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Clostridium difficile Infection: A Re-Emerging Threat

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Abstract

Clostridium difficile infection is an important healthcare-associated infection. The incidence and severity of *C. difficile* infection are increasing. Recent *C. difficile* infection outbreaks with high proportions of severe outcomes have been linked to an emerging, hypervirulent strain of *C. difficile*. Recently recognized risk factors of *C. difficile* infection include fluoroquinolone exposure and gastric acid suppression. Effective prevention measures for *C. difficile* infection include contact precautions and antimicrobial stewardship. Awareness of *C. difficile* infection is critical to providing appropriate clinical care.

Clinical History and Epidemiology

Although antibiotic-associated colitis has been recognized since antibiotics were first introduced into clinical practice and *C. difficile* was first isolated in 1935, *C. difficile* was not identified as the cause of antibiotic-associated colitis until 1978.[1] Initially *C. difficile* infection was thought to be a nuisance infection, a complication of necessary antibiotic therapy, with very little attributable morbidity and mortality. *C. difficile* infection is now recognized as one of the most common healthcare-associated pathogens, rivaling methicillin-resistant *Staphylococcus aureus*.[2]

Since 2000, there have been significant increases in the incidence and severity of *C. difficile* infection in the US, Canada, and Europe.[3] In the US, the number of acute care facility discharges in the National Hospital Discharge Survey where the patient received the International Classification of Diseases, 9th edition (ICD9) code for *C. difficile* infection more than doubled from approximately 130,000 in 2000 to over 290,000 in 2005.[4] The attributable mortality of *C. difficile* infection in recent outbreaks has been as high as 17% and as high as 6% in endemic settings.[5, 6]

These increases in *C. difficile* infection incidence and severity have been associated with the identification of a new, hypervirulent stain of *C. difficile*, commonly referred to as the epidemic strain.[7] Due to the numerous methods available for molecular typing of *C. difficile*, there are many names for this strain: NAP1, 027, and BI.[8] This epidemic strain has a mutation in an important toxin production down regulatory gene, the *tcdC* gene, that renders this gene nonfunctional. As a result, this strain is able to produce up to 16 times more toxin A and 23 times more toxin B *in vitro* than what have historically been the most common strains of *C. difficile*.[7] Other potential virulence factors of the epidemic stain include presence of the genes for binary toxin and high-grade fluoroquinolone resistance.[8]

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Risk factors for *Clostridium Difficile* Infection

Exposure to antimicrobial agents is a well recognized predisposing factor for *C. difficile* infection.[9] Although nearly all antimicrobial agents can predispose *C. difficile* infection, the likelihood of developing *C. difficile* infection is not equal for all antimicrobials. The risk of *C. difficile* infection is related to how much the antimicrobial disrupts the bowel flora (in particular the anaerobic component), how resistant *C. difficile* is to that antimicrobial, and how frequently an antimicrobial is used. Historically cephalosporins, amino-penicillins, and clindamycin were the antimicrobials associated with the greatest risk of *C. difficile* infection.[2] In several of the recent *C. difficile* infection outbreaks, fluoroquinolones, in particular the broader-spectrum fluoroquinolones such as levofloxacin, moxifloxacin, and gatifloxacin, have been strongly associated with risk of *C. difficile* infection.[10] It has been hypothesized that increased used of fluoroquinolones has given the epidemic strain a competitive advantage over other strains of *C. difficile* that are not as resistant to fluoroquinolones.

Another essential risk factor for *C. difficile* infection is exposure to *C. difficile*. Exposure to *C. difficile* most commonly occurs in the healthcare setting.[9] Typically, only ~3% of the healthy US population and approximately 20% of people in a healthcare facility or with recent healthcare exposures may be colonized with *C. difficile*.[11] In addition patients asymptomatically colonized with *C. difficile* appear to be at a lower risk for *C. difficile* infection compared to patients who newly acquire *C. difficile* after admission to a healthcare facility.[12] Although length of stay in a healthcare facility is commonly cited as a risk factor for *C. difficile* infection, length of stay is a surrogate for *C. difficile* exposure within the healthcare facility.[1]

Other important risk factors for *C. difficile* infection include advancing age and increasing severity of underlying illness.[13] In addition the immune system plays an important role in the pathogenesis of *C. difficile* infection. Patients who are asymptomatically colonized with *C. difficile* have higher levels of detectable antibodies against *C. difficile* than those not colonized, and those with higher levels of antibodies against *C. difficile* are less likely to develop *C. difficile* infection after acquiring *C. difficile*.[14]

