Clostridium difficile infection in older adults

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Clostridium difficile infection, the most frequent cause of nosocomial diarrhea, disproportionately affects older adults. The two most important risk factors for developing *C. difficile* infection are antimicrobial exposure and age >65 years old. Risk factors specific to older adults are frequent interactions with healthcare systems and age-related changes in physiology, including immune senescence and changes to the gut microbiome. Metronidazole and oral vancomcyin are the mainstays of conventional treatment for *C. difficil*e infection. Alternative therapies include fidaxomicin, a narrow-spectrum macrocyclic antibiotic, and fectal bacteriotherapy, which offers an excellent therapeutic outcome. Strategies to prevent *C. difficile* infections include enhanced infection control measures and reducing inappropriate antimicrobial use through stewardship.

Clostridium difficile infection, the most common cause of nosocomial diarrhea, remains among the most serious of healthcare-acquired infections [101]. Older adults, frequent users of healthcare, experience the greatest morbidity and mortality from *C. difficile* infection. Presented here is a discussion regarding *C. difficile* infection that highlights aspects distinct to older adults, including their increased susceptibility, treatment challenges and opportunities for prevention.

Microbiology & pathogensis

C. difficile is a Gram-positive, spore-forming bacillus. Individuals acquire *C. difficile* through accidental ingestion of spores acquired from the environment. The human gut microbiome, a frequently overlooked form of host defense, protects most individuals from enteric pathogens, such as *C. difficile* through colonization resistance [1]. Simply stated, colonization resistance is the means through which the host gut microbiota prevents *C. difficile* from gaining a foothold in the intestine, causing it to pass through the body without causing disease. Systemic antibiotics temporarily change the gut microbiome, disrupt colonization resistance and render individuals vulnerable to *C. difficile* infection. Accordingly, systemic antibiotics are the principal risk factor for *C. difficile* infection. Spores ingested by individuals without intact colonization resistance, germinate into vegetative forms that reproduce and secrete the toxins that mediate disease; manifestations range from watery diarrhea to fulminant colitis and death. Most *C. difficile* strains produce two exotoxins, A and B, both of which translocate into the cytosol of target cells, cause active depolymeraization and subsequent cell death. Specifically, the toxins bind and glucosylate a family of Rho GTPase, locking them into an inactive form and blocking downstream signaling pathways, including those required to organize and maintain the actin cytoskeleton [2]. While toxin A was previously thought to be more pathogenic, reports indicate that naturally occurring toxin A^-B^+ *C. difficile* strains cause infection with typical clinical manifestations [3]. Two independent publications confirm that an A^-B^+ mutant causes disease in an animal model, but they differ on whether an A^+B^- mutant causes disease [4,5]. The disparity between their findings may be due to differences in the development of the mutant strains and highlights that experimental manipulation of *C. difficile* is indeed difficult [2].

In the last 10–15 years, reports emerged describing a dramatic increase in the incidence and severity of *C. difficile* infections. These were eventually linked to an epidemic *C. difficile* strain, characterized as toxinotype III, restriction endonuclease group BI, North American pulsed field gel electrophoresis type 1 (NAP1) and ribotype 027 [6,7]. There is also evidence indicating that among Europeans, an age >65 years correlates with an increased risk for *C. difficile* infection due to ribotype 027 [8,9]. The BI/NAP1/027 epidemic strain produces a binary toxin that may cause or be associated with more severe diarrhea and higher fatality rates [10]. It was also found to secrete 16- and 23-fold greater concentrations of toxins A and B, respectively, compared with non-epidemic strains [11]. Initially, these differences were attributed to an 18-base pair deletion in *tcdC*, a gene believed to encode a negative regulator of toxin A and B production. More recent work, however, disputes these findings. Using

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precise genetic manipulation of *C. difficile*, Cartman *et al.* restored the *tcdC* gene to a ribotype 027 strain with a naturally occurring deletion but found no associated decrease in toxin production. The authors suggest that *tcdC* may act as a 'safety catch' for toxin production, rather than affect the amount of toxin produced [12].

Another notable feature of the BI/NAP1/027 epidemic strain is its resistance to fluoroquinolone antibiotics [13]. Widespread use of fluoroquinolones may have conferred a selective advantage for the BI/NAP1/027 epidemic *C. difficile* strain, further contributing to the increased incidence and severity of resulting infections, as well as its global dissemination [14–16]. While more recent evaluations suggests that the BI/NAP1/027 strain may not cause severe disease in a nonoutbreak setting, its emergence and the resulting epidemic continues to have a significant impact on the epidemiology of *C. difficile* infection [17,18].

