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STEM CELL TRANSPLANTATION (R MAZIARZ, SECTION EDITOR)

Rethinking Antimicrobial Prophylaxis in the Transplant Patient in the World of Emerging Resistant Organisms—Where Are We Today?

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Abstract

Purpose of Review The use of prophylactic antibiotics during the neutropenic period in hematopoietic stem cell transplantation has been the standard of care at most institutions for the past 20 years. We sought to review the benefits and risks of this practice.

Recent Findings Emerging data has highlighted the potential costs of antibacterial prophylaxis, from selecting for antibiotic resistance to perturbing the microbiome and contributing to increase risk for *Clostridium difficile* and perhaps graft-versus-host-disease, conditions which may lead to poorer outcomes.

Summary Though in many studies prophylactic antibiotics improved morbidity and mortality outcomes, the potential harms including antibiotic resistance, *Clostridium difficile* infection, and alterations of the gut microbiome should be considered. Future studies aimed to better risk-stratify patients and limit the use of broad-spectrum antibiotics are warranted.

Keywords Hematopoietic stem cell transplant (HSCT) · Bone marrow transplant (BMT) · Neutropenia · Antibiotic prophylaxis · Graft-versus-host-disease (GVHD), microbiome

Abbreviations

BMT	Bone marrow transplant
CDI	*Clostridium difficile* infection
GVHD	Graft-versus-host disease
HSCT	Hematopoietic stem cell transplant
FMT	Fecal microbiota transplant

Introduction

Patients undergoing cytotoxic chemotherapy and hematopoietic stem cell transplant (HSCT) are at risk for bacterial infection during the neutropenic period (absolute neutrophil count (ANC) < 500 cells/mm^3) [1]. Fever, defined as an oral temperature ≥ 38.3 °C (101 °F) or temperature sustained for at least 1 h at ≥ 38.0 °C (100.4 °F) [1], occurs in the majority (up to 80%) of patients who are neutropenic after chemotherapy [2]. Bacteremia is identified in at least 16–20% of patients with severe neutropenia (ANC less than 100 cells/mm^3) [3–7, 8•], often leading to septic shock, and multi-organ failure. Bacterial infections are the most prevalent infectious complication occurring in 20–60% of pediatric and adult patients after allogeneic transplant, causing significant morbidity and mortality [9, 10, 11•, 12].

Various efforts to reduce the incidence of such infections have been attempted over the past few decades, and have included isolation [13, 14], gut decontamination [15], use of granulocyte-stimulating growth factors [16], immunization, and administration of oral and intravenous antibiotics during the afebrile neutropenic period [17]. As a result of numerous studies, the use of prophylactic antibiotics during the period of neutropenia occurring after both induction chemotherapy and HCST has become standard of care at most cancer centers. Such a recommendation is endorsed by American Society for Blood and Marrow Transplantation (ASBMT), Infectious Disease Society of America (IDSA), the National Comprehensive Cancer Network (NCCN), and European Society for Blood and Marrow Transplantation (EBMT) guidelines [1, 18, 19•].

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In recent years, there has been an emerging appreciation of antibiotic resistance and the importance of antibiotic stewardship. Recent research has shed light on the role of the microbiome in health and disease including the influence of its perturbation on graft-versus-host disease (GVHD) and transplant outcome [20•, 21•]. Antibiotic use also comes with toxicity, cost, and microbiologic consequences. A closer look at the use of prophylactic antibiotics has led us to a point where the question should be asked: is the risk worth the benefit of prophylactic antibiotics in stem cell transplant patients?

History of Antibiotic Prophylaxis

The relationship between granulocytopenia and infection has been recognized since the 1960s [3] which led to several bacterial infection prevention trials. Early approaches to antibiotic prophylaxis used non-absorbable antibiotics with the intent of suppressing the endogenous microbial flora and preventing acquisition of exogenous flora. Numerous variably controlled studies were published in the 1970s, each with different combinations of oral non-absorbable antibiotics primarily targeting aerobes in neutropenic patients [13, 22–27]. These studies had diverse outcomes, and not all studies supported the use of such a regimen. In addition, many of the regimens, which were often combinations of oral non-absorbable antibiotics including polymyxin, gentamicin, vancomycin, mycostatin, neomycin, or paromomycin, had significant gastrointestinal intolerance leading to poor compliance and potential risk of re-colonization with more pathogenic organisms [22, 28].

A number of studies in the 1970s and 1980s showed that the use of trimethoprim-sulfamethoxazole (TMP-SMX) was an effective alternative to gut sterilization with non-absorbable antibiotics in preventing bacteremia and reducing days of fever. However, several shortcomings were highlighted, including development of resistant bacteremia, hypersensitivity reactions such as drug fever and hepatitis, and potential for prolonging myelosuppression.

