

Infections à *Clostridium difficile*

Prise en charge des formes graves

G. Nitenberg



Évolution récente des infections à CD

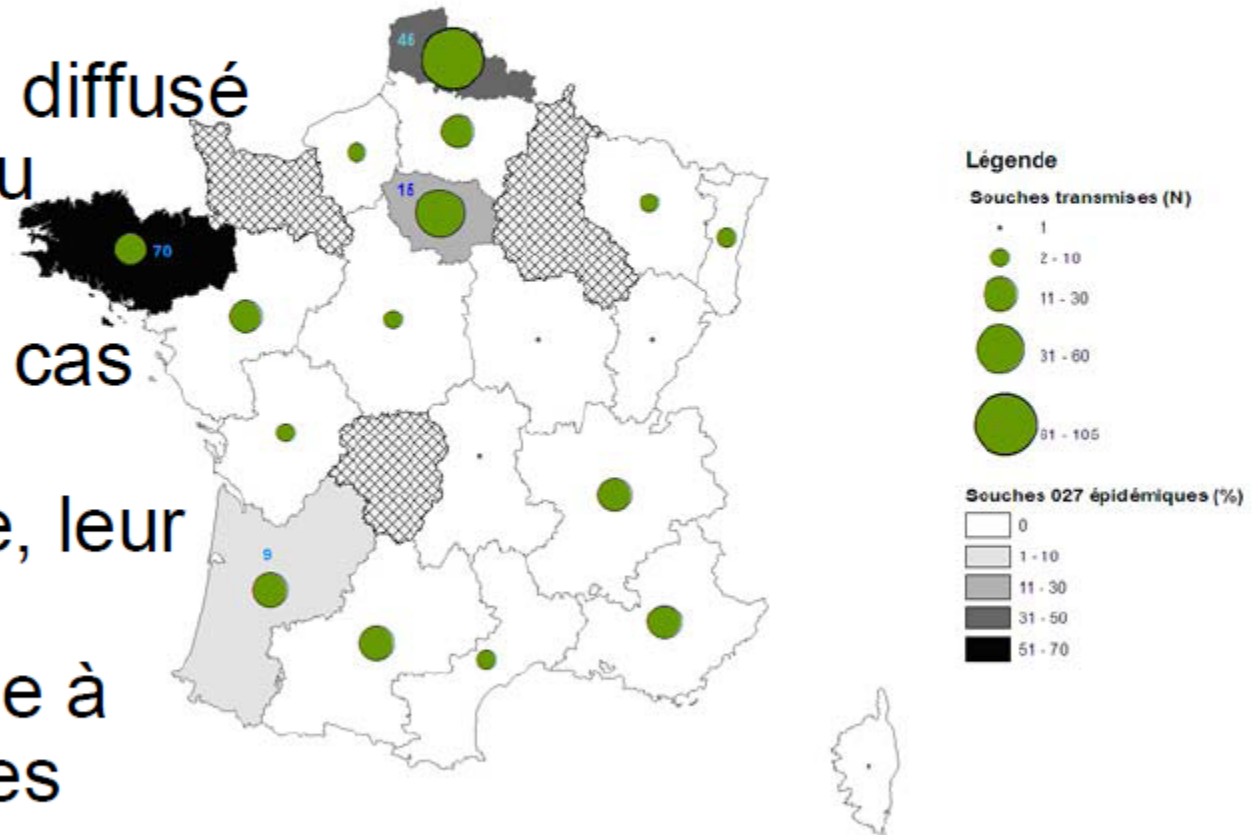
- Augmentation de l'incidence au Québec et USA
 - x 10 dans la cohorte des patients de plus de 65 ans
- Diffusion épidémique en 2005 en Europe
- *Augmentation de la fréquence des cas sévères*
- Augmentation de la mortalité attribuable
- Moindre réponse au métronidazole
- Augmentation des récives et des échecs thérapeutiques

*Loo VG et al, N Engl J Med 2005
McDonald LC et al, N Engl J Med 2005
Warny et al. Lancet 2005*

Infections épidémiques à *Clostridium difficile*

Au 1^{er} juillet 2009 :

- La souche 027 a diffusé sur l'ensemble du territoire
- Les épisodes de cas groupés restent d'ampleur limitée, leur contrôle étant probablement liée à l'appropriation des recommandations

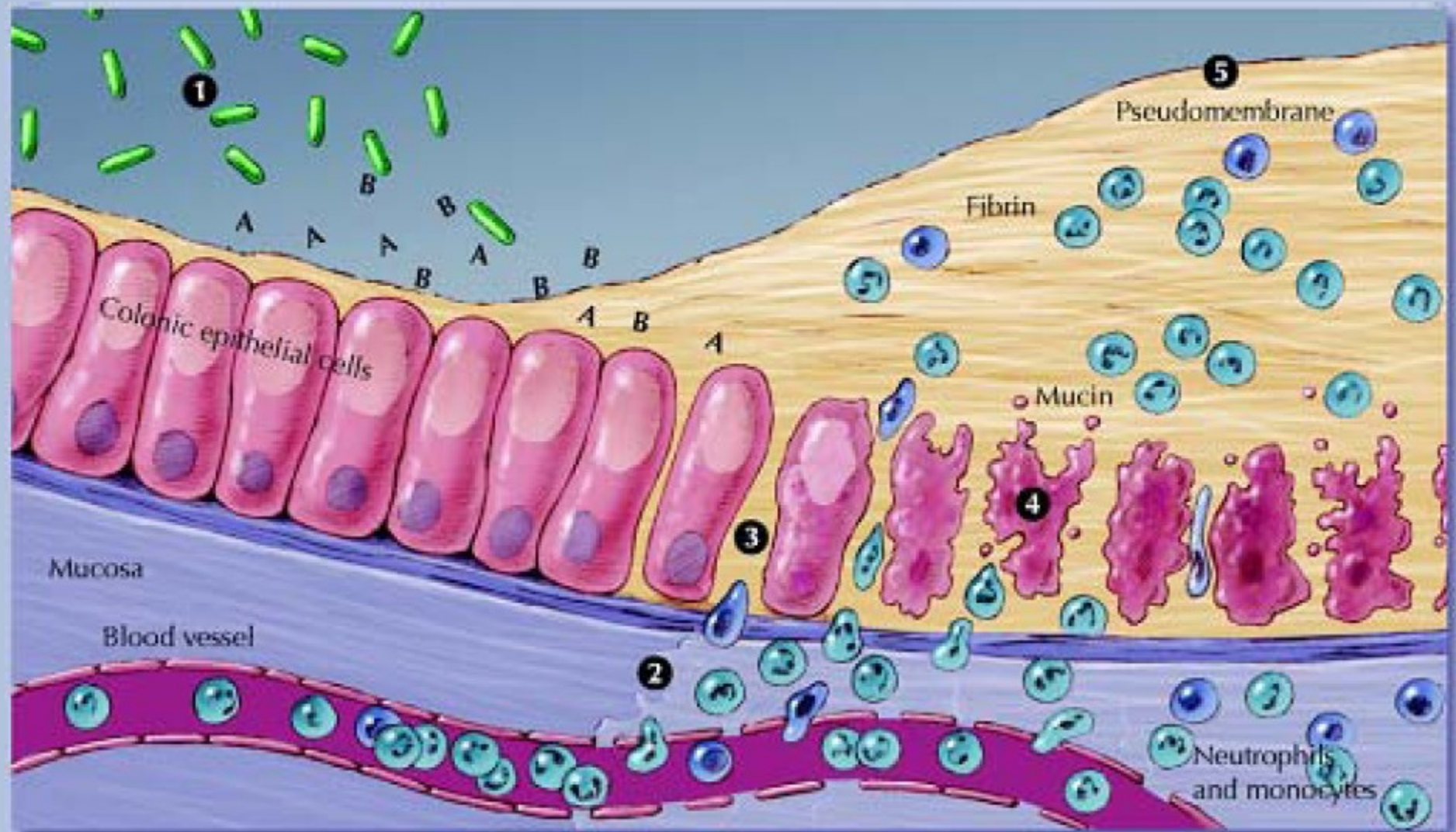


Colite pseudo membraneuse

- Une complication grave de l'antibiothérapie
- (TROP) souvent méconnue
- Un déséquilibre de la flore : une prolifération de *Clostridium difficile* (toxine => nécrose muqueuse)

