C. difficile en réanimation

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Infection • Antimicrobiens • Modélisation • Evolution

AER Lyon 23 nov 2017

Liens d’interets

- Board: Merck, Paratek, Bayer, Gillead, 3M, Maat Pharma
- Symposium: Merck, Biomerieux, Pfizer, astellas, Gillead
- Research grants: Merck, Pfizer, 3M, Astellas.

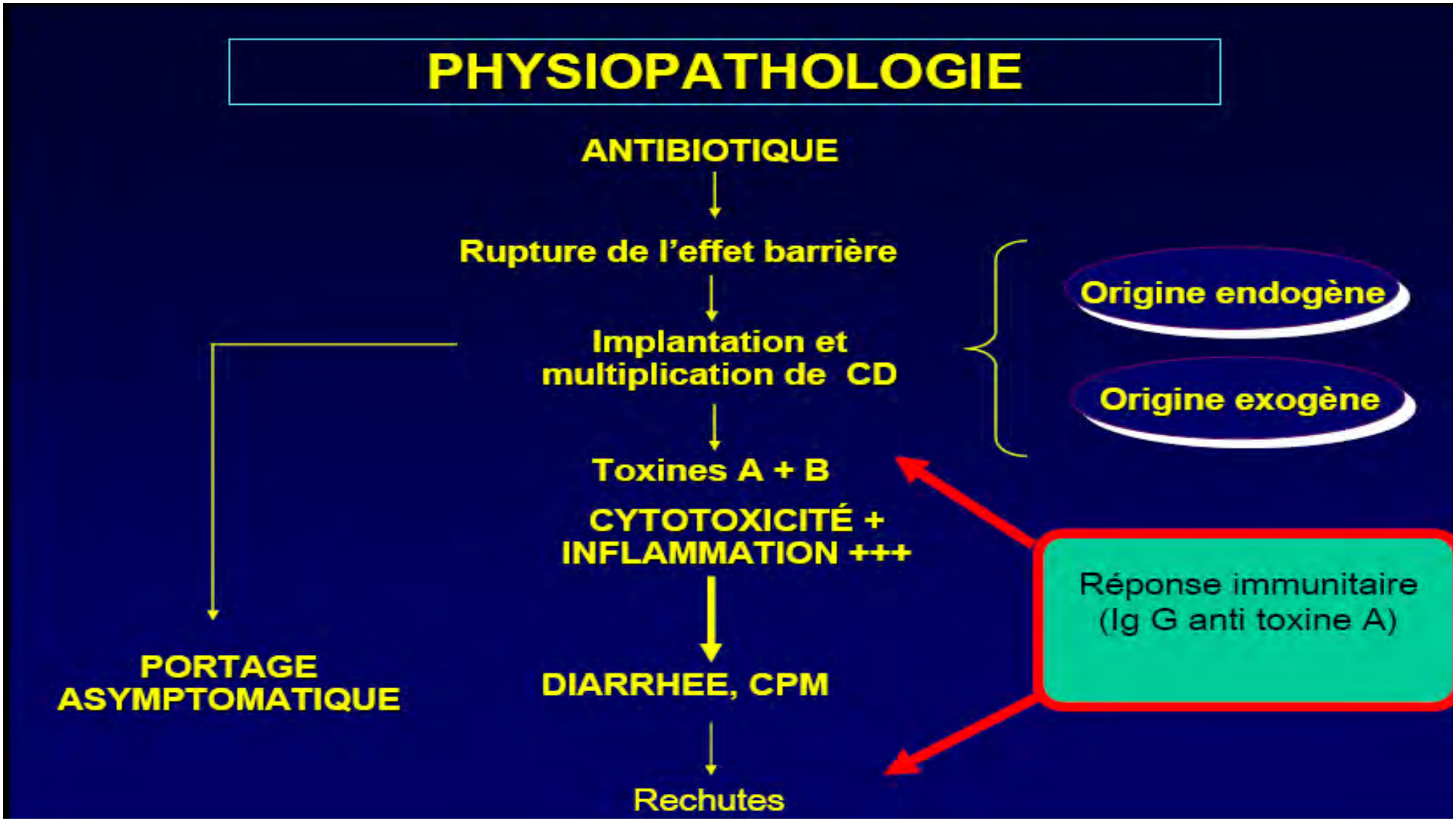
Pré-requis

- **Responsable de 30% des cas de diarrhée post antibiotiques**
- **Responsable de 50 à 80% des cas de colite associée aux antibiotiques**
- **Responsable de 95% des cas de CPM**
- **Cause la plus importante de diarrhée nosocomiale d'origine bactérienne**
- **Manifestations cliniques très variées: portage asymptomatique, diarrhée modérée à CPM gravissime**
- **Rechutes fréquentes**

FACTEURS DE RISQUE D'ICD

Patient	- **Age > 65 ans** - **Co-morbidités** (cancer, insuf. rénale, diabète..) - Immunodépression (hématologie, greffés..) - ATCD d'ICD - Faible taux d'Ac anti toxines
Déséquilibre de flore	- **ATB < 3 mois** - Chimiothérapie - IPP - Lavements, laxatifs…
Exposition à C. difficile	- **Hospitalisations répétées, longs séjours** - Voisin de chambre contaminé - Chambre précédemment occupée par un patient ICD+ -Pression de colonisation

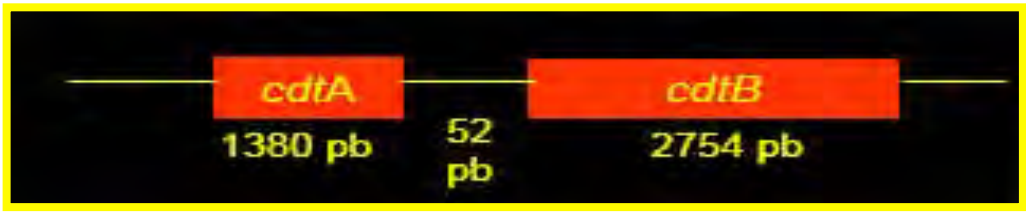
McFarland et al, NEJM1999; Loo V., NEJM 2012


PHYSIOPATHOLOGIE
ANTIBIOTIQUE
Rupture de l'effet barrière
Implantation et multiplication de CD
Origine endogène
Origine exogène
Toxines A + B
CYTOTOXICITÉ + INFLAMMATION +++
Réponse immunitaire (Ig G anti toxine A)
PORTAGE ASYMPTOMATIQUE
DIARRHEE, CPM
Rechutes

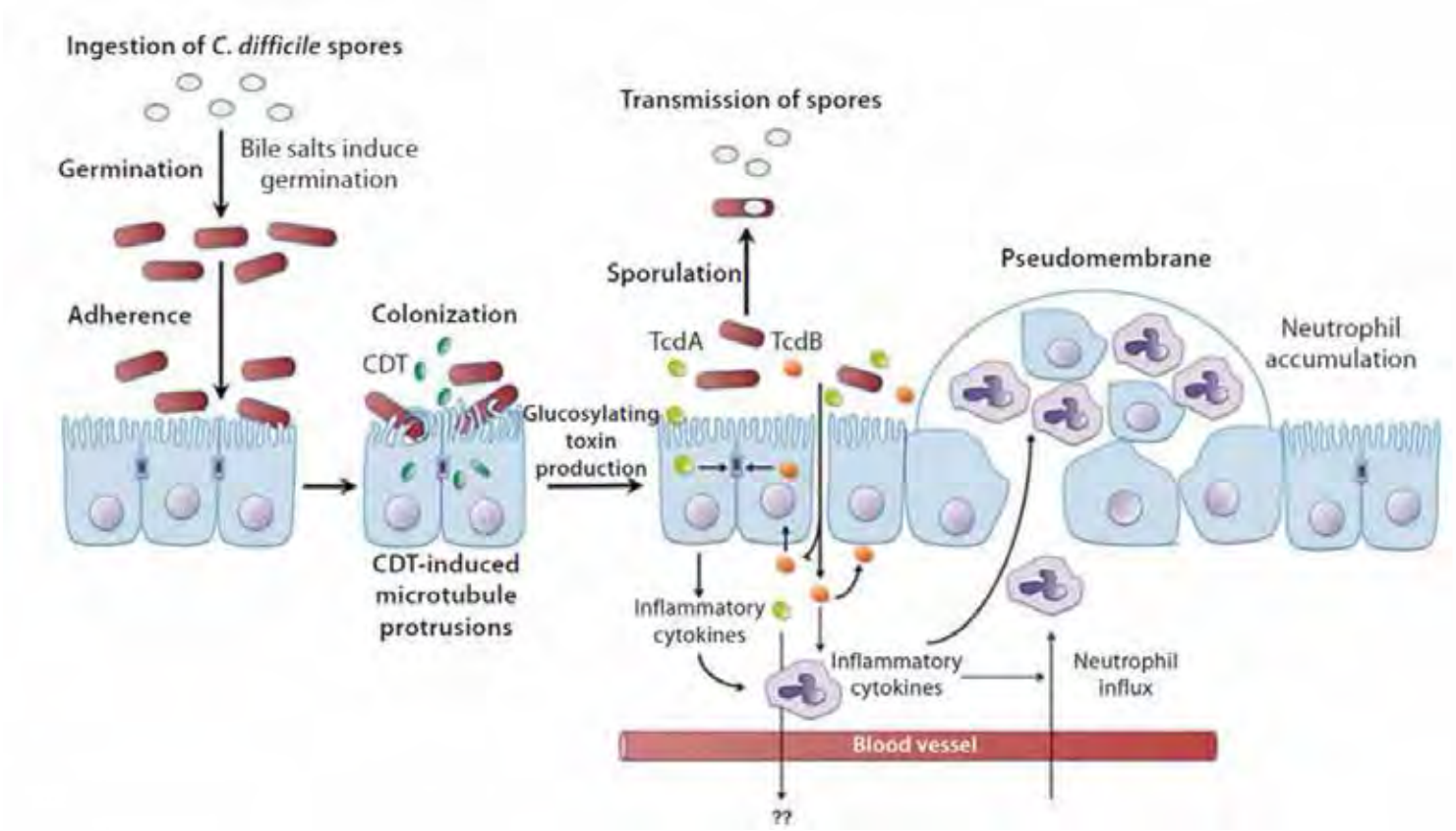
Virulence

- Large clostridial toxines (LCT +++)
  - Toxine A enterotoxine (tcdA)
  - Toxine B cytotoxine (tcdB)

  - Toxine binaire (ADP ribosyl transferase)
    - CDTa sous-unité enzymatique
    - CDTb sous-unité ligand



Physiopathologie

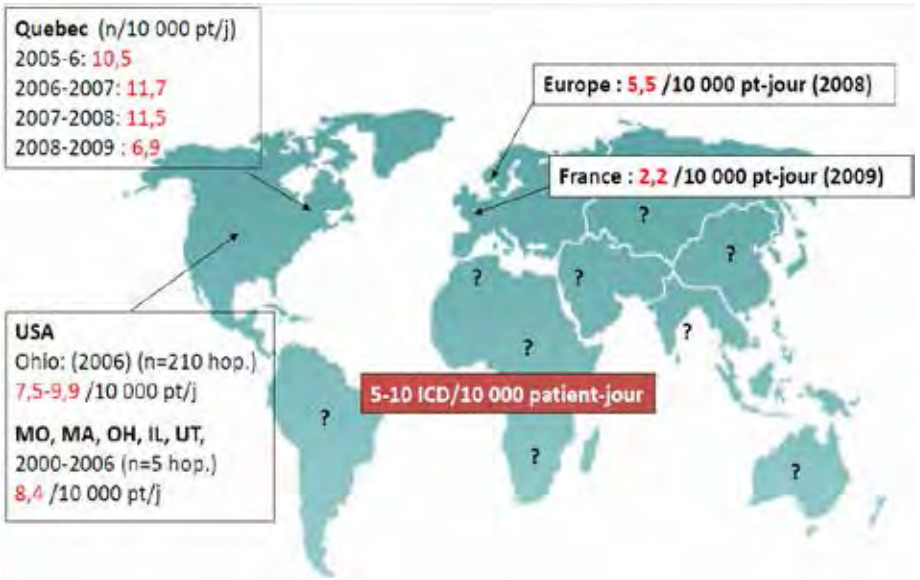


Shen A – J Innate Immun 2012

Epidémiologie et impact médico-économique

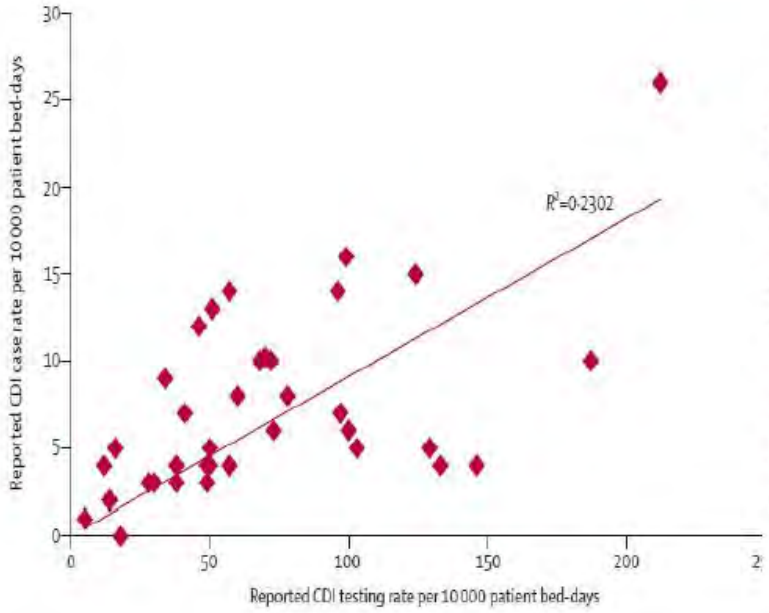
Un problème majeur de santé publique

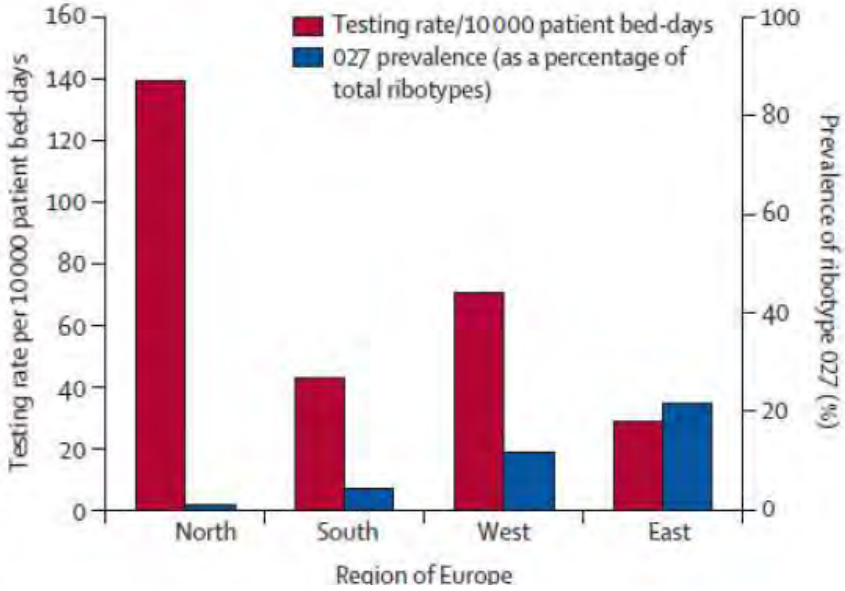
- **Augmentation de l'incidence des ICD**
  - amplifiée par les épidémies (notamment souche 027), la qualité du diagnostic, l'exhaustivité du codage…
- **Augmentation de la sévérité des ICD**
  - de 3 à 30% de mortalité à J30 en Europe
- **Diffusion vers la communauté et vers les structures de long-séjour**
  - ce qui impose de reconsidérer le concept de pathogène nosocomial
- **Impact médico-économique majeur**
  - Augmentation des durées de séjour, impact des récidives
  - Surcoût/épisode : Allemagne (4000 à 9000 €), UK (4000 à 7000£), France (5000 à 11000 €)
  - Projections globales à la hausse (plusieurs milliards d'€ par an en Europe et aux USA)



