C. difficile Associated Diarrhea
Dr. Andreas Widmer, University Hospital, Basel, Switzerland
Sponsored by WHO First Global Patient Safety Challenge, Clean Care is Safer Care

C.difficile Associated Diarrhea

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Hosted by Dr. Kate Ellingson
US Centers for Disease Control

Sponsored by
WHO Patient Safety Challenge
Clean Care is Safer Care

Outline

- Background
- Diseases associtated with *C.difficile*
- Diagnostic issues
- New Strains NAP1/027 078 Binary toxin
- Therapy
- Infection control

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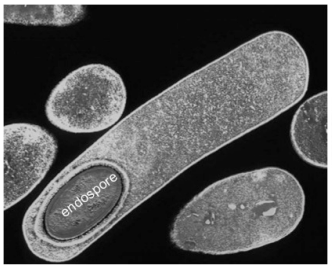
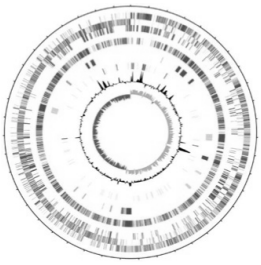
Coloured transmission electron micrograph of *Clostridium difficile* forming an endospore





Aslam S. et al. Lancet Infect Dis 2005;5: 549–57

Nature Genetics 2006;**38**: 779 - 786

History

- 1893 – first case of pseudomembraneous colitis reported as *diphtheritic colitis,* discovered in 1935 by Hall & O'Toole.
- 1935 – *"Bacillus difficile"* isolated.
- 1970s – antibiotic-asociated colitis identified.
- 1978 – *C. difficile* toxins identified in humans.
- 1979 – therapy with vancomycin or metronidazole
- 2000 – increased incidence and virulence
- 2010 – New treatment options, new diagnostic tools

Reservoirs for Toxigenic *C. difficile*

- 15% to 70% of healthy neonates (to age 1 y)
- <3% of healthy adults (up to 15% of inpatients)
- 10% to 20% of hospitalized patients, especially on antibiotics
- Most disease-causing strains are exogenously acquired
- **Spores survive in the environment for at least 6 months**
  - Hospital environment
  - HCW hands

• **Water**	
river	**(88%)**
lake	**(47%)**
sea	**(44%)**
swimming pool	**(50%)**
mains tap 1/18	**(6%)**
• **Soil**	**(21%)**
• **Raw vegetables**	**(2%)**
• **Private residences**	**(2%)**
• **Dogs**	**(10%)**
• **Cats**	**(2%)**
• **4 hospital environments**	**(20%)**

Al Saif et al, J Med Microbiol 1996;45:133-7

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www.webbertraining.com

C.difficile: Basics (-2000)

	Toxin A (enterotoxin)	Toxin B (cytotoxin)
Molecular weight, kD	308	270
Chemical properties	Inactivated by proteases Heat- and acid-labile	Inactivated by proteases Heat- and acid-labile
Mechanism	Causes mucosal damage, Chemo-attraction for neutrophils, Activator of macrophages/mast cells	Inhibits adenylate cyclase Disrupts action filaments
Effects on animals	Hemorrhagic enterocolitis Increased intestinal fluid secretion Increased vascular permeability	**Ten times more potent than toxin A** Increased vascular permeability Lethal in high doses

- ~25% of *C. difficile* isolates are toxin A-/B- (Fekety *JAMA* 1993)

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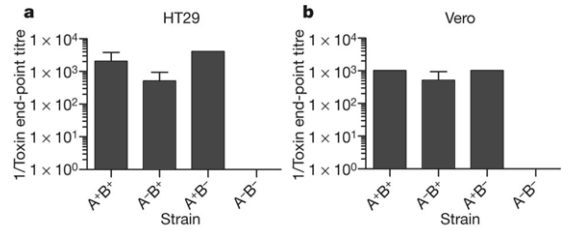
In vitro cytotoxicity of *C.difficile* strain A^+B^+ and the three mutants A^-B^+, A^+B^- and A^-B^-



a, **b**, Supernatants of the parental strain A^+B^+ and the three mutants A^-B^+, A^+B^- and A^-B^- were used in cell culture assays to measure cytotoxicity. HT29 cells (**a**) and Vero cells (**b**) were cultured to a flat monolayer before adding *C. difficile* supernatants in fourfold dilutions series. After a 24-h incubation, toxin end-point titres were determined. Data represent the mean ± standard deviation; *n* =

Toxin A and Toxin B are equivally pathogenic.

SA Kuehne *et al*. Nature. 2010 Oct 7;467(7316):711-3.

Typical Incubation times for Pathogens causing Nosocoimal Diarrhea

4 6 12 24 36 48 72 hrs 5 7 14 18 21 Tage

S.aureus
B.cereus EHEC / ETEC
Toxin Salmonellen
Clostridium perfringens
Vibrio cholerae
Listerien
Shigellen
Rotavirus
Norwalk
Campylobacter ***C.difficile***
Cyclospora cayetanensis
Cryptosporidien
Giardia lamblia
Listerien /Typhus
E.histolytica /Aeromonas

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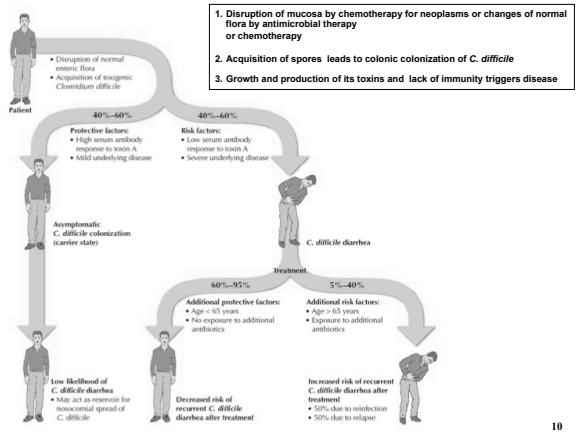
1. Disruption of mucosa by chemotherapy for neoplasms or changes of normal flora by antimicrobial therapy or chemotherapy
2. Acquisition of spores leads to colonic colonization of *C. difficile*
3. Growth and production of its toxins and lack of immunity triggers disease



10

Poutanen SM CMAJ 2004;171(1):51-8

Clinical Pictures of CDAD

Type of infection	Diarrhea	Other symptoms	Clinical exam	endoscopy
Asymptomatic colonization	No	No	normal	normal
CDAD without colitis	Some diarrhea	Abdominal cramps	Some abdominal Tendernes	normal
CDAD with colitis	Profous diarrhea, fecal leucoytes, hemocult pos	Loss of appetite, abnausea, fever, vomiting, dehydratation,	Serious abdominal tendnerness	Localized colitis
Pseudomembranic colitis	Profous diarrhea, fecal leucoytes, hemocult pos	Loss of appetite, nausea, fever, vomiting, abdominal pain, dehydratation,	Tenderness, local peritonitis	Adherent, yellow Plaques 2-10mm, Pseudomembranes (colonoscopy)
Fulminant colitis	Profous diarrhea, fecal leucoytes, hemocult pos development of paralytic ileus	Fever, abdominal pain, peritonitis, septic syndrome, paralytic ileus	Peritonitis Sepsis to septic shock	Contraindicated, CT-scan

