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Prophylaxie antimicrobienne et approches thérapeutiques empiriques et
préemptives pour la prévention des infections chez les receveurs de greffe
allogénique de cellules hématopoïétiques

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Département de Médecine

Service des Maladies Infectieuses

Thèse préparée sous la direction du Professeur Laurent KAISER

**" Prophylaxie Antimicrobienne et Approches Thérapeutiques Empiriques et Préemptives
pour la Prévention des Infections chez les Receveurs de Greffe Allogénique de Cellules
Hématopoïétiques "**

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

Thèse
présentée à la Faculté de Médecine
de l'Université de Genève
pour obtenir le grade de Docteur en médecine
par
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RESUME

Prophylaxie Antimicrobienne et Approches Thérapeutiques Empiriques et Préemptives pour la Prévention des Infections chez les Receveurs de Greffe Allogénique de Cellules Hématopoïétiques

Les complications infectieuses représentent l'une des causes les plus courantes de morbidité et de mortalité chez les receveurs de greffe allogénique de cellules hématopoïétiques. Des stratégies de traitement empirique et préventif contre les agents pathogènes bactériens, fongiques, viraux et parasitaires sont systématiquement mises en œuvre pendant les périodes post-transplantation à haut risque dans la plupart des centres de transplantation. Cette thèse est consacrée aux concepts de base et à la révision des directives actuelles en matière de prophylaxie par antibiotiques et de traitement antibiotique empirique / préventif chez les receveurs de greffe allogénique de cellules hématopoïétiques.

1. INTRODUCTION

Cette thèse a comme but de passer en revue les stratégies de maladies infectieuses en place pour la prévention et la prise en charge des complications des maladies infectieuses chez les patients atteints de tumeurs malignes hématologiques et les receveurs de greffe allogénique de cellules hématopoïétiques. Avec l'augmentation constante du nombre de greffes de cellules hématopoïétiques allogéniques dans le monde entier, en particulier avec l'inclusion de patients plus âgés et plus malades qu'auparavant, un grand nombre de complications liées aux maladies infectieuses se produisent. Ces complications ont un impact significatif sur la morbidité et la mortalité de ces patients.

Ainsi, dès les années 1980, des stratégies antibiotiques prophylactiques ont été développées pour prévenir différents types d'infections chez cette population de patients très fragile. Prophylaxie contre les pathogènes bactériens typiques, y compris les cocci gram-positifs et les bacilles gram-négatifs, les pathogènes fongiques, comme les espèces de *Candida*, et les pathogènes viraux, comme les virus herpès. L'introduction de stratégies de prophylaxie primaire a suivi les résultats de recherches cliniques intensives, certaines dans le contexte d'essais cliniques prospectifs randomisés, mais dans certains cas à la suite d'études rétrospectives observationnelles effectuées dans un seul centre.

La qualité des données qui a guidé nos approches cliniques au cours des dernières décennies n'a pas été bien décrite. De même, des stratégies utilisées depuis de nombreuses décennies ont fait l'objet d'un examen minutieux au cours des dernières années. Par exemple, l'administration d'une prophylaxie antifongique universelle en cas de maladie du greffon contre l'hôte a été fortement critiquée. Surtout lorsque plus de 20 patients peuvent avoir besoin d'une prophylaxie afin de prévenir une seule infection invasive fongique. De même, la poursuite du traitement antibactérien empirique chez les patients atteints de fièvre neutropénique persistante a fait l'objet de discussions et de recherches actives dans ce domaine. De nombreuses autres stratégies ont été critiquées au cours des dernières décennies et la nécessité d'obtenir davantage de données est devenue de plus en plus présente. Cependant, la réalisation d'essais cliniques dans ce domaine n'a pas toujours été une tâche facile. Le nombre de patients

transplantés dans chaque centre ne permet pas à la plupart de ces centres d'effectuer des essais cliniques prospectifs avec une puissance statistique suffisante. De plus, la réalisation d'essais cliniques multicentriques est également entravée par les possibilités de financement disponibles, mais aussi par les différents types de transplantation et les pratiques pertinentes appliquées dans chaque établissement.

