JNI 17es Journées Nationales d'Infectiologie

du mardi 7 au jeudi 9 juin 2016
Lille Grand Palais

Lille
et l'interrégion Nord-Pas-de-Calais-Picardie

Tous les patients sont-ils à risque d'ICD et de récidive d'ICD ?

Prof. Pierre TATTEVIN
Maladies Infectieuses et Réanimation Médicale
Hôpital Pontchaillou, CHU Rennes

Déclaration de liens d'intérêt avec les industries de santé en rapport avec le thème de la présentation (loi du 04/03/2002) :

Intervenant : Tattevin Pierre

Titre : Patients à risque d'infections à *Clostridium difficile*

Consultant ou membre d'un conseil scientifique
Astellas

☑ OUI ☐ NON

Conférencier ou auteur/rédacteur rémunéré d'articles ou documents
Astellas

☑ OUI ☐ NON

Prise en charge de frais de voyage, d'hébergement ou d'inscription à des congrès ou autres manifestations

☐ OUI ☑ NON

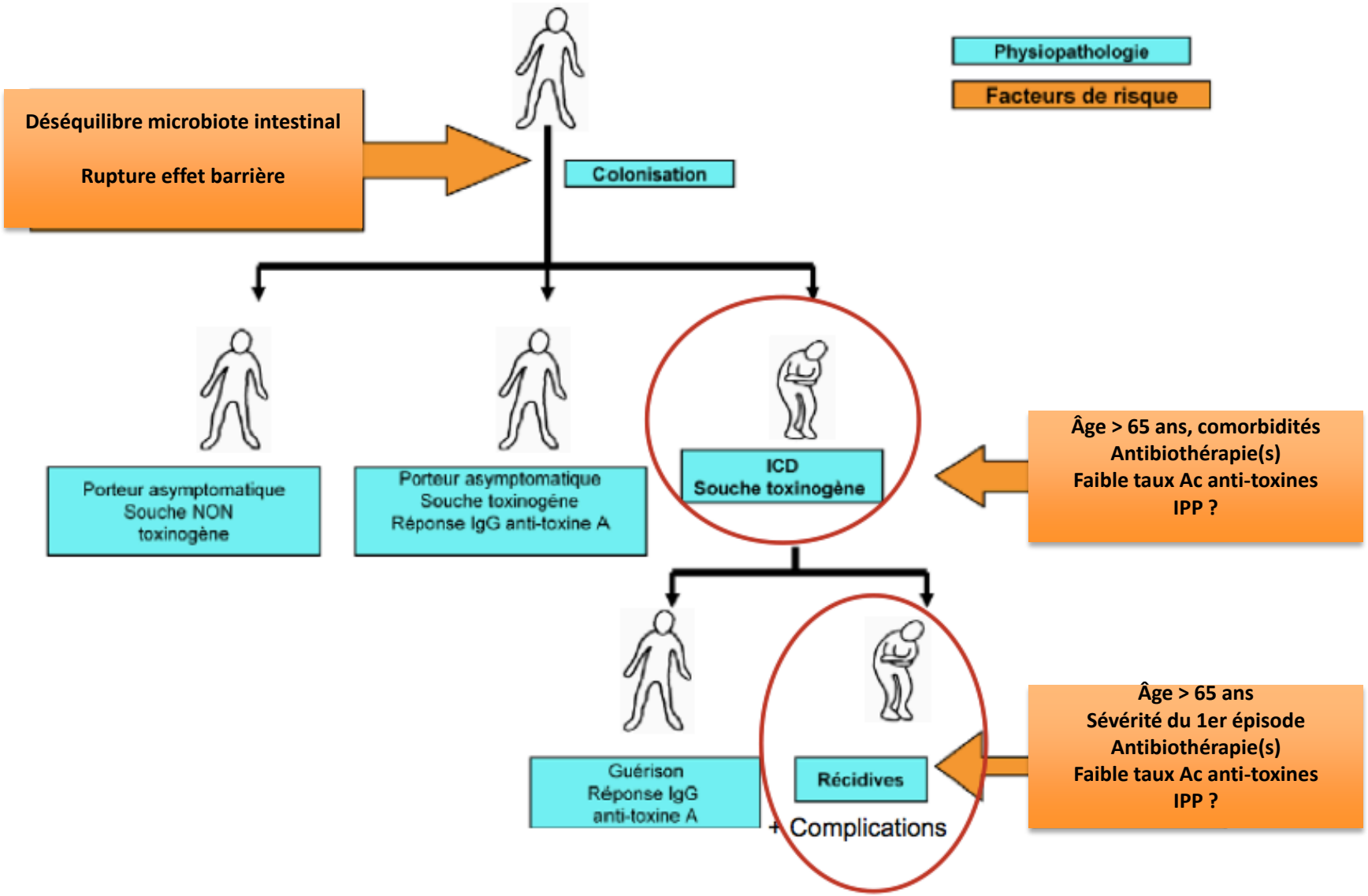
Investigateur principal d'une recherche ou d'une étude clinique
Astellas

☑ OUI ☐ NON

Au menu

- Histoire naturelle
- Facteurs de risque d'ICD
- Facteurs de risque de récurrence d'ICD
- Que faire de ces informations ?

