

Clostridioides difficile

Fidaxomycine pour tout le monde ?

Séminaire d'infectiologie du 19 novembre 2026

20 minutes ; Romain Martischang

1. **Cas clinique et contexte**
2. **Le métronidazole**
3. **La fidaxomycine dans les recommandations**
4. **La fidaxomycine dans l'évidence**
5. **Les schémas prolongés et la transplantation fécale**
6. **Résumé**

Une histoire sans fin



Mme E, 88 ans

Cardiopathie ischémique et valvulaire, pontage aorto-bi-iliaque, AVC, splénectomie, ischémie colique avec colostomie terminale, ésoméprazole

22.07.2026

Infection sévère à *C. difficile* (PCR+EIA+)

- PN à *E. cloacae* BLSE (IMI 5j, 16–22.07.26)
- VAN PO 14 j + MTZ IV 10 j
- Résolution clinique

→

27.08.2026

1re récidive (PCR+EIA+)

- VAN PO 14 j

→

21.09.2026

2re récidive (PCR+EIA+)

? **Traitement ?**

Une histoire sans fin



Quel traitement proposer ?

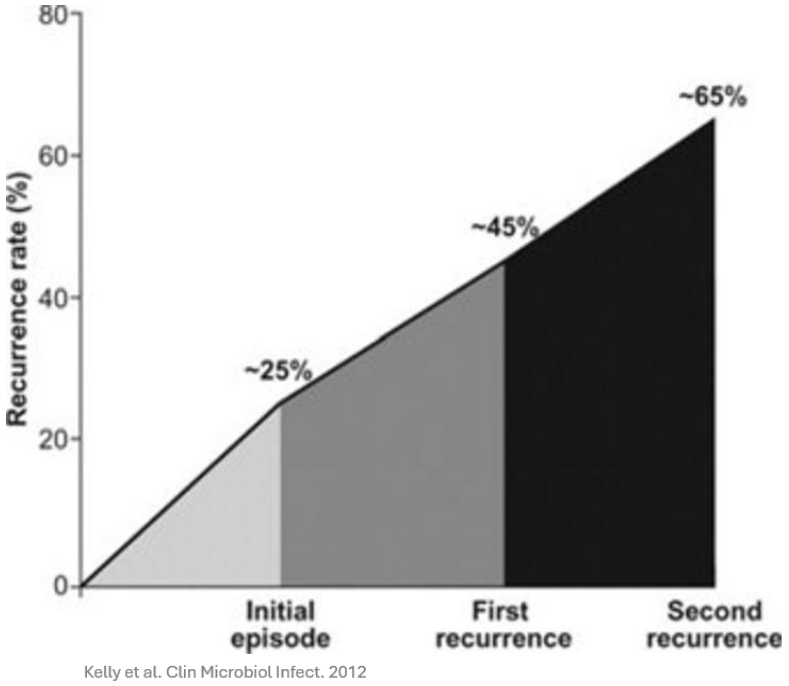
- Vancomycine (schéma prolongé)
- Vancomycine 10J + transplantation fécale
- Vancomycine (schéma prolongé) + transplantation fécale
- Fidaxomycine (schéma prolongé) + transplantation fécale

Contexte épidémiologique & définitions

Prevalence of HAI 7.3%
(European ACH 2016–17; ECDC PPS 2022–2023)

Mortality 3.8% | **rCDI mortality 10.5%**
Okafor. Emerg Infect Dis. 2023

Risque de récurrence



Kelly et al. Clin Microbiol Infect. 2012

	Consensus
CDI sévère	Leucocytes ≥15,000/µL ou Créatinine >132µmol/l *Fièvre >38.5°C (ESCMID, SSI)* *Imagerie (ESCMID, SSI, ECIL-10, AGA)*
CDI sévère-compliquée / fulminant	Hypotension/choc, Iléus ou mégacôlon Perforation ou détérioration rapide *lactate élevés (+- >2mmol/L) (ESCMID, SSI)*
Récurrence	Dans les **8 semaines** suivant une résolution clinique
Réfractaire	Absence de réponse au traitement **dans les 3 à 5 jours**

La place du métronidazole



Métronidazole explicitement NON recommandée

Excepté

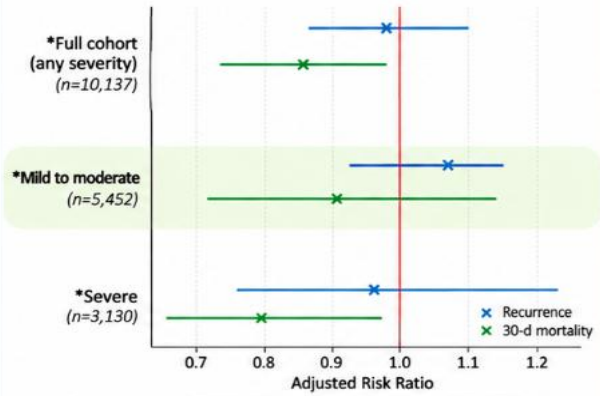
- **Patient à faible risque avec une CDI non sévère** comme alternative, lorsque les coûts ne permettent pas une meilleure option (ACG only)
- Non-sévère si fidaxomycine et vancomycine non disponibles (IDSA, ESCMID)
- IV pour les formes fulminantes ou compliquées (all)

Resistance ~ METRO
(metabolic pathways)

Suboptimal PK ~ METRO
- Absorbed in the small intestine
- Drug inactivation in the colon
- Low concentration in stools