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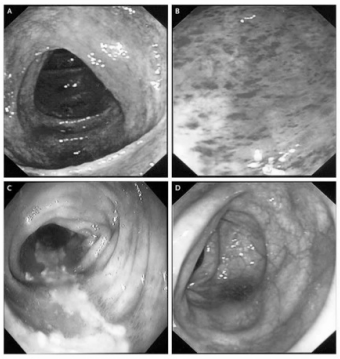
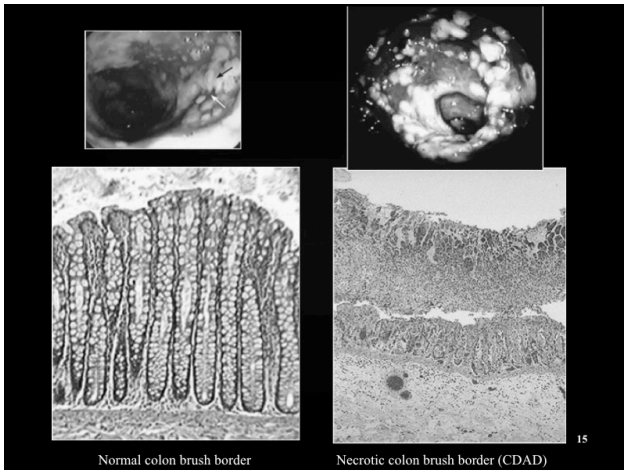
Colonoscopic Images in Two Patients with Antibiotic-Associated Hemorrhagic Colitis by *K.oxytoca*



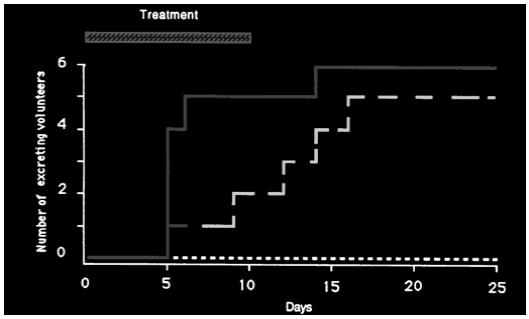
Hogenauer C et al. N Engl J Med 2006;355:2418-2426

13



15

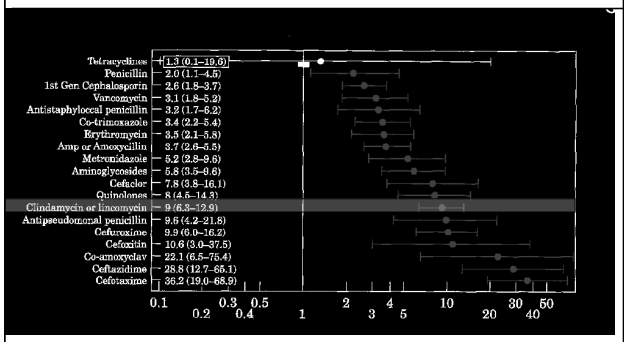
Excretion of *C. difficile* by healthy volunteers treated for 10 days with placebo or antibiotics



Chachaty E. AAC 1992;36:2009-2013

15

Pooled Odds Ratio for each Antibiotic in Relation to CDAD



16

Bignardi GE. J Hosp Infection (1998) 40: I -I 5

Risk of Contributing to CDAD

High Risk	Medium Risk	Low Risk
Fluoroquinoline	Azithromycin	Antifolate and/or sulfonamide
Ciprofloxacin	Clarithromycin	Sulfamethoxazole
Levofloxacin	Erythromycin	Sulfamethoxazole/trimethoprim
Moxifloxacin	Pristinamycin	Sulfasalazine
Norfloxacin	Roxithromycin	Trimethoprim
Ofloxacin	Monobactam	Tetracycline
Lincosamide	Aztreonam	Doxycycline
Clindamycin	Streptogramin	Minocycline
Penicillin (extended spectrum)	Dalfopristin/quinupristin	Tetracycline
Pivampicillin		Tigecycline
Temocillin		

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Mullane KM. Clinical Infectious Diseases 2011;53(5):440–447

High Risk	Medium Risk	Low Risk
Carbapenem	Penicillin (β-lactamase sensitive)	Aminoglycoside
Cilastatin/imipenem	Benzylpenicillin (penicillin G)	Amikacin
Ertapenem	Phenoxymethylpenicillin (penicillin V)	Gentamicin
Imipenem	Penicillin (β-lactamase resistant)	Kanamycin
Meropenem	Cloxacillin	Neomycin
2nd generation cephalosporin	Flucloxacillin	Cell wall synthesis inhibitor
Cefaclor	Oxacillin	Fosfomycin
Cefoxitin	Nafcillin	Glycopeptide
Cefprozil	Penicillin (extended spectrum, combination)	Teicoplanin
Cefuroxime	Amoxicillin	Imidazole
3rd generation cephalosporin	Amoxicillin/clavulanate	Ornidazole
Cefdinir	Amoxicillin/clarithromycin/lansoprazole	Lipopeptides
Cefditoren	Ampicillin	Daptomycin
Cefixime	Ampicillin/sulbactam	Nitrofuran
Cefotaxime	Piperacillin	Nitrofurantoin
Cefpodoxime	Piperacillin/tazobactam	Oxolidinone
Ceftazidime	Ticarcillin/clavulanate	Linezolid
Ceftibuten	1st generation cephalosporin	Polymyxin
Ceftizoxime	Cefadroxil	Colistin
Ceftriaxone	Cefalexin	Rifamycin
4th generation cephalosporin	Cefazolin	Rifampicin
Cefepime	Macrolide	Rifampin

Mullane KM. Clinical Infectious Diseases 2011;53 (5):440–447

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www.webbertraining.com

Risk factors for CDAD

- **Age >65y**
- **Malignant Disease**
  - **Leukemia**
  - **While under chemotherapy**
- **Multiple Antibiotics**
- **Proton pump inhibitors**
- **Long hospital stay**

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Risk factors for Dissemination of *C.difficile*

- **Strain's epidemicity and virulence**
  (Wilcox et al, J Hosp Infect 1997;37:331-343)
- **Susceptibility of the patient**
  (Barbut Bull Soc Fr Microbiol 2002;17 (2)
- **Antibiotic pressures operating on the ward or hospital**
  (Wilcox et al, J Hosp Infect Lett. to the Editor 1997, ECCMID Glasgow 2003)
- **Level of patient's hygiene and clinical status**
  (Worsley M.A., JAC 1998;41,suppl C:59-66)
- **Quality of environmental cleaning (floors, furniture and equipment) and the choice of the cleaning product**
  (Jones et al, Lancet;352:505-6/Wilcox and Fawley, Lancet 2000;356:1324)
- **Compliance with standard and contact precautions: hand hygiene, gloves use, symptomatic patient's isolation**
  (Johnson et al, Am J Med 1990;88:137-40/Struelens et al, Am J Med, 1991;91:138S-144S)

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Table I
Positive predictive value (%) of *Clostridium difficile* toxin tests compared to cytotoxigenic culture, at different prevalences of *C. difficile* disease

Prevalence	Positive predictive value (%)				
	2%	4%	6%	8%	10%
Cytotoxin assay	67.7	81.1	86.8	89.9	92.0
Premier Toxin A + B	39.5	57.1	67.1	73.5	78.0
Vidas *C. difficile* toxin A & B	37.3	54.9	65.1	71.7	76.4
GA *Clostridium difficile* antigen	14.0	24.9	33.7	40.9	47.0
Ridascreen toxin A/B	21.7	36.1	46.4	54.1	60.1
Techlab Toxin A/B II	29.0	45.5	56.1	63.5	69.0
Remel ProSpecT	19.8	33.5	43.6	51.3	57.4
Remel Xpect	69.0	82.0	87.5	90.5	92.4
Techlab Tox A/B Quik Chek	59.1	74.7	81.9	86.0	88.7
Premier Immunocard A + B	16.8	29.2	38.7	46.3	52.4

