Received: 8 July 2020 | Revised: 13 November 2020 | Accepted: 16 November 2020

DOI: 10.1111/ctr.14172

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research
WILEY

REVIEW ARTICLE

Infectious complications in allogeneic hematopoietic cell transplant recipients: Review of transplant-related risk factors and current state of prophylaxis

Mobil Akhmedov

Department of Bone Marrow Transplantation, National Hematology Research Center, Moscow, Russian Federation

Correspondence
Mobil Akhmedov, MD, Department of Bone Marrow Transplantation, National Hematology Research Center, Noviy Zykovskiy proezd 4A, Moscow 125167, Russian Federation.
Email: mobilakhmedov@gmail.com

Abstract

Allogeneic hematopoietic cell transplantation is a complex procedure that carries a significant risk of complications. Infections are among the most common of them. Several direct factors such as neutropenia, hypogammaglobulinemia, lymphopenia, mucosal barrier injury, and graft-versus-host disease have been shown to be associated with increased infectious risk post-transplant. Apart from direct factors, there are also indirect transplant-related factors that are the primary trigger to the formers' development. The most important of them are type of preparative regimen, graft source, donor type, graft-versus-host disease prophylaxis, and graft manipulation techniques. In this review, an attempt has been made to summarize the role of the transplant-related factors in the development of infectious complications and provide evidence underlying the current concept of infectious disease prophylaxis in patients after allogeneic hematopoietic cell transplantation.

KEYWORDS
allogeneic hematopoietic cell transplantation, infections, prophylaxis, risk factors

1 | INTRODUCTION

Infectious complications are a significant cause of morbidity and mortality among allogeneic hematopoietic cell transplant (allotransplant) recipients. The main predisposing factors include pre-transplant conditioning regimen causing neutropenia, hypogammaglobulinemia, lymphopenia, and mucosal barrier injury[1,2] and graft-versus-host disease (GvHD) requiring immunosuppressive treatment which subsequently deepens and prolongs already impaired cellular and humoral immunity.[3]

Three phases of immune reconstitution with a specific pattern of infectious complications are generally accepted in the post-transplantation period (Figure 1):

1. Early pre-engraftment phase lasting approximately 2–4 weeks / 30 days after stem cell infusion;
2. Early post-engraftment phase involving period from the engraftment till 3 months / 100 days after allotransplantation;
3. Late phase extending beyond day + 100 after allotransplantion.[4–6]

The main risk factors in the early pre-engraftment phase are neutropenia, mucosal barrier injury caused by conditioning regimen, and intravenous access devices.[7] During this phase, the general approach is similar to the management of febrile neutropenia, which is common during the therapy of cancer and hematological malignancies. Bacterial pathogens prevail over fungal and viral,[8] and gram-positive infections generally dominate gram-negatives.[7,9,10]

During the early post-engraftment phase, infectious risk is mainly attributed to the development of GvHD and catheter-related bloodstream infections. The main causative pathogens of this phase include adenovirus, BK virus, respiratory viruses, *Pneumocystis jirovecii (PJP)*, *Candida spp*, *Aspergillus spp*, and intestinal tract bacteria.[4,8]

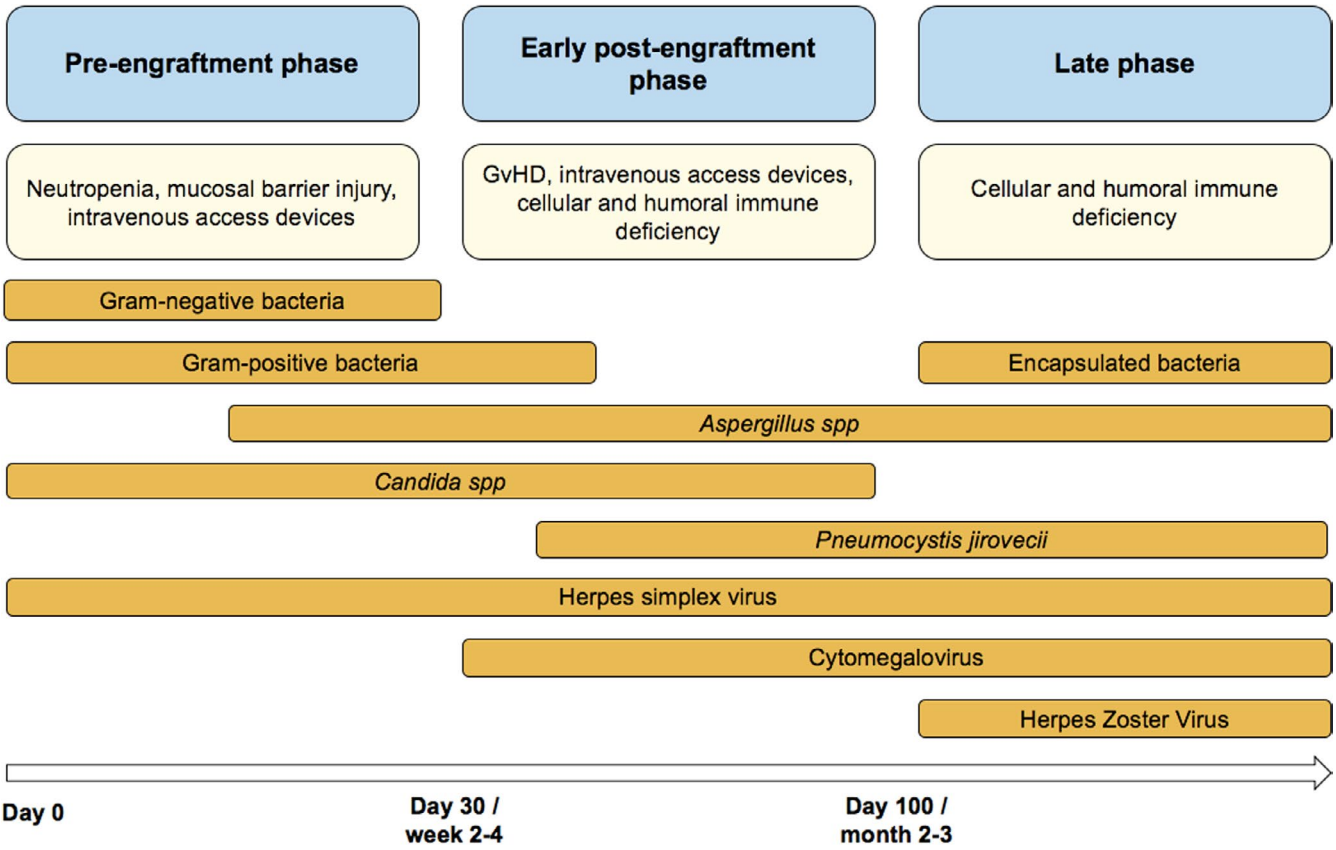

FIGURE 1 Immune reconstitution phases after allotransplant and the most common infectious pathogens

TABLE 1 Transplant-related factors and their impact on the infectious risk after allotransplant

Risk factor	Associated infectious risk
Preparative regimen	Myeloablative conditioning is associated with increased risk of bacterial infections, whereas reduced-intensity conditioning—with an increased incidence of viral infections.
Graft source	• Bone marrow transplantation is linked to increased incidence of bacterial infections; • No difference in the incidence of viral and fungal infections between bone marrow and peripheral blood stem cell transplantations; • Umbilical cord blood transplantation is associated with a higher risk of infectious complications and Human herpesvirus 6 reactivation.
Donor type	• Infectious risk increases in the following order: matched-related donor > matched unrelated donor > mismatched unrelated donor or haploidentical donor.
GvHD prophylaxis	• No difference in the incidence of infectious complications between ATG, PTCy, and alemtuzumab; • Ex vivo graft manipulation strategies seem to be associated with a higher rate of infection-related mortality (more comparative studies needed for confirmation).