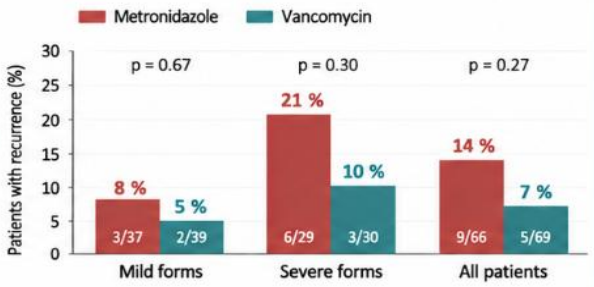
Clinical outcomes (vs vancomycin)

Adjusted RR (95% CI) – Recurrence and 30-day Mortality
Stevens et al., JAMA Intern Med 2017 (Table 2)



***Retrospective of 47'471 PS-matched patients treated for CDI in the VA healthcare system from 2005-2012 (2'068 treated by Vancomycin)*

Recurrence after initial cure
Metronidazole versus vancomycin



RCT 1994–2002
150 patients with *C. difficile* diarrhea, no prior antibiotic
TcdA EIA+
Metronidazole 250 mg q.i.d. vs vancomycin 125 mg q.i.d. / 10d
Test of Cure 21d; EIA TcdA +
Zar et al. CID. 2007;45(3):302–37

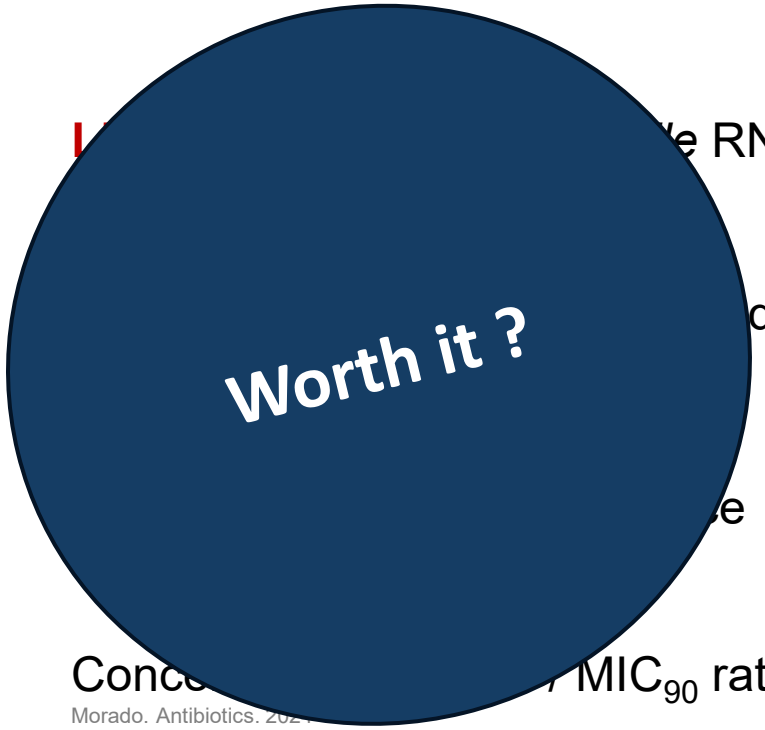
La place de la fidaxomycine …

TABLE 2 Comparison: vancomycin and fidaxomicin[a]

Antibiotic	Fidaxomicin	Vancomycin
Biofilm inhibition	Yes (471, 472)	No
C. difficile MIC_{90}	0.125 mg/L (473)	2 mg/L (473)
Category	Macrocyclic antibiotic	Glycopeptide
Dosage	200 mg PO q12h	125 mg PO q6h
Eagle effect	No	Yes
Efficacy in mild CDI	+++	+++
Efficacy in severe CDI	++	+++
Formulations	Tablets	Powder, tablets
Gut flora disruption	Low	Moderate/high
Mechanism of action	Inhibits RNA polymerase	Inhibits cell wall synthesis
MIC breakpoint	1 mg/L (474)	2 mg/L (475)
Molecular weight	1,058 Da (476)	1,449 Da (477)
PK/PD index	AUC/MIC (474)	AUC/MIC (474)
Post antibiotic effect	Long (474)	Short (474)
Prevention of rCDI	+++	+
Pulsed/tapered regimens	Evidence existing	Evidence existing
Risk of VRE emergence	Low	Moderate/high
Systemic absorption	Minimal	Minimal
Sporulation reduction	++ (464)	– (468)
Toxin reduction	++	–[b]

[a]AUC, area under the curve; Da, dalton; PK/PD, pharmacokinetic/pharmacodynamic; PO, per os; MIC, minimum inhibitory concentration.
[b]–, low.

Di Bella. CMR. 2024.



…e RNA pol

…que

…e

Conc… …/ MIC_{90} ratios ~ 5000:1

Morado. Antibiotics. 202…

La place de la fidaxomycine …
dans l'évidence

Similar efficacy for cure

Fidaxomicin ≈ vancomycin for initial CDI cure

Cure rate: **87–92%**

Cornely et al. Clin Infect Dis. 2012; Louie et al. N Engl J Med. 2011; Cornely et al. Lancet ID. 2012

Better prevention of recurrence

Lower rate of recurrent CDI (rCDI) with fidaxomicin

Day 28 after end of treatment (EOT):

First CDI episode	**AD –10.9%**
First recurrent CDI	**AD –15.8%**

Cornely et al. Clin Infect Dis. 2012

Extended-pulsed fidaxomicin (EPFX): benefit in subgroups

Higher cure rate in older adults

> 60 years (Day 30 EOT): **70% vs 59%** (OR 1.62)

Guery et al. Lancet ID. 2018 (EXTEND trial)

Lower rCDI in very old adults

> 75 years (Day 90, not EOT): **AD –17.5%** (P = 0.037)

Cornely et al. Eur J Clin Microbiol Infect Dis. 2019 (EXTEND subgroup)

