COLITIS PSEUDOMEMBRANOSA

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Clostridium difficile infections: do we know the real dimensions of the problem?

Pierre Tattevin[a,b,*], Sylvie Buffet-Bataillon[c], Pierre-Yves Donnio[c], Matthieu Revest[a], Christian Michelet[a]

A B S T R A C T

Community-associated *Clostridium difficile* infection (CA-CDI) represents 32% of all CDI cases based on U.S. population-based data. The current epidemic strain, NAP1, is the most prevalent strain causing these infections. Although complications, recurrence and death are uncommon, one-fourth of the CA-CDI patients are hospitalized within 7 days after the diagnosis.

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Journal of Infection (2010) 61, 1–8

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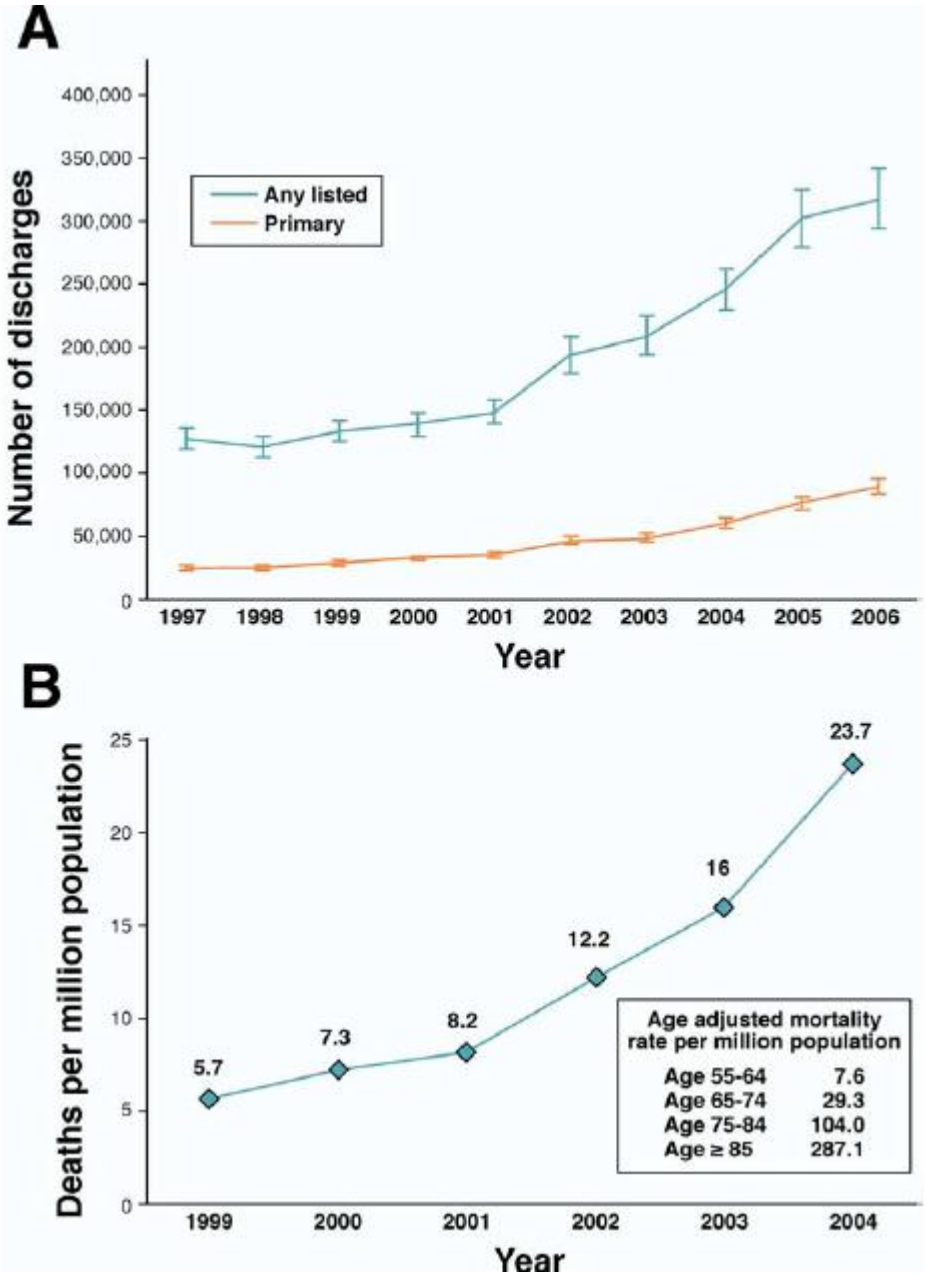
REVIEW

A review of mortality due to *Clostridium difficile* infection

J.A. Karas [a,*], D.A. Enoch [b], S.H. Aliyu [a]

Summary In this review we examine published literature to ascertain mortality in relation to *Clostridium difficile* infection (CDI) and the factors associated with mortality. In the 27 studies that had sufficient data, there were 10975 cases of CDI with great heterogeneity in the methods for reporting mortality. We calculated the overall associated mortality to be at least 5.99% within 3 months of diagnosis. The most important finding is that higher mortality is associated with advanced age, being 13.5% in patients over 80 years. Studies performed after 2000 had a significantly higher mortality than those before this date. We propose minimum standards for reporting mortality in future studies.



Karas JA, Enoch DA, Aliyu SH. A review of mortality due to Clostridium difficile infection. J Infect. 2010 Jul;61(1):1-8.

Factores de Riesgo

- Uso reciente de antibióticos
- Quimioterapia
- Inhibidor de bomba de protones
- Sonda nasogástrica
- Cirugía gastrointestinal
- Pacientes ancianos
- Pacientes inmunocomprometidos

Bourgault AM, Poirier L, Lamothe F, Michaud S, A. Host and pathogen factors for Clostridium difficile infection and colonization. N Engl J Med. 2011 Nov 3;365

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

RESULTS

A total of 4143 patients were included in the study; 117 (2.8%) and 123 (3.0%) had health care–associated *C. difficile* infection and colonization, respectively. Older age and use of antibiotics and proton-pump inhibitors were significantly associated with health care–associated *C. difficile* infection. Hospitalization in the previous 2 months; use of chemotherapy, proton-pump inhibitors, and H_2 blockers; and antibodies against toxin B were associated with health care–associated *C. difficile* colonization. Among patients with health care–associated *C. difficile* infection and those with colonization, 62.7% and 36.1%, respectively, had the North American PFGE type 1 (NAP1) strain.

CONCLUSIONS

In this study, health care–associated *C. difficile* infection and colonization were differentially associated with defined host and pathogen variables. The NAP1 strain was predominant among patients with *C. difficile* infection, whereas asymptomatic patients were more likely to be colonized with other strains. (Funded by the Consortium de Recherche sur le *Clostridium difficile*.)

N Engl J Med 2011;365:1693-703.

