Clostridium difficile infection: still principally a disease of the elderly

Despite recent concerns of *Clostridium difficile* infection in previously low-risk individuals, it remains a disease that disproportionately affects the elderly. Besides advancing age, persons older than 65 years have more risk factors for *C. difficile* infection, poorer responses to treatment, more frequent recurrences, and higher morbidity and mortality. With a rapidly aging population, the need for better diagnostic tests and therapies is crucial. Moreover, the severe consequences of infection in the elderly make prevention as important as treatment.

KEYWORDS: antibiotic-associated diarrhea ■ *Clostridium difficile* ■ elderly

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Despite reports of *Clostridium difficile* infection (CDI) in historically low-risk hosts [1], this common form of antibiotic-associated diarrhea remains primarily a disease of the elderly. Since the year 2000, the incidence and rates of hospitalization and of death have been rising [2], a trend that disproportionately affects people older than 65 years of age [3,4]. Jagai and colleagues demonstrated that in the USA between 1993 and 2004 the rates of hospitalization in the elderly increased from 13/10,000 to 38.78/10,000. Rates increased with age and the highest rate of hospitalization was seen in patients older than 85 years of age [4]. Similarly, elderly patients are more likely to have severe infections, recurrent CDI (RCDI), treatment failure and death from CDI [5–8]. The increasing incidence and severity of disease is caused, in part, by a highly toxigenic strain of *C. difficile* known as restriction-endonuclease analysis group BI/North American pulsed-field gel electrophoresis type 1 strain (BI/NAP1/027) [9,10] that has been shown to have a high attributable mortality in the elderly [11]. This strain produces more toxins A and B *in vitro*, which may explain its virulence [9]. The strain had been identified in the 1980s, and had clindamycin resistance; the strain now also has quinolone resistance [12]. It is speculated that increased use of quinolone antibiotics has contributed to its emergence [13]. Outbreaks of severe CDI have been documented in the USA, Canada, Europe and Japan [14]. In addition to increased numbers and severity of cases of *C. difficile*, there are epidemiologic reports of increased numbers of cases of CDI in previously healthy persons and those without prior antibiotics [1]. The relationship between advancing age and CDI is most likely multifactorial with increased prevalence of comorbid illness, exposure to antibiotics and healthcare settings, as well as age-related changes in host defenses, all playing a role. In light of aging baby boomers and a doubling of the older population projected to occur over the next 20 years [15], the need for improved understanding of CDI treatment and prevention is of paramount importance.

Clinical overview

Clostridium difficile is an anaerobic, Gram-positive, spore-forming bacillus that is acquired via the fecal–oral route. It is the most common cause of nosocomial and antibiotic-associated diarrhea. Alterations of the normal bowel microbiome, usually caused by antibiotics, lead to the loss of colonization resistance allowing overgrowth of *C. difficile.* Infection with toxin-producing strains leads to a spectrum of illness, including asymptomatic carriage, mild diarrhea, pseudomembranous colitis, toxic megacolon, bowel perforation, sepsis and death. Toxin A and B are the most potent virulence factors and their detection in stool is the basis of diagnosis with enzyme immunoassay. Clinical presentation of CDI varies and can occur several weeks after antibiotic therapy or without exposure to antibiotics at all [1,16]. Mild disease consists of mild-to-moderate nonbloody diarrhea and abdominal cramping with minimal systemic symptoms. Severe disease is characterized by profuse, usually nonbloody diarrhea, abdominal pain, fever, nausea, anorexia and malaise. Marked elevations in white blood cell count, hypoalbuminemia and rising creatinine can be seen and are poor prognostic signs [17,18]. Severe

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pseudomembranous colitis may produce little to no diarrhea due to paralytic ileus and toxic megacolon. In the most critical cases, progression to shock, multiorgan failure and death can be rapid.

