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ARTICLE TITLE

Antimicrobial prophylaxis and preemptive approaches for the prevention of infections in the stem cell transplant recipient, with analogies to the hematologic malignancy patient

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DISCLOSURE STATEMENT

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KEYWORDS

Hematopoietic cell transplantation, neutropenia, antibiotic prophylaxis, empirical treatment, preemptive treatment, antibiotics, infectious complications.

KEY POINTS

- Routine antibacterial prophylaxis with a *Pseudomonas*-acting fluoroquinolone is currently recommended by most expert guidelines during prolonged and profound neutropenia.
- Antifungal prophylaxis is routinely administered following allogeneic HCT, against (predominately) *Candida* spp. pre-engraftment and with mold-active azoles post-engraftment, during graft-versus-host disease.
- Anti-herpes simplex / varicella-zoster virus (VZV) prophylaxis is routinely administered in all allogeneic HCT recipients. VZV-prophylaxis may be continued for as long as 1-year following allogeneic HCT.
- Prevention of cytomegalovirus (CMV) disease can include routine CMV prophylaxis or preemptive treatment based on CMV viral activity monitoring.
- Hepatitis B and C positive individuals should not be excluded from donors and recipients of allogeneic HCT transplant.
- Empirical and preemptive antibiotic treatment are frequently used in the management of neutropenic fever.

SYNOPSIS

Infectious complications represent one of the most common causes of morbidity and mortality in allogeneic hematopoietic cell transplant (HCT) recipients. Prophylactic and preemptive treatment strategies against bacterial, fungal, viral, and parasitic pathogens are routinely implemented during high-risk post-HCT periods at most transplant centers. The basic concepts and review of current guidelines of antibiotic prophylaxis and empirical/preemptive antibiotic treatment in allogeneic HCT recipients are reviewed in this chapter.

INTRODUCTION

1. GENERAL CONCEPTS

Infectious complications represent one of the most common causes of morbidity and mortality in allogeneic hematopoietic cell transplant (HCT) recipients. The effect of conditioning chemotherapy during the pre-engraftment period, namely neutropenia and gastrointestinal tract (GIT) mucositis, is similar to other patients treated with intensive chemotherapy regimens, including patients with hematologic malignancies and/or autologous HCT recipients. Hence, most of the recommendations discussed in this chapter for allogeneic HCT recipients during the pre-engraftment period may also apply to most patients treated with intensive chemotherapy regimens with anticipated neutropenia for >7 days [1-4]. Definitions important for the understanding of this chapter are summarized in **Table 1**. Notably, prophylactic and preemptive strategies may vary from consensus guidelines and amongst different institutions, based on HCT practices and local epidemiology.

1.1. Infection risk and timing after hematopoietic cell transplantation

Risk factors for infectious complications heavily depend on the timing after an allogeneic HCT. Historically, three at-risk periods have been identified: (a) pre-engraftment: starting with conditioning initiation until engraftment, (b) early post-engraftment: until day (D) 100 post-HCT, and (c) late post-engraftment: after D100 post-HCT (**Figure 1**). Furthermore, the presence of central venous catheters (CVC) represents another major risk factor for infectious complications.

1.2. Pre-engraftment period.

The main risk factors for infectious complications pre-engraftment include gastrointestinal tract (GIT) mucositis and neutropenia. Mucositis represents the disruption of the GIT mucosa, allowing for gut flora to translocate and cause bloodstream infections (BSI) due to gram-positive cocci (e.g. *viridans*-group *Streptococcus* species, Enterococci), gram-negative bacilli (i.e. *Enterobacteriaceae, Pseudomonas aeruginosa*), and *Candida* species. Chemotherapy induced neutropenia, the second

major risk factor for infections during pre-engraftment, is associated with viral reactivation (i.e. herpes simplex virus, HSV- I and II, and varicella-zoster virus, VZV) and invasive fungal infections (IFI) due to molds, mainly *Aspergillus* species [5,6].

1.3. Early post-engraftment period.

Impaired cellular immunity due to acute graft-versus-host disease (GvHD) with associated treatments represents the major risk factor early post-engraftment. Most common infections include viral infections [i.e. VZV, cytomegalovirus (CMV), Epstein-Barr virus (EBV), or human herpes virus 6 (HHV-6)] and IFI, including *Pneumocystis jirovecii* and invasive mold infections (IMI), with *Aspergillus* species being the most commonly identified molds, followed by the Zygomycetes and *Fusarium* species [5-7]. Furthermore, acute GIT GvHD may lead to gut flora translocation.

1.4. Late post-engraftment period.

The main risk factor for infectious complications in the late post-engraftment period is lack of adequate immune reconstitution, which may take between 6 to 12 months. Furthermore, chronic GvHD and associated treatments further delay cellular immune reconstitution. Reactivation of viral infections (i.e. CMV, EBV, HHV-6) and IFI, including *Pneumocystis jirovecii* and IMI, represent the most frequently encountered infections during this stage. *Aspergillus* species remain the most commonly identified mold during this period as well, albeit the sum of other mold infections (due to the Zygomycetes, *Fusarium* and *Scedosporium* species) are likely proportionally more frequent [5-7]. In addition, impaired humoral immunity increases the risk for infections due to encapsulated bacteria (i.e. *Streptococcus pneumoniae*).

2. ANTIBACTERIAL PROPHYLAXIS

2.1. Antibacterial prophylaxis - Pre-engraftment period.

In a meta-analysis of >100 clinical trials of antibacterial prophylaxis during neutropenia, administration of fluoroquinolones was shown to significantly decrease infection-related mortality, febrile episodes, clinically and microbiologically documented infections, and BSI [8]. In a landmark clinical trial 760 adult patients with cancer and chemotherapy-induced neutropenia were randomized to administration of levofloxacin and placebo [9]. Mortality and tolerability were similar in both groups, whereas patients in the levofloxacin arm were less likely to develop a microbiologically documented bacterial infection and BSI. In a recent meta-analysis of two randomized clinical trials and 12 observational studies performed between 2006 and 2014, primary antibacterial prophylaxis with a fluoroquinolone was not associated with a survival benefit, although an association with lower rates of neutropenic fever and bloodstream infections was demonstrated[10]. Based on the above, administration of primary antibacterial prophylaxis with a fluoroquinolone is recommended by most expert guidelines for high-risk patients treated with chemotherapy and anticipated neutropenia for >7 days, including allogeneic HCT recipients (**Figure 2**) [1,3,4]. Most transplant centers use a fluoroquinolone with anti-*Pseudomonas aeruginosa* activity (ciprofloxacin or levofloxacin) for primary antibacterial prophylaxis. Levofloxacin has a broader antibacterial profile, to include gram-positive cocci, such as viridans-group *Streptococcus* species. Although breakthrough infections have been reported in patients who receive prophylaxis with fluoroquinolones, addition of an antibacterial agent (i.e. amoxicillin, vancomycin) to a fluoroquinolone to improve gram-positive coverage is not recommended [1]. Notably, antibacterial prophylaxis selection should be based on local epidemiology [1,3,10].

2.1.a. Timing of antibacterial prophylaxis.

Timing of antibacterial prophylaxis initiation may vary, beginning anywhere between chemotherapy initiation, stem cell infusion, or the first day of neutropenia, at different centers. A large meta-analysis of >100 clinical trials showed no difference in all-cause mortality when antibacterial prophylaxis was started at the time of chemotherapy initiation or with neutropenia [8]. Current

guidelines suggest that initiation of antibacterial prophylaxis should be considered at the time of cell infusion and continued until neutropenia resolution or initiation of empirical broad-spectrum antibiotic therapy [1,3].

2.1.b. Antibacterial resistance.

Concerns for increased rates of fluoroquinolone resistance have been raised with routine antibacterial prophylaxis with fluoroquinolones [8]. A recent prospective international study in allogeneic and autologous HCT recipients from 65 transplant centers in 25 countries identified fluoroquinolone prophylaxis as a significant risk factor for fluoroquinolone resistance [11]. Continuous vigilance and monitoring of resistance to fluoroquinolones is strongly advised for centers with routine use of these agents for antibacterial prophylaxis [1,10].

2.2. Antibacterial prophylaxis - Post-engraftment period.

Routine antibacterial prophylaxis against encapsulated bacterial pathogens, particularly *Streptococcus pneumoniae,* is recommended until 1-year following HCT (**Figure 2**) [1,3]. The selection of the appropriate agent depends on the local epidemiology and may include administration of penicillin, a macrolide or a fluoroquinolone [1,3]. Gut flora translocation remains a major concern in patients with severe acute and/or chronic GIT GvHD. There are no formal recommendations as to the administration of antibacterial prophylaxis in such patients, however some centers may select to initiate appropriate antibacterial prophylaxis in the setting.

3. ANTIFUNGAL PROPHYLAXIS

3.1. Antifungal prophylaxis - Pre-engraftment.

3.1.a. Fluconazole.