Comparable results in random effects network meta analysis published earlier

(Beinortas et al. Lancet ID. 2018)
(Bednarik et al. Lancet Reg Health 2025)

Results now challenged

No significant benefit in non-RT027 strains

Day 30 EOT

Guery et al. Lancet ID. 2018 (EXTEND trial)

No superiority for 1st or 2nd recurrence

Day 59 (not EOT) vs vancomycin 10d or 31d-TAP

Johnson et al. N Engl J Med. 2026

2016-2024 RCT in patients with only recurrent CDI (and no prolonged systemic antibiotic course) ; But …
Longer treatment duration (VAN-TAP ~ 31J) & shorter follow-up (1M for VAN-TAP),
Unpowered study (almost half of the initial planned population)
Different molecular profile (non-RT027) ? Scarce data
Fidaxomycin more effective for the initial episode ? Controversed …

AD : Absolute Difference
EOT : End Of Treatment
TAP : Tapered & Pulsed

La place de la fidaxomycine …
dans l'évidence

Economic burden of recurrence

Costs of recurrence, hospital stays, and retreatment

Hospitalized CDI: **€189 million**

Modelling studies

Healthcare perspective

Rajasingham et al. CID. 2020;70(5):754–62

Initial non-severe CDI: fidaxomicin (FDX)
Severe CDI: vancomycin (VAN)
1st recurrence: fidaxomicin (FDX)
2nd recurrence: FMT

- 48 treatment strategies
- Additional cost: **+$478/patient**
- **QALY: +0.009/patient**
- **ICER: $31,751/QALY** (< WTP of $100,000)

US societal perspective

Chen et al. Clin Microbiol Infect. 2021;27(10):1448–1454

- Lifetime horizon
- **FDX vs VAN to treat a 1st episode of CDI**
- Additional cost: **+$147/patient**
- **QALY: +0.30/patient**
- **ICER: $495/QALY**
- Cost-saving/dominant (EP-)FDX over VAN (less costly $37,613 vs $39,178, with more QALYs)

Systematic reviews

Burton et al. PharmacoEconomics. 2017;35:1123–1140

- **11/14 (78.6%)** economic evaluations (EE, excl. FMT) favored FDX over VAN
- **5/5 (100%)** EE favored FDX over VAN in patients at **higher risk** of mortality or CDI recurrence

Considerations / Limitations

Recurrence rates from older RCTs
(mostly from Louie et al., Guery et al., and Cornely et al.; latest study not included)

CDI costs may not reflect real-world LOS
(possible confounders overestimating cost-effectiveness of preventing recurrence)

Country-specific costs & WTP thresholds
US WTP: **$5,000 – $100,000**
European WTP: **€20,000 – €50,000**

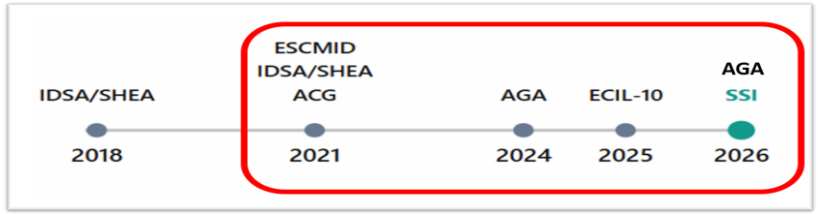
Society perspective (cost-effectiveness) ≠ Institutional perspective (budget saving)

To keep in mind: **industry sponsorship**

Additional note

Generic available in ~2 years in Switzerland
(Helvepharm completed a Swissmedic application in May 2026, but patent extended until 07.2028)

La place de la fidaxomycine …
dans les recommandations



Clostridioides difficile Infection (CDI), extended version

Benoit Guery[1], Werner Albrich[2], Silvio D Brugger[3], Romain Martischang[4], Virginie Prendki[4], Giacomo Stroffolini[5], Sarah Tschudin-Sutter[3].

[1]Infectious Diseases Service, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
[2]Division of Infectious Diseases, Infection Prevention and Travel Medicine, HOCH Health Ostschweiz, St Gallen Cantonal Hospital, St Gallen, Switzerland
[3]Department of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, Zurich, Switzerland
[4]Department of internal medicine, rehabilitation and geriatrics - Hôpitaux Universitaires de Genève
[5]Division of Infectious Diseases, University Hospital Basel, Basel, Switzerland and Department of Clinical Research, University Hospital Basel, and University of Basel, Basel, Switzerland

		1st episode	1st recurrence	>2nd recurrence
Standard of care	1st line	Fidaxomicin 200mg bid 10 days	Vancomycin 125mg qid 10 days	Fecal microbiota transplantation**
	2nd line	Vancomycin 125mg qid 10 days	Fidaxomicin* 200mg bid 10 days	
Risk factors for recurrence		Fidaxomicin 200mg bid 10 days		
Preferred option not available		Vancomycin 125mg qid 10 days	Vancomycin taper pulse§	Vancomycin taper pulse§

		1st line	Multidisciplinary decision
Severe	Oral possible	Fidaxomicin or Vancomycin	Fecal microbiota transplantation
	Oral not possible	Vancomycin local delivery +/- metronidazole iv or tigecycline iv	
Severe-complicated		Vancomycin local delivery +/- metronidazole iv or tigecycline iv	Surgery Fecal microbiota transplantation

*Consider Extended fidaxomicin: 200mg bid on day 1-5, 200mg q48h on day 7-25
**Can be discussed earlier in selected patients
§Vancomycin taper pulse: 2 weeks 125mg qid, 1 week 125mg bid, 1 week 125mg qd, 1 week 125mg q48h, 1 week 125mg q72h

SSI 2026 guidance



Fidaxomicin
Coût publique
1'491.70 CHF/20cp

Limitation de la préparation

Valable dès : 01.02.2023
Limitée: Non
Code d'indication:

Concernant le traitement des diarrhées associées à Clostridium difficile (DACD) chez l'adulte :
- en cas de non-réponse au métronidazole et à la vancomycine ou
- en cas de récidives multiples (≥2) ou
- pour le traitement ultérieur des patients traités précédemment par DIFICLIR en milieu hospitalier.