Chand MA. J Hosp Infect 2011;79:8-12

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Laboratory Testing for *Clostridium difficile* Infection

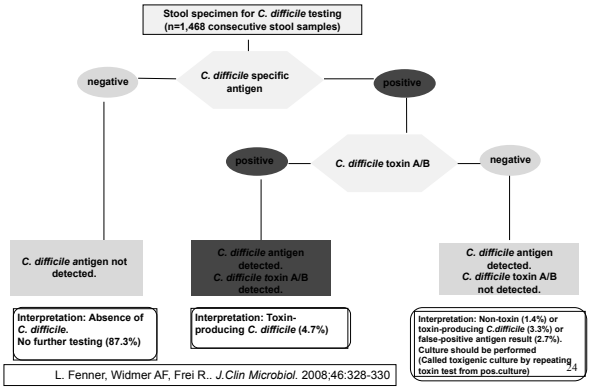
A b s t r a c t
… it is critical that CDI diagnosis be accurate so ongoing epidemiology, disease prevention, and treatment remain satisfactory.
We tested 10 diagnostic assays, including 1 commercial real-time polymerase chain reaction (qPCR) test for the laboratory detection of toxigenic C difficile on 1,000 stool samples. Sensitive culture for toxigenic C difficile using 2 types of media with broth enrichment defined the reference standard.
For the study, 1,000 tests were performed on samples from 919 patients. Of the samples, 146 contained evidence for toxigenic C difficile and represented the true-positive results. Only the US FDA qPCR assay and 1 glutamate dehydrogenase test were not statistically inferior to culture in sensitivity.

The common enzyme immunoassay tests all had sensitivity values less than 50%.
Clinical laboratory professionals need to seriously consider their diagnostic testing and use the assays that perform best for the detection of CDI.

23

Peterson LR & Ari Robicsek,Am J Clin Pathol 2011;136:372-380

Rapid Reliable Testing of *C.difficile*

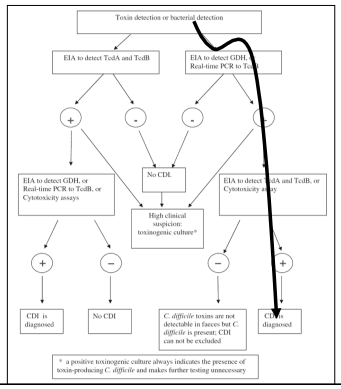


L. Fenner, Widmer AF, Frei R.. *J.Clin Microbiol.* 2008;46:328-330

24

Algorithm to diagnose CDI

European Society of Clinical Microbiology and Infectious Diseases (ESCMID):



Crobach MJT et al (A.Widmer) Clin Microbiol Infect 2009;15:1053-66

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Guideline 2010

American Society for Microbiology

AMERICAN SOCIETY FOR MICROBIOLOGY

A)

GDH assay

positive

negative = Negative for toxigenic *C. difficile*

Toxin A/B assay or Cytotoxin Neutralization

positive = Positive for Toxigenic *C. difficile*

negative

NAAT assay or Toxigenic Culture

positive = Positive for Toxigenic *C. difficile*

negative = Negative for Toxigenic *C. difficile*

GDH = glutamate dehydrogenase antigen **NAAT = nucleic acid amplification test**

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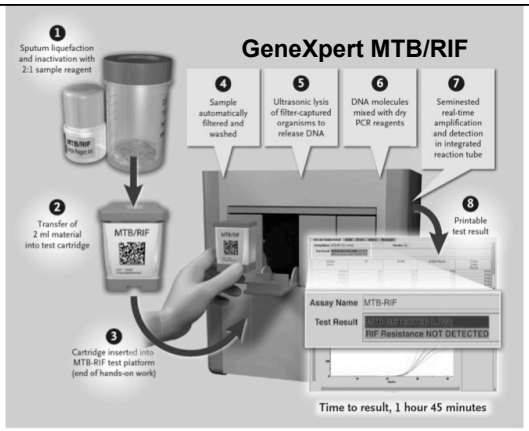
GeneXpert MTB/RIF



27

N Engl J Med 2010,363:1005-15

PCR

Xpert™ *C.difficile**

- Resultate in <1 Std.
- Detection of Toxin B, binary Toxin und *tcdC*-Deletion → NAP1 / PCR Ribotyp 027

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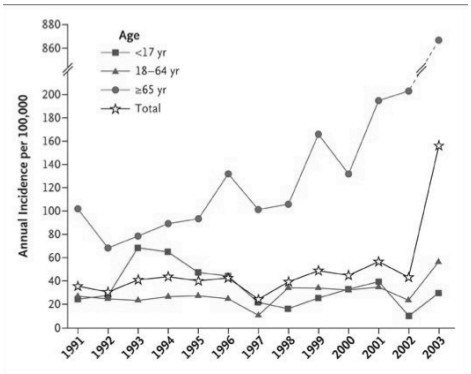
Annual Incidence (per 100,000 Population) of C. difficile Infection in Sherbrooke, Quebec, 1991–2003



31

Kelly C, LaMont J. N Engl J Med 2008;359:1932-1940

Impact of Quinolones on the Incidence of CDI

TABLE 1. Studies examining possible associations between fluoroquinolones and CDI[a]

Study (reference)	Study yr	Setting	*C. difficile* ribotype involved	Quinolone(s)	Study design (no. of positive cases/ total no. of cases)	Logistic regression analysis result(s)	Reported relative contribution to CDI cases (%)
Yip et al. (217)	1998	300-bed U.S. tertiary-care hospital	Unknown	Ciprofloxacin	Retrospective case-control study (27/54)	Ciprofloxacin OR = 9.5 Cephalosporin OR = 6.7	
McCusker et al. (129)	2001	778 beds, Veterans Affairs hospital, Baltimore, MD	Unknown	Levofloxacin, ciprofloxacin, gatifloxacin	Retrospective case-control study (30/60)	Fluoroquinolone OR = 12.7 Cephalosporin OR = 0.4 Clindamycin OR = 2.2	
Gaynes et al. (71)	2002	173-bed acute-care U.S. hospital	Unknown	Switch levofloxacin to gatifloxacin	Retrospective case-control study (37/59)	Clindamycin and increased duration of gatifloxacin therapy	
Muto et al. (139)	2000–2001	Pittsburgh, PA	Polyclonal	Levofloxacin	Retrospective case-control study	Levofloxacin OR = 2.0 (203/203)	31
Loo et al. (121)	2004	12 hospitals in Quebec (8 university and 4 community)	027	Ciprofloxacin, gatifloxacin, moxifloxacin	Prospective matched case-control study (237/237)	Cefotaxime OR = 5.4 Clindamycin OR = 4.8 Fluoroquinolone OR = 3.9 Cephalosporin OR = 3.8	6.7 10
Pepin et al. (154)	2003–2004	Teaching hospital, Sherbrook, Canada	027	Ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin	Retrospective cohort (293/5,619)	Fluoroquinolone adjusted hazard ratio = 3.44 Cephalosporin adjusted hazard ratio = 1.56–1.89 Clindamycin adjusted hazard ratio = 1.77	35.9 10 1.5
Kuzakowa et al. (98)	2002–2003	Community acute-care hospital in Maine	027	Levofloxacin, ciprofloxacin	Matched case-control study (68/127)	Fluoroquinolone OR = 3.22 Cephalosporin OR = 5.19	
McFarland et al. (134)	2004	400-bed Veterans Affairs hospital, Seattle, WA	Unknown	Gatifloxacin	Retrospective matched case-control study (184/184)	Clindamycin OR = 29.9 Penicillin OR = 4.1	
Biller et al. (23)	2003	320, acute-care, nonteaching U.S. hospital	027	Switch levofloxacin to moxifloxacin	Matched case-control study (50/100)	Moxifloxacin OR = 3.14 Cephalosporin OR = NS Clindamycin OR = NS	
Weiss et al. (207)	2007	Two 600-bed tertiary-care hospitals	027	Ciprofloxacin, levofloxacin, moxifloxacin	Case-control study (15/31)	Fluoroquinolone OR = 36.2 Cephalosporin OR = 19.1	
Debast et al. (50)	2005	341-bed community hospital	027	Ciprofloxacin	Prospective case-control study (45/90), including extra control group with non-CDI diarrhea (109)	Fluoroquinolone OR = 26.8 Cephalosporin OR = 7.8 Combination OR = 57.5	33 56

