

Antibiotic Therapy and Gastrointestinal Graft-Versus-Host Disease in the Allogeneic Stem Cell Transplantation Population

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Purpose: Hematopoietic stem cell transplantation patients undergo rigorous courses of myeloablative chemotherapy that increase vulnerability for infections. Complications can arise in the form of graft-vs.-host disease (GvHD) manifesting in various organs, including the skin, lung, liver, and gastrointestinal (GI) tract. Antibiotic therapy is generally begun in order to prevent further complications from infection but may increase the risk for acute GI GvHD. Studies that investigated antibiotic therapy and the subsequent occurrence of GI GvHD in allogeneic stem cell transplantation (aSCT) patients were reviewed. **Methods:** PubMed, Scopus, and CINAHL databases were utilized. Articles published between January 1, 2009, and December 15, 2019, were included in this review. A total of 1,142 articles were retrieved. Duplicates, reviews, letters to the editors, irrelevant interventions/outcomes, and non-English articles were excluded. Inclusion criteria included individuals who were undergoing an aSCT and received antibiotic therapy. A total of seven articles were included for this review after applying the inclusion and exclusion criteria. **Results:** The use of broad-spectrum antibiotics increased the risk of developing GI GvHD. Stool analysis when available showed a decrease in the diversity of the gut microbiome, which in turn led to the increase in acute GvHD. **Implications:** The increased risk of GvHD may have implications for the standard of care therapy, which includes treatment, for infections during SCTs. Providers will need to weigh the risk vs. benefit of antibiotic therapy and exercise judicious selection of antibiotics prior to engraftment.

Hematopoietic stem cell transplantation (HSCT) is a treatment option for many individuals who have been diagnosed with cancers such as leukemia, lymphoma, and myeloma. In particular, allogeneic stem cell transplantations (aSCTs) may be associated with long-term sequelae that can affect an individual's morbidity and mortality (Palua et al., 2010). Graft-vs.-host disease (GvHD) is a complex condition that often arises in various organs, including the skin, lung, liver, and gastrointestinal (GI) tract, and can lead to devastating outcomes (Sung et al., 2018). Naymagon and colleagues (2017) discussed the cumulative incidence of GI GvHD can be as high as 60%; other risk factors include difference in histocompatibility between donor and recipient, patient age, source of donor cells, conditioning, and prophylaxis regimens used. Gastrointestinal graft-vs.-host disease occurs along the GI tract and can cause chronic diarrhea, malnutrition, and failure to thrive.

Patients undergoing HSCT are often exposed to antibiotics during the course of their treatment for either prophylaxis or therapeutic treatment (e.g., for neutropenic fevers; Egan et al., 2019). While the administration of antibiotics may confer a benefit, such as decreased risk of acquiring infection, antibiotics administered during the SCT process (for prophylaxis or treatment) can disrupt the gut microbiome leading to various complications, such as GI GvHD (Shono et al., 2015). This disruption of the gut microbiome, or dysbiosis, has led to studies that analyzed the effects of antibiotics in the SCT population by examining patient stool after antibiotic therapy. This review appraises these studies in the aSCT population to evaluate the risk for GI GvHD and discuss the implications for overall survival.

METHODS

A literature search was conducted with the assistance of a medical librarian on antibiotic therapy during SCT. The databases utilized were PubMed, Scopus, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). Mesh terms included various combinations of spellings and/or terminology of main terms: “antibiotic therapy,” “graft versus host disease,” and “allogeneic stem cell transplant.” All attempts were made to gather

non-English articles translated into English, but articles were excluded if the English version was not available. Articles published between January 1, 2009, and December 15, 2019, were included in this review. A total of 1,142 articles were initially retrieved. Duplicates, reviews, letters to the editors, irrelevant interventions/outcomes, articles on the pediatric population, and non-English articles were excluded. Inclusion criteria included individuals who were undergoing an aSCT and received antibiotic therapy. A total of seven articles were included for this review after applying the inclusion and exclusion criteria (Figure 1).