Vancomycin
Coût publique
86.95 CHF/20cp

2018 IDSA clinical practice guideline
2021 ESCMID update on the treatment guidance document for *Clostridioides difficile* infection in adults
2021 American College of Gastroenterology Guidelines - Prevention, Diagnosis, and Treatment of *Clostridioides difficile* Infections
2021 IDSA clinical practice guideline
2024/2026 American Gastroenterological Association (AGA) - Fecal Microbiota–Based Therapies for Select Gastrointestinal Diseases

La place de la fidaxomycine …
dans les recommandations

Sociétés	IDSA 2021	ESCMID 2021	ACG 2021	ECIL-10 2025	SSI 2026	AGA 2026
1st episode	**F > V**	**F > V** *Consider EPFX for high risk of rCDI (> 65Y + other FdR)*	**F = V**	**F = V** *F > V for high risk of rCDI or complication : severe, HSCT, ABT*	**F > V**	**F = V**
Recurrence	**F > V** *V-TAP acceptable alternative*	**F > V**	**F = V-TAP** *If FDX already used, prefer V-TAP*	**F > V**	**F > V** *If FDX already used, prefer vancomycin, then V-TAP*	**F > V** *If FDX already used, prefer V-TAP or EPFX*

La place de la fidaxomycine …

CAVEAT

Effet souche dépendant ?

Efficacité relative à la vancomycine PO (**R027+** : 80 vs 41%, n=47 vs **R027-** 68 vs 62%, n=309) EXTEND trial. Lancet ID. 2017

Changement épidémiologique avec une diminution de la prévalence de R027, associé à des cas plus sévères. Chakra et al. Open Forum Infect Dis. 2024

AMR

108 patients traités par fidaxomycine (US, 2020-2023), culture, antibiogramme et séquençage

5.6% avec une susceptibilité diminuée à la fidaxomycine

8 cas d'echec clinique, 3 avec acquisition de résistance (et 5 avec un isolat ultérieur absent ou négatif)

(mutation RNA pol) Redmond. CID. 2025

Changement épidémiologique + AMR = besoin de surveiller l'efficacité et la susceptibilité à la fidaxomycine

Les schémas prolongés ?

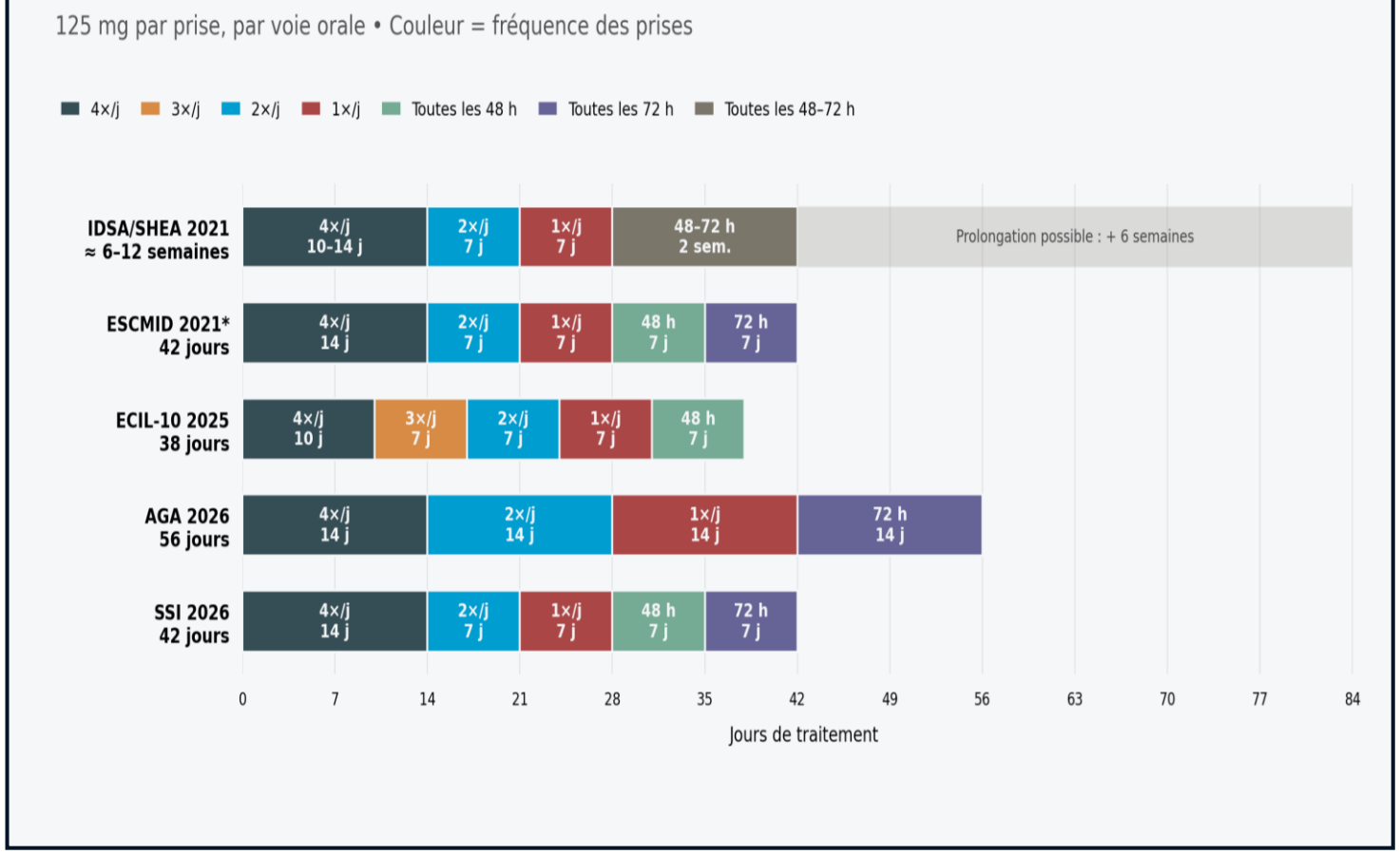
Extended-Pulsed Fidaxomycin (EPFX)

