Changing Epidemiology and Control of *Clostridium difficile* in Older Adults

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Abstract *Clostridium difficile* infection (CDI) presents unique clinical challenges among older adults. Older patients tend to have more severe disease, more treatment failures, and higher rates of relapse. As the burden of CDI in older adults continues to grow, better paradigms for the prevention and treatment of CDI in this vulnerable population will be essential. In this review, we offer an overview of the changing epidemiology of *C. difficile*, with a review of CDI prevention, diagnosis and treatment, with a focus on older patients.

Keywords Elderly · Aged · *Clostridium difficile* · Diarrhea · Infection

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Introduction

Although *Clostridium difficile* was first identified as the major cause of antibiotic-associated diarrhea in the 1970s, more recently *C. difficile* infection (CDI) has emerged as a more frequent, more severe and more difficult to manage clinical entity, especially among older adults [1]. *C. difficile* infection is linked to increased hospital costs and length of stay, and the cost of CDI in the United States is estimated at \$1.1 billion per year [2]. The burgeoning CDI problem is related in large part to healthcare associated spread of *C. difficile*, especially among the elderly [3]. Targeted measures to curtail CDI in this vulnerable population remain essential.

The Changing Epidemiology of *C. difficile*

During the past decade, increases in the incidence and severity of CDI have been reported across the United States, Canada, and Europe, with patients over the age of 65 affected disproportionately [3–7]. In the U.S., hospital discharges listing a diagnosis of CDI doubled between 1996 and 2003 [3]. The increase in severity of CDI has been closely linked to the emergence of the epidemic BI/NAP1 strain of *C. difficile* [4, 6], but may also be linked to the increasing age and presence of comorbidities among hospitalized patients, [3].

Risk Factors Associated with *C. difficile* Infection

Advanced age has repeatedly been identified as a risk factor for the development of CDI [8–10, 11••] and CDI-associated mortality also appears to increase with age [12]. Two-thirds of all patients discharged from a U.S. hospital with a diagnosis of CDI are over the age of 65 years [13].

Other factors associated with an increased risk of CDI include previous hospitalization, increased duration of hospitalization, non-surgical admission, use of broad spectrum or multiple antibiotics, duration of antibiotic use, use of acid suppressive therapy, receipt of chemotherapy, renal insufficiency or hemodialysis, and presence of a nasogastric tube [9, 14–17]. Healthcare associated transmission of *C. difficile* is a significant issue, and patients residing in a room previously occupied by a CDI-positive patient, or in a room adjacent to a patient with CDI, are also at greater risk of CDI [10, 18].

The risk of developing CDI does not disappear following discharge of older patients from the acute care setting, and one recent study found that, 50 % of CDI cases in long-term care facilities (LTCF) occurred more than four weeks following hospital-discharge, underscoring the need for CDI prevention to remain a priority in the LTCF setting [19]. Cases of CDI may also be diagnosed in the outpatient setting, although previous hospital stay remains a significant risk factor [20].

Outcomes in Older Adults

C. difficile infection is associated with an increase in 30-day mortality among hospitalized patients, and older adults with CDI tend to have worse outcomes than their younger counterparts [21]. One report suggests that half of all patients in intensive care units (ICU) with CDI are 65 years of age or older, and that their 30-day mortality is two-thirds higher than in younger patients [22•].

Factors associated with worse outcomes among older patients with CDI include infection with the BI epidemic strain, renal insufficiency, leukocytosis and hypoalbuminemia [17, 21, 23•]. Prolonged exposure to antimicrobials (other than those for the treatment of CDI) is also associated with adverse clinical outcomes, including increased mortality [24].

Readmission following an episode of CDI is a significant problem among older adults. One report suggests that for hospital admissions where CDI is the principle diagnosis, 30-day readmission rates are 5.5 % for patients 65 years and older, compared to rates of 3.3 % for patients aged 18–44 years [25]. Recurrent episodes of CDI are also a common phenomenon in older adults, and risk of recurrence rises with age [26•]. One recent study described lower rates of clinical cure, greater risk of recurrence, and lower sustained clinical response associated with advancing decade after the age of 40 years [23•].

Diagnosis

A case of CDI is defined by a positive stool sample (either assay for toxins A/B, culture or other means), or by endoscopic or histopathologic evidence of pseudomembranous colitis, in a symptomatic patient [27, 28]. *C. difficile*-associated

diarrhea, may be defined as three or more episodes of loose stool per day, for two or more days [29]. Testing for *C. difficile* should be performed only on unformed stool, unless *C. difficile*-associated ileus is suspected [28].