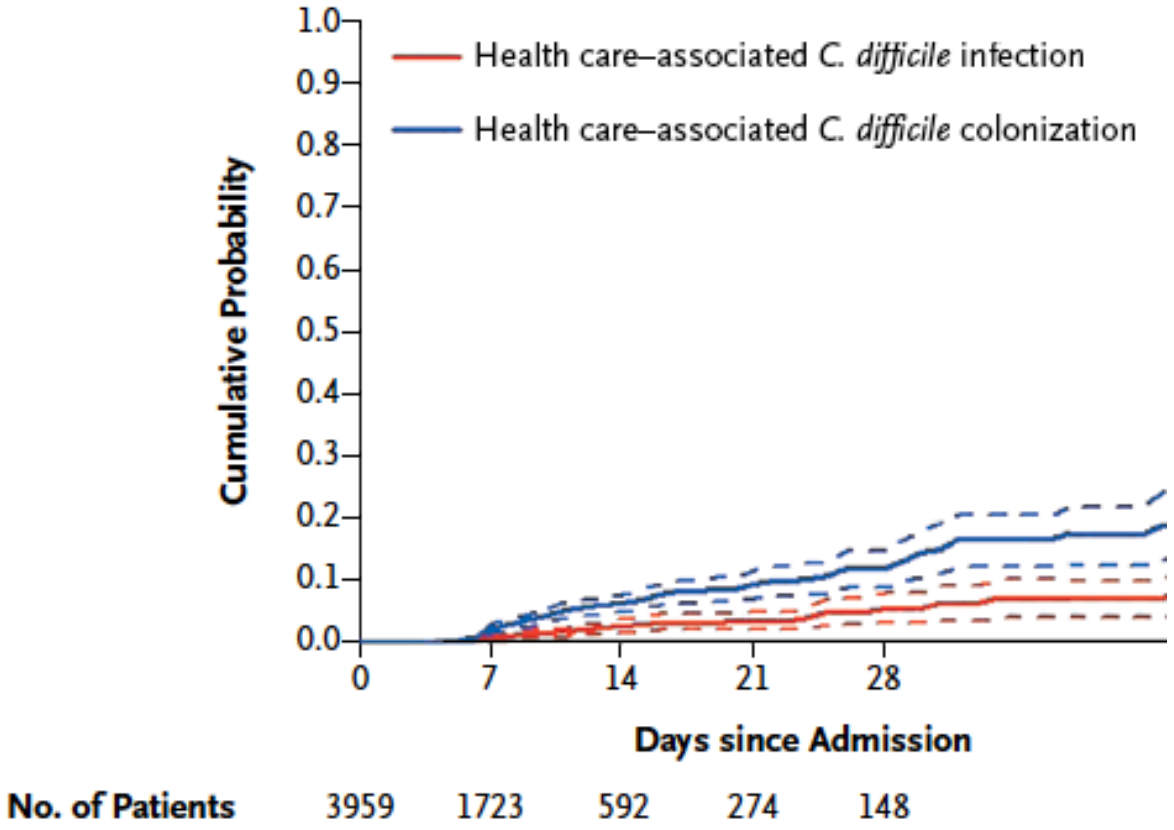
Histoire naturelle



D'après Barbut, Le Monnier et Eckert, Reanimation 2011 ; Kyne L. et al., NEJM 2000 ; Kyne L. et al., Lancet 2001 ; Loo V, NEJM 2011

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

Etude prospective multicentrique Canada/Québec, n = 4 143 adultes (1 prélèvement/semaine)



Loo VG et al. N Engl J Med 2011

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

Variable	Odds Ratio (95% CI)	
	Health Care–Associated *C. difficile* Infection	Health Care–Associated *C. difficile* 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 *C. difficile* ≤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)

Loo VG et al. N Engl J Med 2011

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Loo VG et al. N Engl J Med 2011

Facteurs de risque d'ICD

1. Âge

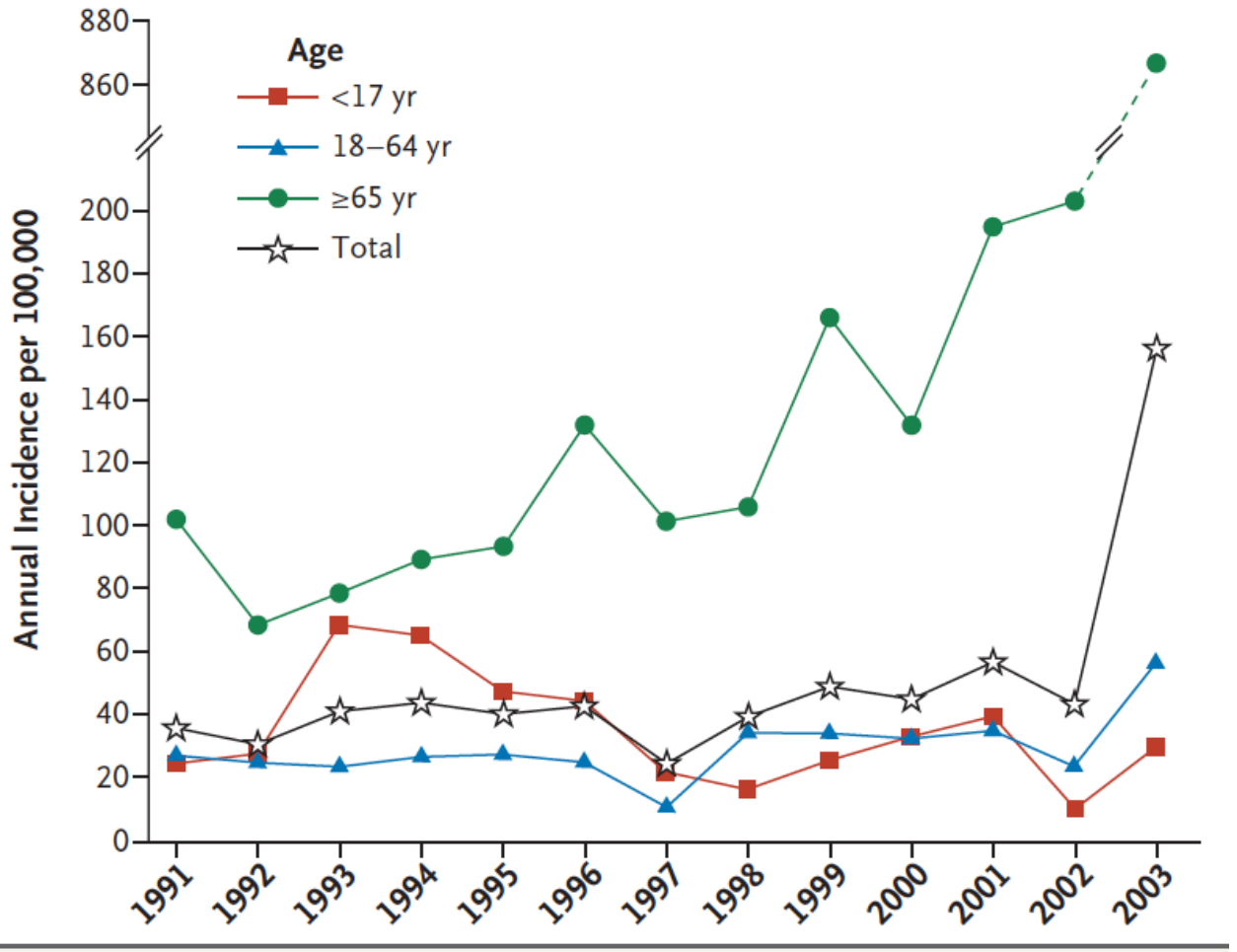

Figure 1. Annual Incidence (per 100,000 Population) of *C. difficile* Infection in Sherbrooke, Quebec, 1991–2003.