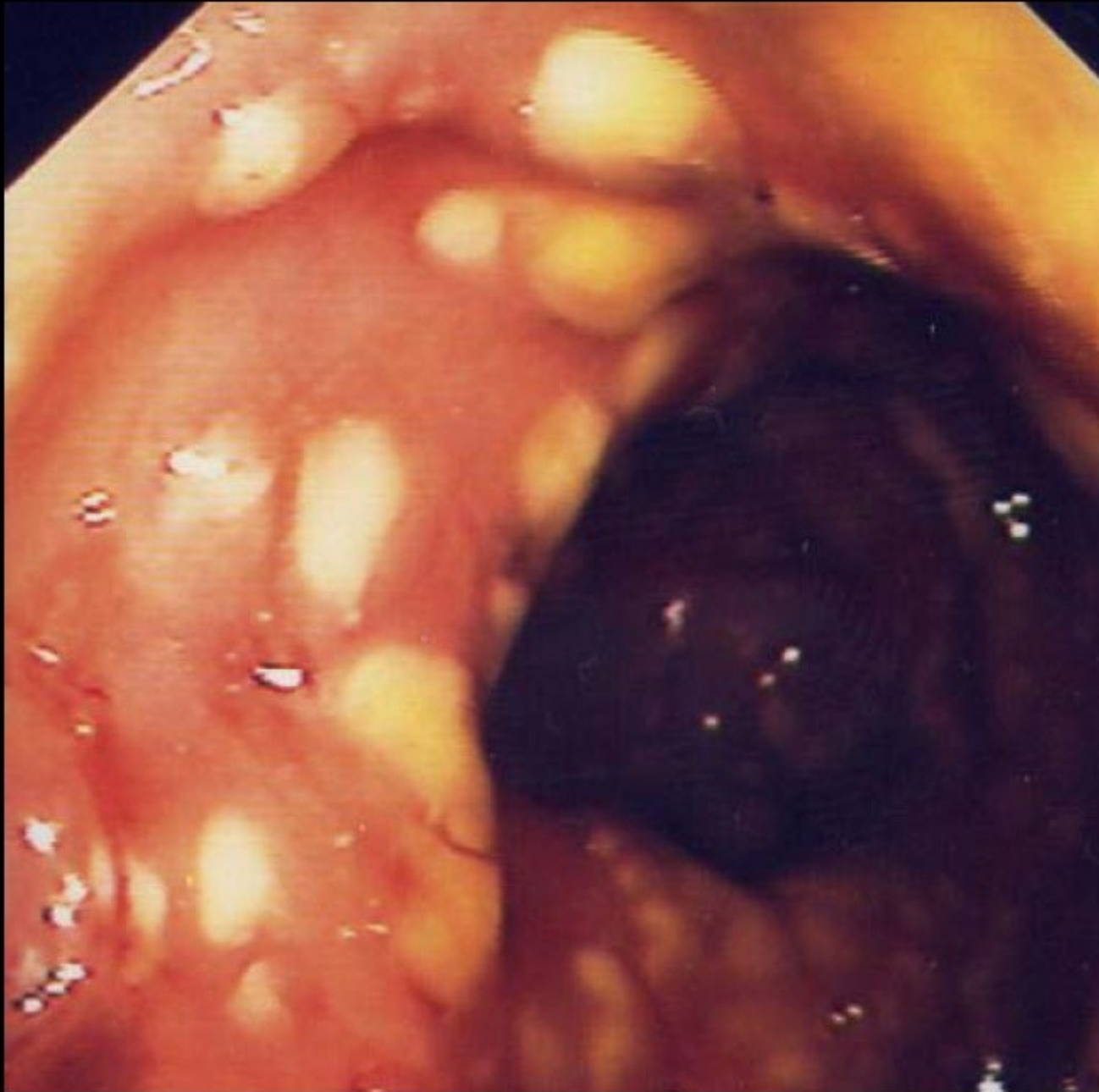
Infection à *Clostridium difficile*

Colites pseudo-membraneuses

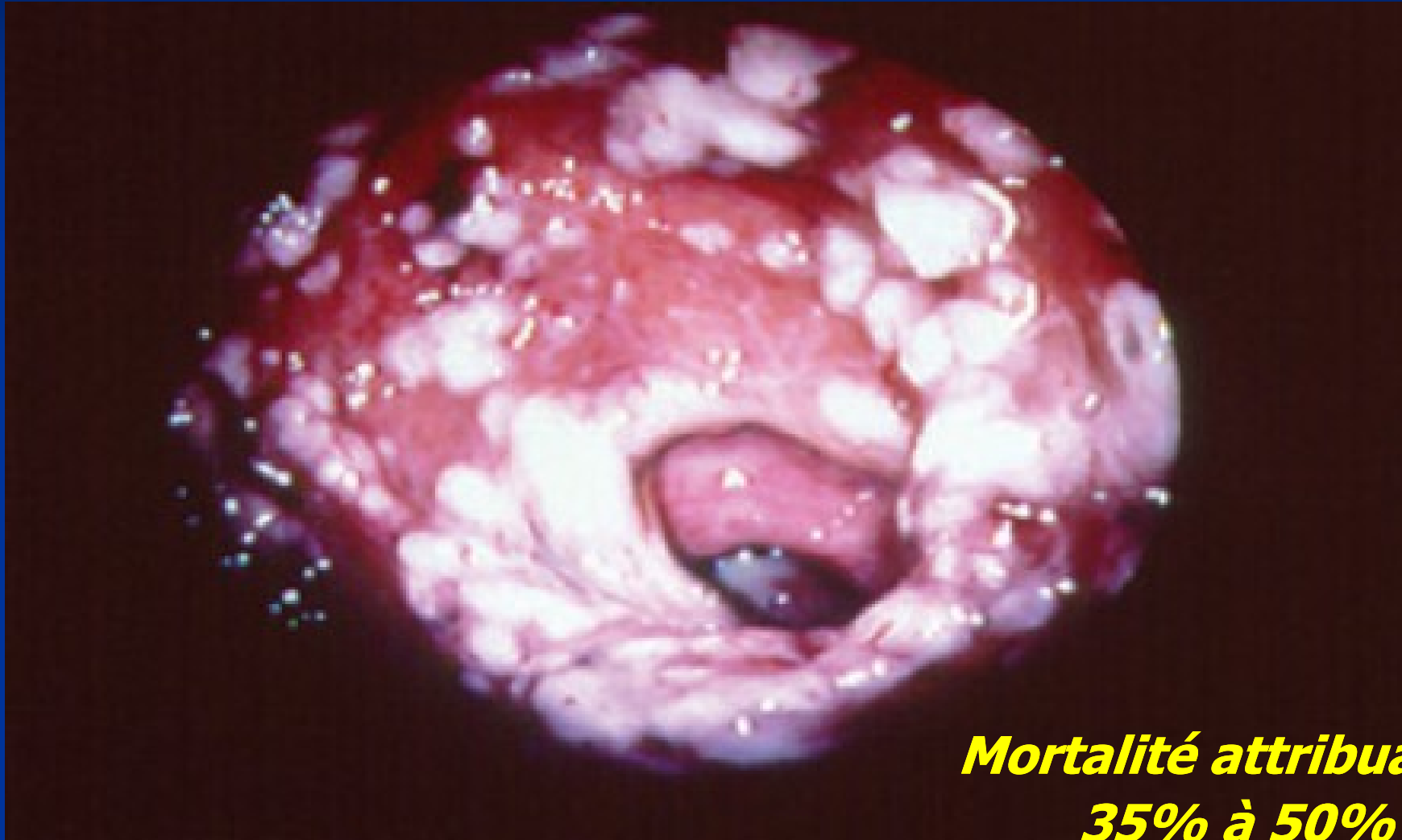


Colite pseudomembraneuse à *C. difficile*

- **Pathologie grave de début brutal**
 - diarrhée profuse (> 7 selles /j)
 - fièvre (75%) - douleurs abdominales (70%)
 - hyperleucocytose (40%) - déshydratation
 - hypoalbuminémie
- **Présence de leucocytes fécaux = 50%**
- **Endoscopie : pseudomembranes** (colon + rectum)
 - plaques jaunes friables (qq mm à 2 cm)

