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REVIEW ARTICLE

Clostridium difficile Diarrhea in the Elderly: Current Issues and Management Options

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Abstract *Clostridium difficile* infection (CDI) is the most common cause of infectious diarrhea in healthcare settings. Along with antimicrobial exposure, advanced age has been shown to be a significant risk factor for the development and recurrence of, and mortality from, CDI. The substantial burden of CDI in the elderly may be related to frequent healthcare exposure, the necessity for more medications, altered intestinal microbiota, and complicated comorbidities. A diagnosis of CDI is based on evidence of toxin, or the *C. difficile* organism itself, in a stool sample in the presence of clinical signs and symptoms. Only symptomatic patients should be tested for CDI, and routine surveillance or repeat testing on asymptomatic patients as a test of cure is discouraged. Antibiotic discontinuation alone can improve or resolve CDI in some patients, and concomitant use of antibiotics is associated with decreased response to CDI treatment. Metronidazole, vancomycin, and fidaxomicin are the therapeutic agents currently available for CDI, with the selection of these agents being based on disease severity, history of recurrence, and cost. The recurrence rate after initial treatment is 20–30 %. The first recurrence can be treated with the same therapeutic agent and, for subsequent recurrences, vancomycin in a tapered and/or pulsed regimen is recommended. Fecal microbiota transplantation has shown remarkable effectiveness for recurrent anti-refractory CDI, although caution is advised in treating immunocompromised hosts and those with toxic megacolon. *C. difficile* can be transmitted directly and indirectly via contact with patients or their environment; therefore, isolation precautions should be initiated at the first suspicion of CDI. *C. difficile* spores can survive for a long time on environmental surfaces, and the patient's room and all equipment used in the room should be disinfected. In order to manage CDI in the elderly, timely diagnosis, appropriate treatment based on severity of illness, and effective infection control are essential.

Key Points

Along with antimicrobial exposure, advanced age has been shown to be a significant risk factor for the development and recurrence of, and mortality from, *Clostridium difficile* infection (CDI).

Only symptomatic patients should be tested for CDI, and routine surveillance or repeat testing on asymptomatic patients as a test of cure is discouraged.

The selection of therapeutic agent is based on disease severity, history of recurrence, and cost.

Isolation precautions should be initiated at the first suspicion of CDI.

1 Introduction

Clostridium difficile infection (CDI) is the most common cause of infectious diarrhea in healthcare settings, with significant morbidity and mortality in developed countries

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[1]. In a number of studies, advanced age, along with antimicrobial exposure, has been shown to be a significant risk factor for the development of CDI [2, 3], as well as CDI mortality and recurrence [4, 5]. Since CDI was first recognized as a toxin-induced diarrheal disease in the 1970s [6], there have been remarkable advances in diagnostic tests and management strategies. In recent years, the US has seen dramatic increases in CDI incidence, disease severity, and mortality [7]. These changes have been partially explained by the appearance of the fluoroquinolone-resistant strain, North American PFGE type 1 and PCR-ribotype 027 (NAP1/027). In one study that explored the molecular epidemiology of outbreaks caused by NAP1/027, the strain was found to be isolated more frequently from older patients (median age 75 years) [8]. Increased recurrence of CDI in the elderly is usually not due to the development of antibiotic resistance, but is considered to be related to decreased host immunity or reinfection due to the persistence of spores in the patient's colon or in the environment. The reason for the substantial burden of CDI in the elderly has not been fully understood; however, it may be related to frequent healthcare exposure, necessity of more medications, altered intestinal microbiota and complicated comorbidities, including decreased renal function or co-existing infections (Table 1). Reported rates of *C. difficile* colonization are higher in the frail elderly population at long-term care facilities, and when CDI outbreaks occur they can be severe [9]. With the rise in use of feeding tubes to maintain nourishment of elderly, frail residents in long-term care facilities, *C. difficile* can also be introduced by this route [10]. A case-controlled study from the UK in patients over 65 years of age showed significantly higher mortality in patients aged 90 years and over [11]. Patients with femur neck fractures, who are generally elderly with poor reserve, were reported to have high mortality (47 %) from CDI [12]. Early recognition of the disease and timely management are crucial for optimizing the care of elderly patients with CDI.

Table 1 CDI in the elderly

Age-associated risk factors
Decline in immune function
Decline in renal function
Altered intestinal microbiota
Multiple complex comorbid conditions
Frequent exposure to healthcare environment
Frequent exposure to antibiotics for co-existing infections
Age-associated clinical outcomes
Higher risk of developing CDI
Higher risk of recurrence in CDI
Higher mortality from CDI