Table 1. Baseline Characteristics of the Study Patients and Characteristics of Samples and Pathogens, According to Clinical Status.*

Variable	Health Care–Associated *C. difficile* Infection (N=117)	Health Care–Associated *C. difficile* Colonization (N=123)	*C. difficile* Colonization on Admission (N=184)	Neither *C. difficile* Infection nor Colonization (N=3719)
Age — yr	67.4±14.1†	63.3±14.7	63.4±14.8	62.1±15.6
Male sex — no. (%)	57 (48.7)	62 (50.4)	94 (51.1)	1871 (50.3)
Score on Charlson comorbidity index‡	2.4±3.9	2.6±2.7	2.3±2.2	1.9±2.2
Hospitalization before current admission — no. (%)§				
Never or >12 mo before	53 (45.3)	59 (48.0)	66 (35.9)	2263 (60.9)
2–12 mo before	34 (29.1)	35 (28.5)	68 (37.0)	925 (24.9)
<2 mo before	30 (25.6)†	29 (23.6)¶	50 (27.2)	530 (14.3)
Medication use — no. (%)‖				
Antibiotic	111 (94.9)†	102 (82.9)¶	122 (66.3)	2612 (70.2)
Chemotherapy	6 (5.1)	9 (7.3)	7 (3.8)	159 (4.3)
Proton-pump inhibitor	74 (63.2)†	62 (50.4)¶	90 (48.9)	1209 (32.5)
H_2 blocker	24 (20.5)	32 (26.0)¶	34 (18.5)	620 (16.7)
Glucocorticoid	13 (11.1)	16 (13.0)	20 (10.9)	262 (7.0)
NSAID	72 (61.5)	82 (66.7)	100 (54.4)	2176 (58.5)
Nasogastric tube — no. (%)‖	15 (12.8)	20 (16.3)	10 (5.4)	437 (11.8)
Samples available for serologic analysis — no./total no. (%)	113/117 (96.6)	122/123 (99.2)	176/184 (95.7)	3559/3719 (95.7)
Positive for antibody against toxin A	17/113 (15.0)	25/122 (20.5)	32/176 (18.2)	607/3559 (17.1)
Positive for antibody against toxin B	34/113 (30.1)	45/122 (36.9)¶	59/176 (33.5)	902/3559 (25.3)
Samples available for isolate analysis — no./total no. (%)	83/117 (70.9)	119/123 (96.7)	181/184 (98.4)	Not applicable
PFGE type				Not applicable
NAP1	52/83 (62.7)	43/119 (36.1)	24/181 (13.3)	
NAP2	1/83 (1.2)	7/119 (5.9)	8/181 (4.4)	
Neither	30/83 (36.1)	69/119 (58.0)	149/181 (82.3)	
Binary toxin				Not applicable
Positive	55/83 (66.3)	50/119 (42.0)	30/181 (16.6)	
Negative	27/83 (32.5)	67/119 (56.3)	149/181 (82.3)	
Discordant**	1/83 (1.2)	2/119 (1.7)	2/181 (1.1)	
tcdC Δ117 Genotype	50/83 (60.2)	45/119 (37.8)	25/181 (13.8)	Not applicable

ANTIBIÓTICOS

2-mercaptobenzimidazole	Doxiciclina	Sulfadimethoxine*	Sulfadiazine*
2-quinoxalinecarboxylic acid	Enoxacin*	Sulfadoxine*	Sulfaguanidine*
6-phenyl-2-thiouracil	Enrofloxacin	Monensin	Sulfamerazine*
Albendazole	Erythromycin*		Sulfamethazine*
Albendazole Amino Sulfone	Etodolac	Narasin	Sulfamethazine-d4*†
Albendazole Sulfone	Fenbendazole	Nicarbazin	Sulfamethizole*
Albendazole Sulfoxide	Fenbendazole Sulfone	Niclosamide	Sulfamethoxazole*
Amoxicilina	Fenbendazole Sulfoxide	Norfloxacin*	Sulfamethoxypyridazine*
Ampicilina	Florfenicol Amine*	Novobiocin	Sulfanilamide*
Bacitracin	Florfenicol*	Ofloxacin*	Sulfanitran
	Flumequine	Orbifloxacin*	Sulfapyridine*
Ceftiofur	Flunixin*	Oxolinic acid*	Sulfaquinoloxaline*
Chloramphenicol*		Oxyphenbutazone	Sulfasalazine*
Chlorotetracycline*	Indomethacin	Oxytetracycline*	Sulfathiazole*
Ciprofloxacina	Ipronidazole-OH	Penicilina G	Sulfisoxazole*
Clindamicina	Josamycin*	Phenylbutazone	Tetraciclina
Cloxacillin*		Ractopamine	Tetramisole*
Danofloxacin*	Lasalocid (pos and neg)	Rafoxanide	Thiabendazole
Decoquinate	Lincomycin*	Ronidazole	Thiamphenicol*
Desethylene Ciprofloxacin*	Lomefloxacin*	Sarafloxacin*	
	Mebendazole	Spiramycin*	Tolfenamic acid
Difloxacin*	Metronidazole	Sulfacetamide*	Triclabendazole
Dimetridazole	Minocycline*	Sulfachloropyridazine*	