Epidemiology

Older adults are disproportionately affected by *C. difficile* infections, including those caused by the BI/NAP1/027 epidemic strain. In 2009, nearly 1% of all hospitalizations in the USA involved *C. difficile* infection [19]. The average age of those patients was 67.9 years compared with 48.1 years for all other hospital stays. The oldest patients (>85 years) experienced the highest rates of *C. difficile* infection-related stays (Figure 1). Just as with hospitalizations, deaths due to *C. difficile* infection have also increased in the USA, rising from 793 in 1999 to 7251 in 2009 [102]. Mortality due to *C. difficile* infection also increases with age, rising from 5% for people 61–70 years to >10% for people >80 years [6]. In 2010, 91% of deaths due to *C. difficile* infection occurred in people >65 years, making it the 18th leading cause of death among USA citizens in this age group [102].

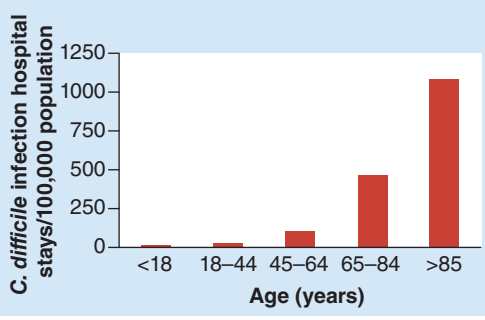

Figure 1. The risk of hospitalization associated with a *Clostridium difficile* infection increases with age.
Data taken from [19].

C. difficile infection may be broadly categorized as healthcare-acquired or community-acquired, with the former being far more common [20]. Community-acquired is defined as *C. difficile* infection in persons who have not been discharged from a healthcare facility in the previous 12 weeks [21]. On average, patients who develop community-acquired infection are significantly younger than those with healthcare-acquired infection, yet the incidence of community-acquired *C. difficile* infection also increases with age [22–24]. The age difference between community- and healthcare-acquired *C. difficile* infection may reflect that older adults experience more frequent admissions to healthcare facilities.

C. difficile infection places a significant financial burden on healthcare systems. In 2009, the aggregate cost associated with hospitalizations related to *C. difficile* infection was an estimated US$8.2 billion, approximately 2.3% of all US hospital costs [19]. Similarly, the European CDC projects costs of €3 million per year for the EU [25]. Given that these figures do not account for *C. difficile* infection in long-term care facilities (LTCFs) [26], they probably underestimate the true financial impact of *C. difficile* infection. Thankfully, recent data indicate stabilization and perhaps a decline in the *C. difficile* infections. Hospitalization rates for *C. difficile* infection in the USA reached a plateau between 2008 and 2009 [19]. In England, *C. difficile* infections have declined by 44% since 2009, with a concurrent reduction in mortality, which may be explained by a decrease in the prevalence of the ribotype 027 strain [27,28].

General risk factors

Aside from exposure to systemic antibiotics, advanced age, followed by gastric acid-suppressive medications are the two most notable risk factors for developing *C. difficile* infection [29–31]. Advanced age and possible reasons for increased vulnerability to *C. difficile* are discussed in detail below. Proton-pump inhibitors were first implicated as a risk factor for hospitalized patients in 2004 [32]. Subsequent research demonstrated that gastric acid suppression, whether due to histamine-2 receptor agonists or proton-pump inhibitors, increased the risk for developing *C. difficile* infection in community-dwelling adults [30]. These findings were significant because they convincingly identified gastric acid suppression as a risk factor distinct from hospitalization and from persons with multiple comorbidities. Interestingly, gastric acid suppression does not appear to increase the risk of severe or recurrent

C. difficile infection [33]. In the nearly 10 years that have elapsed since identification of gastric acid suppression as a risk factor, the mechanisms for this association remain unknown [34,35].

Other risk factors for *C. difficile* infection are an indication of patients' underlying susceptibility (Table 1). Less expected is the recent description of smoking as a risk factor. Current smokers are 80% more likely to develop *C. difficile* infection compared with those who have never smoked [36]. Interestingly, the authors suggest that the presence of *Clostridial* species in cigarette filters may be a route for oral inoculation with spores. Also of interest are recent descriptions of reduced risk for *C. difficile* infection among those on statins [37,38]. Finally, some reports describe culturing *C. difficile* from retail meat products [39,40]. A large-scale study using a consensus method for *C. difficile* culture, however, did not recover the organism from 1755 meat products sampled from nine centers across the USA over 12 months [41]. Coupled with the lack of reports of restaurants or food-associated outbreaks, it is unclear that foodborne *C. difficile* represents a significant clinical risk factor for *C. difficile* infection.