In the late phase, risk factors for infectious complications are mainly associated with immunosuppressive therapy of chronic GvHD and incomplete restoration of cellular and humoral immunity. Encapsulated bacterial and invasive fungal infections, as well as EBV-related post-transplant lymphoproliferations and CMV reactivation, are among the most prevalent infectious complications during this phase.[11] If otherwise not contraindicated after cessation of immunosuppressants allotransplant recipients are generally offered vaccination according to the national immunization record card.

2 | TRANSPLANT-RELATED FACTORS ASSOCIATED WITH A HIGHER RISK OF INFECTIOUS COMPLICATIONS AFTER ALLOTRANSPLANTATION

In addition to the direct factors, such as neutropenia, cellular and humoral immune deficiency, and mucosal injury, predisposing to the development of infections in the post-transplant period, there are also indirect transplant-related factors which are the primary trigger to the development of the formers. The most important

of them are the type of preparative regimen—more aggressive conditioning regimens lead to more severe mucosal injury and prolong neutropenia, graft source—granulocyte colony-stimulating factor–mobilized peripheral blood stem cells are associated with faster engraftment but a higher risk of chronic GvHD, donor type—grafts from mismatched and unrelated donors are associated with delayed B- and T-cell reconstitution, GvHD prophylaxis—antithymocyte immunoglobulin (ATG), post-transplantation cyclophosphamide (PTCy), alemtuzumab may have a different impact on infectious risk due to different pattern of immune reconstitution, graft manipulation—ex vivo T-cell depletion and $CD34^+$ selection strategies are associated with increased risk of graft failure. The impact of these factors is summarized in Table 1 and will be discussed further in detail.

2.1 | Preparative regimen

The pre-transplant conditioning regimen plays a crucial role in the pathogenesis of critical factors, such as neutropenia, mucosal barrier injury, associated with increased risk of infectious complications. Several studies have demonstrated a lower rate of infectious episodes with the use of RIC regimens.[12,13] However, these observations were not confirmed in the pediatric transplantation setting.[14] The large retrospective analysis of the Center for International Blood and Marrow Transplant Research, which included 1775 subjects with acute myeloid leukemia, who had undergone allotransplantation in the first complete remission, found that myeloablative conditioning regimens were associated with an increased incidence of bacterial infections during the first 100 days post-transplant (46% vs. 37%; P = .0004). However, the incidence of viral infections and mainly CMV-viremia was higher in the reduced intensity/non-myeloablative conditioning group (34% vs. 39%; P = .046). Infection density and overall infection rate were also higher in the myeloablative group.[15]

In the European Bone Marrow Transplantation registry study, the use of total body irradiation in the pre-transplant myeloablative conditioning regimen for subjects with acute lymphoblastic leukemia, in addition to improved relapse-free survival compared to the chemotherapeutic myeloablative conditioning, was accompanied by lower rates of non-relapse mortality, and similar rates of infection-related mortality.[16]

2.2 | Graft source

The graft source may also play a role in the development of infections post-transplant. Due to the higher probability of chronic GvHD with peripheral blood stem cells used, there is a tendency for a higher incidence of late fungal and viral infections compared to bone marrow transplantation.[17] Cochrane Database meta-analysis confirmed a higher rate of chronic GvHD in peripheral blood stem cell transplantation. However, these results did not translate in a statistically significant difference in the overall survival or non-relapse mortality.[18] Another prospective randomized trial demonstrated a higher incidence of infections during the first 30 days after bone marrow transplantation compared with hematopoietic stem cell transplantation (47.9% vs. 32.8%; P = .002), that could be related to quicker neutrophil engraftment following latter, or possibly to a higher probability of graft failure following former. Moreover, bacterial infections during the first 2 years post-transplant were more common in the bone marrow transplantation group (84.7% vs. 79.7%; P = .013) with a trend of higher incidence of bloodstream bacterial infections in the first 100 days (44.8% vs. 35.0%; P = .092).[19] The most prevalent pathogens among gram-positive bacteria in the descending order were as follows: coagulase-negative staphylococci, *Clostridium difficile*, *Staphylococcus aureus*, and enterococci; among gram-negatives—*Escherichia coli*, *Klebsiella* spp, *Pseudomonas* spp, *Enterobacter* spp, and *Stenotrophomonas* spp. Another important finding of this study is a similar rate of viral and fungal infections during the first 2 years post-transplant between both graft types that proves the lack of impact of peripheral blood stem cells on infectious risk linked to chronic GvHD. Another study, despite showing significantly higher mortality rate attributed to chronic GvHD following peripheral blood stem cell transplantations (21% vs. 10%; P = .002; P-rate for the overall comparison of causes of death), failed to demonstrate differences in infection-related mortality between peripheral blood stem cell or bone marrow transplantations in unrelated donor setting.[20]

The study held by the Spanish group showed umbilical cord blood transplantations to be associated with a higher rate of infectious complications during the first 100 days after transplant compared to bone marrow or peripheral blood stem cell transplantations (85% vs. 69%; P = .01). However, no statistically significant difference in infection-related mortality and the incidence of infections during the first 3 years post-transplant could be determined between the groups.[21] In addition, cord blood transplantations have been shown to be associated with a higher incidence of Human herpesvirus 6 reactivation that can be attributed to the specific immune reconstitution pattern following this type of transplantations.[22]

2.3 | Donor type

The impact of the donor type on the infectious risk post-transplant is controversial. In a single-center study, the incidence of late infections beyond day 50 after allotransplantation was significantly higher in matched unrelated transplantations compared to related (84.7% vs. 68.2%; P = .009), that translated in a significantly lower non-relapse survival rate (34.4% vs. 49.9%; P = .004).[23] These results, however, were not confirmed in further studies.[24] In a large Center for International Blood and Marrow Transplant Research analysis, which included 2223 subjects with acute myeloid leukemia after allotransplantation, similar overall survival rates were observed between matched related and unrelated transplantations. In contrast, 6-month overall survival was significantly lower in mismatched transplantation group (HR = 1.40; 95% CI 1.15–1.70; P < .001), and

there was a trend of higher infection-related mortality from matched related to matched unrelated and mismatch unrelated transplantations: 10%, 14%, and 20% respectively.[25]