The NEW ENGLAND JOURNAL of MEDICINE

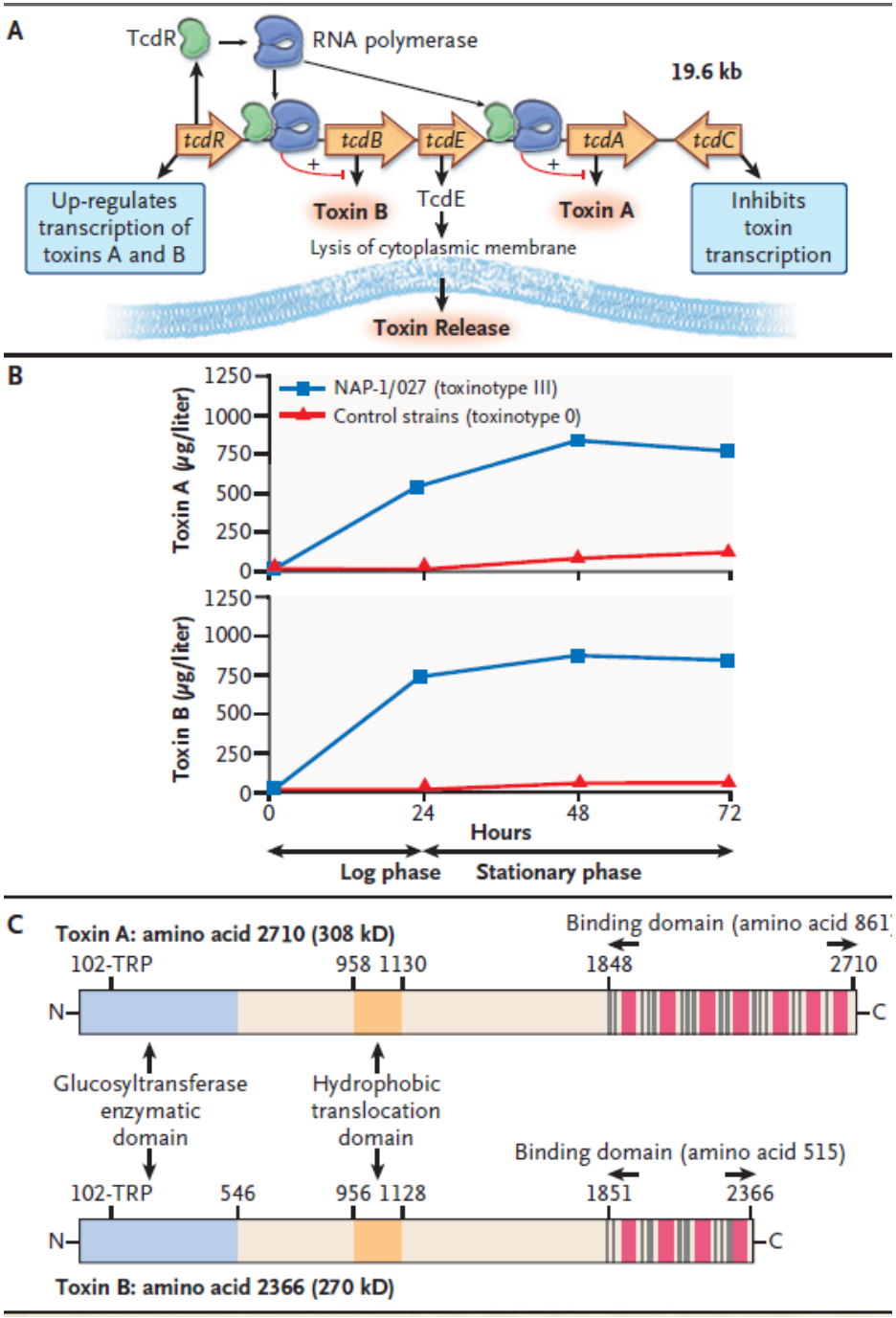
REVIEW ARTICLE

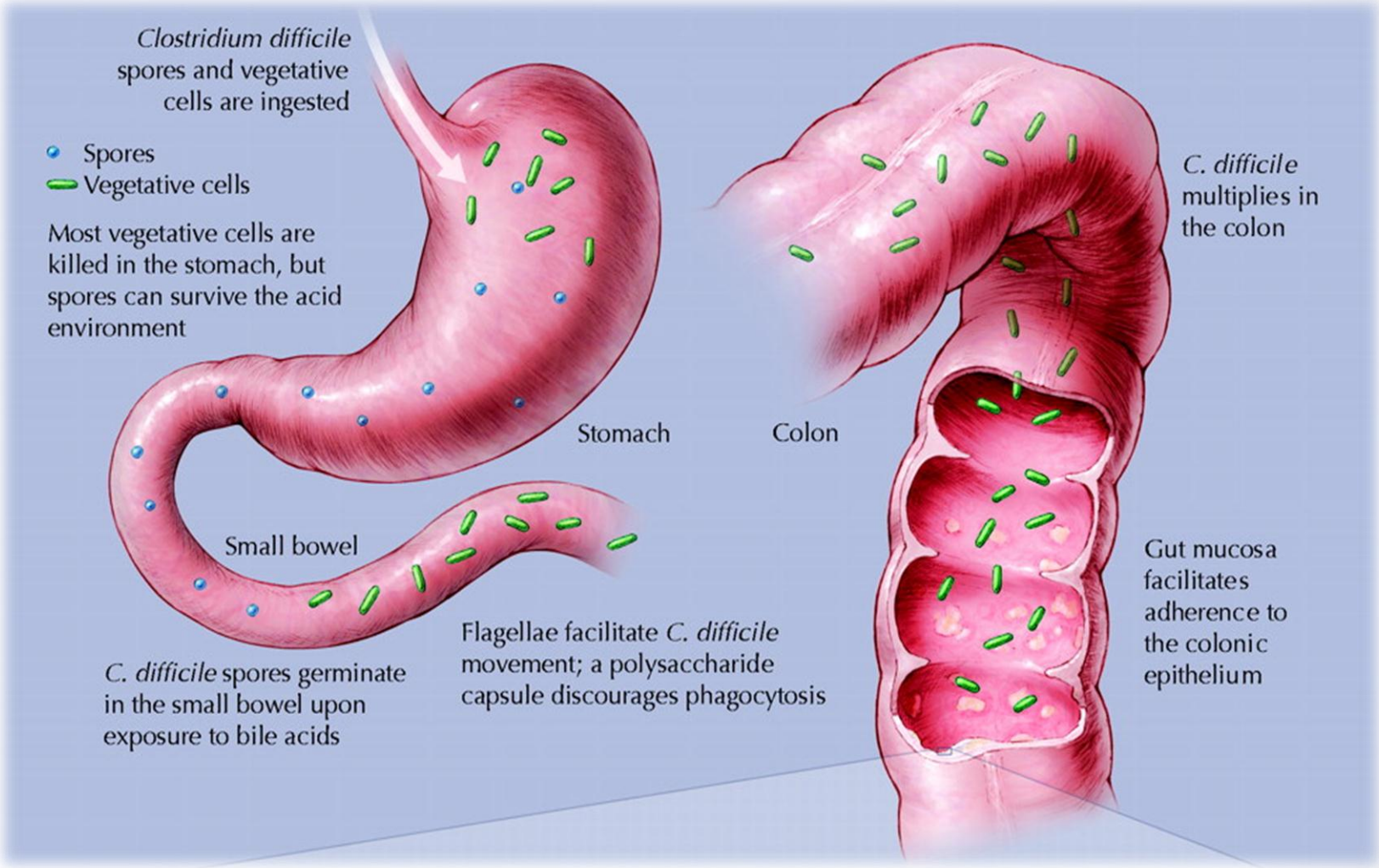
CURRENT CONCEPTS

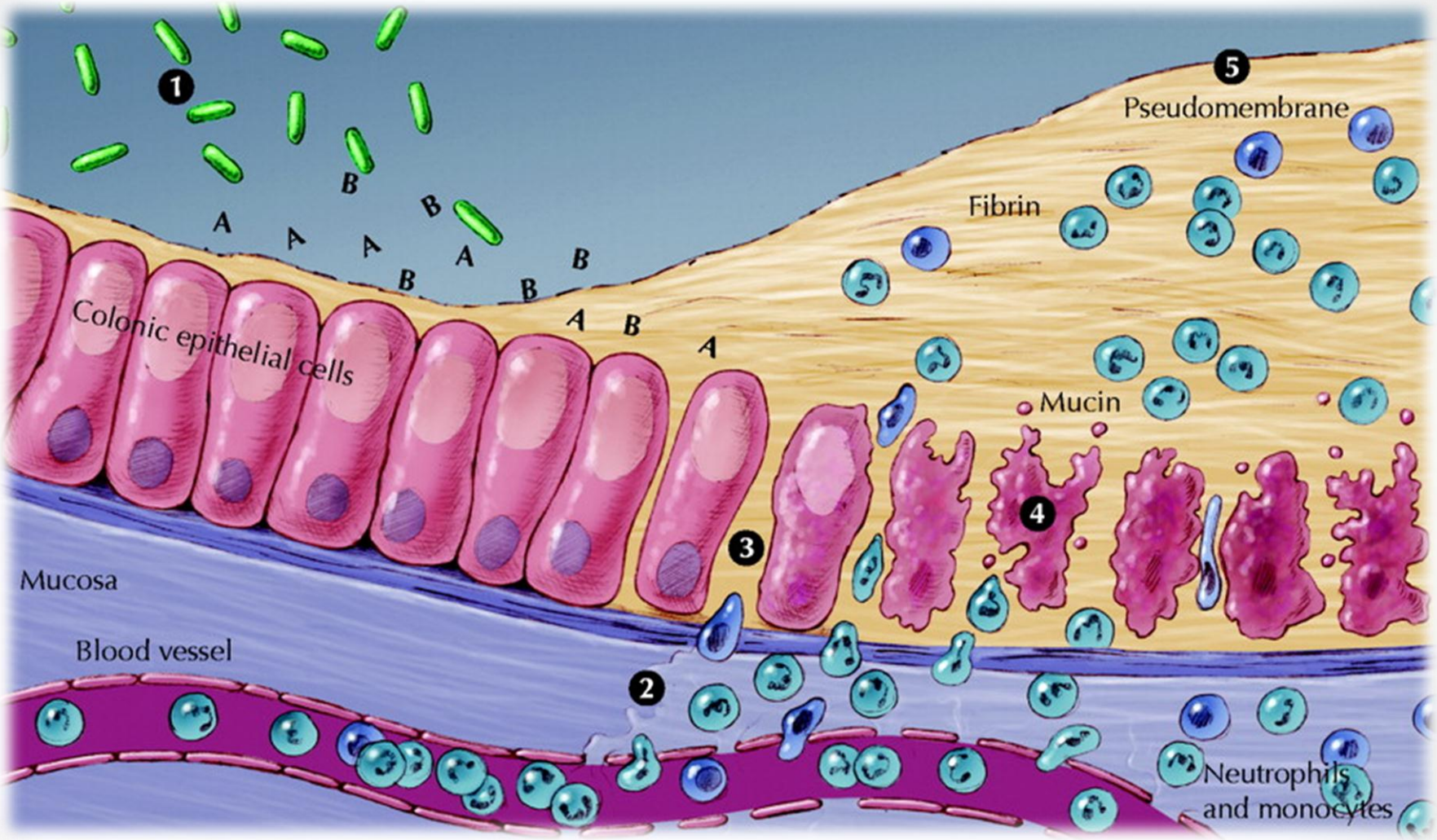
Clostridium difficile — More Difficult Than Ever