[Barbut, ICHE 2009 / Eckert, MMI 2013 / Dubberke, ICHE 2010 / Bauer, Lancet 2010 / Vonberg, JHI 2008 / Wilcox, JHI 1996 / Wiegand, JHI 2012 / Kyne, CID 2002 / Dubberke, EID 2008 / O'Brien, ICHE 2007 / Kuijper, CMI 2006 / Honda, Curr Opin Gastroenterol 2014]

Relation inverse entre la densité de prescription de tests et 027





L'incidence augmente, la proportion de O27 diminue,
en partie artificiellement du fait du nb de tests réalisés

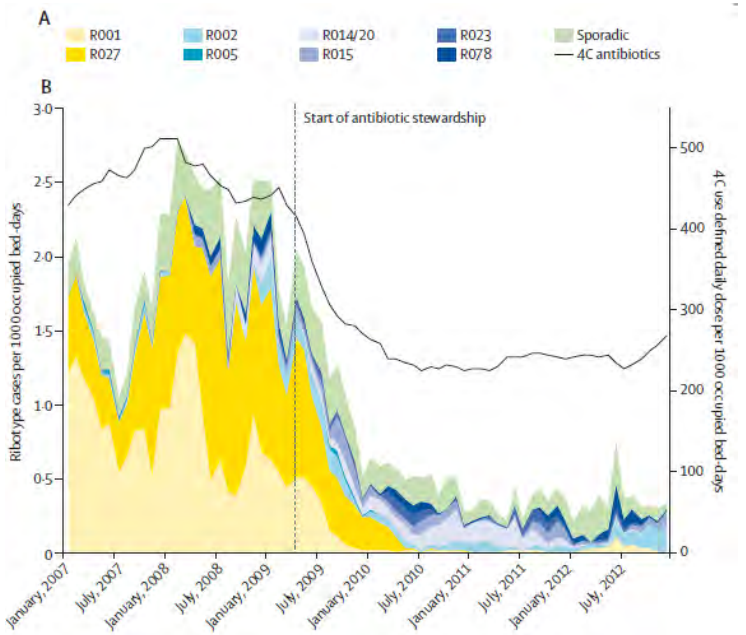
Davies et al - Lancet Inf. Dis 2014, 14, 1208-19

LID 2017

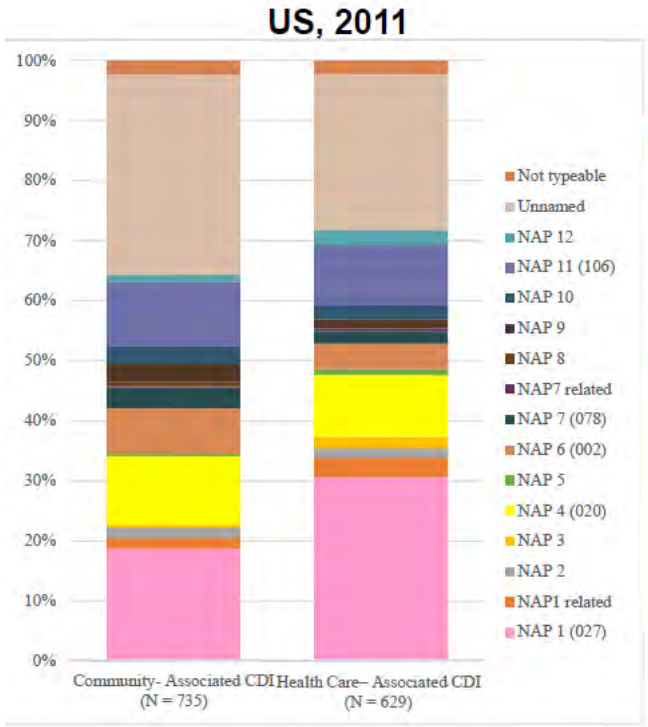
Effect of a national 4C antibiotic stewardship intervention on the clinical and molecular epidemiology of *Clostridium difficile* infections in a region of Scotland: a non-linear time-series analysis

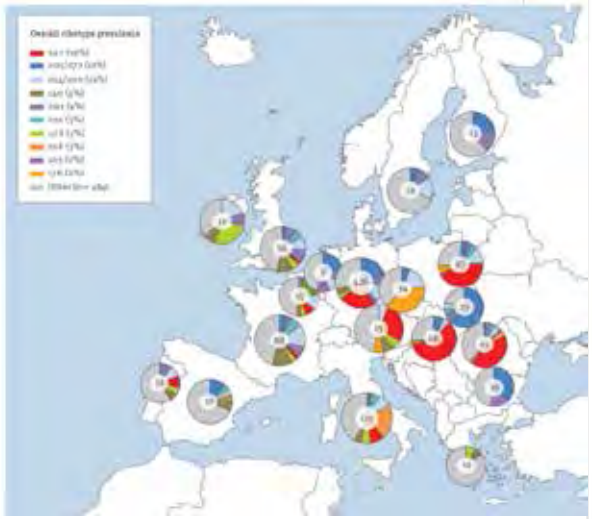
Timothy Lawes, José-María Lopez-Lozano, Cesar A Nebot, Gillian Macartney, Rashmi Subbarao-Sharma, Karen D Wares, Carolyn Sinclair, Ian M Gould

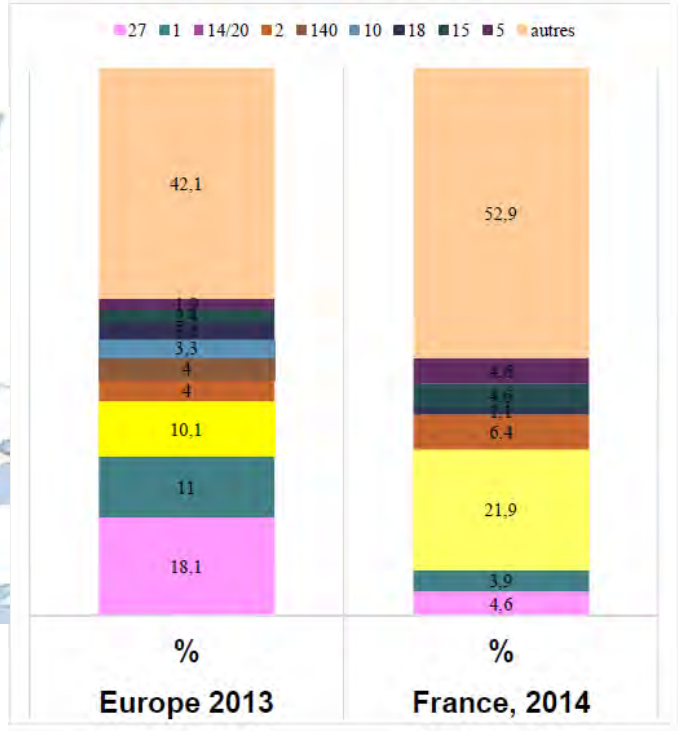
Ecosse, 1997-2012
Programme national de réduction (-50%) de la ciprofloxacine, de la clindamycine, des céphalosporines et de l'amoxicilline-acide clavulanique (2009)
→ Réduction relative de 68 % de l'incidence des ICD hospitalières et de 45% des ICD communautaires