Fluconazole has been the mainstay of antifungal prophylaxis and is currently recommended as primary antifungal prophylaxis during the pre-engraftment period in allogeneic and autologous HCT recipients, based on a large number of data, ease of administration, predictable drug interactions and a benign side-effect profile (**Figure 3**) [1,3]. In the pivotal prospective randomized clinical trials, administration of fluconazole prophylaxis was associated with significantly lower incidence of candidemia and improved overall survival in allogeneic (and autologous) HCT recipients [12-14]. In these clinical trials, fluconazole prophylaxis was started with or at the end of conditioning regimen and continued up to 75-100 days post-transplant [12-14]. Administration of fluconazole for 75 days post-HCT has been associated with a lower incidence of GIT GvHD and a significant 8-year survival benefit compared to placebo [13]. Fluconazole has no activity against *C. krusei* and molds, including *Aspergillus* species. Moreover, increasing resistance to fluconazole among *C. glabrata* strains has been reported [15]. For patients at higher risk for IMI or colonized with fluconazole resistant *Candida* species, alternative approaches, such as administration of mold-active azoles (**3.2.b. Mold-active azoles**) or echinocandins (**3.2.c. Echinocandins**) should be considered [1].

3.1.b. Mold-active azoles.

Attempts to study itraconazole as a potential antifungal prophylactic agent failed, mainly due to poor tolerability, toxicities and drug interactions [16]. Voriconazole was compared to fluconazole as antifungal prophylaxis in allogeneic transplant recipients between D0 and D100 post-HCT in a multi-center prospective randomized clinical trial [17]. Although there was a trend for fewer IA infections in the voriconazole arm, there was no significant benefit in terms of fungal-free survival, IFI incidence, or empirical antifungal treatment [17]. Posaconazole and isavuconazole have not been studied as antifungal prophylaxis during the pre-engraftment period. Despite the lack of strong data, pre-

engraftment antifungal prophylaxis with voriconazole or posaconazole is used in a number of transplant centers considering their extended spectrum of activity, particularly in patients at higher risk for mold infections, such as those with profound and prolonged neutropenia (e.g. cord transplant recipients) or a diagnosis of an IMI prior to HCT [1].

3.1.c. Echinocandins.

Echinocandins have been considered for antifungal prophylaxis, based on their broad spectrum of activity, including fluconazole-resistant *Candida* species and *Aspergillus* species, benign side-effect profile and minimal drug interactions [3,18]. Micafungin was superior to fluconazole as antifungal prophylaxis during neutropenia in >800 pediatric and adult HCT recipients in terms of absence of IFI by the end of antifungal prophylaxis and requirement for empirical antifungal therapy [18]. Although echinocandin use is limited due to requirement for IV administration and sometimes financial costs, micafungin prophylaxis may be considered in patients colonized with azole-resistant *Candida* species, during conditioning to avoid interactions between an azole and the administered chemotherapy, or patients with abnormal liver function and/or at risk for QTc prolongation [1,3].

3.1.d. Amphotericin B products.

Although variable doses of different amphotericin B formulations have been studied, prophylaxis with amphotericin B products is not currently recommended due to lack of beneficial outcomes and toxicity concerns [1,19].

3.2. Antifungal prophylaxis - Post-engraftment.

Current guidelines recommend posaconazole as antifungal prophylaxis in allogeneic HCT recipients with GvHD requiring treatment with high-dose (>1 mg/kg/day) corticosteroids [1,3]. This recommendation is based on the results of an international, double-blind clinical trial, where 600 allogeneic HCT recipients with GvHD were randomized 1:1 to posaconazole and fluconazole

prophylaxis [20]. Posaconazole administration decreased the incidence of breakthrough IFI, IA and IFI-related mortality, but had no effect on overall survival [20]. In another study of patients with acute myeloid leukemia with prolonged neutropenia, administration of posaconazole vs. fluconazole/itraconazole was associated with a lower incidence of proven and probable IFI and IA and improved overall survival [21]. These studies have led to the widespread use of posaconazole as anti-mold prophylaxis in high-risk patients. Multiple concerns have been raised on the generalizability of this approach, considering the: (a) high numbers of patients that need to be treated, particularly at centers with low incidence of IA and IMI, (b) unnecessary exposure to potential drug-associated toxicities and interactions, (c) associated costs, and (d) antibiotic pressure for breakthrough IFI with resistant pathogens [22]. Ultimately, the selection of mold-active prophylaxis in high-risk allogeneic HCT recipients after engraftment remains a decision based on the interpretation of the existing body of literature, local epidemiology and economic considerations at each institution.

3.3. *Pneumocystis jirovecii* prophylaxis

Allogeneic HCT recipients should receive routine prophylaxis against *Pneumocystis jirovecii* [1,3]. Prophylaxis can be started at the time of transplantation or post-engraftment and is continued for a minimum of 6 to 12 months post-HCT [1,3]. A strong body of evidence supports the use of trimethoprim-sulfamethoxazole (TMP-SMX) as the preferred *Pneumocystis* prophylaxis, as a single-strength tablet once daily or a double-strength tablet three times weekly [1,3]. Due to potential myelosuppression, many centers do not initiate PJP prophylaxis with TMP-SMX before engraftment [1,3]. A potentially additional benefit of TMP-SMX is its broad-spectrum of activity to include *Nocardia* and *Toxoplasma* species and common respiratory, urinary tract and GIT pathogens. For patients allergic to TMP-SMX, desensitization should be strongly considered [1,3]. Alternative, albeit inferior to TMP-SMX, options include administration of atovaquone, once monthly aerosolized pentamidine and dapsone. Administration of dapsone should be avoided in patients with severe allergy to TMP-SMX and deficient for G6PD and aerosolized pentamidine has been associated with bronchospasm.

4. ANTIVIRAL PROPHYLAXIS

4.1. Herpes simplex virus (HSV).

Up to 60-80% of HSV-seropositive HCT recipients or patients with acute leukemia can reactivate HSV [1,3]. Anti-HSV prophylaxis with oral acyclovir or valacyclovir is recommended for HCT recipients and patients with acute leukemia (**Figure 4**) [1,3]. Valacyclovir is a valyl ester of acyclovir, with the same spectrum of activity but significantly higher (up to 50-55%) bioavailability. In patients with severe mucositis and/or GIT GvHD who are not able to absorb oral medications, acyclovir can be administered intravenously. Although not approved for prophylaxis in allogeneic HCT recipients in the United States, valacyclovir is used frequently based on its half-life allowing less frequent dosing, high bioavailability, and safety profile [1,3]. Antiviral prophylaxis should be initiated with chemotherapy or conditioning regimen initiation and continued until resolution of neutropenia [1,3]. For patients with frequent episodes of HSV reactivation or allogeneic HCT recipients with GvHD, longer courses of prophylaxis are recommended [1,3].

4.2. Varicella-zoster virus (VZV).

Up to 30% of VZV-seropositive HCT recipients may reactivate VZV, if antiviral prophylaxis is not administered [23]. Antiviral prophylaxis with oral acyclovir or valacyclovir should be administered in all VZV-seropositive HCT recipients, starting at the time of conditioning administration and until at least 1-year post-HCT (**Figure 4**) [1,3,23,24]. Continuation of antiviral prophylaxis for one-year post-HCT has been associated with significant reduction in VZV reactivation and overall mortality [24]. Recent data suggest that prolongation of prophylaxis, even beyond the first year post-HCT, may have a beneficial effect on VZV suppression, without preventing patients to develop protective VZV immunity [23,24]. Longer duration of anti-VZV prophylaxis should be considered in patients with continued immunosuppression, such as patients with chronic GvHD requiring treatment with high-dose corticosteroids [1,3].

4.3. Cytomegalovirus (CMV).

Cytomegalovirus infection is one of the most frequent complications after an allogeneic HCT, associated with significant morbidity and mortality [25-28]. CMV infection/reactivation is defined as the detection of the virus or viral particles in any body fluid or tissue [29]. CMV disease is defined as a viral syndrome and/or end-organ disease due to CMV [29]. CMV infection, as documented by a positive pp65 antigenemia and/or (almost exclusively today) with a CMV quantitative polymerase chain reaction (qPCR) assay, can develop into CMV disease if not treated [25,26,28]. Due to the devastating and complex consequences of CMV infection and disease in allogeneic HCT recipients, prevention of CMV infection has become standard in the management of these patients [25-28].

CMV-seronegative recipients who receive a graft from CMV-seronegative donors have the lowest risk to develop CMV infection. It is strongly recommended that CMV-seronegative recipients receive grafts from CMV-seronegative donors and transfusions of CMV-seronegative and/or leukocyte depleted blood products [1]. CMV-seropositive recipients from a CMV-seronegative donor are at highest risk for CMV reactivation, followed by HCT recipients of CMV-seropositive donors [28]. CMV-seropositive recipients of cord blood grafts are at particularly high risk for CMV reactivation [28]. For CMV-seropositive HCT recipients and/or donors, there are two major approaches to prevent CMV disease: administration of primary anti-CMV prophylaxis and preemptive anti-CMV treatment (**Figure 5**). There have been multiple clinical trials to evaluate the efficacy and safety of both approaches [25,30-34]. In the following sections a brief discussion will follow, focusing on current recommendations and pertinent data on both clinical approaches.

