



Published in final edited form as:

Infect Dis Clin North Am. 2009 September ; 23(3): 727–743. doi:10.1016/j.idc.2009.04.011.

***Clostridium difficile* Infection in the Intensive Care Unit**

David J. Riddle, M.D.^a and Erik R. Dubberke, M.D., M.S.P.H.^b

^aFellow, Department of Medicine, Division of Infectious Diseases, Washington University School of Medicine, St. Louis, Missouri

^bAssistant Professor, Department of Medicine, Division of Infectious Diseases, Washington University School of Medicine, St. Louis, Missouri

Synopsis

Clostridium difficile infection (CDI) is becoming more common worldwide. The morbidity and mortality associated with *C. difficile* is also increasing at an alarming rate. Critically ill patients are at particularly high risk for this disease due to the prevalence of multiple risk factors in the patient population. Treatment of *C. difficile* continues to be a difficult problem in patients with severe or recurrent disease. This article seeks to provide a broad understanding of CDI in the intensive care unit, with special emphasis on risk factor identification, treatment options, and disease prevention.

Keywords

Clostridium difficile; nosocomial infection; pseudomembranous colitis; intensive care; critical care

Introduction

Diarrhea is a common problem in critically ill patients regardless of the disease process that necessitated admission to the intensive care unit (ICU). Overall, up to 40% of patients will develop diarrhea after admission to the ICU [1]. Certain patient populations, such as those suffering extensive burns, may have an incidence of diarrhea greater than 90% [2]. Furthermore, patients that develop diarrhea are at risk of other complications such as dehydration, hemodynamic instability, malnutrition, electrolyte imbalances, and skin breakdown [3]. Enteral feeding is the most common cause of diarrhea in the intensive care setting; however other non-infectious causes include hypoalbuminemia, intestinal ischemia, and medication-induced [4,5]. *Clostridium difficile* infection (CDI) is the most common infectious cause of diarrhea in the ICU [4].

First discovered in 1935 [6], *C. difficile* was not identified as a cause of pseudomembranous colitis in humans until 1978 [7]. Since that time, *C. difficile* has been recognized as the most common cause of nosocomial infectious diarrhea [8]. Recent changes in CDI epidemiology have had a significant impact in the ICU setting. The incidence of CDI is increasing in the ICU, as well as the hospitalized population as a whole [9]. The severity of CDI also is increasing,

© 2009 Elsevier Inc. All rights reserved.

Corresponding Author: Erik R. Dubberke, M.D., Division of Infectious Diseases, Washington University School of Medicine, 660 S. Euclid Ave., Campus Box 8051, St. Louis, Missouri, 63110-1093, Phone:314.454.8293, Fax:314.454.5392, Email: edubberk@im.wustl.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

prompting more admissions to the ICU for management of CDI related complications [10]. Recent data indicates outcomes may be improved by recognizing patients with more severe CDI and prompt initiation of the most appropriate therapy.

Pathogenesis and Epidemiology

C. difficile causes diarrhea through the secretion of exotoxins within the gastrointestinal tract. The production of toxin is necessary for *C. difficile* to cause disease and invasion of *C. difficile* across the colonic mucosa is exceedingly rare. Toxin A causes neutropilic infiltration and damage to the colonic mucosa [11,12]. Toxin B has similar destructive effects on the colonic mucosa, but appears to be roughly 10 times more cytotoxic than toxin A [13]. Necrosis and sloughing of cellular debris into the colonic lumen results from the interaction of the toxins with colonocyte surface receptors that induce the degradation of actin filaments [14]. Toxin induced cytokine release also triggers the exudation of inflammatory cells and proteins from the resulting mucosal ulcerations [15]. The resulting inflammatory exudate forms the pseudomembrane that is nearly pathognomonic for CDI [13].

Roughly 3% of healthy adults are asymptotically colonized with *C. difficile* [16]. Colonization rates increase to as much as 50% in patients residing in long-term care facilities [17]. As many as 60% of patients that acquire the organism in the healthcare setting will remain asymptomatic [18]. Generally, an individual's risk of becoming colonized with *C. difficile* is directly proportional to length of the hospital stay, with mean time to acquisition of the organism of two weeks [19]. Additional studies have found that length of stay is a surrogate for exposure to patients with CDI, and is not an independent risk factor for CDI [20].

Patients that lack previous or established colonization with *C. difficile* are at highest risk for developing symptomatic disease after becoming infected with the organism. A review of several longitudinal studies showed that only about 1% of individuals that were already colonized with *C. difficile* at the time of hospital admission developed diarrhea, but 5% of previously uncolonized individuals had symptomatic disease after new acquisition of the organism [21]. This disparity is thought to be due to a protective effect from anti-toxin antibodies in patients with prior exposure. Patients that are capable of mounting a brisk antibody response to the *C. difficile* toxins after exposure are also less likely to develop symptomatic disease [22].

The overall incidence of CDI varies between centers, but generally about 2% of all hospitalized patients will develop symptomatic infection [23]. In the intensive care setting, CDI is more common with an overall incidence of roughly 4% [24]. Up to 20% of ICU patients that develop symptomatic disease will progress to a fulminant colitis with a mortality rate of nearly 60% [25,26].

Although numerous strains coexist within a single hospital, outbreaks are typically linked to a single strain. The spores of *C. difficile* are difficult to eradicate due to a resistance to many environmental cleaning detergents [27] and can be isolated from environmental swabs taken from a patient's room months after discharge [28]. Although persistence in the environment is well documented, it is typically thought to spread through person-to-person transmission. Health care workers are often responsible for spreading the organism on their hands or medical equipment [18].

The incidence and severity of CDI among hospitalized patients continues to increase worldwide. According to data from the National Inpatient Sample, the number of patients diagnosed with CDI in US hospitals doubled between 2000 and 2005 to 11.2 cases per 10,000 population [9]. The age-adjusted CDI-related mortality showed a similar trend, increasing from 1.2% in 2000 to 2.2% in 2004 [9]. Overall 30 day mortality in patients with CDI in the intensive

care unit is almost 40% during 2004 and 2005. Case control analysis estimated a 6% mortality was directly attributable to CDI in critically ill patients [29].

A hypervirulent strain of *C. difficile*, the North American pulse-field gel electrophoresis type 1 (NAP1) strain, has also been implicated as a cause of the increasing severity of CDI. Epidemics from this strain have occurred across the US, Canada, and Europe [23,30–32]. Patients infected with this strain undergo a higher proportion of urgent colectomies [33] and attributable mortality is estimated to be roughly 17% [34]. A deletion in the toxin regulatory gene, *tcdC*, is thought to allow the NAP1 strain to overproduce toxin A and toxin B by as much as 15 to 20 fold [32]. The NAP1 strain also produces binary toxin, although this virulence factor's role in pathogenesis is currently unknown [31]. Outbreaks of the NAP1 strain are strongly associated with the use of fluoroquinolones, although other antibiotics are also implicated [33,35].

Risk Factors

There are numerous independent risk factors reported for developing symptomatic disease after acquisition of *C. difficile*. The risk factors that are most consistently identified in the literature include antibiotic exposure, age > 60 years, longer duration of hospital stay, severe underlying disease, and gastric acid suppression [36]. Many of these factors are often found in critically ill patients residing in the ICU, making it unsurprising that ICU stay is also a commonly sited risk factor [37]. The most pertinent, potentially modifiable risk factors for intensive care patients are discussed below.