Age-related risk factors

Advanced age is an established risk factor for *C. difficile* infection. Using a large, prospective cohort, Loo *et al.* quantified this risk, determining that for every additional year of age after 18 years, the risk of healthcare-associated *C. difficile* infection increases by approximately 2% [29]. The reasons for this are multifactorial and may relate, in part, to older adults' frequent

Table 1. Nonantibiotic risk factors for acquiring *Clostridium difficile* infection since the advent of the BI/NAP1/027 epidemic strain.

Risk factor	Comments
Well-established	
Advanced age	CDI risk increases ~2% each year for every year >18 years of age [6,91] Age >70 years associates with severe CDI [61] Predicts death due to CDI [42] Predicts initial and recurrent disease [92,93]
Gastric acid suppression	Some studies specifically identify proton-pump inhibitors that are more frequently used than histamine-2 blockers [4,30,94] Does not appear to affect disease severity or outcomes [24] May [91] or may not [24] predict disease recurrence Probably a risk factor for community-acquired CDI [30], although some disparate findings [37]
Low albumin (<3.5 g/dl)	This likely reflects diminished health status [93] Predicts death due to CDI [42] <2.5 g/dl associates with severe disease [61]
Underlying disease severity	Determined by physicians upon patient admission using a modified Horn's index. A score of ≥3 predicts nosocomial CDI [65]
Previous hospital admission	Depending on the study, the time frame extends up to the previous 12 weeks. Suggestive of diminished health and also furnish opportunities for exposure to *C. diffiicile* spores in the environment and for receipt of systemic antimicrobials [20,45,92] Predicts disease recurrence [37]
Residence in a LTCF	LTCFs present opportunities for exposure to *C. difficile* spores and for receipt of systemic antimicrobials [20,95]
Less well-established	
NSAIDs	A recent population-based case–control study specifically implicates diclofenac [96]
Smoking	Both former smokers and current smokers are at an increased risk to acquire CDI compared to never smokers [36]
CDI pressure	Defined as a patient's daily exposure to other patients with CDI on the same ward divided divided by the patient's at risk length of stay [93]
Mechanical ventilation	Predicts CDI [93,97] Predicts disease recurrence [91]
Statins/HMG-CoA reductase inhibitors	Statins are protective against developing CDI while hospitalized [38] and against community-acquired CDI [37]

CDI: Clostridium difficile *infection; LTCF: Long-term care facility.*

interactions with healthcare systems and to age-related changes in physiology. Among older adults specifically, longer courses of antibiotics (>4 weeks) or treatment with more than four agents increased the risk of death due to *C. difficile* infection, as did a low serum albumin and history of coronary artery disease [42].

Frequent interaction with healthcare systems increases the opportunity for exposure to antimicrobials and for contact with physical environments contaminated with *C. difficile* spores. Both symptomatic and asymptomatic carriers of *C. difficile* shed spores onto their skin and into their environment, creating a risk for acquisition from other patients [43–45]. Data from the CDC's Emerging Infectious Program revealed that, in 2010, exposure to healthcare preceded 94% of *C. difficile* infections. Of those, 75% were inpatient exposures, implicating that the remaining 25% of infections were associated with LTCFs and outpatient care settings (Figure 2) [20].

C. difficile infection is endemic in LTCFs, where 3.6% of Americans >65 years old reside [46]. The Ohio Department of Public Health (USA) demonstrated that, in 2006, over half of new cases and three-quarters of recurrent *C. difficile* infections were diagnosed at nursing homes [19]. Compared with those not infected, hospitalized patients infected with *C. difficile* are more likely to be discharged to a LTCF [43]. This reflects the major loss of function reported in 60 and 93% of patients with a primary or secondary *C. difficile* infection, respectively [19]. These patients become a reservoir for *C. difficile* spores, which helps to explain why simply residing in a LTCF poses a risk for developing *C. difficile* infection, particularly within the first several weeks after admission [47]. Furthermore, in the USA, more than 75% of LTCF residents require assistance with at least four activities of daily living [46]. The frequent close contact between residents and healthcare workers presents abundant opportunities for transfer of *C. difficile* spores. Healthcare workers, particularly when understaffed, may unintentionally contribute to transmission of infectious diseases through poor infection control practices [48,49]. Finally, LTCF residents receive 2.9–13.9 courses of antimicrobials per 1000 days of care, and many of them are inappropriate or unnecessary [50–52].