In the 1980s and 1990s, fluoroquinolone prophylaxis was extensively studied for efficacy and compared to oral non-absorbable agents or TMP-SMX in neutropenia, and many studies showed utilization was associated with a decrease in gram-negative bacteremia and mortality [29]. Two meta-analyses in the 1990s examined evidence for fluoroquinolones in neutropenia prophylaxis [30, 31]. While these studies concluded that fluoroquinolones were effective in preventing gram-negative bacteremia in the 19 studies assessed by Cruciani et al. [30] and reducing infection-related outcomes in the 18 studies assessed by Engels, et al. [31], neither meta-analysis found a reduction in overall infection-related mortality. However, a 2005 meta-analysis of 95 prophylaxis trials, 52 of which focused on fluoroquinolone prophylaxis, concluded that antibiotic prophylaxis for neutropenia, especially fluoroquinolone prophylaxis, reduced mortality [7]. An updated meta-analysis was performed in 2012 to assess whether the mortality reduction benefit of antibiotic prophylaxis still held true in the era of antibiotic resistance. The authors again concluded that there was mortality reduction with prophylaxis, particularly with fluoroquinolone use, with a relative risk of infection-related death of 0.61 (95% CI 0.48–0.77) [8•]. Two 2005 studies [32, 33] evaluated the efficacy of levofloxacin for neutropenia prophylaxis, given its extended antimicrobial spectrum. The study by Reuter and colleagues demonstrated that levofloxacin had a favorable impact on infection-related mortality in neutropenia [33]. Of note, most of these studies included highly diverse patient populations, including patients with neutropenia associated with treatment of solid tumors, hematologic malignancies, and autologous stem cell transplant, making it difficult to analyze the relative benefits of fluoroquinolone prophylaxis in a specific population, such as in neutropenic stem cell transplant recipients.

Potential Risks of Antibiotic Prophylaxis

Toxicities Associated with Antibiotics No antibiotic is completely benign, or without risks of toxicities or drug interactions. Fluoroquinolones, the most commonly utilized antibiotic class for bacterial prophylaxis in patients with neutropenia, have many risks including drug resistance [34] and serious musculoskeletal side effects including tendonitis and tendon rupture [35, 36]. Furthermore, they have been associated with severe hepatotoxicity, peripheral neuropathy [37], and corrected QT (QTc) prolongation [38–41]. Of significant concern with prolonged fluoroquinolone use, worsened in an immunocompromised population, is the associated increased risk for *Clostridium difficile* infections. In 2016, the FDA issued an enhanced warning about fluoroquinolone risks, an update to the existing black-box warning label for disabling and potential permanent side effects [40, 41].

Considerations for Drug/Drug Interactions Fluoroquinolones have potential for drug-drug interactions, an important consideration for drug safety and efficacy. Concurrent administration of fluoroquinolones with certain cationic-containing agents such as antacids can inhibit the absorption of the antibiotic and significantly decrease the oral bioavailability of fluoroquinolones [42]. In patients taking warfarin, there is significant concern for increased prothrombin times (INR) and associated increased risks for bleeding in patients concurrently initiated on fluoroquinolones [42]. Patients who take fluoroquinolones with steroids have an increased incidence of tendon rupture [43]. Finally, patients may be at additive risk for QTc prolongation if on fluoroquinolones at the same time as other QTc-prolonging agents.

Antibiotic Resistance In the past two decades, the epidemiology of HSCT-related infections has changed significantly. In the 1980s and 1990s, gram-positive organisms caused the majority of infectious bacterial complications; however, in the past decade gram-negative infections have become the predominant infections in many centers [44–46]. Along with this reversal of ratio between gram-positive and gram-negatives, there has been a dramatic increase in multi-drug-resistant bacteria [47•, 48•, 49•, 50•].