Il est donc nécessaire de réexaminer cette question de l'antibioprophylaxie universelle systématique et du traitement empirique chez ces patients à haut risque, comme les receveurs de greffe allogénique de cellules hématopoïétiques. Par conséquent, dans cette thèse, j'essaierai d'examiner de façon critique l'ensemble de la documentation existante en ce qui concerne l'administration systématique d'antibiotiques primaires prophylactiques et le traitement empirique chez les receveurs de greffe allogénique de cellules hématopoïétiques. Cet examen portera sur les quatre grandes catégories d'agents pathogènes, à savoir les bactéries, les champignons, les virus et les parasites. En outre, un examen des données les plus pertinentes sur la prise en charge de la fièvre neutropénique, en particulier l'administration de traitements antibiotiques prolongés et de traitements antifongiques empiriques. La description des données disponibles et des principales limites sera détaillée dans les tableaux et les figures afin de faciliter la compréhension de ce sujet complexe et alambiqué.

Une partie de ce travail a été publié dans un volume spécial des " Infectious Disease Clinics of North America ", sur la prévention, diagnostic et traitements des complications infectieuses chez les receveurs de greffe allogénique de cellules hématopoïétiques et les patients avec une leucémie aigüe. Il servira de base aux recommandations institutionnelles et de bonne pratique clinique pour les services des Maladies Infectieuses et Hématologie.

2. BACKGROUND

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 thesis 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 thesis 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.

The recommendations included in this work are aligned with the recently published guidelines for the:

- a. management of HCT recipients by the:
 - i. Center for International Blood and Marrow Transplant Research (CIBMTR®),
 - ii. National Marrow Donor Program (NMDP),
 - iii. European Blood and Marrow Transplant Group (EBMT),
 - iv. American Society of Blood and Marrow Transplantation (ASBMT),
 - v. Canadian Blood and Marrow Transplant Group (CBMTG),
 - vi. Infectious Disease Society of America (IDSA),
 - vii. Society for Healthcare Epidemiology of America (SHEA),
 - viii. Association of Medical Microbiology and Infectious Diseases Canada (AMMI), and
 - ix. Centers for Disease Control and Prevention (CDC)
- b. prevention and treatment of cancer related infections by the National Comprehensive Cancer Network, and
- c. use of antimicrobial agents in neutropenic patients with cancer, by the Infectious Disease Society of America [1-3].

These recommendations may be applied with some degree of variability at different institutions, based on several factors, including the type of HCT-associated practices, local epidemiology and susceptibility patterns, and local expertise. Hence, administration of prophylaxis and/or preemptive treatment, selection of antibiotic agent and dosing, and timing of initiation and discontinuation of antibiotic prophylaxis and/or preemptive therapy may differ from consensus guidelines at different cancer/transplant centers.

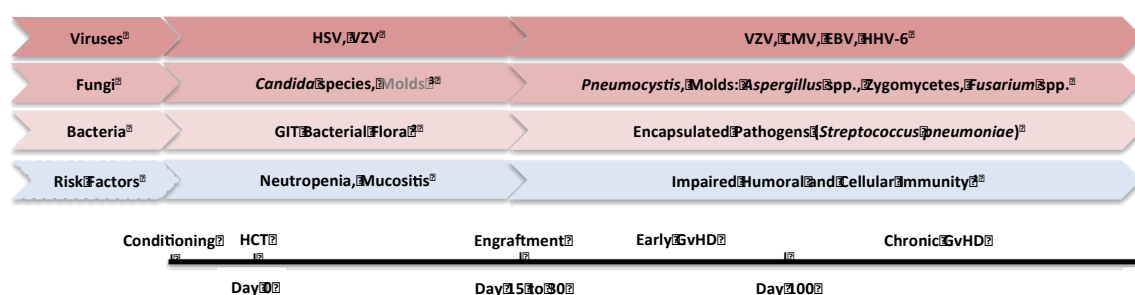
Table 1. Definitions of basic terms used in this thesis.

Term	Definition
Neutropenia	Absolute neutrophil count <500 cells/mm ³
Neutropenic fever	A single episode of fever $\geq 38.3^{\circ}\text{C}$ or two episodes of fever $\geq 38.0^{\circ}\text{C}$ 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

2.1. 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.

Figure 1. Risk factors for infections and common infectious disease complications post-allogeneic hematopoietic cell transplant and associations with timing post-transplant.



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.

¹ Impaired humoral and cellular immunity may last for 6–12 months, depending on multiple variables. Diagnosis of GvHD in the early (acute) or late (chronic) post-engraftment period and associated treatments may further delay cellular immune reconstitution.