[a] NS, not significant.

Freeman J .CLIN MICROBIOL REV 2010, p. 529–549

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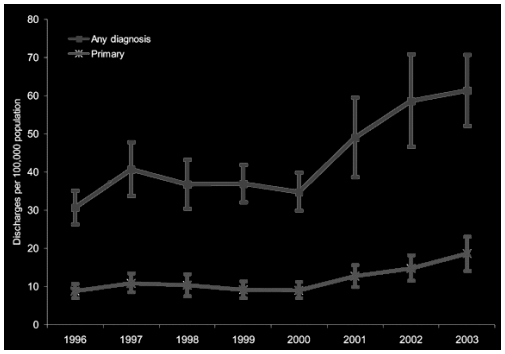
National estimates of US short-stay hospital discharges with *Clostridium difficile* listed as primary or as any diagnosis



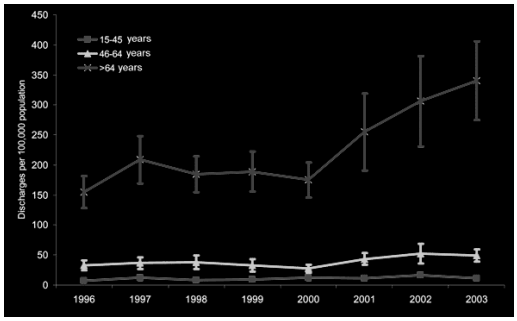
33

Cdiff_McDonald_EID06.ppt

Clifford LMD. EID 2006;12:409-15

Rates of US short-stay hospital discharges with *Clostridium difficile* listed as any diagnosis, by age

Because of low rates and the resulting uncertainty of yearly rate estimates, data for patients <15 years of age are not included.



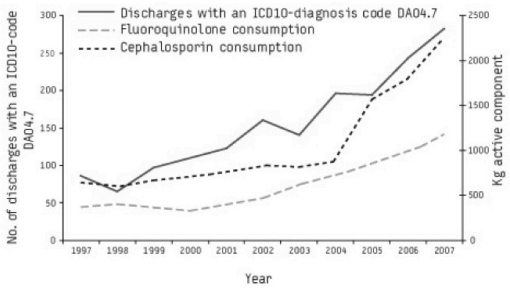
34

Cdiff_McDonald_EID06.ppt

Clifford LMD. EID 2006;12:409-15

FIGURE 1

Annual number of hospital discharges with enterocolitis caused by *Clostridium difficile* (ICD10 diagnosis code DA04.7) and annual consumption of fluoroquinolones and cephalosporins for human use, Denmark, 1997-2007



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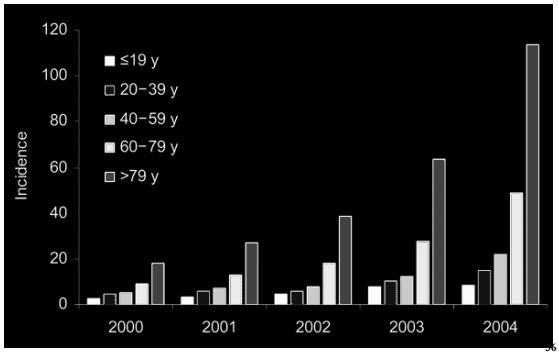
Source: [6]

Clostridium difficile in Discharged Inpatients



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Vonberg RP & Gastmeier P. EID 2007;13:180

C. difficile Ribotype 027 Distribution in Europe

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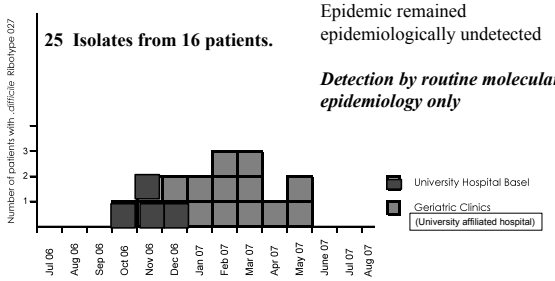
Euro Surveill 2007,12(6)

University of Basel Cluster von CDAD by *C. difficile* Ribotyp 027

25 Isolates from 16 patients.

Epidemic remained epidemiologically undetected

Detection by routine molecular epidemiology only



L. Fenner, A. F. Widmer, A. Stranden, M. Conzelmann, A. Goorhuis, C. Harmanus, E. J. Kuijper R. Frei
Clin Microbiol Infect Dis 2008

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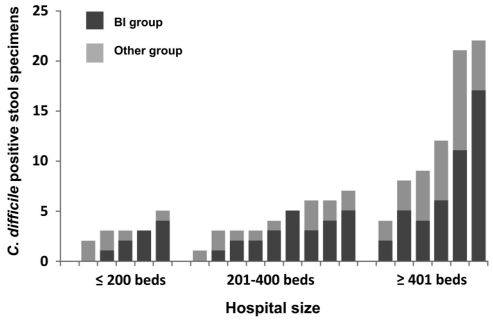
Distribution of The *C. difficile* NAP1/Ribotype 027 cases

among 20 hoSpitals that submitted stool specimens (Chicago and Cook County Departments).