CDI, *Clostridium difficile* infection

2 Epidemiology

There have been several epidemiologic changes in *C. difficile* which appear to have been influenced by the antibiotics predominantly used in each era. In the 1980s, the association between amoxicillin, cephalosporins, clindamycin, or combined antibiotic use and the risk of CDI was identified in many studies [13–22]. Around 1990, prospective observational studies using restriction endonuclease analysis (REA) typing revealed that asymptomatic excretors of *C. difficile* in hospital settings did not have an increased risk of developing subsequent symptomatic disease but could be a source of transmission to other patients who developed diarrhea or colitis from the same REA types of *C. difficile* [23, 24]. In 2002, Montreal and Quebec started to have an epidemic of CDI, with increased morbidity and mortality [25], and between 2003 and 2004, Quebec had 7004 cases of CDI and 1270 people died [26, 27]. In 2005, the dominant strain of this outbreak was characterized as North American PFGE type 1 and PCR-ribotype 027 (NAP1/027), and its alleged hyperproduction of toxins A and B may explain increased morbidity and mortality [28]. It was found to be strongly associated with fluoroquinolone use during the outbreak in Quebec [29]. Soon after the Quebec outbreak, NAP1/027 also became endemic in Europe [28, 30, 31]. During the period between 2000 and 2003 when NAP1/027 was endemic, the rate of CDI was severalfold higher among persons aged >65 years compared with those aged 45–64 years [32]. Between 2011 and 2012 there was an outbreak of severe CDI in Melbourne, and a new hypervirulent strain, RT244, was identified. It has a different mechanism in terms of toxin production and does not have resistance to fluoroquinolones [33]. Recent surveillance studies from Europe suggested that the prevalence of NAP1/027 decreased significantly, which was paralleled by a decrease in CDI rate and mortality [34, 35], while NAP1/027 remains the most predominant strain in the US [36]. Although higher mortality has been observed in NAP1/027 strains, attempting to predict disease severity based on strain type is not recommended because of the wide disease spectrum seen with this strain, ranging from asymptomatic colonization to fulminant disease [37, 38].

According to the National Hospital Discharge Survey 1996–2009, *C. difficile* rates for hospitalized persons aged ≥65 years increased 200 %, with increases of 175 % for those aged 65–74 years, 198 % for those aged 75–84 years, and 201 % for those aged ≥85 years [39]. A recent epidemiologic study showed that, in 2011, incidence estimates, recurrence rate, and death rate were higher among persons 65 years of age than those less than 65 years of age [40]. Although studies showed up to 40–50 % of CDI cases were acquired in long-term care facilities, most occurred at subacute rehabilitation facilities within 30 days of

hospitalization and therefore the number of CDI cases for long-term care facilities may have been overestimated [41–43].

3 Diagnosis

A diagnosis of CDI is based on evidence of toxin, or the *C. difficile* organism itself, in a stool sample in the presence of compatible clinical signs and symptoms. The usual symptoms are watery, loose, or unformed stools generally more than three times within 24 h, often accompanied by fever. Radiographic evidence of ileus or toxic megacolon can also provide clues to the diagnosis, particularly in the absence of diarrhea.

It is recommended that only symptomatic patients be tested for CDI. The sensitivity, specificity, and positive predictive value of the non-culture, laboratory-based assays are lower in asymptomatic patients. Although asymptomatic carriers can be the source of transmission and cause symptomatic disease in other patients, routine surveillance or repeat testing on asymptomatic patients as a test of cure is discouraged because many patients asymptomatically shed *C. difficile* spores for weeks even after CDI is cured [44–46].

A number of laboratory tests are available for the detection of *C. difficile* toxins or organism, and they are currently categorized into six modalities: (1) enzyme immunoassay (EIA) for toxins A and B; (2) EIA for glutamate dehydrogenase (GDH; a protein produced by all *C. difficile* strains); (3) cell cytotoxicity; (4) culture for toxigenic *C. difficile*; (5) nucleic acid amplification test (NAAT; polymerase chain reaction or loop-mediated isothermal amplification); and (6) colonoscopy. Table 2 shows the characteristics of the diagnostic tests [47].

Repeating EIA for toxins A and B used to be recommended to increase its sensitivity; however, a retrospective study using a large number of samples suggested that 90.7 % of patients who had multiple stool samples tested for CDI were accurately diagnosed based on the first stool sample [48]. Due to the variable sensitivity in some of the toxin assay kits, and potential overdetection of colonization by NAAT, multistep test algorithms have been adopted in many institutions to increase the accuracy of CDI diagnosis. Although these algorithms consist of different numbers and types of tests, they share the basic concept of using inexpensive screening tests first (EIA for GDH or toxins A or B, or both), followed by more expensive tests (NAAT, toxigenic culture or cell cytotoxicity) for either discrepant results between two EIA tests or for a negative EIA test.

4 Management

4.1 Discontinuation of Antibiotics

Any antibiotic can disrupt the intestinal microbiota, which has barrier effects to prevent overgrowth of pathogens such as *C. difficile*. Antibiotic discontinuation alone can improve or resolve symptoms in some patients with CDI [49], and withdrawing the offending antibiotics is critically important in treating CDI. Concomitant use of antibiotics is associated with both decreased initial response to CDI therapy and durability of response [50]. When discontinuation of antibiotic therapy is not possible due to concurrent infections, fidaxomicin showed higher clinical cure rates compared with vancomycin [50].

4.2 Treatment

Metronidazole, vancomycin, and fidaxomicin are the therapeutic agents currently available for CDI, with the selection of therapeutic agents being based on disease severity, history of recurrence, and cost (Table 3). Capsule vancomycin is expensive; however, oral vancomycin can be inexpensive by formulating intravenous vancomycin for oral use. Treatment recommendations do not change with the age of the patient. However, according to pharmaceutical company data, following a single 500 mg oral or intravenous dose of metronidazole, subjects aged >70 years with no apparent renal or hepatic dysfunction had a 40–80 % higher mean area under the curve (AUC) of metronidazole active metabolite, with no apparent increase in the mean AUC of the parent compound of metronidazole compared with young healthy controls aged <40 years. In geriatric patients, monitoring for metronidazole-associated adverse events is recommended.