200 mg twice daily for 5 days,
200mg 1x/48 hours for 20 days

Schéma prolongé :

- V-TAP/EPFX : Pas de préférence (IDSA)
- V-TAP : Si fidaxomycine non disponible (ESCMID)
- V-TAP/EPFX : Si antibiothérapie concomitante (ECIL-10)
- Alternative raisonnable si récurrence multiple et FMT refusée par le patient (AGA)

Vancomycin Taper and pulse (V-TAP)



Les schémas prolongés ?
(Extended Pulsed Fidaxomycin)

Indirect Comparison

EXTEND trial – Guery et al.

Recurrence at Day 48

362 patients, > 60 years
(80% 1st episode)

	EPFX	VAN
Recurrence	2%	17%

Cornely et al.

Recurrence at Day 28

666 patients (1st episode)
128 patients (1st recurrence)

	FDX	VAN	RD (FDX – VAN)
1st episode	11.7%	22.6%	–10.9
1st recurrence	19.7%	35.5%	–15.8

Direct Comparison

Rubio-Martin et al. CMI. 2026

Recurrence at 12 weeks

Retrospective study,
19 Spanish centres (2021–2023)

999 patients
(1st episode: 9.5%; recurrence: 16.1%)
FDX: 73.3% | EPFX: 26.7%

	FDX	EPFX	OR (95% CI)
Crude recurrence rate	12.7%	12.8%	1.01 (0.67–1.54)
PS-matched & IPTW analysis			0.90 (0.59–1.39)

✓ **Similar results in subgroup analyses**
(age, number of recurrence, concomitant antibiotics, immunosuppression)

Les schémas prolongés ?
(Taper and Pulse Vancomycin)

Observational data

20 patients with no or failed (n=15) FMT, 80 ans, ~4 CDI, 2013-2017
FU with 125mg qd /8W;
Zhang et al. BMC Infect Dis. 2019

1 récidive par 220 patient-mois

13 interruption de traitement, **31% (n=4) récidive <6 semaines**

RCT : 4W TPVA versus 2W VA

Double-blind clinical trial, 12 Canadian hospitals (2020-2024)
Microbiologically proven CDI with 1st episode OR reccurence with improvement at D10 (n=256, 135 TPVA, 130 VA, stopped early due to recruitment)

Probabilité postérieure d'une supériorité de la TPVA pour prévenir la rCDI à 8 semaines

14.8% TPVA et 17.7% VA, aRR 0.84 [0.48-1.45]

BONNE option pour prévenir une rCDI précoce (J38), mais les bénéfices s'effacent avec le temps

+- bridge pour une FMT



Mais evidence contrastée

Cohorte rétrospective avec appariement sur le score de propension, incluant plus de 61 000 patients hospitalisés, résidents d'établissements de soins de longue durée et patients ambulatoires, traités par vancomycine ou métronidazole pour une infection à C. difficile entre 2006 et 2016.
Aucune différence significative concernant le dépistage, les cultures cliniques et les bactériémies.
Stevens. CID. 2019

La Transplantation fécale

Summary of findings 1. Summary of findings table - Fecal microbiota transplantation (FMT) compared to control in adults with recurrent Clostridioides difficile infection (rCDI)

Fecal microbiota transplantation (FMT) compared to control in adults with recurrent Clostridioides difficile infection (rCDI)

Patient or population: adults with recurrent Clostridioides difficile infection (rCDI)
Setting: inpatient and outpatient
Intervention: fecal microbiota transplantation (FMT)
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 fecal microbiota transplantation (FMT)				
Resolution of rCDI follow-up: range 8 weeks to 17 weeks	401 per 1000	**770 per 1000** (545 to 1000)	**RR 1.92** (1.36 to 2.71)	320 (6 RCTs)	⊕⊕⊕⊖ Moderate[a,b,c]	**NNT = 3**
All-cause mortality follow-up: range 8 weeks to 17 weeks	96 per 1000	**55 per 1000** (21 to 140)	**RR 0.57** (0.22 to 1.45)	320 (6 RCTs)	⊕⊕⊖⊖ Low[e]	FMT may result in a reduction in all-cause mortality; however, the CIs around the summary estimate were wide and possible risk of increased mortality could not be ruled out.
Serious adverse events follow-up: range 8 weeks to 17 weeks	225 per 1000	**164 per 1000** (85 to 317)	**RR 0.73** (0.38 to 1.41)	320 (6 RCTs)	⊕⊕⊕⊖ Moderate[d]	FMT probably results in a slight reduction in serious adverse events; however, the CIs around the summary estimate were wide and included a possibility of increased risk of serious adverse events.
Colectomy	0 per 1000	**0 per 1000** (0 to 0)	Not estimable	(0 studies)	-	None of the included studies reported this outcome.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