Risk factors in the elderly

Recent or current use of antimicrobial therapy is a principal risk factor for the development of CDI. By altering the native intestinal microflora, antibiotics allow for the overgrowth and toxin production of *C. difficile*. This is known as loss of colonization resistance and can occur with any antibiotic. Most commonly associated antibiotics are clindamycin, cephalosporins and penicillins, but more recent reports also implicate fluoroquinolones as high-risk agents [19]. The risk of CDI increases with multiple antibiotic agents and longer courses of treatment, demonstrating the importance of judicious antibiotic use in the prevention of disease. This can be a challenge in the elderly where the burden of acute and chronic illness leads to frequent use of antimicrobials. Furthermore, having multiple comorbidities is itself a risk factor for acquisition of CDI.

Antibiotics alone do not cause CDI. Patients must also be exposed to toxigenic strains of *C. difficile* either by overgrowth of previously indigenous organisms or *de novo* exposure. Although infection is known to occur in community-dwelling elderly people [6], most disease occurs after exposure to healthcare settings. In addition to hospitalization, residence in a long-term care facility (LTCF) is a frequently cited risk factor for the acquisition of CDI [20]. Asymptomatic carriage among residents of nursing homes has been proposed as a possible mechanism of disease transmission [21] and may be present in 4–20% of long-term care residents in the absence of an outbreak [22,23]. During a disease outbreak the rate of asymptomatic carriage has been demonstrated to be as high as 51% with a higher proportion of skin and environmental contamination in carriers compared with noncarriers [21]. Nevertheless, treatment of asymptomatic carriers was not shown to be of benefit and is not recommended [24]. Interestingly, it has been demonstrated that the incidence of CDI in traditional nursing home units is quite low and that most cases of LTCF-associated CDI are in recently admitted patients receiving subacute or rehabilitation care [20]. Thus, the introduction of *C. difficile* from acute care settings accounts for the majority of CDI in nursing homes.

In addition to frequent antibiotic and hospital exposures, host factors that predispose the elderly to CDI include age-related alterations in intestinal microflora and decline in immune function [25,26]. Immunosenescence is a gradual decline in immune function associated with the natural aging process. Bassaris and colleagues demonstrated that the polymorphonuclear cells of elderly subjects had a diminished ability to kill *C. difficile* when compared with those of younger subjects [27]. The ability to mount an adequate immune response with serum IgG antibodies against toxin A has similarly been shown to protect against progression to symptomatic disease after colonization with *C. difficile* [28]. In a study of immune response in elderly hospitalized patients with *C. difficile* (symptomatic, asymptomatic and controls without *C. difficile)*, those with active disease had higher levels of serum antibodies compared with controls. Carriers had intermediate levels of antibodies [29]. This study suggests that inability to mount an antibody response does not predispose to active disease. Thus, the role of immunosenescense is far from clear in development of CDI.

Medications other than antibiotics have also been implicated in the pathogenesis of CDI, especially proton pump inhibitors and H_2 receptor antagonists. By increasing the gastric pH, there is a potential risk for facilitating passage of *C. difficile* in its vegetative form, as spores are relatively acid stable. Antisecretory therapy may also alter the fecal microflora, favoring infection with pathogenic microbes. Although there was initially debate in the literature, many studies have now found an association between acid suppression and increased risk of CDI, a finding confirmed in a recent meta-analysis [30]. Prospective studies are needed to determine whether the associations are causal. Nevertheless, the indications for the use of proton pump inhibitors and H_2 receptor antagonists in the elderly and other patients at high risk for CDI should be examined cautiously. Interestingly, statin drugs have recently been proposed as a potential risk factor in the development of CDI [31]. McGuire and colleagues described how the inhibition of Rho, a GTP-binding protein involved in inflammation, cell cycle regulation and cytoskeletal processes by *C. difficile* toxins A and B, can lead to apoptosis of colonic epithelium. Statins inhibit Rho at an earlier step in the pathway, thus potentially working in a synergistic fashion with toxins A and B to produce CDI. This noteworthy hypothesis warrants further investigation.

