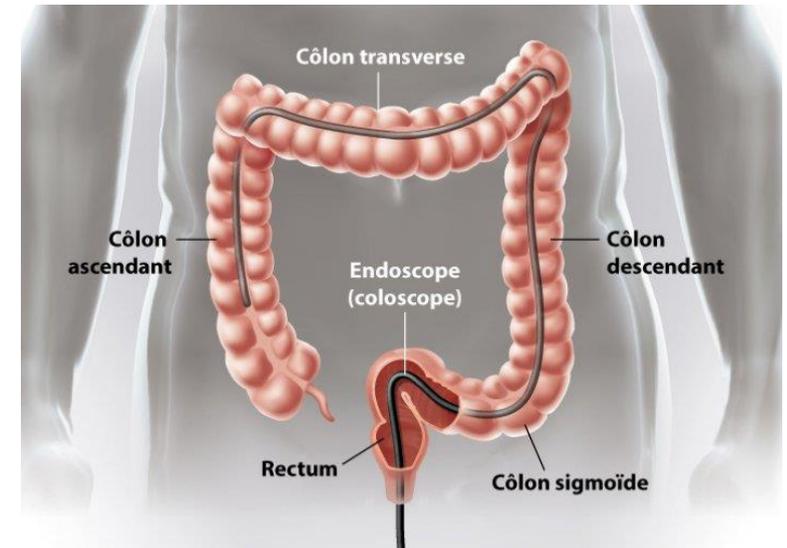
	Sang (sérologies)	Selles
Bactéries	<i>Treponema pallidum</i> (TPHA, VDRL)	<i>Clostridium difficile</i> Coproculture standard : <i>Salmonelle</i> , <i>Yersinia</i> , <i>Shigelle</i> , <i>Campylobacter</i> Bactéries multirésistantes aux antibiotiques ¹
Virus ¹	Virus de l'immunodéficience humaine (HIV) Virus T-lymphotropique humain (HTLV) Virus des hépatites A, B, C et E (HVA HVB HVC HVE) Cytomégalovirus (CMV) ³	Norovirus ² Rotavirus ² (uniquement si le donneur est un enfant < 8 ans)
Parasites	<i>Strongyloïdes stercoralis</i> ⁴ <i>Amibiase</i> ⁴ <i>Trichinella sp.</i> ⁵	<i>Strongyloïdes stercoralis</i> <i>Cryptosporidium sp.</i> (Si patient immunodeprimé) ⁶ <i>Cyclospora sp.</i> ⁶ <i>Entamoeba histolytica</i> ^{6,7} <i>Giardia intestinalis</i> ⁶ <i>Isospora sp.</i> ⁶ <i>Microsporidies</i> ⁶

Voie d'administration

Différence significative ($P=.02$) pour la guérison clinique

Administration colique (lavement ou coloscopie) = **95%** [IC 95% (92%-97%)]

Administration par SNG ou SND = **88%** [IC 95% (82%-94%)]



Modalités d'administration « Frozen vs fresh »

Table 3. Primary Efficacy Outcome in the Modified Intention-to-Treat and Per-Protocol Populations According to Subgroup at 13 Weeks After Last Fecal Microbiota Transplantation

	mITT			Per-Protocol		
	Proportion With Clinical Resolution, No./Total (%)		Difference (95% CI), %	Proportion With Clinical Resolution, No./Total (%)		Difference (95% CI), %
	Frozen	Fresh		Frozen	Fresh	
Overall Population						
Primary efficacy outcome ^a	81/108 (75.0)	78/111 (70.3)	4.7 (-5.2 to ∞) (<i>P</i> < .001)	76/91 (83.5)	74/87 (85.1)	-1.6 (-10.5 to ∞) (<i>P</i> = .01)

Modalités d'administration « Frozen vs fresh »