Exposure to antimicrobials is the most important risk factor for the development of CDI [37]. Preceding antibiotic administration is demonstrated in roughly 95% of inpatient cases [38]. The disruption of the normal flora caused by antibiotics allows *C. difficile* to colonize and overgrow within the gastrointestinal tract. Nearly every antibiotic has been implicated in leading to CDI, however broad spectrum antibiotics with anti-anaerobic activity appear to cause the greatest risk [37]. Prior to the epidemics from the NAP1 strain, clindamycin, ampicillin, and cephalosporins were the most frequently implicated [37,39]. With the increasing use of fluoroquinolones in hospitalized patients, these antibiotics have also emerged as an important cause of CDI [35]. Outbreaks of NAP1 related CDI are more specifically linked to the 8-methoxy fluoroquinolones, moxifloxacin and gatifloxacin. Administration of multiple antibiotics or using longer treatment courses also increases the risk of developing CDI [35, 37].

Several retrospective studies have shown that hospitalized patients are over twice as likely to develop CDI if prescribed proton pump inhibitors (PPIs) [36,40]. This is especially relevant for patients in intensive care units where gastric acid suppression is a routine intervention due to the extremely high incidence of stress related mucosal damage [41]. The usual acidic environment of the stomach is fatal to the vegetative form of *C. difficile* and may make it less likely that the spore form will be able to germinate after passing into the bowel [42]. Once the pH rises above 5, even vegetative *C. difficile* is able to survive gastric exposure [42]. PPIs also appear to cause an alteration in the gastrointestinal flora that may also create a niche for *C. difficile* colonization [43].

Enteral feeding is another common practice in intensive care units that has been implicated as a possible contributing factor in the development of CDI. Up to 60% of patients receiving enteral feeds will develop diarrhea so it is often difficult to distinguish infected from non-infected patients [44]. Several factors associated with tube feeding are thought to increase the risk of infection, including contamination of the formula or equipment during handling [45], or an alteration of the colonic environment associated with the special formulas [46]). In a prospective cohort study involving 152 patients, enteral feeding increased the risk of *C.*

difficile acquisition from 8% to 20% and the risk of developing CDI from 1% to 9% [47]. The finding that enteral feeding doubles the risk of CDI has also been demonstrated in other prospective studies [24,48]. The risk appears to be greatest when the patients were fed with a postpyloric tube [47].

Mechanical ventilation has also been demonstrated as a risk for both the development of CDI and increased disease severity in the few studies that evaluate this risk factor. Mechanical ventilation was associated with the acquisition of *C. difficile* while in the ICU; however statistical significance was not maintained after adjusting for confounders [24]. Ventilator support was found to increase the risk of developing CDI by 2 fold based on multivariable logistic regression on data from 36,086 patients [36]. Post-operative ICU patients that developed CDI had a median duration of ventilator support greater than 24 hours, compared to only 12 hours in the uninfected cohort [49].

Clinical Manifestations

CDI has a wide range of manifestations, causing a self-limited mild diarrheal illness to a fulminant life-threatening colitis [50]. The onset of CDI symptoms may range from 1 day to up to 10 weeks after antibiotics are administered; however most cases begin between within 3 and 7 days of exposure [51–54]. The watery diarrhea of CDI is usually accompanied by low-grade fever and cramping abdominal pain. Although standard definitions of disease severity are lacking, systemic symptoms generally increase with the degree of colitis. Severe cases of colitis can progress to ileus or toxic megacolon that may cause a paradoxical decrease in the amount of diarrhea [51–54] or may result in an acute abdomen [55].

Diagnosis

CDI is diagnosed by confirming the presence of a toxigenic strain of *C. difficile* or one of its toxins in the stool of a patient with symptoms that are consistent with the disease. Unlike most other bacterial infections, isolating the organism in culture is expensive, time consuming, and insufficient to prove disease due to the existence of nontoxigenic *C. difficile* in the stool. The presence of non-toxigenic strains of *C. difficile* can result in a false positive rate that exceeds 10% if culture alone is used to diagnose CDI [56]. Proving the cultured organism is pathogenic requires further analysis to determine the presence of toxin A, toxin B, or the virulence factor genes.

Multiple toxin detecting tests are commercially available for the diagnosis of CDI. The laboratory gold standard for detection of *C. difficile* toxins in the stool is the cytotoxicity cell assay. When filtered diarrheal stool that contains *C. difficile* toxins is added to cultured fibroblasts a characteristic cytopathic effect is seen. The cytotoxicity cell assay is largely considered too impractical for routine use due cost, time delays, and need for cull culture equipment, and has been replaced by enzyme linked immunosorbant assays (ELISAs) in most centers [57]. The ELISAs are relatively inexpensive and can confirm the diagnosis within several hours. Most currently available ELISAs are capable of detecting both toxin A and toxin B and have sensitivities that approach 90% in comparison to the cytotoxicity assay [58]. Another EIA that detects *C. difficile* glutamate dehydrogenase (GDH) is highly sensitive, but must be also be confirmed by a toxin detecting assay since this enzyme is also produced non-toxigenic strains [59].

Up to 20% of critically ill patients may suffer from ileus and lack the diarrhea typically associated with CDI [60]. A lack of diarrhea coupled with an inability of the critically ill patient to communicate with care providers may make diagnosis of CDI extremely difficult. Intensivists will need to maintain a high index of suspicion and must often rely on physical exam and laboratory findings to make the diagnosis. Exam findings such as fever, abdominal

pain, and abdominal distention are likely to be present in severe colitis. Hematology panels may also uncover a significant leukocytosis (often $> 20,000$ cells/mm²) and bandemia [61]. Elevation in serum lactate dehydrogenase is a relatively nonspecific finding for gastrointestinal disease, but may also be a potential clue to the presence of CDI [62,63]. These findings often precede multiorgan dysfunction and should prompt urgent consideration of CDI as a possible cause [61,64,65].

In the uncommon event that the diagnosis of CDI cannot be established through stool testing or compatible clinical syndrome, endoscopy may be a useful adjunct if the diagnosis cannot be delayed. The goal of endoscopy is to visualize the nearly pathognomonic pseudomembrane, however colonic edema, erythema, and mucosal ulcerations may also be consistent with the diagnosis [66,67]. Rectal sparing occurs in up to 25% of patients, but most lesions will be visible within 60 cm from the anus so either flexible sigmoidoscopy or colonoscopy are acceptable methods [68]. Although intestinal perforation appears uncommon in patients with CDI that undergo flexible sigmoidoscopy, this remains an associated risk in severe disease so endoscopic confirmation of the diagnosis should be performed with caution [67].

Computed tomography (CT) is rarely used in the diagnosis of CDI; however it may reveal patterns consistent with colitis and can also be used as supportive evidence for the diagnosis. Findings of colonic wall thickening > 4 mm, wall nodularity, pericolonic stranding, and ascites are common in CDI [69,70]. In a retrospective study using a combination of these criteria to diagnose CDI based on CT scan, the sensitivity was 52% and specificity was 93% compared to stool toxin assays [69]. Bowel wall thickening is the most sensitive finding, but lacks specificity if not supported by other characteristic imaging changes [69]. Less common findings also include distention of the colon, colonic fold effacement, and nodular fold thickening [70]. Characteristic imaging findings are typically associated with other clinical and laboratory abnormalities, but they do not necessarily correlate with severity of the disease [71,72].

Treatment

Treatment of CDI should be based on the severity of the disease. Unfortunately, standardized definitions for disease severity are lacking and current divisions are somewhat subjective and artificial given the illness varies along a continuous spectrum of symptoms. In general, symptoms of CDI can be grouped into three categories: mild to moderate, severe, and severe disease with complications [73,74]. Mild to moderate CDI consists only of diarrhea and abdominal cramping unaccompanied by systemic symptoms. Patients with abundant diarrhea, abdominal pain, leukocytosis, and fever or other systemic symptoms should be considered to have severe CDI. Individuals suffering from severe disease with complications may have any degree of gastrointestinal symptoms that are also accompanied by paralytic ileus, toxic megacolon, or other life threatening conditions. The disease may become progressively more serious even after treatment has been initiated so assessment of disease category must remain a dynamic process.