Management strategies

Mild CDI

As discussed previously, asymptomatic carriers do not benefit from treatment [24], but infection control measures should be instituted. Cessation of the offending antimicrobial therapy may be adequate in mild cases of antibiotic-associated diarrhea. However, if there is documented infection with *C. difficile,* specific treatment is necessary, especially in the frail elderly. Nevertheless, stopping any unnecessary antibiotics should be seriously evaluated as their continuation, even with treatment of CDI, is a risk factor for recurrent infection [7]. The use of vancomycin, the only US FDA-approved drug for the treatment of CDI, is limited by cost and concern for the selection of vancomycin-resistant *Enterococcus* [32,33]. Mild CDI is defined as mild-to-moderate diarrhea; up to six bowel movements a day without signs of systemic toxicity. In cases of mild CDI, initial treatment with metronidazole is appropriate and has been shown to have equivalent efficacy to vancomycin [32]. If symptoms do not improve within 3 days with metronidazole, we recommend instituting therapy with vancomycin.

Severe CDI

Severe CDI is characterized by one or more of the following: severe diarrhea, fever, abdominal pain, leukocytosis and pseudomembranous colitis [34]. In such cases we recommend vancomycin as initial therapy [33].

Fulminant CDI

Fulminant or complicated CDI is broadly defined by systemic toxicity, ileus or toxic megacolon, shock, need for admission to an intensive care unit and/or surgical intervention. Such cases may be fatal. In these severe cases, treatment should be vancomycin orally, via nasogastric tube or via enema, as the clinical situation indicates, as well as intravenous metronidazole. Such patients must be monitored closely as colectomy may be indicated. Advanced age has been demonstrated to be an independent predictor of severe disease and mortality [5,34]. In such cases, initial treatment with vancomycin results in higher cure rates than metronidazole [33]. Cober and Malani demonstrated that in the 'oldest' elderly patients (aged 80 years and older) failure of metronidazole occurred in 27.7% of subjects and was associated with higher white blood cell counts [6]. Thus, in high-risk elderly patients, it may be appropriate to initiate therapy with vancomycin even in the absence of systemic toxicity as delay in aggressive management could lead to worse outcomes.

Surgical intervention is indicated in patients with toxic megacolon, perforation or shock despite maximal medical therapy. Early identification of these patients is crucial. Sailhamer *et al.* demonstrated that patients with fulminant CDI cared for by a surgical service had higher survival rates, perhaps due to more frequent and earlier surgical intervention [34]. Lamontagne and colleagues demonstrated a survival benefit in patients who had emergency colectomy when compared with those treated medically [35]. It is noteworthy that this benefit was seen only in patients aged 65 years and older. Predictors of postoperative mortality include advanced age, elevated lactate, marked leukocytosis, low albumin and renal failure [36]. Therefore, prompt surgical evaluation should occur before the point at which emergent intervention may be futile.

Recurrent CDI

Recurrent CDI is a common clinical challenge and refers to CDI that occurs within approximately 1 month of successful treatment. RCDI occurs in 15–30% of cases and is either caused by relapse (persistence of initial strain of *C. difficile*) or reinfection with a new strain of *C. difficile* [37]. Diarrhea can be quite refractory with the risk of recurrence increasing with each failed treatment course. In one study of 163 patients who had already sustained one recurrence, a second recurrence occurred in 45% of patients [38]. Similarly, in a more recent study of 463 patients in Quebec with RCDI, a second recurrence occurred in a third of patients [39]. The cycle of recurrences can continue for months to years resulting in substantial morbidity, high medical costs, lost wages and decreased quality of life.