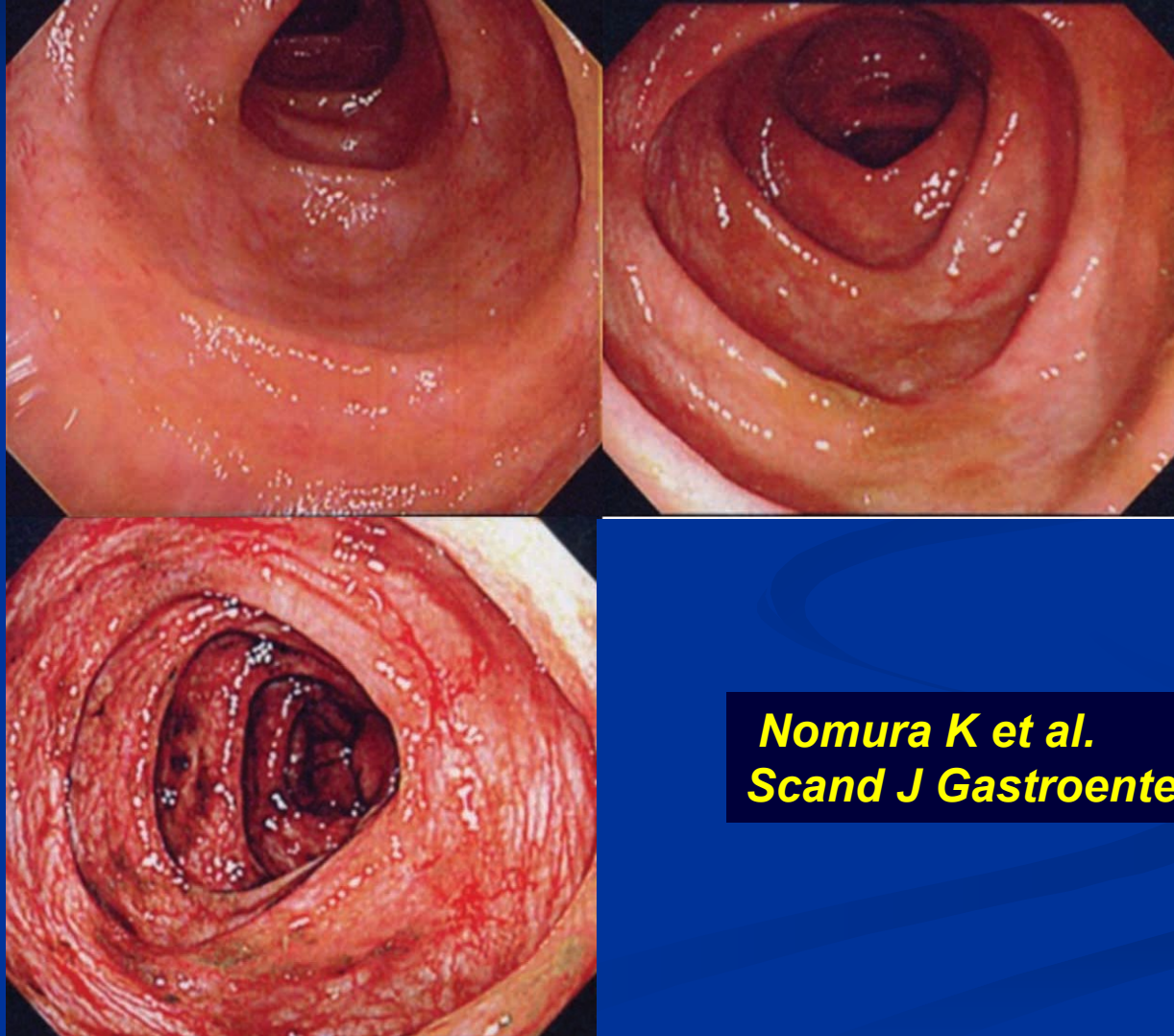


Colite pseudo-membraneuse à *C. difficile*



**Mortalité attribuable :
35% à 50%**

Absence de fausses membranes chez l'immunodéprimé (aplasie)