² Gastrointestinal tract bacterial pathogens include the following: *Streptococcus viridans* species, *Enterococcus* species, *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, *Pseudomonas aeruginosa*.

³ Molds are less commonly observed during pre-engraftment. The most commonly identified molds include the following: *Aspergillus* species, *Zygomycetes*, *Fusarium* species, *Scedosporium* species.

2.2. 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].

2.3. 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.

2.4. 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*).

3. ANTIBACTERIAL PROPHYLAXIS

3.1. Antibacterial prophylaxis - Pre-engraftment period

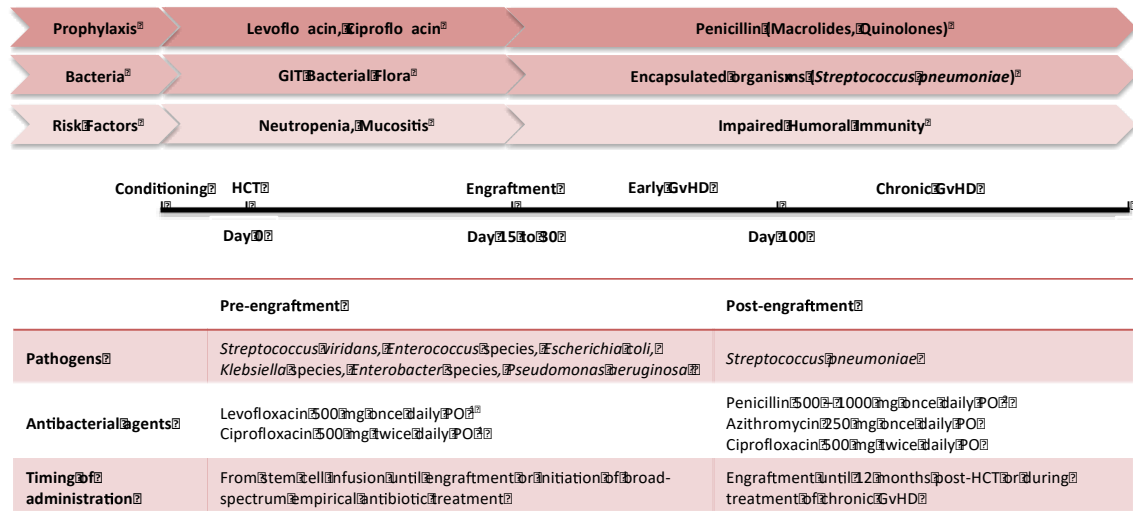
In a meta-analysis of >100 clinical trials of antibacterial prophylaxis during neutropenia, administration of fluoroquinolones was shown to significantly decrease infection-related mortality, febrile episodes, clinically and microbiologically documented infections, and BSI [8]. In a landmark clinical 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].

3.1.a. Timing of antibacterial prophylaxis

Timing of antibacterial prophylaxis initiation may vary, beginning anywhere between chemotherapy initiation, stem cell infusion, or 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].

Figure 2. Review of the risk factors, timing, and prophylactic strategies for bacterial infections post-allogeneic hematopoietic cell transplant.



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

¹Local 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.

²Local epidemiology of *Streptococcus pneumoniae* resistance patterns should be taken into account before selecting the appropriate prophylaxis.

3.1.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].

3.2. Antibacterial prophylaxis - Post-engraftment period

Routine antibacterial prophylaxis against encapsulated bacterial pathogens, particularly *Streptococcus pneumoniae*, is recommended usually until 1-year post-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.