Only RCT, no IS
Minkoff NZ, Cochrane Database of Systematic Reviews 2023;4

La Transplantation fécale

Guideline	PROs	CONs
1st recurrence	Emerging evidence in selected high-risk patients (SSI, AGA) e.g. after severe, fulminant, or refractory CDI and comorbidities	Not recommended (ESCMID, ACG, ECIL-10)
From 2nd recurrence	Recommended (IDSA, ESCMID, ACG, AGA, SSI)	-
Severe/fulminant, Rescue FMT	Rescue therapy may be considered (ESCMID, ACG, AGA, SSI)	-
IS	Non neutropenic : may be considered (ECIL-10) Mildly moderated (AGA)	Severely IS (AGA) Profound neutropenia & LBPs (ECIL-10) CAVEAT GvHD (ECIL-10)

Take home message

- Un coût humain et économique important, principalement lié aux récidives.
- **Études d'efficacité clinique** : la fidaxomycine réduit le risque de récidive.
- **Études coût-efficacité** : favorables à la fidaxomycine, tant pour un premier épisode que pour les récidives.
- **Incertitudes…** sur le coût/bénéfice de la fidaxomycine pour prévenir les récurrences
  - Nouvelles données contradictoires (mais peu de puissance)
  - Arrivée potentielle de génériques
  - Nécessité d'une surveillance continue de l'efficacité & susceptibilité à la fidaxomycine
- **En Suisse** : la fidaxomicine en première intention n'est pas remboursée en ambulatoire avant la deuxième récidive (excepté sur demande de remboursement).

Take home message

- **Fidaxomicine** :
  - **1er épisode :**
    - Hospitalisé surtout si FdR (> 60 ans, antibiothérapie, antécédent d'infection à *C. difficile)*
    - Ambulatoire
      - Réfractaire à la vancomycine
      - Poursuite des patients déjà traités par fidaxomycine en intra-hospitalier
      - Patient à très haut risque (sur demande médicale de prise en charge à l'assurance)
  - **1ère récurrence**
    - Hospitalisé (sauf si déjà traité par fidaxomycine → relais par vancomycine)
    - Ambulatoire (= 1er épisode)
  - **2ème récurrence**
    - Fidaxomycine autorisée, mais …
    - Hospitalisé ➔ vancomycine bridge + FMT
    - Ambulatoire ➔ vancomycine bridge + FMT
  - **Si antibiothérapie concomitante** (Schéma prolongé de vancomycine ou fidaxomycine)

Une histoire sans fin



Mme E, 88 ans

Cardiopathie ischémique et valvulaire, pontage aorto-bi-iliaque, AVC, splénectomie, ischémie colique avec colostomie terminale, ésoméprazole

22.07.2026

Infection sévère à *C. difficile* (PCR+EIA+)

- PN à *E. cloacae* BLSE (IMI 5j, 16–22.07.26)
- VAN PO 14 j + MTZ IV 10 j
- Résolution clinique

→

27.08.2026

1re récidive (PCR+EIA+)

- VAN PO 14 j

→

21.09.2026

2re récidive (PCR+EIA+)

Traitement ?

Question

Quelle prise en charge pour la 2re récidive de C. difficile chez cette patiente âgée avec comorbidités ?

Une histoire sans fin



Attitude

- Vancomycine (schéma prolongé sur 45 jours)
- Prolongation du traitement par vancomycine 2x/j
- Transplantation fécale prévue au CHUV

Hôpitaux Universitaires Genève

Thank you !

Especially to pr. Virginie Prendki & pr. Benoît Guery for their attentive reading



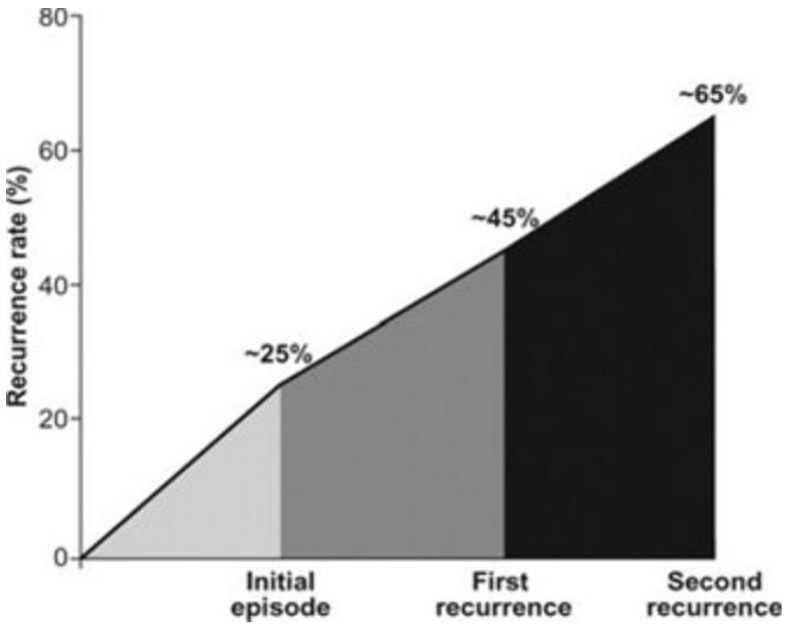
R. Martischang

An expensive burden of disease…

Prevalence of HAI 7.3%
(European ACH 2016–17; ECDC PPS 2022–2023)