RESULTS

The results focus on the time interval during which a patient undergoes conditioning chemotherapy prior to an aSCT infusion (which is termed day 0) and onward (which is delineated by a plus sign, e.g., day +1 means 1 day after the transplantation). During this time period, patients typically receive prophylactic medications along with antibiotic therapy to combat infections (Egan et al., 2019). The term “engraftment” refers to the instance when a patient's absolute neutrophil count is $> 500/\text{mm}^3$ for 3 consecutive days (Sahdev & Abdel-Azim, 2016). The time period prior to engraftment is when the patient is neutropenic and has an increased susceptibility for infection. Fevers during this time of neutropenia are often managed with antibiotic therapy, which varies according to clinician preference. Table 1 summarizes each of the studies included in the review.

Type of Antibiotic Therapy (Including Prophylaxis)

There are no universal standards for first choice antibiotics; however, fluoroquinolones have commonly been used as prophylaxis (Kern et al., 2018). The studies reviewed used a variety of regimens. Three studies addressed the antibiotic regimen as a determinant of intestinal GvHD.

Farowski and colleagues (2018) conducted a prospective cohort study that included 399 patients who underwent an aSCT from January 2007 to April 2013. This study demonstrated that penicillin and carbapenem therapies were individually associated with an increased incidence of intestinal GvHD ($p = .015$ and $p = .001$, respectively) as