4.3.a. Primary CMV prophylaxis.

A large number of antivirals has been studied as primary CMV prophylaxis in allogeneic HCT recipients, including acyclovir, valacyclovir, ganciclovir, foscarnet and valganciclovir [25]. Considering the associated toxicities and costs, CMV prophylaxis is predominately considered in high-risk

patients, such as recipients of cord blood or T-cell depleted grafts [1]. The concept of using high doses of acyclovir/valacyclovir for CMV suppression is used infrequently, due to the indirect activity / low efficacy of these agents against CMV. However, they may provide enough coverage of CMV that a number of minor CMV blood viremia reactivations are blocked. The administration of CMV-active agents, such as ganciclovir/valganciclovir or foscarnet, for CMV prophylaxis has been hindered by several important associated drug-toxicities: cytopenias for ganciclovir/valganciclovir and nephrotoxicity for foscarnet. Recently, three new agents with activity against CMV and better side-effect profile have been considered for primary CMV prophylaxis in allogeneic HCT recipients, including letermovir, brincidofovir, and maribavir [35-38]. Although initially promising, clinical trial results have failed to show a benefit associated with brincidofovir and maribavir, due to dosing and toxicity issues [36-38]. More recently, letermovir for CMV prophylaxis during the first 100 days in adult CMV-seropositive allogeneic HCT recipients was compared to a placebo-based preemptive approach in a large prospective randomized multicenter phase-3 clinical trial [35]. By week 24, clinically significant CMV disease, defined as CMV disease and infection requiring initiation of CMV treatment, and mortality were significantly lower in the letermovir arm vs. placebo. Letermovir has no activity against HSV and VZV, hence additional anti-herpetic prophylaxis is required. Based on the results of this study, the European Conference of Infections in Leukemia (ECIL) has endorsed letermovir for CMV prophylaxis in allogeneic HCT recipients [39]. US guidelines have not included letermovir as yet, as they were published before relevant data were available.

4.3.b. Preemptive CMV therapy.

Due to potential drug toxicities and costs associated with universal primary CMV prophylaxis, most transplant centers today practice a preemptive approach for CMV prevention. Preemptive therapy with ganciclovir, valganciclovir and foscarnet has been validated by several clinical trials [30-34]. A preemptive approach consists of regular monitoring of CMV reactivation with a CMV qPCR assay [1,39]. Weekly CMV qPCR monitoring is usually performed, starting on the day of engraftment and

continued until day-100 following HCT [1,39]. More frequent monitoring should be applied in high-risk patients, such as recipients of umbilical cord blood or T-cell depleted allografts [1,39]. CMV qPCR monitoring should be continued beyond day-100 in patients with GvHD requiring immunosuppressive treatment with corticosteroids [1,39].

4.3.b.1. CMV threshold for preemptive treatment initiation. There are no definitive CMV viral load cutoffs above which preemptive treatment should be started. At most centers, preemptive therapy is started when a CMV qPCR is >500-1000 IU/mL. Cutoffs as low as 150 IU/mL have been used, based on local guidelines and standard operating procedures at each center. In a recently published retrospective study, initiation of preemptive treatment at CMV PCR titers of 135-440 IU/mL was associated with faster viremia resolution and lower rates of prolonged viremia and duration of antiviral treatment [40].

4.3.b.2. Preemptive treatment agent selection. Preemptive therapy can include ganciclovir, valganciclovir or foscarnet [1,3,39]. The agent selection depends on the time of CMV infection post-HCT for an individual patient, and institutional protocols. Due to potential myelosuppression, ganciclovir/valganciclovir are generally avoided in the pre- and early post-engraftment periods, during which foscarnet is usually favored by most transplant centers [1]. Administration of valganciclovir should be avoided in patients with GIT GvHD, due to potential poor absorption in the setting of almost any amount of diarrhea [39]. Foscarnet is avoided in patients with renal function impairment or in case of co-administration with other potentially nephrotoxic agents. Cidofovir may be considered as secondary preemptive treatment approach in specific cases, such as in patients treated with foscarnet for transition to outpatient treatment based on its convenient once weekly dosing, albeit limited data are available [39].

4.3.b.3. Preemptive treatment dosing and duration. Induction dose of CMV preemptive therapy is usually administered for 2-3 weeks with transition to maintenance dose treatment for 2-3 weeks and/or until an undetectable CMV viral load is documented by CMV qPCR [1,39]. Approaches may differ at different centers, according to the study operating procedures at each institution.

4.3.c. Additional concepts.

There are no adequate data to support the use of intravenous administered immunoglobulin or CMV-vaccines for the prevention of CMV infection in allogeneic HCT recipients. Similarly, there are not adequate data on the use of CMV-specific interferon-gamma producing T-cells for the management of CMV infection [1,39].

4.4 Epstein-Barr virus (EBV).

Frequent EBV monitoring with an EBV qPCR assay is recommended during the first 100 days post-allogeneic HCT, particularly for patients at higher risk for post-transplant lymphoproliferative disease, such pediatric patients and cord blood, haplo-identical and T-cell depleted graft recipients [1]. Monitoring of EBV reactivation should be continued beyond day 100, in case of GvHD and associated treatment [1]. The major concern about EBV reactivation is the development of post-transplant lymphoproliferative disorder, associated with the graft type and GvHD prophylaxis regimen selection [1,41]. A preemptive approach for the management of EBV reactivation is applied in most transplant centers. Although EBV viral load thresholds for preemptive treatment initiation are not as well defined, interventions, including reduction of immunosuppression and/or administration of rituximab, are applied for >1,000 copies/mL [1].

4.5. Hepatitis B virus (HBV)

Routine pretransplant and prechemotherapy HBV testing for all HCT donors and recipients is recommended, including: HBV surface antigen (HBsAg), HBV surface antibody (HBsAb), HBV core

antibody (HBcAb) and HBV DNA (**Figure 6**) [1]. Hepatitis B vaccination is recommended in all HBV-naïve patients who undergo chemotherapy and/or HCT [1]. If HBV vaccination cannot be initiated or completed before initiation of chemotherapy or stem cell infusion, HCT-naive recipients should be vaccinated or complete their vaccination as soon as their immunity is restored post-HCT [1]. Patients at risk for HBV primary infection or reactivation should receive prophylaxis with an anti-HBV active agent at the time of conditioning and at least for another 6 months after discontinuation of all immunosuppression [1]. Entecavir and tenofovir are preferred over lamivudine, due to their higher efficacy and resistance barrier [42]. Appropriate antiviral treatment, preferably with entecavir, should be immediately initiated in patients with active HBV viremia at the time of chemotherapy or transplant and close monitoring of liver function and HBV viral load should apply.

4.5.a. HCT donor and HBV.

HBV naïve recipients should preferably receive a graft from HBsAg-negative donors [1]. However, HBV serostatus should not exclude potential HCT donors and HBsAg and/or HBV DNA-positive individuals can be considered as potential HCT donors [1]. Specific treatment and monitoring approaches are in place for HBsAg-positive positive donors and recipients to limit HBV transmission (**Figure 6a**) [1,43].

4.5.b. HCT recipient and HBV.

HBV recipients can be high, moderate and low risk based on their HBV serology constellation:
(i) High-risk: HBsAg and/or HBV DNA positive patients, (ii) moderate risk: HBcAb positive, HBsAg and HBsAb negative patients, particularly those that are HBV DNA positive, and (iii) low-risk: HBsAb and/or HBcAb positive patients. All high-risk HCT recipients should have a liver biopsy prior to their HCT and receive anti-HBV prophylaxis starting before conditioning [1,43]. For moderate risk HCT recipients, HBV DNA should be monitored, and if negative HBV vaccine should be administered. If HBV DNA is positive, patients should receive antiviral prophylaxis. Low-risk patients should have ALT and HBsAb levels monitored once every month and every three months, respectively, as detailed in

Figure 6b [1]. HBcAb and HBsAb-positive recipients with GvHD requiring prolonged steroid treatment courses are at higher risk for HBV reactivation and thus should receive antiviral prophylaxis [1]. Due to ease of administration, benign adverse event profile, and few drug interactions, most centers administer HBV prophylaxis in low risk patients as well.