For all severities of CDI, cessation of the inciting antibiotic is the first step in treatment whenever possible. This should theoretically allow for recovery of the normal colonic flora to help combat the overgrowth of *C. difficile*. Prior to the NAP1 epidemic, stopping the administration of antibiotics resulted in the resolution of diarrhea in nearly one-quarter of patients with CDI [75,76]. Unfortunately, this intervention is rarely possible in the intensive care setting since more than 60% of patients that develop CDI have documented serious concomitant infections [38]. When it is unsafe to stop the inciting antibiotic therapy, it is prudent to change to a more narrow-spectrum regimen when possible.

Metronidazole and vancomycin are most common antibiotics used to treat *C. difficile* in patients with symptomatic infection [77]. Both antibiotics should be administered orally in patients able to tolerate that route. Metronidazole may also be given intravenously since both biliary excretion and exudation across inflamed colonic mucosa allow adequate treatment concentrations to be reached in the colon [78]. The use of intravenous metronidazole is also supported by several published case series and extensive clinical experience [79,80]. Intravenous vancomycin is not effective for CDI since there is minimal bowel excretion fecal drug concentration is low.

Metronidazole has historically been the drug of preference in CDI due to significant cost advantage in comparison to oral vancomycin and equal efficacy demonstrated in prior studies [81,82]. There has also been reluctance to use oral vancomycin due to the concern that it will result in more intestinal colonization with vancomycin resistant enterococci, although this concern has not been substantiated in the literature [83,84]. *C. difficile* continues to be susceptible to both medications *in vitro* [85]; however recent studies indicate that the choice of one drug over the other should now be based on disease severity [74,86].

Metronidazole remains appropriate first-line therapy for mild to moderate disease. In recent studies, oral vancomycin appears to have improved clinical outcomes in patients with severe disease. The decreasing efficacy of metronidazole was illustrated in a prospective observational study of 207 patients with CDI that reported 22% of patients remained symptomatic after 10 days of metronidazole therapy and an additional 27% suffered relapse [87]. In a randomized trial that enrolled 150 patients, metronidazole therapy resulted in a cure rate of only 76%, compared to a 97% cure rate with vancomycin for the treatment of severe CDI [74]. The difference between the two antibiotics was not significant of mild to moderate disease in this study. Due to these findings, vancomycin is preferred initial therapy for patients with severe disease or with risk factors for progressing to severe disease.

In cases of severe CDI with complications, reduced or absent bowel motility may prevent adequate amounts of orally administered vancomycin from reaching the site of infection. Several case reports have supported the intracolonic administration of vancomycin when oral therapy cannot be tolerated [88–90]. Some experts will also use higher doses of oral vancomycin with the goal of improving the chance that adequate fecal concentrations will be reached although this practice has not been studied. Intravenous metronidazole may be added to either oral or intracolonic vancomycin in severely ill patients with ileus, although this approach has also not been adequately evaluated [79,80].

When the colitis is so extreme that the efficacy of antibiotic therapy is in doubt, it is extremely important to consider surgical consultation. Fulminant *C. difficile* colitis that necessitates colectomy is rare, occurring in less than 3% of all patients with CDI [91]. In the ICU patient population, it is not surprising that the incidence of severe colitis is much higher, with 20% of patients requiring colectomy or diversion procedures [25]. Improved mortality rates are seen when surgical intervention is performed within 48-hours of lack of response to medical therapy [92]. With the increased number of rapidly progressing cases secondary to the hypervirulent NAP1 strain of *C. difficile*, surgical consultation is becoming even more urgent. Elderly patients with leukocytosis and elevated lactate appear to benefit the most from early colectomy during NAP1 epidemics [93]. Admission to the hospital for a diagnosis other than CDI, mental status changes, prolongation of attempted medical treatment, and vasopressors support are all predictors of postoperative mortality [93].

Multiple other antibiotics have been considered in the treatment of CDI, but none have demonstrated any significant clinical benefits over the current conventional therapy. Rifaximin, nitazoxanide, and fusidic acid are equally efficacious to vancomycin and/or

metronidazole [82,94–96]. The only benefit noted with teicoplanin was a significant reduction in stool toxin levels in comparison to vancomycin and metronidazole, but there is no corresponding significant clinical benefit [82,95,97] and it is not available in the United States. Combination therapy with metronidazole and rifampin has been evaluated in a single randomized trial of 39 patients, but the only significant finding was an increase in mortality in the combination group [98]. The lack of any significant clinical benefits coupled with reduced physician experience with these medications has resulted in these other antibiotics being rarely used or advocated for CDI.

A novel macrocycle antibiotic, OPT-80, is currently in phase 3 trials evaluating its effectiveness in the treatment of CDI. OPT-80 is minimally absorbed from the gastrointestinal tract and well tolerated in most subjects [99]. Although highly effective against *C. difficile*, OPT-80 leaves the majority of the gram-negative anaerobic flora of the gastrointestinal tract intact [100]. A total of 48 subjects with mild to moderate CDI participated in the trial and were randomized to receive 100mg, 200mg, or 400mg per day of the medication [100]. Although only 77% of patients treated with the lower dose had resolution of diarrhea within 10 days, this climbed to 94% in the high dose treatment group. Only 2 patients suffered disease relapse across all treatment groups. Unfortunately, it is currently unknown if the drug will perform well in patients with severe or complicated disease, but OPT-80 does show some early promise as a potential future alternative to the current conventional therapy.

Another commonly employed strategy in combating CDI is the administration of probiotics. The live microorganisms in the probiotic formula are intended to restore the non-pathogenic flora to the colon, inhibit *C. difficile* toxin production, and stimulate the immune system [101]. The combination of *Saccharomyces* or *Lactobacillus* probiotics with conventional antibiotic therapy has shown no statistically significant benefit for the treatment of CDI in several randomized controlled trials [102–105]. *Saccharomyces boulardii* did appear to reduce the relapse rate of CDI when combined with conventional therapy in one randomized, placebo-controlled trial after subgroup analysis [103]; however this result was unable to be replicated. Although adverse effects of probiotics are rare, occasional case reports of blood stream infections in critically ill patients with central venous catheters are reported, and being critically ill, immunocompromised, and/or having a central venous catheter are considered contraindications for probiotics [106]. These organisms may also become aerosolized and place other patients in the ICU at risk for opportunistic infection [107].

Neutralizing the *C. difficile* toxins has been another attempted treatment strategy. Cholestyramine and colestipol bind *C. difficile* toxins *in vitro*; however clinical trials have shown no efficacy during acute CDI [108]. The only placebo controlled trial evaluating these medications showed no reduction in the stool concentration of either *C. difficile* or its toxins [53]. There is also a potential harm in using these medications during therapy with vancomycin since the drugs can complex with one another and may result in subtherapeutic antibiotic concentrations in the stool [109].

Intravenous immunoglobulin (IVIG) has also been evaluated for the treatment of CDI with the goal of neutralizing the effect of the toxins. A poor humoral response to *C. difficile* toxins is known to be associated with an increased risk of developing symptomatic disease and a higher incidence of relapses [22]. Anti-*C. difficile* toxin antibodies are commonly present in healthy subjects and typically found in pooled immunoglobulin [110]. Although theoretically beneficial, IVIG use is currently only supported by case studies and series [110–113]. These studies are contradicted by a retrospective analysis of 18 pair matched patients with severe CDI that did not show a clear benefit in adding IVIG to standard antibiotic therapy [114]. Unfortunately, this study suffered from methodological difficulties such as not controlling for the length of time between onset of symptoms and administration of IVIG. Due to the

insufficient evidence base, IVIG cannot be generally recommended for the treatment of CDI, although this appears to be an area worth further study, especially in patients with severe disease or multiple relapses.