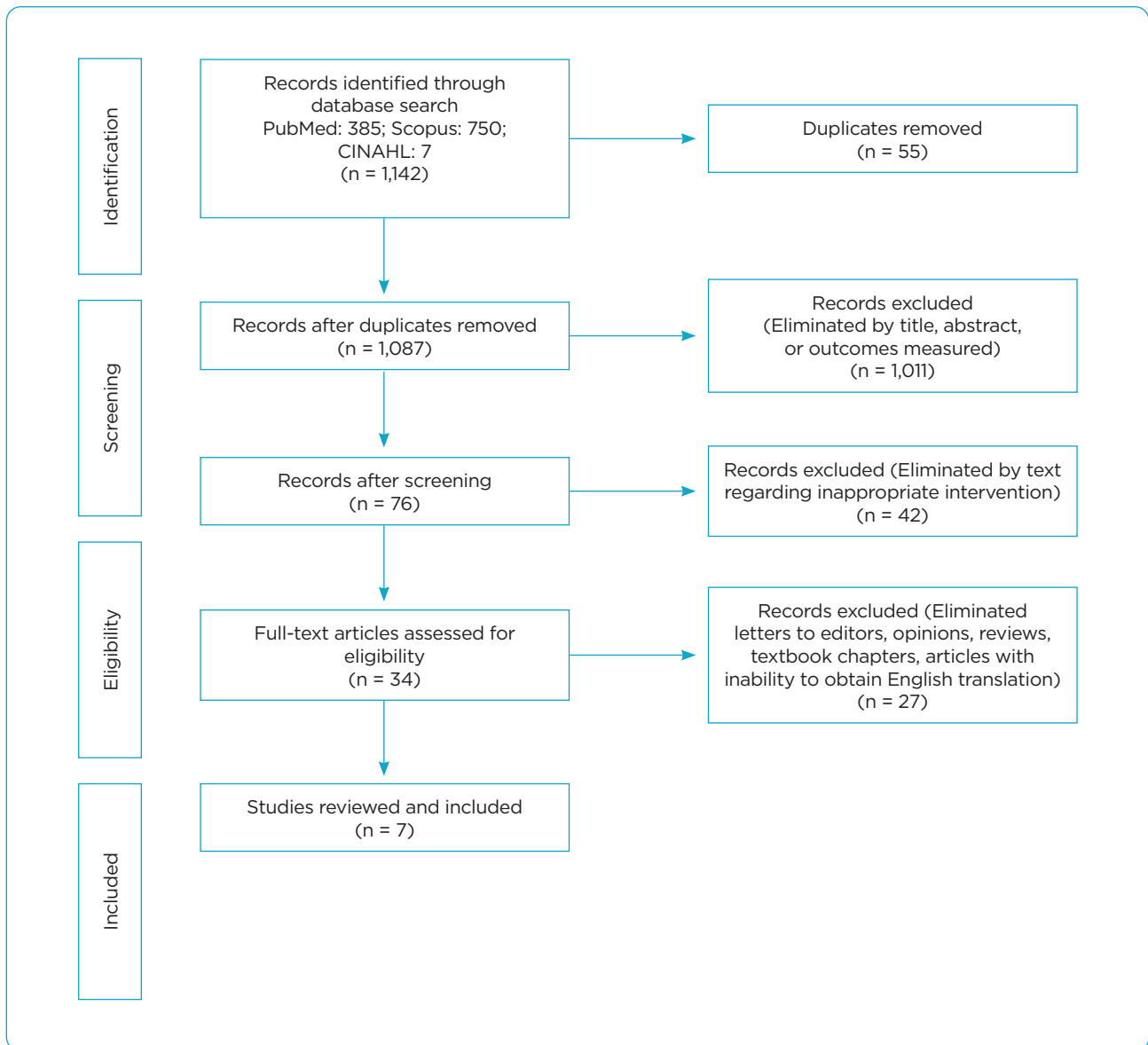


Figure 1. Prisma flow diagram.

compared with glycopeptide or other antibiotics. Further analysis identified that penicillin followed by carbapenem was a greater risk factor for GI GvHD rather than each antibiotic alone ($p = .023$). This sequence of antibiotic administration is contrasted by other studies that grouped findings into classes of antibiotics.

Lee and colleagues (2019) observed a cohort of 211 patients undergoing transplantation in South Korea. This study divided patients into three categories: group 1 had no antibiotics, group 2 had cefepime only, and group 3 had carbapenem antibiotics, which was defined as meropenem or

prepenem with or without previous cefepime. While each group had participants who developed GI GvHD, it occurred mostly in the carbapenem group (32.1%) as compared with the no antibiotics group (11.6%) and the cefepime group (26.4%). These findings were statistically significant ($p = .044$). Out of the 54 individuals who developed intestinal GvHD, 5 (9.3%) did not receive any antibiotics prior to engraftment, 23 (42.6%) received cefepime alone, and 26 (48.1%) were treated with broad-spectrum antibiotics. Lee and colleagues (2019) concluded that the use of broad-spectrum antibiotics such as carbapenem increased GI

Table 1. Evidence Summary

Author	Evidence type	Study details	Study findings	Limitations	Evidence level
Farowski et al., 2018	Prospective cohort study	<ul style="list-style-type: none"> N = 399 Patients from the prospective Cologne Cohort of Neutropenic Patients (CoCoNut) undergoing aSCT from January 2007 to April 2013 	<ul style="list-style-type: none"> Penicillin (HR 1.11; 95% CI = 1.01–1.35; $p = 0.015$) and carbapenem (HR 1.31; 95% CI = 1.25–1.83; $p = .001$) exposure was significantly associated with an increased incidence of iGVHD. Glycopeptide exposure was not associated with iGVHD. The sequence of penicillin derivatives followed by carbapenems was a risk factor for iGVHD rather than the individual components ($p = .023$). 	<ul style="list-style-type: none"> Addition of a microbiome analysis from fecal samples and immunological assessments may improve data. 	Level IV
Han et al., 2019	Prospective study	<ul style="list-style-type: none"> N = 141 Patients undergoing aHSCT Beijing Genomics Institute, Shenzhen, China 	<ul style="list-style-type: none"> Lower microbiota diversity in the aGVHD group compared with the non-aGVHD group at day 0 and day 15 plus or minus 1 ($p = .018$ and $.009$, respectively). Diversity was negatively associated with conditioning intensity ($p = .017$, day 0; $p = .045$, day 15) and β-lactam antibiotic administration ($p = .004$, day 15). 	-	Level IV
Hidaka et al., 2018	Retrospective study on antibiotic use on the incidence of iGVHD occurring before day 100 after aSCT	<ul style="list-style-type: none"> N = 200 Patients who underwent aSCT between January 2010–December 2015 Hokkaido University Hospital, Japan 	<ul style="list-style-type: none"> Antibiotics were classified into carbapenem, quinolone, penicillin, cepem, and glycopeptide. Among 128 patients who developed aGVHD, iGVHD developed in 36 patients. Patients with iGVHD received significantly longer administration of carbapenem and glycopeptide compared with those without it in peri-engraftment period. The use of carbapenem for greater than 7 days was associated with an increased risk of iGVHD. However, use of antibiotics for greater than 7 days was not associated with poor overall survival and high nonrelapse mortality Long use of carbapenem in peri-engraftment period may be a risk for iGVHD. Quinolone included levofloxacin and pazufloxacin. Penicillin included piperacillin-tazobactam and piperacillin. Cepem included cefepime, ceftaxone, and ceftazidime. Glycopeptide included teicoplanin and vancomycin. Oral antibiotics given for febrile neutropenia prophylaxis were also included in this analysis. 	<ul style="list-style-type: none"> Antibiotics used were decided by physician preference. Prospective studies are suggested by the study to confirm the observation that the long use of carbapenem during the peri-engraftment period had an association with the incidence of iGVHD. 	Level IV

