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Review Article

Clostridioides difficile: An Underappreciated Disease in The Long-Term Care Setting

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Abstract

Recurrent *Clostridioides difficile* infections are a major challenge for long term care facilities with a population which is at risk of multiple recurrences despite standard of care antibiotics. There is a need to adopt a different approach by restoring the gut flora to normal and thereby obviating the conditions for *C. difficile* spores to grow and cause disease. The nursing home setting is a particularly difficult setting due to the proximity of residents, the pressure on nursing staff and the multiple risk factors such as antibiotic and proton pump use being present. Live Biotherapeutic Products may be an "old/new" approach to managing and reducing recurrence of CDI.

Introduction

Initially discovered in 1935 by Hall and O'Toole [1] from the stool of a healthy neonate, *Clostridioides difficile* was initially called *Clostridium difficile*. It was not until the late 1970's that the organism was associated as the cause of pseudomembranous colitis (PMC) as well as diarrheal disease [2-4]. Diarrheal disease is now a leading cause of infectious disease mortality in the US, between 1980-2014 deaths from diarrheal diseases increased by 483.96% (95% UI, −17.66% to 622.24%) from 0.41 to 2.41 per 100,000 persons [5]. This observation is likely due to Clostridioides difficile infection (CDI), which continues to be the most commonly known cause of antibiotic-associated diarrhea and healthcare-associated infections [6].

In the US there are almost 500,000 cases of CDI, with 30,000 annually deaths, and the majority of CDI cases occurring in those aged over 65 years [7, 8]. Older patients are disproportionally affected by CDI, they have a higher risk of CDI occurrence and recurrence (rCDI), disease severity, poor response to treatment, and experience worse health outcomes [9-12]. CDI results in prolonged hospital stay, higher rates of discharge to a nursing home and readmission in subsequent months [13, 14]. Those aged over 65 years account for 72% of all CDI recurrence and 83% of all CDI deaths [4], and over the course of a year after rCDI the CDI-associated deaths are almost ten times higher in older patients (25.4%) than non-recurrent CDI (2.7%) [15]. The short and long-term impact of CDI and rCDI among this population is in part due to their higher prevalence of risk factors.

Risk factors among the elderly

Risk factors that contribute to CDI among older patients include frequent interactions with healthcare facilities, hospitaliza-

tions, antibiotic exposure, use of proton pump inhibitors, multiple comorbidities, polypharmacy, changes in microbiome and age-related changes in physiology, and the immune response [11, 16, 17]. Advanced age is recognized as a key risk factor for severe disease, recurrence, and mortality in CDI [18]. Mortality due to *C. difficile* infection increases incrementally with age, from 5% for people 61–70 years to >10% for people >80 years [11]. Antibiotic exposure in older adults (≥65 years old) is high, in 2011 and 2014, older adults ≥65 years old in the United States were prescribed 46 million (1113 prescriptions per 1000 persons) and 51.6 million (1115 prescriptions per 1000 persons) outpatient antibiotic prescriptions, respectively. Prescribing rates for outpatient antibiotics remained stable overall between 2011 and 2014 (P = 0.89). In 2014, Persons aged ≥75 years had a higher prescribing rate (1157 prescriptions per 1000 persons) than persons aged 65–74 (1084 prescriptions per 1000 persons [19].

Additionally, use of medications associated with increased risk of CDI are frequent among the elderly: history of using corticosteroids, proton pump inhibitors, or lipid-lowering therapy, and gastric acid-suppressive medications [7, 11, 15, 20]. Approximately 40% of elderly adults receive PPIs, a study found 78.68% take them for longer periods of time than recommended, and appropriate clinical indications may be lacking for up to 85% of PPIs prescribed [21 22].