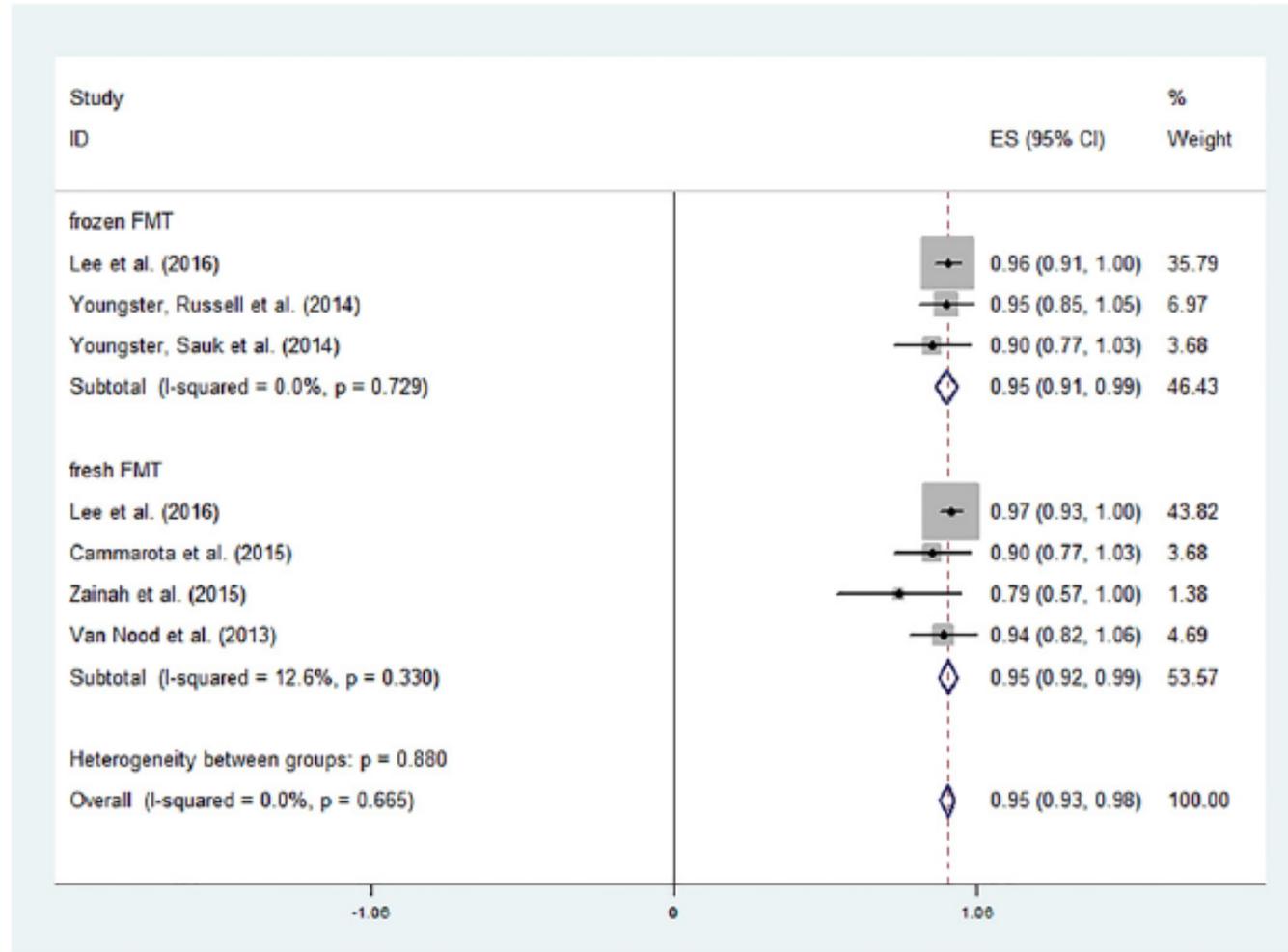


Fig. 3. Meta-analysis plot of pooled second effective rate comparing frozen FMT with fresh FMT.



Modalités d'administration : gélules

Youngster *et al.*, JAMA 2014

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

20 patients (au – 2 récurrences préalables). 15 gélules/j en 1 prise pendant 2 jours

Guérison : **90%** [IC 95% (68%-98%)]

Kao *et al.*, JAMA 2017

Effect of Oral Capsule– vs Colonoscopy-Delivered Fecal Microbiota Transplantation on Recurrent *Clostridium difficile* Infection

Essai **randomisé multicentrique**. Inclus : au – 2 récurrences. Transplant congelé.

116 patients :

- **Guérison clinique identique pour les 2 groupes (96,2%); $P < .001$**
- Perception « non désagréable » dans le groupe gélule (66% vs 44%; difference, 22% [IC 95% (3%-40%)]);
 $P = .01$

Préparation du transplant TMF = médicament = préparation à la pharmacie !

Box 4 Minimum general steps to follow for the preparation of fresh and frozen faecal material

FRESH FAECAL MATERIAL

- ▶ Fresh stool should be used within 6 hours after defecation
- ▶ To protect anaerobic bacteria, the storage and preparation should be as brief as possible
- ▶ Until further processing, the stool sample can be stored at ambient temperature (20°C–30°C)
- ▶ Anaerobic storage and processing should be applied if possible
- ▶ A minimum amount of 30 g of faeces should be used
- ▶ Faecal material should be suspended in saline using a blender or manual effort and sieved in order to avoid the clogging of infusion syringes and tubes
- ▶ A dedicated space, disinfected using measures that are effective against sporulating bacteria, should be used
- ▶ Protective gloves and facial masks should be used during preparation

FROZEN FAECAL MATERIAL

- ▶ At least 30 g of donor faeces and 150 mL of saline solution should be used
- ▶ Before freezing, glycerol should be added up to a final concentration of 10%
- ▶ The final suspension should be clearly labelled and traceable, and stored at –80°C
- ▶ On the day of faecal infusion, faecal suspension should be thawed in a warm (37°C) water bath and infused within 6 hours from thawing
- ▶ After thawing, saline solution can be added to obtain a desired suspension volume
- ▶ Repetitive thawing and freezing should be avoided

TMF : conclusion

❑ Quel rationnel ?

- ICD récidivantes = dysbiose
- TMF restaure le microbiote et « casse le cercle vicieux » de la récurrence

❑ Est-ce que ça marche ? **OUI!**

Beaucoup mieux que les traitements médicamenteux pour les ICD récidivantes

❑ En pratique, comment fait-on ?

cf recommandations françaises et européennes pour la TMF

❑ Perspectives

- En infectiologie :
 - ✓ ICD : plus tôt dans la stratégie thérapeutique?
 - ✓ Eradication BMR
- Hors infectiologie