4.6. Hepatitis C virus (HCV)

Based on current guidelines, HCV seropositivity for the donor or the recipient is not an absolute contraindication for an allogeneic HCT [1]. Close monitoring of these patients and all efforts possible to decrease the risk of transmission and/or progression of HCV infection post-HCT is highly recommended [1]. HCV-seropositive, HCV RNA-positive donors should receive direct-acting antiviral (DAA) HCV-specific treatment, with the ultimate goal to achieve undetectable HCV viral load at the time of harvest [44]. HCV-seropositive, HCV RNA-positive recipients should receive treatment with a DAA agent, when possible [1,44]. There are no definitive data to suggest what time post-HCT DAA HCV-specific treatment should be initiated, but most experts would agree to treatment initiation in about 6 months post-HCT or after all immunosuppressive therapy is tapered [44]. HCV-seropositive recipients with fibrosis, cirrhosis or HCV-associated lymphoproliferative disorder should be treated as soon as possible [44]. HCV-seropositive recipients should be carefully monitored for HCV progression and long-term complications [1,44]. Myeloablative conditioning regimens, particularly those containing cyclophosphamide and total body irradiation, should be avoided due to increased risk of post-HCT complications, including sinusoidal obstruction syndrome [1].

5. PARASITIC PROPHYLAXIS

5.1. *Toxoplasma gondii* prophylaxis

Toxoplasmosis remains an uncommon complication after an allogeneic HCT, due to reactivation of an old infection in the vast majority of cases [1,3]. HCT recipients of T-cell depleted or cord blood grafts and/or with GvHD are at higher risk for *Toxoplasma* reactivation [1]. Administration of TMP-SMX for PCP prophylaxis can also be protective for toxoplasmosis, although dosing of TMP-SMX for prevention of toxoplasmosis has not, as yet, been well defined [1,3]. In patients at high risk for toxoplasmosis not receiving prophylaxis with TMP-SMX, screening by a qPCR for *Toxoplasma* species should be performed, albeit frequency of monitoring has not been established. This is discussed further in Chapter 12.

6. EMPIRICAL ANTIBACTERIAL AND ANTIFUNGAL TREATMENT FOR NEUTROPENIC FEVER

6.1. General concepts of neutropenic fever management.

Neutropenic fever represents the most common complication of neutropenic patients, but a definitive bacterial infection is diagnosed in <25% of these patients [1,2]. Due to the inability of neutropenic patients to generate an adequate immune response and rapid progression to sepsis, prompt initiation of appropriate antibiotic therapy has become the standard of care since decades. Empirical antibacterial treatment should include a bactericidal, well-tolerated and broad-spectrum agent, with activity against gram-positive and gram-negative organisms, including *Pseudomonas aeruginosa* [2]. In this review, neutropenic fever management will be discussed only for high-risk patients. All high-risk patients with neutropenic fever should be admitted to the hospital for prompt initiation of a detailed and comprehensive diagnostic work-up, parallel to antibiotic treatment initiation. Details on the diagnostic work-up of neutropenic fever are presented in **Chapter 5: Work-up for fever during neutropenia.**

6.2. Antibacterial empirical treatment - Initial neutropenic fever.

In high-risk patients with neutropenic fever, intravenous administration of an appropriately dosed β-lactam with antipseudomonal activity: piperacillin-tazobactam, cefepime, imipenem-cilastatin or meropenem, should be promptly initiated [2]. Concerns due to increased 30-day mortality associated with cefepime were raised, based on the results of a meta-analysis [45]. However, a new meta-analysis initiated by the Federal Drug Administration, in which more studies of cefepime in patients with febrile neutropenia were included, did not corroborate the findings of the prior study and hence cefepime remains a first-line agent for the management of febrile neutropenia [2]. Additional concepts considered in the selection of initial antibiotic treatment for neutropenic fever are presented in **Table 2.**

6.3. Antibacterial empirical treatment - Persistent neutropenic fever.

Persistent neutropenic fever, defined as neutropenic fever after 3-5 fays of empirical antibiotic treatment, is a frequent occurrence in allogeneic HCT recipients and leukemia patients receiving induction chemotherapy. High-risk patients with neutropenic fever may remain febrile for an average of 5 days, despite administration of empirical treatment [2]. In most cases, patients will defervesce with resolution of neutropenia without an identified infectious etiology [2]. Persistent neutropenic fever in hemodynamically stable patients should not always generate additional antibiotic changes [2]. However, antibiotic escalation is frequently applied, particularly in unstable patients or patients with persistent profound neutropenia (**Table 3**) [2].

6.4. Duration of empirical antibacterial treatment for neutropenic fever.

Historically, neutropenic patients started on empirical antibiotic treatment for neutropenic fever remain on broad-spectrum empirical antibiotic therapy until both fever and neutropenia are resolved [2,46]. This approach has been recently challenged, considering the lack of robust data and significant improvements in the diagnosis and treatment of infectious complications and in the management of neutropenic patients achieved during the last four decades [47,48]. De-escalation to a fluoroquinolone has been suggested for low-risk patients and in cases of completion of a recommended antibiotic treatment course for a specific infection in an afebrile patient who remains neutropenic [2]. The recently revised ECIL recommendations for the management of patients with febrile neutropenia suggest that empirical antibiotic treatment can be discontinued after ≥72 hours in neutropenic patients who remain afebrile for ≥48 hours [47]. Secondary prophylaxis with a narrower-spectrum agent, such as a fluoroquinolone, may be used, depending on local epidemiology [47,48]. In a recent superiority open-label prospective randomized clinical trial, 158 hematologic malignancy patients or HCT recipients with high-risk febrile neutropenia were randomized 1:1 to two arms: an experimental arm, in which empirical treatment was discontinued ≥72 hours after fever resolution and a control arm, with empirical treatment continued until neutropenia resolution [49]. Less total days of empirical antibiotic treatment and side effects were observed in the experimental group, while days of fever,

recurrent fever and mortality were similar in both arms. Although not definitive, the results of this study can reignite the discussion on the efficacy and safety of empirical treatment discontinuation in certain subsets of neutropenic patients.

6.5. Antifungal empirical treatment.

Empirical antifungal treatment is defined as the initiation of a broad-spectrum antifungal agent in the setting of neutropenic fever that persists after 4-7 days of empirical antibacterial treatment based on high clinical suspicion for an IFI (**Figure 7**) [2]. The concept of empirical antifungal treatment was introduced in the early 1980s with the landmark study by Pizzo et al showing decreased mortality after the introduction of empirical treatment with conventional amphotericin B in patients with neutropenic fever [50]. Empirical antifungal treatment has been widely practiced ever since, with multiple clinical trials validating the use of amphotericin B lipid formulations, broad-spectrum azoles and echinocandins [1,51-53]. However, the low incidence of IFI, treatment associated-toxicities and costs, and improved diagnostic modalities for the detection of IFI have led to the investigation of other approaches, namely antifungal preemptive treatment.

6.6. Antifungal preemptive treatment.

Antifungal preemptive treatment is defined as initiation of early antifungal treatment based on clinical, laboratory and radiographic evidence of an early IFI. This approach has been possible, because of the significant progress attained in the field of IA diagnosis. Identification of the halo-sign, crescent-sign and nodular lesions on chest computed tomography (CT) as signs of IA has led to early diagnosis of IA and prompt initiation of appropriate treatment, leading to improved survival outcomes [54-56]. In addition, fungal biomarkers, such as the GM EIA and b-D glucan have been introduced in clinical practice in the last two decades and may lead to earlier diagnosis of IMI. Maertens et al were the first to assess the feasibility of a preemptive antifungal approach in a cohort of neutropenic patients receiving fluconazole prophylaxis [56]. Initiation of treatment with liposomal

amphotericin B was based on predefined chest CT findings and positive microbiologic evidence, including a positive GM EIA (two consecutive GM EIA tests with an optical density index, ODI >0.5). A 78% reduction in antifungal treatment administration was observed, when compared to empirical antifungal treatment based on pre-defined criteria. This study was followed by a multicenter, open-label randomized non-inferiority clinical trial comparing empirical and preemptive antifungal treatment in hematologic malignancy patients with neutropenia; no allogeneic HCT recipients were included in this trial [57]. An ODI ≥1.5 was considered for GM EIA positivity. Overall survival at 14-days post-neutropenia recovery, IFI-associated mortality, duration of neutropenic fever and length of hospital stay were similar between the two arms. Preemptive antifungal treatment was associated with decreased costs of antifungal therapy by 35%, but more proven and probable IFI (IA and *Candida* infections) compared to empirical antifungal treatment. Notably, almost half patients did not receive any antifungal prophylaxis, which could have contributed to more candidal infections. Although not studied in allogeneic HCT recipients, most centers follow a preemptive antifungal treatment approach in the pre-engraftment period in cases of persistent neutropenic fever.

Figure Legends

Figure 1. Timing of risk factors and infectious complications in allogeneic hematopoietic cell transplant (HCT) recipients, starting with conditioning until 1-year post-HCT.

Figure 2. Bacterial prophylaxis during the first year after an allogeneic hematopoietic cell transplant. (Adapted from Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant.* 2009;15(10):1143-1238; and 2.2016 NGV. Prevention and treatment of Cancer-Related Infections. *National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines)* 2016; https://oralcancerfoundation.org/wp-content/uploads/2016/09/infections.pdf. Accessed 30 September, 2018; with permission.)