Risk factors for RCDI were recently reported in a meta-analysis by Garey *et al.* and include older age, continued use of non-*C. difficile* antibiotics and concomitant use of antacids [7]. In the Quebec study, age and prolonged hospitalization were independent predictors of second recurrence [39]. As with initial infection with *C. difficile*, host factors also play a role in the development of recurrent infections. Kyne *et al.* demonstrated that a robust immune response, as measured by antitoxin A IgM and IgG levels, was protective against the development of RCDI [40]. Persistent loss of colonization resistance caused by alteration in the bowel

microflora is also a likely contributor to RCDI. In a small study, Chang *et al.* compared the fecal microbiota of healthy patients to those with initial CDI and RCDI [41]. The gut flora of patients with RCDI was characterized by significantly reduced phylogenetic diversity and supports altered gut flora as an important mechanism of disease.

Treatment of RCDI is not standardized. First recurrences can most often be treated with a repeat course of the initial agent as recurrence is not known to be associated with antibiotic resistance [37]. However, if recurrence is clinically severe, vancomycin should be used regardless of the initial agent. For repeated recurrences, a tapering dose of vancomycin or pulsed-dosed vancomycin was demonstrated to result in significantly fewer recurrences [38]. Adjuvant therapy with probiotics has also been of interest owing to their potential to re-establish colonization resistance [42]. In a randomized, placebo-controlled study of 124 patients with RCDI, *Saccharomyces boulardii*, in addition to standard antibiotics, significantly decreased the rate of recurrence (34.6 vs 64.7% in placebo group; p = 0.04) [43]. Other alternative approaches include the addition of nonstandard antibiotics, fecal reconstitution with donor stool, and in severe cases, the use of intravenous immunoglobulin [44], although more data are needed before advocating any one approach over another. Novel therapies are much needed. A recent randomized controlled trial of human monoclonal antibodies against CDI showed lower rates of recurrence in the treated group compared with the untreated controls (7 vs 25%) [45].

Prophylaxis

There is no effective means of prophylaxis against CDI. Several probiotics have been studied in prevention of antibiotic-associated diarrhea. *Lactobacillus* GG and *Saccharomyces boulardii* have been demonstrated to decrease associated diarrhea when given in conjunction with antibiotics in multiple controlled trials [46]. However, this does not automatically translate into prevention of CDI. In a controlled study of 135 hospitalized patients receiving antibiotics, those given a probiotic mixture of *Lactobacillus casei*, *Lactobacillus bulgaricus* and *Streptococcus thermophilus* demonstrated no cases of CDI in the treated group compared with nine out of 53 in the placebo group [47]. Two small trials, one of *S. boulardii* and one of *Clostridium butyricum*, showed similar trends in decreased cases of CDI [48,49]. Such studies suggest that probiotics may be shown to prevent CDI, but many more well-designed and replicated studies will be needed before this can be widely accepted.

Prevention: infection control & antibiotic stewardship

Any discussion would be remiss to overlook the importance of infection control and prevention in the fight against CDI. Hand hygiene with soap and water (not alcohol-based hand gels), contact precautions and enhanced cleaning of contaminated surfaces with bleach are mainstays of infection control [50]. Education of healthcare staff on *C. difficile* epidemiology, clinical features and transmission is also recommended. Patients with active infections should be placed in a private room or together with other patients with CDI. Although no less critical, infection control may be a particular challenge in LTCFs where group activities are common and private rooms and/or private bathrooms are limited. Higher rates of fecal incontinence in the elderly also increases the risk of disease transmission. Nevertheless, in the elderly who may consider a LTCF their home, the potential psychosocial consequences of isolation must be weighed against infection control benefits [51].

As exposure to antimicrobials is the principal risk factor for the development of CDI, the judicious use of antibiotics is fundamental to any CDI prevention strategy. In the elderly, who have a high burden of acute and chronic disease with frequent need for medical therapy, this may be difficult, but is no less important. Antibiotic stewardship programs can facilitate the prudent use of antimicrobials with the narrowest spectrum of activity and the shortest duration of therapy [52]. Such programs should be developed in LTCFs where antibiotics are among the most frequently prescribed medications [51].