Although the evidence is anecdotal, it is generally advised that any medications with an antiperistaltic effect be avoided in patients with CDI. Drugs that decrease intestinal motility are thought to increase the risk of severe complications such as toxic megacolon [115]. Unfortunately, the critically ill patient population often requires sedatives and narcotics for pain management or mechanical ventilation. Nevertheless, it is prudent to wean medications with antiperistaltic effects if possible in patients at high risk for developing severe CDI.

Treatment Failure

Patients typically have some symptomatic improvement, including fever resolution, within 48 hours after the initiation of appropriate antibiotic therapy for CDI [116]. A significant reduction in the amount of diarrhea is expected within 6 days of starting therapy in most patients [116]. Failure to respond appropriately after treatment with metronidazole is associated with low serum albumin, continued exposure to the inciting antibiotic, and residence in the intensive care unit [117,118]. One possible physiologic explanation for metronidazole failure comes from the observation that stool concentrations diminish as the colitis improves due to reduced exudation across the non-inflamed colonic mucosa [78]. *in vitro* susceptibilities performed on *C. difficile* strains obtained from the stool of patients that have failed to respond continue to be metronidazole sensitive [119]. Although the emergence of resistance to metronidazole is rare, many clinicians advocate changing therapy to oral vancomycin in this scenario. If patients continue to fail antibiotic therapy with vancomycin, surgical intervention or other less established treatments, such as IVIG, should be considered.

Relapse

Intensivists are likely to encounter CDI relapses in patients that have prolonged stays within the ICU. About one third of patients will develop at least one relapse to CDI regardless of initial treatment choice [120]. Relapses have been reported to occur up to several months after the initial episode, but most occur within the first two weeks of completing therapy. The first relapse is followed by even more episodes of recurrent disease in 50% of patients [121]. The risk factors of recurrent disease are similar to those associated with the first episode of CDI. It remains unresolved if disease relapse is secondary to reactivation of latent *C. difficile* spores, reacquisition of the organism from the environment, or a combination of both scenarios [122].

Treatment of recurrent disease is a difficult problem since it has not been extensively studied and current strategies have questionable effectiveness. Since antibiotic resistance does not appear to be a cause of relapse, the first recurrence is generally managed similarly to the initial disease with either metronidazole or vancomycin depending on disease severity [122].

Treatment with longer courses of oral vancomycin in either a tapering or pulse dosing schedule is generally thought to be appropriate strategies patients that suffer multiple CDI relapses, but this approach is only supported by case studies and not always effective [123,124]. Several recent studies have attempted using rifaximin after a standard treatment course of vancomycin has been completed. All but one patient remained disease free in a case series of 8 patients with a history of multiple CDI relapses that were treated with vancomycin followed by two weeks of rifaximin [125]. The patient that suffered the relapse appeared had a *C. difficile* strain that developed resistance to rifaximin. Another case series treated 6 patients with recurrent CDI with rifaximin alone and five patients had no recurrence after a mean follow-up of 310 days [126]. As noted above, combining probiotics, toxin-binding resins, or IVIG with vancomycin therapy has shown potential in reducing the incidence of multiple relapses in some small studies

and these may be considered on a case-by-case basis. The investigational macrocycle, OTP-80, may also prove beneficial in treating CDI relapses in the future.

Prevention

The most essential aspect of CDI prevention is protecting patients from initial acquisition of the organism in the healthcare setting. As with many other nosocomial pathogens, strict hand hygiene and appropriate contact precautions are the cornerstones of reducing the spread of *C. difficile* between patients. *C. difficile* spores are not eradicated by the commonly used alcohol-based hand sanitizers; however the use of these products has not been associated with any significant increases in the incidence of CDI within centers [127]. Contact precautions that include the use of a gown and gloves when entering a patient's room also results in a significant decrease in new CDI cases [128,129]. The combination of rigorous hand hygiene with contact precautions can decrease the incidence of CDI by as much as 80% [128–130].

Environmental contamination with *C. difficile* spores is also a potential source of disease acquisition in the hospital setting. Rapid identification and treatment of patients is essential in reducing the amount of spores released into the environment since the amount of contamination correlates with the duration of symptoms [131]. Disinfection of the patient's surroundings is difficult since the spore form of *C. difficile* is resistant to standard cleaning products and may persist in patient rooms for months [132,133]. In the absence of an Environmental Protection Agency approved liquid disinfectant with known sporicidal activity, household bleach diluted 1:10 with water may be used and has been shown fatal rapidly fatal to *C. difficile* spores [134]. There is currently no evidence that routine decontamination of patient rooms results in a decrease in CDI, but this step is reasonable to consider in outbreak situations.

Attention should also be directed at reducing each modifiable individual risk factor if possible. The most significant intervention in this area appears to be ensuring the prudent use of antibiotics through formulary restrictions and antimicrobial stewardship programs. During a NAP1 strain outbreak in Quebec, an antimicrobial stewardship program was introduced that resulted in a 54% reduction in antibiotic use and a 60% reduction in the incidence of CDI [135]. When broad spectrum antibiotics are specifically restricted in antimicrobial stewardship programs, CDI rates also fall despite the overall antibiotic use remaining unchanged [136]. More specific interventions that restrict antibiotics that are highly associated with CDI, such as fluoroquinolones and clindamycin, have also proven successful [137–140]. In addition to the control of antibiotic use, prudent use of other medications such as PPIs may also be beneficial.

Conclusion

C. difficile is commonly encountered in the ICU setting and critically ill patients are at significant risk for morbidity and mortality from this pathogen. The incidence and severity of CDI has been increasing with new epidemics secondary to the hypervirulent NAP1 strain. Critically ill patients share many of the risk factors for developing severe CDI so vigilance must be maintained in this patient population in order to prevent and rapidly treat the disease. Clinical manifestations may be variable in the ICU setting due to the high incidence of complicated disease so intensivists should have a high index of suspicion in patients with otherwise unexplained exam or laboratory findings associated with CDI. Treatment of choice for patients with mild to moderate disease remains metronidazole; however patients with severe and complicated disease should be treated with vancomycin. Intracolonic administration of vancomycin, surgical intervention, and less-well established therapies such as IVIG may be beneficial in some patients with severe disease. Prevention efforts remain essential in halting

the spread of this disease within medical centers and focus on hand hygiene, contact precautions, and antimicrobial stewardship programs.

Acknowledgments

This work was supported by grant T32 HD007507 from the NICHD and 1 UL1 RR024992-01 (PI: Polonsky); 1 KL2 RR024994-01 (PI: Fraser) from the NCRR.