Black SR. Infection Control and Hospital Epidemiology, Vol. 32, No. 9 (September 2011), pp. 897 - 902

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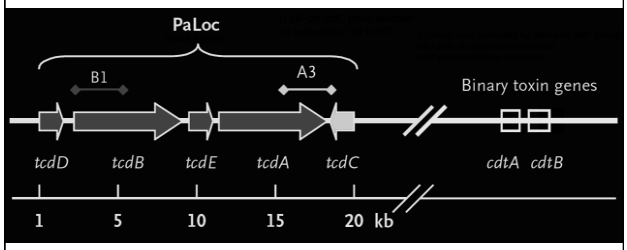
Major Genes in the Pathogenicity Locus (PaLoc) of *Clostridium difficile* NAP1/027 and Relation to the Genes for Binary Toxin



- *tcdA* codes for toxin A
- *tcdB* tocodes for toxin B
- *tcdC* putative negative regulator of toxin production
- *tcdD* positive regulator of toxin production
- *tcdE* holin production: release of toxin, holes in membranes

McDonald, L. et al. N Engl J Med 2005;353:2433-2441
Rupnik M. et al. J Med Microbiol 2005;54:113-7
Geric *J Clin Microbiol* 2003

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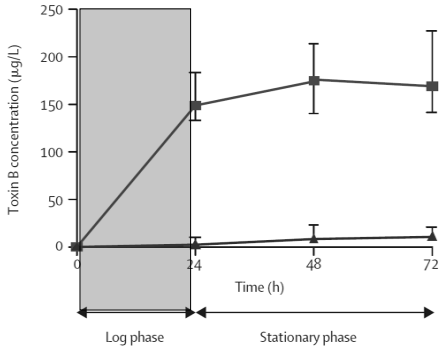
Comparison of Molecular Characteristics of 2 *C. difficile* Isolates with Historical Standard-Type Strains and a Recently Recognized Epidemic Strain, by Selected Characteristics, OH and PA, 2005

Characteristic	Standard Strain	Epidemic Strain	Ohio Strain	Pennsylvania Strain
Toxinotype	0	III	IX	XIV/XV
PFGE* pattern	< 80% related to NAP1†	NAP1	85% related to NAP1	64% related to NAP1
Binary toxin	–	+	+	+
18 bp deletion in *tcdC*	–	+	–	+

***Pulsed-field gel electrophoresis.**
† North American pulsed-field type 1.
McDonald LC. An epidemic, toxin gene-variant strain of *Clostridium difficile*. *N Engl J Med.* 2005;353:2433-2441.
CDC. *MMWR.* 2005;54:1201-1205.

41

Increased Toxin B production *in vitro*

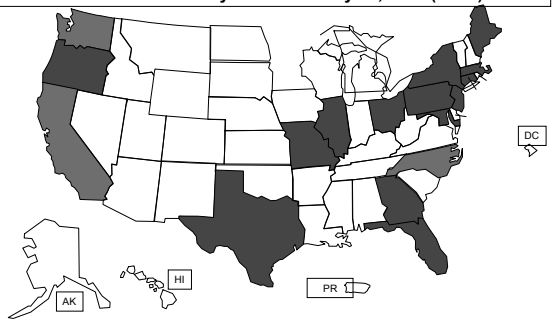


In vitro production of toxins A and B by *C difficile* isolates. Median concentration and IQRs are shown. *C difficile* strains included 25 toxinotype 0 and 15 NAP1/027 strains (toxinotype III) from various locations.

42

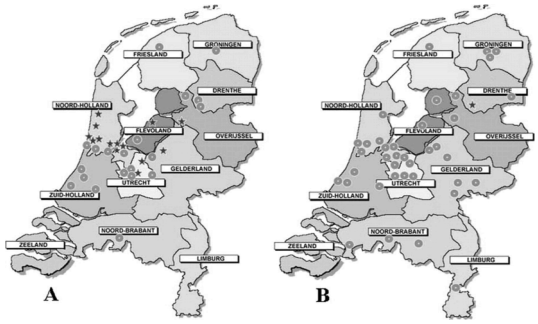
Warny M et al. Lancet 2005;366:1079-84

States with the North American Pulsed Field Type 1 strain of *C. difficile* confirmed by CDC as of May 15, 2006 (N=17)



43

Spread of PCR ribotype 027 across The Netherlands.

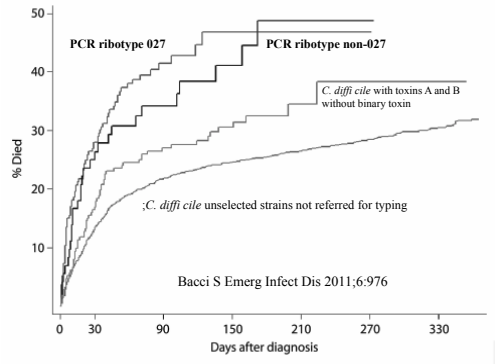


A: Spread of PCR ribotype 027 B, Spread of PCR ribotype 078

Goorhuis A et al. Clin Infect Dis. 2008;47:1162-1170

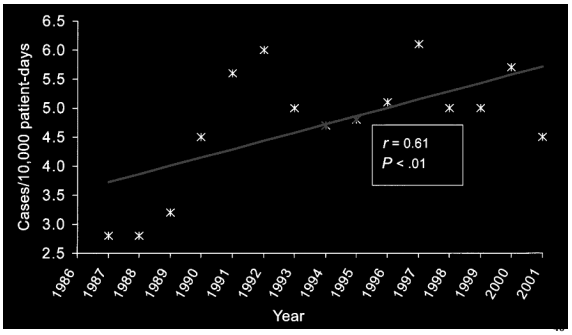
44

Patient survival with *C. difficile* infection by infection group Binary Toxin vs Ribotype 027



45

Annual *Clostridium difficile*–associated disease rates for hospitals with 1500 beds, by ICU surveillance component
(National Nosocomial Infections Surveillance System, 1987–2001)



Cdiff_Nov06.ppt

Archibald LK et al. JID 2004;189:1585-9

Nosocomial incidence of CDAD per 10,000 person-days (Jan-march/ 2005) and crude and adjusted rate ratios

Hospital characteristic	No. of hospitals (*n* = 39)	No. of CDAD cases (*n* = 2012)	No. of CDAD cases per 10,000 person-days[a]	Crude rate ratio (95% CI)	Adjusted rate ratio[b] (95% CI)
Clonal predominance					
Nonclonal[c]	6	143	9.0	1	1
Clonal B-B1	8	297	13.6	1.5 (1.2–1.8)	1.3 (1.1–1.6)
Clonal A	25	1572	21.2	2.4 (2.0–2.8)	2.0 (1.7–2.4)
Proportion of patients with age ≥65 years					
<35%	13	497	13.2	1	1
≥35%	26	1515	20.4	1.5 (1.4–1.7)	1.3 (1.1–1.4)
No. of beds					
<250 beds	15	501	16.9	1	…
≥250 beds	24	1511	18.4	1.1 (0.99–1.2)	…

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Hubert B et al, Clin Inf Dis 2007;44:238-244

Outline

- Background
- Diseases associtated with *C.difficile*
- Diagnostic issues
- New Strains NAP1/027 078 Binary toxin
- Therapy
- Infection control

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Association of CDI Treatment-Concurrent PPI Exposure With Recurrent CDI Within 90 Days

Model		HR (95% CI)	*P* Value
Unadjusted	Step 1: stop antibiotics, if possible	1.42 (1.11-1.82)	.006
Adjusted[a]		1.42 (1.10-1.83)	.008
Age stratified, y[a]			
<60 (n=189)		1.19 (0.56-2.55)	.65
60-80 (n=593)		1.32 (0.94-1.85)	.11
>80 (n=384)		1.86 (1.15-3.01)	.01
Non-CDI antibiotic exposure stratified[a]			
Antibiotic exposure (n=426)		1.71 (1.11-2.64)	.01
No additional antibiotic exposure (n=740)		1.30 (0.94-1.79)	.12

[a] Adjusted for age, incident CDI treatment, additional antibiotic exposure, length of hospital exposure, ischemic heart disease, esophageal disease, rheumatologic disease, peptic ulcer disease, pulmonary disease, and systemic corticosteroid use.

Linsky, A. et al. Arch Intern Med 2010;170:772-778.