Beyond their interactions with the healthcare system, older adults incur age-related physiologic changes that also contribute to their increased risk of *C. difficile* infection. Aging is accompanied by immune senescence. Diminished antibodies against *C. difficile* toxins may permit the development of symptomatic disease, rather than asymptomatic carriage, which may also increase the risk of recurrent infection [53]. Additionally, the gut microbiome of older adults differs to that of younger individuals. Using an *in vitro* assay that tests *C. difficile* growth in fecal emulsions as a functional measure of colonization resistance, Borriello and Barclay found that fecal emulsions derived from geriatric patients were less inhibitory for *in vitro* growth of *C. difficile,* compared with healthy adult volunteers [54]. This suggests that older adults' gut microbiomes have less robust colonization resistance at baseline, which may reflect differences in the relative proportion and diversity of member species. Using microbiological cultivation, Hopkins and Macfarlane found decreased bacterial diversity among the feces of a small cohort of older adults, especially those with *C. difficile* infection, compared with younger adults [55]. Furthermore, Rea *et al.* used pyrosequencing of ribosomal RNA amplicons to describe a similar decrease in microbial diversity observed among older adults colonized or infected with *C. difficile* [56]. Comparison of older and younger adults' gut microbiomes (average ages 73 and 31 years old, respectively) using whole-genome sequencing demonstrated a relative decrease among bacteria from the phylum *Bacteroidetes* and *Clostridium* cluster IX (includes *Veillonella* species) and an increase in those from *Clostridium* cluster XIVa (includes *Eubacterium*, *Lachnospira*, *Ruminococcus* and

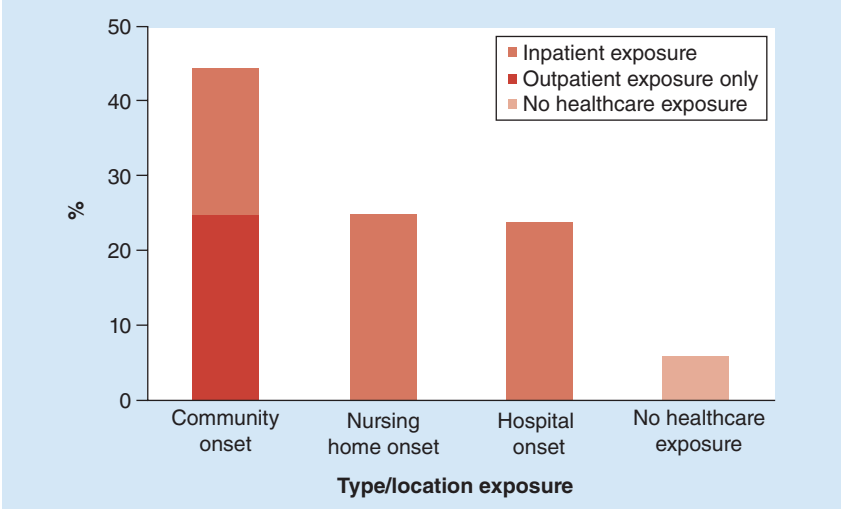

Figure 2. Percentage of *Clostridium difficile* infection cases by inpatient or outpatient status at the time of stool collection and type/location of exposures.
Data taken from [20].

Roseburia species) [57]. While the clinical implications of these data are still unclear, changes in composition of the human gut microbiome in health and disease states is an active and exciting area of investigation.

Disease manifestations & treatment

C. difficile infection may manifest with a range of symptoms including asymptomatic colonization, frequent watery diarrhea (>3 episodes/day) and fulminant colitis requiring colectomy. Prior to the emergence of the epidemic strain, while older adults were at increased risk for developing *C. difficile* infection, the clinical features of the disease were not substantially different between younger and older adults [58,59]. This changed, however, following the outbreak of the BI/NAP1/027 strain, which began in Canada in around 2003 and spread to the USA by 2005 [6,60]. Infection with the BI/NAP1/027 strain was a risk factor for death [6]. Furthermore, in a retrospective chart review conducted between June 2005 and May 2006, Henrich *et al.* determined that age >70 years was a risk factor for severe *C. difficile* infection (odds ratio: 3.24; 95% CI: 1.42–7.38) [61].