Note. aSCT = allogeneic stem cell transplantation; aHSCT = allogeneic hematopoietic stem cell transplantation; iGVHD = intestinal graft-vs.-host disease; aGVHD = acute graft-vs.-host disease; AB = antibiotics; TRM = transplant-related mortality; OS = overall survival.

Table 1. Evidence Summary

Author	Evidence type	Study details	Study findings	Limitations	Evidence level
Lee et al., 2019	Prospective cohort	<ul style="list-style-type: none"> N = 211 Patients undergoing HSCT Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea 	<ul style="list-style-type: none"> Group 1 had no antibiotics during transplant. Group 2 had cefepime only. Group 3 had carbapenem. Intestinal GvHD developed in 54 patients (25.6%), and its occurrence differed according to the use and spectrum of antibiotics (11.6% in group 1 vs. 26.4% in group 2 vs. 32.1% in group 3; $p = .044$). Among the 54 patients with iGVHD, 5 (9.3%) did not receive antibiotics before engraftment, 23 (42.6%) were treated with cefepime alone, and 26 (48.1%) were treated with broad-spectrum antibiotics. 	<ul style="list-style-type: none"> Variance in the timing of stool collection and measurement at only a single point. A larger cohort size may be needed for validation of study. 	Level IV
Shono et al., 2016	Retrospective study from 1992 to 2015	<ul style="list-style-type: none"> N = 857 Patients undergoing aHSCT at Memorial Sloan Kettering Cancer Center from 1992 to 2015 Memorial Sloan Kettering Cancer Center, New York, New York 	<ul style="list-style-type: none"> Treatment of neutropenic fever with imipenem-cilastatin and piperacillin-tazobactam antibiotics was associated with increased GvHD-related mortality at 5 years (21.5% for imipenem-cilastatin-treated patients vs. 13.1% for untreated patients, $p = .025$; 19.8% for piperacillin-tazobactam-treated patients vs. 11.9% for untreated patients, $p = .007$). However, two other antibiotics also used to treat neutropenic fever, aztreonam and cefepime, were not associated with GvHD-related mortality ($p = .78$ and $p = .98$, respectively). 	<ul style="list-style-type: none"> Retrospective, single-center nature of the approach. 	Level IV
Weber et al., 2017	Retrospective study	<ul style="list-style-type: none"> N = 621 A total of 621 adult patients undergoing aSCT in Regensburg, Germany (n = 380) and New York, New York (n = 241) Patients undergoing an aSCT University Medical Center of Regensburg in Germany and Memorial Sloan Kettering Cancer Center in the US 	<ul style="list-style-type: none"> In the Regensburg cohort, it was observed that there was a significantly higher rate of death from severe acute and/or chronic GvHD in the early (23%, 44/190) compared with the late AB (16%, 26/160) and the no AB groups (3%, 1/30; $p = .003$). The same association was seen in the New York cohort: Death from severe acute and/or chronic GvHD was observed in 26% (12/46) in the early, 12% (16/137) in the late, and 5% (3/58) in the no AB groups ($p = .01$). 	<ul style="list-style-type: none"> Prospective trials of antibiotic prophylaxis should be initiated to investigate different strategies or even no gut decontamination aiming at the protection of gut microbiota. 	Level IV
Weber et al., 2019	Retrospective analysis	<ul style="list-style-type: none"> N = 161 Patients undergoing an aSCT 	<ul style="list-style-type: none"> Rifaximin followed by additional systemic antibiotics was associated with differences in clinical outcome variables, such as GI GvHD, TRM, and OS, compared with all other types of systemic antibiotic treatment. This resulted in a lower rate of severe GI GvHD ($p = .05$). 	<ul style="list-style-type: none"> In the setting of aSCT, the composition of intestinal microbiota is influenced by several factors, such as intestinal epithelial damage related to chemotherapy conditioning, parenteral nutrition, and the patient's own eating habits. 	Level IV