O27 est plus rare en France

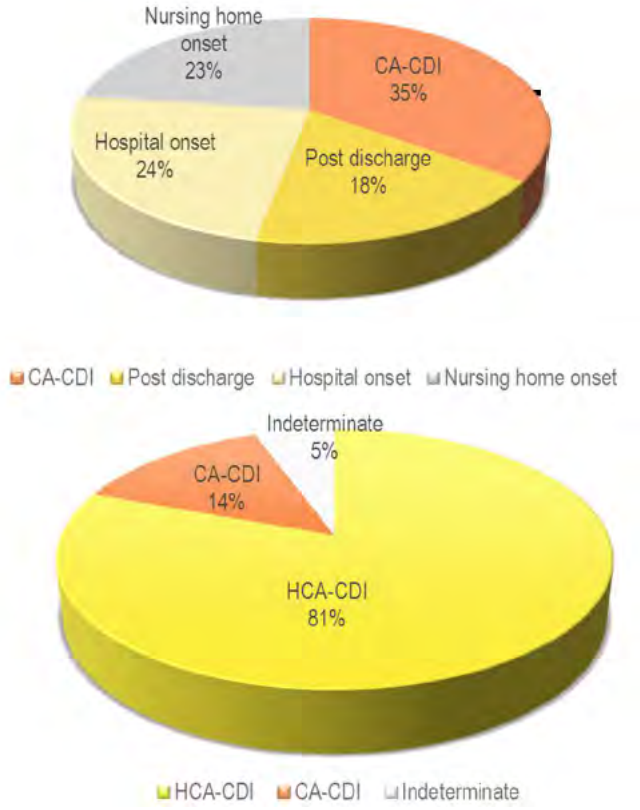






1- Lessa NEJM 2015; 2- Davies LID 2014 and 3-Davies Eurosurv 2016

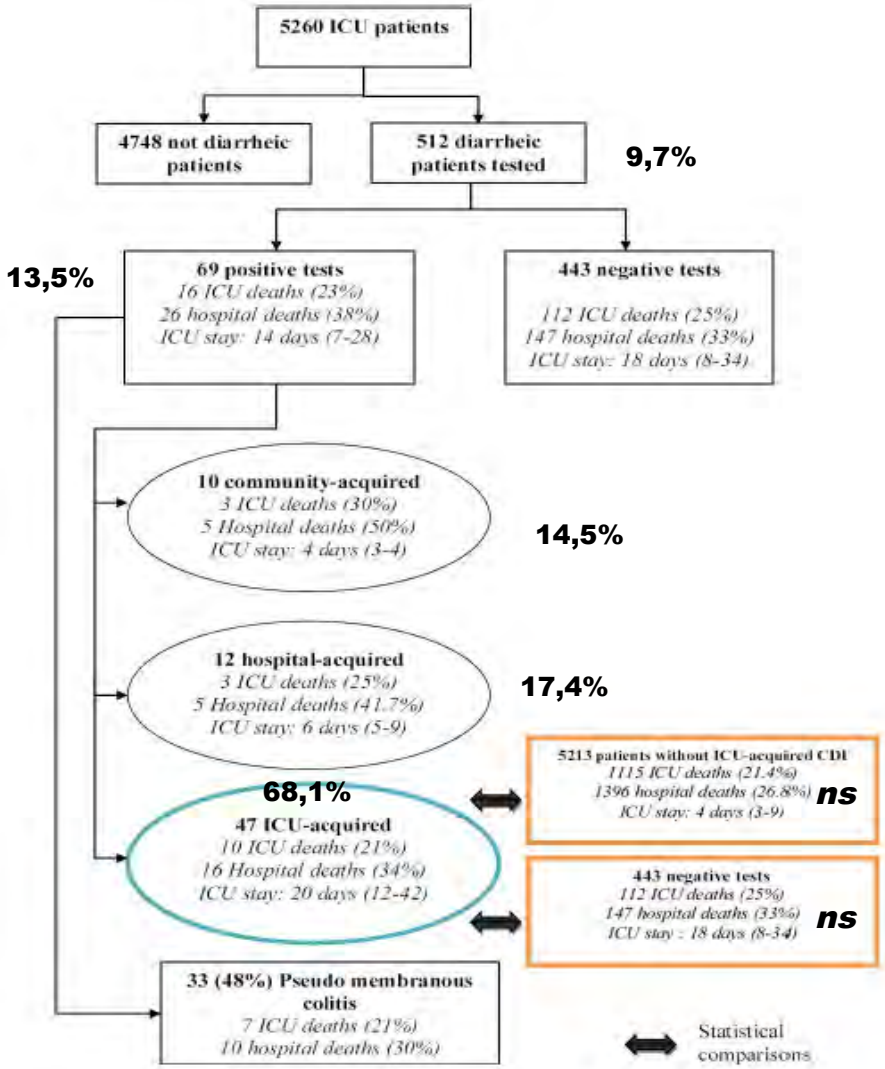
Origine des ICD



USA – Lessa et al NEJM 2015

82% des CA ICD ont un contact avec le système de santé ds les 12 semaines

Europe: Bauer et al – Lancet 2011



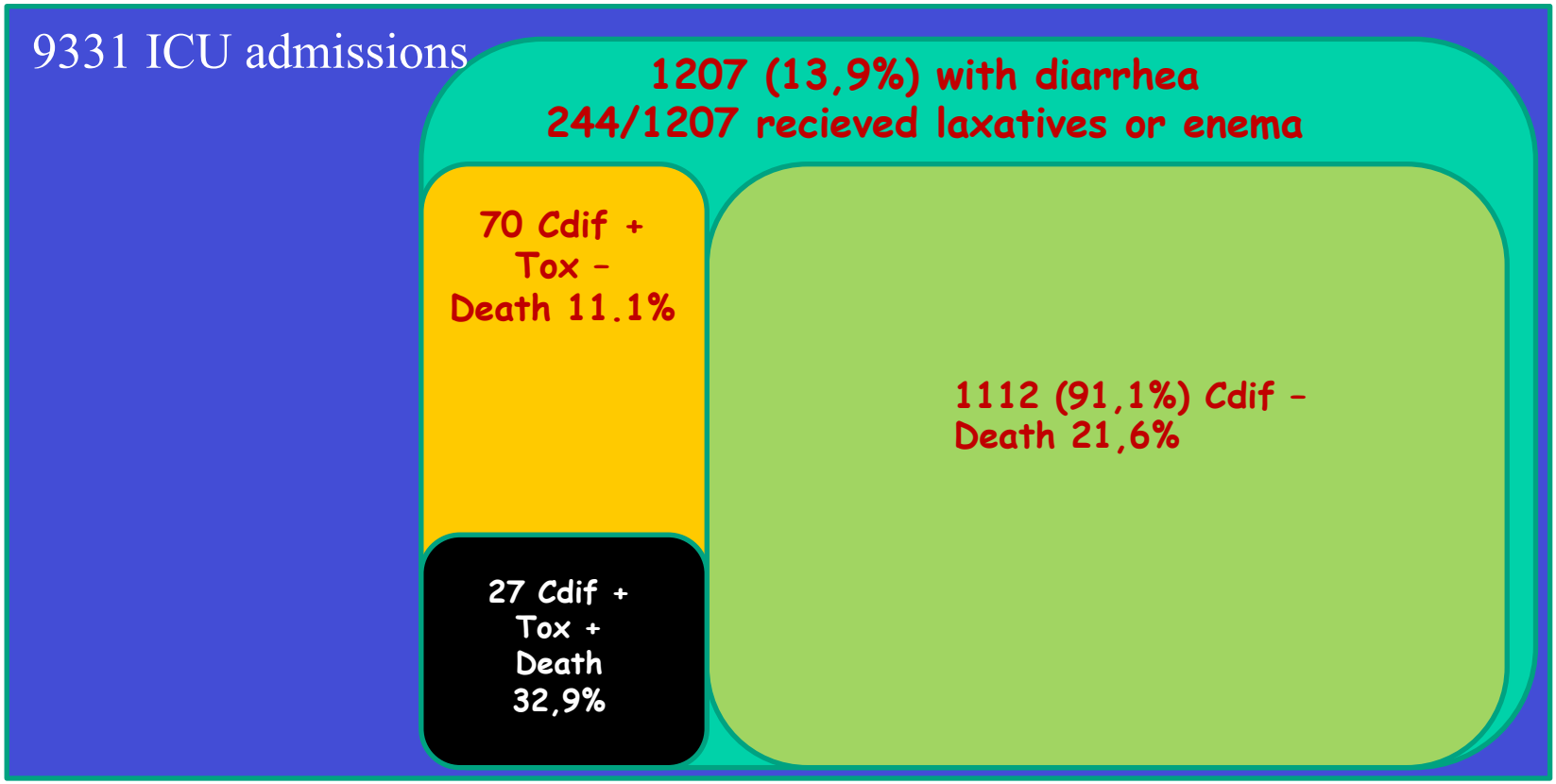
CRITICAL CARE
Zahar et al. Critical Care 2012, 16:R215

En réanimation

OUTCOME RÉA

Diarrhea is common in ICU associated with poor outcome and rarely associated with *C difficile*

Tirlapur N et al - Sci Rep. 2016 Apr 20;6:24691



Predictors of poor outcome

Table 3. Multivariate Analysis for Severe *Clostridium difficile* Disease Among Cases With Strain Typing Results, 2009–2011

Risk Factors[a]	AOR (95% CI)	*P* Value
Cases with strain typing results (n = 2057)		
Age>65 y	1.69 (1.31–2.18)	<.0001
Healthcare-associated epidemiologic classification[b]	1.75 (1.32–2.34)	.0001
Emergency department visit during 12 wk prior to infection	1.31 (1.01–1.69)	.04
Charlson index	1.08 (.98–1.20)	.14
Medications during 14 d prior to infection		
Immunosuppressive treatment	1.42 (1.05–1.92)	.02
Any antibiotic	1.38 (1.08–1.76)	.01
NAP1 strain	1.74 (1.36–2.22)	<.0001

Table 5. Multivariate Analysis for 14-Day Mortality After *Clostridium difficile* Infection Among Cases With Strain Typing Results, 2009–2011

Risk Factors[a]	AOR (95% CI)	*P* Value
Cases with strain typing results (n = 2057)		
Age >65 y	2.98 (1.45–6.11)	.003
White race	0.46 (.23–.95)	.04
Epidemiologic classification		
Healthcare facility–onset	3.80 (1.62–8.94)	.002
Community-onset healthcare facility–associated	2.33 (1.01–5.36)	.05
Community-associated (reference)		
Charlson score	2.03 (1.44–2.86)	<.0001
NAP1 strain	2.12 (1.22–3.68)	.008

See et al - Clinical Infectious Diseases 2014;58(10):1394–400

Diagnostic bactériologique

1 – selles liquides (éviter écouvillon rectal)

2 – mise en évidence des toxines dans la selle

3 – mise en évidence de la bactérie

Méthodes diagnostiques

	Se	Sp
Référence:		
Culture toxigenique (1€)	+++	
Test de cytotoxicité		+++
Routine:		
GDH (glutamate deshydrogenase) (13€)	+++	
Test immuno-enzymatique – EIA (toxines) (10€)		+++
PCR (30-40€)	+++	

- → dépistage rapide (GDH) + test confirmatoire

10186 patients/ tests de référence

	Group 1 (CTA positive)	Group 2 (CC positive, CTA negative)	Group 3 (all negative)	Group 1 vs group 2 p values	Group 1 vs group 3 p values	Group 2 vs group 3 p values
n	435	207	5880	..	..	..
Female (%)	243/435 (56%)	118/207 (57%)	3154/5876* (54%)	..	..	..
Mean age, (years; SD)	69 (20)	66 (21)	64 (21)	..	..	..
Mean white cell count (x10³/L; SD)	12·4 (8·9)	10·1 (5·8)	9·9 (10·7)	0·0004	<0·0001	0·6970
Mean rise in creatinine (%; SD)	37% (63)	52% (147)	33% (85)	0·1238	0·2270	0·0028
>100% rise in creatinine (%)	40/316 (13%)	21/169 (12%)	447/4729 (9%)	..	..	..
Mean albumin (g/L; SD)	31 (7)	32 (8)	34 (8)	0·5226	<0·0001	0·0017
Albumin <20 g/L (%)	13/344 (4%)	11/166 (7%)	241/4855 (5%)	..	..	..
Died (%)	72/435 (16·6%)	20/207 (9·7%)	503/5880 (8·6%)	0·022	<0·0001	0·530
Mean length of stay before sample (days; SD)	18·0 (29)	14·1 (24)	10·7 (21)	0·1584	<0·0001	0·0157
Mean length of stay after sample (days; SD)	19·4 (25)	18·6 (27)	14·2 (22)	0·9498	<0·0001	0·0022
Death rate per 1000 inpatient days	9·03	5·33	6·26	0·0195	0·0033	0·4224

CTA=cytotoxin assay. CC=cytotoxigenic culture. *Sex was not recorded for four patients in this group.

Table 2: **Clinical characteristics of first episodes of inpatients with available clinical outcome results**

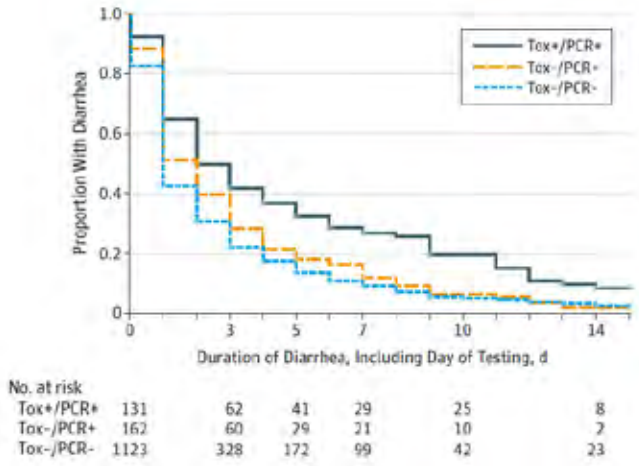
NB: CC tres sensible; CTA très spécifique

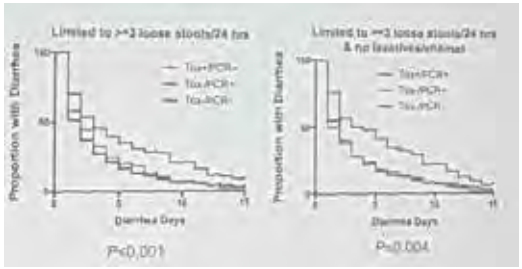
Planche et al – LID 2013

Overdiagnosis with PCR tests?

1416 pat (522 ICU)

Outcome	*C difficile* Positive		*C difficile* Negative	
	Tox+/PCR+ (n = 131)	Tox−/PCR+ (n = 162)	Tox−/PCR− (n = 1123)	*P* Value[a]
***C difficile*-Related Complication or Death Within 30 d, No. (%)**				
Complication[b]	10 (7.6)	0	3 (0.3)	<.001
Death[c]	11 (8.4)	1 (0.6)	0	<.001
Complication or death	18 (13.7)	1 (0.6)	3 (0.3)	<.001
Repeat *C difficile* Testing Within 14 d, No. (%)				
Retested	14 (10.7)	61 (37.7)	374 (33.3)	<.001
Positive toxin test result	3 (2.3)	13 (8.0)	17 (1.5)	<.001
Repeat *C difficile* Testing at 15-30 d, No. (%)				
Tested	26 (19.8)	18 (11.1)	106 (9.4)	.001
Positive toxin test result	14 (10.7)	5 (3.1)	10 (0.9)	<.001
Treatment Within 14 d				
Metronidazole or oral vancomycin, No. (%)[d]	131 (100)	66 (40.7)	361 (32.1)	<.001





Polage et al – Jama intern med 2015; 175(11):1792-801

Overdiagnosis with PCR tests?

1416 pat (522 ICU)

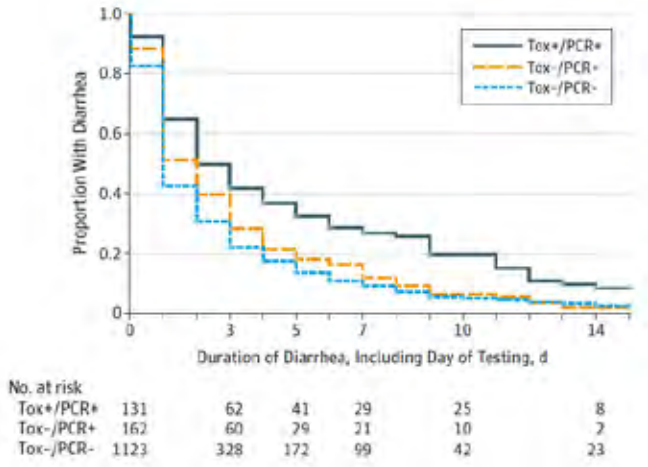
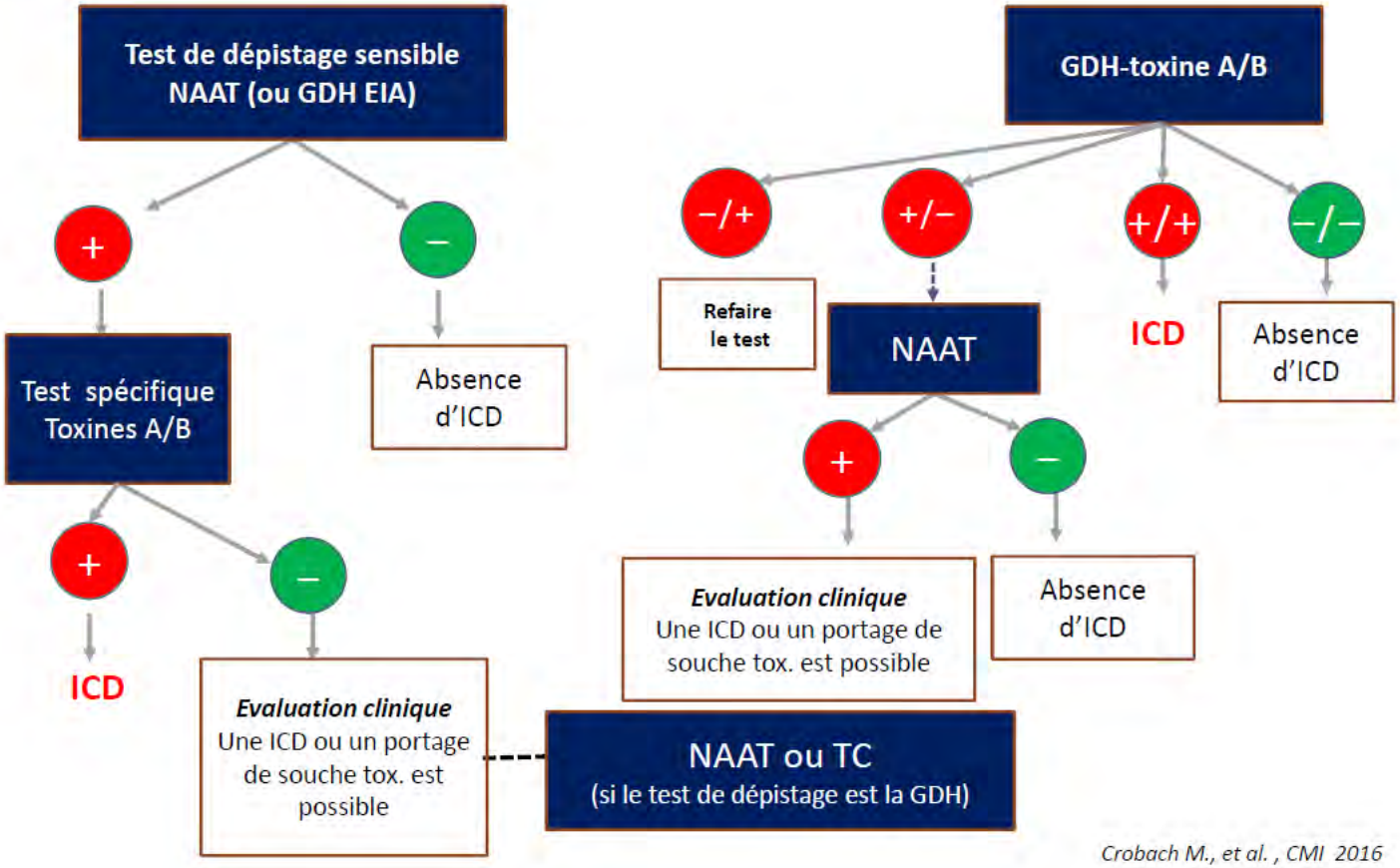


Table 1. Baseline Characteristics of the Study Population by *Clostridium difficile* Test Group