4. ANTIFUNGAL PROPHYLAXIS

4.1. Antifungal prophylaxis - Pre-engraftment

4.1.a. Fluconazole

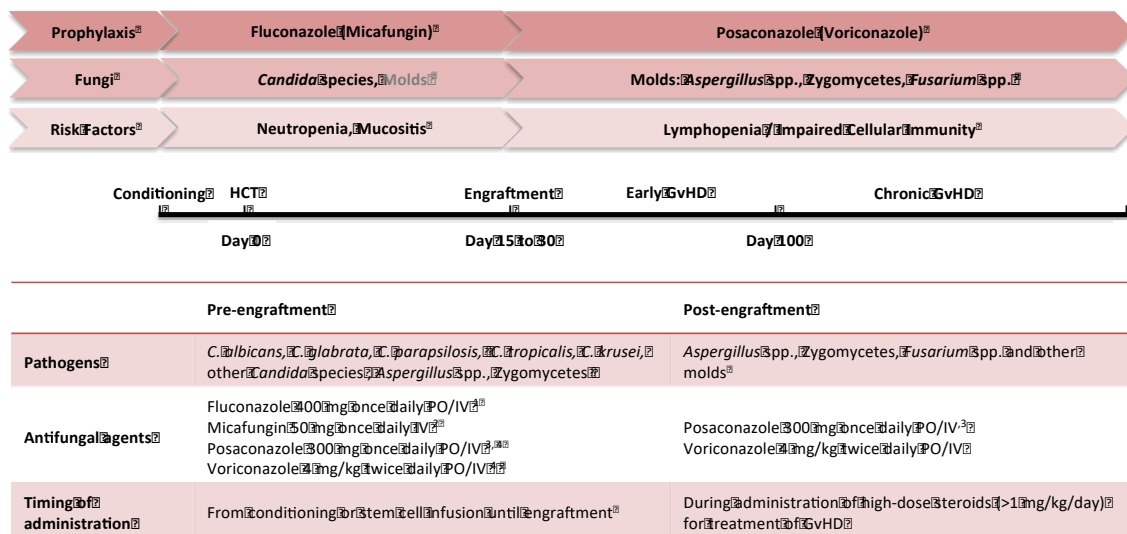
Fluconazole has been the mainstay of antifungal prophylaxis and is currently recommended as primary antifungal prophylaxis during the pre-engraftment period in allogeneic and autologous HCT recipients, based on a large number of data, ease of administration, predictable drug interactions and a benign 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-acting azoles (**4.1.b. Mold-acting azoles**) or echinocandins (**4.1.c. Echinocandins**) should be considered [1].

4.1.b. Mold-acting 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].

Figure 3. Review of the risk factors, timing, and prophylactic strategies for invasive fungal infections post-allogeneic hematopoietic cell transplant.



HCT: Hematopoietic Cell Transplant, GVHD: Graft-versus-Host Disease, GIT: Gastrointestinal Tract, PO: Orally, IV: Intravenously.
¹ Fluconazole at 200mg once daily are occasionally used at certain institutions.
² Miconazole may be used in case of prolonged neutropenia and/or patients colonized with fluconazole-resistant *Candida* species.
³ Posaconazole delayed release tablets are preferred to posaconazole suspension for PO administration, due to better absorption.
⁴ Voriconazole and posaconazole prophylaxis may be used pre-engraftment in patients at high-risk for an invasive mold infection (IMI) or patients with a diagnosis of an IMI prior to HCT.

4.1.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].

4.1.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].

4.2. 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-acting 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.

4.3. *Pneumocystis jirovecii* prophylaxis

Allogeneic HCT recipients should receive routine prophylaxis against *Pneumocystis jirovecii* pneumonia (PJP) [1, 3]. Prophylaxis can be started at the time of transplantation or post-engraftment, based on institutional protocols and is continued for a minimum of 6 to 12

months post-HCT [1, 3]. A strong body evidence supports the use of trimethoprim-sulfamethoxazole (TMP-SMX) as the preferred PJP prophylaxis [1, 3]. The recommended dose of TMP-SMX includes a single-strength tablet once daily or a double-strength tablet three times weekly [1, 3]. Due to potential myelosuppression associated with TMP-SMX, 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 options include administration of atovaquone, once monthly aerosolized pentamidine and dapsone. Administration of dapsone should be avoided in patients allergic to TMP-SMX and deficient for G6PD and aerosolized pentamidine has been associated with bronchospasm.