Leffler DA et al. N Engl J Med 2015

Facteurs de risque d'ICD

2. Antibiotiques

Class	Association with *C. difficile* Infection
Clindamycin	Very common
Ampicillin	Very common
Amoxicillin	Very common
Cephalosporins	Very common
Fluoroquinolones	Very common
Other penicillins	Somewhat common
Sulfonamides	Somewhat common
Trimethoprim	Somewhat common
Trimethoprim–sulfamethoxazole	Somewhat common
Macrolides	Somewhat common

Leffler DA et al. N Engl J Med 2015

Cumulative Antibiotic Exposures Over Time and the Risk of *Clostridium difficile* Infection

Vanessa Stevens,[1,3,4] Ghinwa Dumyati,[2] Lynn S. Fine,[2] Susan G. Fisher,[3] and Edwin van Wijngaarden[3]

Class—any during hospitalization[g]	CDI positive *n* (%)	CDI negative *n* (%)	Adjusted hazard ratio[i] (95% CI)
Aminoglycosides	22 (9)	837 (8)	0.9 (.3, 3.0)
Cephalosporins			
First- and second-generation	94 (39)	3883 (39)	2.4 (1.4, 4.1)
Third- and fourth-generation	74 (31)	1527 (15)	3.1 (1.9, 5.2)
Clindamycin	34 (14)	876 (9)	1.9 (.8, 4.4)
Macrolides	48 (20)	1266 (13)	1.5 (.7, 3.1)
Metronidazole	37 (15)	981 (10)	0.3 (.1, 0.9)
Penicillins	30 (12)	993 (10)	1.9 (.9, 4.0)
β-Lactamase inhibitor combinations	120 (50)	3013 (30)	2.3 (1.5, 3.5)
Quinolones	132 (55)	3471 (35)	4.0 (2.7, 5.9)
Sulfas	33 (14)	1158 (12)	1.9 (1.1, 3.4)
Vancomycin	120 (50)	2741 (28)	2.6 (1.7, 4.0)

Stevens D et al. Clin Infect Dis 2011

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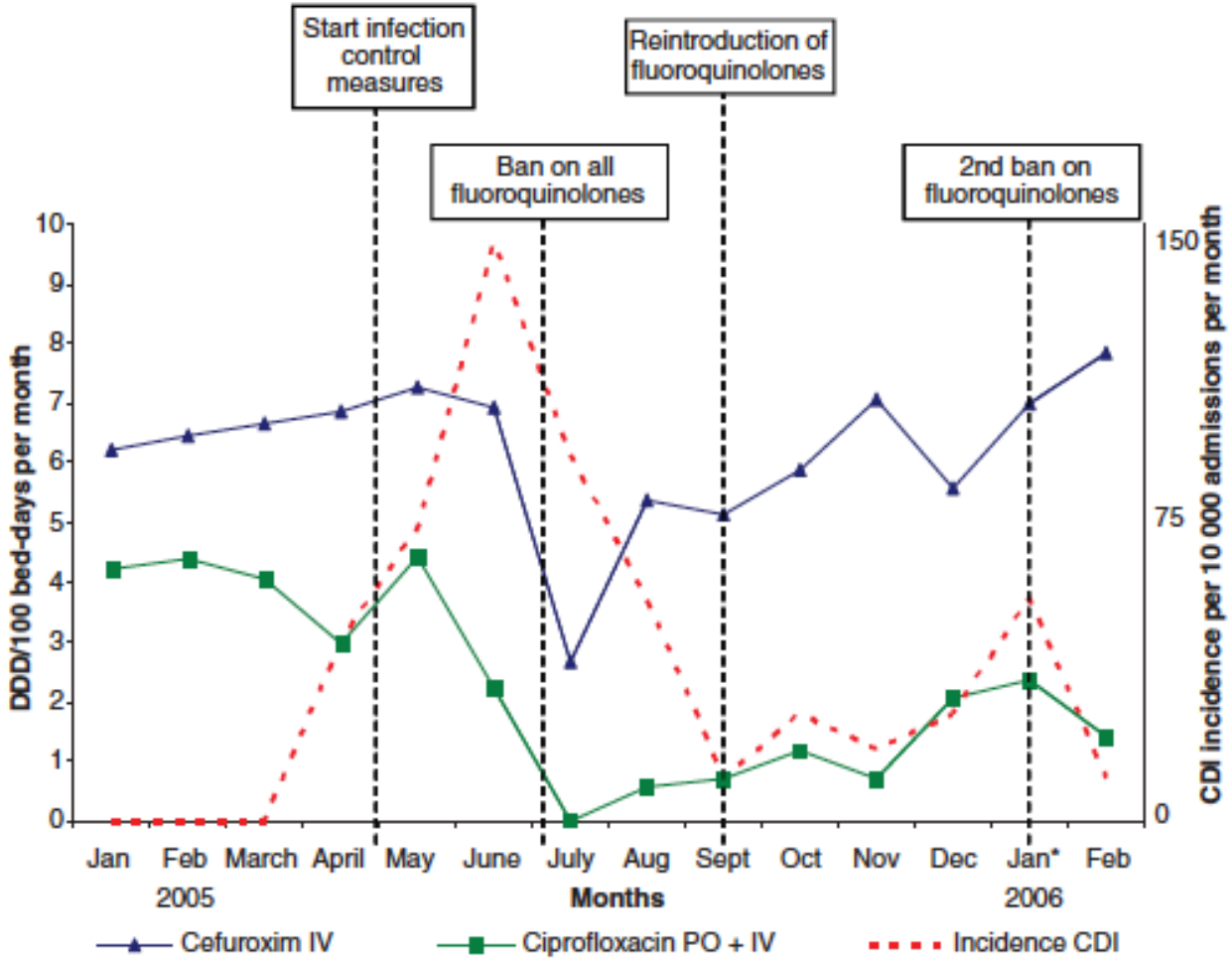
	CDI positive *n* (%)	CDI negative *n* (%)	Adjusted hazard ratio (95% CI)
Defined daily doses[e], median (IQR)	14.8 (21.2)	7.2 (12.3)	—
<3.0	18 (7)	1502 (15)	Ref
3.0 to 7.79	49 (20)	3702 (37)	1.2 (.7, 2.1)
7.80 to 21.0	89 (37)	2952 (30)	2.8 (1.7, 4.6)
>21.0	85 (35)	1757 (18)	5.3 (3.1, 9.0)
Antibiotic days, median (IQR)[f]	14.0 (23.0)	7.0 (9.0)	—
<4	22 (9)	2208 (22)	Ref
4 to 7	41 (17)	3071 (31)	1.4 (.8, 2.4)
8 to 18	87 (36)	3097 (31)	3.0 (1.9, 5.0)
>18	91 (38)	1537 (16)	7.8 (4.6, 13.4)
Number of antibiotics, median (IQR)[f]	3.0 (4.0)	2.0 (2.0)	—
1	31 (13)	3744 (38)	Ref
2	54 (22)	2507 (25)	2.5 (1.6, 4.0)
3 or 4	70 (29)	2505 (25)	3.3 (2.2, 5.2)
5 or more	86 (36)	1157 (12)	9.6 (6.1, 15.1)

Stevens D et al. Clin Infect Dis 2011

Successful combat of an outbreak due to *Clostridium difficile* PCR ribotype 027 and recognition of specific risk factors