References

1. Kelly TW, Patrick MR, Hillman KM. Study of diarrhea in critically ill patients. *Crit Care Med* 1983;11:7–9. [PubMed: 6848311]
2. Thakkar K, Kien CL, Rosenblatt JI, et al. Diarrhea in severely burned children. *JPEN J Parenter Enteral Nutr* 2005;29:8–11. [PubMed: 15715268]
3. Ringel AF, Jameson GL, Foster ES. Diarrhea in the intensive care patient. *Crit Care Clin* 1995;11:465–477. [PubMed: 7788541]
4. Liolios A, Oropello JM, Benjamin E. Gastrointestinal complications in the intensive care unit. *Clin Chest Med* 1999;20:329–345. [PubMed: 10386260]viii
5. Wiesen P, Van Gossum A, Preiser JC. Diarrhoea in the critically ill. *Curr Opin Crit Care* 2006;12:149–154. [PubMed: 16543792]
6. Hall IC, O'Toole E. Intestinal flora in ew-born infants with a description of a new pathogenic anaerobe, *Bacillus difficilis*. *American Journal of Diseases in Children* 1935;49:390–402.
7. Bartlett JG, Chang TW, Gurwith M, et al. Antibiotic-associated pseudomembranous colitis due to toxin-producing clostridia. *N Engl J Med* 1978;298:531–534. [PubMed: 625309]
8. Barbut F, Corthier G, Charpak Y, et al. Prevalence and pathogenicity of *Clostridium difficile* in hospitalized patients. A French multicenter study. *Arch Intern Med* 1996;156:1449–1454. [PubMed: 8678714]
9. Zilberberg MD. *Clostridium difficile*-related hospitalizations among US adults, 2006. *Emerg Infect Dis* 2009;15:122–124. [PubMed: 19116073]
10. Labbe AC, Poirier L, Maccannell D, 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;52:3180–3187. [PubMed: 18573937]
11. Pothoulakis C, Sullivan R, Melnick DA, et al. *Clostridium difficile* toxin A stimulates intracellular calcium release and chemotactic response in human granulocytes. *J Clin Invest* 1988;81:1741–1745. [PubMed: 2838520]
12. Triadafilopoulos G, Pothoulakis C, O'Brien MJ, et al. Differential effects of *Clostridium difficile* toxins A and B on rabbit ileum. *Gastroenterology* 1987;93:273–279. [PubMed: 3596162]
13. Riegler M, Sedivy R, Pothoulakis C, et al. *Clostridium difficile* toxin B is more potent than toxin A in damaging human colonic epithelium in vitro. *J Clin Invest* 1995;95:2004–2011. [PubMed: 7738167]
14. Voth DE, Ballard JD. *Clostridium difficile* toxins: mechanism of action and role in disease. *Clin Microbiol Rev* 2005;18:247–263. [PubMed: 15831824]
15. Meyer GK, Neetz A, Brandes G, et al. *Clostridium difficile* toxins A and B directly stimulate human mast cells. *Infect Immun* 2007;75:3868–3876. [PubMed: 17517880]
16. Barbut F, Petit JC. Epidemiology of *Clostridium difficile*-associated infections. *Clin Microbiol Infect* 2001;7:405–410. [PubMed: 11591202]
17. Riggs MM, Sethi AK, Zabarsky TF, et al. Asymptomatic carriers are a potential source for transmission of epidemic and nonepidemic *Clostridium difficile* strains among long-term care facility residents. *Clin Infect Dis* 2007;45:992–998. [PubMed: 17879913]
18. McFarland LV, Mulligan ME, Kwok RY, et al. Nosocomial acquisition of *Clostridium difficile* infection. *N Engl J Med* 1989;320:204–210. [PubMed: 2911306]
19. Clabots CR, Johnson S, Olson MM, et al. Acquisition of *Clostridium difficile* by hospitalized patients: evidence for colonized new admissions as a source of infection. *J Infect Dis* 1992;166:561–567. [PubMed: 1323621]

20. Dubberke ER, Reske KA, Olsen MA, et al. Evaluation of Clostridium difficile-associated disease pressure as a risk factor for C difficile-associated disease. *Arch Intern Med* 2007;167:1092–1097. [PubMed: 17533213]
21. Shim JK, Johnson S, Samore MH, et al. Primary symptomless colonisation by Clostridium difficile and decreased risk of subsequent diarrhoea. *Lancet* 1998;351:633–636. [PubMed: 9500319]
22. Kyne L, Warny M, Qamar A, et al. Asymptomatic carriage of Clostridium difficile and serum levels of IgG antibody against toxin A. *N Engl J Med* 2000;342:390–397. [PubMed: 10666429]
23. Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality. *N Engl J Med* 2005;353:2442–2449. [PubMed: 16322602]
24. Lawrence SJ, Puzniak LA, Shadel BN, et al. Clostridium difficile in the intensive care unit: epidemiology, costs, and colonization pressure. *Infect Control Hosp Epidemiol* 2007;28:123–130. [PubMed: 17265392]
25. Grundfest-Broniatowski S, Quader M, Alexander F, et al. Clostridium difficile colitis in the critically ill. *Dis Colon Rectum* 1996;39:619–623. [PubMed: 8646945]
26. Kyne L, Merry C, O'Connell B, et al. Factors associated with prolonged symptoms and severe disease due to Clostridium difficile. *Age Ageing* 1999;28:107–113. [PubMed: 10350405]
27. Gerding DN, Muto CA, Owens RC Jr. Measures to control and prevent Clostridium difficile infection. *Clin Infect Dis* 2008;46(Suppl 1):S43–S49. [PubMed: 18177221]
28. Kim KH, Fekety R, Batts DH, et al. Isolation of Clostridium difficile from the environment and contacts of patients with antibiotic-associated colitis. *J Infect Dis* 1981;143:42–50. [PubMed: 7217711]
29. Kenneally C, Rosini JM, Skrupky LP, et al. Analysis of 30-day mortality for clostridium difficile-associated disease in the ICU setting. *Chest* 2007;132:418–424. [PubMed: 17573523]
30. Severe Clostridium difficile-associated disease in populations previously at low risk—four states, 2005. *MMWR Morb Mortal Wkly Rep* 2005;54:1201–1205. [PubMed: 16319813]
31. McDonald LC, Killgore GE, Thompson A, et al. An epidemic, toxin gene-variant strain of Clostridium difficile. *N Engl J Med* 2005;353:2433–2441. [PubMed: 16322603]
32. Warny M, Pepin J, Fang A, et al. Toxin production by an emerging strain of Clostridium difficile associated with outbreaks of severe disease in North America and Europe. *Lancet* 2005;366:1079–1084. [PubMed: 16182895]
33. Muto CA, Pokrywka M, Shutt K, et al. A large outbreak of Clostridium difficile-associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased fluoroquinolone use. *Infect Control Hosp Epidemiol* 2005;26:273–280. [PubMed: 15796280]
34. Pepin J, Valiquette L, Cossette B. Mortality attributable to nosocomial Clostridium difficile-associated disease during an epidemic caused by a hypervirulent strain in Quebec. *Cmaj* 2005;173:1037–1042. [PubMed: 16179431]
35. Pepin J, Saheb N, Coulombe MA, 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;41:1254–1260. [PubMed: 16206099]
36. Dubberke ER, Reske KA, Yan Y, et al. Clostridium difficile--associated disease in a setting of endemicity: identification of novel risk factors. *Clin Infect Dis* 2007;45:1543–1549. [PubMed: 18190314]
37. Bignardi GE. Risk factors for Clostridium difficile infection. *J Hosp Infect* 1998;40:1–15. [PubMed: 9777516]
38. Marra AR, Edmond MB, Wenzel RP, et al. Hospital-acquired Clostridium difficile-associated disease in the intensive care unit setting: epidemiology, clinical course and outcome. *BMC Infect Dis* 2007;7:42. [PubMed: 17517130]
39. Gurwith MJ, Rabin HR, Love K. Diarrhea associated with clindamycin and ampicillin therapy: preliminary results of a cooperative study. *J Infect Dis* 1977;135(Suppl):S104–S110. [PubMed: 850083]
40. Cunningham R, Dale B, Undy B, et al. Proton pump inhibitors as a risk factor for Clostridium difficile diarrhoea. *J Hosp Infect* 2003;54:243–245. [PubMed: 12855243]