5. ANTIVIRAL PROPHYLAXIS

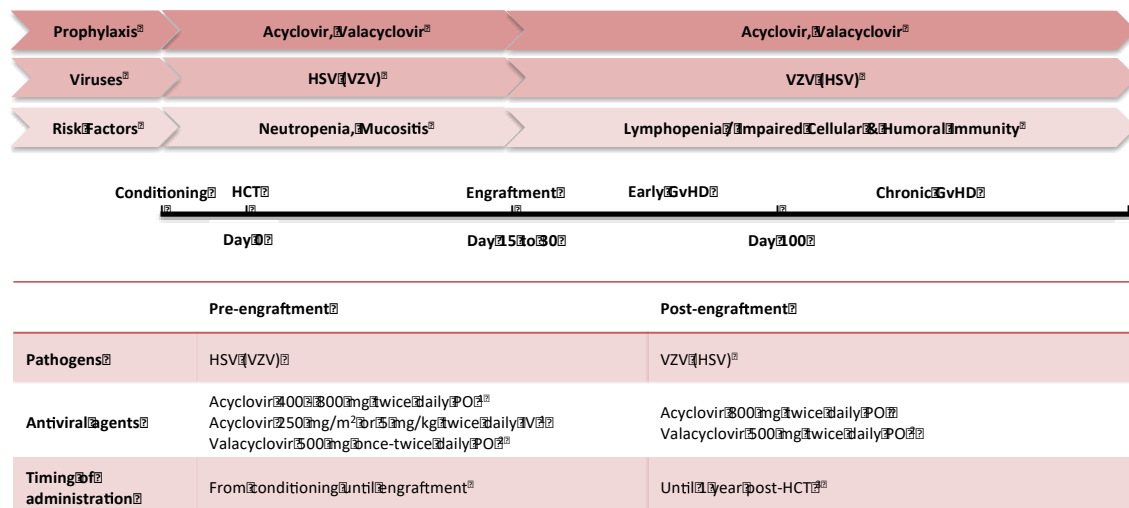
5.1. Herpes simplex virus (HSV)

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].

5.2. 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 [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 prolonged treatment courses with high-dose corticosteroids [1, 3].

Figure 4. Review of the risk factors, timing, and prophylactic strategies for herpes simplex and varicella-zoster viruses infections post-allogeneic hematopoietic cell transplant.



HCT: Hematopoietic Cell Transplant, GVHD: Graft-versus-Host Disease, HSV: Herpes Simplex Virus, VZV: Varicella-zoster Virus, PO: Orally, IV: Intravenously.

¹Acyclovir pre-engraftment can be used either PO or IV, depending on the severity of mucositis and ability of patient for oral intake.

²Valacyclovir can be used instead of acyclovir, although it is not approved in the United States for prophylaxis in allogeneic HCT recipients.

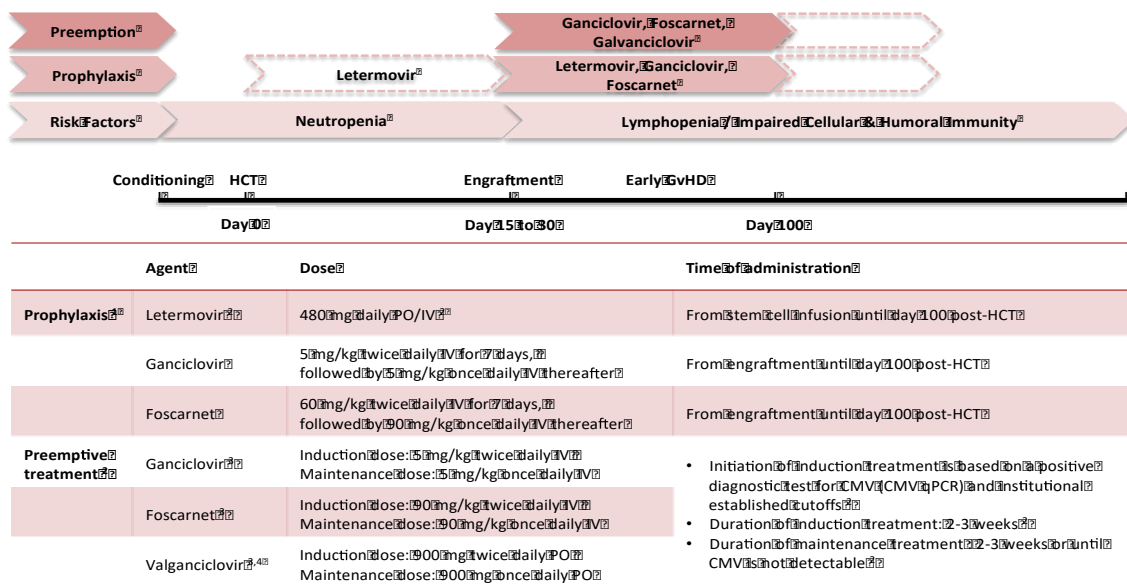
³Longer courses of prophylaxis should be considered in allogeneic HCT recipients with chronic GVHD requiring continued immunosuppressive treatments.

