

# *Clostridium difficile:* What You Need to Know!

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## Objective

- Discuss risk factors for development of *C. difficile* infection

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## Outline

- Epidemiology and Pathogenesis
- Clinical Presentation
- Diagnosis and Management
- Infection Control and Prevention
- Summary



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# Epidemiology

- *Clostridium difficile* is the causative agent of antibiotic associated colitis (CDAD)
- Identified in 1978 and attributed to Clindamycin
- 1989-1992 – Highly clindamycin resistant "J strain" implicated in a large outbreak in the USA
- Penicillins, cephalosporins, and fluoroquinolones became implicated with their widespread use
- 2003-2006 – rise of hypervirulent strains, refractory to standard therapy (NAP1/BI/027) in USA and Europe
- NAP1 associated with fluoroquinolone use

Barnett, JG. *Ann Intern Med* 2006; 145:758  
 Bartlett, JG et al. *Gastroenterology* 1978; 75:778  
 Miller et al. *CID* 2010; 50:194  
 Pepin et al. *CID* 2005; 50: 194

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# Epidemiology



- Incidence of CDAD per 100,000 persons rose 4-fold from 1991 to 2003 and 10-fold in those over age 65
- In hospitalized patients the incidence rose from 3-12 per 1000 person to 25-43 per 1000 person during the same time period
- Cases were associated with more severe disease requiring ICU care and colectomy for toxic megacolon
- Mortality rates as high as 16%
- 2005: strain 078 identified in Netherlands and associated with disease in a younger population and community associated

Leo et al. *NEJM*. 2005; 353:2442  
 Pepin et al. *CMAJ*. 2004; 171:466  
 Goorhuis et al. *CID* 2008; 47:1162

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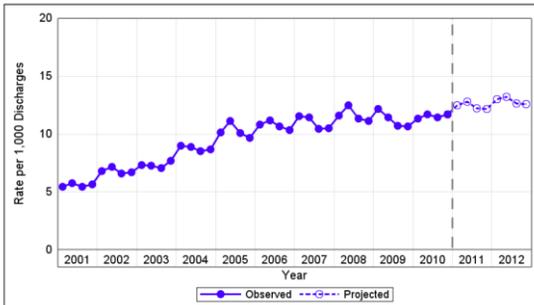
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National Rate of CDAD hospitalization per 1000 non-maternal, adult discharges



[http://www.hcup-us.ahrq.gov/reports/projections/CDI\\_Regional\\_projections\\_Final.pdf](http://www.hcup-us.ahrq.gov/reports/projections/CDI_Regional_projections_Final.pdf)

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### Yearly morality rates

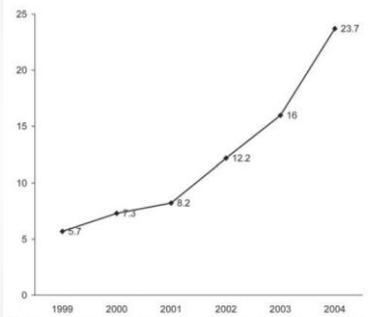


Figure. Yearly *Clostridium difficile*-related mortality rates per million population, United States, 1999–2004. *Redelings et al. EID 2007;13:9*

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### Microbiology

- Gram Positive Rod
- Anaerobic
- Spore forming
- Toxin producing
- Difficult to culture
- Extra-colonic—spore form
  - Resistant to heat, acid, Abx
- Colonic – vegetative form
  - Toxin A (enterotoxin)
  - Toxin B (cytotoxin)
    - Essential for virulence
- *C. difficile* is part of this microbial ecosystem in up to 70% of infants and 3% of normal adults




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### Pathogenesis

- Normal colonic bacterial flora disrupted by antibiotics or anti-neoplastic agents with antimicrobial activity
- Colonization with toxigenic strain of *C. difficile* (not typically covered by most antibiotics)
- Mucosal injury and inflammation
  - Exotoxins A and B
  - Binds to intestinal epithelial cells
  - Causes disruption of cell structure (cytoskeleton) of WBCs and mucosal epithelial layers
  - Destroys the "tight junction" between cells
  - Fluid leak, mucosal injury, and inflammation

*Price et al. Curr Microbiol. 1987; 16:55.*  
*Brito et al. J Infect Dis. 2002;185(9):1297*  
*Hecht et al. Gastroenterology. 1992;102(2):416*  
*Sears et al. Microbiol Rev. 1996;60(1):167.*