Another recently recognized risk factor for *C. difficile* infection is exposure to gastric acid suppressing agent.[13, 15] The mechanism linking gastric acid suppression and *C. difficile* infection is not completely understood. Some potential explanations for why gastric acid suppression may increase the risk of *C. difficile* infection include gastric acid, although not sporicidal, may inhibit the germination of spores after they reach the small intestine, and gastric acid suppression has been associated with an alteration of bowel flora.[15, 16] Alternatively, gastric acid suppression may be a marker for severity of underlying illness.[13]

Clinical Manifestations and Diagnosis of *Clostridium Difficile* Infection

C. difficile infection ranges from a mild, self-limited illness to a severe, life-threatening colitis. The hallmark of *C. difficile* infection is diarrhea. Onset of diarrhea may occur days after the initial antimicrobial exposure or as late as eight weeks after the antimicrobials are discontinued.[17] Other common signs and symptoms include fever, nausea, abdominal cramping, and abdominal tenderness. Rarely *C. difficile* infection may present with ileus or an acute abdomen. These patients tend to be acutely ill and may require emergent colectomy. Other markers for severe *C. difficile* infection include leukocytosis, hypotension, acute kidney failure, and an elevated serum lactate.[8, 11, 17]

The diagnosis of *C. difficile* infection typically relies on a high index of clinical suspicion (i.e., presence of symptoms and predisposing factors) and laboratory confirmation of *C.*

difficile toxin(s) in the stool. Several types of stool assays are currently available to diagnose *C. difficile* infection. The most commonly used assays in the US are toxin enzyme immunoassays (EIAs). Toxin EIAs are inexpensive, easy to perform, and rapid (results within a few hours). The major disadvantage of toxin EIAs is a decreased sensitivity (70–80%) compared to other methods for detecting *C. difficile* or its toxins.[17] Of note, some toxin EIAs detect only toxin A and others detect both toxins A and B. Because some strains of *C. difficile* only produce toxin B a toxin A and B assay is preferred.

The cell culture cytotoxicity assay is the clinical laboratory gold standard test for *C. difficile* infection because of better sensitivity and specificity compared to toxin EIAs, but limitations include by increased costs, personnel time to run the assay, the requirement for specialized equipment, and it may take as long as 72 hours for final results. Another option is EIAs to detect glutamate dehydrogenase, an enzyme produced by *C. difficile*. The glutamate dehydrogenase EIA is relatively inexpensive, results are available within an hour, and it may be more sensitive than the toxin EIAs. However, this assay is not specific as other bacteria and non-pathogenic *C. difficile* strains can produce glutamate dehydrogenase. Some investigators use the glutamate dehydrogenase EIA as an initial screen.[18] The cell culture cytotoxicity assay is then run on glutamate dehydrogenase positive stool samples. The rationale behind this method is to have a rapid screen with a high negative predictive value, and then confirm positive results with the more expensive and sensitive cytotoxicity assay.

Anaerobic stool culture, when performed correctly, is the most sensitive method to detect *C. difficile*. Anaerobic stool culture also provides *C. difficile* isolates for strain typing if needed. Disadvantages of stool culture are the need to determine if the *C. difficile* isolate produces toxin (i.e., toxigenic culture), expense, and it can take as long as five day to have final results. Polymerase chain reaction (PCR) for *C. difficile* is being investigated as a new diagnostic strategy. Real-time PCR detects toxigenic *C. difficile* in stool in a few hours with higher sensitivity than that of toxin EIAs and cell culture cytotoxicity assays.[19] Potential disadvantages of PCR include increase in costs and currently not all labs are able to perform PCR.

An unresolved issue is the number of additional stool specimens necessary if an initial test is negative. Repeat testing is often performed because of concerns regarding the relatively low sensitivity of toxin EIAs. However, no test is 100% specific for *C. difficile* infection. Repeat testing increases the likelihood of having a false positive test result. Of note, the negative predictive value for toxin EIAs based on the reported prevalence of *C. difficile* infection in patients on antibiotics with diarrhea in acute care hospitals in the U.S. (10 to 20%) is still ≥94%. Therefore, when the clinical suspicion for *C. difficile* infection is low, repeated toxin testing is unnecessary.[2]

Treatment

In general, all patients with *C. difficile* infection should receive appropriate supportive therapy when needed, such as intravenous fluids if the patient is dehydrated. The offending antibiotic should be discontinued whenever possible; this alone is curative in as many as 23% of cases of *C. difficile* infection.[20] Patients acutely ill with *C. difficile* infection will need specific treatment for *C. difficile* infection.