4.2.1 Mild to Moderate Disease

CDI is considered to be mild to moderate when the white blood cell count is 15,000 cells/mL or lower and the serum creatinine level is less than 1.5 times the baseline level [51]. Oral metronidazole is often chosen for mild to moderate disease because of its low cost, and many studies have indicated slow clinical response or decreased efficacy of metronidazole [52, 53]. In a recent study, vancomycin showed better treatment success compared with metronidazole [54]. For these reasons—faster response, lower relapse rates, and increased toxicity—vancomycin has replaced metronidazole as the drug of choice.

Table 2 Characteristics of diagnostic tests for *Clostridium difficile* infection [42, 44, 45]

Diagnostic test	Sensitivity (%)	Specificity (%)	Advantage	Disadvantage
EIA for toxins A and B	60–89	93–99	Inexpensive, rapid turnaround time	Variable sensitivity
EIA for GDH	71–100	67–99	Inexpensive, rapid turnaround time	Low specificity, does not distinguish between toxigenic and nontoxigenic strains
NAAT	88–100	88–97	High sensitivity, rapid turnaround time	Expensive, does not distinguish between colonization and infection
Toxigenic culture	95–100	96–100	High sensitivity, high specificity	Slow turnaround time, requires technical expertise, does not distinguish between colonization and infection
Cell cytotoxicity	77–86	97–100	High specificity, gold standard	Slow turnaround time, requires technical expertise
Colonoscopy to detect pseudomembranous colitis	51	100	High specificity	Invasive

EIA enzyme immunoassay, *GDH* glutamate dehydrogenase, *NAAT* nucleic acid amplification test

Table 3 Recommended medical therapy for *Clostridium difficile* infection [39, 62]

Disease severity	Therapeutic agent	Dose	Duration
Mild to moderate[a]	Vancomycin (first-line agent)	125 mg PO qid	10–14 days
	Metronidazole (second-line agent)	500 mg PO tid	10–14 days
Severe[a]	Vancomycin	125 mg PO qid	10–14 days
	OR		
	Fidaxomicin	200 mg PO bid	10 days
Severe complicated	Vancomycin	125 mg PO qid	10–14 days
	AND		
	Metronidazole	500 mg IV q8h	
	W/WO		
	Vancomycin enema	500 mg in 100 mL normal saline PR q6h	
First recurrence[a]	Same as for initial episode		
Second recurrence and thereafter	Vancomycin taper	125 mg PO qid	10 days
		125 mg PO bid	7 days
		125 mg PO daily	7 days
		125 mg PO every 2–3 days	2–4 weeks
	AND/OR		
	Vancomycin pulse	PO every 2–3 days	
		500 mg/day	7 days
		250 mg/day	7 days
		125 mg/day	7 days
	OR		
	Fidaxomicin	200 mg PO bid	10 days

Recommendations are the authors' expert opinion based on the US and European national guidelines [39, 62]

PO orally, *IV* intravenously, *bid* twice daily, *PR* rectally, *tid* three times daily, *qid* four times daily, *qxh* every *x* hours, *W/WO* with and without

[a] Consider fidaxomicin if high risk of recurrence, e.g. elderly, renal insufficiency, concomitant antibiotics

4.2.2 Severe Disease

CDI is considered severe when the white blood cell count is greater than 15,000 cells/mL and serum creatinine is greater than 1.5 times baseline. Multiple studies have suggested that oral vancomycin is superior to oral metronidazole in treating severe CDI [46, 53, 55]. As an alternative, fidaxomicin can be used for severe CDI as it showed equivalent treatment response and a lower rate of later recurrence compared with vancomycin [56]. Fidaxomicin is not recommended for mild disease due to its high cost; however, it is recommended for use when the risk of recurrence is high.

4.2.3 Severe Complicated Disease

Severe complicated disease is defined as CDI with ileus, toxic megacolon, or shock. Elderly patients are at greater risk of severe disease and often have comorbid conditions that imperil their recovery. Oral vancomycin remains the drug of choice; however, oral administration may not be feasible in those with severe complicated CDI. Rectal administration of vancomycin and/or intravenous administration of metronidazole are often used as adjunctive therapies, although evidence of efficacy is limited due to the lack of randomized trials. Patients with severe complicated CDI should be evaluated promptly for surgical intervention. Studies regarding surgical management have been limited by the small sample size and lack of a standardized approach. While early surgical intervention can reduce mortality [57, 58], the risks associated with surgical procedures are high in those with severe complicated CDI, and the optimal timing of surgical intervention has been very difficult to determine [59]. The advocated surgical approach has been total or subtotal colectomy with end ileostomy. In one study, loop ileostomy with colonic lavage followed by postsurgical vancomycin administration via ileostomy also achieved reduced mortality and preservation of the colon [60].