5.3. 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 a mainstay 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, based on regular monitoring of CMV viral activity (**Figure 5**). There have been multiple clinical trials to evaluate the efficacy and safety of both approaches [25]. In the following sections a brief discussion will follow, focusing on current recommendations and pertinent data on both clinical approaches (**5.3.1a. Primary CMV prophylaxis & 5.3.b. Preemptive CMV treatment**).

Figure 5. Review of the risk factors, timing, and prophylactic strategies for cytomegalovirus post-allogeneic hematopoietic cell transplant.



HCT: Hematopoietic Cell Transplant; GvHD: Graft-versus-Host Disease; CMV: Cytomegalovirus; PO: orally; IV: Intravenously; PCR: Quantitative.

¹Letermovir 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. It is not included in current US guidelines. It has been endorsed by the European Leukemia 2017 guidelines. Letermovir has no activity against HSV and VZV, hence additional prophylaxis for these viruses is required. Due to significant interactions, half the dose of Letermovir is recommended in patients who receive concomitantly cyclosporine.

²Preemptive CMV treatment consists of regular monitoring of CMV reactivation with a CMV PCR assay in CMV-seropositive recipients or recipients who received a graft from a CMV-seropositive donor. Weekly CMV PCR 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, such as recipients of umbilical cord blood or -cell depleted allografts and continued beyond Day 100 in patients with GvHD requiring immunosuppressive treatment with corticosteroids. 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.

³Doses need to be adjusted based on renal function.

⁴Valganciclovir is not recommended in patients with severe renal impairment (creatinine clearance < 30 mL/min).

5.3.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 initial concept of using higher doses of acyclovir or valacyclovir for CMV suppression has been abandoned, due to the low efficacy of these agents against CMV. The administration of CMV-active agents, such as ganciclovir/valganciclovir or foscarnet, for CMV prophylaxis has been hindered by the associated drug-toxicities, namely 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 brincidofovir (an orally administered cidofovir-prodrug, 400-times more active against CMV than cidofovir, not associated with nephrotoxicity), maribavir (a UL97 viral protein kinase inhibitor) and letermovir (a viral terminase subunit terminator) [30-33]. Although initially promising, clinical trial results have failed to show a benefit associated with brincidofovir and maribavir, due to dosing and toxicity issues [31-33]. More recently, letermovir was studied for CMV prophylaxis during the first 100 days in adult CMV-seropositive allogeneic HCT recipients [30]. In a large prospective randomized multicenter phase-3 clinical trial, administration of letermovir during the first 14 weeks post-allogeneic HCT was compared to a placebo-based preemptive approach. 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 prophylaxis for these viruses 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 [34].

5.3.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 [35-38]. A preemptive approach consists of regular monitoring of CMV reactivation with a CMV

qPCR assay [1, 34]. Weekly CMV qPCR monitoring is usually performed, starting on the day of engraftment and continued until day-100 post-HCT [1, 34]. More frequent monitoring should be applied in high-risk patients, such as recipients of umbilical cord blood or T-cell depleted allografts [1, 34]. CMV qPCR monitoring should be continued beyond day-100 in patients with GvHD requiring immunosuppressive treatment with corticosteroids at a dose >1 mg/kg/day [1, 34].

5.3.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 [39].

5.3.b.2. Preemptive treatment agent selection. Preemptive therapy can include ganciclovir, valganciclovir or foscarnet [1, 3, 34]. The agent selection depends on the time of CMV infection post-HCT and institutional protocols. Due to potential myelosuppression associated, ganciclovir and 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 [34]. 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 [34].

5.3.b.3. Preemptive treatment dosing and duration. Induction dose of CMV preemptive therapy is usually administered for a minimum of 2 to 3 weeks [1, 34]. Transition to maintenance dose usually occurs after 2 to 3 weeks of induction-dose treatment and is continued for another 2 to 3 weeks and/or until an undetectable CMV viral load is documented

by CMV qPCR [1, 34]. 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 and treatment administration [1, 34].

5.4 Epstein-Barr virus (EBV)

Weekly EBV monitoring with an EBV qPCR assay is recommended during the first 100 days post-allogeneic HCT [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 (PTLD), associated with the graft type and GvHD prophylaxis regimen selection [1, 40]. 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].