41. Brett S. Science review: The use of proton pump inhibitors for gastric acid suppression in critical illness. *Crit Care* 2005;9:45–50. [PubMed: 15693983]
42. Jump RL, Pultz MJ, Donskey CJ. Vegetative *Clostridium difficile* survives in room air on moist surfaces and in gastric contents with reduced acidity: a potential mechanism to explain the association between proton pump inhibitors and *C. difficile*-associated diarrhea? *Antimicrob Agents Chemother* 2007;51:2883–2887. [PubMed: 17562803]
43. Thorens J, Froehlich F, Schwizer W, et al. Bacterial overgrowth during treatment with omeprazole compared with cimetidine: a prospective randomised double blind study. *Gut* 1996;39:54–59. [PubMed: 8881809]
44. Bliss DZ, Guenter PA, Settle RG. Defining and reporting diarrhea in tube-fed patients--what a mess! *Am J Clin Nutr* 1992;55:753–759. [PubMed: 1550053]
45. Thurn J, Crossley K, Gerdt A, et al. Enteral hyperalimentation as a source of nosocomial infection. *J Hosp Infect* 1990;15:203–217. [PubMed: 1971627]
46. Rolfe RD. Role of volatile fatty acids in colonization resistance to *Clostridium difficile*. *Infect Immun* 1984;45:185–191. [PubMed: 6735467]
47. Bliss DZ, Johnson S, Savik K, et al. Acquisition of *Clostridium difficile* and *Clostridium difficile*-associated diarrhea in hospitalized patients receiving tube feeding. *Ann Intern Med* 1998;129:1012–1019. [PubMed: 9867755]
48. Asha NJ, Tompkins D, Wilcox MH. Comparative analysis of prevalence, risk factors, and molecular epidemiology of antibiotic-associated diarrhea due to *Clostridium difficile*, *Clostridium perfringens*, and *Staphylococcus aureus*. *J Clin Microbiol* 2006;44:2785–2791. [PubMed: 16891493]
49. Crabtree T, Aitchison D, Meyers BF, et al. *Clostridium difficile* in cardiac surgery: risk factors and impact on postoperative outcome. *Ann Thorac Surg* 2007;83:1396–1402. [PubMed: 17383346]
50. Kelly CP, Pothoulakis C, LaMont JT. *Clostridium difficile* colitis. *N Engl J Med* 1994;330:257–262. [PubMed: 8043060]
51. Beaulieu M, Williamson D, Pichette G, et al. Risk of *Clostridium difficile*-associated disease among patients receiving proton-pump inhibitors in a Quebec medical intensive care unit. *Infect Control Hosp Epidemiol* 2007;28:1305–1307. [PubMed: 17926283]
52. Hurley BW, Nguyen CC. The spectrum of pseudomembranous enterocolitis and antibiotic-associated diarrhea. *Arch Intern Med* 2002;162:2177–2184. [PubMed: 12390059]
53. Mogg GA, Burdon DW, Keighley M. Oral metronidazole in *Clostridium difficile* colitis. *Br Med J* 1979;2:335. [PubMed: 476461]
54. Tedesco FJ. Pseudomembranous colitis: pathogenesis and therapy. *Med Clin North Am* 1982;66:655–664. [PubMed: 7043127]
55. Triadafilopoulos G, Hallstone AE. Acute abdomen as the first presentation of pseudomembranous colitis. *Gastroenterology* 1991;101:685–691. [PubMed: 1860633]
56. Peterson LR, Kelly PJ. The role of the clinical microbiology laboratory in the management of *Clostridium difficile*-associated diarrhea. *Infect Dis Clin North Am* 1993;7:277–293. [PubMed: 8345170]
57. Gelone SP, Fishman N, Gerding DN, et al. *Clostridium difficile* epidemiology: Results of an international web-based survey project. In SHEA '06 Chicago.
58. Musher DM, Manhas A, Jain P, et al. Detection of *Clostridium difficile* toxin: comparison of enzyme immunoassay results with results obtained by cytotoxicity assay. *J Clin Microbiol* 2007;45:2737–2739. [PubMed: 17567791]
59. Wilkins TD, Lyerly DM. *Clostridium difficile* testing: after 20 years, still challenging. *J Clin Microbiol* 2003;41:531–534. [PubMed: 12574241]
60. Sheth SG, LaMont JT. Gastrointestinal problems in the chronically critically ill patient. *Clin Chest Med* 2001;22:135–147. [PubMed: 11315452]
61. Wanahita A, Goldsmith EA, Marino BJ, et al. *Clostridium difficile* infection in patients with unexplained leukocytosis. *Am J Med* 2003;115:543–546. [PubMed: 14599633]
62. Grossmann EM, Longo WE, Kaminski DL, et al. *Clostridium difficile* toxin: cytoskeletal changes and lactate dehydrogenase release in hepatocytes. *J Surg Res* 2000;88:165–172. [PubMed: 10644484]

63. Lamontagne F, Labbe AC, Haeck O, et al. Impact of emergency colectomy on survival of patients with fulminant *Clostridium difficile* colitis during an epidemic caused by a hypervirulent strain. *Ann Surg* 2007;245:267–272. [PubMed: 17245181]
64. Peled N, Pitlik S, Samra Z, et al. Predicting *Clostridium difficile* toxin in hospitalized patients with antibiotic-associated diarrhea. *Infect Control Hosp Epidemiol* 2007;28:377–381. [PubMed: 17385141]
65. Wanahita A, Goldsmith EA, Musher DM. Conditions associated with leukocytosis in a tertiary care hospital, with particular attention to the role of infection caused by *clostridium difficile*. *Clin Infect Dis* 2002;34:1585–1592. [PubMed: 12032893]
66. Adams SD, Mercer DW. Fulminant *Clostridium difficile* colitis. *Curr Opin Crit Care* 2007;13:450–455. [PubMed: 17599017]
67. Mylonakis E, Ryan ET, Calderwood SB. *Clostridium difficile*--Associated diarrhea: A review. *Arch Intern Med* 2001;161:525–533. [PubMed: 11252111]
68. Tedesco FJ, Corless JK, Brownstein RE. Rectal sparing in antibiotic-associated pseudomembranous colitis: a prospective study. *Gastroenterology* 1982;83:1259–1260. [PubMed: 7129030]
69. Kirkpatrick ID, Greenberg HM. Evaluating the CT diagnosis of *Clostridium difficile* colitis: should CT guide therapy? *AJR Am J Roentgenol* 2001;176:635–639. [PubMed: 11222194]
70. Kunimoto D, Thomson AB. Recurrent *Clostridium difficile*-associated colitis responding to cholestyramine. *Digestion* 1986;33:225–228. [PubMed: 3956890]
71. Ash L, Baker ME, O'Malley CM Jr, et al. Colonic abnormalities on CT in adult hospitalized patients with *Clostridium difficile* colitis: prevalence and significance of findings. *AJR Am J Roentgenol* 2006;186:1393–1400. [PubMed: 16632736]
72. Boland GW, Lee MJ, Cats AM, et al. *Clostridium difficile* colitis: correlation of CT findings with severity of clinical disease. *Clin Radiol* 1995;50:153–156. [PubMed: 7889703]
73. Cohen, SH.; Gerding, DN.; Johnson, S., et al. *Clostridium difficile* Infection: Clinical Practice Guidelines by SHEA and IDSA. IDSA 45th Annual Meeting; San Diego, California.
74. Zar FA, Bakkanagari SR, Moorthi KM, et al. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. *Clin Infect Dis* 2007;45:302–307. [PubMed: 17599306]
75. Bartlett JG. Treatment of antibiotic-associated pseudomembranous colitis. *Rev Infect Dis* 1984;6 (Suppl 1):S235–S241. [PubMed: 6718937]
76. Olson MM, Shanholtzer CJ, Lee JT Jr, et al. Ten years of prospective *Clostridium difficile*-associated disease surveillance and treatment at the Minneapolis VA Medical Center, 1982–1991. *Infect Control Hosp Epidemiol* 1994;15:371–381. [PubMed: 7632199]
77. Miller MA. Clinical management of *Clostridium difficile*-associated disease. *Clin Infect Dis* 2007;45 (Suppl 2):S122–S128. [PubMed: 17683016]
78. Bolton RP, Culshaw MA. Faecal metronidazole concentrations during oral and intravenous therapy for antibiotic associated colitis due to *Clostridium difficile*. *Gut* 1986;27:1169–1172. [PubMed: 3781329]
79. Friedenber F, Fernandez A, Kaul V, et al. Intravenous metronidazole for the treatment of *Clostridium difficile* colitis. *Dis Colon Rectum* 2001;44:1176–1180. [PubMed: 11535859]
80. Johnson S, Peterson LR, Gerding DN. Intravenous metronidazole and *Clostridium difficile*-associated diarrhea or colitis. *J Infect Dis* 1989;160:1087–1088. [PubMed: 2584759]
81. Teasley DG, Gerding DN, Olson MM, et al. Prospective randomised trial of metronidazole versus vancomycin for *Clostridium-difficile*-associated diarrhoea and colitis. *Lancet* 1983;2:1043–1046. [PubMed: 6138597]
82. Wenisch C, Parschalk B, Hasenhundl M, et al. Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of *Clostridium difficile*-associated diarrhea. *Clin Infect Dis* 1996;22:813–818. [PubMed: 8722937]
83. Al-Nassir WN, Sethi AK, Li Y, et al. Both oral metronidazole and oral vancomycin promote persistent overgrowth of vancomycin-resistant enterococci during treatment of *Clostridium difficile*-associated disease. *Antimicrob Agents Chemother* 2008;52:2403–2406. [PubMed: 18443120]