Characteristic	*C difficile* Positive		*C difficile* Negative	
	Tox+/PCR+[b] (n = 131)	Tox−/PCR+[b,c] (n = 162)	Tox−/PCR−[b,d] (n = 1123)	*P* Value[a]
Age, median (IQR), y	64 (52-71)	58 (48-68)	59 (47-71)	.12
Female sex, No. (%)	64 (48.9)	83 (51.2)	530 (47.2)	.61
Comorbidities, median (IQR)	4 (2-6)	4 (2-5)	3 (2-5)	.01
WBC count ≥15 000 cells/μL on day 1 ±1 d, No./total No. tested (%)[e]	54/129 (41.9)	50/154 (32.5)	323/1101 (29.3)	.01
Creatinine level >1.5 mg/dL on day 1 ±1 d, No./total No. tested (%)[e]	36/127 (28.3)	45/156 (28.8)	297/1102 (27.0)	.85
Albumin level <2.5 g/dL on day 1 ±1 d, No./total No. tested (%)[e]	29/48 (60.4)	50/70 (71.4)	318/475 (66.9)	.46
Diarrhea present on day 1 ±1 d, No. (%)[e]	121 (92.4)	143 (88.3)	927 (82.5)	.004
Stool count on day 1, median (IQR)[e]	5 (3-6)	3 (2-5)	3 (2-5)	<.001
C difficile toxin B, median (IQR), ng/mL	640.8 (172.5-1194.0)	1.1 (0.3-2.5)	NA	<.001
Hypervirulent *C difficile* ribotype RT027/078, No. (%)	68 (51.9)	39 (24.1)	NA	<.001
C difficile binary toxin positive, No. (%)	71 (54.2)	45 (27.8)	NA	<.001
Log_{10} *C difficile* DNA copies/mL, median (IQR)	7.3 (6.6-7.7)	4.9 (4.4-6.2)	NA	<.001
High lactoferrin level, No./total No. tested[n]	43/117 (36.8)	19/142 (13.4)	9/188 (4.8)	<.001

Polage et al – Jama intern med 2015; 175(11):1792-801

Recommandations ECCMID 2016



Crobach M., et al. , CMI 2016

Diarrhée simple post-antibiotique à *C. difficile*

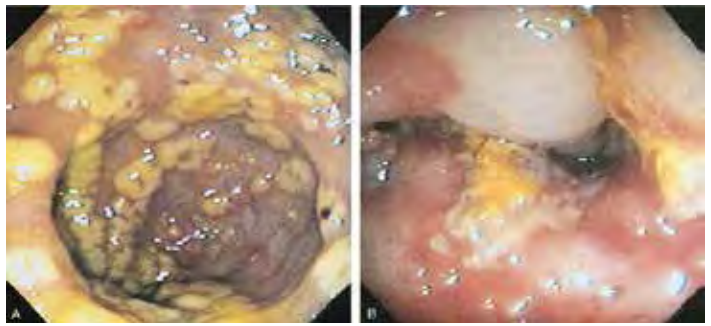
- Diarrhée modérée à abondante survenant pendant l ’antibiothérapie où dans les 2 semaines suivant son arrêt
- Absence de signes généraux
- Endoscopie : muqueuse normale ou érosive sans pseudomembrane
- Guérison après simple retrait de l ’ATB dans 25% des cas

- Rechutes :
  - 20% après un premier épisode
  - 60 % après une première rechute

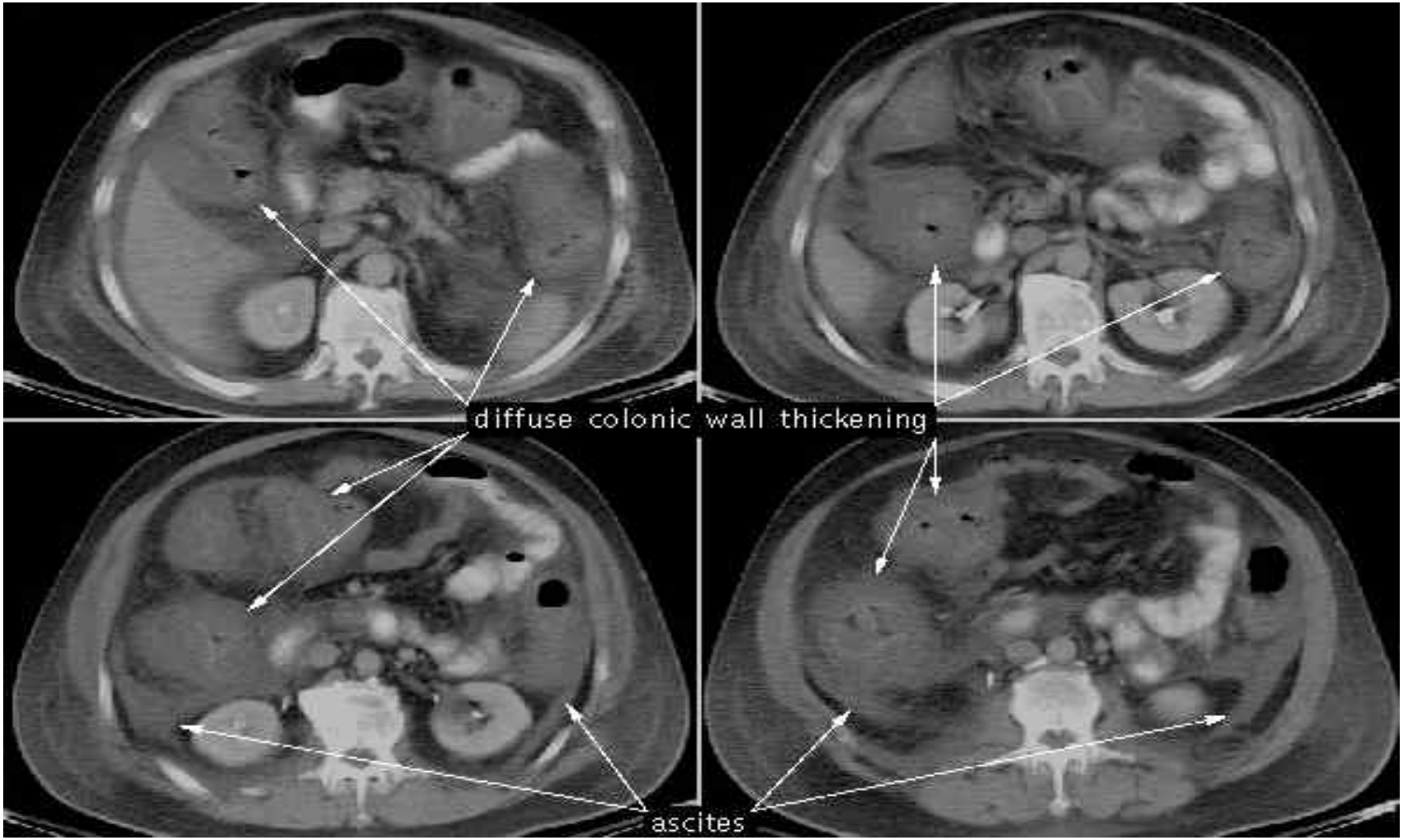
Colite pseudomembraneuse à *C. difficile*

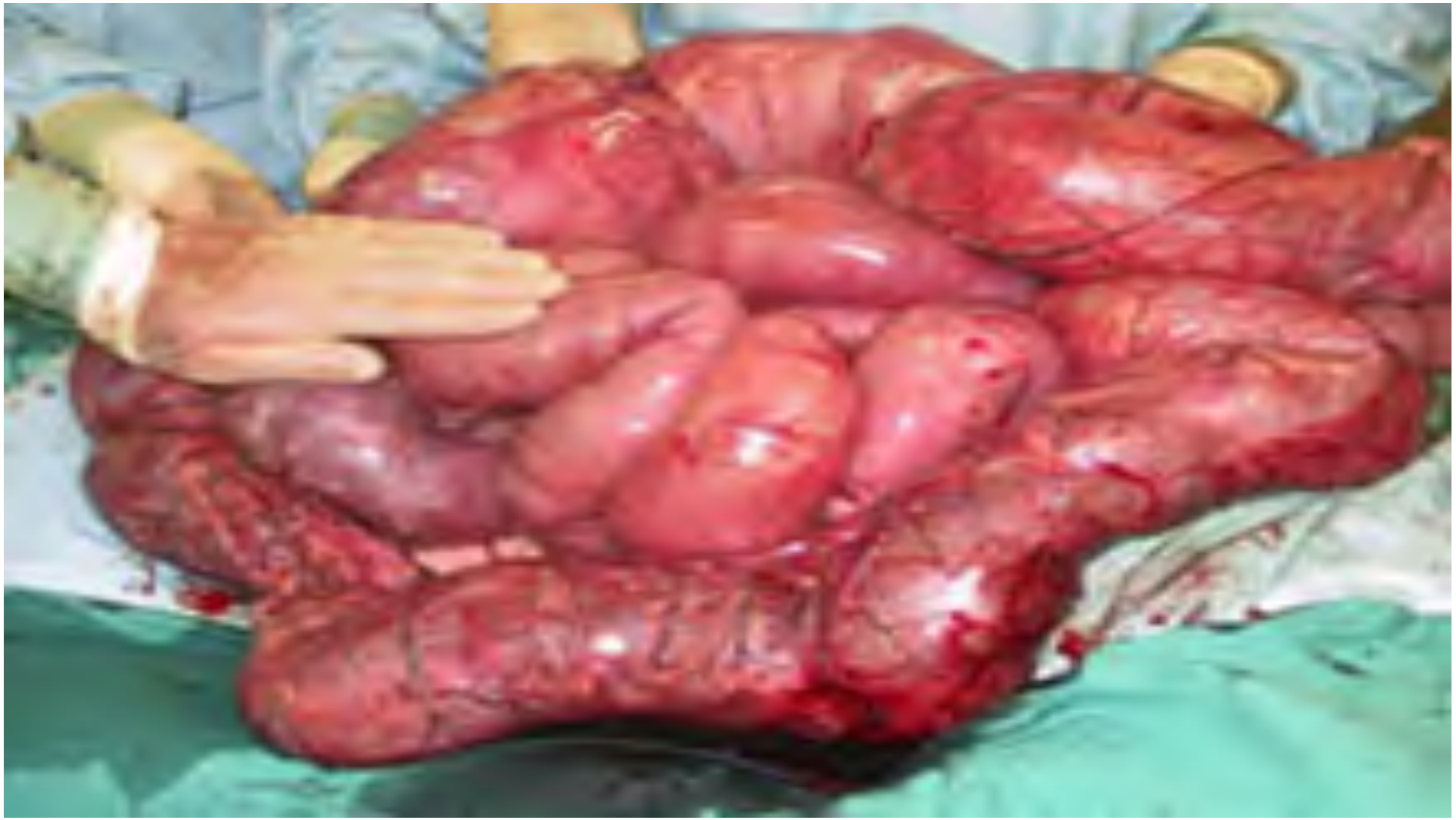
- **Pathologie grave de début brutal**
  - **diarrhée profuse (> 7 selles /j)**
  - **fièvre (75%) - douleurs abdominales (70%)**
  - **hyperleucocytose (40%) – Syndrome inflammatoire**
  - **Déshydratation-hypoalbuminémie**

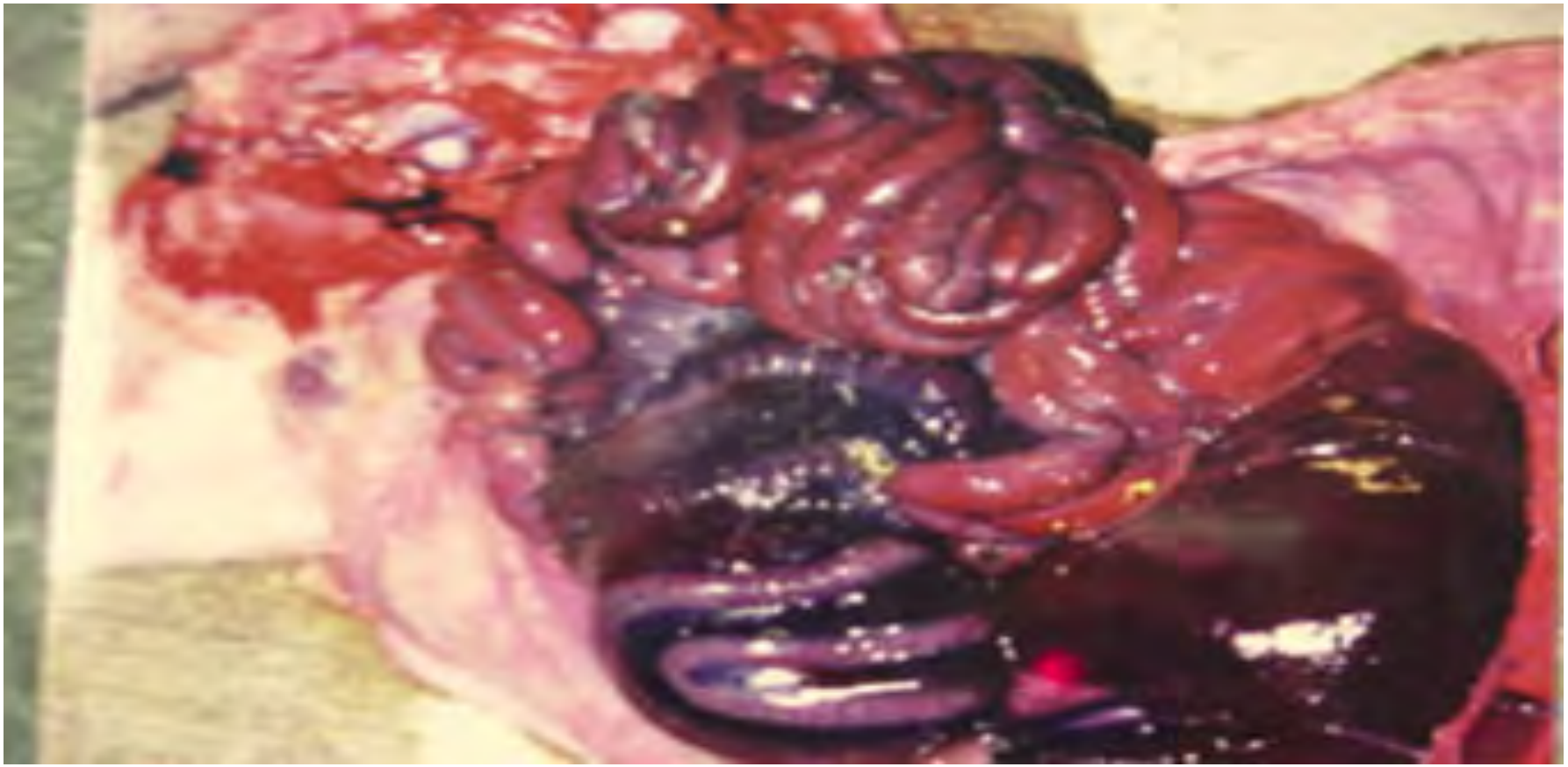
- **Présence de leucocytes fécaux = 50%**
- **Distension abdominale, ascite**
- **Endoscopie : pseudomembranes (colon + rectum)**
  - **plaques jaunes friables (qq mm à 2 cm)**
- **Complications**
  - **Choc infectieux**
  - **Mégacolon toxique - perforation**