Meta-analyses as described above have suggested that using broad-spectrum prophylactic antibiotics decreases mortality in neutropenic HSCT patients; however, the use of such antibiotics has led to the emergence of resistant bacteria. Routine fluoroquinolone use for prophylaxis has been associated with the broad emergence of fluoroquinolone-resistant bacterial isolates. A single-center study reported results encompassing a 9-year period in which fluoroquinolone resistance in gram-negative organisms was observed to increase from 16 to 35% [47•]. A retrospective review of infections in 42 patients undergoing HSCT in 2002 showed that the majority of early post-transplant infections were due to coagulase-negative *staphylococci* (CoNS) and gram-negative bacilli resistant to ciprofloxacin [51]. A 2009 study demonstrated that, in one center, greater than 70% of bacterial isolates were fluoroquinolone-resistant [46]. Additionally, widespread use of fluoroquinolones has also been associated with the emergence and increased incidence of Methicillin-resistant *Staphylococcus aureus* (MRSA) [52], CoNS [53], viridans streptococci such as *Streptococcus mitis* [52], quinolone-resistant gram-positive bacteria [54], and multi-drug resistant (MDR) Enterobacteriaceae [53, 55]. Colonization with multi-drug-resistant organisms (MDRO) has been shown to lead to worse outcomes, including higher non-relapse mortality (NRM) of 25.4 versus 3% ($P < 0.001$) in those patients with MDROs versus the non-colonized patients, respectively [56•]. A recent prospective, intercontinental study from 65 centers assessed gram-negative rod (GNR) resistance in HSCT, reporting that 50% of isolated GNRs were resistant to fluoroquinolones and non-carbapenems, and 18.5% were carbapenem-resistant [57•]. A striking 35.2% of GNRs were multi-drug resistant. As a result of increased resistance to these antibiotics, carbapenems are now widely used for empiric therapy in febrile neutropenia. Consequently, carbapenem-resistant bacteria are now emerging as pathogens as well [58, 59].

Most data on antibiotic resistance patterns in HSCT recipients is from bloodstream infections. Although other infections such as pneumonia and skin infections are common post transplant, often no specific microbiological diagnosis is made and the impact of prophylaxis on drug-resistant infections may be underestimated.

Perturbation of the Microbiome A growing body of research has shown a clear correlation between microbiome diversity and transplant complications that are influenced by exposure to systemic antibiotics. In a longitudinal study of 94 allogeneic-HSCT recipients by Taur and colleagues, loss of microbial diversity and development of microbial domination by Proteobacteria, *Enterococcus* and *Streptococcus* correlated with risk of life-threatening bacteremia [60]. In this study, 11 of 22 patients with bacteremia were shown to have initial intestinal domination of a matching organism (e.g., vancomycin-resistant *Enterococcus*) prior to bacteremia. Diversity loss was correlated with administration of systemic antibiotics, in particular fluoroquinolones, vancomycin, and anti-anaerobic agents.

Multiple studies have demonstrated that decreased microbiota diversity and domination by *Enterococcus* species leads to reduced overall survival [61••, 62]. Metagenomic analysis of stool microbiome shows predominately commensal bacteria at the time of hospital admission, but shifts toward enterococci after transplantation. This shift in microbiome is prominent in patients receiving antibiotics for prophylaxis or treatment, with the biggest shift seen in patients with active gastrointestinal GVHD [63••].

GVHD is a major source of non-relapse-related mortality following allogeneic HSCT and thus limits the overall efficacy of transplantation [21•]. During GVHD, various immune cells are activated and attack target healthy tissues and organs, including the gastrointestinal tract. This leads to systemic exposure of intestinal microbial contents. Patients post-transplant are at particular risk prior to immune reconstitution. Evidence from recent studies suggests that the composition of the gut microbiota also influences the risk for GVHD via microbe-immune cell interactions [21•, 64], and suggests an association between loss of diversity, intestinal inflammation, and GVHD [65–68]. Furthermore, studies have shown that the presence of certain bacteria, such as the anaerobic species *Blautia*, may be associated with reduced GHVD-related mortality and improved overall survival [69], whereas the depletion of other species, such as non-pathogenic clostridial commensal species, is associated with an increase incidence of GVHD [70•].

Clostridium difficile infection (CDI), also associated with perturbation of the microbiome, is a frequent early complication after HSCT, particularly in recipients of myeloablative conditioning. Studies estimate a CDI incidence of 6–27% in the HSCT population [71–73]. A 2017 study identified that intestinal colonization with three bacterial groups, *Bacteroidetes*, *Lachnospiraceae*, and *Ruminococcaceae*, was associated with a 60% lower risk for CDI [74]. Several large retrospective studies of adult HSCT patients have shown that the use of broad-spectrum antibiotics is a risk factor for CDI. Receiving antibiotics in the prior 1 month led to a 53% increased risk of CDI infection [71] with patients typically receiving four different antibiotics [73].

The results of many of these studies imply that while widespread adoption of quinolone prophylaxis may have prevented many infections, it did so at the cost of selecting for more resistant infections as well as leading to perturbations of the gut microbiome which may be associated with an increase in transplant complications. For this reason, the question should be asked: are we at a tipping point where the risk of prophylactic antibiotics in the setting of induction chemotherapy and transplant outweighs the benefits? (Fig. 1a).