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## Transmission

- C. difficile carriers (20-50% of hospitalized adults) act as reservoir for environmental contamination
- Fecal oral route through ingestion of spores
- Organism survives in patient rooms, on hands, stethoscopes, and fomites
- Patient to patient transmission
- About half of transmission are associated with symptomatic infection

*Gerding et al. Infect Control Hosp Epi 1995; 16:459*  
*Kim et al. JID 1981; 143:42*  
*McFarland et al. NEJM 1989; 320:204*  
*Samore et al. Am J Med 1996; 100:32*

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## Risk Factors

- Prior antibiotic us (within 5 days of start and up to 10 weeks after cessation)
- Hospitalization
- Advance age
- Severe illness
- Gastric acid suppression
- Enteral feeding, GI surgery, obesity, chemotherapy
- Recurrence: >75 yrs old; >10 unformed stools/day, Cr. >1.2mg/dL

*Loo et al. NEJM 2011; 365:1693*  
*Kone et al. ICHE 2002; 23:653*  
*Bliss et al. Ann Intern Med 1998; 129:1012*  
*Kamihara et al. Arch Intern Med 1992; 152:1715*  
*Bishara et al. CID 2013; 57:489*

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## Community Associated CDAD

- No hospitalization within 1 year
- Women, younger age and healthier
- No prior antibiotic exposure within 12 weeks (1/3<sup>rd</sup>)
- Little or no outpatient exposure (50-60%)
- PPI use (1/3<sup>rd</sup>)
- Exposure to antibiotics in animal feed?

*Khanna et al. Am J Gastroenterol 2012;107:89*  
*Chinnis et al. JAMA Intern Med 2013;173:1339*  
*CDC. MMWR. 2005;54:1201*  
*Gould et al. CID 2010; 51:577*

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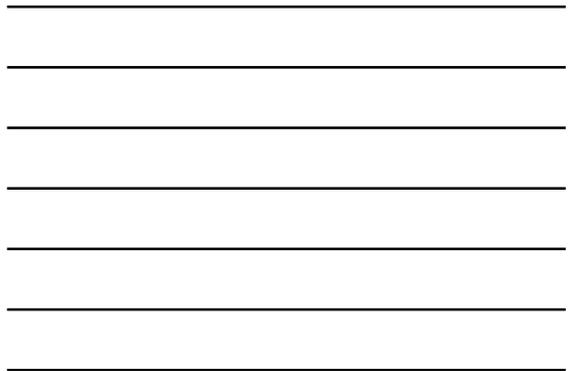




# Alternative therapies

- Anion-binding resins (tolevamer, colestipol, cholestyramine)
- IVIG –contains *C. difficile* antitoxin
- Probiotics –*Lactobacillus* (*Bifidobacteria*) or *Saccharomyces boulardii*
  - Suppression of *C. diff* growth
  - Inhibit toxin production and binding to colonic wall
  - Immunomodulation
- Fecal biotherapy
  - Severe and recurrent disease
  - Human synthetic stool (33 enteric pathogens)
  - Stool from healthy donors
  - Via enema, UGI (NGT), colonoscopy

Tedesco *Am J Gastroenterol*. 1982;77(4):220.  
 Kravtsov *et al. Johns Hopkins Med J*. 1978;148(3):67.  
 Mogg *et al. Scand J Infect Dis Suppl*. 1980;  
 Juang *et al. Am J Infect Control*. 2007;35(2):131.  
 Hempel *et al. JAMA*. 2012 May;307(18):1939-49.  
 Ritchie *et al. PLoS One*. 2012;7(4):e34938. Epub 2012 Apr 18.  
 Goldenberg *et al. Cochrane Database Syst Rev*. 2013;5:CD006095.  
 Protof *et al. Microbiome*. 2013;1(1):3.  
 Yoon *et al. J Clin Gastroenterol*. 2010;44(8):542.



MAJOR ARTICLE

## Recurrent *Clostridium difficile* Colitis: Case Series Involving 18 Patients Treated with Donor Stool Administered via a Nasogastric Tube

Johannes Ans,<sup>1</sup> Charles E. Gessert,<sup>2</sup> and Johan S. Bakker<sup>1</sup>  
 Department of Gastroenterology, <sup>1</sup>Division of Education and Research, and <sup>2</sup>Department of Infectious Diseases, St. Mary's-O'Leary Clinic Health System, Duluth, Minnesota

*Clostridium difficile*-associated diarrhea and colitis have emerged as major complications associated with use of systemic antimicrobials. In this study, the medical records for 18 subjects who received donor stool by nasogastric tube for recurrent *C. difficile* infection during a 9-year period at a single institution were retrospectively reviewed. During the period between the initial diagnosis of *C. difficile* colitis and the stool treatments, the 18 subjects received a total of 64 courses of antimicrobials (range, 2–7 courses; median, 3 courses). During the 90 days after receipt of treatment with stool, 2 patients died of unrelated illnesses. One of the 16 survivors experienced a single recurrence of *C. difficile* colitis during 90-day follow-up. No adverse effects associated with stool treatment were observed. Patients with recurrent *C. difficile* colitis may benefit from the introduction of stool from healthy donors via a nasogastric tube.

