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Scientific Comment

Clostridium difficile infection is a frequent but well-controlled event after hematopoietic cell transplantation[☆]



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Clostridium difficile infection (CDI) is the most common cause of nosocomial diarrhea and represents a frequent and important source of gastrointestinal morbidity after hematopoietic stem cell transplantation (HSCT). Patients undergoing HSCT have several risk factors for the development of CDI, including multiple prior hospitalizations, frequent use of wide spectrum antibiotics, disease- and treatment-related immunosuppression and mucosal barrier disruption secondary to conditioning regimens, particularly when they are myeloablative or include total body irradiation. Consequently, patients undergoing HSCT have an incidence of CDI that is higher than the general hospitalized population; it is as high as 15–30% after allogeneic HSCT.¹

The majority of reports of CDI in HSCT patients originate from transplant centers located in developed countries. The manuscript by Pilcante et al.² is the first report of the incidence, risk factors and outcomes of CDI in patients undergoing HSCT in an academic medical center in Chile.

The results presented are compatible with other reports, confirming the global importance of CDI in HSCT patients. When compared to previous reports, the incidence of CDI observed in this study appears to be in the lower portion of the reported spectrum, possibly as a result of multiple factors, including antibiotic use patterns, cultural dietary habits, and possibly the degree of *C. difficile* colonization affecting the general hospitalized patient population of Chile. Recent reports by Kinnebrew³ and Bruminhent⁴ show high rates of colonization by *C. difficile* at the time of admission

for the HSCT procedure in two US centers. Development of CDI was preceded by colonization, with rare cases of CDI developing in patients without previous colonization. It is possible that lower colonization rates at admission were the main determinant for a lower incidence of CDI in Chilean patients undergoing HSCT. As in other publications, the majority of CDI cases occurred early in the transplant period, with 40% of cases occurring within the first seven days. However, the median time to CDI was longer than other studies, suggesting that late infections had a larger effect in this cohort. Again, prior hospitalizations, antibiotic use patterns and the rate of colonization may have had an impact on these results.

While previous studies have observed an association of CDI with the development of acute GVHD (aGVHD), and increased risk of gastrointestinal aGVHD,⁵ this finding has not been consistent. It has been postulated that CDI may represent the initial insult that stimulates the immune response against the gastrointestinal tract. However, the higher rate of aGVHD could have occurred due to increased testing in patients with CDI as part of the clinical evaluation of diarrhea in the post-transplant setting. Moreover, patients with aGVHD require frequent hospitalizations and have increased risk of infectious complications and antibiotic use. In a recent study, Guddati et al. reported that patients with GVHD had a higher rate of *C. difficile* colonization in post-engraftment hospitalizations,⁶ likely as a result of the increased need for medical interventions and inpatient care.

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[☆] See paper by Pilcante et al. on pages 388–94.

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The association observed between CDI and longer time to neutrophil engraftment in allogeneic HSCT observed in the study by Pilcante et al. needs to be interpreted with caution.² One previous study identified the use of umbilical cord blood grafts as a risk factor for CDI, likely as a result of their slower engraftment.⁷ However, the presence of a correlation between CDI and delayed engraftment is not sufficient to establish a causal relationship. The reverse causation could be possible (delayed engraftment causing increase in CDI) or both CDI and slower engraftment could be the result of other risk factors (i.e. intensity of conditioning chemotherapy, myelosuppressive antibiotics, prior bone marrow damage or immunosuppression, etc.). Subsequent studies should focus on the specific sequence of events and the presence or other clinical and laboratory risk factors for delayed engraftment.

Diarrheal illness is a common event in the post HSCT period, and CDI should be considered high in the differential diagnosis. While earlier literature suggested that CDI in HSCT recipients was more severe and was associated with increased non-relapse mortality,⁸ recent retrospective analyses suggest that the majority of cases of CDI are mild to moderate and respond well to antibiotic therapy.^{5,9} The outcomes reported by Pilcante et al. confirm that most patients experience mild diarrheal illness that responds to a single course of antibiotics.² Moreover, transplant outcomes and overall survival do not appear to be affected by the incidence of CDI. These and other results suggest that while CDI is common after HSCT, it is rarely a life-threatening event. Over the last decade, heightened awareness, improved testing methods and early treatment of CDI in HSCT recipients have contributed to a reduction in the severity of the diarrheal illness associated thereby limiting its impact on post-transplant outcomes.

Conflicts of interest

The author declares no conflicts of interest.

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