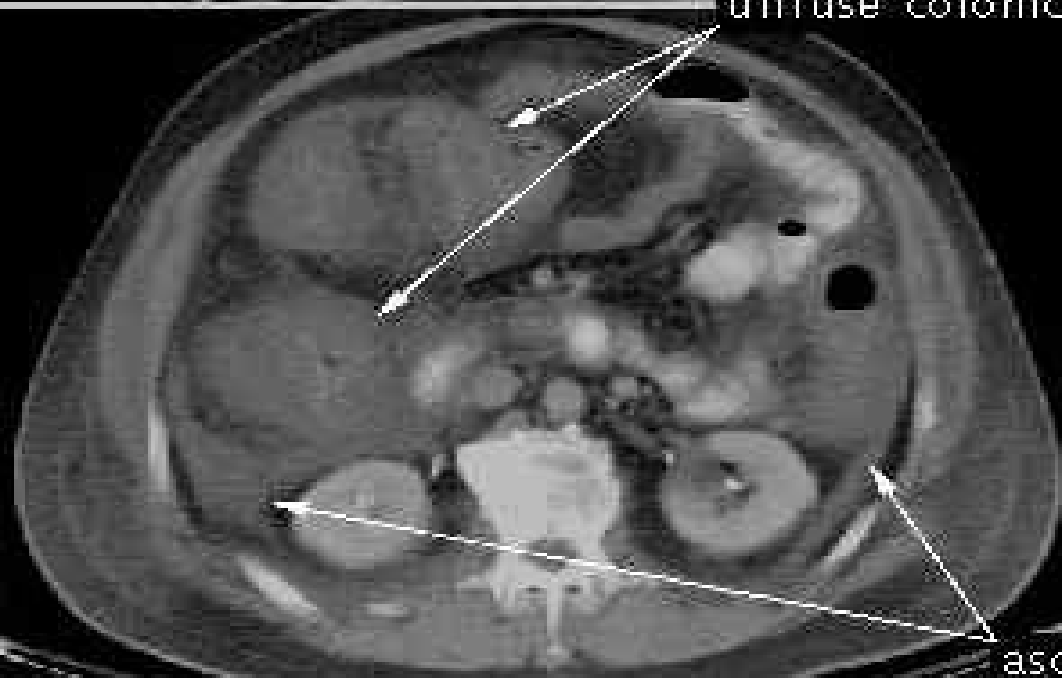
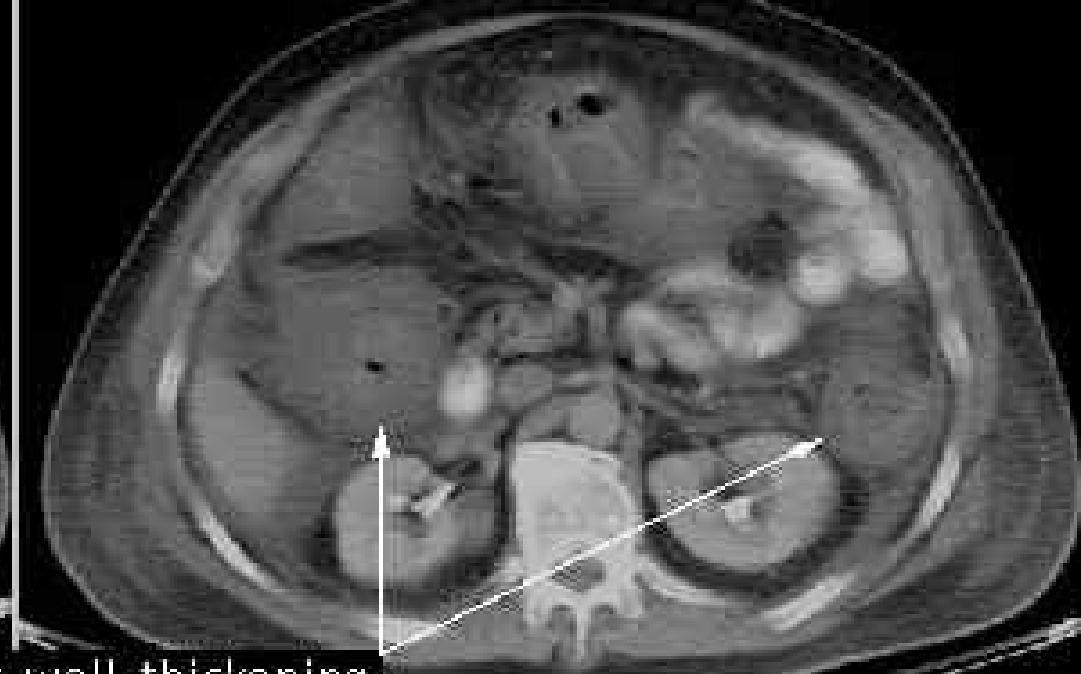
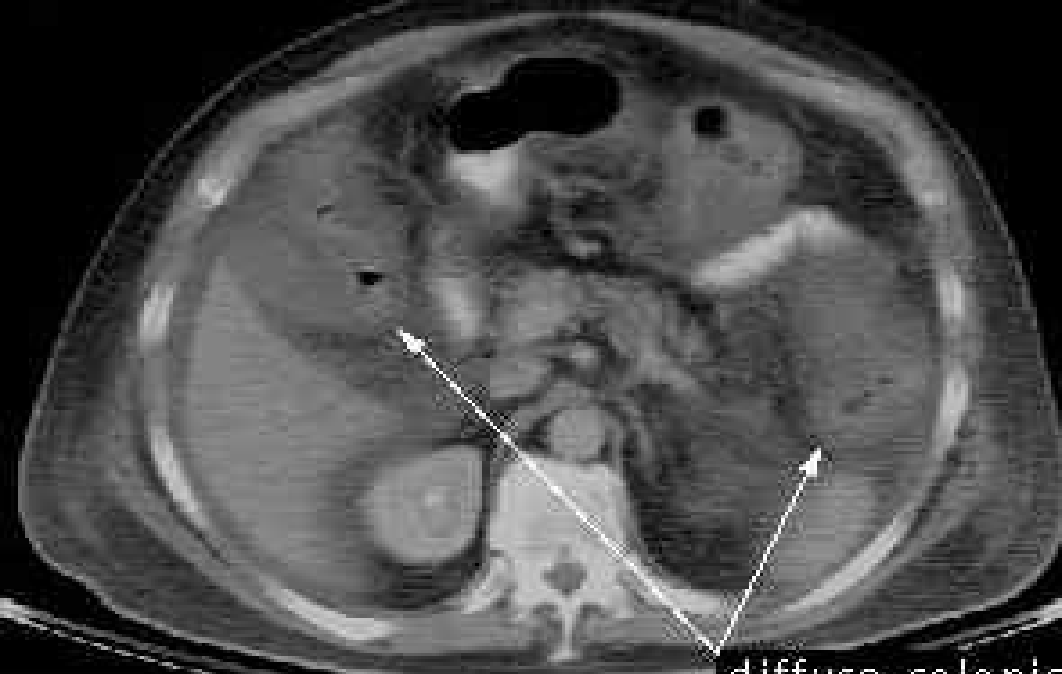
**Nomura K et al.
Scand J Gastroenterol 2009; 44: 74-8**

Complications

Mégacôlon
Perforation
Choc septique
Décès

Récidive





diffuse colonic wall thickening

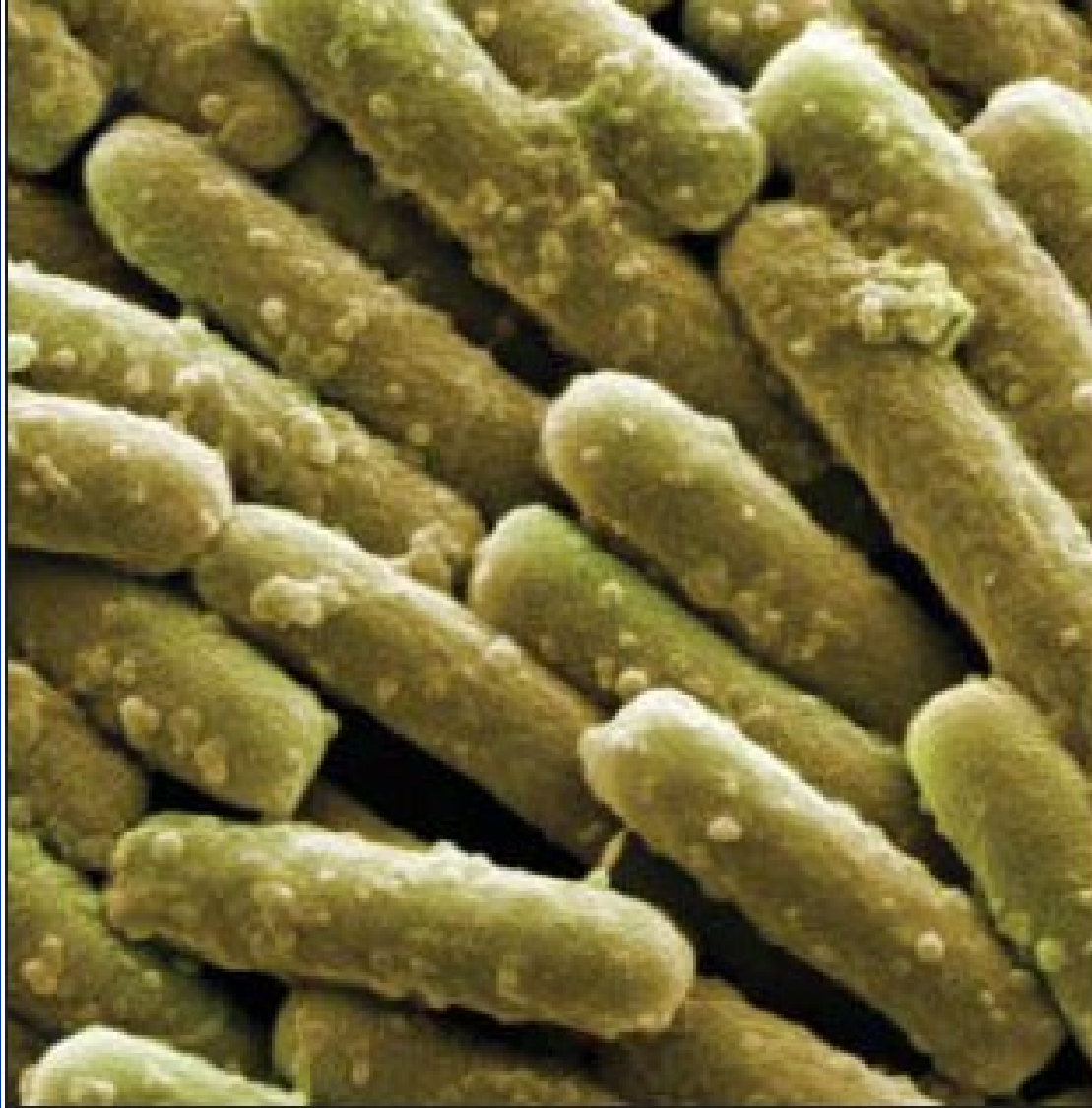
ascites



Risk factors for **severe** CD disease

Table 5. Binary logistic regression model to identify independent associations of laboratory values and pertinent variables with severe CDAD, 285 patients*