Older adults are also at greater risk for recurrent *C. difficile* infection. In 2009, among individuals discharged from hospitals in the USA with a diagnosis of *C. difficile* infection, the risk of readmission due to recurrent disease increased with age (Figure 3) [62]. A recently described model based on a clinical trial with nearly 1000 adults with *C. difficile* infection predicts that the risk of recurrent disease rises from <20% for those <40 years to just over 30% for those >80 years [63]. Furthermore, the first episode of disease recurrence becomes a predictor of additional episodes, regardless of whether they are due to relapse or due to reinfection with the same or a different strain [53]. Currently, identifying those at risk for recurrent infection may be achieved through a clinical prediction rule that assigns one point each for age >65 years, severe underlying disease and additional antibiotic use [64]. This scoring system considers patients with a score >2 as high risk for recurrent disease with an accuracy of approximately 72%. Older adults' increased risk of recurrent *C. difficile* infections probably reflects immune senescence and age-related changes in the gut microbiome, as discussed above. Aside from age, other risk factors for recurrent disease include continued exposure to non-*C. difficile*-specific antibiotics after diagnosis, as well as administration of gastric acid-suppressive medications [65].

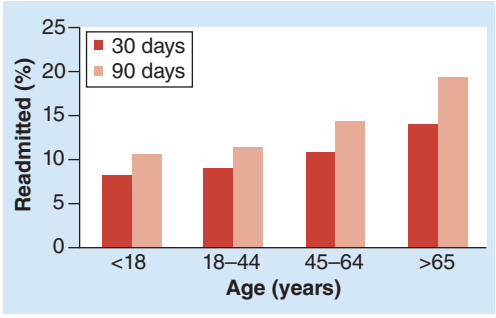

Figure 3. Following a *Clostridium difficile* infection-related hospital stay, the risk of readmission at 30 and 90 days due to *C. difficile* infection increases with age.
Data taken from [62].

Treatment recommendations do not vary with the age of the patient. Cessation of the inciting antibiotic remains an important aspect of management. The Society for Healthcare Epidemiology of America/Infectious Disease Society of America (SHEA/IDSA) and European Society of Clinical Microbiology and Infectious Disease (ESCMID) guidelines recommend similar medical treatments for initial episodes and first recurrence episodes of *C. difficile* infection (Table 2) [21,66]. Subsequent recurrences of *C. difficile* infection are challenging and may, as detailed in both the SHEA/IDSA and ESCMID guidelines, respond to tapered vancomycin therapy. While some studies have raised concerns for an increased rate of failure among older adults treated with oral metronidazole, these findings seem to indicate treatment failure for individuals with severe disease rather than an age-related deficit [53,67]. A novel medication, fidaxomicin, has potent activity against *C. difficile* but spares most other bacterial groups in the gut microbiome [68]. Compared with oral vancomycin, fidaxomicin leads to fewer episodes of first recurrences of *C. difficile* infection [63]. Interestingly, the BI/NAP1/027 epidemic strain may obviate the benefits of fidaxomicin compared with oral vancomycin; the reasons for different outcomes depending on strain are unclear [69,70].

Fecal bacteriotherapy, also termed fecal transplant, is a therapeutic option that is gaining wider acceptance in both Europe and the USA. The premise is that instillation of normal fecal bacteria into the intestine of a person afflicted with *C. difficile* infection will permit rapid recovery of the gut microbiome and colonization resistance. The procedure relies upon obtaining healthy stool and administering it to the patient via nasogastric tube, enema or via colonoscopy. Donor feces usually comes from a close contact

Table 2. Recommendations for the treatment of *Clostridium difficile* infection[†].

Clinical situation	Description	Recommended treatments
All		Stop inciting antibiotics whenever possible
Initial episode: nonsevere	>3 unformed or watery stools per day and a stool test result positive for toxigenic *C. difficile* or its toxins, or pseudomembranous colitis on colonoscopic or histopathologic examination	Metronidazole, 500 mg by mouth three-times a day for 10–14 days
Initial episode: severe	Leukocytosis with white blood cell count >15,000 cell/ml and a serum creatinine >1.5-times the premorbid level	Vancomcyin 125 mg by mouth four-times a day for 10–14 days[‡]
Initial episode: severe and complicated	Hemodynamic instability, ileus or toxic megacolon[§] Fever (>38.5°C), rigors, peritonitis, band neutropihils >20% of leukocytes; elevated serum lactate, pseudomembranous colitis, colonic wall thickening, pericolonic fat stranding, ascitics without another cause[¶]	Vancomycin 500 mg four-times a day by mouth or through nasogastric tube; metronidazole 500 mg intravenously If complete ileus, consider adding rectal installation of vancomycin Surgical consultation
Indications for colectomy		Colonic perforation Failure to respond to antibiotic treatment with a deteriorating clinical status, including toxic megacolon or severe ileus
Recurrent disease: first episode		Same as for initial episode
Recurrent disease: subsequent episodes		Vancomycin taper or pulse therapy[#]