Allogeneic hematopoietic cell transplantation from haploidentical donor despite the benefit of quick and almost universal donor availability is also associated with higher infectious risk. In a retrospective single-center study including 187 subjects, who underwent allotransplantation with PTCy, 100-day and 1-year infection-related mortality were significantly higher in haploidentical group compared to matched related and unrelated group (8.9% vs. 1.4%; $P = .03$ и 15.9% vs. 3.8%; $P = .01$, respectively). No significant difference could be detected in bacterial or fungal infections rates between the groups; however, a trend of higher incidence of bacteremia (20.5% vs. 9.2%; $P = .06$) and urinary tract infections (18.2% vs. 8.5%; $P = .09$) was observed in the haploidentical group. CMV-infections, BK virus-associated hemorrhagic cystitis, and BK-viremia were also significantly higher in the haploidentical cohort (59.1% vs. 23.8%; $P = .01$; 40.9% vs. 8.4%; $P = .01$; and 15.9% vs. 0.8%; $P = .01$ respectively).[26]

2.4 | GvHD prophylaxis

GvHD prophylaxis strategies such as in vivo T-cell depletion with ATG, PTCy, or alemtuzumab and ex vivo graft manipulation techniques, such as CD34 positive selection and T- and/or B-cell depletion, are also considered among the most important transplant-related factors determining the risk of infectious complications. There is a distinct pattern of immune reconstitution after allotransplantation using ATG or PTCy as GvHD prophylaxis[27]; however, these differences in reconstitution profiles do not seem to translate in the infectious risk discrepancy. For instance, two large European Bone Marrow Transplantation Society analyses could detect no difference in the incidence of infectious complications following allotransplantation using either PTCy or ATG in haploidentical or mismatched unrelated transplantations.[28,29] Anti-CD52 monoclonal antibody alemtuzumab used as a GvHD prophylaxis in transplant setting for aplastic anemia demonstrated similar overall survival and infection-related mortality rates compared to ATG (42.6% vs. 47.6%; $P = .131$; *P*-rate for all causes of death).[30]

Ex vivo graft manipulation is a promising technology for the prevention of GvHD without compromising the disease control. However, transplant-related mortality (mostly infection-related) could achieve up to 36%–40% with CD34 positive selection,[31,32] 20%–30% with CD3/CD19 depletion,[33,34] and 0%–20% or up to 39% in the elderly group when using TCRab/CD19 depletion technique.[35-38] Several studies comparing different types of in vivo and ex vivo T-cell depletion strategies have already been published. In the study conducted by the European Bone Marrow Transplantation Society and Memorial Sloan Kettering Cancer Center, no statistically significant difference in relapse-free or overall survival could be detected after allotransplantation from HLA-identical donors in first complete remission of acute myeloid leukemia using either CD34 positive selection or ATG as GvHD prophylaxis. However, infection-related mortality was significantly higher in the ex vivo graft manipulation group (31% vs. 17%; $P = .04$).[39] Another study revealed a trend of higher incidence of infectious episodes after haploidentical transplantations using CD34 positive selection and ATG compared to PTCy (146 vs. 91; $P = .06$) with the most remarkable difference in viral (56.2% vs. 54.9%; $P = .035$) and fungal infections (8.2% vs. 3.3%; $P = .008$).[40]

3 | ANTIBACTERIAL PROPHYLAXIS

There are two main sources of bacterial infections during the early pre-engraftment phase: gut microflora responsible for gram-negative infections, and indwelling intravenous access devices responsible mostly for gram-positive infections. Antibacterial prophylaxis, oral hygiene, neutropenic diet, and gut decontamination decrease the infections rate and chemotherapy-induced febrile episodes.[2,41-43]

Fluoroquinolones due to lower incidence of gram-negative bacteremia and acceptable safety profile are currently the most widely used antibiotics for prophylaxis during neutropenia.[41,44] In addition, fluoroquinolone prophylaxis has been shown to reduce the frequency of neutropenic fevers and infection-related mortality in cytotoxic therapy-related neutropenic patients,[45] as well as the relative risk of death in patients after allotransplantion.[46] Although recent meta-analysis done by European Conference on Infections in Leukemia (ECIL) could not demonstrate overall survival benefit, it revealed decreased incidence of bloodstream infections and febrile neutropenia episodes with fluoroquinolone prophylaxis in patients with hematological malignancies.[47] Finally, the most recent systematic review could not reveal overall survival benefit either but could detect a reduced rate of bacteremia and infection-related mortality with fluoroquinolone prophylaxis in patients with cancer and hematopoietic cell transplantation. No significant difference was observed in the rate of *Clostridium difficile* infections and other adverse events compared with placebo or non-absorbable antibiotics.[48] Alongside this evidence, the joint guidelines of the American Society of Clinical Oncology and Infectious Diseases Society of America[49] and National Comprehensive Cancer Network guidelines[50] currently recommend fluoroquinolone prophylaxis for high-risk patients who are expected to have profound, protracted neutropenia.

Nevertheless, the main problem with the use of fluoroquinolone prophylaxis is the development of resistant bacteria. A single-center study demonstrated that 10% of all subjects who received levofloxacin prophylaxis during autologous or allogeneic hematopoietic cell transplantation had extended-spectrum beta-lactamase (ESBL)—producing Enterobacteriaceae in rectal swabs and 32% of them subsequently developed breakthrough levofloxacin-resistant bacteremia post-transplant compared to 0.4% subjects not colonized with ESBL Enterobacteriaceae ($P = .01$). All bloodstream ESBL producing Enterobacteriaceae were levofloxacin-resistant and had identical genotypic profiles with gut colonizing species.[51] Levofloxacin prophylaxis may have led to the selection of resistant bacteria resulting

in a subsequent breakthrough bloodstream infections observed in this study. Indirect evidence of that is the fact that ciprofloxacin may impair gut microbiota diversity,[52] that could potentially impact transplant outcomes. For instance, gut microbiome diversity determined by bacterial 16S rRNA sequencing has been shown to directly impact overall survival of allotransplant recipients: 36% for low, 60% for intermediate, and 67% for high diversity groups (P = .019).[53] Although no effect of ciprofloxacin (in contrast to vancomycin, metronidazole, and β-lactam antibiotics) on intestinal diversity was detected in this work, further studies are needed to make definitive conclusions.