4.2.4 Recurrent Disease

CDI recurrence can be due to either reinfection or relapse. Risk factors for recurrence include advanced age, concomitant or post-CDI antibiotic use, prolonged or recent stay in a healthcare facility, proton-pump inhibitor use, presence of comorbidities, absence of an antitoxin A antibody response, and infection with the NAP1/027 strain [61–63]. It is believed that recurrence is more likely induced by a failure of host immune response to mount protective immunity, or a failure in reconstituting the microbiota rather than antimicrobial treatment failure. The immunological senescence that accompanies aging may lead to impaired immune responses to *C. difficile* and contribute to the significant association between advancing age and increased risk of CDI recurrence [64]. Recurrence occurs in 20–30 % of patients with CDI after initial treatment. The Infectious Diseases Society of America (IDSA) guidelines and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommend treating the first recurrence of CDI with the same therapeutic agent as used in the initial episode. For subsequent recurrences, both guidelines recommend vancomycin in a tapered and/or pulsed regimen, and the ESCMID guideline also recommends fidaxomicin as an option. Tapered or pulsed vancomycin therapy is often used in clinical practice, although there are no randomized trials and there is no standardized regimen or duration [44, 65]. Metronidazole is not recommended due to the risk of neuropathy from prolonged use.

4.2.5 Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) has continued to show remarkable clinical effectiveness, especially for recurrent and refractory CDI without serious adverse events. Overall response rates are approximately 90 % [66–70]. The rationale for this therapy is to re-establish normal gut microbiota and restore its colonization resistance by instillation of donor stool into the gastrointestinal tract of patients with CDI. FMT has been performed via nasojejunal tube, enema, gastroscope, colonoscope, or frozen fecal capsule preparation. A recent case series suggested that FMT was also effective for severe CDI [71]. In the ESCMID guideline, FMT in combination with oral antibiotic treatment is strongly recommended for multiple recurrent CDIs unresponsive to repeated antibiotic treatment [65]. However, caution is advised in treating immunocompromised hosts and those with toxic megacolon since severe outcomes and deaths have been reported [71].

4.2.6 Probiotics

Probiotics are generally well tolerated and have few adverse effects, with the exception of rare cases of fungemia with *Saccharomyces boulardii* [72, 73] or bacteremia [74] in immunocompromised hosts. Although there have been a number of studies published on probiotics in CDI prevention using various organisms and doses, the effectiveness as adjunctive therapy for CDI prevention or treatment is still unclear (Fig. 1). A recent systematic review concluded that probiotics, such as *Saccharomyces boulardii* and *Lactobacillus* GG, are effective for the primary prevention of CDI with moderate-quality evidence [75].

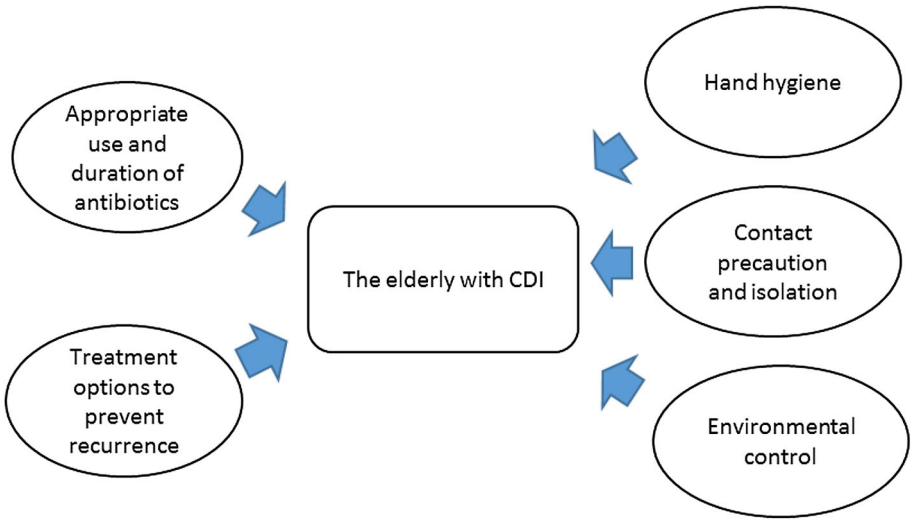

Fig. 1 CDI prevention strategies for the elderly. CDI, *Clostridium difficile* infection

5 Infection Control

5.1 Hand Hygiene

Spores of *C. difficile* are resistant to alcohol-based hand rubs and antibacterial soap. Healthcare providers' hands are frequently contaminated with *C. difficile* after patient contact, and wearing gloves to provide a physical barrier is critically important to reduce the transmission of *C. difficile* [76].

5.2 Isolation and Contact Precaution

C. difficile can be transmitted directly and indirectly via contact with patients or their environment. Isolation precautions should be initiated at the first suspicion of CDI. Ideally, a patient with *C. difficile* should be isolated in a private room with a bathroom, and if private rooms are not available then the alternative is to cohort patients with *C. difficile* in the same room. If cohorting and separation are not feasible, strict contact precautions are necessary, including dedication of a bathroom to one patient and a bedside commode to the other. Although one study suggested that the use of gloves alone may be as effective as the use of gloves and gowns in preventing the transmission of *C. difficile* [77], current guidelines recommend the use of both gloves and gowns [78]. Although it is currently recommended that contact precaution may be discontinued when the patient no longer has diarrhea [79], an observational study has shown that skin contamination and environmental shedding of *C. difficile* often persist at the time of resolution of diarrhea, and persistent shedding is common 1–4 weeks after therapy [80]. Therefore, some experts recommend extending contact precautions for several days after diarrhea stops, or continuing them until hospital discharge if local rates of CDI are high.