LTC facilities

CDI has become an important condition not only in hospitals but also in long term care facilities (LTCFs) and in the community setting [9, 23-26]. Of more than 55.8 million elderly adults in the U.S. (65 or older), 1.3 million live in nursing homes, representing 2.3% of the elderly population [27]. An additional 818,800 elderly Americans reside in residential care facilities [28]. Discharge to a LTCF is the second most common type of hospital discharge (13%) [29], and in their study, Dubberke et al. found that 32% of hospitalized patients with CDI were discharged to a LTCF compared to 23% without CDI [30]. In a two-center study, compared to matched controls, elderly patients with CDI were more likely to be discharged to a nursing home or LTCF, experience functional decline or die during admission [31].

Frequently, cases of CDI have their onset in LTCFs, and many hospital-onset cases are transferred to LTCFs [32]. Residents of these facilities are at high-risk for CDI due to the combination of multiple risk factors of the vulnerable population, including antibiotic exposure, multiple comorbidities, and nature of the communal living setting [26]. In addition, asymptomatic carriage of toxigenic *C. difficile*, exposure to *C. difficile* spores, and rCDI are prevalent in this setting [26, 33, 34]. Moreover, factors such as dementia or poor functional status of residents in LTCFs also affect the ability to implement measures to prevent transmission [26].

While diarrhea is the most common symptom of CDI, older adults (>65 years) with CDI may present with atypical clinical features, such as acute confusion, altered mental status or other nonspecific symptoms of infection, including weakness and loss of physical functional capacity [18]. Delirium was twice as frequent in hospitalized elderly with CDI as in controls in a two-center study [31]. Altered mental status was the presenting symptom in one sixth of patients in a study, including cases from the community, hospitals, and long-term care facilities (LTCF) [35].

Recurrent *C difficile* infections (rCDI) are a major challenge for LTCFs with a population which is at risk of multiple recurrences despite standard of care antibiotics. There is a need to adopt a different approach by restoring the gut flora to normal and thereby obviating the conditions for *C. difficile* spores to grow and cause disease. The nursing home setting is a particularly difficult setting due to the proximity of residents, the pressure on nursing staff and the multiple risk factors such as antibiotic and proton pump use being present. LBP's may be an "old/new" approach to managing and reducing recurrence of CDI.

rCDI and the elderly

Between 20 and 35% of patients with index CDI will experience a recurrence (usually within 30 days) [15, 20, 36-40], Furthermore, of the patients who have a recurrence, up to 60% will experience subsequent recurrences [41, 42] The existing standard of care does not reduce the recurrence rates due to the damaged gut microbiome and subsequent dysbiosis [43]. Medically complex patients are often encountered in clinical practice. Based on Medicare fee-for-service claims data from 2009 to 2017, 25% of older patients aged ≥65 years with rCDI died within 1 year of experiencing CDI (CDI-related mortality). This mortality rate is nearly 10 times that of CDI-related mortality after a first episode of CDI (2.7%) [15].

The combination of higher comorbidity burden and worse clinical outcomes from CDI/rCDI in older patients is critical to address. CDI incidence increases with age, and older adults are 3 times more likely to develop complicated CDI (eg, fulminant colitis and admission to an intensive care unit) [44]. In addition, the increasing number of older patients with comorbidities is increasing, making clinical challenges and complexity of medical decision making.

Microbiome and CDI

The gut microbiota composition changes with aging, leading to a reduction in the protective microbial diversity and a decrease in resistance to *C.difficile* colonization [17, 45]. Dysbiosis, changes in gut physiology and function are associated with aging, and the decline in the immune system contributes to putting elderly people at risk for CDI. Disruptions to gut microbiota composition and diversity can result in microbiome disruption, termed dysbiosis, and subsequent intestinal proliferation of opportunistic pathogens such as *C. difficile*. This shift in gastrointestinal flora can occur after certain antibiotics, proton pump inhibitors, and immunosuppressants. In light of the changing gut microbiome, the challenge of managing CDI is increasing, especially as the antibiotics that are currently recommended, do not restore the microbial flora. The increasing contemporary interest and a target of preventive strategies is the manipulation of the gut microbiome. The microbiome is a vast ecosystem of microbes that can influence human health and disease. The intestinal flora changes with age, especially as the presence of anaerobes decreases [46, 47].