Due to increasing emergence of fluoroquinolone-resistant organisms, several attempts have been made to discover new prophylactic strategies in patients with hematological malignancies and allotransplant recipients. Third-generation oral cephalosporin cefpodoxime as an alternative to fluoroquinolone-based approach has recently demonstrated similar rates of neutropenic fever and antibiotic prophylaxis failure compared to levofloxacin in a single-center retrospective study. Moreover, there was a similar rate of *C difficile* and multi-drug resistant infections and 100-day survival among both groups.[54] Although the higher rate of infections caused by *Pseudomonas aeruginosa* was detected in cefpodoxime group, this finding was not observed in another study of cefpodoxime or cefdinir versus levofloxacin prophylaxis in patients with myelodysplastic syndromes.[55] Despite these promising results, cephalosporin prophylaxis did not reduce infection-related mortality in patients with cancer and allotransplant recipients in a recent systematic review.[48]

4 | ANTIFUNGAL PROPHYLAXIS

The majority of fungal infections tend to develop in the early post-engraftment and late phase that could be attributed to GvHD and immunosuppressive treatment. During this period, the most common yeast fungal infections are due to *Candida spp*, whereas *Aspergillus spp* prevail among molds.[56] Contamination pattern also differs: while the development of yeast fungal infections is associated with intravenous access devices and gut mucosal injury, aspiration of airborne spores is the main route of molds penetration.[8] For this reason, the installation of High-Efficiency Particulate Air filters in bone marrow transplantation departments is crucial. The incidence of invasive fungal infections after hematopoietic cell transplantation, according to a multicenter study in the USA involving 23 centers, was 3.4%, and the frequency of fungal infections after autologous cell transplantation was significantly lower than after allotransplantation with the most common infections in the entire cohort being invasive aspergillosis (43%), invasive candidiasis (28%), and zygomycosis (8%).[56]

4.1 | Antifungal prophylaxis during pre-engraftment phase

Currently, fluconazole is recommended for the antifungal prophylaxis in the early pre-engraftment phase post-transplant by most guidelines.[49,57] However, ECIL recommends fluconazole prophylaxis only for transplant centers with a low incidence of mold infections (below 5%) and only when combined with mold-directed diagnostic approach (either antigen or computer tomography scan based), or a mold-directed empirical therapy approach.[57] In a randomized prospective placebo-controlled trial prolonged overall survival as well as reduced incidence of invasive fungal infections and gut GvHD were observed in subjects receiving fluconazole as antifungal prophylaxis after allotransplantion.[58]

Voriconazole, another azole antifungal, got previously provisional recommendation by ECIL-3 for antifungal prophylaxis in allotransplant recipients; however, a multicenter prospective randomized trial of voriconazole versus fluconazole prophylaxis did not meet its primary endpoint—180-day fungal-free survival (75% vs. 78%; P = .49). Nevertheless, trends of reduced incidence of fungal infections (7.3% vs. 11.2%; P = .12), invasive aspergillosis (9 vs. 17; P = .09), and empirical antifungal therapy (24.1% vs. 30.2%, P = .11) were detected in the voriconazole arm.[59] Another prospective randomized trial of voriconazole versus itraconazole prophylaxis in allotransplant recipients demonstrated a statistically significant difference in the composite primary endpoint—the success of prophylaxis, defined as the ability to tolerate study drug for at least 100 days, with survival without proven/probable invasive fungal infection to day 180 favoring voriconazole arm. The success of prophylaxis, as well as a number of subjects, tolerated prophylaxis for 100 days was significantly higher with voriconazole (48.7% vs. 33.2%; P = .01; and 53.6% vs. 39.0%; median total duration 96 vs. 68 days; P = .01, respectively) compared to itraconazole. However, no difference could be detected in the incidence of invasive fungal infections and 6-months overall survival between the groups (1.3% vs. 2.1%; P = .54 and 81.9% vs. 80.9%; P = .17, respectively).[60]

Due to the lack of sufficient data of posaconazole prophylaxis in allotransplant recipients during pre-engraftment phase, no definitive conclusions can be made to date regarding its use. In addition, in a small prospective randomized trial oral posaconazole was not superior to amphotericin B lipid complex in regards to incidence of invasive fungal infections in allotransplant recipients (5% vs. 0%; P = .48); however, nephrotoxicity was a major concern with amphotericin use (53% vs. 5%; P = .001).[61] In another randomized multicenter trial posaconazole has been shown to reduce invasive fungal infection rate compared to fluconazole or itraconazole in patients with acute myeloid leukemia or myelodysplastic syndromes receiving induction therapy (8% vs. 2%; P = .001).[62] Clinical trial comparing antifungal prophylaxis with posaconazole and itraconazole in allotransplant recipients is currently actively enrolling subjects (NCT03631602).

There is also a lack of sufficient data of echinocandin prophylaxis in allotransplant recipients. Despite significant shortcomings such as no formulation available other than intravenous, echinocandins demonstrate better safety profile and lower number of potential drug interactions compared to azole family antifungals. Although preliminary results of the prospective randomized trial have revealed superiority of micafungin 50 mg OD over fluconazole 400 mg OD as prophylaxis in hematopoietic stem cell

transplantation recipients,[63] further analysis revealed several shortcomings of this study and namely inadequate follow-up period and predominance of patients with a lower risk of invasive fungal infections development (autologous stem cell transplant recipients) causing potentially unreliable interpretation of the study results in allogeneic setting.[64] Another prospective randomized trial by the Japanese group was not able to demonstrate the superiority of micafungin 150 mg OD over micafungin 400 mg OD as antifungal prophylaxis in allotransplant recipients. Nevertheless, the rate of empirical antifungal therapy for breakthrough infections was higher in the fluconazole group (4% vs. 12%; P = .06).[65] In patients undergoing induction therapy for acute myeloid leukemia or myelodysplastic syndromes, micafungin 100 mg OD was superior to posaconazole 800 mg/daily in terms of prophylaxis failure defined as premature discontinuation due to infection, intolerance, adverse event, or death (34.5% vs. 52.7%; P = .0118). Whereas micafungin prophylaxis failures were mostly due to antifungal treatment, posaconazole failures were largely linked to adverse events or gastrointestinal intolerance.[66] In summary, micafungin is currently recommended as antifungal prophylaxis in allotransplant recipients in transplantation centers with a low incidence of mold infections.[57]

4.2 | Antifungal prophylaxis during post-engraftment phase

As mentioned earlier, the main predisposing factor for fungal infections post-transplant is immunosuppressive therapy of GvHD. Posaconazole is currently recommended by most of the guidelines for antifungal prophylaxis during this period.[57,67] These recommendations are based on the results of the randomized control trial which demonstrated a trend of lower incidence of invasive fungal infections (5.3% vs. 9.0%; P = .07), as well as lower incidence of proven/probable invasive aspergillosis (2.3% vs. 7.0%; OR 0.31; 95% CI, 0.13–0.75; P = .006) and breakthrough fungal infections (2.4% vs. 7.6%, P = .004) with 112 days posaconazole prophylaxis compared to fluconazole. In addition, rates of adverse reactions were similar between the groups (36% vs. 38%).[68] Other mold-active azoles such as voriconazole and itraconazole can be used as prophylaxis during this period alternatively to posaconazole. For the same reason, fluconazole should be avoided in the late post-engraftment phase. No sufficient data supporting prophylactic use of echinocandins post-transplant currently exist.

The median time for PJP pneumonia onset after allotransplantation is about nine months, and mortality rate despite treatment is still high achieving up to 89% in the first six months post-transplant.[69,70] PJP prophylaxis in allotransplant recipients is similar to that of HIV/AIDS patients with the main agents being trimethoprim/sulfamethoxazole, pentamidine, and atovaquone.[71,72] In clinical practice, prophylaxis usually starts from the time of documented engraftment and lasts till the rise in $CD4^+$ lymphocyte count above 200/μl, providing no active immunosuppressive treatment.