Although oral vancomycin remains the only antimicrobial with a Food and Drug Administration (FDA) indication for the treatment for *C. difficile* infection, comparative trials historically have demonstrated oral metronidazole has identical response rates and relapse rates.[11] Because of cost considerations and concerns about selecting for vancomycin resistant enterococci (VRE), many professional societies have recommended oral metronidazole as an equivalent or in preference to oral vancomycin for *C. difficile* infection

treatment. However, several recent randomized control trials indicate oral vancomycin may be better than oral metronidazole for patients with severe *C. difficile* infection.[20] One caveat, however, there are no validated methods to identify patients at greatest risk for developing complications due to *C. difficile* infection.

The Infectious Diseases Society of America and Society for Healthcare Epidemiology of America are in the process of updating their C. *difficile* infection treatment guidelines.[21] Treatment recommendations will likely be based on the clinical presentation of *C. difficile* infection. Patients with mild or moderate *C. difficile* infection can be treated with oral metronidazole 500 mg three times daily or 250mg four times daily for 10 to 14 days. Patients with severe *C. difficile* infection should receive oral vancomycin 125 mg four times daily.

A third treatment category is severe, complicated *C. difficile* infection. These are patients with the most severe manifestations of *C. difficile* infection such as ileus, toxic megacolon, hemodynamic instability, or acute kidney failure due to *clostridium difficile* infection. For these cases, a higher dose of vancomycin, up to 500 mg orally or via gastric tube four times daily, combination with intravenous metronidazole 500mg four times daily is recommended.[20] The rationale for giving higher doses of oral vancomycin plus the addition or intravenous metronidazole is to get active drug to the colon as quickly as possible. In the absence of severe, complicated *C. difficile* infection there is no need to provide oral vancomycin at a dose higher than 125mg four times daily or to give combination therapy.

Alternative routes of vancomycin administration may be necessary in patients if the gastrointestinal tract is not functioning properly, e.g. ileus or vomiting. Intravenous vancomycin does not achieve high enough levels in the stool to treat *C. difficile* infection and should never be used for the treatment of *C. difficile* infection. Alternative approaches to administering enteral vancomycin include continuous drips via tubes inserted into the small bowel and vancomycin enemas. A wide range of vancomycin doses, concentrations, and frequency of administration are reported in the literature, and are almost always administered in conjunction with intravenous metronidazole with or without oral vancomycin.

An adjunctive therapy for severe, complicated *C. difficile* infection is intravenous immunoglobulin because antibodies against *C. difficile* are present in intravenous immunoglobulin. Doses range from 250mg/kg to 500mg/kg as a one-time bolus.[11, 20] In extreme cases, surgery may be needed for the treatment of severe, complicated *C. difficile* infection. Indications for surgery include perforation, significant bowel obstruction or progressive deterioration despite appropriate medical therapy. Prompt assessment of need for surgical therapy is warranted since fulminant *C. difficile* infection can be fatal despite aggressive management.

Recurrent Clostridium Difficile Infection

Approximately 20% of patients with an initial episode of *C. difficile* infection will develop at least one recurrence and 65% of patients with at least two recurrences will develop additional recurrences.[10, 20] Risk factors for recurrent *C. difficile* infection are similar to those for the first episode: advanced age, increased severity of underlying illness, and repeat or continued antibiotic exposures. Of note, studies indicate that at least half, if not more, recurrences of *C. difficile* infection are due to reacquisition of *C. difficile* rather than reactivation of spores that remain in the colon at the end of therapy.

Recurrent *C. difficile* infection can be extremely frustrating to manage, in particular because there are few well studied treatment strategies that have shown any benefit. Luckily,

resistance to metronidazole and vancomycin is extremely rare, and has not been reported after initial treatment with either of these antimicrobials. First recurrences of mild or moderate *C. difficile* infection can be treated with metronidazole. Severe cases of recurrent *C. difficile* infection should be treated with vancomycin. Tapering or pulsed regimen of vancomycin has been commonly tried for multiple recurrent *C. difficile* infection. This regimen was based on one study, which revealed lower rate of recurrence rate of *C. difficile* infection in patients treated with tapering or pulsed vancomycin.[22]

Other adjunctive therapies for recurrent *C. difficile* infection have been poorly studied or have not been effective. Probiotic agents (e.g. *Lactobacillus spp.* or *Saccharomyces spp.*) have been the best studied adjunctive therapies with several randomized, placebo controlled trials.[20] Unfortunately, the trials indicate probiotics have minimal, if any, role in the prevention of additional *C. difficile* infection recurrences. Rifaximin, a nonabsorbed rifamycin derivative, has more selective activity against *C. difficile* than other bowel flora.[23] This may help prevent recurrences by allowing normal bowel flora to regenerate as the infection is being treated. The development of resistance while on therapy has historically been a problem with rifamycin derivatives, and may be an issue with rifaximin.[22]