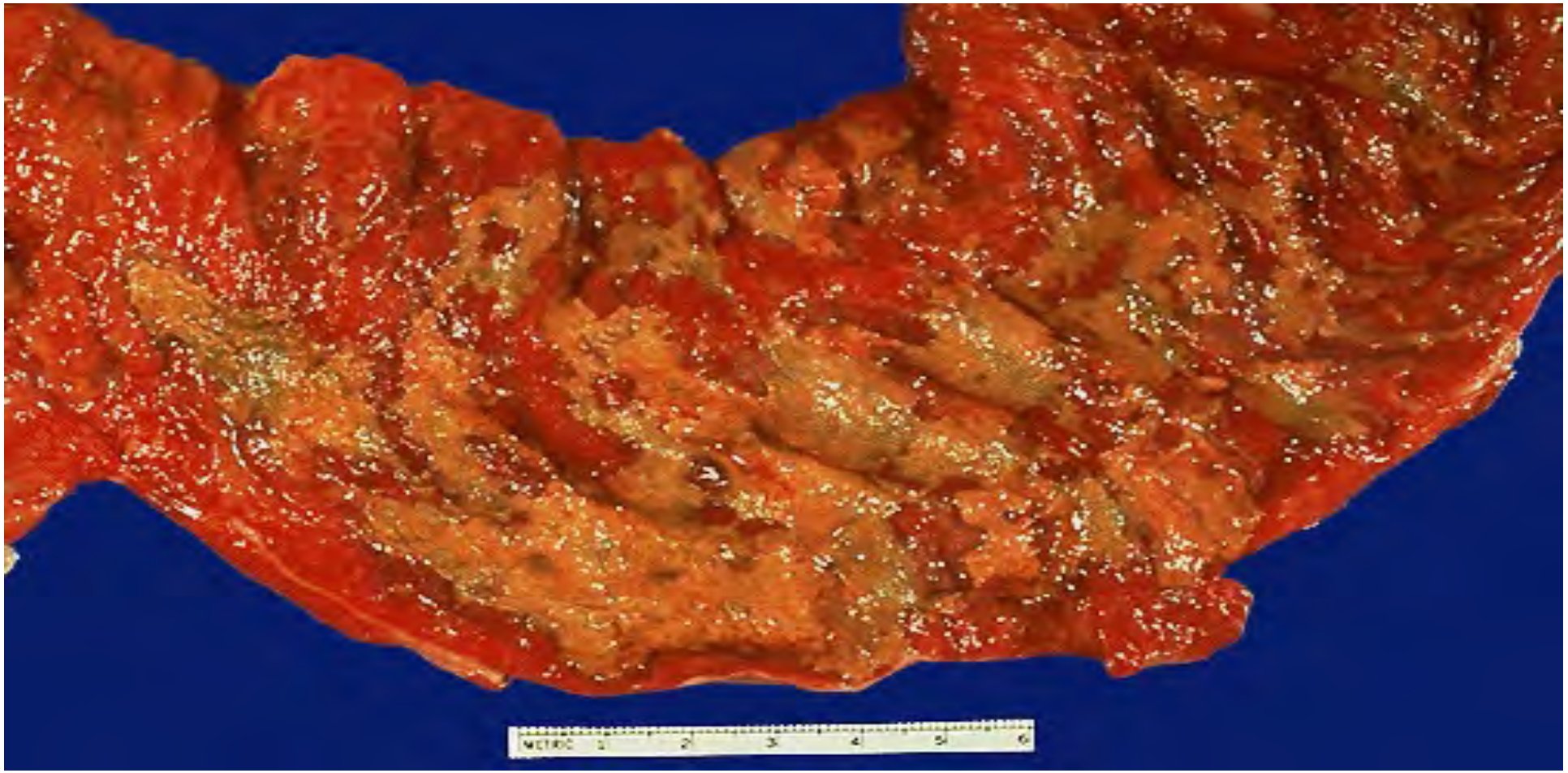


Morrisson RH Clin Infect Dis 2011; Modena S et al. J Clin Gastroenterol 2006; 40: 49-54; Chilton CH et al – J Antimicrobial Chemother 2012 Jan 25th ; Pepin J et al - Am J Gastroenterol. 2007 Dec;102(12):2781-8


diffuse colonic wall thickening
ascites







TRT Cl difficile

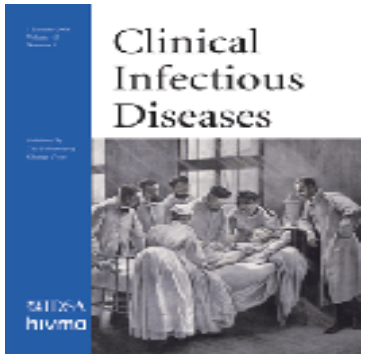
- Réhydratation et arrêt ATB
- Pas de modificateurs du transit ou d'anti-secrétoires
- Metronidazole per os ou vancomycine?
- Autres traitements?
- Transplantation fécale?
- Timing de la chirurgie pour les formes les plus graves?
- Prévention de la transmission et des récidives:
  - Immunotherapie, vaccination
  - Mesure hygiène,manuportage

MAJOR ARTICLE

Risk Factors Associated With Complications and Mortality in Patients With *Clostridium difficile* Infection

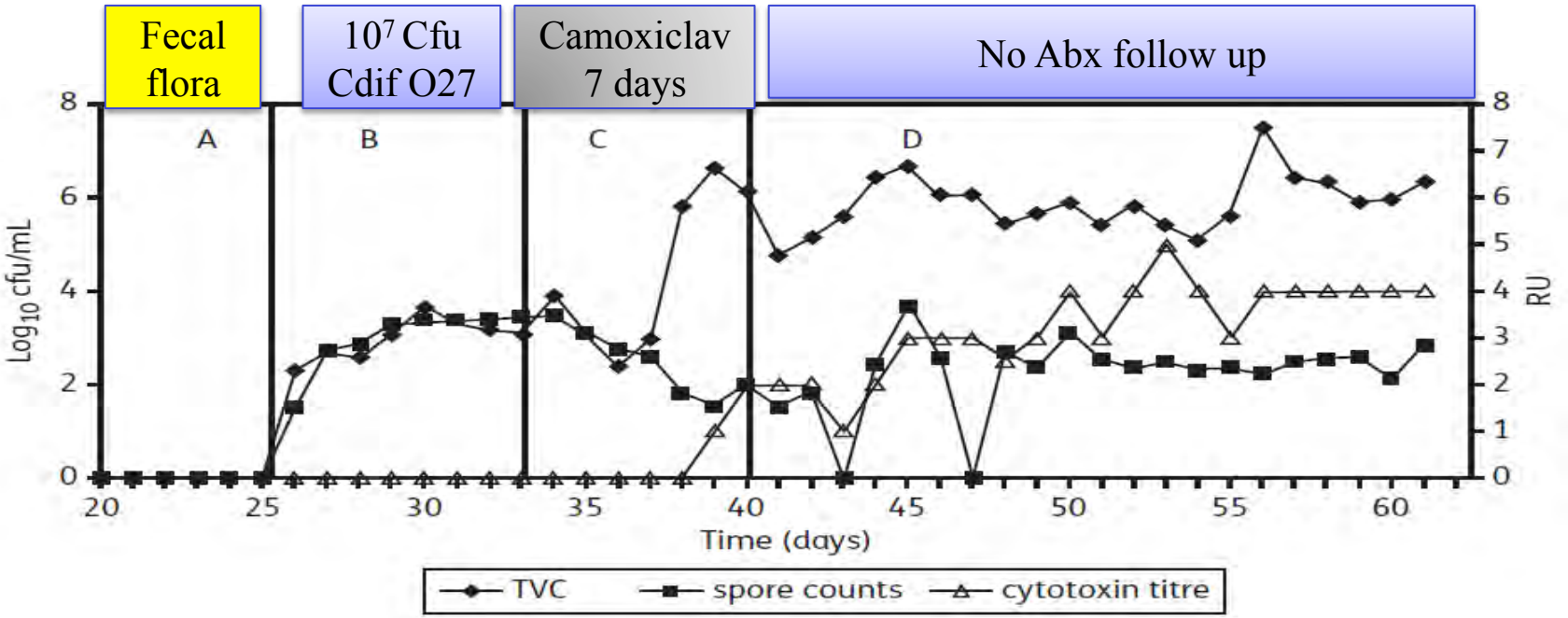
Rosemary H. Morrison,[1] Natalie S. Hall,[2] Mina Said,[2] Tamar Rice,[2] Harold Groff,[3] Stephanie K. Brodine,[1] Donald Slymen,[1] and Edith R. Lederman[1,3,4]

[1]San Diego State University Graduate School of Public Health, [2]Pharmacy Department, and [3]Division of Infectious Diseases, Naval Medical Center San Diego, California; and [4]Infectious Disease Clinical Research Program, Uniformed Services University of the Health Sciences, Bethesda, Maryland



Variable (no. for all complications, mortality alone)	Association with complications, including mortality			Association with mortality alone		
	OR	95% CI	*P*	OR	95% CI	*P*
Age ≥80 years						
Yes (14, 10)	4.20	2.11–8.35	<.001[a]	7.91	3.31–18.89	<.001[a]
No (33, 13)	1.00[b]	—	—	1.00[b]	—	—
Admitted for CDI						
Yes (27, 10)	4.17	2.23–7.80	<.001[a]	2.16	.91–5.13	.08
No (19, 13)	1.00[b]	—	—	1.00[b]	—	—
Corticosteroid use						
Yes (14, 6)	2.31	1.17–4.54	.015[a]	1.79	.68–4.69	.23
No (33, 45)	1.00[b]	—	—	1.00[b]	—	—
Prior antibiotic use						
Yes (40, 20)	1.80	.78–4.14	.17	2.06	.60–7.06	.25
No (7, 3)	1.00[b]	—	—	1.00[b]	—	—
Prior acid suppression						
Yes (33, 19)	2.86	1.49–5.49	.002[a]	5.60	1.88–16.72	.002[a]
No (14, 4)	1.00[b]	—	—	1.00[b]	—	—

Co-amoxiclav induces proliferation and cytotoxin production of *Clostridium difficile* ribotype 027 in a human gut model



Chilton CH et al – J Antimicrobial Chemother 2012 Jan 25th

Gravité clinique et poursuite des ATB

TABLE 3. Relationship of Disease Severity and Continuation of Antibiotics With Patient Response to Treatment by Day 5 and Day 14

	Disease Severeity (n)			Continued Antibiotics (n)		
	Mild	Severe	P*	Yes	No	P*
Patient responded† by day 5						
No	5	13		10	8	
Yes	7	2	0.01	7	2	0.26
Patient responded† by day 14						
No	3	4		7	0	
Yes	9	11	0.92	10	10	0.02

*P values calculated using Fisher's Exact test (2-sided).

†Definition of response: first of 2 consecutive days when the patient had any number of solid bowel movements or <3 loose or watery bowel movements. Pain resolution was considered the first of 2 consecutive days when the score was <3.

Modena S et al. J Clin Gastroenterol 2006; 40: 49-54

Vancomycine ou metronidazole

- Vancomycine
  - CMI_{90}:1.0-2.0 mg/l
  - La plus haute jamais rapportée: 16 mg/L
- Metronidazole
  - CMI ≤ 2 mg/L
  - Pelaez 2005: 415 souches
    - CMI_{90} 4mg/L CMI > 32:6% cas
  - *Mais pas de corrélation bio-clinique*

Wang et al – Diagn Microbiol Infect Dis 1999; 34:1; Aspevall et al – AAC 2006; 50:1890;. Pelaez et al – AAC 2005; 49:1147

PK metronidazole

- Oral Metronidazole
  - Absorption rapide: pic 1-2 h → paroi colique
  - Concentration fécale

    Diarrhée liquide: 9.3 µg/g (range 0.8-24)

    Selles moulées:1.2 µg/g (range 0-10.2)

    Porteurs asymptomatiques ≈ 0
- IV Metronidazole
  - 3 patients → 6.3 µg/g à 24 µg/g
  - Données cliniques publiées plutôt négatives (QS)

Bolton RP et al – Gut 1986; 27:1169; Dion YM et al – Ann Surg 1980; 192:221; Johnson S et al – Ann Intern Med 1992; 117:297

PK Vancomycine

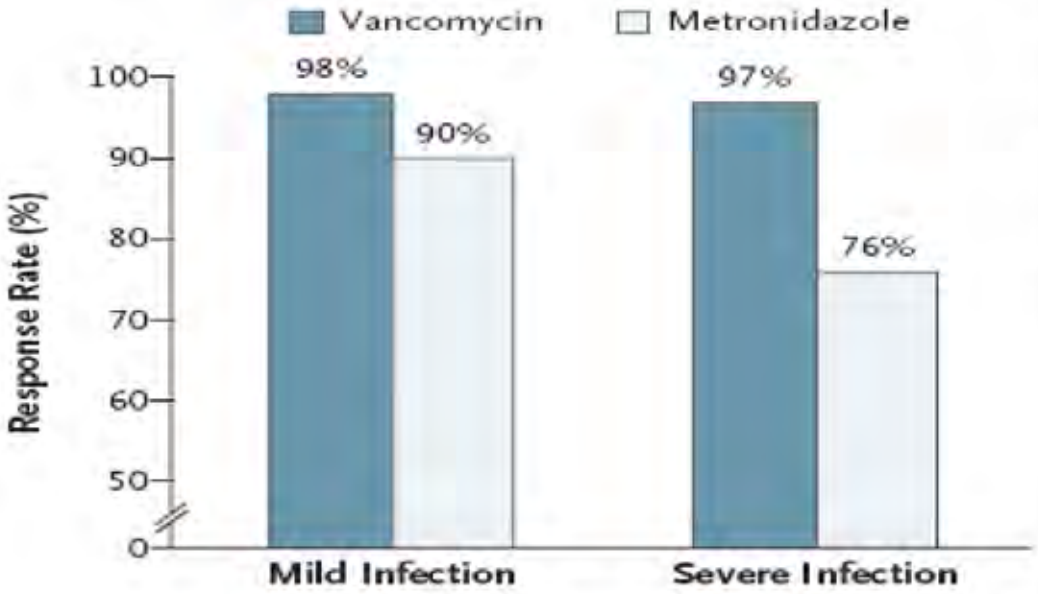
- Oral Vancomycine
  - Pos :125 mg X 4 → > 3000 µg/g dans les selles
  - Atteint la valve ileo-caecale en moins de 6 heures
  - En cas d'ileus????
    - Pic retardé???
    - Posologies plus élevées
- IV Vancomycine
  - 0 ou presque…

Pepin J - Clin Infect Dis 2008; 46:1493; Johnson et al – Ann Intern Med 1992; 117:297; Tedesco F – Lancet 1978- 2:226

A Comparison of Vancomycin and Metronidazole for the Treatment of *Clostridium difficile*–Associated Diarrhea, Stratified by Disease Severity

CID 2007; 45: 302

Fred A. Zar,[1] Srinivasa R. Bakkanagari,[2] K. M. L. S. T. Moorthi,[2] and Melinda B. Davis[1]



- **Métronidazole**
  - **250 mg x 3 / j**
- **Vancomycine**
  - **125 mg x 4 / j**
- **Infection sévère:**
  - pseudomembranes à la coloscopie
  - admission en réa
  - âge > 60 ans
  - T > 38,3 ° C
  - Alb < 25 g/l
  - GB > 15000/mm^3

Metronidazole IV vs oral vs Vancomycin oral

Mild forms, oral route always possible

TABLE 2 The three treatment groups and CDI patients receiving no antimicrobial treatment by demographics, severity of comorbidity, and underlying condition[a]

Characteristic or underlying condition	Met p.o. ($n = 121$)	Met i.v. ($n = 42$)	Van p.o. ($n = 42$)	No antimicrobial treatment ($n = 60$)	P
Characteristic					
Median (range) age (yr)	75.0 (22–95)	75.3 (43–92)	75.0 (27–98)	73.5 (21–94)	0.99
No. (%) of patients by:					
Sex (male)	45 (37.2)	20 (47.6)	19 (45.2)	13 (21.7)	0.41
Comorbidity (moderate/severe)	62 (51.2)	24 (57.1)	24 (57.1)	36 (60)	0.71
Underlying condition					
Cerebral dysfunction	52 (43.0)	17 (40.5)	19 (45.2)		0.91
Cardiovascular disease	92 (76.0)	31 (73.8)	37 (88.1)		0.2
Pulmonary disease	27 (22.3)	13 (31.0)	15 (35.7)		0.19
Renal disease	36 (29.8)	11 (26.2)	14 (33.3)		0.77
Liver disease	10 (8.3)	5 (11.9)	5 (11.9)		0.69
Surgery in previous 3 mo	21 (17.4)	6 (14.3)	5 (11.9)		0.68
Medical invasive device	11 (9.1)	3 (7.1)	4 (9.5)		0.91
Current neoplasia	11 (9.1)	5 (11.9)	3 (7.1)		0.75
Diabetes mellitus	39 (32.2)	14 (33.3)	11 (26.2)		0.73
HIV infection	0 (0)	0 (0)	0 (0)		

[a] The three treatment groups were metronidazole (Met) p.o. ($n = 121$), metronidazole i.v. ($n = 42$), and vancomycin p.o. ($n = 42$).