Clinical Infectious Diseases 2003



Donor exclusion criteria for fecal microbiota transplant

Absolute
<b>Risk of infectious agent</b>
Known HIV, hepatitis B or C infections
Known exposure to HIV or viral hepatitis (within the previous 12 months)
High-risk sexual behaviors
Use of illicit drugs
Tattoo or body piercing within six months
Incarceration or history of incarceration
Known current communicable disease (eg, upper respiratory tract infection)
Risk factors for variant Creutzfeldt-Jakob disease
Travel (within the last six months) to areas of the world where diarrheal illnesses are endemic or risk of traveler's diarrhea is high
<b>Gastrointestinal comorbidities</b>
History of inflammatory bowel disease
History of IBS, idiopathic chronic constipation, or chronic diarrhea
History of gastrointestinal malignancy or known polyps
<b>Factors that can or do affect the composition of the intestinal microbiota</b>
Antibiotics within the preceding three months
Major immunosuppressive medications (eg, calcineurin inhibitors, empergans)
Glucocorticoids, biological agents, etc)
Systemic antiparasitic agents
<b>Additional recipient-specific considerations</b>
Recent ingestion of a potential allergen (eg, nuts) where recipient has a known allergy to the (donor agent)
<b>Relative exclusion criteria that might be appropriate to consider</b>
History of major gastrointestinal surgery (eg, gastric bypass)
Metabolic syndrome
Systemic autoimmunity (eg, multiple sclerosis, connective tissue disease)
Atopic diseases including asthma and eczema, eosinophilic disorders of the gastrointestinal tract
Chronic pain syndromes (eg, chronic fatigue syndrome, fibromyalgia)

HIV, human immunodeficiency virus; IBS, irritable bowel syndrome.  
 Data from Bakker JS, Gessert CE, Protof C, et al. Treating *Clostridium difficile* infection with fecal microbiota transplantation. *Clin Gastroenterol Hepatol* 2012; 9:1044.

UpToDate

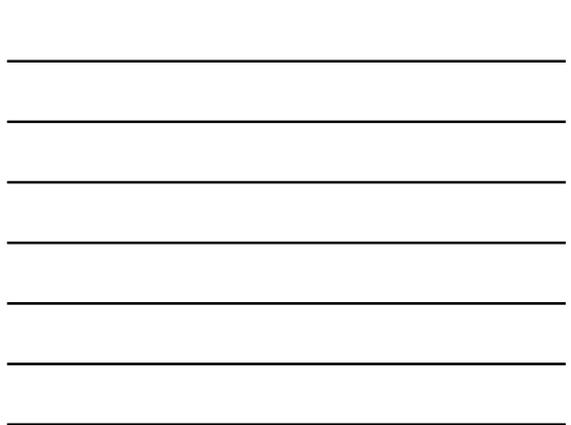




TABLE 1. Mean *Clostridium difficile* Colony Counts after Different Hand Hygiene Interventions According to the Whole-Hand Protocol

Intervention	Mean count (95% CI), log <sub>10</sub> CFU/mL
Warm water and plain soap	1.99 (1.80–2.09)
Cold water and plain soap	1.90 (1.58–2.22)
Warm water and antibacterial soap	2.31 (2.04–2.58)
Antiseptic hand wipe	3.25 (3.04–3.45)
Alcohol-based handrub	3.74 (3.40–4.07)
No intervention	3.82 (3.54–4.10)

NOTE. CI, confidence interval; CFU, colony-forming unit.

*Oughnon et al. Infect Control Hosp Epidemiol. 2009 Oct;30(10):939-44*

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## Summary

- Patients with *C. difficile* infections need to be in Isolation and on CONTACT precautions
- Handwashing with soap/water is more effective than alcohol based hand-gels for killing *C. difficile* spores
- Environmental cleansing with Chlorine based solutions are effective
- Health care providers should practice wise ABX stewardship to prevent the development of *C. difficile* infections

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## QUESTIONS ?



Disclaimer: "The views expressed in this publication/presentation are those of the author(s) and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the US Government."

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