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Step 1: stop antibiotics, if possible

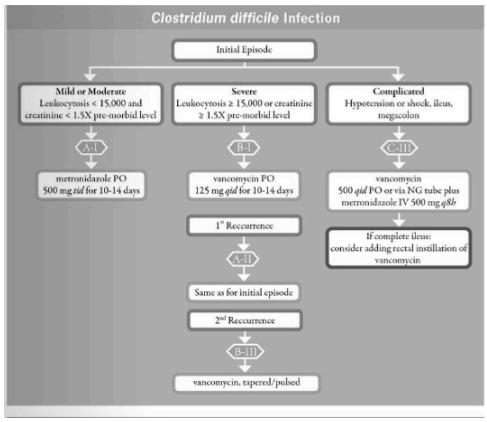
Table 2. Effect of Concomitant Antibiotic (CA) Therapy During Treatment and/or Follow-up Periods

Endpoint study period	No CA	≥1 CA	Difference, % (95% CI)	*P*
Clinical cure (*n* = 999)				
Treatment (days 1–10)	92.57 (747/807)	84.38 (162/192)	8.19 (2.98–13.89)	<.001
Recurrence (*n* = 794)				
Treatment (days 1–10)	17.88 (118/660)	23.88 (32/134)	−6.00 (−14.04 to 1.46)	.11
Follow-up (days 11–40)	17.74 (118/665)	24.81 (32/129)	−7.06 (−15.3 to 0.60)	.06
At any time (days 1–40)	17.57 (107/609)	23.24 (43/185)	−5.67 (−12.63 to 0.92)	.08
Global cure (*n* = 999)				
At any time (days 1–40)	74.72 (541/724)	65.82 (181/275)	8.91 (2.54–15.37)	.005

NOTE. Data are % (proportion) of subjects unless otherwise specified.

Mullane KM. Clinical Infectious Diseases 2011;53(5):440–447

50



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IDSA guidelines 2010

Table 2. Suggested Approaches to Therapy.*

Initial episode

Mild-to-moderate infection

Metronidazole at a dose of 500 mg orally 3 times daily for 10 to 14 days

Severe infection or unresponsiveness to or intolerance of metronidazole

Vancomycin at a dose of 125 mg orally 4 times daily for 10 to 14 days

First recurrence

Mild-to-moderate infection

Metronidazole at a dose of 500 mg orally 3 times daily for 10 to 14 days

Severe infection or unresponsiveness to or intolerance of metronidazole

Vancomycin at a dose of 125 mg orally 4 times daily for 10 to 14 days

Second recurrence†

Vancomycin in tapered and pulsed doses

125 mg 4 times daily for 14 days

125 mg 2 times daily for 7 days

125 mg once daily for 7 days

125 mg once every 2 days for 8 days (4 doses)

125 mg once every 3 days for 15 days (5 doses)

Third recurrence

Vancomycin at a dose of 125 mg orally 4 times daily for 14 days, followed by rifaximin at a dose of 400 mg twice daily for 14 days

Other options for recurrent infection

Intravenous immune globulin at a dose of 400 mg per kilogram of body weight once every 3 weeks for a total of 2 or 3 doses

Therapy with other microorganisms, including "fecal transplantation"

Suggested Approaches to Therapy

Kelly C, LaMont J. N Engl J Med 2008;359:1932-1940

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Treatment Failures and Recurrences of C. difficile Infection with Metronidazole and Vancomycin Therapy

Table 1. Treatment Failures and Recurrences of *C. difficile* Infection with Metronidazole and Vancomycin Therapy.*

Variable	No. of Studies	Treatment Failure	Recurrence
		no./total no. (%)	
Metronidazole			
Year 2000 or before	4	18/718 (2.5)	48/715 (6.7)
After 2000	5	275/1508 (18.2)	332/1162 (28.6)
Combined periods	9	293/2226 (13.2)	380/1877 (20.2)
Vancomycin			
Year 2000 or before	11	22/637 (3.5)	112/624 (17.9)
After 2000	2	2/71 (2.8)	36/181 (19.9)
Combined periods	13	24/708 (3.4)	148/805 (18.4)

Kelly C, LaMont J. N Engl J Med 2008;359:1932-1940

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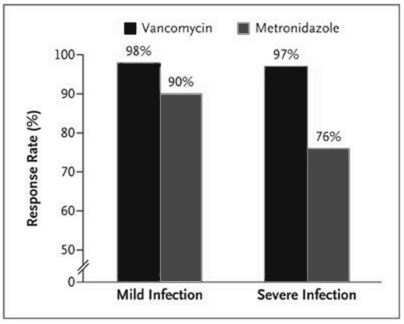
Response Rates to Vancomycin and Metronidazole Therapy, According to the Severity of *C. difficile* Infection



Kelly C, LaMont J. N Engl J Med 2008;359:1932-1940

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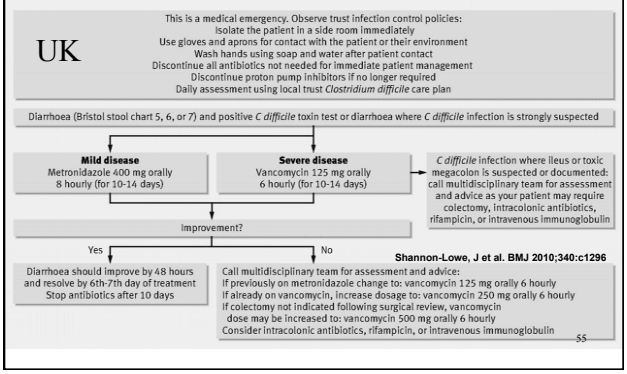
C. difficile Associated Diarrhea
Dr. Andreas Widmer, University Hospital, Basel, Switzerland
Sponsored by WHO First Global Patient Safety Challenge, Clean Care is Safer Care

Suggested management cascade for *C. difficile* infection

- **Severe disease: one or more**
- **- white blood cell count >15x109/l,**
- **- acutely rising serum creatinine (>50% baseline),**
- **- temperature >38.5{degrees}C,**
- **- clinical or radiological evidence of severe**



Shannon-Lowe, J et al. BMJ 2010;340:c1296

55

Treatment guidance document for CDAD

European Society of Clinical Microbiology and Infectious Diseases (ESCMID):

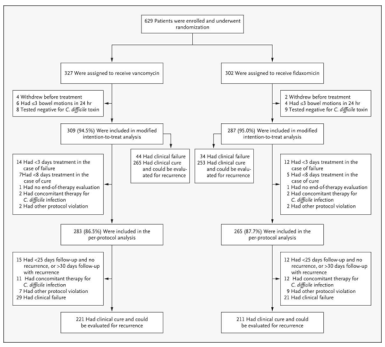
- ORAL
  - **non-severe: metronidazole 500 mg tid orally for 10 days (A-I)**
  - severe: vancomycin 125 mg qid* orally for 10 days (A-I)
  - *Oral vancomycin may be replaced by teicoplanin 100 mg bid, if available.
- IV
  - non-severe: metronidazole 500 mg tid intravenously for 10 days (A-III)
  - severe: metronidazole 500 mg tid intravenously for 10 days (A-III)
  - **+ intracolonic vancomycin 500 mg in 100 mL of normal saline every 4–12 h (C-III) and/orvancomycin 500 mg qid by nasogastric tube (C-III)**

Cohen SH et al. Clin Infect Dis. 2010;31:431–455; Debast SB et al. Clin Microbiol Infect 2009; 15: 1067–1079

