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EDITORIAL ARTICLE

Impact of *Clostridioides Difficile* Infection on Stem Cell Transplant Outcomes – Practical Considerations for Prevention and Treatment

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Introduction

Hematopoietic stem cell transplantation (HSCT) has transformed outcomes for patients with hematologic malignancies, offering a curative path where few options exist. Yet, this life-saving procedure brings profound vulnerability—most notably, a heightened risk of infectious complications. Among these, *Clostridioides difficile* infection (CDI) stands out as a formidable threat, with reported incidence rates reaching up to 34% among allogeneic HSCT recipients[1]. In a recent Center for International Blood and Marrow Transplant Research registry study that examined 826 patients transplanted between 2013 and 2018, Ramanathan et al reported a cumulative incidence of CDI by day 100 of 18.7% (99% CI: 15-22.7%) and 10.2% (99% CI: 9.2-11.1%) in pediatric and adult patients, respectively. CDI was associated with inferior overall survival (OS) ($p = 0.0018$) and a 2.58-fold [99% CI: 1.43-4.66; $p < 0.001$] increase in infection-related mortality (IRM)[2]. Driven by the combination of broad-spectrum antibiotic use and immunosuppression, the increased incidence of CDI disrupts recovery from transplant, prolongs hospitalization, and contributes to serious complications like graft-versus-host disease (GVHD) and infection-related mortality. IRM increased to more than fourfold when a combination of CDI and GVHD were considered in the study[2]. CDI has been shown by several studies to be associated with worse clinical outcomes after allogeneic transplant and warrants a dynamic, evidence-based approach to prevention and treatment. In this editorial, we explore the impact of CDI in transplant recipients and critically examine current and emerging prevention and treatment strategies, recognizing that CDI is associated with increased morbidity and mortality in addition to greater health care costs. We evaluate best-practice interventions such as antimicrobial stewardship, oral vancomycin prophylaxis, fecal microbiota transplant (FMT), and treatment strategies that incorporate oral vancomycin and fidaxomicin. The editorial underscores the necessity for evidence based multifaceted strategies to mitigate the burden of CDI in transplant recipients and improve patient outcomes.

Detrimental Impact of *Clostridioides Difficile* Infection on HSCT Outcomes

The detrimental impact of *Clostridioides difficile* infection on allogeneic transplant outcomes is increasingly recognized, extending beyond a self-limited diarrheal illness to influencing recovery trajectories and long-term prognosis. One of the most concerning associations is the link between CDI and the subsequent development of acute graft-versus-host disease (GVHD), particularly the gastrointestinal type. Multiple studies have demonstrated that CDI is associated with up to a two-fold increased risk of grade II-IV acute GVHD, implicating a complex interplay between gut microbiota disruption and immune dysregulation in the immunocompromised host[2,3]. Beyond immunologic sequelae, CDI contributes to prolonged hospitalization and increased healthcare costs[4,5]. Although often self-limited, CDI can result in serious complications such as toxic megacolon, intestinal perforation, that warrant surgical intervention. While the direct relationship between CDI and overall survival or infection-related mortality remains a subject of ongoing investigation, emerging data suggest a potentially damaging impact[2,5]. Significantly, the challenge of disentangling CDI from other post-transplant complications such as GVHD, limits causal inference; nonetheless, there is no doubt that CDI contributes to increased morbidity and complicates the transplant course[5,6].

Antimicrobial Stewardship

Given the substantial burden of *Clostridiodes difficile* infection in allo-transplant recipients, prevention strategies have become an essential part of supportive care. One approach that is gaining favorability is the early de-escalation of broad-spectrum antibiotics to reduce the risk of CDI[7,8]. The underlying rationale is to minimize disruption of the intestinal microbiota, thereby reducing the susceptibility to C. difficile colonization and infection. European guidelines now recommend narrowing antibiotic coverage after 48 hours in clinically stable patients without documented infection, reflecting

a shift toward microbiome-preserving antimicrobial stewardship[9]. Studies have shown that, when implemented with appropriate safeguards, early de-escalation of antibiotics reduces CDI incidence without increasing the risk of recurrent fever or serious bacterial infection in HSCT patients[7,10]. Still, there are important limitations to consider. Premature or unsupported de-escalation may delay treatment of occult infections, potentially resulting in adverse patient outcomes. Therefore, practical application of this strategy relies on careful patient selection, close clinical surveillance, and access to timely diagnostic tools. While not universally applicable, shortened antibiotic course in well-selected patients offers a practical, microbiome-conscious strategy for mitigating CDI risk in the transplant setting.