5 | ANTIVIRAL PROPHYLAXIS

The main goal of antiviral prophylaxis post-transplant is the reduction of the viral reactivation in seropositive recipients. About 80% of adult allotransplant recipients are Herpes Simplex types 1/2 (HSV 1/2) seropositive, and the reactivation rate can achieve up to 80%.[73] For this reason, acyclovir or valacyclovir prophylaxis has been recommended for decades against HSV types 1/2 reactivation during the first 30 days.[74,75] Prolongation of prophylaxis for up to 1 year or until complete immune reconstitution allows to prevent Varicella-zoster viral reactivation.[76,77]

Ideally, to prevent cytomegaloviral (CMV) reactivation, all CMV-seronegative recipients should be transplanted from CMV-seronegative donors. Moreover, all brood products for these patients should also be obtained from seronegative donors or preliminary lymphodepleted. Several attempts have been made in search of suitable prophylaxis. However, due to impaired CMV-specific T-cell response and myelotoxicity with the use of ganciclovir,[78] and novel diagnostic methods that have led to the development of equally effective pre-emptive therapy approach,[79] ganciclovir, valganciclovir, or even foscarnet are not currently recommended for routine CMV prophylaxis in allotransplant recipients.

Maribavir another anti-CMV drug that inhibits the UL97 viral protein kinase has demonstrated promising results in the multicenter randomized, double-blind, placebo-controlled, dose-ranging study—lower incidence of CMV infection compared to placebo (46%) was detected in each of the maribavir groups: 100 mg twice daily (7%; P = .001), 400 mg once daily (11%; P = .007), and 400 mg twice daily (19%; P = .038). Anti-CMV therapy was also used less often in subjects receiving each respective dose of maribavir (15%; P = .001; 30%; P = .051; 15%; P = .002) compared with placebo (57%).[80] However, in the intention-to-treat analysis of further placebo-controlled phase 3 trial no difference was observed in the incidence of CMV disease (4% vs. 5%; OR 0.90; 95% CI 0.42–1.92) suggesting no benefit of maribavir prophylaxis in allotransplant recipients.[81]

Finally, in 2017 results of phase 3 double-blind placebo-controlled trial of letermovir (an antiviral agent that inhibits CMV replication by binding to components of the terminase complex) prophylaxis in allotransplant recipients demonstrated a significantly lower incidence of CMV infection (37.5% vs. 60.6%, P = .001) with no difference in adverse events rate[82] leading to subsequent approval by Food and Drug Administration as CMV prophylaxis in high-risk allotransplant recipients.

6 | CONCLUSIONS

The main transplant-related factors associated with a higher infectious risk are myeloablative conditioning regimens, bone marrow, and umbilical cord blood transplantations, and HLA-disparity. A similar rate of infectious episodes between different types of in-vivo T-cell depletion strategies indirectly proves the donor type's independent role on the infectious risk. Further studies need to address

this problem prospectively. There is also a high necessity of comparative studies of ex vivo graft manipulation techniques and their impact on the infectious risk.

Antibacterial prophylaxis with fluoroquinolones is still considered a gold standard according to major guidelines. Several shortcomings of this approach include failure to demonstrate overall survival benefit and emergence of resistant species. Due to controversies observed to date, further studies evaluating the impact of fluoroquinolones on the gut microbiota diversity and subsequently on the transplant outcomes are needed. Despite promising results in single studies prophylaxis with third-generation cephalosporins did not reduce infection-related mortality in a meta-analysis.

Fluconazole is still a mainstay of antifungal prophylaxis in allotransplant recipients in the pre-engraftment phase. Micafungin can be used alternatively; however, both approaches are recommended for transplant centers with a low incidence of mold infections. Otherwise, or in case of known invasive fungal infection during induction treatment, voriconazole, itraconazole, or posaconazole should be preferred. Despite limited data, physicians are encouraged to use mold-active antifungals during the post-engraftment phase. Further prospective studies better defining the current state of antifungal prophylaxis in allotransplant recipients are needed, including trials of novel drugs such as isavuconazole.

Novel antiviral agents active against CMV with acceptable safety profile have already demonstrated promising results in randomized trials as prophylaxis in allotransplant recipients. However, due to inability of letermovir to prevent reactivation of HSV types 1/2 or VZV this approach still needs dual antiviral coverage. Therefore, further translational studies in search of universal antiviral agents for prophylaxis in allotransplant recipients with reasonable toxicity profiles are needed.

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The author confirms that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