S. B. Debast[1], N. Vaessen[2], A. Choudry[2], E. A. J. Wiegers-Ligtvoet[3], R. J. van den Berg[2] and E. J. Kuijper[2]



Debast SB et al. Clin MIcrobiol 2009

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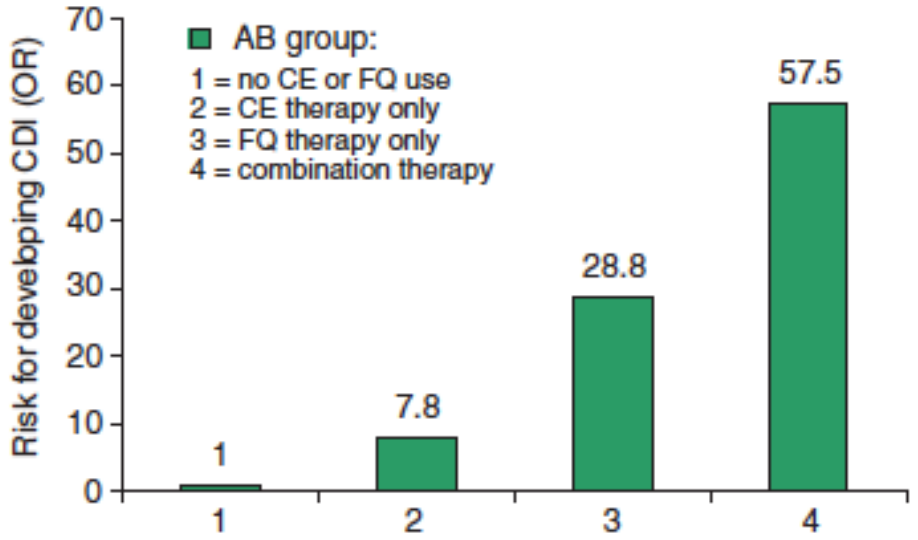


FIG. 2. Risk for development of *Clostridium difficile* infection (CDI), stratified by cephalosporin (CE) and fluoroquinolone (FQ) therapy within the preceding 3 months.

Proportion des ICD attribuables aux céphalosporines, 56%; aux quinolones, 33%

Debast SB et al. Clin MIcrobiol 2009

Bed Occupancy Rates and Hospital-Acquired *Clostridium difficile* Infection: A Cohort Study

Lauren C. Ahyow, MBChB, MPH, MFPH;[1] Paul C. Lambert, PhD;[2,3] David R. Jenkins, MBBS, MSc, FRCPath;[4] Keith R. Neal, FRCP, FFPHM, DM;[5] Martin Tobin, PhD, FFPH[2,6,7]

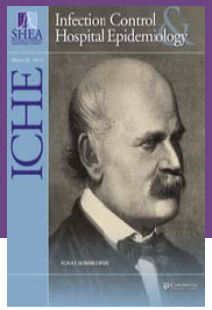


TABLE 4. Adjusted Hazard Ratios (HRs) for *Clostridium difficile* Infection Comparing Bed Occupancy

Level of bed occupancy (%)	Adjusted HR (95% CI)
0–69.9	(1)
70–79.9	1.30 (0.95–1.76)
80–89.9	1.56 (1.18–2.04)
90–99.9	1.52 (1.16–1.98)
100	1.55 (1.19–2.01)

NOTE. HR adjusted for ward clustering (similarities between patients on the same ward), age, antibiotic policy period, and ward type. CI, confidence interval.

Ahyow LC et al. Infect Control Hosp Epidemiol 2013

Récidives

- **La récidive d'ICD est banale: 25% des cas dans les 30 jours suivant le traitement dans les essais cliniques (moins dans la 'vraie vie' ?)**

- **La récidive semble être liée à une association de :**
  - Echec de **rétablissement du microbiote intestinal**
  - Persistance intra-luminale de **spores de *C. difficile***
  - **Réponse immunitaire défaillante** de l'hôte à l'organisme infectieux et/ou à ses toxines