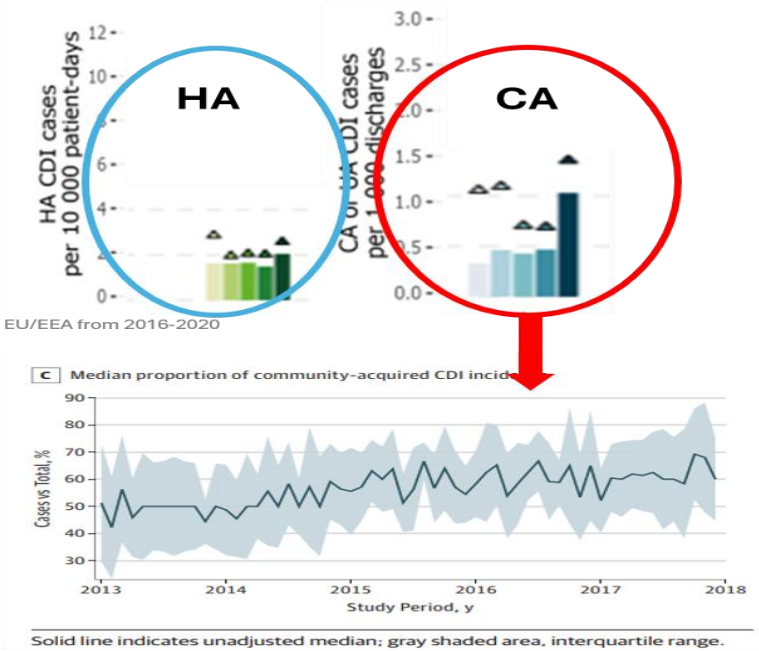
Mortality 3.8% | **rCDI mortality 10.5%**
Okafor. Emerg Infect Dis. 2023

Risque de récurrence



Kelly et al. Clin Microbiol Infect. 2012

Evolution épidémiologique



Solid line indicates unadjusted median; gray shaded area, interquartile range.
Cohort of 2mio patients in 43 U.S. hospitals

Évolution moléculaire

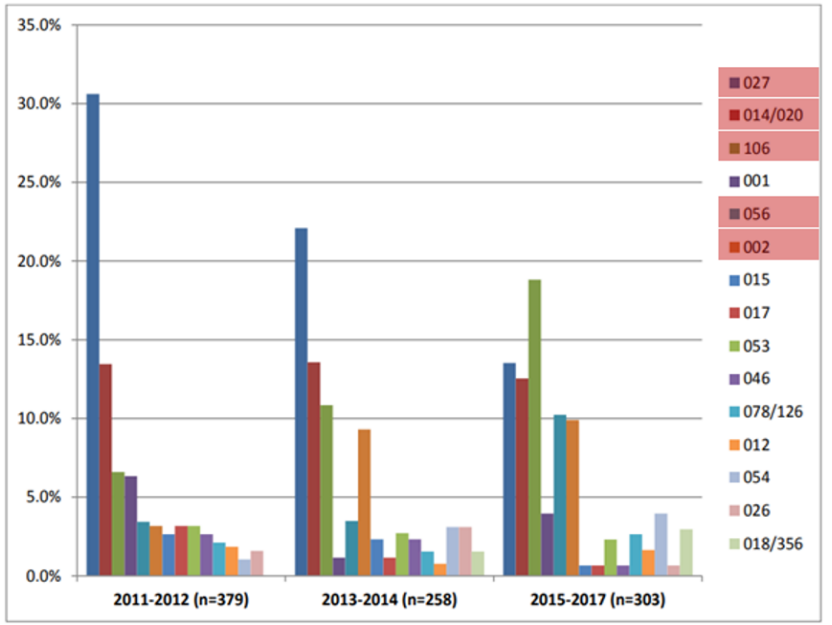


Fig. 1. Change in proportion of the most frequent PCR ribotypes over the three time periods.

940 C.difficile isolates from 26 U.S. hospitals

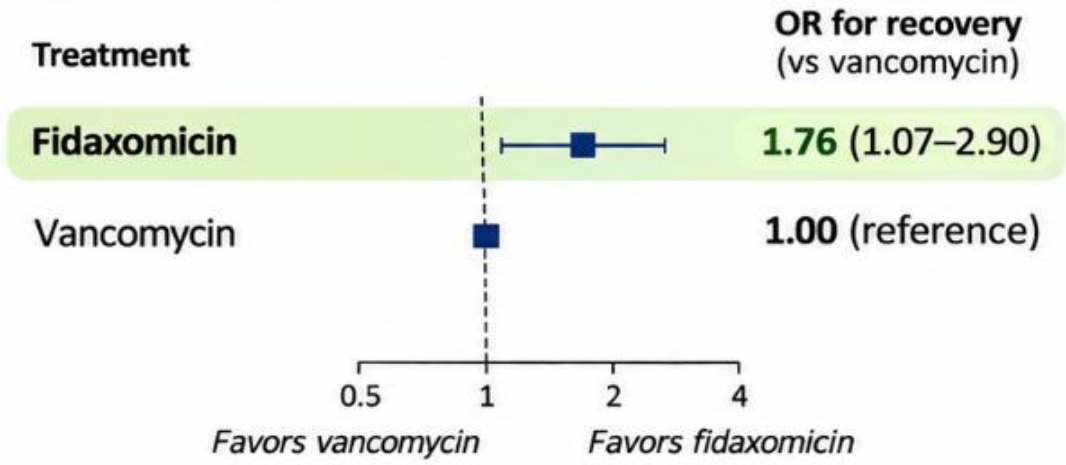
La place de la fidaxomycine …
dans l'évidence