While there is not a gold standard test for detection of *C. difficile*, both cell culture cytotoxicity neutralization assay (CCNA) and toxigenic culture are highly sensitive and specific, although not frequently used in clinical laboratories [30–32]. *C. difficile* toxin detection enzyme immunoassays (CDT-EIA) were, for many years, the main testing strategy at the great majority of clinical laboratories in the U.S. [32]. However, these CDT-EIAs demonstrate highly variable sensitivity (69–99 %) with low positive predictive values (PPVs) (less than 50 % in some reports) when the prevalence of CDI is relatively low [33]. In fact, CDT-EIA testing alone can yield false positives at a rate of 10–20 % compared to cell cytotoxicity assay, with variability attributed to inaccuracies in the specific test used [34].

Many clinical laboratories now utilize two-stage testing strategies; combining highly sensitive rapid screening tests, either CDT-EIAs and/or glutamate dehydrogenase antigen enzyme immunoassays (GDH-EIA), with a more specific confirmatory test, such as Nucleic acid amplification testing (NAAT) [34–36] [31]. NAAT for the gene responsible for toxin B production (*tcdB*) improves specificity for toxigenic *C. difficile* to 94 %, but does not directly detect free toxin [34]. Meanwhile, a two-step algorithm, coupling GDH-EIA and CDT-EIA, followed by NAAT for *tcdB* in samples with discordant EIA results, can minimize the weaknesses inherent in each modality [37].

Several key issues make diagnostic testing for recurrent CDI difficult to interpret. The natural history of clinical recovery from CDI includes prolonged shedding of the organism in stool. The duration of asymptomatic shedding varies, but up to 50 % of patients have positive stool assays six weeks after the completion of therapy [38, 39]. Long-term colonization can also occur after a successfully-treated episode of CDI [40]. During the early recovery period, recurrent symptoms can occur from a transient functional bowel disorder (FBD) in as many as 35 % of patients, and rarely this can lead to a persistent postinfectious irritable bowel syndrome (IBS) [41]. It is important to distinguish between symptoms due to recurrent CDI and another cause such as FBD or IBS, as current guidelines advise against treatment of asymptomatic carriage / shedding [42]. Given these issues, testing of stool from asymptomatic patients, and “tests of cure” are not clinically useful and are not recommended [28].

Unfortunately, with the use of currently available diagnostic tests it may be difficult to distinguish asymptomatic shedding from symptomatic CDI. Proper identification of actual CDI requires integrating the clinical presentation and symptoms with testing results. Decisions regarding treatment in this setting are thus left to the individual clinician.

Treatment

Medications for the Treatment of CDI

The approach to the treatment of CDI in older adults presents unique challenges. When selecting a treatment regimen, clinicians should be mindful that older patients have more severe disease, more treatment failures and a higher relapse rate.

Treatment of CDI is recommended for symptomatic patients only; asymptomatic carriers of *C. difficile* do not require treatment with antimicrobials, and prophylactic therapy for those at high risk of CDI is also not recommended [27, 28, 43, 44]. In fact, there is some suggestion that asymptomatic colonization with *C. difficile* may decrease the risk of developing symptomatic CDI [45].

Virtually all antibiotics are associated with increased risk of developing CDI [46]. For symptomatic patients receiving antimicrobial therapy at the time of diagnosis of CDI, removal of the precipitating agent may allow for repopulation of the colon with normal flora, although this is usually not sufficient for treatment. However, if the indication to continue antimicrobials is not clear, it is prudent to stop the offending agent(s).

Metronidazole is the primary first-line therapy for the treatment of mild to moderate, uncomplicated CDI [28]. Early studies indicated that oral metronidazole and oral vancomycin had equivalent efficacy for the treatment of CDI, similar rates of relapse and with similar tolerability [47, 48]. However, gastrointestinal complaints are common among patients taking metronidazole, including reports of a metallic taste, and prolonged, high-dose, metronidazole has been associated with symptoms of peripheral neuropathy, which can rarely persist for up to two-years after use [49].

Vancomycin has emerged as the preferred agent in patients with severe CDI (markers for severe disease include fever, leukocytosis with a white blood cell count (WBC) of 15,000 cells/ μ L or higher, or a serum creatinine level greater than or equal to 1.5 times the baseline level) [28, 50–52]. Oral or rectal administration of vancomycin plus intravenous metronidazole, are often used in combination, in cases of severe, complicated CDI [28].