Figure 3. Antifungal prophylaxis during the first year after an allogeneic hematopoietic cell transplant. (Adapted from Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant.* 2009;15(10):1143-1238; and 2.2016 NGV. Prevention and treatment of Cancer-Related Infections. *National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines)* 2016; https://oralcancerfoundation.org/wp-content/uploads/2016/09/infections.pdf. Accessed 30 September, 2018; with permission.)

Figure 4. Anti-herpetic prophylaxis during the first year after an allogeneic hematopoietic cell transplant. (Adapted from Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant.* 2009;15(10):1143-1238; and 2.2016 NGV. Prevention and treatment of Cancer-Related Infections. *National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines)* 2016; https://oralcancerfoundation.org/wp-content/uploads/2016/09/infections.pdf. Accessed 30 September, 2018; with permission.)

Figure 5. Cytomegalovirus prophylaxis and preemptive treatment during the first year after an allogeneic hematopoietic cell transplant . (Adapted from Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant.* 2009;15(10):1143-1238; and 2.2016 NGV. Prevention and treatment of Cancer-Related Infections. *National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines)* 2016; https://oralcancerfoundation.org/wp-content/uploads/2016/09/infections.pdf. Accessed 30 September, 2018; with permission.)

Figure 6. Management of hepatitis B virus (HBV) infection in allogeneic hematopoietic cell transplant recipients (HCT): (a) in case of HBV DNA / HBV surface antigen (HBsAg) positive HCT donors and (b) HBsAg / HBV core antibody positive HCT recipients. (Adapted from Tomblyn M,

Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant.* 2009;15(10):1143-1238; and 2.2016 NGV. Prevention and treatment of Cancer-Related Infections. *National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines)* 2016; https://oralcancerfoundation.org/wp-content/uploads/2016/09/infections.pdf. Accessed 30 September, 2018; with permission.)

References

1. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant.* 2009;15(10):1143-1238.
2. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. *Clin Infect Dis.* 2011;52(4):e56-93.
3. 2.2016 NGV. Prevention and treatment of Cancer-Related Infections. *National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines)* 2016; https://oralcancerfoundation.org/wp-content/uploads/2016/09/infections.pdf. Accessed 30 September, 2018.
4. 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.* 2018:JCO1800374.
5. Kontoyiannis DP, Marr KA, Park BJ, 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.
6. Marr KA, Carter RA, Crippa F, Wald A, Corey L. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. *Clin Infect Dis.* 2002;34(7):909-917.
7. Kontoyiannis DP, Wessel VC, Bodey GP, Rolston KV. Zygomycosis in the 1990s in a tertiary-care cancer center. *Clin Infect Dis.* 2000;30(6):851-856.
8. Gafter-Gvili A, Paul M, Fraser A, Leibovici L. Effect of quinolone prophylaxis in afebrile neutropenic patients on microbial resistance: systematic review and meta-analysis. *J Antimicrob Chemother.* 2007;59(1):5-22.
9. 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.
10. Mikulska M, Averbuch D, Tissot F, et al. Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines. *Journal of Infection.* 2018;76(1):20-37.
11. Averbuch D, Tridello G, Hoek J, et al. Antimicrobial Resistance in Gram-Negative Rods Causing Bacteremia in Hematopoietic Stem Cell Transplant Recipients: Intercontinental Prospective Study of the Infectious Diseases Working Party of the European Bone Marrow Transplantation Group. *Clin Infect Dis.* 2017;65(11):1819-1828.
12. Goodman JL, Winston DJ, Greenfield RA, et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. *N Engl J Med.* 1992;326(13):845-851.
13. 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.
14. Slavin MA, Osborne B, Adams R, et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation--a prospective, randomized, double-blind study. *J Infect Dis.* 1995;171(6):1545-1552.
15. Pfaller MA, Diekema DJ, Gibbs DL, et al. Results from the ARTEMIS DISK Global Antifungal Surveillance study, 1997 to 2005: an 8.5-year analysis of susceptibilities of Candida species and other yeast species to fluconazole and voriconazole determined by CLSI standardized disk diffusion testing. *J Clin Microbiol.* 2007;45(6):1735-1745.

16. Marr KA, Crippa F, Leisenring W, et al. Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants. *Blood.* 2004;103(4):1527-1533.
17. 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.
18. van Burik JA, 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.
19. Cordonnier C, Mohty M, Faucher C, et al. Safety of a weekly high dose of liposomal amphotericin B for prophylaxis of invasive fungal infection in immunocompromised patients: PROPHYSOME Study. *Int J Antimicrob Agents.* 2008;31(2):135-141.
20. 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.
21. 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.
22. De Pauw BE, Donnelly JP. Prophylaxis and aspergillosis--has the principle been proven? *N Engl J Med.* 2007;356(4):409-411.
23. Boeckh M, Kim HW, Flowers ME, 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.
24. Erard V, Guthrie KA, Varley C, et al. One-year acyclovir prophylaxis for preventing varicella-zoster virus disease after hematopoietic cell transplantation: no evidence of rebound varicella-zoster virus disease after drug discontinuation. *Blood.* 2007;110(8):3071-3077.
25. Chen K, Cheng MP, Hammond SP, Einsele H, Marty FM. Antiviral prophylaxis for cytomegalovirus infection in allogeneic hematopoietic cell transplantation. *Blood Adv.* 2018;2(16):2159-2175.
26. Green ML, Leisenring W, Xie H, et al. Cytomegalovirus viral load and mortality after haemopoietic stem cell transplantation in the era of pre-emptive therapy: a retrospective cohort study. *Lancet Haematol.* 2016;3(3):e119-127.
27. Yong MK, Ananda-Rajah M, Cameron PU, et al. Cytomegalovirus Reactivation Is Associated with Increased Risk of Late-Onset Invasive Fungal Disease after Allogeneic Hematopoietic Stem Cell Transplantation: A Multicenter Study in the Current Era of Viral Load Monitoring. *Biol Blood Marrow Transplant.* 2017;23(11):1961-1967.
28. Ljungman P. The role of cytomegalovirus serostatus on outcome of hematopoietic stem cell transplantation. *Curr Opin Hematol.* 2014;21(6):466-469.
29. Ljungman P, Boeckh M, Hirsch HH, et al. Definitions of Cytomegalovirus Infection and Disease in Transplant Patients for Use in Clinical Trials. *Clin Infect Dis.* 2017;64(1):87-91.
30. Boeckh M, Gooley TA, Myerson D, Cunningham T, Schoch G, Bowden RA. Cytomegalovirus pp65 antigenemia-guided early treatment with ganciclovir versus ganciclovir at engraftment after allogeneic marrow transplantation: a randomized double-blind study. *Blood.* 1996;88(10):4063-4071.
31. Einsele H, Reusser P, Bornhauser M, et al. Oral valganciclovir leads to higher exposure to ganciclovir than intravenous ganciclovir in patients following allogeneic stem cell transplantation. *Blood.* 2006;107(7):3002-3008.
32. van der Heiden PL, Kalpoe JS, Barge RM, Willemze R, Kroes AC, Schippers EF. Oral valganciclovir as pre-emptive therapy has similar efficacy on cytomegalovirus DNA load reduction as intravenous ganciclovir in allogeneic stem cell transplantation recipients. *Bone Marrow Transplant.* 2006;37(7):693-698.
33. Ayala E, Greene J, Sandin R, et al. Valganciclovir is safe and effective as pre-emptive therapy for CMV infection in allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant.* 2006;37(9):851-856.