The prevalence of *C. difficile* in stool is the highest among those living in nursing homes with 20% to 50% of residents affected, compared to 1.6% in the general community and 9.5% in the outpatient setting [48]. Thus, this continued dysbiosis and colonization requires another approach, fecal microbiome transplantation has gained support over the past decade such that several companies have examined ways to restore the disturbed flora. Fecal microbiome transplantation (FMT) was first reported in the 4th century by Ge Hong but was re-visited in 1958 by Eisemann and colleagues [49]. In the past decade there have been multiple studies, most showing a clear benefit of FMT. However, the source and manipulation of the product has been the focus of discussion and concern as secondary infections have been reported. In view of these worries a different approach was undertaken with support from the FDA. The new products are classed as live biotherapeutic products (LBP). Currently two products are FDA approved.

Management of C. difficile using a "old-new" approach

Ferring Pharmaceuticals developed a human derived fecal transplant called REBYOTA, a Live Biotherapeutic Product (LBP) which is a single dose rectally administered product which was approved by the FDA in November of 2022. This product contained a broad consortium of species including Bacteroides. This latter group of organisms are considered to be keystone taxa and vital to the development of an environment which protects against *C. difficile* [50]. Latterly, Seres Therapeutics had an ethanol processed product, VOWST approved. This product only contains spores of Firmicute species and not Bacteroides. Vowst requires a regimen of three-days of four capsules given orally daily after a bowel preparation and the capsules must be taken on an empty stomach.

Both products, although human derived, are screened against 29 pathogens dictated by the FDA. Of note in the older patient population the efficacy of REBYOTA (formerly RBX2660) as a single dose was specifically reported in an ad hoc analysis of a population of >65-year-old patients who had various underlying conditions. These data derived from the PUNCH CD III study of 289 patients of which 71% [126/177] achieved clinical success measured as recurrence free at 8 weeks. This compared with 62% [53/85] who received placebo. When these patients were evaluated by underlying condition, cardiac (69%), kidney (68%) or gastrointestinal (67%) the REBYOTA patients showed better clinical responses than the placebo recipients. Treatment Emergent Adverse Events were reported by 52% (n=94/180) of REBYOTA (RBX2660)-treated participants compared with 44% (n=38/87) of placebo-treated participants. The increased incidence of TEAEs after REBYOTA (RBX2660) treatment was largely due to mild events. 40% of REBYOTA (RBX2660)-treated participants experienced mild events compared with 30% of placebo-treated participants. Serious adverse events (SAEs) were infrequent and reported in a similar percentage of placebo- and REBYOTA (RBX2660)-treated participants [51]. This post hoc subgroup analysis of PUNCH CD3 showed that REBYOTA (RBX2660) is efficacious and safe in a broad range of older adults with rCDI with varying comorbidity burden.

In the ECOSPOR III Seres reported that VOWST had >65-year-old subjects in their study but did not specifically separate these data. The <65year old and >65-year-old subjects responded similarly with an overall efficacy of 88% [52]. There have been no direct comparisons involving the two products as both were deemed efficacious and safe by the FDA. Other aspects of the products should be considered when prescribing an LBP such as ease of delivery single dose without need for a bowel preparation nor need for empty stomach delivery [53, 54], and cost, REBYOTA currently costing $9,500 per course, while VOWST is $17,000 for the 3-day regimen and accessibility [55], both products are readily ordered and delivered to point of need.

Conclusion

Recurrent *C. difficile* infections are a major challenge for long term care facilities with a population which is at risk of multiple recurrences despite standard of care antibiotics. There is a need to adopt a different approach by restoring the gut flora to normal and thereby obviate the conditions for *C. difficile* spores to grow and cause disease. The nursing home setting is a particularly difficult setting due to the proximity of residents, the pressure on nursing staff and the multiple risk factors such as antibiotic and proton pump use being present. LBP's may be an "old/new" approach to managing and reducing recurrence of CDI.

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Conflict of Interest

NT has no disclosures. GT is a consultant to Spero Therapeutics, Ferring Pharmaceuticals and Taro Pharmaceuticals.

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