Facteurs de risque de récidive d'ICD

La spirale des récurrences

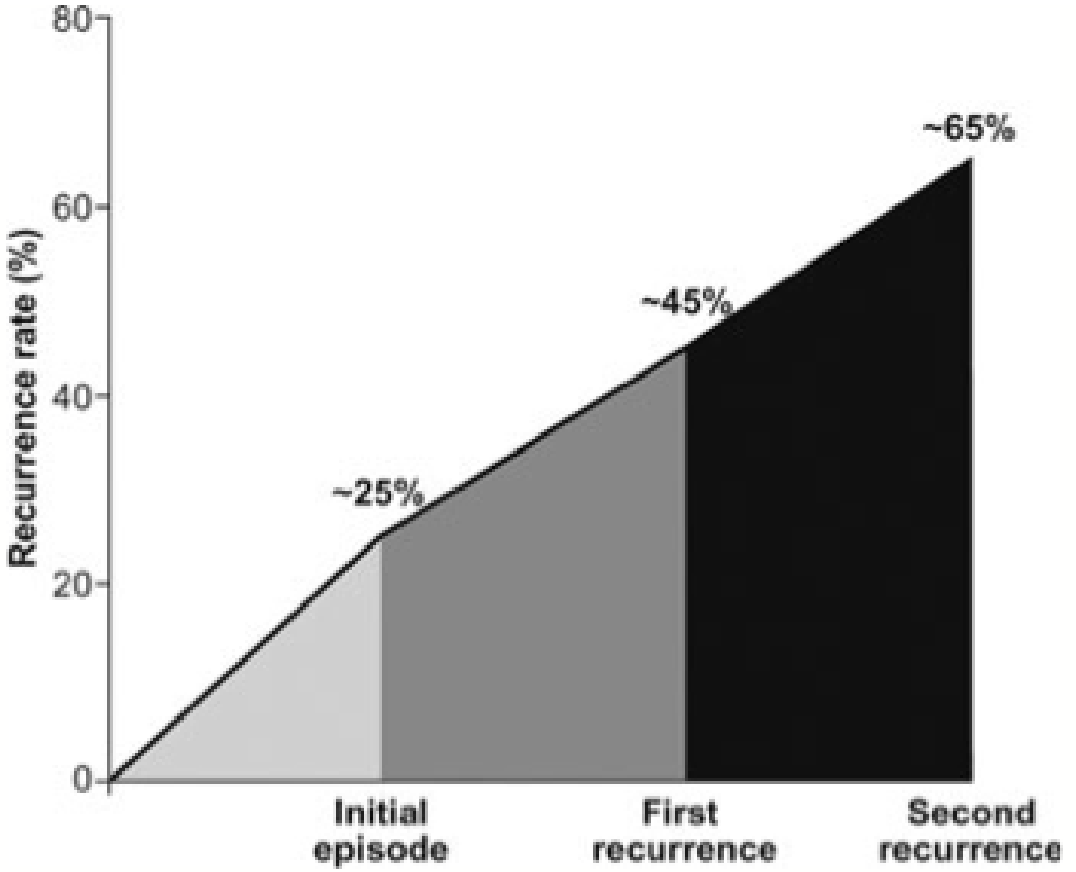
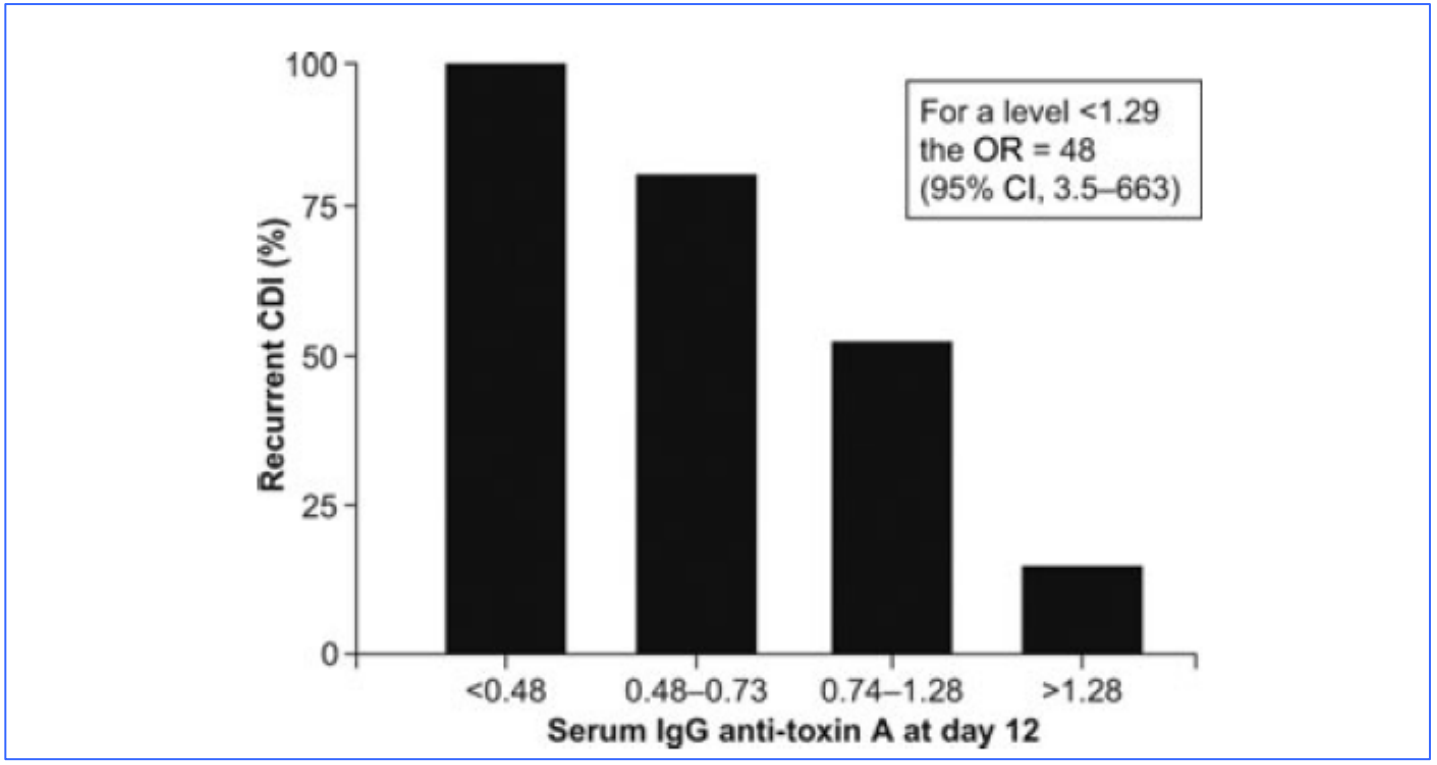


FIG. 2. Frequency of recurrent *Clostridium difficile* infection (CDI) following an initial episode and first and second recurrence

Kelly CP. Clin Microbiol Infect 2012

L’importance de l’immunité humorale

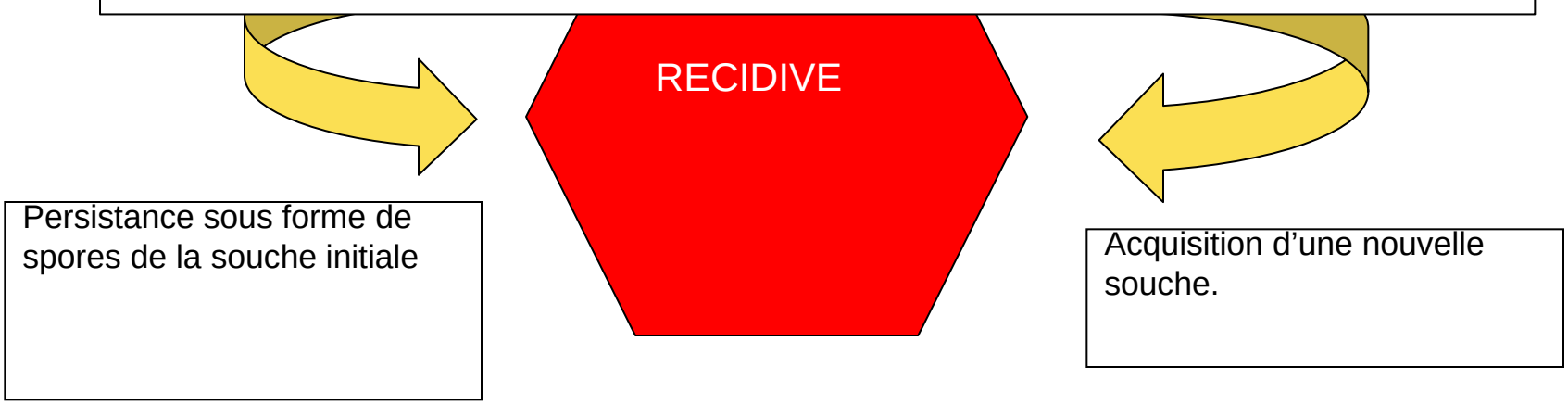


Kelly CP. Clin Microbiol Infect 2012

Récidives : rechute ou ré-infection ?