34. Busca A, de Fabritiis P, Ghisetti V, et al. Oral valganciclovir as preemptive therapy for cytomegalovirus infection post allogeneic stem cell transplantation. *Transpl Infect Dis.* 2007;9(2):102-107.
35. 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.
36. 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.
37. Marty FM, Winston DJ, Rowley SD, et al. CMX001 to prevent cytomegalovirus disease in hematopoietic-cell transplantation. *N Engl J Med.* 2013;369(13):1227-1236.
38. Marty FM, Winston DJ, Chemaly R. Brincidofovir for Prevention of Cytomegalovirus (CMV) after Allogeneic Hematopoietic Cell Transplantation (HCT) in CMV-Seropositive Patients: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Phase 3 Trial. *Biol Blood Marrow Transplant.* 2016;22(3).
39. Update E-C. 7th European Conference on Infections in Leukaemia. 2017; http://www.ecil-leukaemia.com/telechargements/ECIL%207%20CMV%20final%20slides.pdf. Accessed September 30, 2018.
40. Tan SK, Waggoner JJ, Pinsky BA. Cytomegalovirus load at treatment initiation is predictive of time to resolution of viremia and duration of therapy in hematopoietic cell transplant recipients. *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology.* 2015;69:179-183.
41. Kanakry JA, Kasamon YL, Bolanos-Meade J, et al. Absence of post-transplantation lymphoproliferative disorder after allogeneic blood or marrow transplantation using post-transplantation cyclophosphamide as graft-versus-host disease prophylaxis. *Biol Blood Marrow Transplant.* 2013;19(10):1514-1517.
42. Shang J, Wang H, Sun J, et al. A comparison of lamivudine vs entecavir for prophylaxis of hepatitis B virus reactivation in allogeneic hematopoietic stem cell transplantation recipients: a single-institutional experience. *Bone Marrow Transplant.* 2016;51(4):581-586.
43. Lubel JS, Angus PW. Hepatitis B reactivation in patients receiving cytotoxic chemotherapy: diagnosis and management. *Journal of gastroenterology and hepatology.* 2010;25(5):864-871.
44. Torres HA, Chong PP, De Lima M, et al. Hepatitis C Virus Infection among Hematopoietic Cell Transplant Donors and Recipients: American Society for Blood and Marrow Transplantation Task Force Recommendations. *Biol Blood Marrow Transplant.* 2015;21(11):1870-1882.
45. Yahav D, Paul M, Fraser A, Sarid N, Leibovici L. Efficacy and safety of cefepime: a systematic review and meta-analysis. *Lancet Infect Dis.* 2007;7(5):338-348.
46. Pizzo PA. Management of fever in patients with cancer and treatment-induced neutropenia. *N Engl J Med.* 1993;328(18):1323-1332.
47. Averbuch D, Orasch C, Cordonnier C, et al. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia. *Haematologica.* 2013;98(12):1826-1835.
48. Orasch C, Averbuch D, Mikulska M, et al. Discontinuation of empirical antibiotic therapy in neutropenic leukaemia patients with fever of unknown origin is ethical. *Clin Microbiol Infect.* 2015;21(3):e25-27.
49. Aguilar-Guisado M, Espigado I, Martin-Pena A, et al. Optimisation of empirical antimicrobial therapy in patients with haematological malignancies and febrile neutropenia (How Long study): an open-label, randomised, controlled phase 4 trial. *Lancet Haematol.* 2017;4(12):e573-e583.
50. Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG. Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. *Am J Med.* 1982;72(1):101-111.

51. Walsh TJ, Finberg RW, Arndt C, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *N Engl J Med.* 1999;340(10):764-771.
52. Walsh TJ, Pappas P, Winston DJ, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med.* 2002;346(4):225-234.
53. Walsh TJ, Teppler H, Donowitz GR, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med.* 2004;351(14):1391-1402.
54. Caillot D, Casasnovas O, Bernard A, et al. Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. *J Clin Oncol.* 1997;15(1):139-147.
55. Greene RE, Schlamm HT, Oestmann JW, et al. Imaging findings in acute invasive pulmonary aspergillosis: clinical significance of the halo sign. *Clin Infect Dis.* 2007;44(3):373-379.
56. Maertens J, Theunissen K, Verhoef G, et al. Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. *Clin Infect Dis.* 2005;41(9):1242-1250.
57. Cordonnier C, Pautas C, Maury S, et al. Empirical versus preemptive antifungal therapy for high-risk, febrile, neutropenic patients: a randomized, controlled trial. *Clin Infect Dis.* 2009;48(8):1042-1051.
58. Paul M, Silbiger I, Grozinsky S, Soares-Weiser K, Leibovici L. Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. *The Cochrane database of systematic reviews.* 2006(1):CD003344.

Table 1. Definitions of basic terms used in this chapter.

Term	Definition
Neutropenia	Absolute neutrophil count <500 cells/mm^3
Neutropenic fever	A single episode of fever ≥38.3^{O}C or two episodes of fever ≥38.0^{O}C during neutropenia
Engraftment	Absolute neutrophil count >500 cells/mm^3 for 3 consecutive days
Pre-engraftment period	Time between infusion of stem cells until Absolute neutrophil count >500 cells/mm^3
Early post-engraftment period	Time between engraftment and Day+100 post-transplant
Late post-engraftment period	Time after Day+100 of infusion of stem cells until (usually) 1 year post-transplant
Antibiotic prophylaxis	Prophylaxis administered to prevent an infectious complication
Empirical treatment	Administration of an antibiotic agent to empirically treat a suspected infection, based on clinical suspicion
Preemptive treatment	Administration of antibiotic therapy at the onset of an infectious complication, as suggested by an early positive screening test

Table 2. Considerations for initial empirical antibiotic treatment for neutropenic fever [2].

Antibiotic	Indication
Aminoglycosides	• Routine inclusion of an aminoglycoside in the initial antibiotic regimen is not recommended. • In case of hemodynamic instability, an aminoglycoside should be added, until more microbiological and clinical data are available. • Meta-analysis showed that addition of an aminoglycoside to a beta-lactam for the treatment of sepsis did not improve survival and was associated with more side effects than monotherapy [58].

Antibiotics with activity against resistant gram-positive cocci (MRSA, VRE)	• Routine administration of antibiotics ((vancomycin, daptomycin, linezolid)) with activity against resistant gram-positive cocci (MRSA, VRE) should not be included in the initial empirical treatment regimen
	• Administration of agents with activity against resistant gram-positive cocci should be considered in case of:
	  • clinical suspicion for a CVC-associated, skin and soft tissue, or a positive blood culture for gram-positive cocci
	  • patients with known colonization, prior infection or high clinical suspicion for resistant gram-positive organisms
	  • *Streptococcus viridan*s bacteremia if the prevalence of penicillin-resistant *Streptococcus viridans* species is high
	• If blood cultures remain negative, treatment with these agents can be discontinued after 2-3 days

Agents with activity against MDR gram-negative organisms (ESBL, CPE)	• A carbapenem is preferred in patients with colonization, prior infection or clinical suspicion for an ESBL producing) organism • In patients with colonization, prior infection or clinical suspicion for CPE producing organisms, empirical antibiotic therapy should be adjusted (i.e. colistin, prolonged administration of a carbapenem) after discussion with the Infectious Disease consultation team and based on the local epidemiology and antibiotic susceptibility profile
Ceftazidime	• Ceftazidime is not included in the list of preferred empirical treatments, due to its lack of activity against gram-positive pathogens

MRSA: Methicillin Resistant *Staphylococcus aureus*, VRE: Vancomycin Resistant *Enterococcus*, CVC: Central Venous Catheter, MDR: Multidrug Resistant, ESBL: Extended-spectrum B-Lactamase, CPE: Carbapenemase Enzyme.

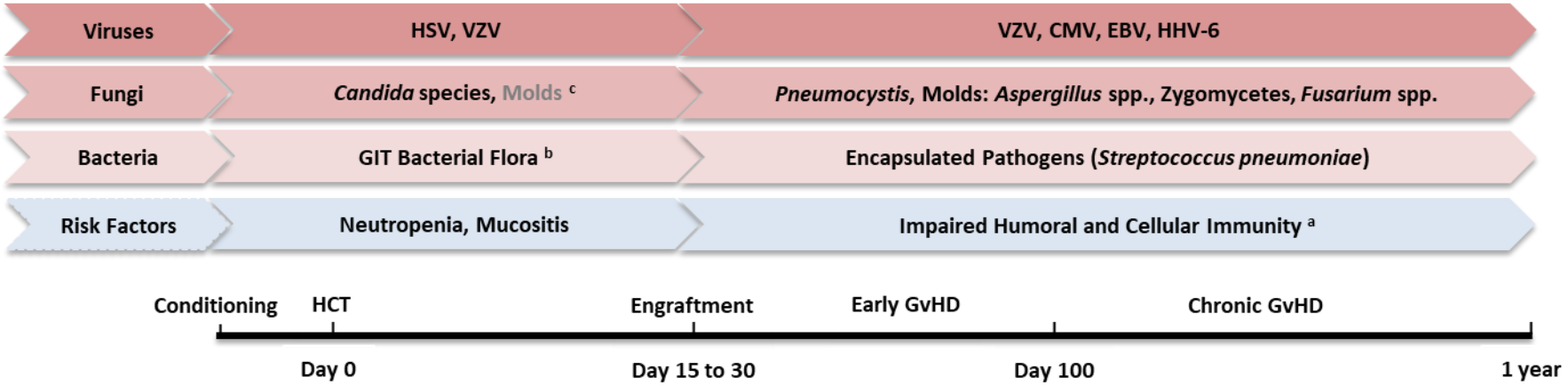
From Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. *Clin Infect Dis.* 2011;52(4):e56-93; with permission.

Table 3. Considerations for empirical antibiotic treatment for persistent neutropenic fever [2].