Ciarán P. Kelly, M.D., and J. Thomas LaMont, M.D.

N Engl J Med 2008;359:1932-40.


A
TcdR
RNA polymerase
19.6 kb
tcdR
tcdB
tcdE
tcdA
tcdC
+
+
Up-regulates transcription of toxins A and B
Toxin B
TcdE
Toxin A
Inhibits toxin transcription
Lysis of cytoplasmic membrane
Toxin Release
B
NAP-1/027 (toxinotype III)
Control strains (toxinotype 0)
Toxin A (μg/liter)
Toxin B (μg/liter)
1250
1000
750
500
250
0
0
24
48
72
Hours
Log phase
Stationary phase
C
Toxin A: amino acid 2710 (308 kD)
Binding domain (amino acid 861
102-TRP
958 1130
1848
2710
N
C
Glucosyltransferase enzymatic domain
Hydrophobic translocation domain
Binding domain (amino acid 515)
102-TRP
546
956 1128
1851
2366
N
C
Toxin B: amino acid 2366 (270 kD)


Clostridium difficile spores and vegetative cells are ingested
Spores
Vegetative cells
Most vegetative cells are killed in the stomach, but spores can survive the acid environment
Stomach
Small bowel
C. difficile spores germinate in the small bowel upon exposure to bile acids
Flagellae facilitate *C. difficile* movement; a polysaccharide capsule discourages phagocytosis
Colon
C. difficile multiplies in the colon
Gut mucosa facilitates adherence to the colonic epithelium


1
A
A
A
B
A
B
B
B
B
A
B
A
Colonic epithelial cells
Mucosa
Blood vessel
2
3
4
5
Pseudomembrane
Fibrin
Mucin
Neutrophils
and monocytes

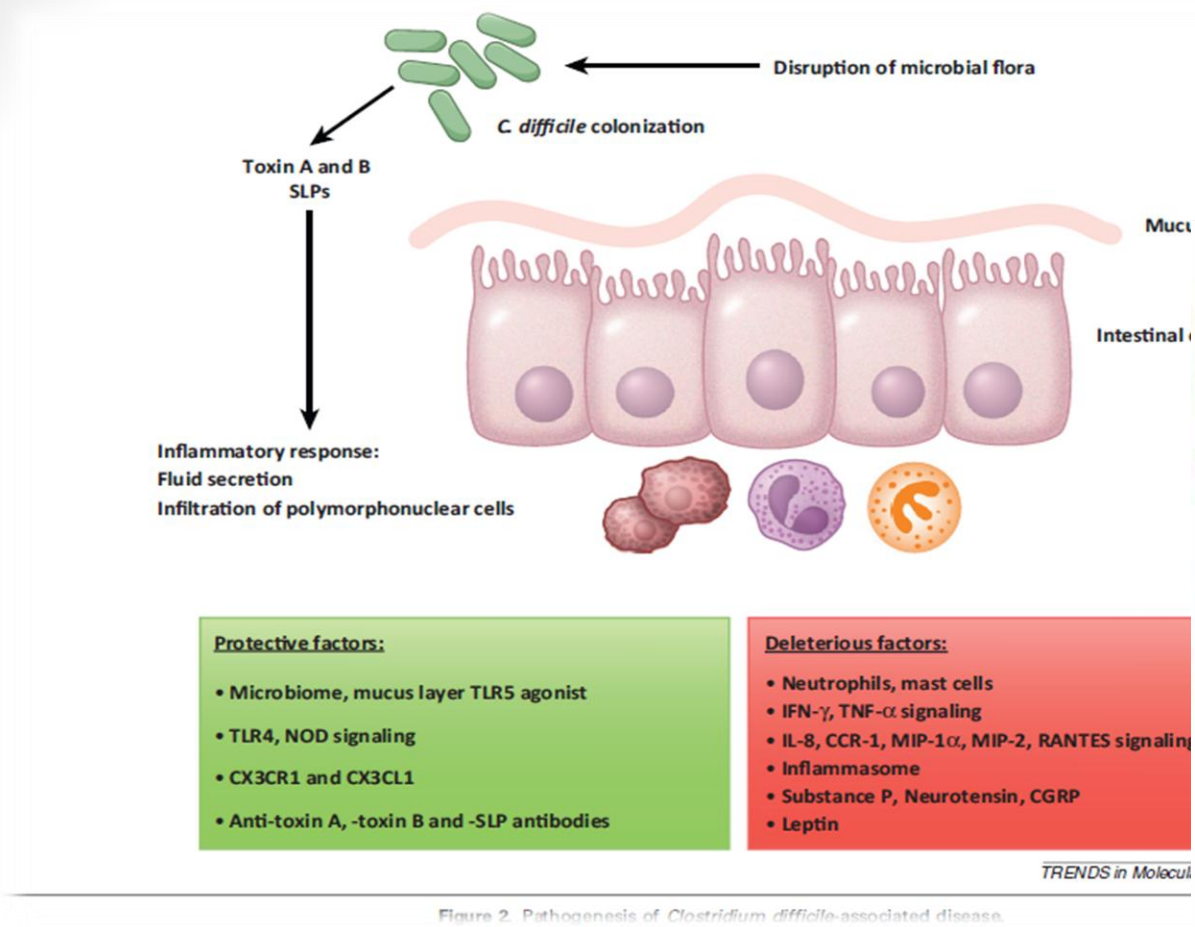
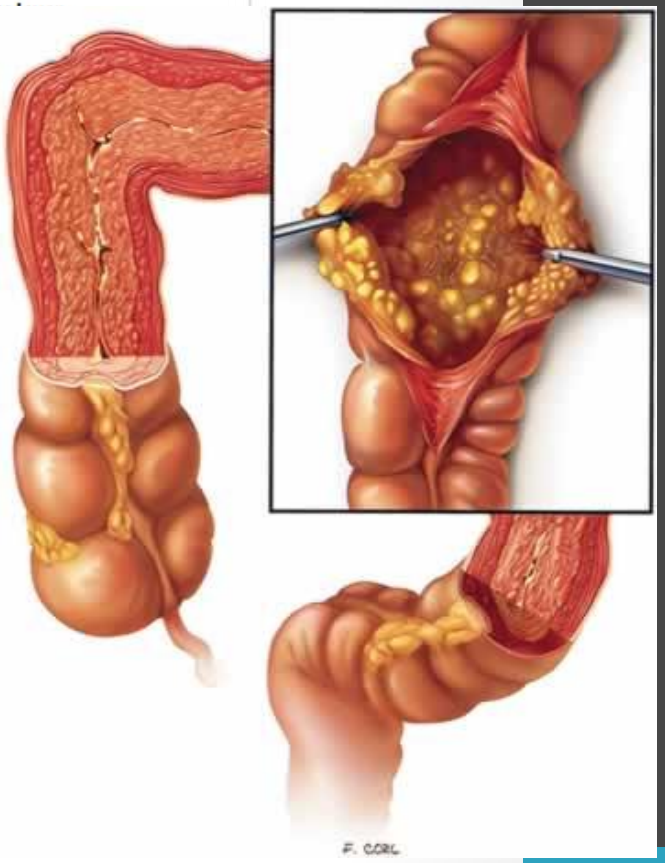