La récidive n'est pas un problème secondaire à une résistance aux antibiotiques:

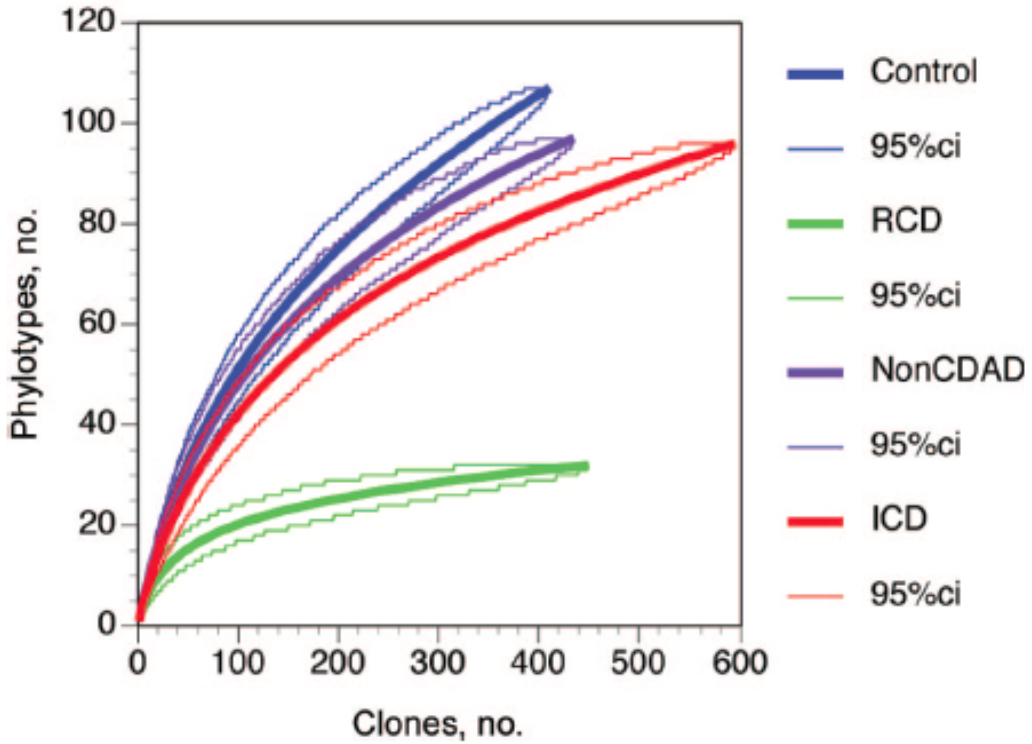
- **Tests *in vitro***
- **Réponse clinique préservée au traitement antérieur**



Bauer et al. Clin Microbiol Infect 2009; 15:1067-79

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

Ju Young Chang,[1,a] Dionysios A. Antonopoulos,[1,a] Apoorv Kalra,[3] Adriano Tonelli,[3] Walid T. Khalife,[2] Thomas M. Schmidt,[1] and Vincent B. Young[1,3,4,a]

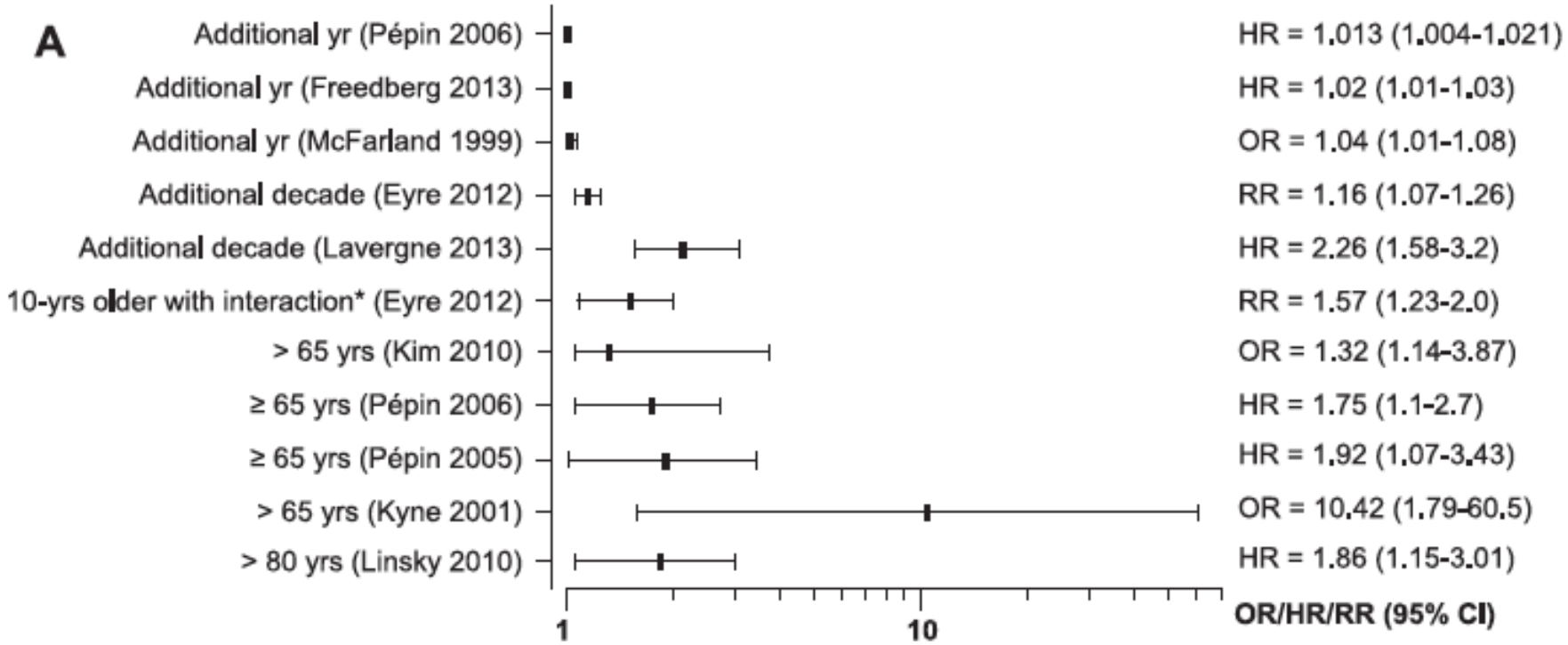


En comparaison avec le groupe contrôle et un premier épisode d'ICD, les patients ayant une ICD récidivante ont une diminution significative de la diversité des espèces du microbiote intestinal.

Young Chang J et al. J Infect Dis 2008

Risk Factors for Recurrence, Complications and Mortality in *Clostridium difficile* Infection: A Systematic Review

Claire Nour Abou Chakra, Jacques Pepin, Stephanie Sirard, Louis Valiquette*



Forest plots of associations of age, antibiotic use and PPIs with recurrence of CDI.