Random-effects network meta-analysis
Bednarik et al. Lancet Reg Health. 2025

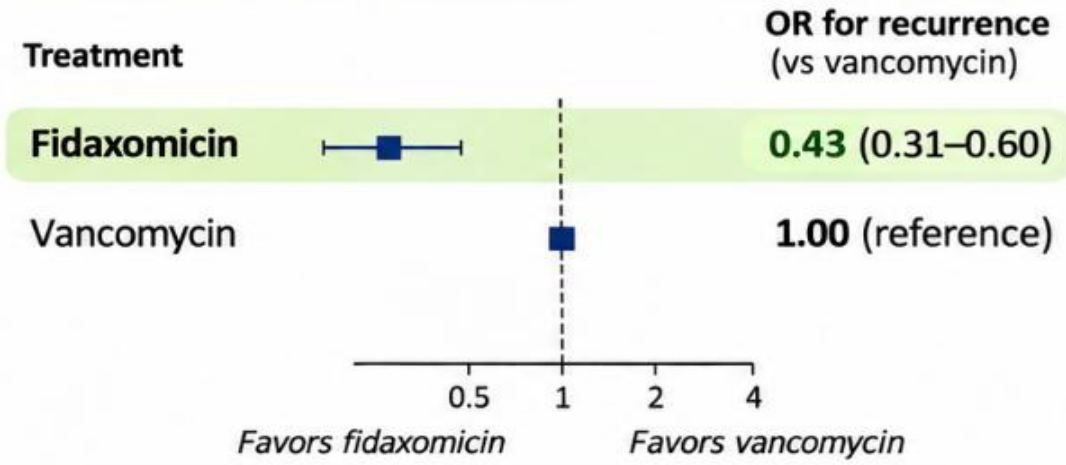
73 RCTs
(28 interventions)

27,959 patients

Outcome 1: Cure rate



Outcome 2: Recurrence



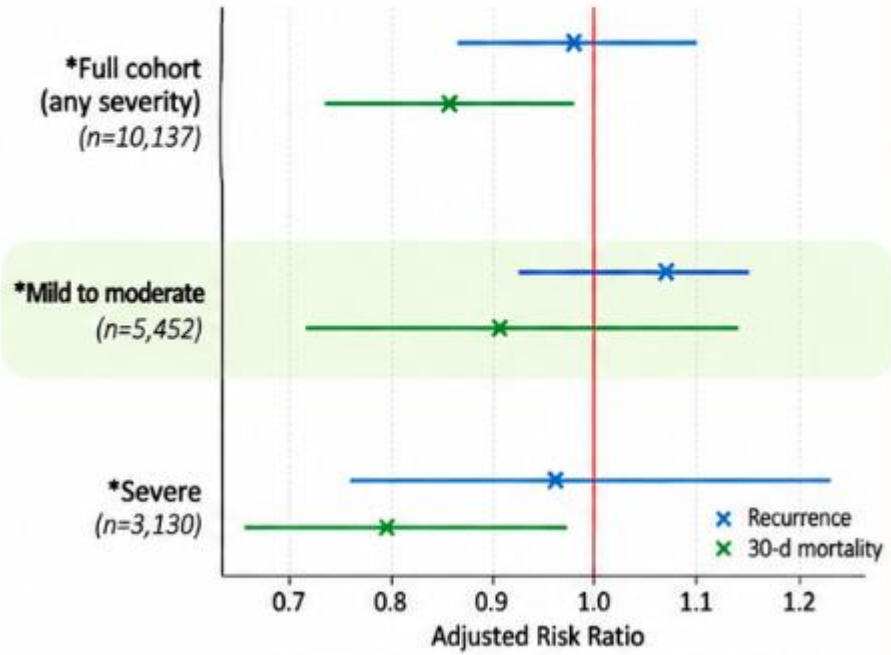
The fall of metronidazole

Resistance ~ METRO
(metabolic pathways)

Suboptimal PK ~ METRO
- Absorbed in the small intestine
- Drug inactivation in the colon
- Low concentration in stools

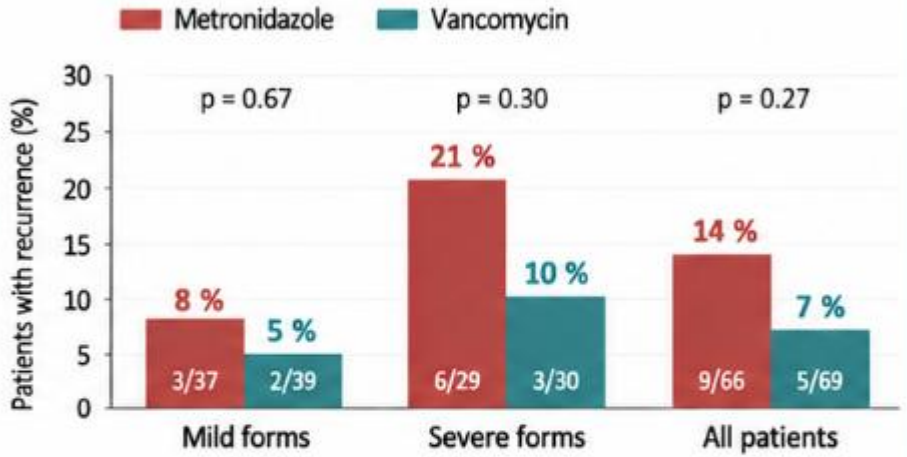
Clinical outcomes (vs vancomycin)

Adjusted RR (95% CI) – Recurrence and 30-day Mortality
Stevens et al., JAMA Intern Med 2017 (Table 2)



***Retrospective of 47'471 PS-matched patients treated for CDI in the VA healthcare system from 2005-2012 (2'068 treated by Vancomycin)*

Recurrence after initial cure
Metronidazole versus vancomycin



RCT 1994–2002
150 patients with *C. difficile* diarrhea, no prior antibiotic
TcdA EIA+
Metronidazole 250 mg q.i.d. vs vancomycin 125 mg q.i.d. / 10d
Test of Cure 21d; EIA TcdA +
Zar et al. CID. 2007;45(3):302–37