5.3 Environmental Control

C. difficile spores can survive on environmental surfaces for as long as 5 months. Stethoscopes, thermometers, blood pressure cuffs, bedrails, call buttons, telephones, TV controls, light controls, bed sheets, scales, commodes, toilets, windowsills, tube feedings, and flow control devices for IVs can all be contaminated [81]. The patient's room and all equipment used in the room should be disinfected with bleach [78, 82]. Ultraviolet irradiation has been shown to be effective in deactivating *C. difficile* endospores [83], and appears to be equivalent to bleach in decreasing environmental contamination with *C. difficile* spores [84, 85].

6 Conclusions

Advanced age is a major risk factor for developing CDI and it is associated with increased morbidity and mortality, as well as a higher risk of recurrence. Frequent exposure to healthcare environments, multiple comorbidities, increased use of antibiotics, age-related decrease in immune response, and altered intestinal microbiota are possible explanations for the disproportionate burden of CDI in elderly individuals. Timely diagnosis, appropriate treatment based on the severity of illness, and effective infection control are essential in managing CDI in the elderly.

Compliance with Ethical Standards

Sherwood Gorbach is a consultant for Seres Health, Cempra Pharmaceuticals, Medimmune and Cubist, and also serves as a member of the Scientific Advisory Board for Seres Health and Cempra

Pharmaceuticals. He is a former employee of Cubist. Shira Doron serves on the speakers bureau for Merck and Cubist Pharmaceuticals, and is also a consultant and serves on the speakers bureau for Allergan. Masako Mizusawa has no conflicts of interest.