Conclusion

Infectious diarrhea due to *C. difficile* has increased in incidence and severity with wide-reaching impacts in the community and in healthcare settings. Despite reports of disease in previously low-risk hosts, the impact of CDI continues to disproportionately affect the elderly with higher rates of severe CDI, RCDI and death. The influence of CDI on functional independence is also of key importance in the aged where discharge to LTCFs is common [8], even in previously community-dwelling elderly people [6]. Therefore, in the elderly, the prevention of infection is as essential as, if not more important than, CDI treatment alone. As the

aging US population continues to grow, so too does the need for improved understanding of all aspects of CDI.

Future perspective

In light of the increasing incidence, rate of relapse and severity of disease, innovative approaches to the prevention and treatment of CDI are being sought. Novel antibiotics other than vancomycin and metronidazole currently under investigation include rifaximin, nitazoxanide, difimicin and ramoplanin, although none have been shown to be superior to standard therapy. There is also promise in nonantibiotic strategies that circumvent the loss of colonization resistance inherent in any antibiotics therapy. Anion-exchange resins are able to bind toxins A and B, but do not have any intrinsic antibiotic activity. Tolevamer is one such agent that in clinical trials was inferior to metronidazole and vancomycin, but demonstrated a lower rate of RCDI in those patients that did respond [53]. As they are developed, probiotics and prebiotics may play a significant role in the prevention of infection or in the treatment of recurrent disease. We also eagerly anticipate a *C. difficile* vaccine for high-risk patients, including the elderly, which is currently in development.

Finally, the maintenance of a normal population of fecal flora is probably the most important factor in preventing CDI and thwarting recurrent infection. Perhaps the epitome of nonantibiotic therapy is the reconstitution of colonization resistance with donor stools. Although limited in its present application for the treatment of RCDI, we believe fecal transplantation will become more readily available and accepted in the years to come. As we gain more understanding regarding the nature of the healthy colonic microbiome, synthetic stool that is intrinsically resistant to CDI could be developed. Artificial stool could avoid the potential infectious risks associated with donor stools and would be more palatable for patients and providers alike.

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Executive summary

Clinical overview

- *Clostridium difficile* infection (CDI) is the most common cause of nosocomial and antibiotic-associated diarrhea.
- Alteration in bowel microflora can lead to overgrowth of toxin-producing *C. diffficile.*
- CDI can occur weeks after antibiotic exposure or without exposure to antibiotics.
- Leukocytosis, hypoalbuminemia and renal failure indicate poor prognosis.

Risk factors in the elderly

- CDI disproportionately affects the elderly.
- Antibiotic exposure is the most important risk factor for development of CDI.
- Exposure to healthcare settings, such as nursing homes and hospitals, increases the risk of CDI.
- Treatment of asymptomatic carriers of *C. difficile* has not shown any benefit.
- Immunosenescence may play a role in the development of CDI in the elderly.

Management strategies

- Cessation of offending antibiotics may be adequate in mild cases, but specific treatment is often needed, especially in frail elderly patients.
- Metronidazole has similar efficacy to vancomycin in mild disease.
- Severe infection should be treated with vancomycin at the outset.
- Fulminant disease may be fatal. Treatment should be with oral vancomycin and intravenous metronidazole.
- Surgical intervention is indicated in patients with toxic megacolon, perforation or shock, despite maximal medical therapy.
- Recurrent CDI is a common challenge and can occur due to relapse with the initial strain or acquisition of a new strain.
- Initial recurrence can be treated with a repeat course of metronidazole or vancomycin. Refractory cases may require long, tapering regimens.
- There is no effective means for prophylaxis against CDI.
- Infection control and antibiotic stewardship are cornerstones in CDI management.

Future perspective

- Novel antibiotics as well as nonantibiotic strategies are being evaluated in the treatment of CDI.
- Probiotics may play a significant role in the prevention of infection or recurrence.
- Immunization against *C. difficile* is an area of active research.
- Reconstitution of a healthy population of fecal flora through donor stool or perhaps synthetic stool is an important factor in the prevention of CDI and warrants further study.

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