Abou Chakra CN et al. PLoS One 2014

Risk Factors for Recurrence, Complications and Mortality in *Clostridium difficile* Infection: A Systematic Review

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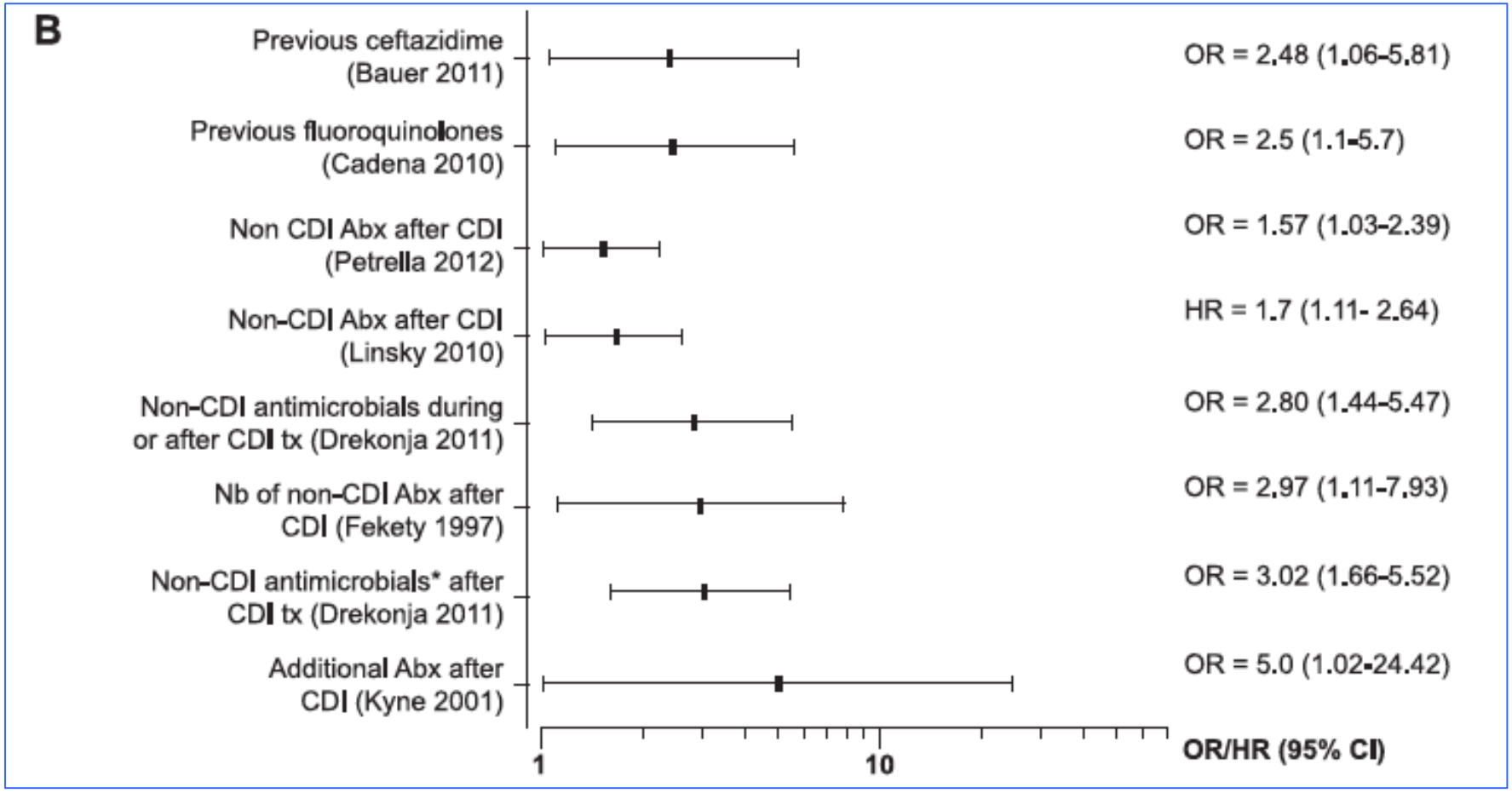

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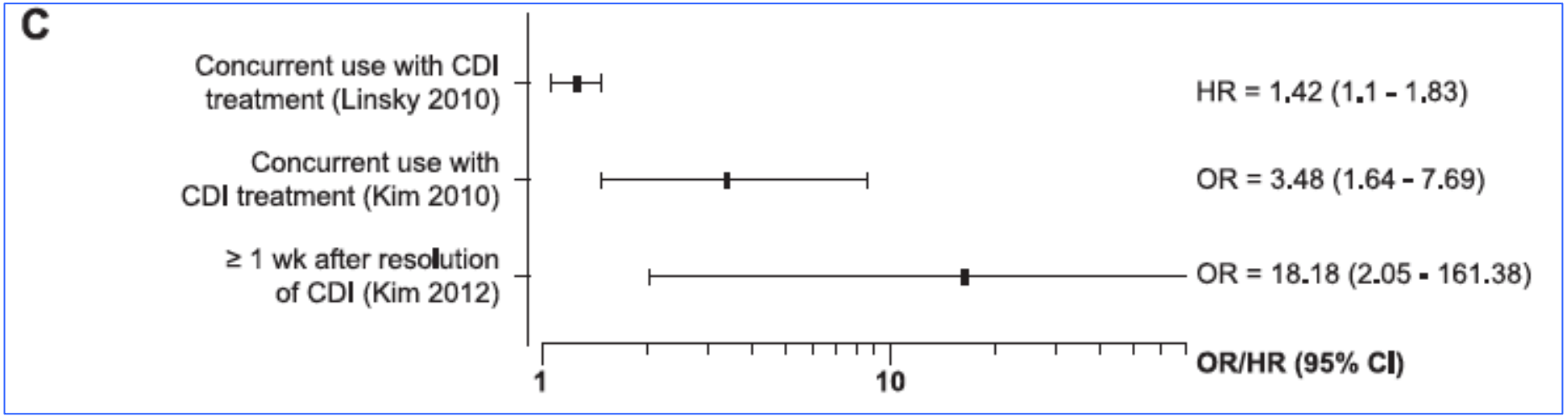


Forest plots of associations of age, antibiotic use and PPIs with recurrence of CDI.