ORCID

Mobil Akhmedov https://orcid.org/0000-0002-9646-690X

REFERENCES

1. Leather HL, Wingard JR. Infections following hematopoietic stem cell transplantation. *Infect Dis Clin North Am*. 2001;15(2):483-520. https://doi.org/10.1016/S0891-5520(05)70157-4
2. Santos CAQ, Rhee Y, Czapka MT, Kazi AS, Proia LA. Make sure you have a safety net: updates in the prevention and management of infectious complications in stem cell transplant recipients. *J Clin Med*. 2020;9(3):865. https://doi.org/10.3390/jcm9030865
3. Arnaout K, Patel N, Jain M, El-Amm J, Amro F, Tabbara IA. Complications of allogeneic hematopoietic cell transplantation. *Cancer Invest*. 2014;32(7):349-362. https://doi.org/10.3109/07357907.2014.919301
4. Wingard JR, Hsu J, Hiemenz JW. Hematopoietic stem cell transplantation: an overview of infection risks and epidemiology. *Infect Dis Clin North Am*. 2010;24(2):257-272. https://doi.org/10.1016/j.idc.2010.01.010
5. Ogonek J, Kralj Juric M, Ghimire S, et al. Immune reconstitution after allogeneic hematopoietic cell transplantation. *Front Immunol*. 2016;7:507. https://doi.org/10.3389/fimmu.2016.00507
6. van den Brink MRM, Velardi E, Perales M-A. Immune reconstitution following stem cell transplantation. *Hematol Am Soc Hematol Educ Program*. 2015;2015:215-219. https://doi.org/10.1182/asheducation-2015.1.215
7. Gudiol C, Garcia-Vidal C, Arnan M, et al. Etiology, clinical features and outcomes of pre-engraftment and post-engraftment bloodstream infection in hematopoietic SCT recipients. *Bone Marrow Transplant*. 2014;49(6):824-830. https://doi.org/10.1038/bmt.2014.37
8. Sahin U, Toprak SK, Atilla PA, Atilla E, Demirer T. An overview of infectious complications after allogeneic hematopoietic cell transplantation. *J Infect Chemother*. 2016;22(8):505-514. https://doi.org/10.1016/j.jiac.2016.05.006
9. Mikulska M, Raiola AM, Galaverna F, et al. Pre-engraftment bloodstream infections after allogeneic hematopoietic cell transplantation: impact of T cell-replete transplantation from a haploidentical donor. *Biol Blood Marrow Transplant*. 2018;24(1):109-118. https://doi.org/10.1016/j.bbmt.2017.08.024
10. Kikuchi M, Akahoshi Y, Nakano H, et al. Risk factors for pre- and post-engraftment bloodstream infections after allogeneic hematopoietic cell transplantation. *Transpl Infect Dis*. 2015;17(1):56-65. https://doi.org/10.1111/tid.12345
11. Espinoza JL, Wadasaki Y, Takami A. Infection complications in hematopoietic stem cells transplant recipients. Do Genetics Really Matter? *Front Microbiol*. 2018;9:2317. https://doi.org/10.3389/fmicb.2018.02317
12. Kim S-H, Kee SY, Lee D-G, et al. Infectious complications following allogeneic stem cell transplantation: reduced-intensity vs. myeloablative conditioning regimens. *Transpl Infect Dis*. 2013;15(1):49-59. https://doi.org/10.1111/tid.12003
13. Ringdén O, Erkers T, Aschan J, et al. A prospective randomized toxicity study to compare reduced-intensity and myeloablative conditioning in patients with myeloid leukaemia undergoing allogeneic haematopoietic stem cell transplantation. *J Intern Med*. 2013;274(2):153-162. https://doi.org/10.1111/joim.12056
14. Satwani P, Baldinger L, Freedman J, et al. Incidence of viral and fungal infections following busulfan-based reduced-intensity versus myeloablative conditioning in pediatric allogeneic stem cell transplantation recipients. *Biol Blood Marrow Transplant*. 2009;15(12):1587-1595. https://doi.org/10.1016/j.bbmt.2009.08.006
15. Ustun C, Kim S, Chen M, et al. Increased overall and bacterial infections following myeloablative allogeneic HCT for patients with AML in CR1. *Blood Adv*. 2019;3(17):2525-2536. https://doi.org/10.1182/bloodadvances.2019000226
16. Dholaria B, Labopin M, Angelucci E, et al. Outcomes of total body irradiation- versus chemotherapy-based myeloablative conditioning regimen in haploidentical hematopoietic cell transplantation with post-transplant cyclophosphamide for acute lymphoblastic leukemia: ALWP of the EBMT Study. *Blood*. 2019;134(Supplement_1):320. https://doi.org/10.1182/blood-2019-122258
17. Anderson D, DeFor T, Burns L, et al. A comparison of related donor peripheral blood and bone marrow transplants: importance of late-onset chronic graft-versus-host disease and infections. *Biol Blood Marrow Transplant*. 2003;9(1):52-59. https://doi.org/10.1053/bbmt.2003.50000
18. Holtick U, Albrecht M, Chemnitz JM, et al. Bone marrow versus peripheral blood allogeneic haematopoietic stem cell transplantation

for haematological malignancies in adults. *Cochrane Database Syst Rev*. 2014;(4):CD010189. https://doi.org/10.1002/14651858.CD010189.pub2