Figure 2. Pathogenesis of *Clostridium difficile*-associated disease.



Enfermedad mediada por toxinas

Bloomfield MG, Sherwin JC, Gkrania-Klotsas E. Risk factors for mortality in Clostridium difficile infection in the general hospital population: a systematic review. J Hosp Infect. 2012 Sep;82(1):1-12.

Anaerobe 16 (2010) 527–532

Contents lists available at ScienceDirect

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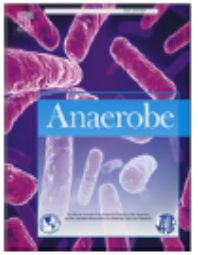


Pathogenesis and Toxins

Repetitive domain of *Clostridium difficile* toxin B exhibits cytotoxic effects on human intestinal epithelial cells and decreases epithelial barrier function

Mateja Zemljic [a,c], Maja Rupnik [a,b,*], Melania Scarpa [c], Gregor Anderluh [d], Gorgio Palù [c], Ignazio Castagliuolo [c]

A B S T R A C T

We have used recombinant repetitive domain of *Clostridium difficile* toxin B obtained from two different strains, rec-TcdB3$_{10463}$ and rec-TcdB3$_{8864}$ and a model intestinal epithelial cell line(s) to characterize their cytotoxic and cytopathic effect and influence on tight-junction organization. Both recombinant receptor binding domains caused intestinal epithelial cell damage, decreased transepithelial electrical resistance and induced translocation of ZO-1 from tight-junction proteins although less efficiently as holotoxins. Recombinant repetitive TcdB domains also caused stimulation of interleukin IL-8 synthesis in HT-29 cells.

This is the first description of glucosyltransferase independent toxicity of TcdB and these C-terminal mediated effects may contribute to the pathophysiology of *C. difficile* infection.

International Journal of Infectious Diseases (2007) 11, 5–10

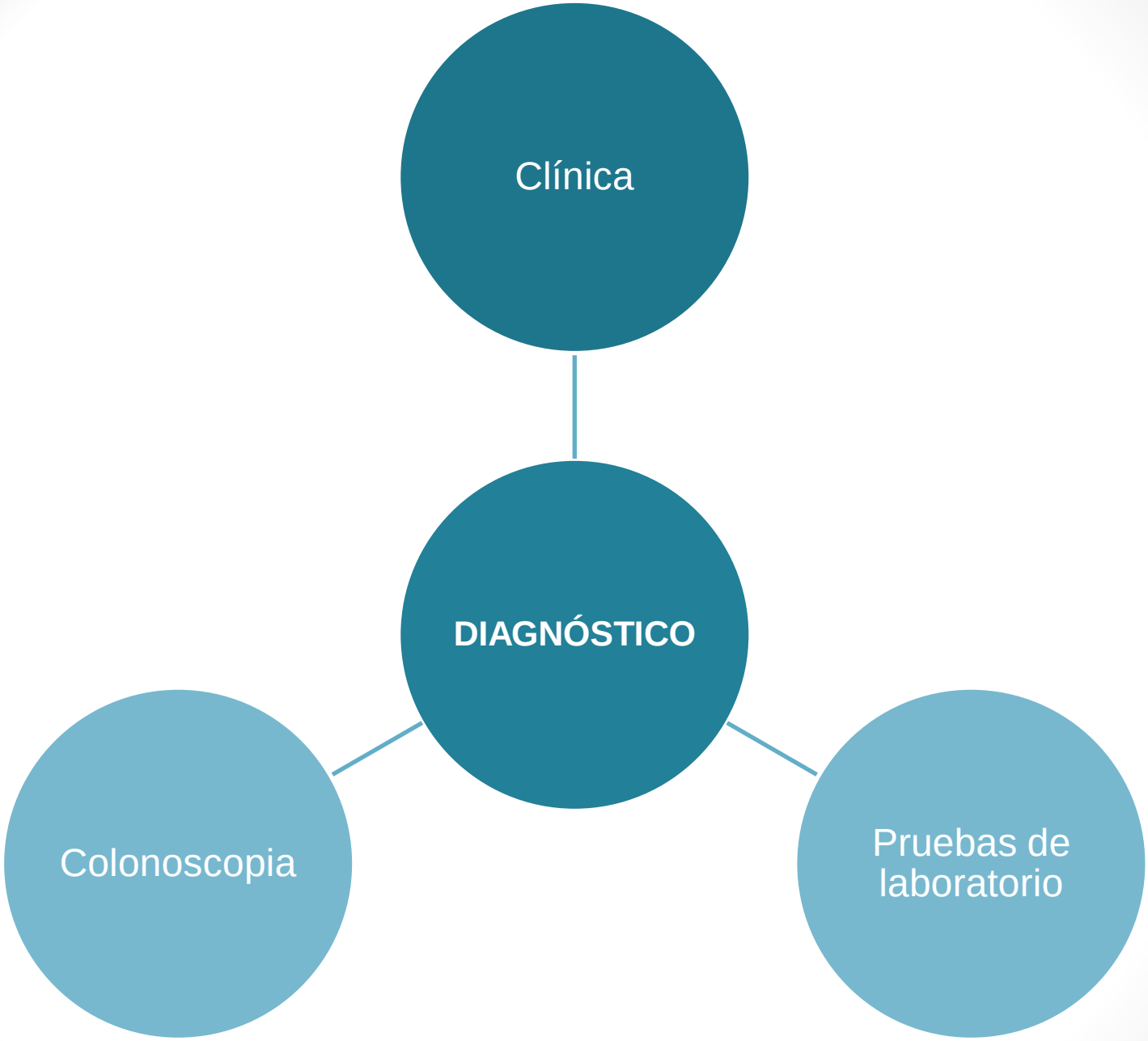
http://intl.elsevierhealth.com/journals/ijid