Variable	OR	95% CI
Age >70 y	3.24†	1.42–7.38
Female	1.16	0.51–2.62
Antimicrobial-drug use	1.04	0.35–3.12
Malignancy	0.90	0.37–2.18
Chemotherapy	1.02	0.27–3.92
Steroid use	1.13	0.48–2.68
Hemodialysis	0.5	0.8–3.01
Max leukocyte count >20,000/μL	2.77†	1.28–6.0
Max glucose level >150 mg/dL	1.46	0.63–3.4
ALT >40 U/L	1.47	0.58–3.7
Min albumin level <2.5 g/dL	3.44†	1.56–7.6
Max creatinine level >2 mg/dL	2.47†	1.04–5.8
Small bowel obstruction or ileus	3.06‡	1.00–9.5
Abnormal abdominal CT scan	13.54†	5.72–32.07
Prior hospitalization	1.39	0.61–3.18
SNF/rehabilitation stay	1.11	0.46–2.68



New recommendations advise that treatment of *Clostridium difficile* infection should be based on disease severity. A once-uncommon strain has mutated, causing more severe disease.

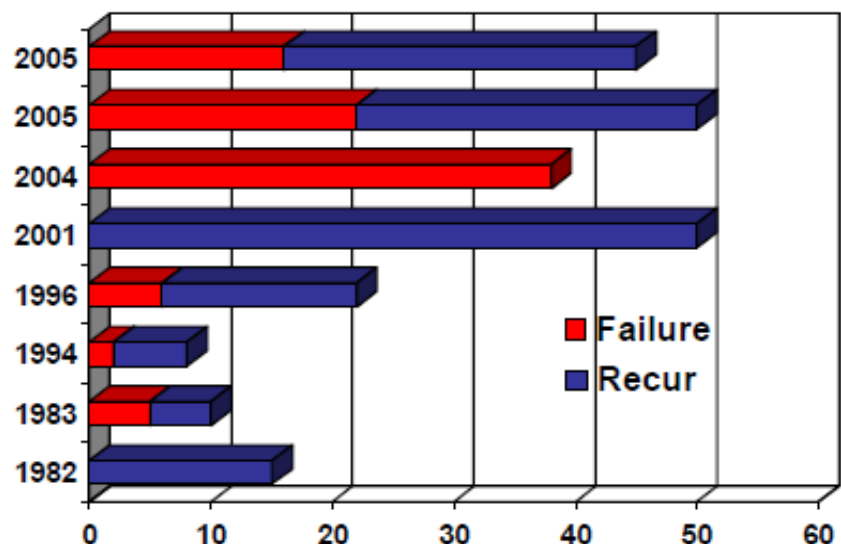
Voelker R JAMA 2010

Evolution récente des infections à *C. difficile* en Amérique du Nord (2003-2008)

- moins bonne réponse au métronidazole
 - ✓ Plus d'échecs thérapeutiques
(9.6% en 2002 vs 25.7% en 2004)
 - ✓ Plus de rechutes

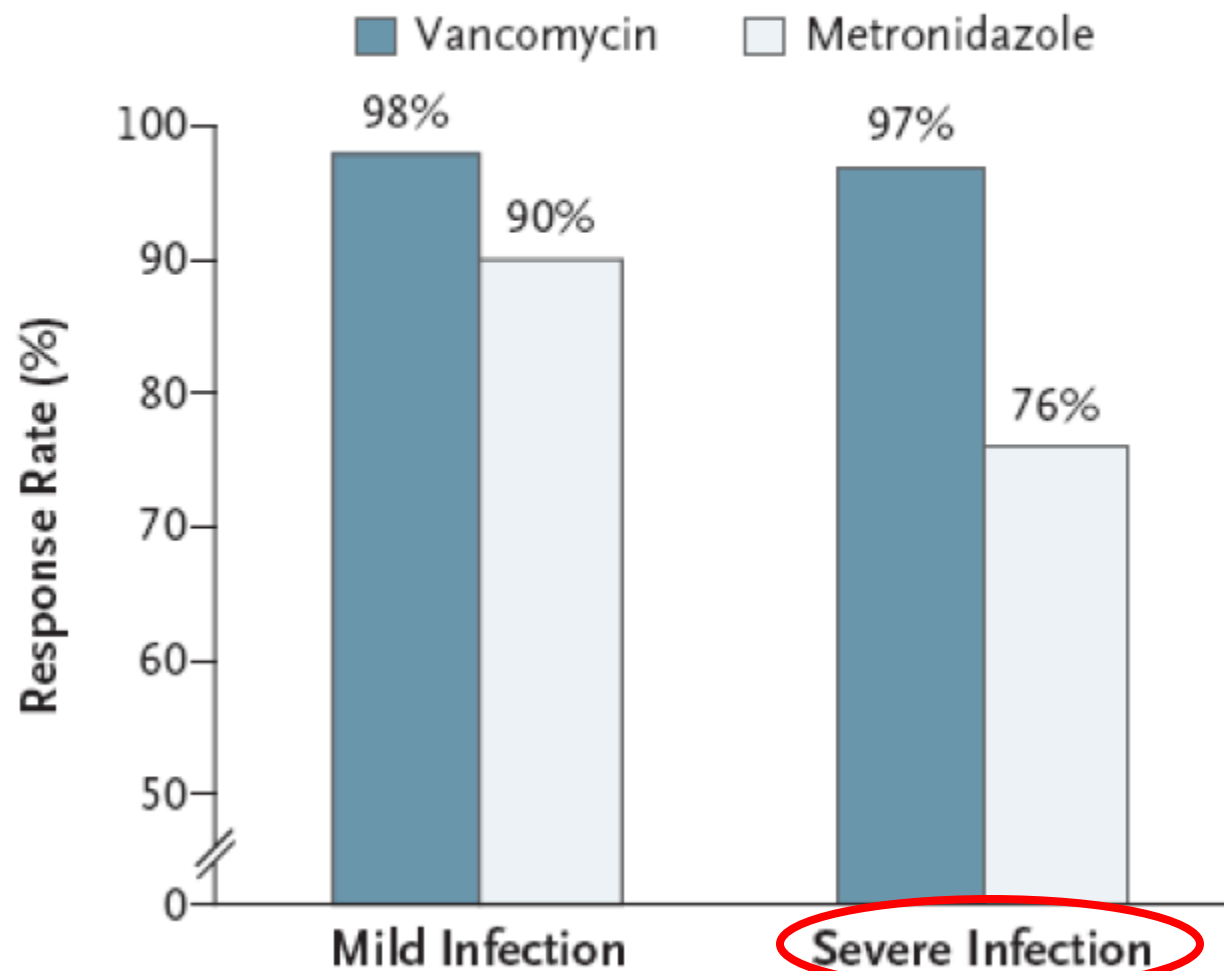
Musher DM et al., *CID*, 2005
Pepin J et al., *CID*, 2005
Aslam et al. *Lancet Inf. Dis*, 2005