19. Young J-AH, Logan BR, Wu J, et al. Infections following transplantation of bone marrow or peripheral-blood stem cells from unrelated donors. *Biol Blood Marrow Transplant*. 2016;22(2):359-370. https://doi.org/10.1016/j.bbmt.2015.09.013
20. Anasetti C, Logan BR, Lee SJ, et al. Peripheral-blood stem cells versus bone marrow from unrelated donors. *N Engl J Med*. 2012;367(16):1487-1496. https://doi.org/10.1056/NEJMoa1203517
21. Parody R, Martino R, Rovira M, et al. Severe infections after unrelated donor allogeneic hematopoietic cell transplantation in adults: comparison of cord blood transplantation with peripheral blood and bone marrow transplantation. *Biol Blood Marrow Transplant*. 2006;12(7):734-748. https://doi.org/10.1016/j.bbmt.2006.03.007
22. Chevallier P, Hebia-Fellah I, Planche L, et al. Human herpes virus 6 infection is a hallmark of cord blood transplant in adults and may participate to delayed engraftment: a comparison with matched unrelated donors as stem cell source. *Bone Marrow Transplant*. 2010;45(7):1204-1211. https://doi.org/10.1038/bmt.2009.326
23. Ochs L, Shu XO, Miller J, et al. Late infections after allogeneic bone marrow transplantations: comparison of incidence in related and unrelated donor transplant recipients. *Blood*. 1995;86(10):3979-3986.
24. Rieger CT, Rieger H, Kolb HJ, et al. Infectious complications after allogeneic stem cell transplantation: incidence in matched-related and matched-unrelated transplant settings. *Transpl Infect Dis*. 2009;11(3):220-226. https://doi.org/10.1111/j.1399-3062.2009.00379.x
25. Saber W, Opie S, Rizzo JD, Zhang M-J, Horowitz MM, Schriber J. Outcomes after matched unrelated donor versus identical sibling hematopoietic cell transplantation in adults with acute myelogenous leukemia. *Blood*. 2012;119(17):3908-3916. https://doi.org/10.1182/blood-2011-09-381699
26. Chang J, Hsiao M, Blodget E, Akhtari M. Increased risk of 100-day and 1-year infection-related mortality and complications in haploidentical stem cell transplantation. *J Blood Med*. 2019;10:135-143. https://doi.org/10.2147/JBM.S201073
27. Retière C, Willem C, Guillaume T, et al. Impact on early outcomes and immune reconstitution of high-dose post-transplant cyclophosphamide vs anti-thymocyte globulin after reduced intensity conditioning peripheral blood stem cell allogeneic transplantation. *Oncotarget*. 2018;9(14):11451-11464. https://doi.org/10.18632/oncotarget.24328
28. Battipaglia G, Labopin M, Kröger N, et al. Posttransplant cyclophosphamide vs antithymocyte globulin in HLA-mismatched unrelated donor transplantation. *Blood*. 2019;134(11):892-899. https://doi.org/10.1182/blood.2019000487
29. Ruggeri A, Sun Y, Labopin M, et al. Post-transplant cyclophosphamide versus anti-thymocyte globulin as graft- versus-host disease prophylaxis in haploidentical transplant. *Haematologica*. 2017;102(2):401-410. https://doi.org/10.3324/haematol.2016.151779
30. Samarasinghe S, Clesham K, Iacobelli S, et al. Impact of T-cell depletion strategies on outcomes following hematopoietic stem cell transplantation for idiopathic aplastic anemia: a study on behalf of the European blood and marrow transplant severe aplastic anemia working party. *Am J Hematol*. 2019;94(1):80-86. https://doi.org/10.1002/ajh.25314
31. Aversa F, Tabilio A, Velardi A, et al. Treatment of high-risk acute leukemia with T-cell-depleted stem cells from related donors with one fully mismatched HLA haplotype. *N Engl J Med*. 1998;339(17):1186-1193. https://doi.org/10.1056/NEJM199810223391702
32. Aversa F, Terenzi A, Tabilio A, et al. Full haplotype-mismatched hematopoietic stem-cell transplantation: a phase II study in patients with acute leukemia at high risk of relapse. *J Clin Oncol*. 2005;23(15):3447-3454. https://doi.org/10.1200/JCO.2005.09.117
33. Bethge WA, Faul C, Bornhäuser M, et al. Haploidentical allogeneic hematopoietic cell transplantation in adults using CD3/CD19 depletion and reduced intensity conditioning: an update. *Blood Cells Mol Dis*. 2008;40(1):13-19. https://doi.org/10.1016/j.bcmd.2007.07.001
34. Hale GA, Kasow KA, Madden R, et al. Mismatched family member donor transplantation for patients with refractory hematologic malignancies: long-term follow-up of a prospective clinical trial. *Blood*. 2006;108(11):3137. https://doi.org/10.1182/blood.V108.11.3137.3137
35. Lang PJ, Schlegel PG, Meisel R, et al. TCR-alpha/beta and CD19 depleted haploidentical stem cell transplantation following reduced intensity conditioning in children: first results of a prospective multicenter phase I/II clinical trial. *Blood*. 2016;128(22):389. https://doi.org/10.1182/blood.V128.22.389.389
36. Maschan M, Shelikhova L, Ilushina M, et al. TCR-alpha/beta and CD19 depletion and treosulfan-based conditioning regimen in unrelated and haploidentical transplantation in children with acute myeloid leukemia. *Bone Marrow Transplant*. 2016;51(5):668-674. https://doi.org/10.1038/bmt.2015.343
37. Locatelli F, Merli P, Pagliara D, et al. Outcome of children with acute leukemia given HLA-haploidentical HSCT after αβ T-cell and B-cell depletion. *Blood*. 2017;130(5):677-685. https://doi.org/10.1182/blood-2017-04-779769
38. Prezioso L, Manfra I, Bonomini S, et al. Haploidentical hematopoietic stem cell transplantation in adults using the αβTCR/CD19-based depletion of G-CSF-mobilized peripheral blood progenitor cells. *Bone Marrow Transplant*. 2019;54(2):698-702. https://doi.org/10.1038/s41409-019-0608-z
39. Malard F, Labopin M, Cho C, et al. Ex vivo and in vivo T cell-depleted allogeneic stem cell transplantation in patients with acute myeloid leukemia in first complete remission resulted in similar overall survival: on behalf of the ALWP of the EBMT and the MSKCC. *J Hematol Oncol*. 2018;11(1):127. https://doi.org/10.1186/s13045-018-0668-3
40. Ciurea SO, Mulanovich V, Saliba RM, et al. Improved early outcomes using a T cell replete graft compared with T cell depleted haploidentical hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2012;18(12):1835-1844. https://doi.org/10.1016/j.bbmt.2012.07.003
41. Bucaneve G, Micozzi A, Menichetti F, et al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. *N Engl J Med*. 2005;353(10):977-987. https://doi.org/10.1056/NEJMoa044097
42. Imran H, Tleyjeh IM, Arndt CAS, et al. Fluoroquinolone prophylaxis in patients with neutropenia: a meta-analysis of randomized placebo-controlled trials. *Eur J Clin Microbiol Infect Dis*. 2008;27(1):53-63. https://doi.org/10.1007/s10096-007-0397-y
43. Hayes-Lattin B, Leis JF, Maziarz RT. Isolation in the allogeneic transplant environment: how protective is it? *Bone Marrow Transplant*. 2005;36(5):373-381. https://doi.org/10.1038/sj.bmt.1705040
44. Gafter-Gvili A, Fraser A, Paul M, et al. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. *Cochrane Database Syst Rev*. 2012;1:CD004386. https://doi.org/10.1002/14651858.CD004386.pub3
45. Bow EJ. Fluoroquinolones, antimicrobial resistance and neutropenic cancer patients. *Curr Opin Infect Dis*. 2011;24(6):545-553. https://doi.org/10.1097/QCO.0b013e32834cf054
46. Cullen M, Baijal S. Prevention of febrile neutropenia: use of prophylactic antibiotics. *Br J Cancer*. 2009;101(Suppl 1):S11-S14. https://doi.org/10.1038/sj.bjc.6605270
47. Mikulska M, Averbuch D, Tissot F, et al. Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL

critical appraisal of previous guidelines. *J Infect*. 2018;76(1):20-37. https://doi.org/10.1016/j.jinf.2017.10.009