In case of empirical treatment with cefepime or piperacillin-tazobactam and/or ESBL-producing gram-negative organism colonization, treatment should be broadened to either imipenem-cilastatin or meropenem, to include coverage against ESBL-producing pathogens
In case of MRSA and/or VRE or penicillin-resistant *Streptococcus viridans* colonization/infection, treatment with vancomycin (daptomycin or linezolid) should be instituted
In case of CPE-producing gram-negative organism colonization / infection, antibiotic treatment should be adjusted based on antibiogram results and after consultation with the Infectious Disease consultation team
In patients with persistent neutropenic fever despite broad-spectrum antibacterial treatment, less common bacterial pathogens should be considered, including *Stenotrophomonas maltophilia* or *Nocardia* species
In patients with a definitive diagnosis of a specific infection, antibiotic treatment should be tailored based on culture and antibiotic susceptibility results
In patients with hemodynamic instability, addition of an aminoglycoside (i.e. amikacin) should be considered

ESBL: Extended-spectrum B-Lactamase, MRSA: Methicillin Resistant *Staphylococcus aureus*, VRE: Vancomycin Resistant *Enterococcus*, CPE: Carbapenemase Enzyme.

Figure 1.



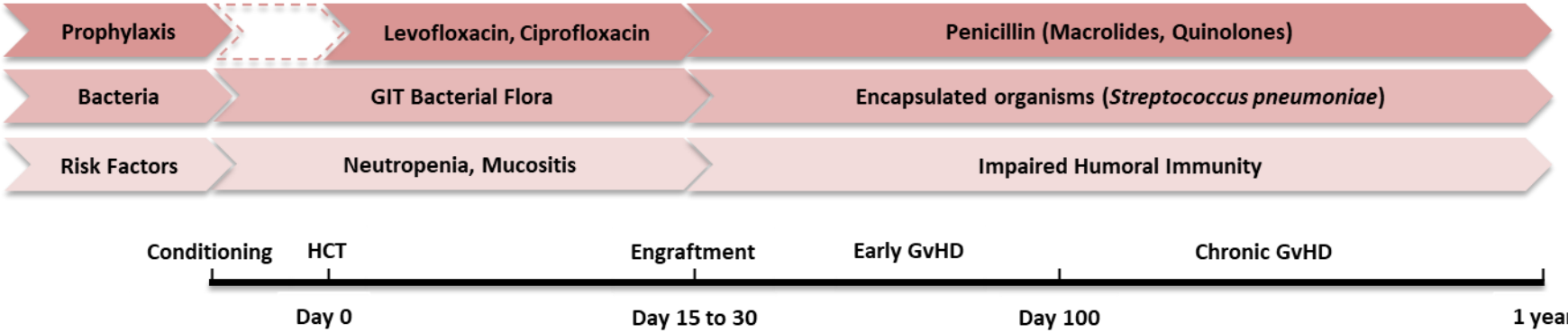
HCT: Hematopoietic Cell Transplant, GvHD: Graft-versus-Host Disease, GIT: Gastrointestinal Tract, HSV: Herpes simplex virus, VZV: Varicella-zoster virus, CMV: Cytomegalovirus, EBV: Epstein-Barr virus, HHV-6: Human herpes virus 6.

[a] Impaired humoral and cellular immunity may last for 6-12 months. Diagnosis of GvHD in the early (acute) or late (chronic) post-engraftment period and associated treatments may further delay cellular immune reconstitution.

[B] Gastrointestinal tract bacterial pathogens include, but are not limited to, the following: *Streptococcus viridans* species, *Enterococcus* species, *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, *Pseudomonas aeruginosa*.

[c] Molds are less commonly observed during pre-engraftment than post-engraftment. Prolonged profound neutropenia pre-engraftment may be associated with more mold infections [4-6]. The most commonly identified molds include the following: *Aspergillus* species, Zygomycetes, *Fusarium* species, *Scedosporium* species.

Figure 2.



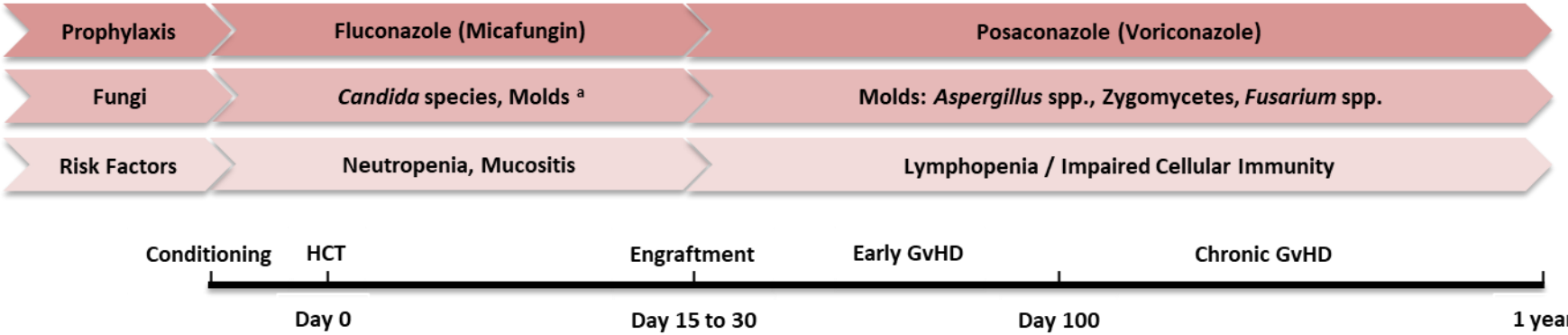
	Pre-engraftment	Post-engraftment
Pathogens	*Streptococcus viridans, Enterococcus* species, *Escherichia coli, Klebsiella* species, *Enterobacter* species, *Pseudomonas aeruginosa* [a]	*Streptococcus pneumoniae*
Antibacterial agents	Levofloxacin 500 mg once daily PO [b] Ciprofloxacin 500 mg twice daily PO [b]	Penicillin 500 – 1000 mg once daily PO [b] Azithromycin 250 mg once daily PO Ciprofloxacin 500 mg twice daily PO
Timing of administration	From stem cell infusion (or conditioning at some centers) until engraftment or initiation of broad-spectrum empirical antibiotic treatment	From engraftment until 12 months post-HCT and/or during treatment of chronic GvHD

HCT: Hematopoietic Cell Transplant, GvHD: Graft-versus-Host Disease, GIT: Gastrointestinal Tract, PO: Orally.

[a] Gastrointestinal tract bacterial pathogens include, but are not limited to, the listed pathogens.

[b] Local epidemiology should be taken into account in terms of antibacterial prophylaxis agent selection. At centers where fluoroquinolones are routinely used for antibacterial prophylaxis, regular monitoring of fluoroquinolone resistance should be applied. Local epidemiology of *Streptococcus pneumoniae* resistance patterns should be taken into account before selecting the appropriate prophylaxis.

Figure 3.

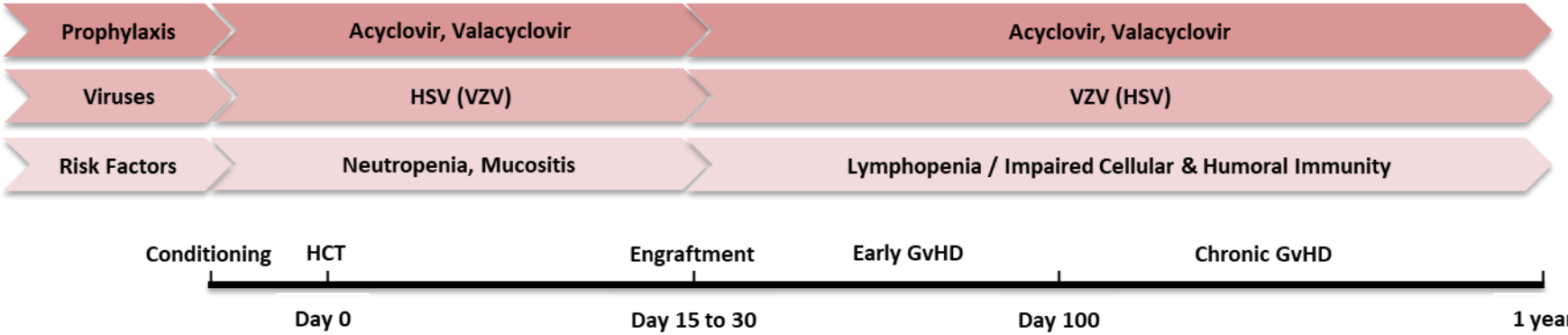


	Pre-engraftment	Post-engraftment
Pathogens	*C. albicans, C. glabrata, C. parapsilosis, C. tropicalis, C. krusei,* other *Candida* species , *Aspergillus* species, Zygomycetes	*Aspergillus* species, Zygomycetes, *Fusarium* species, *Scedosporium* species and other molds
Antifungal agents	Fluconazole 400 mg once daily PO/IV [b] Micafungin 50 mg once daily IV [c]	Posaconazole 300 mg once daily PO/IV [d,e] Voriconazole 4 mg/kg twice daily PO/IV [e]
Timing of administration	From conditioning or stem cell infusion until engraftment	During administration of high-dose steroids (>1 mg/kg/day) for treatment of GvHD

HCT: Hematopoietic Cell Transplant, GvHD: Graft-versus-Host Disease, GIT: Gastrointestinal Tract, PO: Orally, IV: Intravenously.