Metronidazole



Infections à *Clostridium difficile*

Traitement

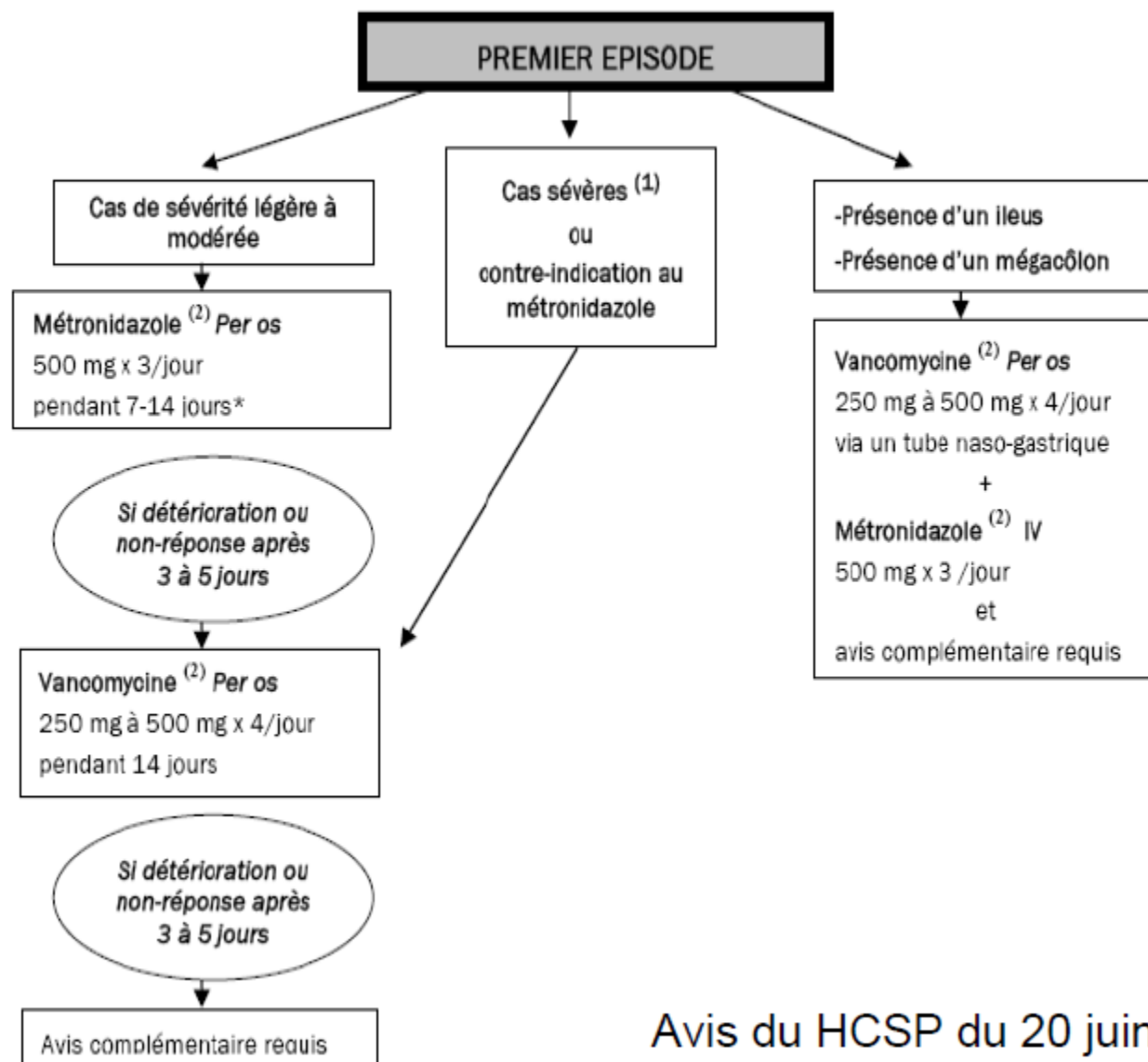


Kelly CP et LaMont JT. 2008

Tt des Complications (1)

- Inability to take medications by mouth:
 - vancomycin (500 mg every 6 h by retention enema or nasogastric tube)
 - and IV metronidazole (500 mg 4 times daily) ?

Traitement des infections à *Clostridium difficile*

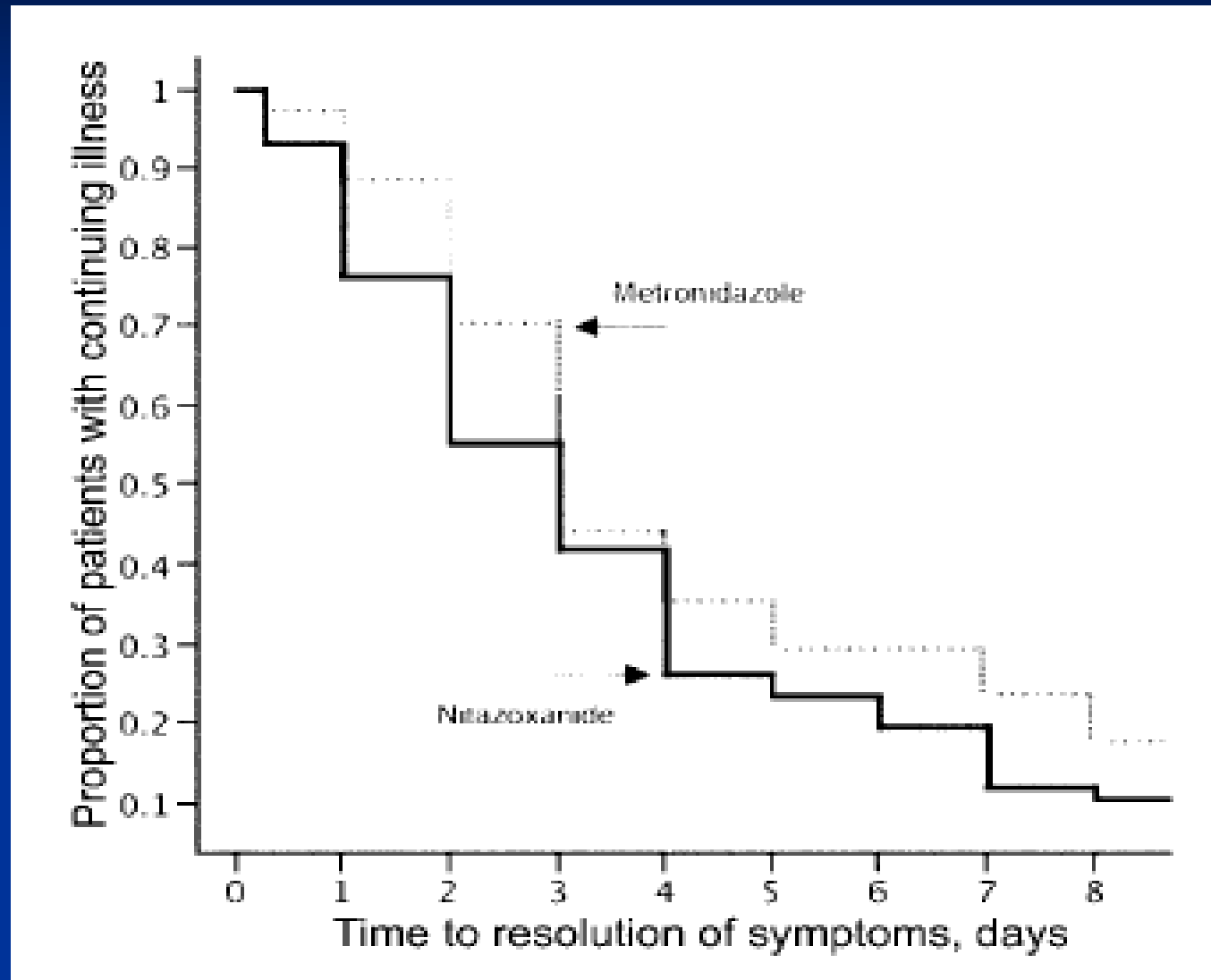


Avis du HCSP du 20 juin 2008

Traitement à venir...

