

Prevention and Management of *Clostridium difficile* epidemics

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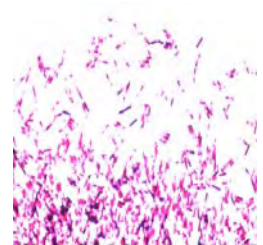
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Clostridium difficile

Spore-forming, obligate, anaerobic gram-positive rods

Toxins:

- 308 kDa enterotoxin (TcdA)
- 269 kDa cytotoxin (TcdB)
- binary toxin (BT)



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Clostridium difficile Associated Disease, Mortality & Cost

- Asymptomatic colonization
- Diarrhea (0.5 to 20%) & Relapses
- Complications:
 - Pseudomembranous colitis (>35 %)
 - Toxic megacolon (>65%)
 - Protein-losing enteropathy
 - Reactive arthritis
- Cost:
 - UK: 5-15 000 €/case;
 - EU: 3 billion €/yr



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Risk factors for *C. difficile*-associated diarrhea

- Antibiotic administration
- Chemotherapy
- Elderly age
- Bedridden
- Duration of hospital (ICU) stay
- Underlying disease
- Antacids, PPI ?
- Intestinal surgery, obstruction and/or tube feeding

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Toxigenic *Clostridium difficile*: Detection Assays

- Gold standard: stool cytotoxin assay (48 h) & selective culture for toxigenic *C. difficile* (96 h)
- ELISA: toxin A and/or B: 30-80 % sensitivity
- Immuno-chromatography (20 min): GDH combined with toxin: sensitivity > 90 % with PPV >99%
- Real-time PCR (<24 h): in house test with similar performance

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ESGCD Paneuropean Study of CDAD Barbut 16th ECCMID 2006

Incidence CDAD/10,000 patient-days varies widely between 23 hospitals:

2.45 ± 1.8 (range : 0.14- 7.1)

Hospitals NL : 0.13-0.14
Hospitals F: 0.5-1.2
Hospitals G, B: 2-7



USA : 12.1 CDAD /10,000 patients days (range 3-25.1) (Sohn, ICHE 2005)
Québec : 12.8 /10,000 patients-days (INSPQ report, 2005)

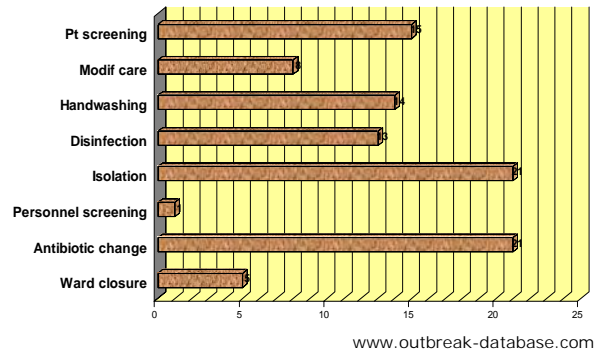
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C.difficile Sources of Nosocomial Infection

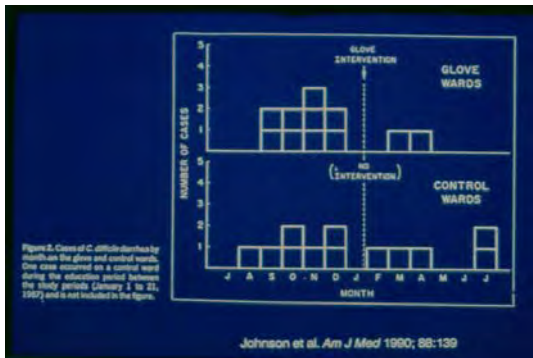
- **Endogenous :**
 - Antibiotic exposure: amplification & toxin production
- **Exogenous: (spores!)**
 - Cross-colonisation by healthcare workers (hands)
 - Indirect contact with surfaces & fomites
 - Medical instruments

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Percent C.difficile Outbreaks with Control Measures



Protective Efficacy of Gloves for C.difficile Transmission



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A Large Outbreak of C. difficile – Associated Disease with Unexpected Proportion of Deaths and Colectomies at a Teaching Hospital

■ From 1999 to 2000-2001:

- *C. difficile* - associated disease increased from 2.7 to 6.8 cases per 1,000 discharges ($P < 0.001$).
- Severe disease increased from 5.6% patients with nosocomial *C. difficile* to 8.8% cases, resulting in 18 of 37 deaths ($P = 0.004$).

Muto et al., Infect Control Hosp Epidemiol 2005; 26: 273-80

Etiologic Fractions for Antibiotics Associated with C. difficile Disease

Drug	Proportion of disease presumably caused by drug
Clindamycin	10.0%
Ceftriaxone	6.7%
Levofloxacin	30.8%

Muto et al., Infect Control Hosp Epidemiol 2005; 26: 273-80
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Clostridium difficile-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity

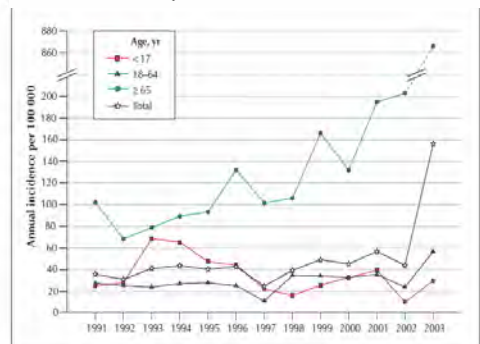
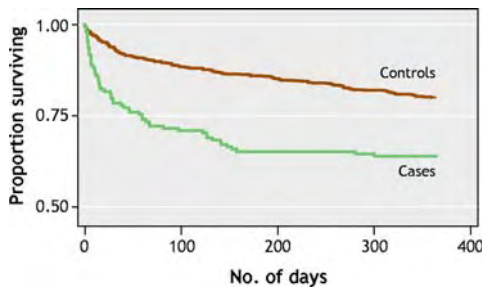


Fig. 1: Annual incidence (per 100 000 population) of *Clostridium difficile*-associated diarrhea (CDAD) in Sherbrooke, Que., 1991–2003.