[a] Molds are less commonly observed during pre-engraftment than post-engraftment. Prolonged profound neutropenia pre-engraftment may be associated with more mold infections [4-6].
[b] Fluconazole at 200 mg once daily are occasionally used at certain institutions [1].
[c] Micafungin may be used in case of prolonged neutropenia and/or patients colonized with fluconazole-resistant *Candida* species.
[d] Posaconazole is the only broad-spectrum azole validated for antifungal prophylaxis post-engraftment [18]. Posaconazole delayed release tablets are preferred to posaconazole suspension for PO administration, due to better absorption.
[e] Voriconazole and posaconazole prophylaxis may be used for pre-engraftment antifungal prophylaxis in patients at high-risk for an invasive mold infection (IMI) or patients with a diagnosis of an IMI prior to HCT [1].

Figure 4.



	Pre-engraftment	Post-engraftment
Pathogens	HSV (VZV)	VZV (HSV)
Antiviral agents	Acyclovir 400 - 800 mg twice daily PO [a] Acyclovir 250 mg/m^2 or 5 mg/kg twice daily IV [a] Valacyclovir 500 mg once-twice daily PO [b]	Acyclovir 800 mg twice daily PO Valacyclovir 500 mg twice daily PO [b]
Timing of administration	From conditioning until engraftment	From engraftment until 1 year post-HCT [c]

HCT: Hematopoietic Cell Transplant, GvHD: Graft-versus-Host Disease, HSV: Herpes simplex virus, VZV: Varicella-zoster virus, PO: Orally, IV: Intravenously.

[a] Acyclovir pre-engraftment can be used either PO or IV, depending on the severity of mucositis and ability for oral intake.
[b] Valacyclovir can be used instead of acyclovir, although it is not approved in the United States for prophylaxis in allogeneic HCT recipients.
[c] Longer courses of prophylaxis should be considered in allogeneic HCT recipients with chronic GvHD requiring continued immunosuppressive treatments.

Figure 5.

	Agent	Dose	Time of administration
Prophylaxis	Letermovir [a]	480 mg daily PO/IV	From stem cell infusion until day 100 post-HCT
	Ganciclovir	5 mg/kg twice daily IV for 7 days, followed by 5 mg/kg once daily IV thereafter	From engraftment until day 100 post-HCT
	Foscarnet	60 mg/kg twice daily IV for 7 days, followed by 90 mg/kg once daily IV thereafter	From engraftment until day 100 post-HCT
Preemptive treatment [b]	Ganciclovir [c]	Induction dose: 5 mg/kg twice daily IV Maintenance dose: 5 mg/kg once daily IV	• Initiation of induction treatment is based on a positive diagnostic test for CMV (CMV qPCR) and institutional established cutoffs [b] • Duration of induction treatment: 2-3 weeks [b] • Duration of maintenance treatment : 2-3 weeks or until CMV is not detectable [b]
	Foscarnet [c]	Induction dose: 90 mg/kg twice daily IV Maintenance dose: 90 mg/kg once daily IV	
	Valganciclovir [c,d]	Induction dose: 900 mg twice daily PO Maintenance dose: 900 mg once daily PO	

HCT: Hematopoietic Cell Transplant, GvHD: Graft-versus-Host Disease, CMV: Cytomegalovirus, PO: rally, IV: Intravenously; qPCR: Quantitative.

[a] Letermovir was approved by the United States (US) Food and Drug Administration for CMV prophylaxis in high-risk allogeneic HCT recipients, based on the results of a prospective randomized clinical trial [28]. It is not included in current US guidelines. It has been endorsed by the European Conference of Infections in Leukemia 2017 guidelines for CMV prophylaxis. Letermovir has no activity against HSV and VZV, hence additional prophylaxis for these viruses is required.

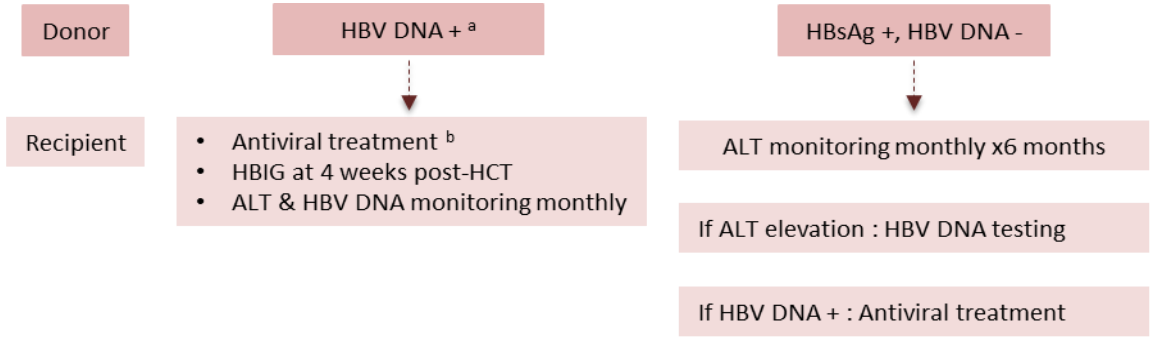
[b] Preemptive CMV treatment consists of regular monitoring of CMV reactivation with a CMV qPCR assay. Weekly CMV qPCR monitoring is recommended between the day of HCT or engraftment and until day 100 post-HCT. More frequent monitoring should be applied in high-risk patients (recipients of umbilical cord blood or T-cell depleted allografts) and continued beyond day 100 in patients with GvHD requiring immunosuppressive treatment. There are no definitive CMV viral load cutoffs above which preemptive treatment should be started. Historically CMV PCR >500-1,000 IU/mL are used for preemptive treatment initiation. CMV viral load cutoffs to initiate preemptive therapy, duration of induction and maintenance treatment may vary across institutions.

[c] Doses need to be adjusted based on renal function.

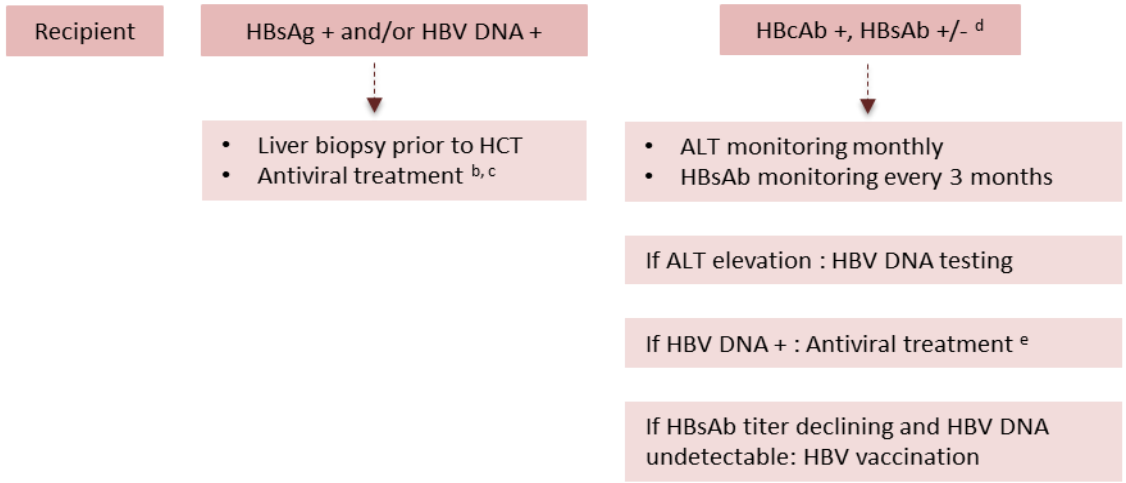
[d] Valganciclovir can be used instead of ganciclovir IV if there are no concerns about absorption, particularly in patients with GvHD.

Figure 6.

6a.



6b.



HBV: Hepatitis B Virus, HBsAg: HBV surface antigen, HBsAb: HBV surface antibody, HBcAb: HBV core antibody, HCT: Hematopoietic Cell Transplant, ALT: Alanine Aminotransferase.

[a] Donor: If donor is HBV DNA positive prior to stem cell harvest, treatment for 4 weeks should be administered, or until HBV DNA is undetectable.
Recipient: In case recipient is not vaccinated for HBV, HBV vaccination shuld be administered, if feasible before HCT. If vaccination is not feasible or complete prior to HCT or HBsAb titer <10 IU/L, HBIG should be administered with stem cell infusion.
[b] Entecavir and tenofovir are preferred over lamivudine.
[c] Antiviral treatment should be initiated before conditioning regimen.
[d] HCT recipients who are HBcAb+ / HBsAb- should receive HBV vaccination prior to HCT, if they HBV DNA is undetectable.
[e] Antiviral treatment should be administered for a minimum of 6 months post discontinuation of immunosuppressive treatment.