Potential Strategies to Minimize the Use and Adverse Consequence of Prophylactic Antibiotics

A number of approaches to minimize prophylactic antibiotic use in transplant patients have been studied. Some centers have made efforts to improve risk stratification of patients with neutropenia in an effort to use antibiotics more wisely. Such strategies have included avoiding prophylaxis in patients on chemotherapy regimens with lower incidence of mucositis [75], reverting to the use of non-absorbable antimicrobials with fewer effects on the gut microbiome (such as rifaximin), omitting fluoroquinolone prophylaxis [76•] and fecal microbiota transplant (FMT) or probiotic use after stem cell transplant in an effort to reconstitute the gut ecology and minimize colonization with multi-drug-resistant pathogens.

Rifaximin may be an effective candidate for gut decontamination because of its broad-spectrum activity with limited intestinal absorption. Recent studies have shown that rifaximin helps maintain commensal gut flora and decrease gut inflammation. One center in Germany replaced standard ciprofloxacin/metronidazole with rifaximin for HSCT prophylaxis [77]. In the retrospective review of 394 patients over a 7-year period, Weber and colleagues showed lower 1-year transplant-related mortality, and improved overall survival

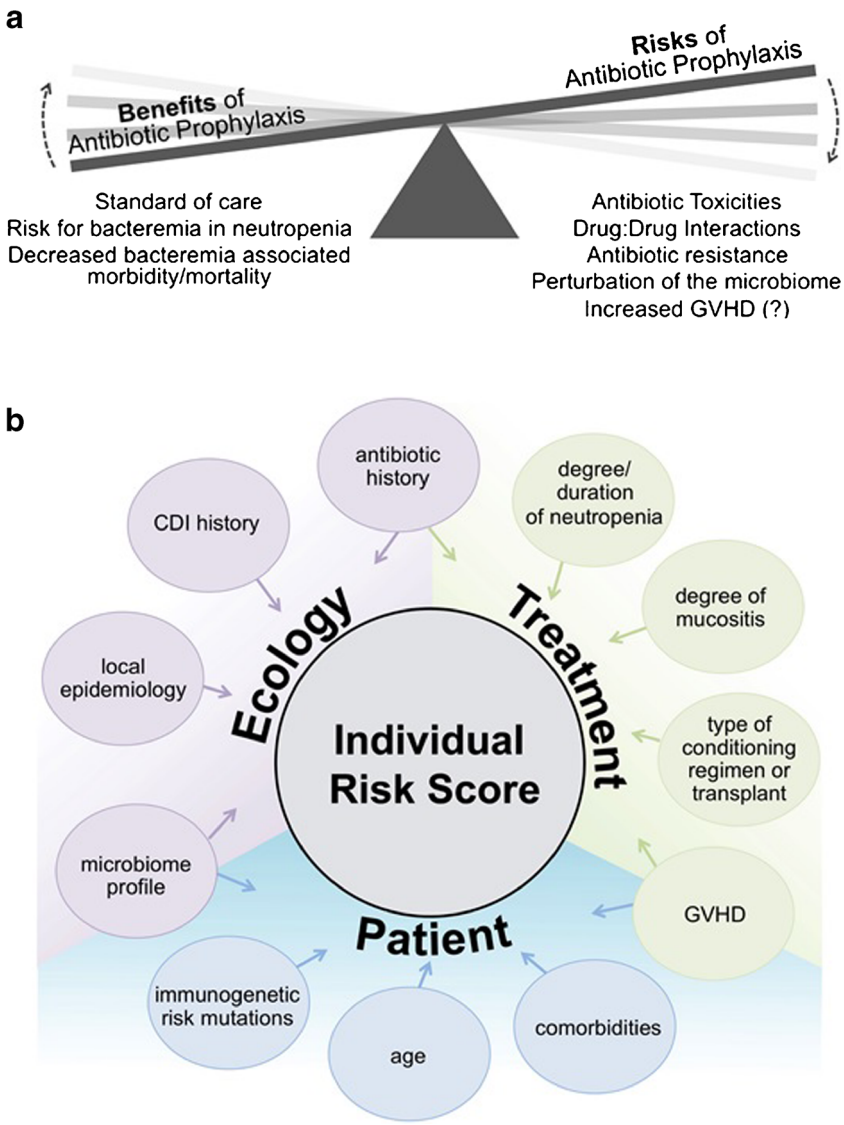

Fig. 1 **a** The benefits and risks of antibiotic prophylaxis in neutropenia. **b** Strategic determination of individual risk using ecological, treatment-related, and patient-specific factors

after this change. Rifaximin use was correlated with lower rates of enterococcus colonization and a more diverse gut microbiome, suggesting its advantage may come from preserving the intestinal microbiota composition.