PERSPECTIVE

Toxin A-negative, toxin B-positive *Clostridium difficile*

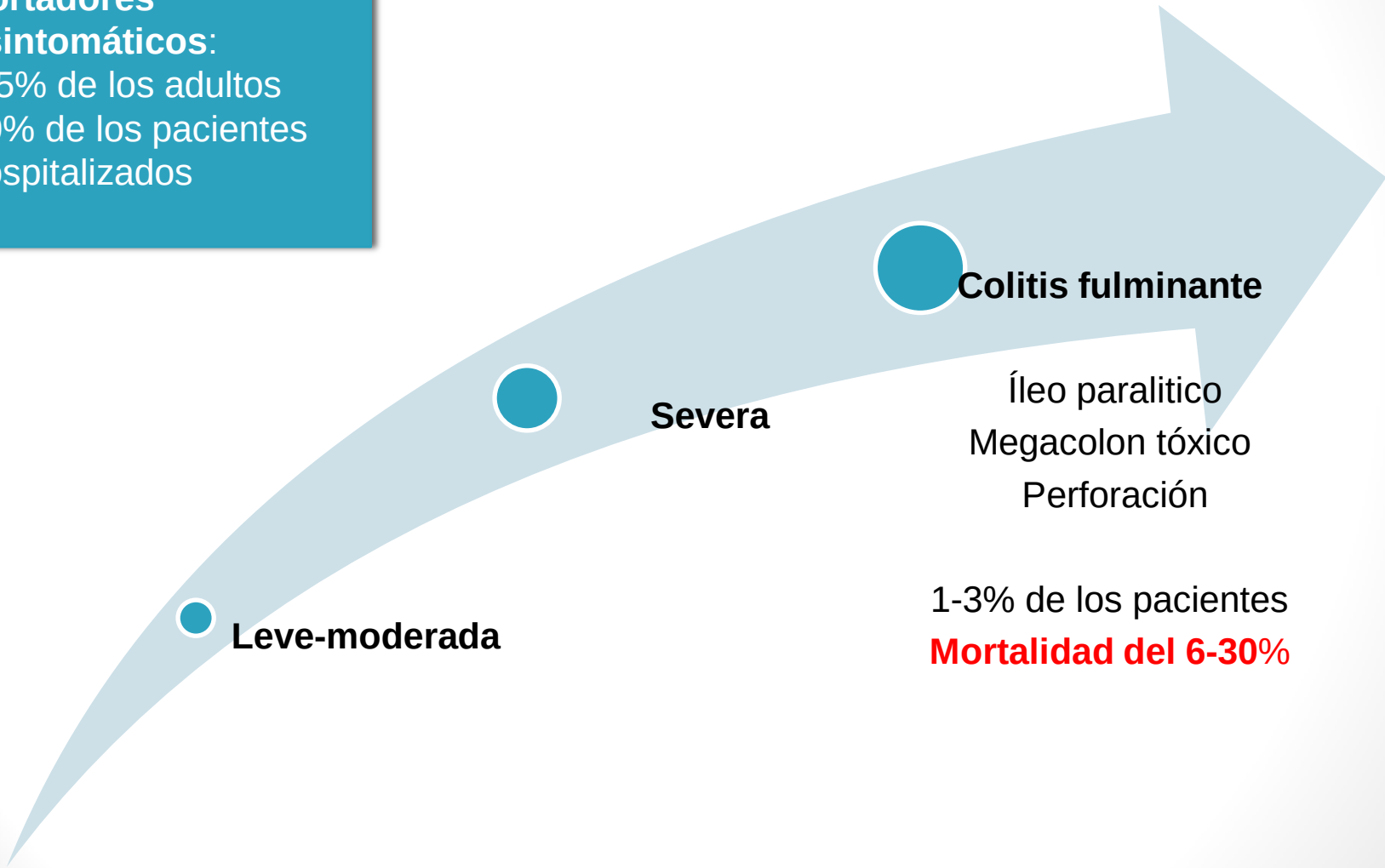
Denise Drudy [a,*], Séamus Fanning [a], Lorraine Kyne [b]

Summary *Clostridium difficile* is a major cause of infectious diarrhea in hospitalized patients. Many pathogenic strains of *Clostridium difficile* produce two toxins TcdA and TcdB, both of which are pro-inflammatory and enterotoxic in human intestine. Clinically relevant toxin A-negative, toxin B-positive (A^-B^+) strains of *Clostridium difficile* that cause diarrhea and colitis in humans have been isolated with increasing frequency worldwide. This perspective describes these important toxin variant strains and highlights the need to use *Clostridium difficile* diagnostic methods that can detect both TcdA and TcdB.


Clínica
DIAGNÓSTICO
Colonoscopia
Pruebas de laboratorio

Manifestaciones Clínicas

Portadores asintomáticos:
3-5% de los adultos
50% de los pacientes hospitalizados



Manifestaciones Clínicas

- **Diarrea** (3 deposiciones acuosas por mas de 2 días)
- **Cólicos abdominales**
- **Sin síntomas sistémicos**
- **Colonoscopia normal**

Leve-moderado

Manifestaciones clínicas

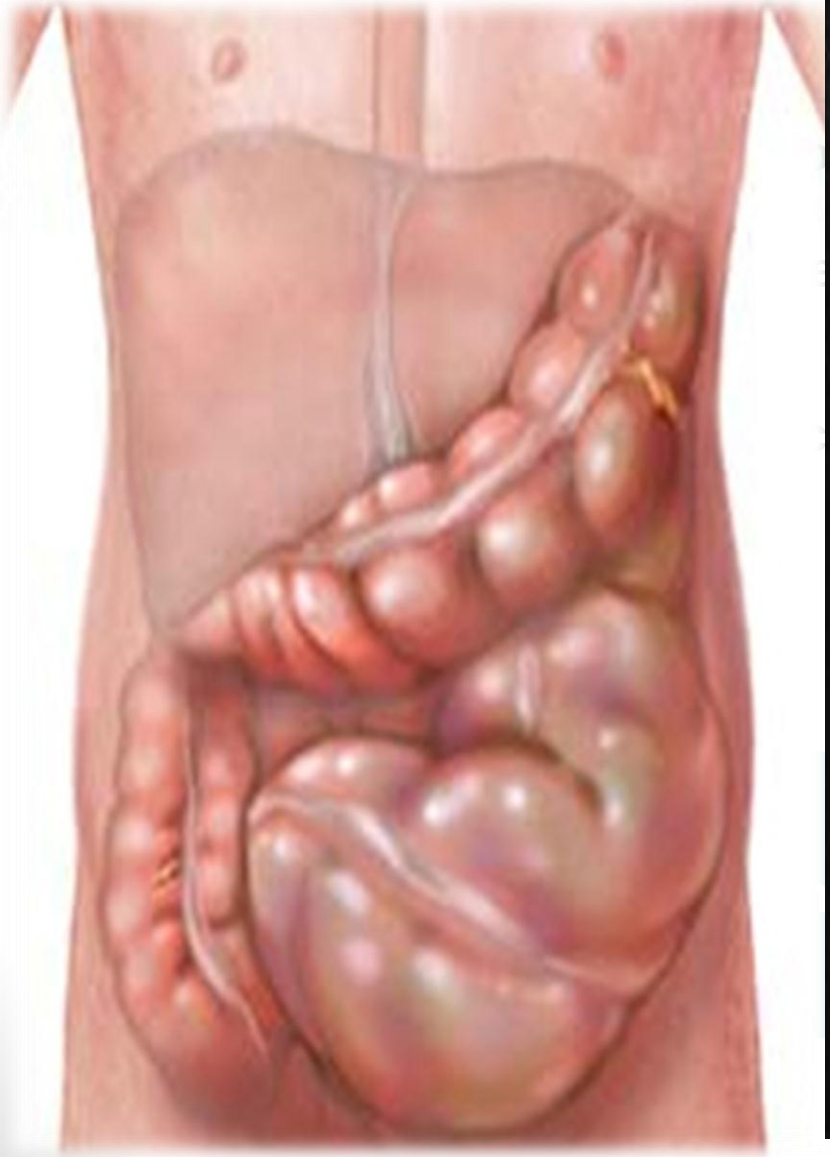
- **Diarrea** (≥15 deposiciones día)
- **Distensión y cólicos abdominales**
- **Síntomas sistémicos:** fiebre, astenia, leucocitosis y leucocitos fecales
- **Colonoscopia: pseudomembranas**