Abou Chakra CN et al. PLoS One 2014

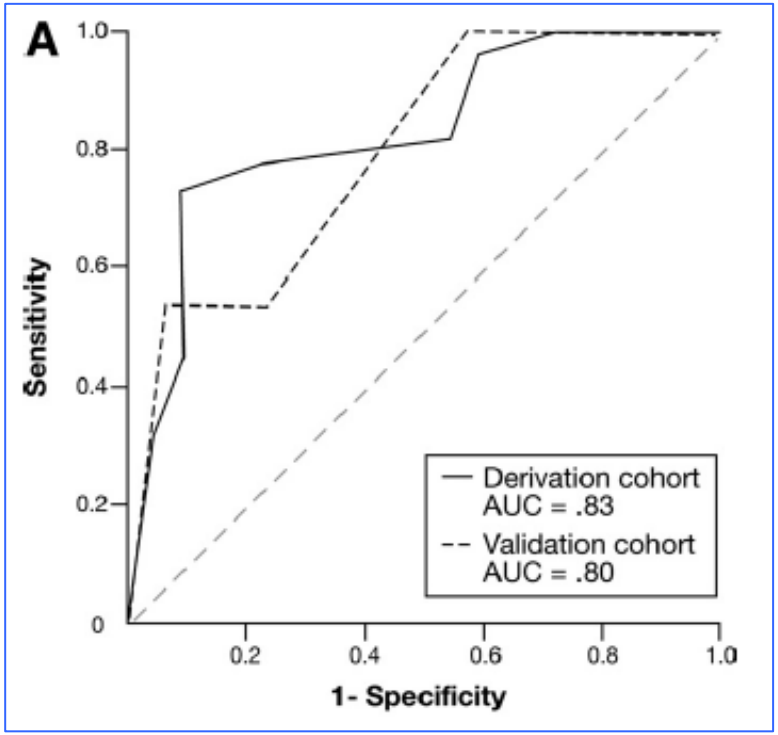
Prospective Derivation and Validation of a Clinical Prediction Rule for Recurrent *Clostridium difficile* Infection

MARY Y. HU,* KIANOOSH KATCHAR,* LORRAINE KYNE,‡ SEEMA MAROO,* SANJEEV TUMMALA,* VALLEY DREISBACH,* HUA XU,* DANIEL A. LEFFLER,* and CIARÁN P. KELLY*

Table 2. Predictors of Recurrent *C difficile* Infection in the Derivation Cohort

Variable	β coefficient	OR	95% CI	Points
Age >65 *y*	1.81	6.12	1.03–36.58	1
Horn index severe or fulminant	2.26	9.56	1.19–76.68	1
Additional antibiotic use	2.31	10.03	1.47–68.26	1

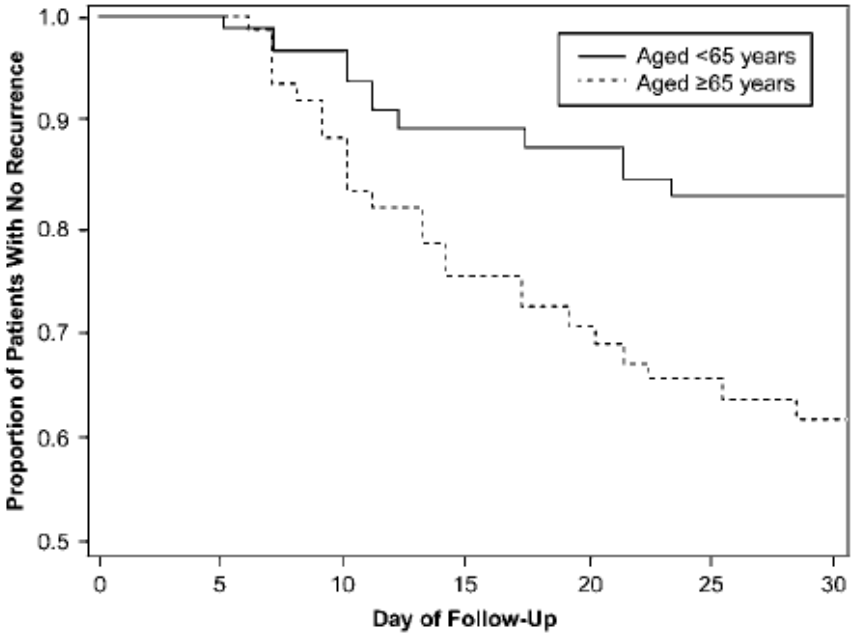
	Recurrence			
	Predicted (derivation cohort) (n = 44)		Observed (validation cohort) (n = 64)	
Score	n	%	n	%
0	0/7	0	0/9	0
1	5/15	33.3	6/36	16.7
2	10/14	71.4	5/16	31.3
3	7/8	87.5	2/3	66.7

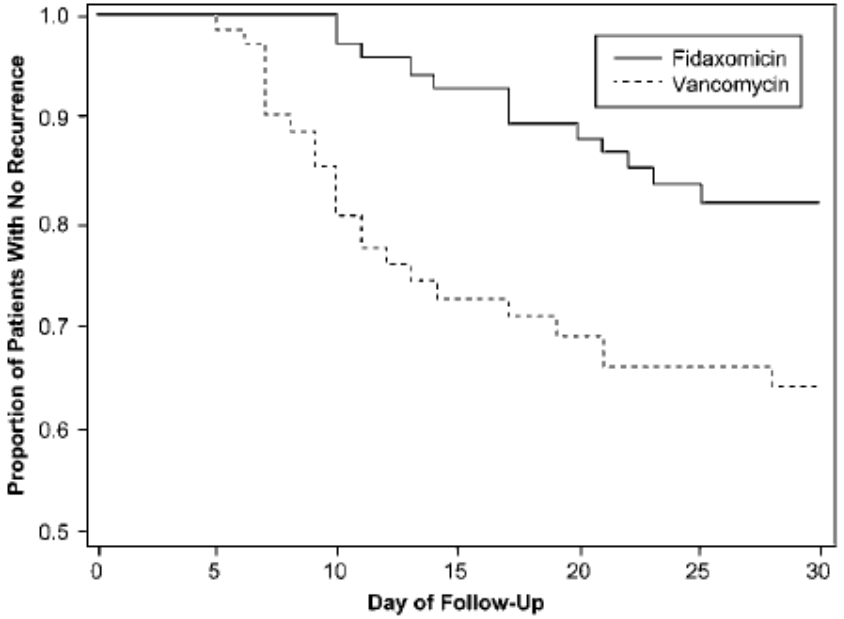


Hu MY et al. Gastroenterology 2009

Treatment of First Recurrence of *Clostridium difficile* Infection: Fidaxomicin Versus Vancomycin

Oliver A. Cornely,[1] Mark A. Miller,[2] Thomas J. Louie,[3,4] Derrick W. Crook,[5,6] and Sherwood L. Gorbach[7,8]





Cornely O et al. Clin Infect Dis 2012

Conclusions

- **FDR hétérogènes selon l'étape (colonisation => ICD => récidive)**

- **Deux FDR non modifiables puissants pour ICD & récidive**
  - **Âge** (seuil 65 ans)
  - **Comorbidités**

- **FDR modifiables**
  - Antibiothérapie avec **effet dose & classe** (céphalos/quinolones)
  - Possiblement les IPP

- **Scores prédictifs de récidive pour affiner les choix de traitement ?**

Merci de votre attention !