UK: M. Wilcox, Department of Microbiology, Old Medical School Leeds General Infirmary, Leeds Teaching Hospitals & University of Leeds, Leeds, UK.
Sweden: L. Burman, Swedish Institute for Infectious Disease Control, Stockholm.
Belgium: M. Delmée, Universite' Catholique de Louvain, Bruxelles.
Germany: T. Welte, Department of Infectious Diseases, Hannover Medical School, Hannover.
France: B. Guery – Hopital Calmette – Pavillon Christiaens. Lille Cedex, France.
Spain: E. Bouza, Servicio de Microbiologı´a Cli´nica y E. Infecciosas Madrid, Spain.
Hungary: Z. Maszar´ovics, Department of Hygiene, Department of Infectious Diseases Markhot Ferenc County Hospital, Eger, Hungary.
Switzerland: A. F. Widmer. Facharzt fu´r Innere Medizin und Infektiologie Universita¨tsspital, Basel, Switzerland.Clin Microbiol Infect 2009; 15: 1067–1079

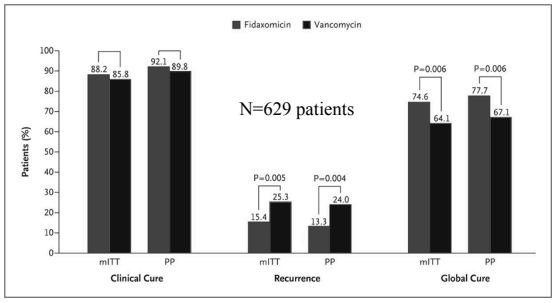
56

Fidaxomicin versus Vancomycin for *C.difficile* Infection
A randomized controlled clinical trial



Louie TJ et al. N Engl J Med 2011;364:422-431

Results: Rates of Primary and Secondary End Points
Fidaxomicin vs Vancomycin



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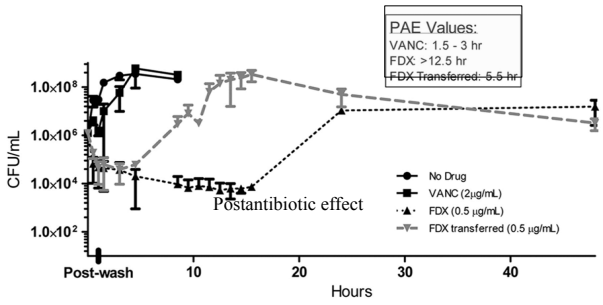
Louie TJ et al. N Engl J Med 2011;364:422-431

Recovery kinetics of C. difficile LC3 following a 1-h exposure to fidaxomicin (OPT-80) and vancomycin (VANC)

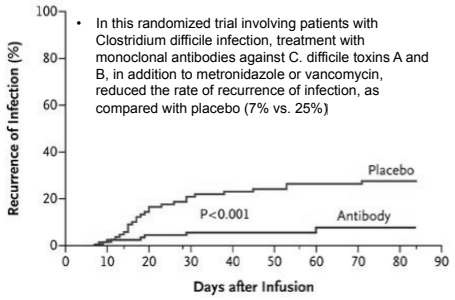


Babakhani, F. et al. 2011. Antimicrob. Agents Chemother. 55(9):4427-4429

59

Time to Recurrence of *C.difficile* Infection: Monoclonal antibody vs placebo: RCT

- In this randomized trial involving patients with Clostridium difficile infection, treatment with monoclonal antibodies against C. difficile toxins A and B, in addition to metronidazole or vancomycin, reduced the rate of recurrence of infection, as compared with placebo (7% vs. 25%)



Lowy I et al. N Engl J Med 2010;362:197-205

No. at Risk				
Antibody	101	93	89	85
Placebo	99	77	66	62

60

Parks T. N Engl J Med. 2010 Apr 15;362(15):1444;

A Webber Training Teleclass
Hosted by Dr. Kate Ellingson, CDC, Atlanta
www.webbertraining.com

Outline

- Background
- Diseases associated with *C.difficile*
- Diagnostic issues
- New Strains NAP1/027 078 Binary toxin
- Therapy
- Infection control

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Clostridium difficile infection

- **HICPAC Contact Isolation for *Clostridium difficile* infection**
  - Colonization with multiresistant bacteria
  - Risk of MR bacteria: transfer from healthcare facility where MRB are prevalent
  - Major abcess, cellulitis or decubiti
  - Acute diarrhea in an incontinent or diapered patient
  - RSV infection, croup or bronchiolitis in young infants
- **SHEA / IDSA** *CDC Guidelines July 2007* *SHEA-IDSA Guidelines 2010*
  16. Accommodate patients with CDI in a private room with contact precautions (B-III).

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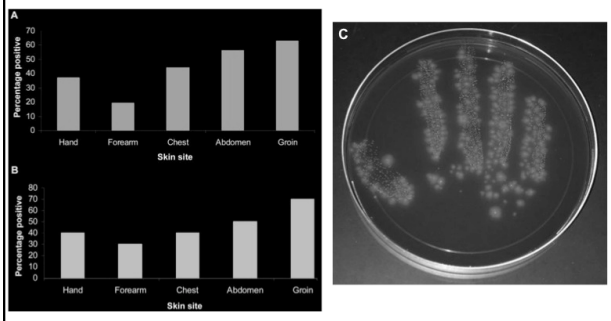
Clostridium difficile-associated disease



Frequency of *Clostridium difficile* contamination of skin sites of 27 patients with *C. difficile*-associated disease (CDAD) *(A)* and frequency of acquisition on sterile gloves after contact with skin sites of a subset of 10 patients *(B)*. *C,* Typical illustration of acquisition of *C. difficile* on sterile gloves after contact with a CDAD-affected patient's groin. The larger yellow colonies outlining the fingers are *C. difficile*. Of note, the patient had showered 1 h before collection of the culture specimen.

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C.difficile_CID_08

Bobulsky GS et al, Clin Infect Dis 2008;46:447-450

Glove use

- **Prevent heavy hand's contamination**

3 CFU/min wearing gloves
16 CFU/min not wearing gloves
(Pittet et al, Arch Intern Med 1999;159:821-6)

- **Decrease incidence of CDAD and asymptomatic carriers**

7.7 cases/1000 ptt discharges before to
1.5 cases/1000 ptt discharges during intervention
p=.015
(Johnson et al, Am J Med 1990;88:137-40)

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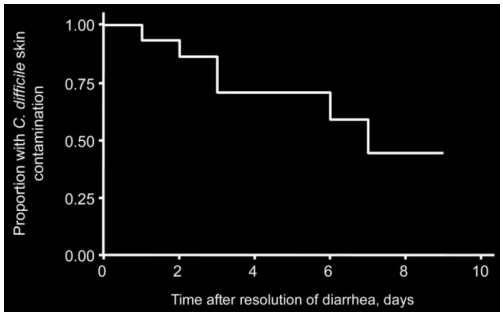
Kaplan-Meier Estimation of Time from resolution of diarrhes to negative culture results



Kaplan-Meier estimation of time from resolution of diarrhea (day 0) to negative results of culture specimens of abdomen and/or chest skin of patients with *Clostridium difficile*-associated disease.

65

C.difficile_CID_08

Bobulsky GS et al, Clin Infect Dis 2008;46:447-450

Does the environment need to be disinfected?