[†]Based on both the Society for Healthcare Epidemiology of America/Infectious Disease Society of America and European Society of Clinical Microbiology and Infectious Disease treatment guidelines.
[‡]Where available, teicoplanin 100 mg by mouth twice a day may replace oral vancomycin.
[§]Per the Society for Healthcare Epidemiology of America/Infectious Disease Society of America Guidelines.
[¶]Per the European Society of Clinical Microbiology and Infectious Disease Guidelines.
[#]Vancomycin 125 mg by mouth four-times a day for 10–14 days followed by vancomycin 125 mg by mouth twice a day for 1 week, 125 mg by mouth once daily for 1 week and then 125 mg by mouth every 2–3 days for 2–8 weeks.
Data taken from [21,66].

of the patient, including an intimate partner, relative or household contact. Beyond convenience, obtaining stool from a close contact of the patient minimizes the risk of introducing a new pathogens and is associated with lower relapse rate compared with feces obtained from unrelated volunteers [71,72]. A recent randomized controlled trial, however, used a prescreened pool of healthy donors with excellent results [73]. In total, 15 of 16 patients (93%) in the fecal bacteriotherapy arm were cured of their *C. difficile* infection with one to two instillations of donor feces. Analysis of the microbiome recovered from patients following successful treatment revealed an increase in bacteria from the phylum *Bacteroidetes*, *Clostridium* cluster IV (includes *Clostridium leptum* spp.), *Clostridium* cluster XIVa (includes *Eubacterium*, *Lachnospira*, *Ruminococcus* and *Roseburia* spp.) and a decrease in bacteria from *Proteobacteria*. Fecal bacteriotherapy seems to be a safe and well-tolerated therapy to treat patients with *C. difficile* infection, including older adults with recurrent disease [74].

Prevention

Preventing *C. difficile* infection involves both minimizing transmission and reducing patients' vulnerability. The longevity and tenacity of *C. difficile* spores in the environment contributes to the risk of acquisition during institutionalization [21]. *C. difficile* spores may remain dormant on environmental surfaces for months, far longer than any other nosocomial pathogen [21]. Furthermore, the spores contaminate a variety of environmental surfaces in hospitals and LTCFs, including toilets, bedrails, equipment used to obtain vital signs and bedside curtains, with some indications that they may even be

airborne [75]. Given that *C. difficile* spores are resistant to most surface disinfectants and that environmental staff may not appropriately clean many surfaces, it is not surprising that occupying a room in which the previous patient had *C. difficile* infection is a significant risk factor for acquiring a new *C. difficile* infection [76].

A variety of strategies have been employed to combat the persistence of *C. difficile* spores in the environment, ranging from improved cleaning methods to new disinfectant technologies. Chlorine-containing cleaning agents are an effective means to reduce the environmental burden and, at least to some extent, the incidence of *C. difficile* infection [21]. In a hospital with a high rate of *C. difficile* infection (24.2 cases/10,000 patient days), daily cleaning of all rooms with bleach wipes reduced the incidence of hospital-acquired *C. difficile* infection to 3.6 cases/10,000 patient days [77]. The drawbacks to using chlorine-containing agents include the strong odor, possible hypersensitivity, a corrosive effect on equipment over time, achieving sufficient contact time on surfaces and that its application is operator dependent [21]. Among new technologies, adding hydrogen peroxide vapor to terminal cleaning of hospital rooms appears to have reduced facility-wide *C. difficile* infection rates from 0.88 to 0.55 cases/1000 patient days in one retrospective quasiexperimental study [78]. While effective, drawbacks associated with using hydrogen peroxide vapor include the expense of purchasing specialized equipment and associated consumables, as well as the need to seal rooms [21]. Ultraviolet radiation may also hold promise as a means to reduce environmental contamination, although it has not yet been shown to reduce *C. difficile* infection rates. Also relatively expensive, ultraviolet radiation has the distinct advantage that it requires the patient to be absent from the room for only a short period, making it a practical means to reduce the environmental pathogens during a patient's stay. While this may not confer an advantage for hospitals, in which the length of stay is relatively short, it may hold promise as a means to reduce the burden of *C. difficile* spores in LTCFs and similar facilities [44].