Anion binding resins such as cholestyramine and colestipol has been used in the treatment of recurrent *C. difficile* infection because they bind to *C. difficile* toxin *in vitro*. A single randomized control trial showed no benefit over placebo.[24] If used, clinicians should be aware these anion binding resins also bind to vancomycin, in addition to other drugs, and these agents should not be administered simultaneously.

Treatment of *C. difficile* infection through restoration of gastrointestinal flora by the administration of fecal flora from a healthy volunteer has shown promise. Restoration of gastrointestinal flora by stool infusion may lead to prevention of overgrowth of *C. difficile*. Several case reports and case series indicate a success rate over 90%.[25] However, lack of supportive data and obvious aesthetic drawbacks limit the practical applicability of this method.

Prevention

Controlling *C. difficile* infection in the hospital environment is a challenge. Effective hospital infection control programs to prevent *C. difficile* infection combine patient isolation, reinforcement of proper hand hygiene technique, environmental decontamination, antimicrobial stewardship, and careful epidemiological monitoring of *C. difficile* infection cases, rates, and trends.[26]

C. difficile spores are transferred between patients primarily via the hands of healthcare workers.[2] Research indicates hospitalized patients are at greater risk of *C. difficile* infection if there is another *C. difficile* infection patient concurrently admitted on the same ward.[27] Thus, contact precautions (disposable gowns and gloves, disposable or designated medical equipment where possible) and isolation (private rooms) of symptomatic patients are recommended as an essential component of *C. difficile* infection control. Glove use has been shown to reduce the spread of *C. difficile*.[2] An area of controversy is the preferred method of hand hygiene after caring for a patient with *C. difficile* infection. Alcohol-based hand sanitizers are not sporicidal, but the use of these products in U.S. hospitals does not appear to result in increases in *C. difficile* infection rates or outbreaks.[28] Nevertheless, soap and water may be substituted for alcohol-based products during *C. difficile* infection outbreaks to ensure effective hand hygiene.[2]

C. difficile spores frequently contaminate the hospital environment of patients with *C. difficile* infection, and spores may be found even in rooms that have not housed a *C. difficile*

infection patient recently.[29] Environmental decontamination is an important but poorly understood aspect of *C. difficile* infection control. Hypochlorite solutions (i.e., bleach) are sporicidal, but bleach is corrosive and the fumes may be irritating to patients and staff. Several studies have indicated use of a 1:10 of a 6% hypochlorite solution for disinfection reduced rates of *C. difficile* infection during outbreaks. Disinfection with bleach may be a useful component in *C. difficile* infection control during an outbreak but impractical and unnecessary for routine hospital disinfection.[2]

As noted previously, certain antimicrobial agents, particularly clindamycin, amoxicillin/ampicillin, cephalosporins, and fluoroquinolones, are associated with increased risk of *C. difficile* infection. Improved antimicrobial prescribing practices and restriction of high-risk antimicrobials are among the most effective methods of reducing the incidence of *C. difficile* infection. A recent study demonstrated that an antimicrobial stewardship program that focused on improved antimicrobial prescribing in addition to limiting the use of antibiotics associated with *C. difficile* infection was successful in combating an outbreak due to the epidemic strain of *C. difficile*.[2, 30] The implementation of antimicrobial stewardship is strongly encouraged as an essential component of an effective *C. difficile* infection prevention and control program.[2]

Summary

Treatment and prevention of *C. difficile* infection are challenging. Current increases in *C. difficile* infection severity, the emergence of the hypervirulent epidemic strain, and increasing *C. difficile* infection rates make *C. difficile* one of the most important hospital-associated pathogens. While many issues regarding the detection, treatment, and prevention of *C. difficile* infection remain poorly studied or unresolved, much new research has been published since the emergence of the epidemic strain. The Society for Healthcare Epidemiology of America (SHEA) and Infectious Disease Society of America (IDSA) recently published practical recommendations on the prevention of *C. difficile* infection in acute care facilities, and updated comprehensive *C. difficile* infection guidelines from SHEA and IDSA are expected in the spring of 2009. Collaboration between clinicians, healthcare epidemiologists, and infection prevention and control professionals is essential to determine appropriate treatment strategies and preventive measures at your healthcare facility.

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