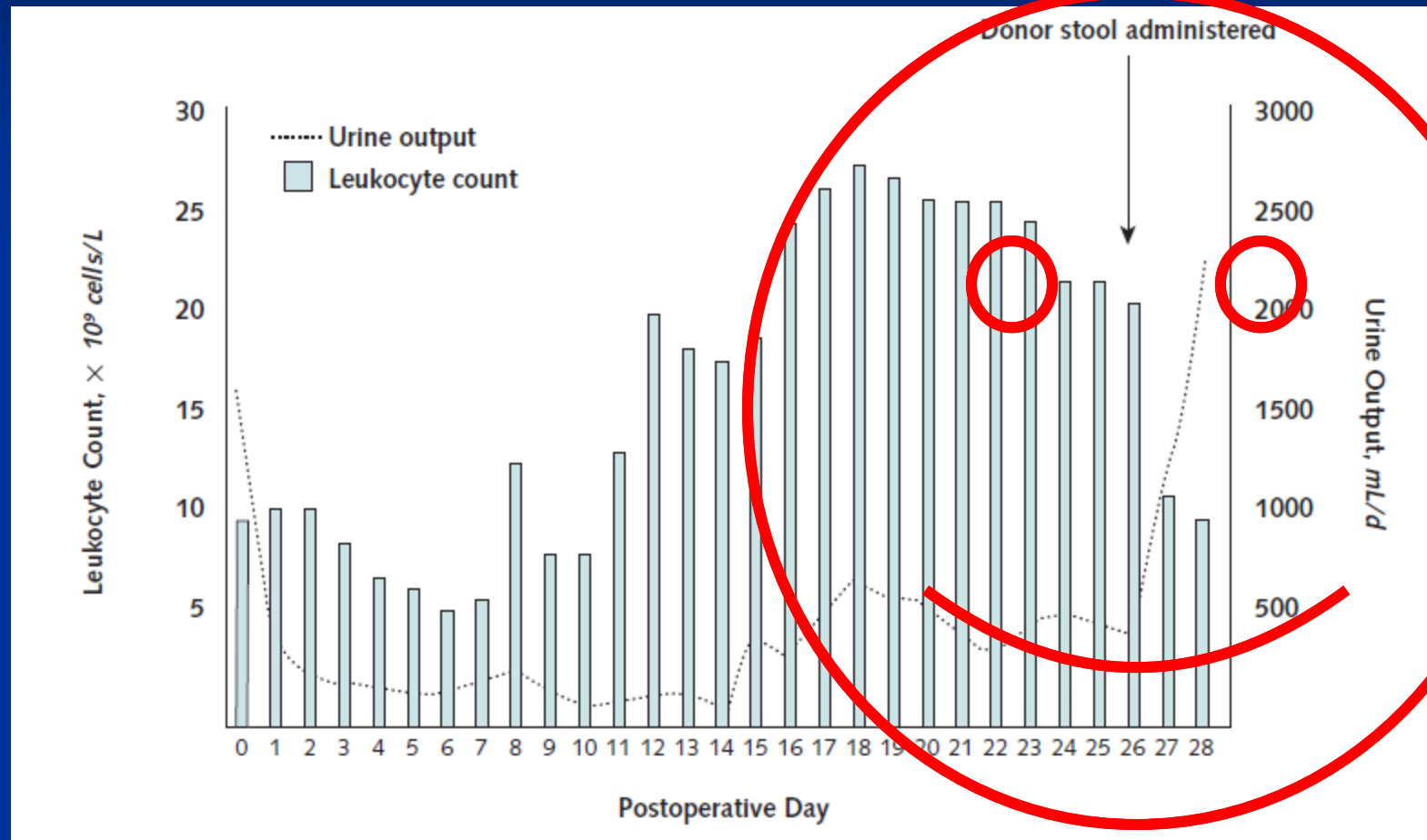
ATB	Chélateur de toxine	Restauration de la flore	Augmenter le système immunitaire
Rifaximin	Tolevamer	Prébiotique	Ig IV
Nitazoxanide	Cholestyramine	Probiotique <i>Saccharomyces boulardii</i> <i>Lactobacillus</i> <i>Bifidobacterium</i>	Vaccin
Ramoplanine		Feces synthétique	
Daptomycine		Feces autologue	

Nitazoxanide et diarrhée à CD



Musher DM et al. CID 2006; 43: 421-7

Successful Treatment of Fulminant CD Infection with Fecal Bacteriotherapy



Holman RP Ann Int Med 2008; 148: 632-3

Tt des Complications (2)

- Delayed response and critical illness: consider IVIG (400 mg/kg of body weight) or surgical consultation for possible colectomy, especially if :
 - leukemoid reaction (leukocyte count $> 20\,000$ cells/mL),
 - renal failure, septic shock,
 - or any combination of these occurs

Colites pseudo-membraneuses fulminantes à *C. 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
 - totale ou subtotale
 - bénéfice plus net chez les patients en choc septique
 - à réaliser précocement si indiquée (avant lactates > 5 mmol/l)

ICAAC 2006 - D'après J. Pépin, communication orale 539







CDAD in the ICU : risk factors of death

VARIABLES	OR	95%CI	P
Age, years (per 1-year increment)	1.10	1.02–1.19	0.011
SOFA score at infection onset (per 1-point increment)	1.40	1.13–1.75	0.002
Organ failure (any)*	-	-	0.998

#Hosmer and Lemeshow goodness-of-fit statistic = 7.1 (8 DF) (p = 0.53)
OR, odds ratio
CI, confidence interval
*Organ failure occurred in 100% who died from CDAD, as such, there is no odds ratio and confidence interval

Fulminant *Clostridium difficile* Colitis

Care & mortality

Factor	Mortality, No. (%)	OR (95% CI)	P Value
Age, y			
≥70	47 (40.2)		
<70	22 (26.8)	2.2 (1.0-4.8)	.04
WBC count, /μL			
≥35 000 or <4000	38 (46.3)		
<35 000 and ≥4000	31 (26.5)	4.2 (1.9-9.1)	<.001
Neutrophil bands, %			
≥10	53 (40.5)		
<10	16 (23.5)	2.8 (1.3-6.5)	.01
Vasopressors			
Yes	48 (52.2)		
No	21 (19.6)	4.0 (1.9-8.5)	<.001
Intubation			
Yes	45 (52.9)		
No	24 (21.1)	4.7 (2.1-10.5)	<.001
Oral vancomycin			
Yes	19 (21.6)		
No	50 (45.0)	0.25 (0.11-0.55)	<.001
Colectomy			
Yes	24 (32.0)		
No	45 (36.3)	0.49 (0.21-1.1)	.08

Fulminant *Clostridium difficile* Colitis

Care & mortality

Table 4. Mortality in Patients With Fulminant *Clostridium difficile* According to Grouped Risk Factors