Note: aSCT = allogeneic stem cell transplantation; aHSCT = allogeneic hematopoietic stem cell transplantation; iGVHD = intestinal graft-vs.-host disease; aGVHD = acute graft-vs.-host disease; AB = antibiotics; TRM = transplant-related mortality; OS = overall survival.

GvHD as compared with narrow-spectrum antibiotics such as cefepime.

In a retrospective study of 857 aSCT patients treated for neutropenic fever at Memorial Sloan Kettering Cancer Center from 1992 to 2015, Shono and colleagues (2016) reported the effects of antibiotics with two cohorts: those who received antibiotics and those who did not. Grade 2 to 4 GI GvHD (grade 1 = least severe; grade 4 = most severe) occurred more often with piperacillin-tazobactam and imipenem-cilastatin antibiotic treatments as compared with the no antibiotic group ($p = .0167$ and $p = .0165$, respectively). Piperacillin-tazobactam and imipenem-cilastatin were also associated with an increase incidence of both upper ($p = 0.002$ and $p = .045$, respectively) and lower ($p = .019$ and $p = .036$, respectively) GI GvHD.

Length and Timing of Treatment

Timing was addressed by Weber and colleagues (2017) in a retrospective study with two separate cohorts in Germany ($n = 380$) and New York ($n = 241$), with a total of 621 participants. This study reported that early administration of antibiotics affected rates of death from GvHD. Early antibiotic exposure was defined as day -7 to day 0 (day 0 = infusion of stem cells). Late antibiotic exposure was defined as subsequent days after the infusion indicated by a "+". Three groups were analyzed: group 1 had early exposure ($n = 236$ or 38%), group 2 had exposure to antibiotics from day of infusion (day 0) onwards ($n = 297$ or 48%), and group 3 had no systemic antibiotic treatment throughout the course of their SCT other than prophylactic medications ($n = 88$ or 14%). Both New York and German cohorts experienced higher rates of death from severe acute and/or chronic GvHD with early antibiotic therapy in Germany (33%, $p = .003$) and in New York (37%, $p = .01$) as compared with groups 2 and 3.

Length of treatment was addressed by Hidaka and colleagues (2018) in a retrospective study ($n = 200$) that examined the length of antibiotic administration in patients who underwent an aSCT and developed GI GvHD before day 100 after the aSCT. Antibiotics were classified as carbapenem, quinolone, penicillin, cephem, and glycopeptides. Hidaka and colleagues evaluated the association of GI GvHD and antibiotic therapy in 10-day in-

tervals based on antibiotic usage: day -7 to day +2, day 0 to day +9, and for 10 days up until 3 days after engraftment. In this study, 128 patients developed acute GvHD, and among those, 36 developed GI GvHD. While Hidaka found no differences in antibiotic treatments between patients with and without GI GvHD between day -7 and day +2 and day 0 and day +9, patients with GI GvHD received longer treatments of carbapenem ($p = .045$) and glycopeptides ($p = .004$). In a multivariate analysis, use of carbapenem for greater than 7 days was associated with an increased risk of GI GvHD ($p = .012$); however, extended use of carbapenem did not adversely affect overall survival or mortality.