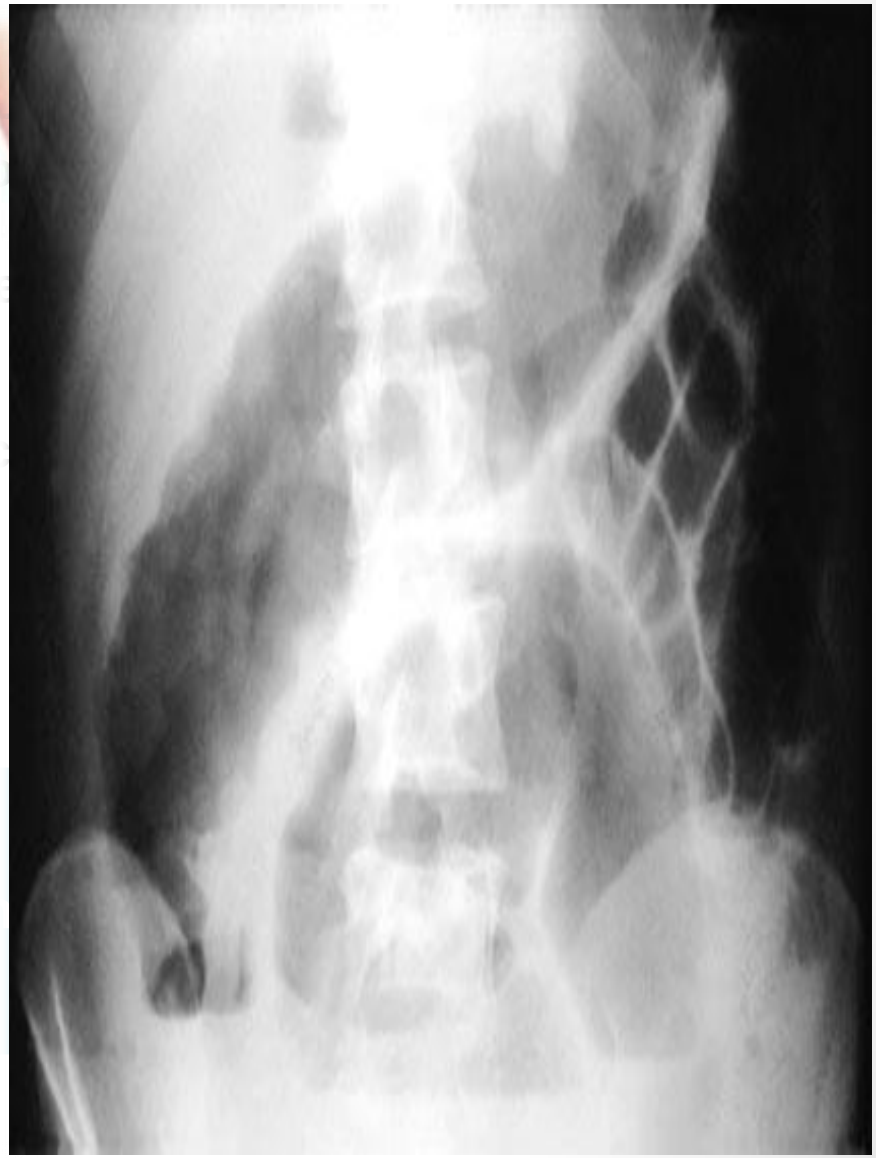
Severo

Complicaciones:

Deshidratación, Alteraciones Electrolíticas, Hipotensión, Hipoalbuminemia, Artritis Reactiva Poliarticular

Manifestaciones Clínicas





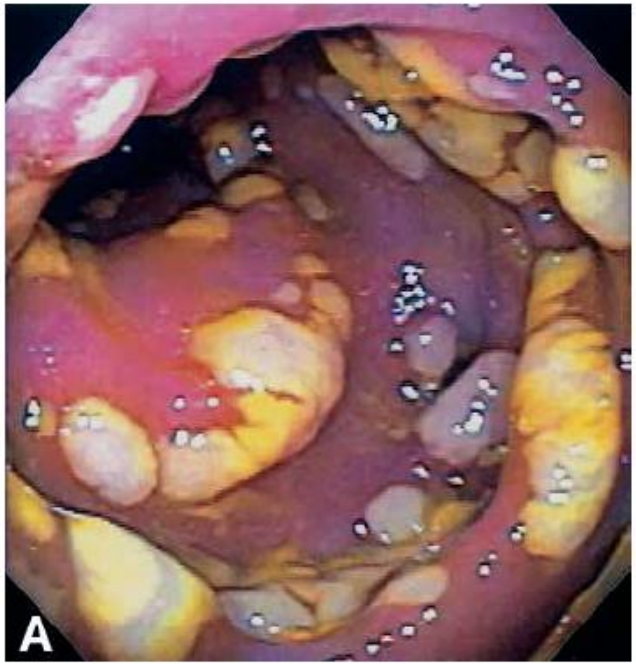
Pruebas de Laboratorio

Tabla 19-1 Métodos de detección de *Clostridium difficile*

Prueba	Sensibilidad (%)	Especificidad (%)
Análisis de citotoxicidad celular	92,7-100	99-100
Cultivo tisular	96,4	99,1
ELISA para toxina A + B	66-96,2	93,5-100
ELISA para toxina A	65,4-88,3	65,4-100
Reacción en cadena de la polimerasa	87-91,5	96-100

Adaptada de Aslam y Musher.

Aslam S, Musher DM. An update on diagnosis, treatment, and prevention of Clostridium difficile-associated disease. Gastroenterol Clin North Am. 2006 Jun;35(2):315-35.