5.5. Hepatitis B virus (HBV)

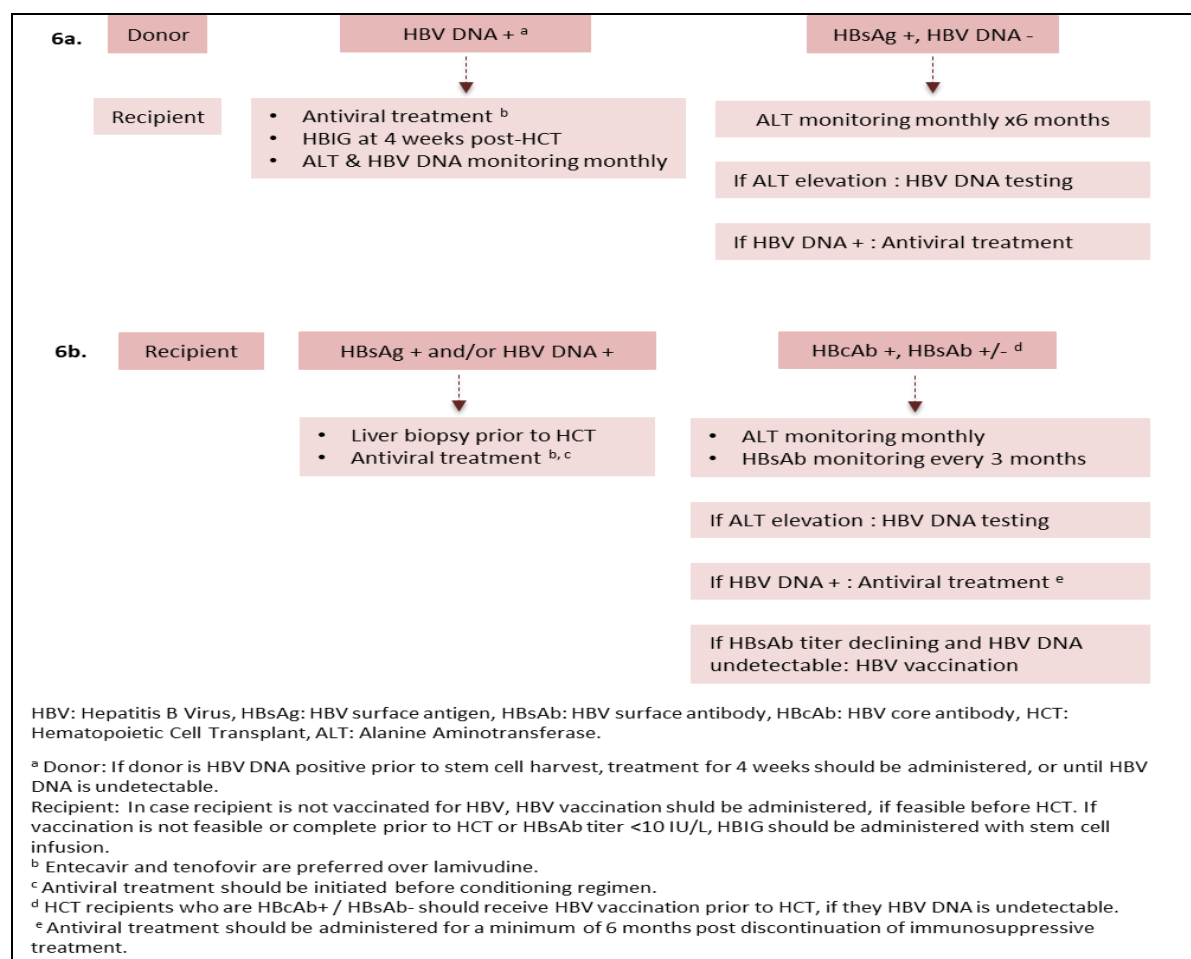
Routine pretransplant and prechemotherapy HBV testing for all HCT donors and recipients is recommended, including: HBV surface antigen (HBsAg), HBV surface antibody (HBsAb), HBV core antibody (HBcAb) and HBV DNA (**Figure 6**) [1]. Hepatitis B vaccination is recommended in all HBV-naïve patients who undergo chemotherapy and/or HCT [1]. If HBV vaccination cannot be initiated or completed before initiation of chemotherapy or stem cell infusion, HCT-naïve 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 [41]. 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.

5.5.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 donors and recipients to limit HBV transmission.

Figure 6. Review of the risk factors, timing, and prophylactic strategies for hepatitis B virus post-allogeneic hematopoietic cell transplant.



5.5.b. HCT recipients 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, 42]. 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 [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.