Fidaxomicin is the newest drug approved for the treatment of CDI. Similar rates of clinical cure have been seen with fidaxomicin compared to vancomycin, although there is some data to suggest lower risk of recurrence with fidaxomicin; a 60 % lower risk of recurrence in one study, and better rates of clinical cure in the presence of concomitant antibiotics [23•, 53–56]. There is limited data on other adjunctive therapies for the treatment of CDI, including nitazoxanide and rifaximin, and these agents will not be discussed in detail here.

Complicated CDI

Fulminant CDI is characterized by abdominal pain, fever, hypotension, tachypnea, lactic acidosis and significant leukocytosis (WBC count of $>20,000$ cells/mm³) and can result in serious complications, including bowel perforation, megacolon, and death [57, 58]. Prompt surgical evaluation should be undertaken in any patient with these signs or symptoms, as emergent colectomy can be lifesaving in these patients. A new surgical approach for treatment of fulminant CDI has become popular: loop ileostomy followed by antegrade vancomycin enemas. This approach is potentially life-saving and also can avoid a total colectomy—a recent study achieved preservation of the colon in 93 % of patients treated this way [59]. Among older adults with fulminant CDI, factors associated with increased 30-day mortality include age over 75 years, lack of leukocytosis, and development of septic shock [22••].

Elderly patients with CDI experience a higher rate of relapse, as well as more treatment failures on standard therapy [60–62]. Treatment failures may be due to the kinetics of toxin production, and the inability to get effective levels of drug to the colon before toxin has bound [63, 64]. Increasing minimum inhibitory concentration (MIC) values for metronidazole have been observed in some strains, however this does not seem to be an issue with vancomycin [64].

Recurrent CDI is a particular problem in older adults [23•, 26•, 60]. Lower concentrations of antibodies to toxins A and B, after an episode of CDI, have been associated with risk of recurrence [65, 66], and immunosenescence in older adults may be related to their increased risk of recurrent CDI. Recurrent CDI is sometimes treated with extended courses of therapy, adjunctive antimicrobials, which will not be addressed here, or fecal microbiota transplantation (FMT), which is addressed below.

Human Gut Microbiota, Probiotics and Fecal Microbiota Transplantation

The human gut microbiota is a diverse ecosystem with at least 300–500 species of bacteria [67], which is thought to be protective against invasion by pathogens. Figure 1 illustrates the pathogenesis of CDI: broad-spectrum antibiotics alter the microbiota into a susceptible state, *C. difficile* is introduced, and CDI ensues. Following infection in some individuals, the gut microbiota remains susceptible and recurrent CDI can occur, either as a relapse from the same strain or reinfection from another strain, and may ultimately lead to further recurrent episodes of CDI, refractory to traditional approaches to therapy [68].

Probiotics are live microorganisms which, when administered in adequate doses, can assist in restoring the normal colonic microbiota, which is an essential aspect of preventing

Fig. 1 Pathogenesis of *Clostridium difficile* infection (CDI). This figure illustrates how the normal microbiota (upper left corner) is altered by antibiotics to a susceptible state in which CDI can occur. It

also shows the cycle of recurrence that occurs in some individuals and how, even after successful treatment of CDI, persistent shedding can occur. (Figure courtesy of Vincent B. Young, MD, PhD)

CDI recurrence [69]. While the role of probiotics in the treatment of CDI has not been well-defined, one double-blind, placebo-controlled trial reported that therapy with high-dose oral vancomycin plus a probiotic (*Saccharomyces boulardii*) was 67 % more effective in preventing CDI recurrences than vancomycin alone [70]. There have been reports of fungemia associated with probiotic use [69], but probiotics are generally well tolerated without major side effects [71].

Fecal microbiota transplantation (FMT) similarly restores colonic microbiota to a healthy state, by transplanting healthy donor stool into an infected patient, and is emerging as a promising solution to this recalcitrant problem. Fecal microbiota transplantation was first performed successfully for CDI treatment in 1983, via rectal enema [72], however the procedure received slow acceptance. Since then, numerous case reports and case series have been published. A large systematic review by Gough et al. [73] included published articles, abstracts, as well as unpublished data, on 317 patients with recurrent CDI. The routes used for FMT in this review included rectal enema (35 %), Nasojejunal tube/gastroscope (23 %), and colonoscopy (42 %). Despite significant

variability between reports regarding FMT infusion site, amount of donor stool, and donor stool preparation, the results were resounding; 92 % of patients had resolution of their recurrent CDI, with 89 % resolution after a single treatment. Of the 4 % of patients who had relapsed CDI after initial FMT, 87.5 % had resolution with repeat FMT. There were no serious adverse effects directly attributable to FMT, but symptoms of an irritable colon (constipation, diarrhea, cramping, bloating) were reported shortly after FMT and were usually transient. Since this systematic review, several additional case series have been published describing FMT via colonoscopy [74, 75] and rectal enema [76], with similar success rates of 86–93 %. One study used a standard frozen preparation for FMT from a single universal donor for the majority of cases [75].