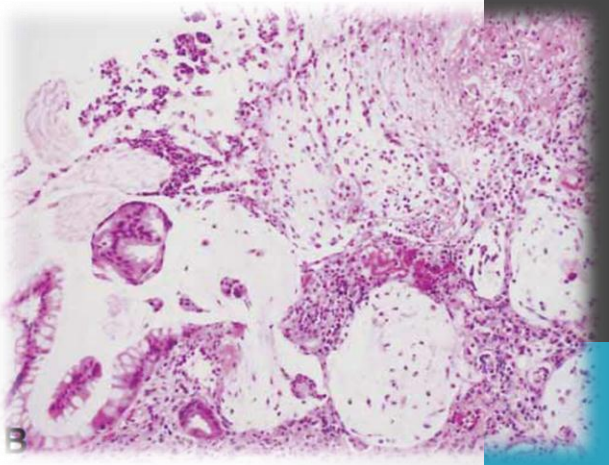
Colonoscopia

- Se encuentra en recto y colon izquierdo 77% de los casos, en el **10% están circunscritas exclusivamente al colon derecho**.

Table 3. Histology of Pseudomembranous Colitis

Stage	Findings
Type I, or early lesion	Patchy epithelial necrosis Exudate of fibrin and neutrophils into colonic lumen
Type II	Volcano or summit lesion erupting from a focus of epithelial ulceration Normal surrounding mucosa
Type III	Diffuse epithelial necrosis and ulceration overlying pseudomembrane

Data from Price and Davies.[14]



Boardman, Amy. "Diagnosis and management of pseudomembranous colitis and clostridium difficile-associated disease." *Primary care update for ob/gyns* 5, no. 5 (1998): 219-228.

Diagnostico Diferencial

DIARREA ASOCIADA A ANTIBIÓTICO POR C. DIFFICILE

DIARREA ASOCIADA A ANTIBIÓTICO DE CAUSA DESCONOCIDA

TRATAMIENTO

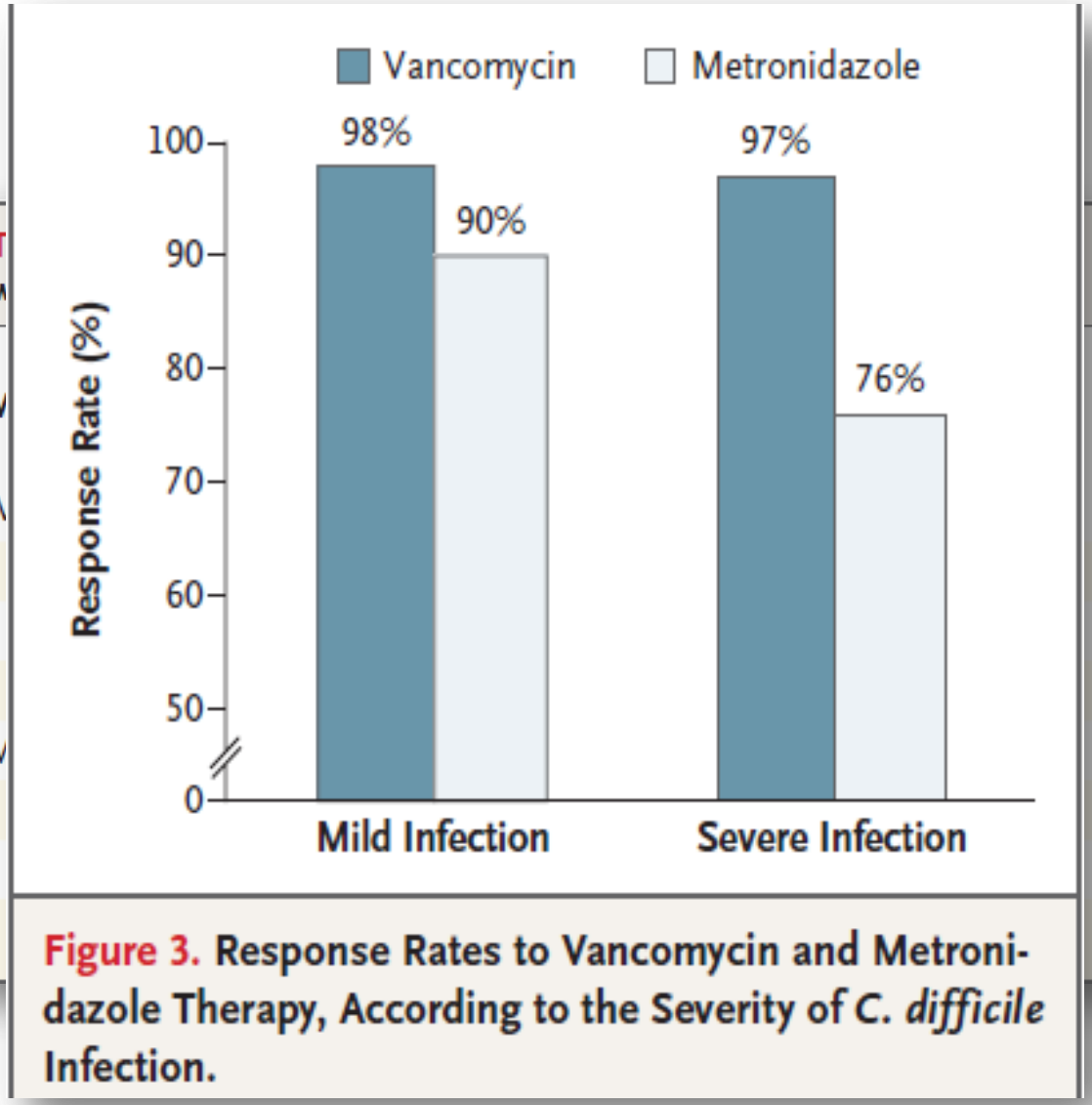


Figure 3. Response Rates to Vancomycin and Metronidazole Therapy, According to the Severity of *C. difficile* Infection.

Kelly CP, LaMont JT. **Clostridium difficile--more difficult than ever**. N Engl J Med. 2008 Oct 30;359(18):1932-40

Episodio Inicial

Leve- moderado	Severo/ función intestinal normal	severo/ íleo
• **Metronidazol** 500 mg oral. 3 veces al día, por 10-14 días.	• **Vancomicina** 125 mg (efectiva solo enteral). 4 veces al día, por 10-14 días	• **Vancomicina** 125 mg. (efectiva solo enteral) 4 veces al día por 10-14 días **+ Metronidazol IV** • Sin respuesta al tratamiento médico: Cirugía

Kelly CP, LaMont JT. **Clostridium difficile--more difficult than ever**. N Engl J Med. 2008 Oct 30;359(18):1932-40

Recurrencias

1ra recurrencia	2da recurrencia	3ra recurrencia
• **Igual al tratamiento inicial.**	• **Vancomicina:** • 125 mg oral,4 veces al día por 14 días • 125 mg 2 veces al día por 7 días • 125 mg 1 vez al día por 7 días • 125 mg cada 2 días por 8 días • 125 mg 1 vez cada 3 días por 15 días	• **Vancomicina** 125 mg oral QID por 14 días seguido de Rifaximina 400 mg 2 veces al día por 14 días.

Kelly CP, LaMont JT. **Clostridium difficile--more difficult than ever**. N Engl J Med. 2008 Oct 30;359(18):1932-40

Otras Opciones de Tratamiento

- **Inmunoglobulina humana combinada** IV 400 mg/ Kg 1 vez cada 3 semanas. Total 2-3 dosis.
- **“Transplante fecal”**

Kelly CP, LaMont JT. **Clostridium difficile--more difficult than ever**. N Engl J Med. 2008 Oct 30;359(18):1932-40

GRACIAS