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References

1. Guerrant RL, Hughes JM, Lima NL, Crane J. Diarrhea in developed and developing countries: magnitude, special settings, and etiologies. Rev Infect Dis. 1990;12(Suppl 1):S41–50.
2. To KB, Napolitano LM. Clostridium difficile infection: update on diagnosis, epidemiology, and treatment strategies. Surg Infect. 2014;15:490–502.
3. Lo Vecchio A, Zacur GM. Clostridium difficile infection: an update on epidemiology, risk factors, and therapeutic options. Curr Opin Gastroenterol. 2012;28:1–9.
4. Garey KW, Sethi S, Yadav Y, DuPont HL. Meta-analysis to assess risk factors for recurrent *Clostridium difficile* infection. J Hosp Infect. 2008;70:298–304.
5. Abou Chakra CN, Pepin J, Sirard S, Valiquette L. Risk factors for recurrence, complications and mortality in *Clostridium difficile* infection: a systematic review. PloS One. 2014;9:e98400.
6. Bartlett JG, Chang TW, Gurwith M, Gorbach SL, Onderdonk AB. Antibiotic-associated pseudomembranous colitis due to toxin-producing clostridia. N Engl J Med. 1978;298:531–4.
7. Lessa FC, Gould CV, McDonald LC. Current status of *Clostridium difficile* infection epidemiology. Clin Infect Dis. 2012;55:S65–70.
8. Labbé A-C, Poirier L, MacCannell D, Louie T, Savoie M, Béliveau C, et al. *Clostridium difficile* Infections in a Canadian tertiary care hospital before and during a regional epidemic associated with the BI/NAP1/027 strain. Antimicrob Agents Chemother. 2008;52:3180–7.
9. Strausbaugh LJ, Sukumar SR, Joseph CL, High KP. Infectious disease outbreaks in nursing homes: an unappreciated hazard for frail elderly persons. Clin Infect Dis. 2003;36:870–6.
10. Chait M M. The new era of *C. difficile*-associated diarrhea. Ann Longterm Care. 2008;16.
11. Karas JA, Bradshaw S, Mahmud W, Enoch DA. Mortality in hospitalized older adults associated with Clostridium difficile infection at a district hospital. Infect Dis Rep. 2010;2:e8. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3892575/. Accessed 30 Jun 2015.
12. Kakwani R, Chakrabarti D, Khan R, Sinha A, Tawari G. Morbidity and mortality due to *C. difficile* infection in fracture neck of femur patients. J Bone Joint Surg Br. 2010;92-B:273.
13. Finegold SM. Anaerobic infections and Clostridium difficile colitis emerging during antibacterial therapy. Scand J Infect Dis Suppl. 1986;49:160–4.
14. Pierce PF, Wilson R, Silva J, Garagusi VF, Rifkin GD, Fekety R, et al. Antibiotic-associated pseudomembranous colitis: an epidemiologic investigation of a cluster of cases. J Infect Dis. 1982;145:269–74.
15. Beesley J, Eastham EJ, Jackson RH, Nelson R. Case report. Clindamycin associated pseudomembranous colitis. Acta Paediatr Scand. 1981;70:129–30.
16. Aronsson B, Möllby R, Nord CE. *Clostridium difficile* and antibiotic associated diarrhoea in Sweden. Scand J Infect Dis Suppl. 1982;35:53–8.
17. Rocca JM, Pieterse AS, Rowland R, Hecker R, Rich GE. *Clostridium difficile* colitis. Aust N Z J Med. 1984;14:606–10.
18. Aronsson B, Möllby R, Nord CE. Diagnosis and epidemiology of *Clostridium difficile* enterocolitis in Sweden. J Antimicrob Chemother. 1984;14 Suppl D:85–95.
19. Golledge CL, McKenzie T, Riley TV. Extended spectrum cephalosporins and *Clostridium difficile*. J Antimicrob Chemother. 1989;23:929–31.
20. Hyams JS, Feder H, Krause PJ, Frick J, McLaughlin JC, Furth T, et al. Occurrence of *Clostridium difficile* toxin-associated gastroenteritis following antibiotic therapy for otitis media in young children. Pediatr Infect Dis. 1984;3:433–6.
21. Gerding DN, Olson MM, Peterson LR, Teasley DG, Gebhard RL, Schwartz ML, et al. *Clostridium difficile*-associated diarrhea and colitis in adults. A prospective case-controlled epidemiologic study. Arch Intern Med. 1986;146:95–100.
22. Bohnen JM, Matlow AG, Cohen MM. Pseudomembranous colitis and wound infection following perioperative use of multiple antibiotics. Can J Surg J Can Chir. 1985;28:432–3.
23. McFarland LV, Mulligan ME, Kwok RY, Stamm WE. Nosocomial acquisition of *Clostridium difficile* infection. N Engl J Med. 1989;320:204–10.
24. Johnson S, Clabots CR, Linn FV, Olson MM, Peterson LR, Gerding DN. Nosocomial *Clostridium difficile* colonisation and disease. Lancet. 1990;336:97–100.
25. Eggertson L, Sibbald B. Hospitals battling outbreaks of *C. difficile*. CMAJ. 2004;171:19–21.
26. Erban J. *C. difficile*: will lessons be learned? CMAJ. 2005;172:1161.
27. Eggertson L. *C. difficile*: by the numbers. CMAJ. 2004;171:1331–2.
28. Warny M, Pepin J, Fang A, Killgore G, Thompson A, Brazier J, et al. Toxin production by an emerging strain of *Clostridium difficile* associated with outbreaks of severe disease in North America and Europe. Lancet. 2005;366:1079–84.
29. Pépin J, Saheb N, Coulombe M-A, Alary M-E, Corriveau M-P, Authier S, et al. Emergence of fluoroquinolones as the predominant risk factor for *Clostridium difficile*-associated diarrhea: a cohort study during an epidemic in Quebec. Clin Infect Dis. 2005;41:1254–60.
30. Joseph R, Demeyer D, Vanrenterghem D, van den Berg R, Kuijper E, Delmée M. First isolation of *Clostridium difficile* PCR ribotype 027, toxinotype III in Belgium. Euro Surveill. 2005;10(E051020):4.
31. Kuijper EJ, van den Berg RJ, Debast S, Visser CE, Veenendaal D, Troelstra A, et al. *Clostridium difficile* ribotype 027, toxinotype III, the Netherlands. Emerg Infect Dis. 2006;12:827–30.
32. McDonald LC, Owings M, Jernigan DB. *Clostridium difficile* infection in patients discharged from US short-stay hospitals, 1996–2003. Emerg Infect Dis. 2006;12:409–15.
33. Lim SK, Stuart RL, Mackin KE, Carter GP, Kotsanas D, Francis MJ, et al. Emergence of a ribotype 244 strain of *Clostridium difficile* associated with severe disease and related to the epidemic ribotype 027 strain. Clin Infect Dis. 2014;58:1723–30.
34. Bauer MP, Notermans DW, van Benthem BHB, Brazier JS, Wilcox MH, Rupnik M, et al. *Clostridium difficile* infection in Europe: a hospital-based survey. Lancet. 2011;377:63–73.
35. Wilcox MH, Shetty N, Fawley WN, Shemko M, Coen P, Birtles A, et al. Changing epidemiology of *Clostridium difficile* infection following the introduction of a national ribotyping-based surveillance scheme in England. Clin Infect Dis. 2012;55:1056–63.
36. See I, Mu Y, Cohen J, Beldavs ZG, Winston LG, Dumyati G, et al. NAP1 strain type predicts outcomes from *Clostridium difficile* infection. Clin Infect Dis. 2014;58:1394–400.
37. Petrella LA, Sambol SP, Cheknis A, Nagaro K, Kean Y, Sears PS, et al. Decreased cure and increased recurrence rates for