While case reports and case series have been encouraging, there was a lack of high quality data in field of FMT, until recently. In 2013 van Nood and colleagues published a randomized controlled trial for FMT via duodenal infusion for recurrent CDI [77]. Patients were randomized to receive vancomycin for 5 days followed by FMT (n=16), vancomycin alone for 14 days (n=13), or vancomycin for 14 days

with bowel lavage (rapid administration of a large volume of polyethylene glycol solution) (n=13). The primary outcome was cure defined as absence of diarrhea or persistent diarrhea from another cause with three consecutive negative stool tests for *C. difficile* toxin. The study was stopped early after an interim analysis, as 94 % of patients in the FMT group achieved cure, most of those after only one infusion, versus 31 % in the vancomycin alone or vancomycin with bowel lavage groups, respectively. Based on these findings, off-protocol FMT was offered to 18 patients in the other treatment arms and this achieved an 83 % cure rate. Although further study is needed to fully ascertain the safety and efficacy of FMT for recurrent CDI, it shows promise as an excellent treatment for this difficult disease.

The regulatory status of FMT in the United States was previously ill-defined, but currently the FDA is requiring that any center wanting to perform FMT must apply for an expanded access IND as described in the code of federal regulations: 21 CFR 312 Subpart I [21 CFR 312.300].

Prevention of Healthcare Associated Transmission of CDI

C. difficile is a common environmental contaminant in healthcare facilities, including nursing homes, and there is a strong association between the level of environmental contamination and healthcare associated transmission [78]. Spores can survive on hard surfaces for up to five months, and have been found on the floors, toilets, bedding and furniture in rooms of patients with CDI [79].

Strategies to reduce patient exposure to *C. difficile* (contact precautions, environmental cleaning, hand hygiene) and strategies to prevent alteration of the normal fecal microbiota (antimicrobial stewardship) are vital to prevent CDI. These strategies are often implemented as part of infection control bundles [80, 81]. Current SHEA/IDSA guidelines recommend the following to prevent the spread of CDI: private rooms when possible for patients with CDI, barrier precautions for patients with CDI (gowns and gloves), emphasis on hand hygiene with soap and water, and environmental decontamination of rooms with a 1:10 sodium hypochlorite solution [27, 28]. The use of barrier precautions for patients with asymptomatic colonization of *C. difficile* is not generally recommended [27, 28]. Some of these precautions may be difficult to implement in the LTCF setting.

C. difficile has been isolated from the hands of asymptomatic healthcare workers, and transmission by healthcare workers is likely an important source of nosocomial spread [79]. Alcohol-based hand rubs (ABHR) have activity against the vegetative form of *C. difficile*, but are not sporicidal, although this deficit may be offset by improved hand hygiene

compliance seen with the use of ABHR. Some evidence suggests that hand hygiene adherence improves dramatically when alcohol-based hand cleansers are available, without significantly impacting rates of CDI [82–84].

Antimicrobial Stewardship

Antibiotic use is the strongest risk factor for the development of CDI, especially with multiple agents, or prolonged use, although virtually all antibiotics can precipitate CDI [46]. An Antimicrobial Stewardship Program (ASP) can help to reduce rates of CDI by establishing guidelines and clinical pathways for prudent antimicrobial use, de-escalating therapy when possible, optimizing dosing and reducing duration of treatment [85].

Conclusion

As CDI has increased in frequency and severity in the U.S. and many other parts of the world, older adults have been disproportionately affected. Older patients tend to have more severe disease, more treatment failures and a higher relapse rate. As the population ages, elderly patients will continue to be at risk of CDI acquisition in both the acute care and long term care setting. Thoughtful approaches to prevention and treatment will remain essential.

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Compliance with Ethics Guidelines

Conflict of Interest Natasha Bagdasarian, Krishna Rao, and Preeti N. Malani declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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