Prophylactic Use of Oral Vancomycin

In addition to antibiotic management, the prophylactic use of oral vancomycin has emerged as a potential strategy to reduce *Clostridioides difficile* infection in autologous and allogeneic transplant recipients[11,12]. Given the high incidence and morbidity of CDI in this population, expanding the resources for prevention remains a priority. Oral vancomycin is an effective drug due to its minimal systemic absorption and favorable safety profile, which lowers the concerns of systemic toxicity. In a recent multicenter observational study, a significant reduction in CDI incidence was shown among allo-HSCT recipients receiving oral vancomycin prophylaxis, with a 23.6% incidence of CDI in the control group versus 1.4% in the prophylaxis group[11]. These findings suggest that oral vancomycin may serve as a valuable adjunct to existing infection prevention protocols. However, broader implementation requires careful consideration. The most pressing concern is the potential emergence of vancomycin-resistant Enterococci, which may complicate future infection management[13]. Although preliminary data are promising, robust evidence from large randomized controlled trials is needed to confirm efficacy, optimize dosing strategies, and identify patient subgroups that are likely to benefit from this strategy. Until such data are available, the use of oral vancomycin should remain individualized and guided by institutional epidemiology and risk-stratification guidelines.

Prophylactic Fecal Microbiota Transplantation Pre-transplant

Another emerging strategy for *Clostridiodes difficile* infection prevention in high-risk transplant recipients is the use of fecal microbiota transplantation before transplant[14]. This approach is grounded in growing evidence that disruption of the gut microbiome plays a key role in susceptibility to CDI and other post-transplant complications, including bloodstream infections[2,15]. Pre-transplant FMT aims to restore intestinal microbial diversity and reduce susceptibility to *C. difficile* colonization by re-introducing a balanced and resilient microbial community. Although FMT is FDA-approved for recurrent CDI[16], its prophylactic use in the HSCT setting remains investigational. In a single-arm pilot study of 25 allo-HSCT recipients, it was demonstrated that oral FMT capsules given after conditioning led to partial restoration of gut microbial diversity within two weeks; however, only two cases of CDI were observed in the post-transplant setting, limiting definitive conclusions[17]. Importantly, long-term outcomes, optimal timing pre-transplant, and ideal delivery route (oral, enema) have not been established[18]. Therefore, clinical evidence supporting its pre-transplant prophylactic use is still limited, and broader implementation of FMT faces several practical challenges. Most importantly, there are safety concerns that exist for the immunocompromised state of HSCT recipients, particularly in terms of the risk of transmitting infections through donor fecal material[18]. As a result, any consideration of FMT for transplant patients must be approached with rigorous screening protocols and careful patient selection.

First Line *Clostridioides Difficile* Infection Treatment

When *Clostridiodes difficile* infection occurs in transplant recipients, an effective first-line treatment is essential in reducing morbidity and preventing recurrence. In this high-risk population, oral vancomycin and fidaxomicin are generally preferred over

metronidazole due to their higher efficacy and lower recurrence rates[16]. In a multicenter retrospective study of 108 allo-HSCT recipients with CDI, metronidazole was associated with a higher treatment failure rate, compared to oral vancomycin (38.2% vs. 6.2%), underscoring vancomycin's role as a more effective first-line agent[3]. Moreover, fidaxomicin, a narrow-spectrum antibiotic with a minimal impact on commensal gut flora, offers additional benefits—particularly in its ability to sustain clinical response and reduce recurrence in high-risk groups such as HSCT recipients[3,20]. However, cost remains a substantial barrier to fidaxomicin use. A standard 10-day course of fidaxomicin can exceed $4300, in comparison to $75 for oral vancomycin, leading many institutions to restrict fidaxomicin use to recurrent or high-risk cases[21]. As a result, the choice of first-line therapy is shaped not only by clinical evidence but also by considering access, affordability, and institutional practice policies.