Clostridium difficile infection caused by the epidemic *C. difficile* BI strain. Clin Infect Dis. 2012;55:351–7.
38. Sirard S, Valiquette L, Fortier L-C. Lack of association between clinical outcome of *Clostridium difficile* infections, strain type, and virulence-associated phenotypes. J Clin Microbiol. 2011;49:4040–6.
39. Centers for Disease Control and Prevention. QuickStats: rates of *Clostridium difficile* infection among hospitalized patients aged ≥65 years,* by Age Group—National Hospital Discharge Survey, United States, 1996–2009. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6034a7.htm?s_cid=mm6034a7_w. Accessed 16 Feb 2015.
40. Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, et al. Burden of *Clostridium difficile* infection in the United States. N Engl J Med. 2015;372:825–34.
41. Campbell RJ, Giljahn L, Machesky K, Cibulskas-White K, Lane LM, Porter K, et al. *Clostridium difficile* infection in Ohio hospitals and nursing homes during 2006. Infect Control Hosp Epidemiol. 2009;30:526–33.
42. Kim JH, Toy D, Muder RR. *Clostridium difficile* infection in a long-term care facility: hospital-associated illness compared with long-term care-associated illness. Infect Control Hosp Epidemiol. 2011;32:656–60.
43. Mylotte JM, Russell S, Sackett B, Vallone M, Antalek M. Surveillance for *Clostridium difficile* infection in nursing homes. J Am Geriatr Soc. 2013;61:122–5.
44. Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31:431–55.
45. Fekety R, Silva J, Kauffman C, Buggy B, Deery HG. Treatment of antibiotic-associated *Clostridium difficile* colitis with oral vancomycin: comparison of two dosage regimens. Am J Med. 1989;86:15–9.
46. McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent *Clostridium difficile* disease. Am J Gastroenterol. 2002;97:1769–75.
47. Gerding DN, Johnson S, Peterson LR, Mulligan ME, Silva J. *Clostridium difficile*-associated diarrhea and colitis. Infect Control Hosp Epidemiol. 1995;16:459–77.
48. Deshpande A, Pasupuleti V, Patel P, Ajani G, Hall G, Hu B, et al. Repeat stool testing to diagnose *Clostridium difficile* infection using enzyme immunoassay does not increase diagnostic yield. Clin Gastroenterol Hepatol. 2011;9(665–9):e1.
49. Olson MM, Shanholtzer CJ, Lee JT, Gerding DN. Ten years of prospective Clostridium difficile-associated disease surveillance and treatment at the Minneapolis VA Medical Center, 1982–1991. Infect Control Hosp Epidemiol. 1994;15:371–81.
50. Mullane KM, Miller MA, Weiss K, Lentnek A, Golan Y, Sears PS, et al. Efficacy of fidaxomicin versus vancomycin as therapy for *Clostridium difficile* infection in individuals taking concomitant antibiotics for other concurrent infections. Clin Infect Dis. 2011;53:440–7.
51. Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31:431–55.
52. Wilcox MH, Howe R. Diarrhoea caused by *Clostridium difficile*: response time for treatment with metronidazole and vancomycin. J Antimicrob Chemother. 1995;36:673–9.
53. Al-Nassir WN, Sethi AK, Nerandzic MM, Bobulsky GS, Jump RLP, Donskey CJ. Comparison of clinical and microbiological response to treatment of *Clostridium difficile*-associated disease with metronidazole and vancomycin. Clin Infect Dis. 2008;47:56–62.
54. Johnson S, Louie TJ, Gerding DN, Cornely OA, Chasan-Taber S, Fitts D, et al. Vancomycin, metronidazole, or tolevamer for *Clostridium difficile* infection: results from two multinational, randomized, controlled trials. Clin Infect Dis. 2014;59:345–54.
55. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. Clin Infect Dis. 2007;45:302–7.
56. Louie TJ, Miller MA, Mullane KM, Weiss K, Lentnek A, Golan Y, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. N Engl J Med. 2011;364:422–31.
57. Ferrada P, Velopulos CG, Sultan S, Haut ER, Johnson E, Praba-Egge A, et al. Timing and type of surgical treatment of *Clostridium difficile*-associated disease: a practice management guideline from the Eastern Association for the Surgery of Trauma. J Trauma Acute Care Surg. 2014;76:1484–93.
58. Stewart DB, Hollenbeak CS, Wilson MZ. Is colectomy for fulminant *Clostridium difficile* colitis life saving? A systematic review. Colorectal Dis. 2013;15:798–804.
59. Klobuka AJ, Markelov A. Current status of surgical treatment for fulminant *Clostridium difficile* colitis. World J Gastrointest Surg. 2013;5:167–72.
60. Neal MD, Alverdy JC, Hall DE, Simmons RL, Zuckerbraun BS. Diverting loop ileostomy and colonic lavage: an alternative to total abdominal colectomy for the treatment of severe, complicated *Clostridium difficile* associated disease. Ann Surg. 2011;254:423–7 **(discussion 427–9)**.
61. Garey KW, Sethi S, Yadav Y, DuPont HL. Meta-analysis to assess risk factors for recurrent *Clostridium difficile* infection. J Hosp Infect. 2008;70:298–304.
62. Vardakas KZ, Konstantelias AA, Loizidis G, Rafailidis PI, Falagas ME. Risk factors for development of *Clostridium difficile* infection due to BI/NAP1/027 strain: a meta-analysis. Int J Infect Dis. 2012;16:e768–73.
63. Kyne L, Warny M, Qamar A, Kelly CP. Association between antibody response to toxin A and protection against recurrent *Clostridium difficile* diarrhoea. Lancet. 2001;357:189–93.
64. Kelly CP. Can we identify patients at high risk of recurrent *Clostridium difficile* infection? Clin Microbiol Infect. 2012;18(Suppl 6):21–7.
65. Debast SB, Bauer MP, Kuijper EJ. European Society of Clinical Microbiology and Infectious Diseases, European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for *Clostridium difficile* infection. Clin Microbiol Infect. 2014;20:1–26
66. Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent *Clostridium difficile* infection. Clin Infect Dis. 2011;53:994–1002.
67. Cammarota G, Ianiro G, Bibbò S, Gasbarrini A. Fecal microbiota transplantation: a new old kid on the block for the management of gut microbiota-related disease. J Clin Gastroenterol. 2014;48(Suppl 1):S80–4.
68. Youngster I, Russell GH, Pindar C, Ziv-Baran T, Sauk J, Hohmann EL. Oral, capsulized, frozen fecal microbiota transplantation for relapsing *Clostridium difficile* infection. JAMA. 2014;312:1772–8.
69. Van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. N Engl J Med. 2013;368:407–15.
70. Youngster I, Sauk J, Pindar C, Wilson RG, Kaplan JL, Smith MB, et al. Fecal microbiota transplant for relapsing *Clostridium difficile* infection using a frozen inoculum from unrelated donors: a randomized, open-label, controlled pilot study. Clin Infect Dis. 2014;58:1515–22.