TABLE 3 Findings of the comparative analyses between the three treatment regimens with respect to the primary and secondary endpoints[a]

Endpoint	No. (%) of patients			P^b
	Met p.o. ($n = 121$)	Met i.v. ($n = 42$)	Van p.o. ($n = 42$)	
Primary				
Recovery	100 (82.6)	22 (52.4)	34 (81)	<0.001
Continuing diarrhea	12 (9.9)	4 (9.5)	4 (9.5)	1
All-cause death	9 (7.4)	16 (38.1)	4 (9.5)	<0.001

Wenisch et al – AAC 2012 January 17th

Traitement « classique » de la diarrhée à CD

- Standard:
  - Metronidazole *per os* pendant 7 à 10 jours
  - 500 mg x 3/jour
  - Formes peu graves
- Graves ou recidivantes:
  - Vancomycine *per os,* 7 à 10 jours
  - 125 mg x 4/jour
  - Doses plus élevées pour les épisodes sévères
  - Standard (?) pour les patients
    - avec albumine <25 g/l
    - En USI
- La résistance clinique de CD au metronidazole et à la vancomycine n'est pas rapportée
- … mais le changement d'antibiotiques est recommandé par certains en cas de persistance des symptômes au delà d'une semaine

En cas d'iléus sévère et megacolon toxique

- Metronidazole IV et Vancomycine Per os en augmentant les doses
- +- Lavement à la Vancomycine *(500 mg dans 100 ml – sonde de Foley++)*
- Immunoglobulines? *(0.2 à 0.4 g/kg)*

Adapté de Gerdings et al – Clin Infect Dis 2008; 46:S32

Intracolonic vancomycin?

	Therapy with adjunctive intracolonic vancomycin No. (%) or average ± s.d.	Therapy without intracolonic vancomycin No. (%) or average ± s.d.	*P* value*
Total Number	26 (20.5 %)	101 (79.5 %)	
Average Severity Score Index (range 0–9)	5.69 ± 1.4	5.02 ± 1.0	0.03
Length of hospital stay (days): average + SD	39.1 ± 30.6	27.1 ± 33.3	0.09
Death	10 (38.5)	39 (38.6 %)	1.00
Oral vancomycin	21 (80.8 %)	44 (43.6 %)	0.0008
Oral metronidazole	13 (50.0 %)	76 (75.2 %)	0.012
IV metronidazole	25 (96.2 %)	45 (44.6 %)	<0.0001
Admission to or transfer to the ICU	24 (92.3 %)	70 (69.3 %)	0.022
Fever (>101 ° F)	10 (38.5 %)	37 (33.7 %)	0.86
Ileus	12 (46.2 %)	29 (28.7 %)	0.10
Toxic megacolon	9 (34.6 %)	4 (4.0 %)	<0.0001
Colectomy	4 (15.4 %)	1 (1.0 %)	0.006

*Because of multiple hypotheses testing, a p value ≤ 0.01 determined statistical significance
SD standard deviation, *IV* intravenous, *ICU* intensive care unit, *VRE* vancomycin resistant enterococcus, *MRSA* methicillin resistant *Staphylococcus aureus*

- Retrospective 127 patients
- Dose et durée variable
- Patients plus graves et mortalité similaire…

Akamine et al BMC-ID 2016 7;16:316

Fidaxomicin (Dificlir™)

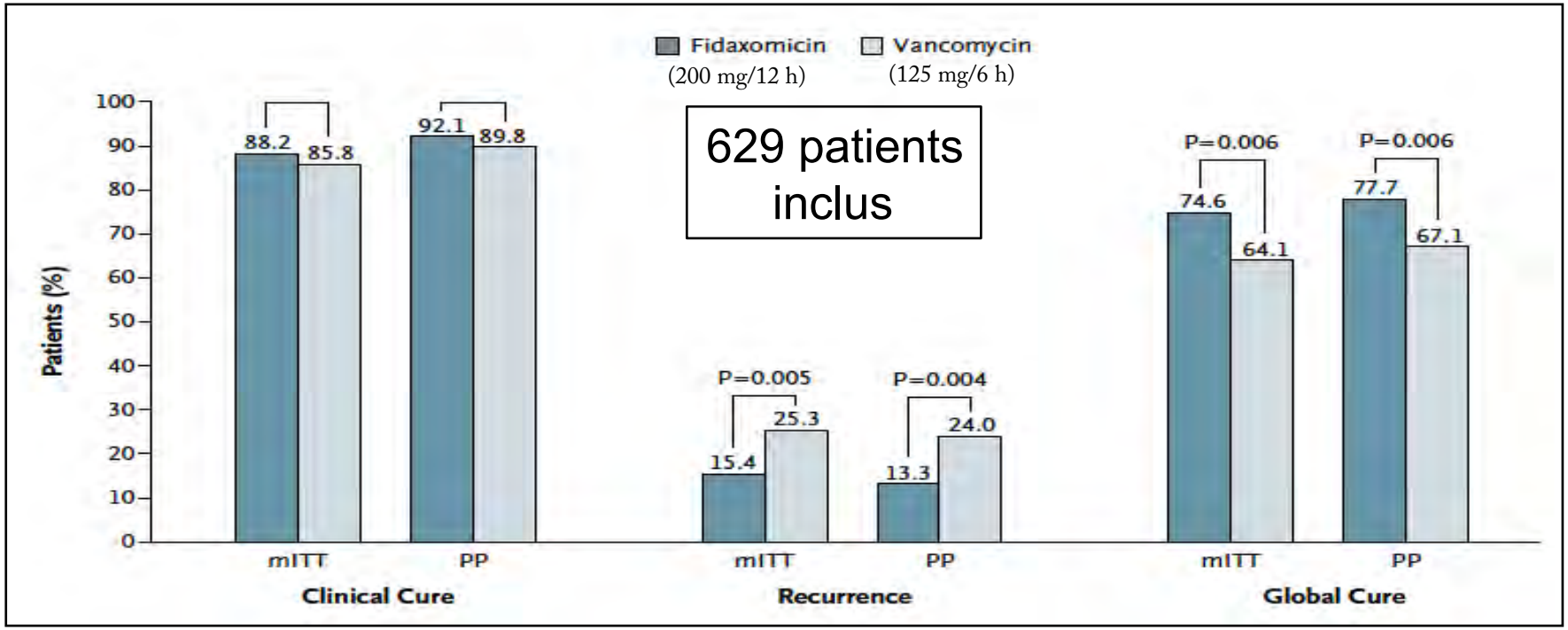
- **Macrocyclique/CMI_{90}: 0,25 µg/ml**
- **Concentration fecale: 1225.1±759.0 µg/g**
- **Inhibe la sporulation de Cdif**
- **200 mg 2 fois par jour 10 jours**
- **Au moins aussi efficace voir plus que Vancomycine (125mg X 4) dans le sous-groupe qui reçoit des antibiotiques**
- **Peu d'impact sur la flore digestive, pas d'activité sur BGN, *Bacteroides* sp., ERV**
- **Moins de récidives**
- **Peu de données en réanimation: PK correcte ds la sonde gastrique**
- **$3360 pour 10 j de traitement aux USA**

Mullane Clin Infect Dis 2011; Cornelly Lancet Infect Dis 2012;

Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection

Thomas J. Louie, M.D., Mark A. Miller, M.D., Kathleen M. Mullane, D.O., Karl Weiss, M.D., Arnold Lentnek, M.D., Yoav Golan, M.D., Sherwood Gorbach, M.D., Pamela Sears, Ph.D., and Youe-Kong Shue, Ph.D., for the OPT-80-003 Clinical Study Group*

N Engl J Med 2011;364:422-31.



Fin de traitement
(2 jours après)

Dans les 4 sem après la fin du traitement

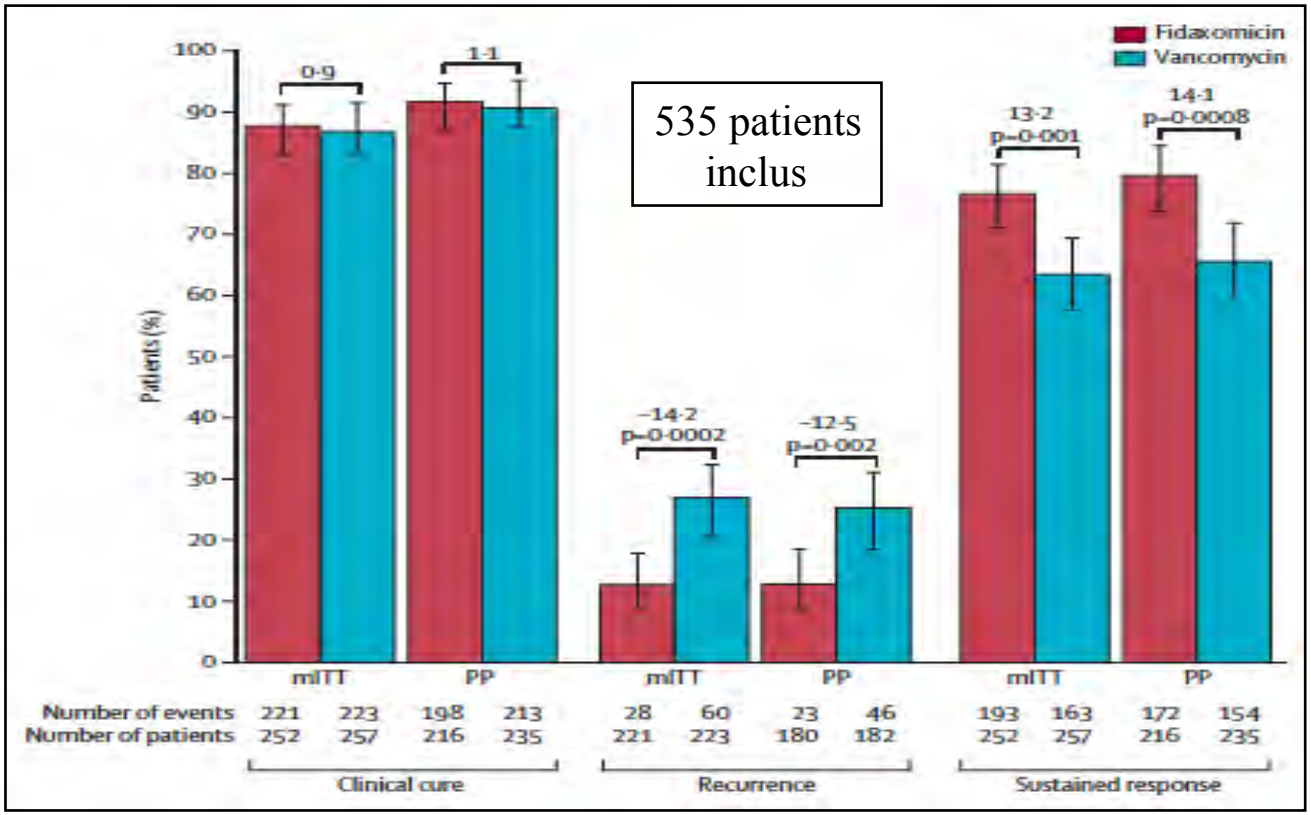
A J28 post traitement

Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial

Lancet Infect Dis 2012; 12: 281–89

Oliver A Cornely, Derrick W Crook, Roberto Esposito, André Poirier, Michael S Somero, Karl Weiss, Pamela Sears, Sherwood Gorbach, for the OPT-80-004 Clinical Study Group

535 patients inclus



Efficacy of Fidaxomicin Versus Vancomycin as Therapy for *Clostridium difficile* Infection in Individuals Taking Concomitant Antibiotics for Other Concurrent Infections

Endpoint	% (proportion) of subjects			
study period	Fidaxomicin	Vancomycin	Difference (95% CI)	*P*
Any CA				
Clinical cure				
Treatment	90.00 (81/90)	79.41 (81/102)	10.59 (0.23–20.34)	.04
Recurrence				
Treatment	17.19 (11/64)	30.00 (21/70)	12.81 (26.41 to 1.66)	.08
Follow-up	21.31 (13/61)	27.94 (19/68)	6.63 (20.98 to 8.29)	.38
At any time	16.85 (15/89)	29.17 (28/96)	12.31 (23.90 to 0.12)	.048
Global Cure				
At any time	72.73 (96/132)	59.44 (85/143)	13.29 (2.11–24.05)	.02
No high-risk CA[b]				
Clinical cure				
Treatment	92.22 (403/437)	91.97 (424/461)	0.25 (3.32 to 3.79)	.89
Recurrence				
Treatment	12.22 (44/360)	24.25 (89/367)	12.03 (17.50 to 6.42)	<.001
Follow-up	11.85 (43/363)	23.64 (87/368)	11.80 (17.20 to 6.26)	<.001
At any time	11.59 (40/345)	23.86 (84/352)	12.27 (17.79 to 6.61)	<.001
Global cure				
At any time	80.79 (328/406)	68.26 (299/438)	12.52 (6.66–18.25)	<.001

Mullane *et al,* Clin Inf Dis 2011

Tigecycline?