Fecal Microbiota Transplantation for Recurrent *Clostridioides Difficile* Infection post-transplant

For transplant recipients with recurrent *Clostridioides difficile* infection, especially after neutrophil engraftment and during immunosuppression tapering, fecal microbiota transplantation has emerged as a highly effective treatment option. Recurrent CDI often reflects persistent disruption of the gut microbiome, and FMT serves to restore gut microbial diversity and improve intestinal function[22]. Studies have shown high rates of sustained clinical response following FMT in this setting, with evidence supporting its ability to re-establish microbial balance in the post-transplant gut[15,23]. In multiple case reports, FMT has been associated with improved survival outcomes, demonstrating success rates for resolution of recurrent CDI in post-HSCT recipients[24,25]. Careful patient selection, standardized delivery methods, and comprehensive donor screening remain critical. While infection risk is a valid concern in immunocompromised hosts, this risk declines after neutrophil recovery and tapering of immunosuppressants. When applied under appropriate clinical conditions, FMT offers a microbiome-targeted solution to recurrent CDI, bridging the gap between infection control and restoration of gut homeostasis in HSCT recipients.

Conclusion

In conclusion, *Clostridioides difficile* infection remains a significant and persistent challenge in the context of transplant, associated with increased morbidity, prolonged hospitalization, and worse survival. Its role in triggering overlapping complications such as GVHD that contribute to increased infection-related mortality only heightens the urgency for effective prevention and treatment strategies. A multi-faceted approach is essential. Antimicrobial optimization with appropriate consideration for the early de-escalation of broad-spectrum antibiotics plays a central role in preserving the gut microbiome and limiting the risk of CDI. The use of oral vancomycin/fidaxomicin as CDI prophylaxis is promising, especially for high-risk patients, though further studies are needed to clarify its long-term safety. Fecal microbiota transplantation, both in the setting of transplant and post-transplant, represents a compelling microbiome-targeted strategy with encouraging results. Finally, for treatment, the first-line use of oral vancomycin or fidaxomicin over metronidazole is supported by evidence[16] and should be considered the standard in this vulnerable population. Moving forward, clinical practice should be guided by emerging data, patient-specific risk profiles, and careful integration of novel therapies. Future research must focus on refining these strategies through prospective trials that utilize microbiome-conscious approaches to CDI prevention and management. Ultimately, addressing CDI with evidence-based, patient-centered strategy will be critical to improving outcomes and enhancing the safety of stem cell transplantation.

References:

1. Dubberke ER, Reske KA, Olsen MA, Bommarito KM, Seiler S, Silveira FP, et al. Risk for Clostridium difficile infection after allogeneic hematopoietic cell transplant remains elevated in the postengraftment period. Transplant Direct. 2017;3(4):e145.

2. Ramanathan M, Kim S, He N, Chen M, Hematti P, Abid MB, et al. The incidence and impact of Clostridioides difficile infection on transplant outcomes in acute leukemia and MDS after allogeneic hematopoietic cell transplant-a CIBMTR study. Bone Marrow Transplant. 2023;58(4):360-6.

3. Piekarska A, Sadowska-Klasa A, Mensah-Glanowska P, Sobczyk-Kruszelnicka M, Drozd-Sokołowska J, Waszczuk-Gajda A, et al. Effective treatment of Clostridioides difficile infection improves survival and affects graft-versus-host disease: a multicenter study by the Polish Adult Leukemia Group. Sci Rep. 2024;14(1):5947.

4. Alonso CD, Treadway SB, Hanna DB, Huff CA, Neofytos D, Carroll KC, et al. Epidemiology and outcomes of Clostridium difficile infections in hematopoietic stem cell transplant recipients. Clin Infect Dis. 2012;54(8):1053-63.

5. Shah NN, McClellan W, Flowers CR, Lonial S, Khoury H, Waller EK, et al. Evaluating risk factors for Clostridium difficile infection in stem cell transplant recipients: a national study. Infect Control Hosp Epidemiol. 2017;38(6):651-7.

6. Weber S, Scheich S, Magh A, Wolf S, Enßle JC, Brunnberg U, et al. Impact of Clostridioides difficile infection on the outcome of patients receiving a hematopoietic stem cell transplantation. Int J Infect Dis. 2020;99:428-36.

7. Chen YH, Sun A-E, Narain K, Chang WC, Yang C, Chen PH, et al. Efficacy and safety of early antibiotic de-escalation in febrile neutropenia for patients with hematologic malignancy: a systematic review and meta-analysis. Antimicrob Agents Chemother. 2025;69(4):e0159724.

8. Gustinetti G, Raiola AM, Varaldo R, Galaverna F, Gualandi F, Del Bono V, et al. De-escalation and discontinuation of empirical antibiotic treatment in a cohort of allogeneic hematopoietic stem cell transplantation recipients during the pre-engraftment period. Biol Blood Marrow Transplant. 2018;24(8):1721-6.