An attractive model would be to assign an individual risk score to patients to allow clinicians to tailor the strategy of neutropenic prophylaxis. Such a model would take into account risk factors for infection such as the patients' age, comorbid conditions, immunogenetics, and microbiome, and integrate this information with a profile of the hospital microbial ecosystem, yielding an overall individual risk score (Fig. 1b). Although some of these elements are easily accessible with current informatics (i.e., age, comorbid conditions, *Clostridium difficile* infection history, conditioning regimen), others may be more difficult to quantify (i.e., degree of mucositis, degree and duration of neutropenia) and some, such as immunogenetic risk and personal microbiome profile, are not currently easily measurable.

The advent of new microbiological diagnostic tools such as MALDI-TOF allows for specific diagnoses to be made in hours instead of days. Capitalizing on this ability to rapidly identify pathogens could allow for "real-time" analysis and monitoring of patients' bacterial milieu and microbiome for use in predictive modeling for prophylaxis guidance.

Given the link between low microbiome diversity and transplant complications, one approach would be to do microbiome profiling, that is, risk-stratify patients based on microbial diversity of stool samples post transplant into low-, intermediate-, and high-diversity groups. Avoiding broad-spectrum antibiotic use in the lower-diversity groups and using narrower-spectrum antibiotics in the higher-risk groups would help protect diversity.

Multiple studies have now shown that intestinal domination precedes bacteremia [60, 78]. As metagenomic analysis techniques advance to allow rapid and inexpensive testing of clinical samples, we may soon be able to monitor an individual's microbiome in real time and identify adverse changes in diversity. When decreasing diversity and domination of pathogenic bacteria are identified, prophylactic antibiotics could be initiated.

Although this approach is still very new, preliminary microbiome-based models to predict infection risk have shown good prognostic value. In one study, 28 patients with non-Hodgkin's lymphoma had fecal microbiome sampling prior to allogeneic HSCT [79]. Using high-throughput DNA sequencing and machine-learning methods, a risk index was developed to predict post-transplant bloodstream infection incidence with 90% sensitivity and specificity [79].

Another potential method of risk stratification involves genetic risk assessment. Recent evidence suggests that some individual susceptibility to infections is due to genetic polymorphisms. While most of the studies have been done on immunocompetent patients, several polymorphisms in immunomodulatory genes have been associated with increased risk for bacterial infections in HSCT patients [80–82]. Further identification of such genetic markers could be another method to identify high-risk patients and tailor antimicrobial prophylactic therapy accordingly.

We are realizing more and more that infection risks in HSCT are complex and involve interactions between numerous patient, ecological, and treatment factors. To address these emerging challenges in infection risk management, we anticipate in the future taking an updated approach to antimicrobial prophylaxis in this unique population that is tailored to the individual patient.

This targeted approach would involve selecting a prophylactic regimen from a spectrum of options, ranging from no prophylaxis for lower-risk patients to gut decontamination with rifaximin to current fluoroquinolone-based regimens to broad-spectrum regimens for highest-risk patients in the appropriate clinical settings. In the future, it could also incorporate other "prophylactic" strategies including probiotics, FMT from a healthy donor or from the patients' own banked stool, or administration of a cocktail of specific commensal bacteria known to be protective against bloodstream infection. An individualized prophylactic strategy would be dynamic and adjusted to changing needs: a single patient might transition between different prophylaxis regimens based on risk-profile modifications.

Conclusions

Antibiotic prophylaxis in the setting of peri-transplant neutropenia has been a relatively standard approach to bacterial infection prevention in the past 30 years. Emerging data highlights some of the risks of this practice including rising rates of antibiotic resistance and a new understanding of the potentially adverse relationship of antibiotic use with both a restricted microbiome and GVHD. Addressing these issues will require an ongoing reevaluation of the practice of prophylactic antibiotics in neutropenia. While many technologies that would aid us in risk stratification of neutropenic transplant patients are still in the development phase, studies oriented toward improved risk assessment using tools we currently have in our armamentarium such as stratification according to patient characteristics, degree of neutropenia, and comorbidities, and with real-time monitoring are needed in order to safely limit antibiotic prophylaxis use in the stem cell transplant population.

Compliance with Ethical Standards

Conflict of Interest Lucy E. Horton declares no potential conflicts of interest.

Nina M. Haste reports that spouse (Brandon Taylor, PhD) is employed by Novartis.

Randy A. Taplitz is on the advisory board for Merck.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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