Gut Diversity

Han and colleagues (2019) conducted a prospective study ($n = 141$) with aSCT patients to study the effects of antibiotics on the microbiome of the gut. Stool and blood samples were collected between day 0 and day 15 to evaluate for gut diversity, and GvHD was evaluated by a retrospective review of the patients' charts. Han and colleagues (2019) reported that gut diversity at day 0 was lower in the acute GvHD group as opposed to the non-acute GvHD group ($p = .018$). The study found that patients who developed acute GvHD had decreased *Lachnospiraceae* (family of *Clostridiales*). By day 15, gut diversity continued to be lower compared with the group without acute GvHD ($p = .005$).

In the antibiotic comparison cohort in Korea, Lee and colleagues (2019) showed a significant decrease in commensal bacteria with patients given carbapenem ($p < .05$). To show the relationship between gut diversity and GI GvHD, the patients were divided into 2 groups: a GI GvHD group ($n = 10$) and no GI GvHD group ($n = 11$). The group without GI GvHD showed no significance difference in pre- or post-SCT gut diversity ($p = .332$). The group with GI GvHD showed a statistically significant ($p = .001$) reduction in gut diversity before and after SCT after antibiotic exposure.

Effect on Mortality

Mortality outcomes as a result of the development of severe GvHD were an additional finding from this review. In a 13-year study at Memorial Sloan Kettering Cancer Center, Shono and colleagues (2016) demonstrated that patients who were

treated with imipenem-cilastatin (21.5%; $p = .025$) and piperacillin-tazobactam (19.8%; $p = .007$) antibiotics during periods of neutropenic fevers were at increased risk of GvHD-associated mortality at 5 years as opposed to those patients treated with aztreonam ($p = .78$) and cefepime ($p = .98$). The New York/Regensburg study by Weber and colleagues (2017) indicated that overall survival decreased when antibiotics were given early vs. late. In the Regensburg cohort, 23% (44/190) died from GvHD as compared with 16% (26/160) with late antibiotics and 3% (1/30; $p = .003$) with no antibiotic administration. In the New York cohort, 25% (12/46) died from early antibiotic administration, 12% (16/137) in the late administration group, and 5% (3/58) in the group without antibiotics ($p = .01$). Hidaka and colleagues' study showed the use of antibiotics greater than 7 days did not have an association with overall survival. Lee and colleagues (2019) showed that a longer duration of antibiotic therapy was associated with notable outcomes (although not statistically significant), such as higher transplantation-related mortality ($p < .001$), lower rate of relapse ($p = .022$), greater tendency of GI GvHD ($p = .08$), and lower overall survival ($p = .08$). Weber and colleagues (2019) demonstrated that imipenem-cilastatin and piperacillin-tazobactam led to the dysbiosis of the microbiome composition, resulting in an increased GvHD-related mortality rate vs. the administration of aztreonam or cefepime (limited-spectrum antibiotics), which was not associated with GvHD-related mortality.

DISCUSSION

Type of Antibiotic Therapy

It has been a long-standing practice to prescribe broad-spectrum antibiotics in SCT patients for prophylaxis and during times of suspected infection. The potential effects of this practice have shown to increase risk associated with the development of GI GvHD. More specifically, Farowski and colleagues (2018) showed the increased risk of GI GvHD with penicillin followed by carbapenem was an independent risk factor for GI GvHD, while Lee and colleagues (2019) attributed an increased incidence in GI GvHD to carbapenem antibiotics (meropenem or prepenem). Shono and colleagues (2016) also showed an increased incidence in GI GvHD with the use

of piperacillin-tazobactam and imipenem-cilastatin antibiotic treatments.

These studies agree that broad-spectrum antibiotics are the likely source of risk associated with GI GvHD. Antibiotics with broad-spectrum activity have a greater propensity for disrupting the gut microbiome, allowing harmful gut bacteria to blossom and increasing the risk of acute GI GvHD (Han et al., 2019; Lee et al., 2019). Limited-spectrum activity antibiotics, such as aztreonam or cefepime, are not associated with GI GvHD-related mortality, likely due to the sparing of commensal GI bacteria (Shono et al., 2016). One such example is seen in the study conducted by Holler and colleagues (2014), where microbiome shifts occurred during periods of antibiotic treatment and were more pronounced when associated with GI GvHD. While antibiotics are necessary in the aSCT population due to neutropenic fevers, it may be beneficial to be selective so that further complications do not arise from the development of GI GvHD.