No. of Risk Factors	Elderly ^a	Abnormal WBC Count ^a	Cardiopulmonary Failure ^a	No. (%) of Patients			
				Mortality ^b (n=199)		Mortality After Colectomy ^c (n=75)	
0	-	-	-	0/6 (0)	0/6 (0)	0/2 (0)	0/2 (0)
1	+	-	-	0/10 (0)	4/45 (8.9)	0/3 (0)	0/11 (0)
	-	+	-	2/23 (8.7)		0/6 (0)	
	-	-	+	2/12 (16.7)		0/2 (0)	
2	+	+	-	11/40 (27.5)	37/99 (37.4)	1/17 (5.9)	16/45 (35.6)
	-	+	+	18/41 (43.9)		12/25 (60)	
	+	-	+	8/18 (44.4)		3/3 (100)	
3	+	+	+	28/49 (57.1)	28/49 (57.1)	8/17 (47.1)	8/17 (47.1)

Fulminant *Clostridium difficile* Colitis

Care & mortality

Table 5. Colectomy and Mortality in 136 Patients Admitted to the Hospital With Fulminant *Clostridium difficile* by Hospital Department

	No. (%) of Patients		<i>P</i> Value
	Surgical Department ^a	Nonsurgical Department ^a	
Colectomy	40/47 (85.1)	10/89 (11.2)	<.001
Mortality	6/47 (12.8)	35/89 (39.3)	.001
Mortality after colectomy	5/40 (12.5)	7/10 (70.0)	<.001

Conclusions (1)

- Le tableau clinique des colites graves à CD
 - est aspécifique
 - souvent trompeur (absence de diarrhée)
 - entraîne un retard diagnostique et thérapeutique
- Il faut avoir l'examen des selles « facile » chez tous les sujets à risque avec un tableau abdominal bâtarde.
- Au moindre doute, le TDM abdominal permet le diagnostic dans la majorité des cas.

Conclusions (2)

- Actuellement, le traitement médical repose sur la vancomycine intra digestive.
- L'hospitalisation en réanimation et la concertation médico-chirurgicale permanente doivent être la règle.
- La chirurgie est salvatrice en cas de non amélioration dans les 48-72h
- La colectomie totale semble l'intervention de choix, mais n'empêche pas une mortalité élevée

Comparison of Patients With Fulminant *Clostridium difficile* Colitis Who Underwent Colectomy vs Medical Treatment Alone

Table 1. Comparison of Patients With Fulminant *Clostridium difficile* Colitis Who Underwent Colectomy vs Medical Treatment Alone

Parameter	No Colectomy (n=124)	Colectomy (n=75)	P Value
Age, mean (SD), y	68.4 (17.0)	68.0 (12.9)	.85
Male, No. (%)	61 (49.2)	35 (46.7)	.77
Risk factors, No. (%)			
Diabetes mellitus	38 (30.6)	21 (28.0)	.75
Renal disease	29 (23.4)	21 (28.0)	.50
Immunosuppression	67 (54.0)	33 (44.0)	.17
Recurrent <i>C difficile</i> colitis	52 (41.9)	13 (17.3)	<.001 ^a
Clinical features, No. (%)			
Abdominal findings			
Abdominal pain	55 (44.4)	57 (76.0)	<.001
Abdominal distension	38 (30.6)	56 (74.7)	<.001 ^a
Abdominal tenderness	44 (35.5)	51 (68.0)	<.001
Peritonitis	8 (6.5)	28 (37.3)	<.001 ^a
WBC count, mean (SD), /μL	29 000 (19 600)	36 700 (22 300)	.01
Neutrophil bands, mean (SD), %	16.4 (15.1)	20.9 (15.1)	.04
Neutrophil bands ≥10%, No. (%)	74 (59.7)	57 (76.0)	.02
Albumin, mean (SD), mg/dL	2.03 (0.7)	1.91 (0.6)	.19
Creatinine, mean (SD), mg/dL	2.2 (1.5)	2.3 (1.7)	.77
Intubation, No. (%)	44 (35.5)	41 (54.7)	.01
Vasopressors, No. (%)	57 (46.0)	35 (46.7)	>.99
CT results, No. (%)			
Scan positive	74/84 (88.1)	66/66 (100)	<.001 ^a
Colon thickening	64 (76.2)	62 (93.9)	<.001
Colon dilation	13 (15.5)	21 (31.8)	.002
Free fluid	36 (42.9)	43 (65.2)	<.001
Free air	0 (0)	6 (9.1)	.003
Oral vancomycin, No. (%)	49 (39.5)	39 (52.0)	.11
Mortality, No. (%)	45 (36.3)	24 (32.0)	.65

Abbreviations: CT, computed tomography; WBC, white blood cell.

SI conversion factors: To convert albumin to grams per liter, multiply by 10; creatinine to micromoles per liter, multiply by 88.4; WBC count to $\times 10^9/L$, multiply by 0.001.

^aIndependent predictors of colectomy on multivariate analysis.

Sailhamer, E. A. et al. Arch Surg 2009;144:433-439.

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Independent Predictors of Mortality in 199 Patients With Fulminant *Clostridium difficile* Colitis

Table 3. Independent Predictors of Mortality in 199 Patients With Fulminant *Clostridium difficile* Colitis

Factor	Mortality, No. (%)	OR (95% CI)	P Value
Age, y			
≥70	47 (40.2)		
<70	22 (26.8)	2.2 (1.0-4.8)	.04
WBC count, /μL			
≥35 000 or <4000	38 (46.3)		
<35 000 and ≥4000	31 (26.5)	4.2 (1.9-9.1)	<.001
Neutrophil bands, %			
≥10	53 (40.5)		
<10	16 (23.5)	2.8 (1.3-6.5)	.01
Vasopressors			
Yes	48 (52.2)		
No	21 (19.6)	4.0 (1.9-8.5)	<.001
Intubation			
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Colectomy			
Yes	24 (32.0)		
No	45 (36.3)	0.49 (0.21-1.1)	.08

Abbreviations: CI, confidence interval; OR, odds ratio; WBC, white blood cell.
SI conversion factor: To convert WBC count to $\times 10^9/L$, multiply by 0.001.

Sailhamer, E. A. et al. Arch Surg 2009;144:433-439.

Mortality in Patients With Fulminant *Clostridium difficile* According to Grouped Risk Factors

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				Mortality ^b (n=199)		Mortality After Colectomy ^c (n=75)	
0	–	–	–	0/6 (0)	0/6 (0)	0/2 (0)	0/2 (0)
1	+	–	–	0/10 (0)	4/45 (8.9)	0/3 (0)	0/11 (0)
	–	+	–	2/23 (8.7)		0/6 (0)	
	–	–	+	2/12 (16.7)		0/2 (0)	
2	+	+	–	11/40 (27.5)	37/99 (37.4)	1/17 (5.9)	16/45 (35.6)
	–	+	+	18/41 (43.9)		12/25 (60)	
	+	–	+	8/18 (44.4)		3/3 (100)	
3	+	+	+	28/49 (57.1)	28/49 (57.1)	8/17 (47.1)	8/17 (47.1)

Abbreviations: WBC, white blood cell; –, negative; +, positive.

^a Abnormal WBC count indicates a white blood cell count of 35 000/μL or more or less than 4000/μL (to convert to ×10⁹/L, multiply by 0.001) or neutrophil bands of 10% or more; cardiopulmonary failure, a requirement for vasopressors or intubation; and elderly, age of 70 years or older.

^b *P* < .001 for mortality according to the number of risk factors present.

^c *P* = .04 for mortality after colectomy according to the number of risk factors present.

Sailhamer, E. A. et al. Arch Surg 2009;144:433-439.

Colectomy and Mortality in 136 Patients Admitted to the Hospital With Fulminant *Clostridium difficile* by Hospital Department

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Mortality	6/47 (12.8)	35/89 (39.3)	.001
Mortality after colectomy	5/40 (12.5)	7/10 (70.0)	<.001

^a Nonsurgical department indicates admitted to and remained in the nonsurgical department; surgical department, admitted or transferred to the surgical department.

Sailhamer, E. A. et al. Arch Surg 2009;144:433-439.