Besides direct contact with contaminated environmental surfaces, people may also acquire *C. difficile* infection through contact with healthcare workers. While alcohol hand rub effectively kills most nosocomial pathogens, *C. difficile* spores are resistant to alcohol. The best means to remove spores from hands is the mechanical action associated with using soap and water. In response to low rates of hand hygiene employed by healthcare workers, several organizations, including the CDC and the WHO, have launched campaigns to improve hand hygiene at healthcare facilities. The 'Cleanyourhands' campaign in 187 acute trusts in England and Wales found that, in the setting of a high-profile political drive, increased procurement of soap and alcohol rub correlated with decreased rates of *C. difficile* infection and bacteremia due to methicillin-resistant *Staphylococcus aureus* [79]. Routine use of gloves may also be an effective means to reduce nosocomial transmission of *C. difficile* spores [21].

In addition to reducing the burden of spores in the environment, a key aspect of preventing *C. difficile* infection in older adults is to minimize their vulnerability by avoiding unnecessary antibiotic exposure. In the USA, >50% of antimicrobials prescribed in hospitals and 25–75% of those prescribed in LTCFs may be inappropriate or unnecessary [51,80,81]. Beyond *C. difficile* infection, adverse consequences of inappropriate antimicrobial use include selection for resistant pathogens, increased risk for drug–drug interactions and greater costs. Improving antimicrobial use through antimicrobial stewardship reduces *C. difficile* infections in both acute and long-term care settings. Prior to the emergence of the BI/NAP1/027 epidemic *C. difficile* strain, a teaching hospital in the UK reduced the incidence of *C. difficile* infection on a single geriatric ward by nearly 50% through restrictions on intravenous cephalosporins [82]. When enhanced infection-control measures proved ineffective at reducing the incidence of the BI/NAP1/027 epidemic strain, two Canadian hospitals implemented an educational initiative to direct the choice of empiric antimicrobial therapy away from specific agents associated with *C. difficile* infection. Comparisons of the same 4-week period over 3 years showed a reduction in total antimicrobial use by over 20% and in the incidence of *C. difficile* infection by 60% [83]. Three hospitals in Northern Ireland achieved similar results during an outbreak of the BI/NAP1/027 epidemic strain by restricting only fluoroquinolones [84]. Antimicrobial stewardship in a LTCF that reduced total antibiotic use by 30% and fluoroquinolones by 28% led to a decline in the rate of positive *C. difficile* tests [85]. These and similar studies concur with the SHEA/IDSA recommendations to use antimicrobial stewardship as a means to reduce *C. difficile* infection [21].

Conclusion & future perspective

Among the causes of morbidity and mortality among older adults, *C. difficile* infection stands out because most instances are iatrogenic. Not only do older adults experience increased disease severity, they are also more likely to have recurrent infection with courses of treatment that may last for months. Developing a diagnostic test to identify patients at high risk for recurrent disease may augment medical management of these individuals. For example, notifications through the electronic medical record may alert healthcare providers of patients with a high risk for recurrence, perhaps reducing the likelihood of further antimicrobial prescriptions, apart from those used for treating *C. difficile* infection.

Fecal bacteriotherapy is an effective option to treat both initial and recurrent *C. difficile* infection. While it has yet to receive an endorsement from the SHEA, IDSA or ESCMID, fecal bacteriotherapy is gaining acceptance by healthcare providers in the USA [86]. The American College of Gastroenterology's *C. difficile* Infection guidelines offer a conditional recommendation to consider fecal bacteriotherapy among patients who failed pulsed-oral vancomycin (i.e., more than three recurrences) [87]. Over the next few years, larger hospitals and referral centers may develop fecal bacteriotherapy centers, coordinating the efforts of infectious disease physicians and gastroenterologists. Furthermore, as fecal bacteriotherapy centers become more common, we may also see the advent of clinical studies comparing the source of the sample (household contact, genetically related family member, prescreened donors), preparation of the sample (blender, filtration) and recipient, (bowel lavage, duration without antibiotics) and method of administration (capsule, instillation via nasogastric, duodenal or jejunal tube, enema or colonoscopy).