Length and Timing of Treatment

The length and timing of antibiotic treatment also correlates with the risk of GI GvHD and adverse outcomes. In the studies reviewed, the longer the duration of therapy, the greater the risk of developing GI GvHD. This effect is likely due to the depletion of the gut microbiome from prolonged antibiotic exposure (Holler et al., 2014). This is consistent with findings by Weber and colleagues (2017), which showed that early antibiotic exposure had higher rates of death from severe acute and/or chronic GvHD. While Hidaka and colleagues (2018) did not observe carbapenem to affect overall survival, use of carbapenem for greater than 7 days did increase the risk of GI GvHD.

Gut Diversity

It has been suggested that a decrease in the diversity of the gut microbiota is a contributing factor in the development of GI GvHD (Kolb et al., 2018). There are certain bacterial species that have characteristics beneficial to the gut, while others cause harm if given the opportunity. Findings from Han and colleagues (2019) and Lee and colleagues (2019) indicate the decrease in overall gut diversity as a result of the depleted gut microbiome af-

ter antibiotic therapy subsequently increases the risk of acute GI GvHD. Specifically, Han and colleagues (2019) discussed how patients who developed acute GvHD had decreased *Lachnospiraceae*. Specific changes in intestinal microbiota composition were also observed by Lee and colleagues (2019) who noted the use of carbapenem led to an overgrowth of *Melissococcus* and *Anaerotruncus*. These organisms are likely disadvantageous to the gut microbiome given the increased risk of GI GvHD in the carbapenem group. While the study of the gut microbiome is an ever-growing field, there are other bacteria that have been shown to be beneficial. Jenq and colleagues (2015) studied the genus *Blautia* in depth and showed that it too was associated with improved overall survival and a decrease in the severity of GvHD. There is also evidence to suggest that a transplant donor's gut diversity may influence the incidence of GvHD in a recipient (Liu et al., 2017).

Effect on Mortality

The mortality outcomes from the development of severe GvHD in SCT patients were an additional finding from this review. The findings parallel those related to the development of GI GvHD and can be attributed to the same causes: the choice and timing of antibiotics, duration of therapy, and depletion of the gut microbiome.

Limitations

This article is aimed to help the advanced practitioner with understanding the potential effects of antibiotic use in the setting of aSCT. This review did not delineate between different types of transplantations, that is, haploidentical, cord, matched unrelated/related donor, etc. As previously mentioned, there are other risk factors associated with an increased risk of GI GvHD, such as difference in histocompatibility between donor and recipient, patient age, source of donor cells, and conditioning regimens used that were not the area of focus and could benefit from future studies.

CONCLUSION AND IMPLICATIONS FOR PRACTICE

Gastrointestinal graft-vs.-host disease in the aSCT population can be detrimental. The microbiome disruption caused by the administration of antibi-

otic therapy, more so broad-spectrum antibiotics, has been shown to lead to an increase in acute GI GvHD as well as GvHD-associated mortality. This review highlighted the associations between antibiotic therapy and GI GvHD in aSCT patients. The studies in this review present evidence to suggest antibiotic therapy increases the risk of acute GI GvHD, and the timing and duration of antibiotic therapy can also contribute to the risk of and mortality associated with acute GI GvHD.

Judicious use of antibiotics is suggested; however, the restrictive usage of antibiotics during neutropenic fevers may lead to sepsis or death. Therefore, the risks and benefits of early antibiotic therapy must be weighed. Pillinger and colleagues (2020) reviewed studies looking at de-escalation of broad-spectrum antibiotics in cancer patients with febrile neutropenia and fever of unknown origin and found evidence supporting de-escalation without differences in recurrent fever. Furthermore, the gut microbiome is vast and warrants further studies to examine, on a larger scale, how antibiotics can influence various species that may harm the existing gut flora leading to GI GvHD. Other areas of exploration that may be beneficial include the effects of fecal transplants improving the gut microbiome in GI GvHD patients and the effects of nutrition improving gut diversity during the transplantation process. ●

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Disclosure

The authors have no conflicts of interest to disclose.

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