Pépin J CMAJ 2004; 171: 468

Kaplan-Meier plot showing probability of death since diagnosis among inpatients in whom nosocomial *Clostridium difficile*-associated disease (CDAD) developed and among matched control subjects without CDAD



Pepin, J. et al. CMAJ 2005;173:1037-1042

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Mortality at 30 days among inpatients with CDAD, Québec, by Age and Comorbidity

Variable	Mortality at 30 d		
	No. (%) of case subjects	No. (%) of control subjects	Attributable mortality (95% CI), %
Age, yr			
18-64	1/16 (6.3)	2/64 (3.1)	3.2 (-7.4 to 29.3)
65-74	12/62 (19.4)	13/257 (5.1)	14.3 (5.0 to 26.9)
≥ 75	24/83 (28.9)	31/335 (9.3)	19.7 (9.8 to 31.2)
Charlson Comorbidity Index score			
0	0/11 (0)	1/55 (1.8)	-1.8 (-30.4 to 11.0)
1-3	16/69 (23.2)	16/305 (5.2)	17.9 (8.4 to 30.1)
4-6	15/59 (25.4)	23/225 (10.2)	15.2 (4.0 to 28.9)
≥ 7	6/22 (27.3)	6/71 (8.5)	18.8 (0.4 to 42.5)

Note: CI = confidence interval.

Pepin, J. et al. CMAJ 2005;173:1037-1042

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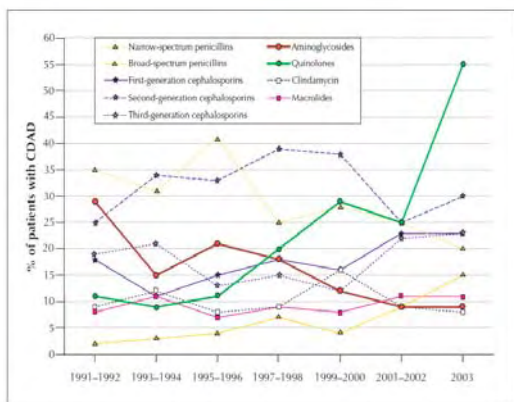


Fig. 2: Proportions of patients with CDAD by class of antibiotic received in the 2 months preceding the diagnosis of CDAD, 1991-2003.

Pépin J. CMAJ 2004; 171:466¹⁵

Pandemic *Clostridium difficile* Type 027

- Large and difficult to control outbreaks in North America, United Kingdom, the Netherlands, Belgium and France in 2004-06
- Severe course;
- Increased rate of metronidazole treatment failure
- High mortality
- Ribotype 027, clonally-related

McDonald C. *Infect Control and Epidemiol.* 2005;26:672-5;

CDR weekly 2005;15(24): news.

Kuijper EJ. *Ned Tijdschr Geneesk.* 2005; 49:2087-9

Eurosurveillance 2005-06

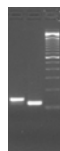
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Characteristics of Pandemic Strain of *C. difficile* ribotype 027

Characteristics:

- tcdA* and *tcdB*
- tcdC* (toxin regulator gene)
- ermB*
- binary toxin

positive
18 bp deletion
negative
positive



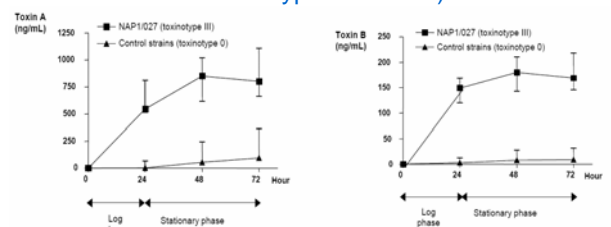
Genotyping:

- PCR-ribotyping
- Toxinotyping
- PFGE

027
IIIb
Diverse

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In vitro Production of Toxins A and B by *C. difficile* Isolates (25 toxinotype III/027 strains and 25 toxinotype 0 isolates)



16 (toxin A) and 23 (toxin B) times increase of toxin concentrations

Waruy et al. 2005; Lancet 366: 1079-84

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Prevention of Nosocomial *C.difficile*

- Quantify the attributable fraction due to imported cases, endogenous infection, environmental acquisition and patient-to-patient transmission (surveillance & typing)
- Barrier precautions (gloves & gowns) for diarrheal patients; if failure: cohorting/ward closure
- Prudent antibiotic use
- Environmental decontamination with hypochlorite
- Hand hygiene with soap then alcohol rub
- Systematic *C.difficile* detection and culture for nosocomial diarrhea; refer strains to ref lab for typing
- Screening & isolation for diarrheal patients transferred from institutions with epidemic strain ?

Kuijper E *Clin Microbiol Infect* 2006;12(suppl. 6):2-18