Further investigations into the gut microbiome will continue to identity specific bacteria that confer colonization resistance. Using a mouse model, Lawley *et al.* have identified six bacterial species, three of which are novel, that together are able to restore colonization resistance to the gut microbiome of mice experimentally infected with *C. difficile* [88]. Coming from distinct branches of the phylogenetic tree that comprises the gut microbiome, these bacteria are *Staphylococcus warneri*, *Enterococcus hirae*, *Lactobacillus reuteri*, *Anaerotspies* species nov., *Bacteroidetes* species nov. and *Enterohabdus* species nov. [88]. Translating this work into clinical trials may eventually foster development of an evidence-based probiotic formulation targeted specifically for people with *C. difficile* infection. Ideally, administration of live microorganisms as a medical therapy would be approved and regulated by the US FDA with the organisms that can be quantified and identified by genus, species and strain.

There are ongoing efforts to develop a vaccine effective against *C. difficile* infection. A candidate vaccine against toxoids A and B administered as a series of four intramuscular injections over 8 weeks cured recurrent infection in patients who had previously been oral vancomcyin for 7, 9 and 22 months [89]. Some hurdles to vaccine development include whether to target toxin A, B or both, and to determine if systemic (IgG) or mucosal (IgA) antibodies are most effective at disease prevention. For an excellent review of vaccines against *C. difficile* that also addresses immunologic and biotherapeutic approaches, please see [90].

Further research and clinical studies will continue to bring advances in the treatment and eventually, prevention of *C. difficile* infection. Currently, however, our best efforts to reduce the risk of this disease must focus on enhanced infection-control measures, specifically rigorous hand hygiene and stringent environmental decontamination, coupled with reducing older adults' vulnerability through good antimicrobial stewardship practices in all healthcare settings.

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Executive summary

Pathology

- *Clostridium difficile* is a Gram-positive, spore-forming bacillus that causes disease following ingestion by a susceptible host.
- The gut microbiome prevents *C. difficile* from gaining a foothold in the intestine through colonization resistance.
- Systemic antibiotics disrupt the gut microbiome, rendering hosts vulnerable to *C. difficile* infection.
- An epidemic strain of *C. difficile* emerged in the last 10–15 years. It causes more severe disease and is resistant to fluoroquinolones.

Epidemiology

- Older adults are disproportionately affected by *C. difficile* infection.
- Nearly 1% of all hospitalizations involve *C. difficile* infection.
- *C. difficile* infections place a significant financial burden on healthcare systems.

General risk factors

- Antibiotic exposure and advanced age are the two greatest risk factors for *C. difficile* infection.
- Gastric acid suppression appears to be strongly correlated with *C. difficile* infection, although the mechanism is unclear.
- Most other risk factors reflect diminished health status (albumin ≤3.5 g/dl, underlying disease severity and mechanical ventilation).

Age-related risk factors

- Older adults' frequent interactions with healthcare systems increase their opportunity for exposure to *C. difficile* spores.
- Older adults frequently receive antibiotics, placing them at risk for *C. difficile* infection.
- With aging comes immune senescence and, perhaps, a less robust gut microbiome.

Disease manifestations & treatment

- *C. difficile* infection may manifest with a range of symptoms including asymptomatic colonization, watery diarrhea and fulminant colitis requiring colectomy.
- Older adults experience more severe disease and are at greater risk for recurrent disease.
- Metronidazole and oral vancomycin are the mainstays of treatment.
- While expensive, fidaxomicin reduces the likelihood of a first disease recurrence.
- Fecal transplant is an excellent therapy that is garnering greater attention.

Prevention

- *C. difficile* spores are difficult to remove using routine cleansing agents and may remain viable on environmental surfaces for months.
- Reducing the burden of *C. difficile* in the environment is critical to disease prevention.
- Healthcare workers may serve as vectors; hand hygiene using soap and water is the best means to remove spores from their hands.
- Preventing unnecessary antimicrobial use through stewardship also reduces *C. difficile* infections.

Conclusion & future perspective

- Morbidity and mortality due to *C. difficile* is mostly iatrogenic.
- Fecal transplant centers may offer highly effective treatment for *C. difficile* infection, particularly for recurrent episodes.
- Current research efforts may lead to an effective, evidence-based probiotic therapy to treat *C. difficile* infection.
- There are ongoing efforts, including clinical trials, to develop a vaccine that will treat, and possibly prevent, *C. difficile* infection.

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