84. Salgado CD, Giannetta ET, Farr BM. Failure to develop vancomycin-resistant *Enterococcus* with oral vancomycin treatment of *Clostridium difficile*. *Infect Control Hosp Epidemiol* 2004;25:413–417. [PubMed: 15188848]
85. Wong SS, Woo PC, Luk WK, et al. Susceptibility testing of *Clostridium difficile* against metronidazole and vancomycin by disk diffusion and Etest. *Diagn Microbiol Infect Dis* 1999;34:1–6. [PubMed: 10342100]
86. Louie, T.; Gerson, M.; Grimard, D., et al. Results of a phase III trial comparing tolevamar, vancomycin and metronidazole in patients with *Clostridium difficile*-associated diarrhea (CDAD); 47th Annual ICAAC, Chicago;
87. Musher DM, Aslam S, Logan N, et al. Relatively poor outcome after treatment of *Clostridium difficile* colitis with metronidazole. *Clin Infect Dis* 2005;40:1586–1590. [PubMed: 15889354]
88. Apisarnthanarak A, Razavi B, Mundy LM. Adjunctive intracolonic vancomycin for severe *Clostridium difficile* colitis: case series and review of the literature. *Clin Infect Dis* 2002;35:690–696. [PubMed: 12203166]
89. Malnick SD, Zimhony O. Treatment of *Clostridium difficile*-associated diarrhea. *Ann Pharmacother* 2002;36:1767–1775. [PubMed: 12398575]
90. Nathanson DR, Sheahan M, Chao L, et al. Intracolonic use of vancomycin for treatment of *clostridium difficile* colitis in a patient with a diverted colon: report of a case. *Dis Colon Rectum* 2001;44:1871–1872. [PubMed: 11742178]
91. Rubin MS, Bodenstern LE, Kent KC. Severe *Clostridium difficile* colitis. *Dis Colon Rectum* 1995;38:350–354. [PubMed: 7720439]
92. Ali SO, Welch JP, Dring RJ. Early surgical intervention for fulminant pseudomembranous colitis. *Am Surg* 2008;74:20–26. [PubMed: 18274423]
93. Byrn JC, Maun DC, Gingold DS, et al. Predictors of mortality after colectomy for fulminant *Clostridium difficile* colitis. *Arch Surg* 2008;143:150–154. [PubMed: 18283139]discussion 155
94. Musher DM, Logan N, Hamill RJ, et al. Nitazoxanide for the treatment of *Clostridium difficile* colitis. *Clin Infect Dis* 2006;43:421–427. [PubMed: 16838229]
95. Nelson R. Antibiotic treatment for *Clostridium difficile*-associated diarrhea in adults. *Cochrane Database Syst Rev*. 2007CD004610
96. Wullt M, Odenholt I. A double-blind randomized controlled trial of fusidic acid and metronidazole for treatment of an initial episode of *Clostridium difficile*-associated diarrhoea. *J Antimicrob Chemother* 2004;54:211–216. [PubMed: 15163651]
97. de Lalla F, Nicolin R, Rinaldi E, et al. Prospective study of oral teicoplanin versus oral vancomycin for therapy of pseudomembranous colitis and *Clostridium difficile*-associated diarrhea. *Antimicrob Agents Chemother* 1992;36:2192–2196. [PubMed: 1444298]
98. Lagrotteria D, Holmes S, Smieja M, et al. Prospective, randomized inpatient study of oral metronidazole versus oral metronidazole and rifampin for treatment of primary episode of *Clostridium difficile*-associated diarrhea. *Clin Infect Dis* 2006;43:547–552. [PubMed: 16886144]
99. Louie T, Miller M, Donskey C, et al. Clinical outcomes, safety, and pharmacokinetics of OPT-80 in a phase 2 trial with patients with *Clostridium difficile* infection. *Antimicrob Agents Chemother* 2009;53:223–228. [PubMed: 18955525]
100. Louie TJ, Emery J, Krulicki W, et al. OPT-80 eliminates *Clostridium difficile* and is sparing of bacteroides species during treatment of *C. difficile* infection. *Antimicrob Agents Chemother* 2009;53:261–263. [PubMed: 18955523]
101. Ng SC, Hart AL, Kamm MA, et al. Mechanisms of action of probiotics: Recent advances. *Inflamm Bowel Dis*. 2008
102. Lawrence SJ, Korzenik JR, Mundy LM. Probiotics for recurrent *Clostridium difficile* disease. *J Med Microbiol* 2005;54:905–906. [PubMed: 16091446]
103. McFarland LV, Surawicz CM, Greenberg RN, et al. A randomized placebo-controlled trial of *Saccharomyces boulardii* in combination with standard antibiotics for *Clostridium difficile* disease. *Jama* 1994;271:1913–1918. [PubMed: 8201735]
104. Surawicz CM, McFarland LV, Greenberg RN, et al. The search for a better treatment for recurrent *Clostridium difficile* disease: use of high-dose vancomycin combined with *Saccharomyces boulardii*. *Clin Infect Dis* 2000;31:1012–1017. [PubMed: 11049785]