71. Kelly CR, Ihunnah C, Fischer M, Khoruts A, Surawicz C, Afzali A, et al. Fecal microbiota transplant for treatment of *Clostridium difficile* infection in immunocompromised patients. Am J Gastroenterol. 2014;109:1065–71.
72. Thygesen JB, Glerup H, Tarp B. *Saccharomyces boulardii* fungemia caused by treatment with a probioticum. BMJ Case Rep. 2012;2012: pii:bcr0620114412.
73. Muñoz P, Bouza E, Cuenca-Estrella M, Eiros JM, Pérez MJ, Sánchez-Somolinos M, et al. Saccharomyces cerevisiae Fungemia: an emerging infectious disease. Clin Infect Dis. 2005;40:1625–34.
74. Mehta A, Rangarajan S, Borate U. A cautionary tale for probiotic use in hematopoietic SCT patients—*Lactobacillus acidophilus* sepsis in a patient with mantle cell lymphoma undergoing hematopoietic SCT. Bone Marrow Transplant. 2013;48:461–2.
75. Johnston BC, Ma SSY, Goldenberg JZ, Thorlund K, Vandvik PO, Loeb M, et al. Probiotics for the prevention of *Clostridium difficile*-associated diarrhea systematic review and meta-analysis. Ann Intern Med. 2012;157:878–88.
76. Johnson S, Gerding DN, Olson MM, Weiler MD, Hughes RA, Clabots CR, et al. Prospective, controlled study of vinyl glove use to interrupt *Clostridium difficile* nosocomial transmission. Am J Med. 1990;88:137–40
77. Lawrence SJ, Puzniak LA, Shadel BN, Gillespie KN, Kollef MH, Mundy LM. *Clostridium difficile* in the intensive care unit: epidemiology, costs, and colonization pressure. Infect Control Hosp Epidemiol. 2007;28:123–30.
78. Guide to preventing *Clostridium difficile* infections. Association for Professionals in Infection Control and Epidemiology; 2013;15–7.
79. Siegel JD, Rhinehart E, Jackson M, Chiarello L, Health Care Infection Control Practices Advisory Committee. 2007 guideline for isolation precautions: preventing transmission of infectious agents in health care settings. Am J Infect Control. 2007;35:S65–164
80. Sethi AK, Al-Nassir WN, Nerandzic MM, Bobulsky GS, Donskey CJ. Persistence of skin contamination and environmental shedding of *Clostridium difficile* during and after treatment of *C. difficile* infection. Infect Control Hosp Epidemiol. 2010;31:21–7.
81. Messina G, Ceriale E, Lenzi D, Burgassi S, Azzolini E, Manzi P. Environmental contaminants in hospital settings and progress in disinfecting techniques. Biomed Res Int. 2013;2013. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3830765/. Accessed 2 Feb 2015.
82. Eckstein BC, Adams DA, Eckstein EC, Rao A, Sethi AK, Yadavalli GK, et al. Reduction of *Clostridium difficile* and vancomycin-resistant Enterococcus contamination of environmental surfaces after an intervention to improve cleaning methods. BMC Infect Dis. 2007;7:61.
83. Nerandzic MM, Cadnum JL, Pultz MJ, Donskey CJ. Evaluation of an automated ultraviolet radiation device for decontamination of *Clostridium difficile* and other healthcare-associated pathogens in hospital rooms. BMC Infect Dis. 2010;10:197.
84. Ghantoji SS, Stibich M, Stachowiak J, Cantu S, Adachi JA, Raad II, et al. Non-inferiority of pulsed xenon UV light versus bleach for reducing environmental *Clostridium difficile* contamination on high-touch surfaces in *Clostridium difficile* infection isolation rooms. J Med Microbiol. 2015;64:191–4.
85. Petersson LP, Albrecht U-V, Sedlacek L, Gemein S, Gebel J, Vonberg R-P. Portable UV light as an alternative for decontamination. Am J Infect Control. 2014;42:1334–6.