1. Gut models: No intraluminal *C. difficile* proliferation or toxin production[1]
2. Excretion into the bile in high concentrations and only minimally disrupts the normal intestinal microbiome[2]
3. Limited clinical studies[3]
4. ESCMID guideline only marginally supports recommendation for use of tigecycline as a last resort drug for sCDI (grade C-III evidence)[4]

1- Nord CE et al - Antimicrob Agents Chemother 304 2006;50:3375–80.;.
2- Aldape MJ et al. -J Antimicrob Chemother 2015;70:153–9.
3- Gergely SB et al - Clin Microbiol Infect 317 2016;22:990-5.;
4- Crobach MJT et al - ESCMID guidance document for Clostridium difficile infection. Clin Microbiol Infect 2016; 22(s4): s63-s81.

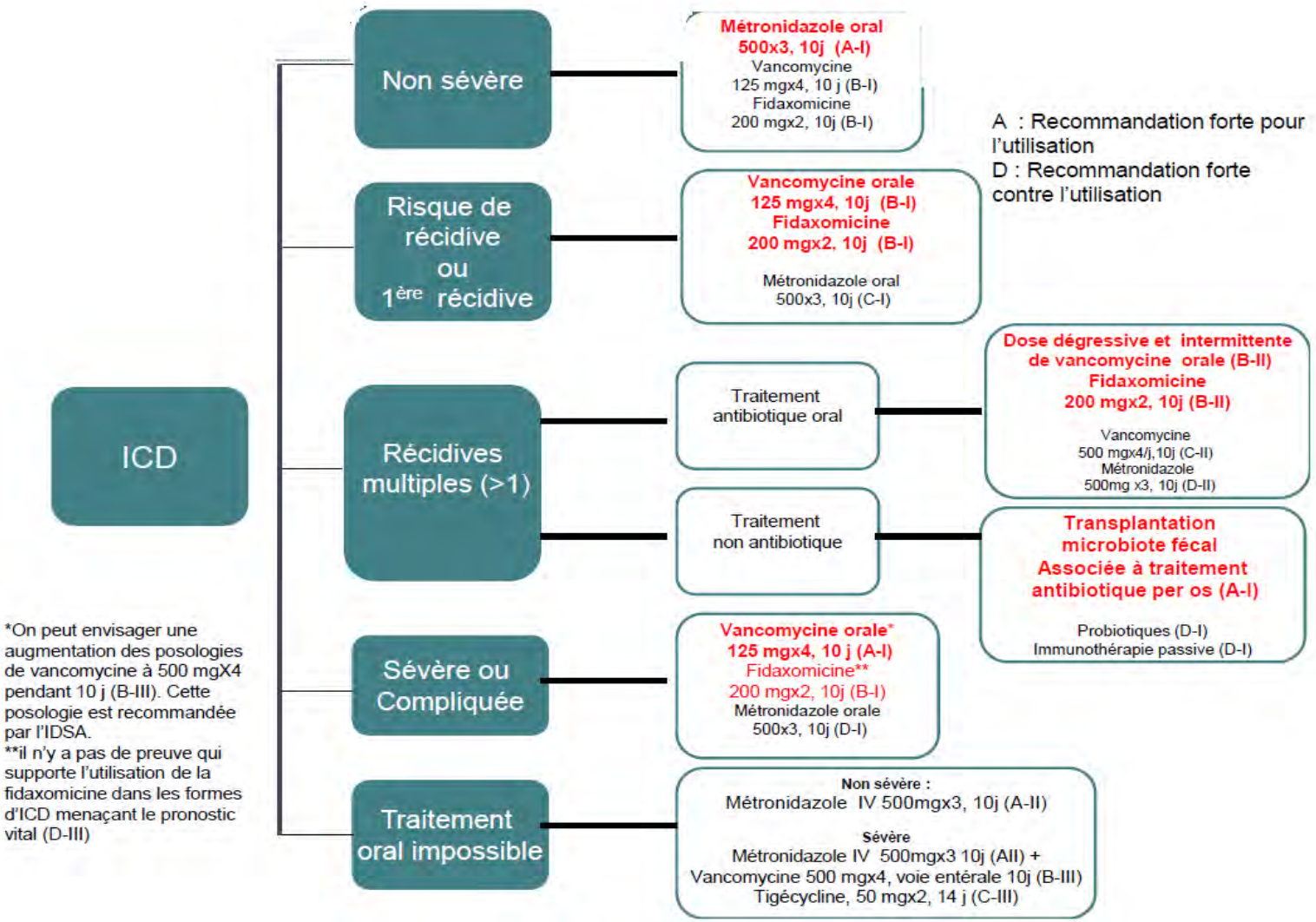
The role of Tigecycline in the management of *Clostridium difficile* infection: a retrospective cohort study

Eliza Manea et al CMI 2017 DOI: 10.1016/j.cmi.2017.06.005

	All included patients			Treated for seven days or more		
	Tigecycline + Vancomycin (n=62)	Vancomycin (n=204)	p*	Tigecycline + Vancomycin (n=47)	Vancomycin (n=204)	p*
Length of CDI therapy in days (mean, SD)	10 (4.8)	13 (6.07)	<0.001	12 (4.2)	13 (6.07)	0.09
Underlying diseases						
Concomitant infection	30 (48)	55 (27)	0.002	23 (49)	55 (27)	0.006
Severity criteria						
Toxic megacolon	6 (10)	1 (0.5)	<0.001	4 (9)	1 (0.5)	0.003
Sepsis	19 (31)	7 (3)	<0.001	16 (34)	7 (3)	<0.001
Age over 65 years	39 (63)	119 (58)	0.5	30 (64)	119 (58)	0.6
Fever	32 (52)	71 (35)	0.001	26 (55)	71 (35)	0.01
Acute renal insufficiency	18 (29)	31 (15)	0.01	14 (30)	31 (15)	0.03
WBC >15x10^9/L	36 (58)	62 (30)	<0.001	28 (60)	62 (30)	<0.001
Albumin <3 g/L	65 (74)	100 (49)	<0.001	36 (77)	100 (49)	0.001
Median ATLAS score (IQR)	5 (4-6)	3 (2-4)	<0.001	5 (4-6)	3 (2-4)	0.005
Severe CDI (according to SHEA guidelines)	39 (63)	73 (36)	<0.001	30 (64)	73 (36)	<0.001
Severe complicated CDI (according to SHEA guidelines)	10 (16)	2 (1)	<0.001	6 (13)	2 (1)	<0.001
Outcomes						
Favourable outcome	48 (77)	193 (95)	<0.001	40 (85)	193 (95)	0.05
Recurrence	8 (13)	39 (19)	0.2	7 (15)	39 (19)	0.6

	All included patients (n=266)		PS adjusted (n=266)		PS matched cohort (n=86)	
Variables	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Charlson index (per one point increase)	0.8 (0.6-1.0)	0.08	0.8 (0.6-1.1)	0.1	1.0 (0.9-1.3)	0.6
Severe CDI (according to SHEA guidelines)	0.9 (0.3-3.1)	0.9	1.9 (0.3-3.2)	0.9	1.1 (0.5-2.3)	0.7
Toxic megacolon	1x10^{-9} (0.0-0.1)	<0.01	6.0 x10^{-9} (0.0-0.1)	<0.01	2.1x10^{-9} *	0.9
ATLAS score (per one point increase)	0.8 (0.6-1.1)	0.2	0.8 (0.6-1.1)	0.1	0.9 (0.7-1.2)	0.5
Treatment with tigecycline	0.5 (0.2-1.5)	0.2	0.4 (0.1-1.3)	0.1	1.0 (0.6-1.5)	0.8

"Adding tigecycline to CDI standard therapy did not increase the clinical cure nor reduced the rate of CDI recurrences"


ICD
Non sévère
Métronidazole oral
500x3, 10j (A-I)
Vancomycine
125 mgx4, 10 j (B-I)
Fidaxomicine
200 mgx2, 10j (B-I)
Risque de récidive ou 1ère récidive
Vancomycine orale
125 mgx4, 10j (B-I)
Fidaxomicine
200 mgx2, 10j (B-I)
Métronidazole oral
500x3, 10j (C-I)
Récidives multiples (>1)
Traitement antibiotique oral
Dose dégressive et intermittente de vancomycine orale (B-II)
Fidaxomicine
200 mgx2, 10j (B-II)
Vancomycine
500 mgx4/j,10j (C-II)
Métronidazole
500mg x3, 10j (D-II)
Traitement non antibiotique
Transplantation microbiote fécal
Associée à traitement antibiotique per os (A-I)
Probiotiques (D-I)
Immunothérapie passive (D-I)
Sévère ou Compliquée
Vancomycine orale*
125 mgx4, 10 j (A-I)
Fidaxomicine**
200 mgx2, 10j (B-I)
Métronidazole orale
500x3, 10j (D-I)
Traitement oral impossible
Non sévère :
Métronidazole IV 500mgx3, 10j (A-II)
Sévère
Métronidazole IV 500mgx3 10j (AII) +
Vancomycine 500 mgx4, voie entérale 10j (B-III)
Tigécycline, 50 mgx2, 14 j (C-III)
A : Recommandation forte pour l'utilisation
D : Recommandation forte contre l'utilisation
*On peut envisager une augmentation des posologies de vancomycine à 500 mgX4 pendant 10 j (B-III). Cette posologie est recommandée par l'IDSA.
**il n'y a pas de preuve qui supporte l'utilisation de la fidaxomicine dans les formes d'ICD menaçant le pronostic vital (D-III)

Indications de la chirurgie

Chirurgie en urgence/Colectomie

Perforation
Colite fulminante
Choc réfractaire
Péritonite

Chirurgie retardée

Mégacolon toxique (>6cm)
Colite sévère chez les sujets agés
Colite inflammatoire
Aggravation des défaillances d'organes

Bobo & Kollef - Chest 2011; 140:1643

Colites pseudo-membraneuses fulminantes à *Clostridium difficile*

- Étude rétrospective, 2003-2005
- CHU Sherbrooke et hôpital Maisonneuve-Rosemont (Québec)
- 165 patients admis en réanimation pour une colite pseudo-membraneuse
- Mortalité à 30 jours
  - 87/165 (53 %)
  - 38 des 87 décès (44 %) dans les 48 heures suivant l'admission en réanimation
- Intérêt de la colectomie ?

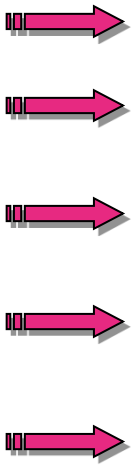
Lamontagne F et al. Ann Surg 2007; 245: 267-72

Colectomie et CPM

TABLE 3. Thirty-Day Mortality According to Whether a Colectomy Was Performed in Some Subgroups of Patients With Fulminant *Clostridium difficile*-Associated Disease (CDAD)

Characteristic	Had a Colectomy (died/total)	Did Not Have a Colectomy (died/total)	*P*
Age			
39–64 yr	3/10 (30%)	9/28 (32%)	0.90
65–74 yr	6/14 (43%)	19/31 (61%)	0.25
≥75 yr	4/14 (29%)	46/68 (68%)	0.006
Immunosuppression*			
No	6/27 (22%)	45/89 (51%)	0.001
Yes	7/11 (64%)	29/38 (76%)	0.41
Shock requiring vasopressor amines			
No	1/11 (9%)	25/61 (41%)	0.04
Yes	12/27 (44%)	49/66 (74%)	0.006
Peak white cell count ($\times 10^9$/L)			
<20	2/2 (100%)	14/34 (41%)	0.11
20.0–49.9	6/28 (21%)	39/71 (55%)	0.002
≥50	5/8 (63%)	21/22 (95%)	0.02
Peak lactate (mmol/L)			
≤2.1	3/8 (38%)	13/29 (45%)	1.00
2.2–4.9	3/18 (17%)	23/46 (50%)	0.03
≥5	6/7 (86%)	33/35 (94%)	0.43
Not done	1/5 (20%)	5/17 (29%)	1.00

*Systemic corticosteroids for as least 1 month, leukemia, lymphoma, organ transplant, neutropenia, or any combination thereof.



age ≥ 75 years
AOR, 6.5; 95% CI, 1.7–24.3

immunosuppression
AOR, 7.9; 95% CI, 2.3–27.2

shock requiring vasopressors
AOR, 3.4; 95% CI,1.3– 8.7

leukocytosis ≥ 50 X 109/L
AOR, 18.6; 95% CI, 3.7–94.7

lactate ≥ 5 mmol/L
AOR, 12.4; 95% CI, 2.4–63.7

Emergency colectomy were less likely to die AOR, 0.22; 95%CI, 0.07– 0.67, P =0.008

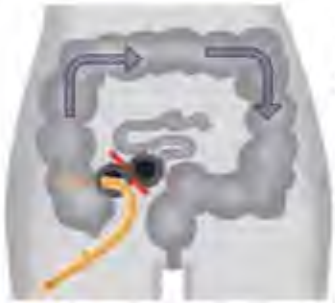
Lamontagne F et al. Ann Surg 2007; 245: 267-72

Diverting Loop Ileostomy and Colonic Lavage

Neal MD et al - Annals of Surgery Volume 254, Number 3, September 2011

A diagnosis of CDAD as determined by history of ongoing or recent diarrhea and one of the following:
1. Positive toxin assay
2. Endoscopic findings
3. CT scan findings consistent with *C. difficile* colitis (pancolitis +/− ascites)

Plus any one of the following criteria:
1. Peritonitis
2. Worsening abdominal distention/pain
3. Sepsis
4. New onset ventilatory failure
5. New or increasing vasopressor requirement
6. Mental status changes
7. Unexplained clinical deterioration
8. Nonimproving or worsening while blood cell count more than 20 or less than 3 despite appropriate antibiotic therapy for 96 hours
9. Nonimproving and worsening bandemia (>10%) despite appropriate antibiotic therapy for 96 hours



1. Creation of diverting loop ileostomy.
2. Intraoperative antegrade colonic lavage with 8 liters of warmed PEG3350/electrolyte solution via ileostomy.
3. Postoperative antegrade colonic enemas with vancomycin (500 mg in 500 mL X 10 days) via ileostomy.

	Ileostomy/Lavage	Colectomy	*P*
Age, y	65.3 ± 13	62.1 ± 14	0.28
Sex	45% women	45% women	1.0
APACHE-II (mean ± SD)	29.7 ± 5.5	28.5 ± 7.1	0.39
While blood cell count (mean ± SD)	25.4 ± 12.1	27.1 ± 13.2	0.54
Band count (mean ± SD)	21.4 ± 12.2	21.3 ± 12.9	0.97
Albumin (mean ± SD)	2.0 ± 0.8	2.2 ± 0.8	0.26
Intensive care unit	38/42 (90%)	38/42 (90%)	0.64
Intubated	27/42 (64%)	26/42 (62%)	0.82
Vasopressors	31/42 (74%)	32/42 (76%)	0.81
Immunosuppression	19/42 (45%)	17/42 (40%)	0.66
Postoperative death	8/42 (19%)	21/42 (50%)	0.006*

*Odds ratio = 0.24 (0.09–0.63).