48. Egan G, Robinson PD, Martinez JPD, et al. Efficacy of antibiotic prophylaxis in patients with cancer and hematopoietic stem cell transplantation recipients: a systematic review of randomized trials. *Cancer Med*. 2019;8(10):4536-4546. https://doi.org/10.1002/cam4.2395
49. Taplitz RA, Kennedy EB, Bow EJ, et al. Antimicrobial prophylaxis for adult patients with cancer- related immunosuppression: ASCO and IDSA clinical practice guideline update. *J Clin Oncol. Published online*. 2018;14(11):692-695.
50. Baden LR, Bensinger W, Angarone M, et al. Prevention and treatment of cancer-related infections. *J Natl Compr Cancer Netw*. 2012;10(11):1412-1445. https://doi.org/10.6004/jnccn.2012.0146
51. Satlin MJ, Chavda KD, Baker TM, et al. Colonization with levofloxacin-resistant extended-spectrum β-lactamase-producing enterobacteriaceae and risk of bacteremia in hematopoietic stem cell transplant recipients. *Clin Infect Dis*. 2018;67(11):1720-1728. https://doi.org/10.1093/cid/ciy363
52. Dethlefsen L, Huse S, Sogin ML, Relman DA. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. *PLOS Biol*. 2008;6(11):e280. https://doi.org/10.1371/journal.pbio.0060280
53. Taur Y, Jenq RR, Perales M-A, et al. The effects of intestinal tract bacterial diversity on mortality following allogeneic hematopoietic cell transplantation. *Blood*. 2014;124(7):1174-1182. https://doi.org/10.1182/blood-2014-02-554725
54. Doan VP, Yeh JC, Gulbis AM, Aitken SL, Ariza-Heredia E, Ahmed S. Levofloxacin versus cefpodoxime for antibacterial prophylaxis in allogeneic stem cell transplantation. *Biol Blood Marrow Transplant*. 2019;25(8):1637-1641. https://doi.org/10.1016/j.bbmt.2019.04.013
55. Yemm KE, Barreto JN, Mara KC, Dierkhising RA, Gangat N, Tosh PK. A comparison of levofloxacin and oral third-generation cephalosporins as antibacterial prophylaxis in acute leukaemia patients during chemotherapy-induced neutropenia. *J Antimicrob Chemother*. 2018;73(1):204-211. https://doi.org/10.1093/jac/dkx338
56. Kontoyiannis D, Marr K, Park B, et al. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001–2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. *Clin Infect Dis*. 2010;50(8):1091-1100. https://doi.org/10.1086/651263
57. Maertens JA, Girmenia C, Brüggemann RJ, et al. European guidelines for primary antifungal prophylaxis in adult haematology patients: summary of the updated recommendations from the European Conference on Infections in Leukaemia. *J Antimicrob Chemother*. 2018;73(12):3221-3230. https://doi.org/10.1093/jac/dky286
58. Marr KA, Seidel K, Slavin MA, et al. Prolonged fluconazole prophylaxis is associated with persistent protection against candidiasis-related death in allogeneic marrow transplant recipients: long-term follow-up of a randomized, placebo-controlled trial. *Blood*. 2000;96(6):2055-2061.
59. Wingard JR, Carter SL, Walsh TJ, et al. Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. *Blood*. 2010;116(24):5111-5118. https://doi.org/10.1182/blood-2010-02-268151
60. Marks DI, Pagliuca A, Kibbler CC, et al. Voriconazole versus itraconazole for antifungal prophylaxis following allogeneic haematopoietic stem-cell transplantation. *Br J Haematol*. 2011;155(3):318-327. https://doi.org/10.1111/j.1365-2141.2011.08838.x
61. Chaftari A-M, Hachem RY, Ramos E, et al. Comparison of posaconazole versus weekly amphotericin B lipid complex for the prevention of invasive fungal infections in hematopoietic stem-cell transplantation. *Transplantation*. 2012;94(3):302-308. https://doi.org/10.1097/TP.0b013e3182577485
62. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med*. 2007;356(4):348-359. https://doi.org/10.1056/NEJMoa061094
63. van Burik J-a h, Ratanatharathorn V, Stepan DE, et al. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. *Clin Infect Dis*. 2004;39(10):1407-1416. https://doi.org/10.1086/422312
64. Cornely OA, Ullmann AJ, Karthaus M. Choosing a study population for the evaluation of antifungal prophylaxis. *Clin Infect Dis*. 2005;40(11):1699. https://doi.org/10.1086/429823
65. Hiramatsu Y, Maeda Y, Fujii N, et al. Use of micafungin versus fluconazole for antifungal prophylaxis in neutropenic patients receiving hematopoietic stem cell transplantation. *Int J Hematol*. 2008;88(5):588-595. https://doi.org/10.1007/s12185-008-0196-y
66. Epstein DJ, Seo SK, Huang Y-T, et al. Micafungin versus posaconazole prophylaxis in acute leukemia or myelodysplastic syndrome: a randomized study. *J Infect*. 2018;77(3):227-234. https://doi.org/10.1016/j.jinf.2018.03.015
67. Baden LR, Swaminathan S, Angarone M, et al. Prevention and treatment of cancer-related infections, Version 2.2016, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Cancer Netw*. 2016;14(7):882-913. https://doi.org/10.6004/jnccn.2016.0093
68. Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med*. 2007;356(4):335-347. https://doi.org/10.1056/NEJMoa061098
69. De Castro N, Neuville S, Sarfati C, et al. Occurrence of Pneumocystis jiroveci pneumonia after allogeneic stem cell transplantation: a 6-year retrospective study. *Bone Marrow Transplant*. 2005;36(10):879-883. https://doi.org/10.1038/sj.bmt.1705149
70. Ullmann AJ, Schmidt-Hieber M, Bertz H, et al. Infectious diseases in allogeneic haematopoietic stem cell transplantation: prevention and prophylaxis strategy guidelines 2016. *Ann Hematol*. 2016;95(9):1435-1455. https://doi.org/10.1007/s00277-016-2711-1
71. Hughes WT, Rivera GK, Schell MJ, Thornton D, Lott L. Successful intermittent chemoprophylaxis for Pneumocystis carinii pneumonitis. *N Engl J Med*. 1987;316(26):1627-1632. https://doi.org/10.1056/NEJM198706253162604
72. Stern A, Green H, Paul M, Vidal L, Leibovici L. Prophylaxis for Pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients. *Cochrane Database Syst Rev*. 2014;(10):CD005590. https://doi.org/10.1002/14651858.CD005590.pub3
73. Meyers JD, Flournoy N, Thomas ED. Infection with herpes simplex virus and cell-mediated immunity after marrow transplant. *J Infect Dis*. 1980;142(3):338-346. https://doi.org/10.1093/infdis/142.3.338
74. Gluckman E, Lotsberg J, Devergie A, et al. prophylaxis of herpes infections after bone-marrow transplantation by oral acyclovir. *Lancet Lond Engl*. 1983;2(8352):706-708. https://doi.org/10.1016/s0140-6736(83)92248-1
75. Dignani MC, Mykietiuk A, Michelet M, et al. Valacyclovir prophylaxis for the prevention of Herpes simplex virus reactivation in recipients of progenitor cells transplantation. *Bone Marrow Transplant*. 2002;29(3):263-267. https://doi.org/10.1038/sj.bmt.1703354
76. Boeckh M, Kim HW, Flowers MED, Meyers JD, Bowden RA. Long-term acyclovir for prevention of varicella zoster virus disease after allogeneic hematopoietic cell transplantation–a randomized double-blind placebo-controlled study. *Blood*. 2006;107(5):1800-1805. https://doi.org/10.1182/blood-2005-09-3624
77. Oshima K, Takahashi T, Mori T, et al. One-year low-dose valacyclovir as prophylaxis for varicella zoster virus disease after

allogeneic hematopoietic cell transplantation. A prospective study of the Japan Hematology and Oncology Clinical Study Group. *Transpl Infect Dis*. 2010;12(5):421-427. https://doi.org/10.1111/j.1399-3062.2010.00541.x

78. Li CR, Greenberg PD, Gilbert MJ, Goodrich JM, Riddell SR. Recovery of HLA-restricted cytomegalovirus (CMV)-specific T-cell responses after allogeneic bone marrow transplant: correlation with CMV disease and effect of ganciclovir prophylaxis. *Blood*. 1994;83(7):1971-1979.
79. Boeckh M, Nichols WG, Chemaly RF, et al. Valganciclovir for the prevention of complications of late cytomegalovirus infection after allogeneic hematopoietic cell transplantation: a randomized trial. *Ann Intern Med*. 2015;162(1):1-10. https://doi.org/10.7326/M13-2729
80. Winston DJ, Young J-A, Pullarkat V, et al. Maribavir prophylaxis for prevention of cytomegalovirus infection in allogeneic stem cell transplant recipients: a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. *Blood*. 2008;111(11):5403-5410. https://doi.org/10.1182/blood-2007-11-121558
81. Marty FM, Ljungman P, Papanicolaou GA, et al. Maribavir prophylaxis for prevention of cytomegalovirus disease in recipients of allogeneic stem-cell transplants: a phase 3, double-blind, placebo-controlled, randomised trial. *Lancet Infect Dis*. 2011;11(4):284-292. https://doi.org/10.1016/S1473-3099(11)70024-X
82. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. *N Engl J Med*. 2017;377(25):2433-2444. https://doi.org/10.1056/NEJMoa1706640

How to cite this article: Akhmedov M. Infectious complications in allogeneic hematopoietic cell transplant recipients: Review of transplant-related risk factors and current state of prophylaxis. *Clin Transplant*. 2020;00:e14172. https://doi.org/10.1111/ctr.14172