9. van Prehn J, Reigadas E, Vogelzang EH, Bouza E, Hristea A, Guery B, et al. European Society of Clinical Microbiology and Infectious Diseases: 2021 update on the treatment guidance document for Clostridioides difficile infection in adults. Clin Microbiol Infect. 2021;27 Suppl 2:S1-s21.

10. Snyder M, Pasikhova Y, Baluch A. Early antimicrobial de-escalation and stewardship in adult hematopoietic stem cell transplantation recipients: retrospective review. Open Forum Infect Dis. 2017;4(4):ofx226.

11. Fusco B, Tomita-Barber J, Mazzaferro N, Tyno A, McEntee N, Greenberg P, et al. Prophylactic vancomycin in the primary prevention of Clostridium difficile in allogeneic stem cell transplant. Transpl Infect Dis. 2025;27(3):e70025.

12. Williams MJ, Atienza S, Franzen E, Rathod H, Mejaki B, Graff J, et al. Evaluation of primary oral vancomycin prophylaxis against Clostridioides difficile infection during autologous stem cell transplantation. Open Forum Infect Dis. 2024;11(11):ofae622.

13. Maraolo AE, Mazzitelli M, Zappulo E, Scotto R, Granata G, Andini R, et al. Oral vancomycin prophylaxis for primary and secondary prevention of Clostridioides difficile infection in patients treated with systemic antibiotic therapy: a systematic review, meta-analysis and trial sequential analysis. Antibiotics (Basel). 2022;11(2).

14. Peery AF, Kelly CR, Kao D, Vaughn BP, Lebwohl B, Singh S, et al. AGA Clinical Practice Guideline on Fecal Microbiota-Based Therapies for Select Gastrointestinal Diseases. Gastroenterology. 2024;166(3):409-34.

15. DeFilipp Z, Hohmann E, Jenq RR, Chen YB. Fecal microbiota transplantation: restoring the injured microbiome after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2019;25(1):e17-e22.

16. Johnson S, Lavergne V, Skinner AM, Gonzales-Luna AJ, Garey KW, Kelly CP, et al. Clinical practice guideline by the Infectious Diseases Society of

America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of Clostridioides difficile infection in adults. Clinical Infectious Diseases. 2021;73(5):e1029-e44.

17. Bilinski J, Grzesiowski P, Sorensen N, Madry K, Muszynski J, Robak K, et al. Fecal microbiota transplantation in patients with blood disorders inhibits gut colonization with antibiotic-resistant bacteria: results of a prospective, single-center study. Clin Infect Dis. 2017;65(3):364-70.

18. Metafuni E, Di Marino L, Giammarco S, Bellesi S, Limongiello MA, Sorà F, et al. The role of fecal microbiota transplantation in the allogeneic stem cell transplant setting. Microorganisms. 2023;11(9).

19. Cammarota G, Ianiro G, Kelly CR, Mullish BH, Allegretti JR, Kassam Z, et al. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. Gut. 2019;68(12):2111-21.

20. Alsoubani M, Chow JK, Rodday AM, Kent D, Snydman DR. Comparative effectiveness of fidaxomicin vs vancomycin in populations with immunocompromising conditions for the treatment of Clostridioides difficile infection: a single-center study. Open Forum Infect Dis. 2024;11(1):ofad622.

21. Jiang Y, Sarpong EM, Sears P, Obi EN. Budget impact analysis of fidaxomicin versus vancomycin for the treatment of Clostridioides difficile infection in the United States. Infect Dis Ther. 2022;11(1):111-26.

22. Habibi S, Rashidi A. Fecal microbiota transplantation in hematopoietic cell transplant and cellular therapy recipients: lessons learned and the path forward. Gut Microbes. 2023;15(1):222 9567.

23. Kaźmierczak-Siedlecka K, Skonieczna-Żydecka K, Biliński J, Roviello G, Iannone LF, Atzeni A, et al. Gut microbiome modulation and faecal microbiota transplantation following allogenic hematopoietic stem cell transplantation. Cancers (Basel). 2021;13(18).

24. de Castro CG, Jr., Ganc AJ, Ganc RL, Petrolli MS, Hamerschlack N. Fecal microbiota transplant after hematopoietic SCT: report of a successful case. Bone Marrow Transplant. 2015;50(1):145.

25. Neemann K, Eichele DD, Smith PW, Bociek R, Akhtari M, Freifeld A. Fecal microbiota transplantation for fulminant Clostridium difficile infection in an allogeneic stem cell transplant patient. Transpl Infect Dis. 2012;14(6):E161-5.