Colon preservation: 39/42…

An institutional comparison of total abdominal colectomy and diverting loop ileostomy and colonic lavage in the treatment of severe, complicated C.difficile infections.

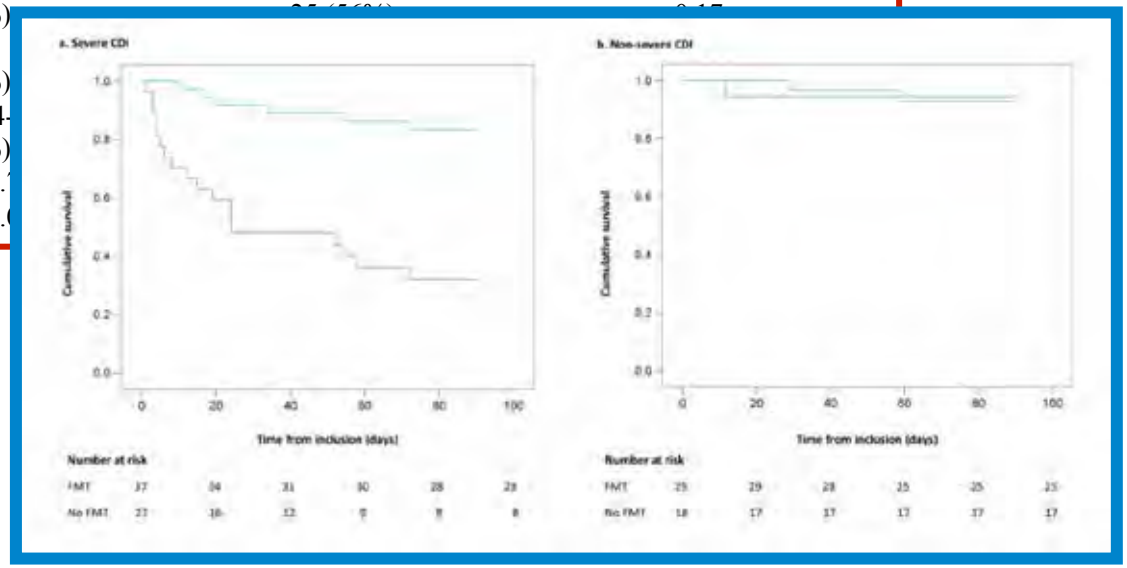
	TAC, N=13	Loop ileostomy, N=10	P-value*
30-day mortality, N (%)	**3 (23)**	**3 (30)**	**1.00**
1-year mortality, N (%)	**6 (46)**	**4 (40)**	**1.00**
CDI recurrence, N (%)	**3 (23)**	**4 (40)**	**0.57**
CDI rec >30-day survivors, N (%)	**3 (30)**	**4 (57)**	**0.35**
Colon preservation >1y survivors, N(%)		6 (100)	
Return of intestinal continuity in >1-year survivors, N (%)	3 (43)	5 (83)	0.27

Fashandi AZ et al Am J Surg. 2017 Mar;213(3):507-511.

Au delà des antibiotiques…

Early Faecal Microbiota Transplantation Improves Survival in Severe Clostridium difficile Infections.

Characteristic	FMT (N=66)	No-FMT (N=45)	*P value*
Age: median (IQR)	81 (69-87)	83 (72-88)	0.84
Charlson comorbidity index (median, range)c	2 (1-3)	2 (1-4)	0.17
Bedridden patients — no. (%)	27 (41%)	18 (40%)	0.92
Use of proton-pump inhibitor — no. (%)	30 (45%)	22 (49%)	0.72
Antibiotic use before CDI— no. (%)f	57 (87%)	38 (84%)	0.78
Hospital/retirement home-acquired CDI — (%)	44 (67%)	28 (62%)	0.63
Binary toxin — no. (%)	34 (51%)	27 (60%)	0.37
Ribotype O27 — no. (%)	28 (42%)		
Median recurrences — no. (range)	0 (0-0)		
Severe colitis — no. (%)	37 (56%)		
Median leukocyte count (IQR)	11.1 (7.4-		
Leukocyte count > 15,000 cells/ml— no. (%)	25 (38%)		
Median albumin (g/l)	31.3 (25.1		
Serum creatinine	91.8 (64.(		



Hocquart M et al - Clin Infect Dis. 2017 Aug 24. doi: 10.1093/cid/cix762. [Epub ahead of print]

Prevention des récidives

- (probiotiques)
- Transplantation fecale
- Anticorps monoclonaux
- (Vaccin)

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

E. van Nood et al. NEJM 2013

- Inclus : rechute après traitement bien conduit
- Donneurs « sains » du jour
- Randomisation :
  - VA 500 x 4/j pdt 4 j puis lavage duodénal puis transplantation (seconde cure si 1ère inefficace)
  - VA 500 x 4/j pdt 14 j per os
  - VA 500 x 4/j pdt 14 j per os + un lavage duodénal à J4-J5
- Critère de jugement : guérison sans rechute (10 sem)
- Arrêt à l'analyse intermédiaire

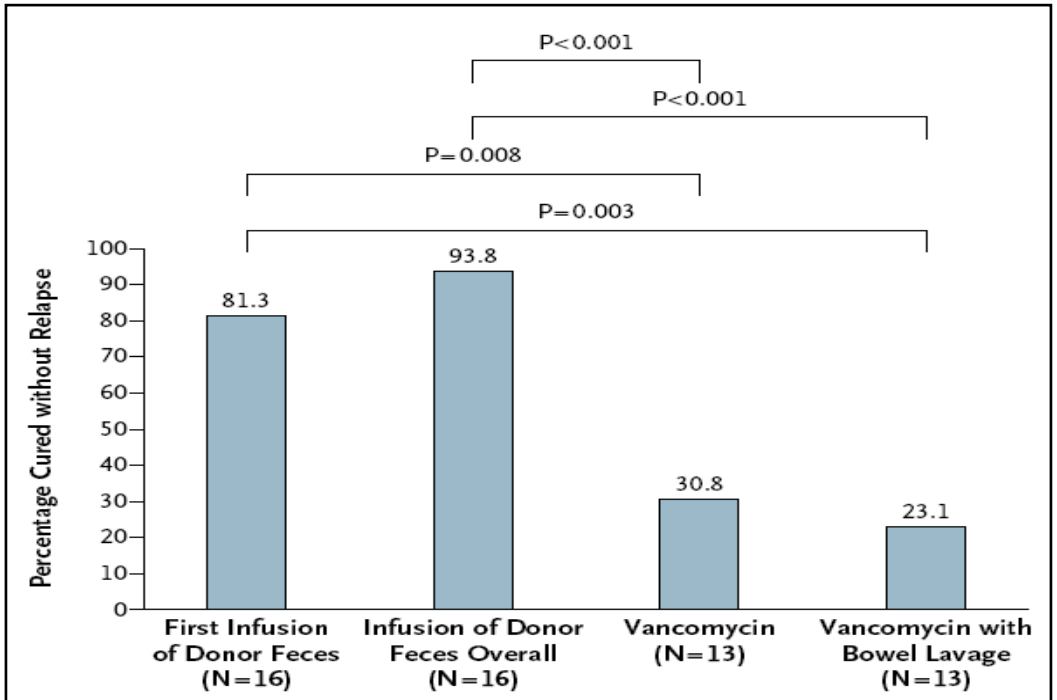
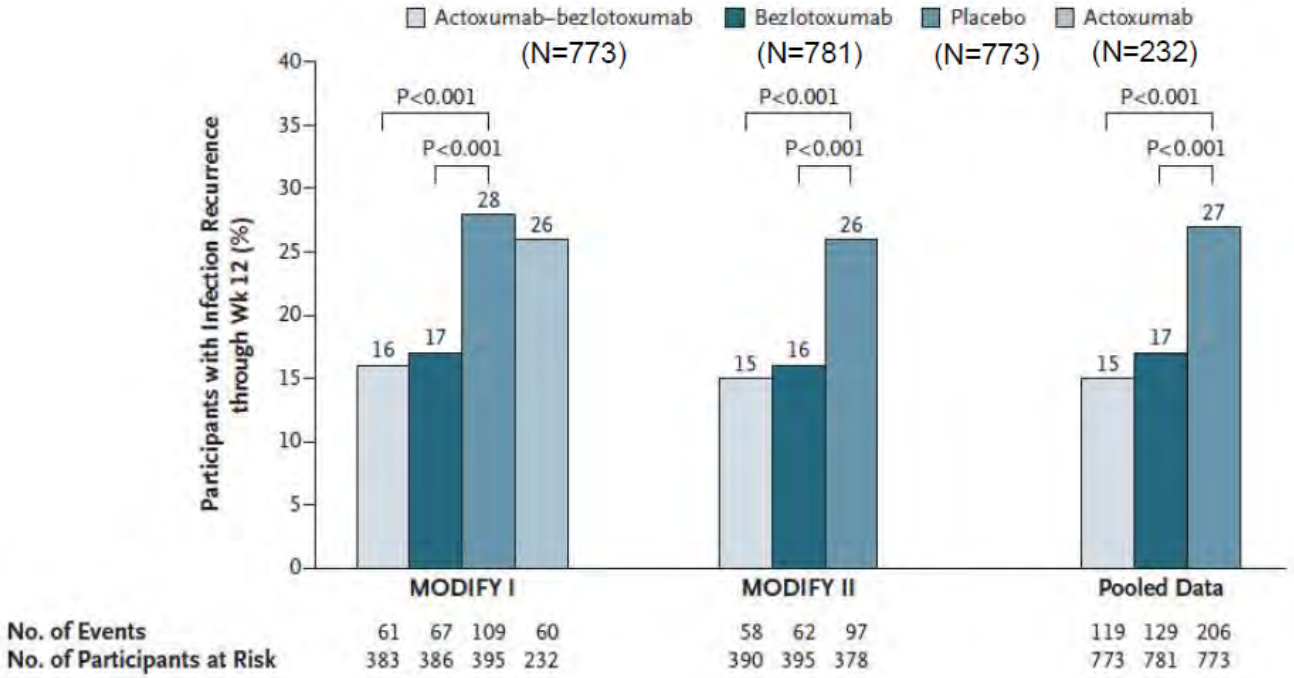


Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.

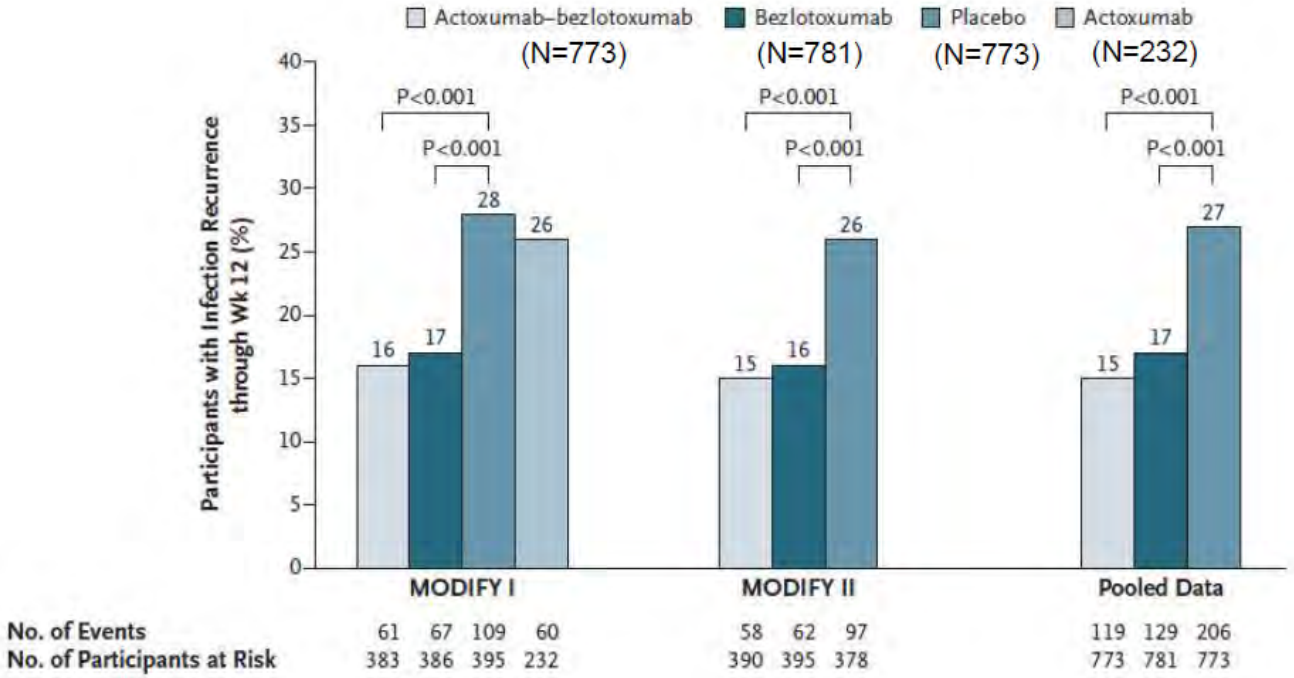
ANTICORPS MONOCLONAUX ANTI-TOXINE DE *C. DIFFICILE (ZINPLAVA)*



- Humanized Mab anti-*C. difficile* toxins A et B de *(MSD)*
  - Anti toxin A (ACTO), anti-toxin B (BEZLO)

Wilcox M. *et al.*, NEJM 2017, 376, 305-317

ANTICORPS MONOCLONAUX ANTI-TOXINE DE *C. DIFFICILE (ZINPLAVA)*



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Prévention

Politique de réduction de l'utilisation des antibiotiques
Dépistage précoce
Isolement géographique
Désinfection quotidienne des locaux (Javel)
Gants pour tout contact
Renforcement de l'hygiène des mains au retrait des gants (lavage au savon doux + GHA)

Conclusion

Fréquent
O27 rare en France (sous surveillance)
EIA seul pas suffisamment sensible. PCR peu être trop sensible
Ne prélevez que les patients diarrhéiques (sans laxatifs)

Vancomycine dans les formes graves (augmentation des posologies)
Place de la fidaxomicine en réa….à définir…intérêts potentiels++

Metronidazole IV seul non, en association peut être, Tyge IV (?)
Lavement à la vanco (prudent?); Ig IV?

Chirurgie à décider au cas par cas → intérêt de l'ileostomie + lavage + vancomycine

Prévention+++

contamination croisée; Lavage des mains, surfaces+++
dépistage précoce (PCR)?
Usage raisonné des antibiotiques
des anti-acides
Immunothérapie des sujets à risque….

Place de la transplantation fécale en réanimation…