Clostridioides difficile infection: curbing a difficult menace

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A high incidence and severity of primary and recurrent *Clostridioides difficile* infection (CDI) continue to plague healthcare systems and people worldwide.[1] Prior to the coronavirus disease 2019 (COVID-19) pandemic, CDI was the most common infection seen in hospitals, and to date, it continues to be the most common bacterial infection in hospitals.[2] Targeting CDI by a multimodal approach by understanding its disease course, pathophysiology, appropriate treatment with benefits, and adverse events, health care delivery to be able to effectively administer treatments across care settings is paramount to curb the difficult menace that CDI is.[1]

Therapeutic advances in gastroenterology have solicited and published articles as part of a special collection aiming to focus on the epidemiology, testing, management (antibiotic, antibody treatment, and microbiome-based therapies), the economic burden, and transitions of care aspects related to CDI.

Clinical and epidemiological studies demonstrate a migration of CDI from being a hospital illness to also being a community illness.[2] Fu *et al.*[3] describe the epidemiology of community-acquired and recurrent CDI. The incidence of community-acquired CDI has been increasing with antibiotics being a common risk factor and several patients developing community-acquired CDI without antibiotic exposure suggesting other risk factors in the community such as proton pump inhibitor use, conditions such as inflammatory bowel disease (IBD), and an aging population with comorbidities. In addition, the rates of recurrent infection continue to be high with a trend toward a decrease in the last decade likely owing to advances in treatment modalities.[3] Most recurrences happen within 8 weeks and delayed recurrences can be seen. The actual impact of the COVID-19 pandemic on the incidence of CDI needs to be completely determined with larger population-based studies.[3] Gupta *et al.* outline the economic burden of CDI suggesting that CDI adds from 3 to 20 days to a hospitalization with an additional cost of over five billion dollars annually in the United States and similar high expenses worldwide.

Germane to the pathogenesis of CDI is a disruption of the gut microbiome owing to risk factor exposure. Sehgal *et al.*[4] outline the relationship between the gut microbiome and primary as well as recurrent CDI. The gut microbiome has a stable composition in healthy adults with risk factors for CDI (mentioned above) leading to a disruption of the colonization resistance conferred by a diverse microbiome. A disruption in the colonization resistance leads to colonization with and proliferation of the *C. difficile* bacterium causing disease.[4] Interestingly, the presence of *C. difficile* by itself leads to microbial dysbiosis. Prevention and correction of microbial dysbiosis have implications in CDI management with microbiome restoration.[5] Fettucciari *et al.*[6] describe the role of the spore form, the life cycle of the spore to the vegetative form, and the role of *C. difficile* toxins in its pathogenesis. Sehgal *et al.*[7] also review a high-risk patient population, those with IBD and the pathogenesis, diagnosis, and outcomes of CDI in those with underlying IBD. Those with underlying IBD are at a high risk of CDI and have higher rates of recurrent infections. In addition, there is a high risk of complications including IBD flares, IBD treatment nonresponse, and surgery.

Another important aspect of CDI pathogenesis is the role of bile acids. Mullish and Allegretti[8]

outline bile acids as a key metabolite of the gut microbiome and review the association of changes between bile acid composition and CDI. Alterations in the gut microbiome lead to changes in bile acid metabolism, resulting in an altered gut bile acid milieu, an enrichment of primary bile acids, and a depletion of secondary bile acids, leading to the pathogenesis of an active infection causing colitis and also recurrent infections.[8,9] Reversing these alterations has been associated with treatment success with newer microbiome-based therapies.[5]

The treatment guidelines for management of CDI have changes over the last three decades. Chaar and Feuerstadt[10] review the evolution of clinical guidelines for antimicrobial management of CDI including initial guidelines from the 1990s, a second wave from 2009 up to 2013, and a modern era of treatment guidelines from 2014 to date. Initial guidelines recommended metronidazole as a preferred treatment which changed to vancomycin owing to high failure rates with metronidazole. Vancomycin was chosen as a preferred treatment in the second wave of guidelines, especially for severe CDI. In the modern iteration of the guidelines, fidaxomicin is preferred over vancomycin owing to sustained treatment success with fewer recurrences. Vancomycin taper and pulse regimens are recommended for recurrent infections, and there is an emphasis on immune-enhancing regimens such as bezlotoxumab and microbiome restoration. Treatment options are nuanced based on risk factors for recurrence.10 The emphasis on metronidazole and rifaximin continues to decrease.

An immunosenescence state is associated with development of primary and recurrent CDI with age greater than 65 years being a risk factor. An enhanced humoral immune response against the *C. difficile* toxins has been shown to be protective against recurrent CDI. Sehgal and Khanna11 review the relationship between this decreased immune response and CDI outcomes and how this has been translated to therapy for patients. Bezlotoxumab is a monoclonal antibody against toxin B and when given in conjunction with antibiotics for CDI, reduces the risk of recurrence. This benefit is seen in patients with one or more high-risk factors for recurrence: age >65 years; immunocompromised state; history of CDI in the last 6 months, or presence of severe CDI.[11]

Sandhu and Chopra[5] review the clinical success from and challenges with fecal microbiota transplantation (FMT), a commonly used treatment modality to prevent recurrent CDI. This is a 2-pronged approach to effectively break the cycle of recurrent CDI. The risk of recurrent CDI is greater than 50–60% after three or more episodes despite guideline-based antibiotic therapy. Microbiome restoration with FMT achieves high cure rates, but the practice is heterogeneous and there have been adverse events noted with infection transmission as outlined. In addition, Yadav and Khanna[12] outline the safety of FMT for CDI focusing on pathobionts and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Common adverse events are mostly gastrointestinal in nature with high rates of diarrhea and postinfection irritable bowel syndrome.[13] While FMT is generally safe, it is dependent on donor screening for existing and emerging pathogens and staying ahead of emerging threats such as COVID-19.[14] Microbiome restoration with FMT has been successfully performed during the COVID-19 pandemic with careful donor screening.[15]

Gupta and Ananthakrishnan[16] also present the cost-effectiveness of different treatment modalities for CDI. It appears based on modeling studies that fidaxomicin may be the most cost-effective treatment strategy for an initial episode of nonsevere CDI and vancomycin for severe CDI, and fidaxomicin for a first recurrence and antibiotics followed by FMT for any subsequent episodes. The delivery of healthcare appropriately to patients is influenced by the transitions of care for these patients as they move in between care settings such as outpatient settings, emergency rooms, acute care, and long-term care settings.[17] The importance of aspects of transitions of care including communication, accountability, system barriers, barriers in knowledge, and training all impacts appropriate transitions of care in this vulnerable patient population. Involvement of a transition team to oversee these transitions and avoiding barriers has the potential to improve care of patients with CDI.

Author contributions

Sahil Khanna: Conceptualization; Supervision; Writing – original draft; Writing – review & editing.

Ryan Pardi: Data curation; Writing – original draft; Writing – review & editing.

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