105. Wullt M, Hagslatt ML, Odenholt I. Lactobacillus plantarum 299v for the treatment of recurrent Clostridium difficile-associated diarrhoea: a double-blind, placebo-controlled trial. *Scand J Infect Dis* 2003;35:365–367. [PubMed: 12953945]
106. Lherm T, Monet C, Nougier B, et al. Seven cases of fungemia with Saccharomyces boulardii in critically ill patients. *Intensive Care Med* 2002;28:797–801. [PubMed: 12107689]
107. Cassone M, Serra P, Mondello F, et al. Outbreak of Saccharomyces cerevisiae subtype boulardii fungemia in patients neighboring those treated with a probiotic preparation of the organism. *J Clin Microbiol* 2003;41:5340–5343. [PubMed: 14605200]
108. Ariano RE, Zhanel GG, Harding GK. The role of anion-exchange resins in the treatment of antibiotic-associated pseudomembranous colitis. *Cmaj* 1990;142:1049–1051. [PubMed: 2186849]
109. Taylor NS, Bartlett JG. Binding of Clostridium difficile cytotoxin and vancomycin by anion-exchange resins. *J Infect Dis* 1980;141:92–97. [PubMed: 7365273]
110. Salcedo J, Keates S, Pothoulakis C, et al. Intravenous immunoglobulin therapy for severe Clostridium difficile colitis. *Gut* 1997;41:366–370. [PubMed: 9378393]
111. Hassoun A, Ibrahim F. Use of intravenous immunoglobulin for the treatment of severe Clostridium difficile colitis. *Am J Geriatr Pharmacother* 2007;5:48–51. [PubMed: 17608247]
112. McPherson S, Rees CJ, Ellis R, et al. Intravenous immunoglobulin for the treatment of severe, refractory, and recurrent Clostridium difficile diarrhea. *Dis Colon Rectum* 2006;49:640–645. [PubMed: 16525744]
113. Warny M, Denie C, Delmee M, et al. Gamma globulin administration in relapsing Clostridium difficile-induced pseudomembranous colitis with a defective antibody response to toxin A. *Acta Clin Belg* 1995;50:36–39. [PubMed: 7537003]
114. Juang P, Skledar SJ, Zgheib NK, et al. Clinical outcomes of intravenous immune globulin in severe clostridium difficile-associated diarrhea. *Am J Infect Control* 2007;35:131–137. [PubMed: 17327194]
115. Bartlett JG. Clinical practice. Antibiotic-associated diarrhea. *N Engl J Med* 2002;346:334–339. [PubMed: 11821511]
116. Fekety R, Shah AB. Diagnosis and treatment of Clostridium difficile colitis. *Jama* 1993;269:71–75. [PubMed: 8416409]
117. Fernandez A, Anand G, Friedenber F. Factors associated with failure of metronidazole in Clostridium difficile-associated disease. *J Clin Gastroenterol* 2004;38:414–418. [PubMed: 15100520]
118. Nair S, Yadav D, Corpuz M, et al. Clostridium difficile colitis: factors influencing treatment failure and relapse--a prospective evaluation. *Am J Gastroenterol* 1998;93:1873–1876. [PubMed: 9772047]
119. Sanchez JLGD, Olson MM, Johnson S. Metronidazole susceptibility in Clostridium difficile isolates recovered from cases of C.difficile-associated disease treatment failures and successes. *Anaerobe* 1999;5:201–204.
120. Fekety R, McFarland LV, Surawicz CM, et al. Recurrent Clostridium difficile diarrhea: characteristics of and risk factors for patients enrolled in a prospective, randomized, double-blinded trial. *Clin Infect Dis* 1997;24:324–333. [PubMed: 9114180]
121. McFarland LV. Alternative treatments for Clostridium difficile disease: what really works? *J Med Microbiol* 2005;54:101–111. [PubMed: 15673502]
122. Barbut F, Richard A, Hamadi K, et al. Epidemiology of recurrences or reinfections of Clostridium difficile-associated diarrhea. *J Clin Microbiol* 2000;38:2386–2388. [PubMed: 10835010]
123. McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent Clostridium difficile disease. *Am J Gastroenterol* 2002;97:1769–1775. [PubMed: 12135033]
124. Tedesco FJ, Gordon D, Fortson WC. Approach to patients with multiple relapses of antibiotic-associated pseudomembranous colitis. *Am J Gastroenterol* 1985;80:867–868. [PubMed: 4050760]
125. Johnson S, Schriever C, Galang M, et al. Interruption of recurrent Clostridium difficile-associated diarrhea episodes by serial therapy with vancomycin and rifaximin. *Clin Infect Dis* 2007;44:846–848. [PubMed: 17304459]

126. Garey KW, Salazar M, Shah D, et al. Rifamycin antibiotics for treatment of *Clostridium difficile*-associated diarrhea. *Ann Pharmacother* 2008;42:827–835. [PubMed: 18430792]
127. Boyce JM, Ligi C, Kohan C, et al. Lack of association between the increased incidence of *Clostridium difficile*-associated disease and the increasing use of alcohol-based hand rubs. *Infect Control Hosp Epidemiol* 2006;27:479–483. [PubMed: 16671029]
128. Johnson S, Gerding DN, Olson MM, et al. Prospective, controlled study of vinyl glove use to interrupt *Clostridium difficile* nosocomial transmission. *Am J Med* 1990;88:137–140. [PubMed: 2301439]
129. Zafar AB, Gaydos LA, Furlong WB, et al. Effectiveness of infection control program in controlling nosocomial *Clostridium difficile*. *Am J Infect Control* 1998;26:588–593. [PubMed: 9836844]
130. Muto CA, Blank MK, Marsh JW, et al. Control of an outbreak of infection with the hypervirulent *Clostridium difficile* BI strain in a university hospital using a comprehensive "bundle" approach. *Clin Infect Dis* 2007;45:1266–1273. [PubMed: 17968819]
131. Gerding DN, Johnson S, Peterson LR, et al. *Clostridium difficile*-associated diarrhea and colitis. *Infect Control Hosp Epidemiol* 1995;16:459–477. [PubMed: 7594392]
132. Kaatz GW, Gitlin SD, Schaberg DR, et al. Acquisition of *Clostridium difficile* from the hospital environment. *Am J Epidemiol* 1988;127:1289–1294. [PubMed: 2835900]
133. Wilcox MH, Fawley WN, Wigglesworth N, et al. Comparison of the effect of detergent versus hypochlorite cleaning on environmental contamination and incidence of *Clostridium difficile* infection. *J Hosp Infect* 2003;54:109–114. [PubMed: 12818583]
134. Perez J, Springthorpe VS, Sattar SA. Activity of selected oxidizing microbicides against the spores of *Clostridium difficile*: relevance to environmental control. *Am J Infect Control* 2005;33:320–325. [PubMed: 16061137]
135. Valiquette L, Cossette B, Garant MP, et al. Impact of a reduction in the use of high-risk antibiotics on the course of an epidemic of *Clostridium difficile*-associated disease caused by the hypervirulent NAP1/027 strain. *Clin Infect Dis* 2007;45(Suppl 2):S112–S121. [PubMed: 17683015]
136. Fowler S, Webber A, Cooper BS, et al. Successful use of feedback to improve antibiotic prescribing and reduce *Clostridium difficile* infection: a controlled interrupted time series. *J Antimicrob Chemother* 2007;59:990–995. [PubMed: 17387117]
137. Climo MW, Israel DS, Wong ES, et al. Hospital-wide restriction of clindamycin: effect on the incidence of *Clostridium difficile*-associated diarrhea and cost. *Ann Intern Med* 1998;128:989–995. [PubMed: 9625685]
138. Davey P, Brown E, Fenelon L, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev*. 2005CD003543
139. Khan R, Cheesbrough J. Impact of changes in antibiotic policy on *Clostridium difficile*-associated diarrhoea (CDAD) over a five-year period in a district general hospital. *J Hosp Infect* 2003;54:104–108. [PubMed: 12818582]
140. O'Connor KA, Kingston M, O'Donovan M, et al. Antibiotic prescribing policy and *Clostridium difficile* diarrhoea. *Qjm* 2004;97:423–429. [PubMed: 15208430]