Intervention	Reduction of initial contamination or Incidence of CDAD	References
Unbuffered hypochlorite (500 ppm) Phosphate buffered hypochlorite (1600 ppm pH 7,6)	5 X 100 X	Kaatz, Am J Epidemiol 1988
Unbuffered 1:10 hypochlorite solutions	Before 8.6/1000 pt-d After 3.3/1000 pt-d	Mayfield, CID 2000
Diluted aldehyde-containing disinfectant + other infection control measures	4 X p=0.04 Before 1.5/1000 adm After 0.3/1000 adm	Struelens, Am J Med 1991

No gluoprotamin. No Quats. No Amines
Widmer AF & Frei R.. Infect Control Hosp Epidemiol Nov 2003
Widmer AF & Frei R. Disinfection. Manual of Clinical Microbiology, ASM 2007 /2011

Cases with *C.difficile*:
Disinfection with an active disinfectant against spores necessary

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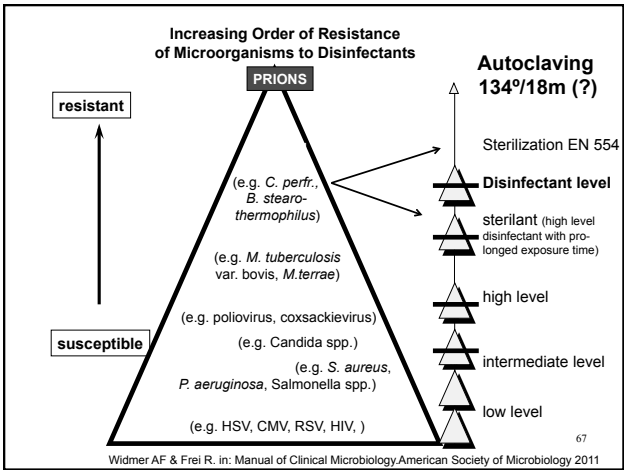
C. difficile Associated Diarrhea
Dr. Andreas Widmer, University Hospital, Basel, Switzerland
Sponsored by WHO First Global Patient Safety Challenge, Clean Care is Safer Care



Widmer AF & Frei R. in: Manual of Clinical Microbiology.American Society of Microbiology 2011

Oxygen-releasing Agents

e.g. Magnesium monoperoxyphthalate hexahydrate (MMPP) 80.0 g

Directions for use		
Surfaces	0,5 % -	1 hrs.
Surfaces during epidemics (NLV)	4,0 % -	1 hrs.
HBV	0,5 % -	5 min.
HIV	0,25 % -	5 min.
BVDV* (Surrogate virus for Hep C).	0,5 % -	1 min.
Rotavirus	0,25 % -	1 min.
Poliovirus	1,0 % -	1 hrs.
Adeno-, Vaccinia-, Papovaviruses	0,25 % -	5 min.
Bacterial spores	**1,0 % -**	**4 hrs.**
M.tuberculosis	0,5 % -	1 hrs.

Available in powder only
Smells like in Swimming Pool

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ORIGINAL ARTICLE

Systematic Review of Measurement and Adjustment for Colonization Pressure in Studies of Methicillin-Resistant *Staphylococcus aureus*, Vancomycin-Resistant Enterococci, and *Clostridium difficile* Acquisition

Adebola O. Ajao, MPH;[1] Anthony D. Harris, MD, MPH;[1,2] Mary-Claire Roghmann, MD, MS;[1,2] J. Kristie Johnson, PhD;[3] Min Zhan, PhD;[1] Jessina C. McGregor, PhD;[4] Jon P. Furuno, PhD[1]

OBJECTIVE. Colonization pressure is an important infection control metric. The aim of this study was to describe the definition and measurement of and adjustment for colonization pressure in nosocomial-acquisition risk factor studies of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and *Clostridium difficile*.

METHODS. We performed a computerized search of studies of nosocomial MRSA, VRE, and *C. difficile* acquisition published before July 1, 2009, through MEDLINE. Studies were included if a study outcome was MRSA, VRE, or *C. difficile* acquisition; the authors identified risk factors associated with MRSA, VRE, or *C. difficile* acquisition; and the study measured colonization pressure.

RESULTS. The initial MEDLINE search yielded 505 articles. Sixty-six of these were identified as studies of nosocomial MRSA, VRE, or *C. difficile* acquisition; of these, 18 (27%) measured colonization pressure and were included in the final review. The definition of colonization pressure varied considerably between studies: the proportion of MRSA- or VRE-positive patients (5 studies), the proportion of MRSA- or VRE-positive patient-days (6 studies), or the total or mean number of MRSA-, VRE-, or *C. difficile*–positive patients or patient-days (7 studies) in the unit over periods of varying length. In 10 of 13 studies, colonization pressure was independently associated with MRSA, VRE, or *C. difficile* acquisition.

CONCLUSION. There is a need for a simple and consistent method to quantify colonization pressure in both research and routine clinical care to accurately assess the effect of colonization pressure on cross-transmission of antibiotic-resistant bacteria.

Infect Control Hosp Epidemiol 2011;32(5):481-489

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Wash or Disinfect Hands after care of *C.difficile* diseased patients?

- Pro and contra wash
  - + Physically removes bacteria and spores
  - + effective based on good studies
  - - Less effective against vegetative bacteria
  - - Poor compliance / time consuming
- Pro and contra Alcohol
  - - No activity against spores
    (alcohol used in the lab to select spores from cultures)
  - + Enhanced compliance
  - + No evidence that washing stops epidemics faster

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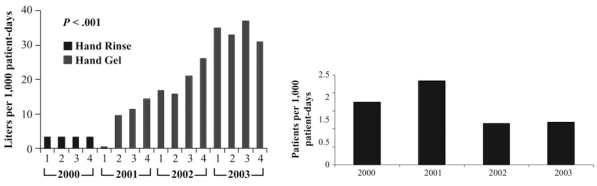
Wash hands if soiled e.g. after taking care of a patient with diarrhea

Lack of Association Between the Increased Incidence of *C.difficile*–Associated Disease and the Increasing Use of Alcohol-Based Hand Rubs



Use of alcohol hand rub by healthcare workers, in liters per 1,000 patient-days, per quarter, 2000-2003.

Number of patients with 1 or more tests positive for *Clostridium difficile* toxin per 1,000 patient-days, 2000-2003.

Boyce JM. Infect Control Hosp Epidemiol 2006;27:479-483

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A Webber Training Teleclass
Hosted by Dr. Kate Ellingson, CDC, Atlanta
www.webbertraining.com

Laboratory-Acquired *C.difficile* Ribotype 027: A New Risk for Laboratory Workers?

- *Clostridium difficile* is not recognized as a pathogen that presents a risk of acquisition in the laboratory, and no particular safety precautions are commended for working with this microorganism
- We report 2 cases of laboratory acquisition of *C. difficile* infection
- After these laboratory-acquired infections occurred, we decided that technicians and researchers should work with *C. difficile* ribotype 027 only in class II biosafety cabinets.We also recommend the use of disposable gloves and gowns, disinfection of hands with water and soap, and decontamination of materials and instruments with chlorine-containing disinfectants.
- **Bouza E & Ed J. Kuijper. Clinical Infectious Diseases 2008; 47:1493–4 (Dec)**

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CONCLUSIONS

- The incidence of CDAD has significantly increased over the last 5 years worldwide
- Epidemics are common today
  - NAP1/027 / 078 and Binary Toxin
  - Age >65y
  - Worldwide:
    - Canada, USA, France, Belgium, Germany, Switzerland, the Netherlands and more
      (Kuijper,…… Widmer Frei……: Eurosurveillance 2007
- Identification of outbreaks and control of CDAD requires
  - epidemiological surveillance AND
  - state of the art microbiology and molecular microbiology
  - And state of the art infection control

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