5.6. 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]. As HCV infection can have devastating complications in an allogeneic HCT recipient, it is important to carefully monitor these patients and make all efforts possible to decrease the risk of transmission and/or progression of HCV infection post-HCT [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 and minimize possible HCV transmission to the recipient [43]. HCV-seropositive, HCV RNA positive recipients should receive treatment with a DAA agent, when possible [1]. Although not a lot of data on DAA HCV treatment in allogeneic HCT recipients are currently available, some preliminary data suggest that DAA HCV treatment can be effective and safe in the setting as well [43, 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 [43, 44]. HCV-seropositive recipients with fibrosis, cirrhosis or HCV-associated lymphoproliferative disorder should be treated as soon as possible [43, 44]. HCV-seropositive recipients should be

carefully monitored for HCV progression and long-term complications, including fibrosis, cirrhosis and hepatocellular carcinoma [1, 43, 44]. In such cases, 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, 45].

6. PARASITIC PROPHYLAXIS

6.1. *Toxoplasma gondii* prophylaxis

Toxoplasmosis remains a fairly uncommon complication after an allogeneic HCT, particularly in the setting of GvHD, T-cell depletion or cord blood grafts [1, 3]. Toxoplasmosis reactivation is significantly more frequent than primary transmission of *Toxoplasma gondii* from the donor. 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 case of TMP-SMX allergy or administration another PJP prophylaxis is used, screening by a qPCR for *Toxoplasma* species should be performed in high-risk patients for initiation of preemptive therapy, albeit frequency of monitoring has not been established.

7. EMPIRICAL ANTIBACTERIAL AND ANTIFUNGAL TREATMENT FOR NEUTROPENIC FEVER

7.1. General concepts of neutropenic fever management

Neutropenic fever represents the most common complication of neutropenic patients, but a definitive bacterial infection is diagnosed <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 (**Table 2**). 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.

7.2. 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 or meropenem, should be promptly initiated (**Table 2**) [2]. The following additional concepts should be strongly considered in the selection of initial antibiotic treatment for neutropenic fever [2]:

Aminoglycosides. Inclusion of an aminoglycoside in the initial antibiotic regimen is not routinely recommended. A recent meta-analysis showed that addition of an aminoglycoside did not significantly improve survival and was associated with more side effects than monotherapy [46]. However, in case of hemodynamic instability, an aminoglycoside should be added, until more microbiological, resistance, and clinical data are available.

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 [46].
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 • <i>Streptococcus viridans</i> bacteremia if the prevalence of penicillin-resistant <i>Streptococcus viridans</i> 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	• 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

(ESBL, CPE)	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.

Antibiotics with activity against resistant gram-positive cocci. Administration of antibiotics with activity against resistant gram-positive cocci (i.e. methicillin resistant *Staphylococcus aureus*, MRSA or vancomycin resistant *Enterococcus* species, VRE) should not be included in the initial empirical treatment regimen [2]. Administration of agents with activity against resistant gram-positive cocci (e.g. vancomycin, daptomycin or linezolid) should be considered in case of: (a) clinical suspicion for a CVC-associated, skin and soft tissue or respiratory tract infection, or a positive blood culture for gram-positive cocci, and (b) patients with known colonization, prior infection or high clinical suspicion for resistant gram-positive organisms (i.e. MRSA, VRE). If vancomycin or another agent with activity against MRSA is initiated and blood cultures remain negative, treatment with this agent can be discontinued after 2-3 days [2].

Streptococcus viridans bacteremia is a common complication in the setting of mucositis and, if not promptly treated, has been associated with shock and acute respiratory distress syndrome [47]. The prevalence of penicillin-resistant *Streptococcus viridans* species has ranged between 10-25% and addition of vancomycin may be warranted when clinical suspicion for a penicillin-resistant *Streptococcus viridans* bacteremia is high.

Multi-drug resistant (MDR) gram-negative organisms. A carbapenem should be preferred in patients with known colonization, prior infection or high clinical suspicion for an MDR gram-

negative (e.g. producing an extended spectrum β -lactamase, ESBL) organism. In patients with known colonization, prior infection or high clinical suspicion for carbapenemase enzyme producing (CPE) 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 the antibiotic susceptibility profile, if available.

Cefepime. Cefepime remains a first-line agent for the management of febrile neutropenia. Despite concerns about suboptimal outcomes associated with the agent based on the results of a meta-analysis, a new meta-analysis initiated by the Federal Drug Administration (FDA) did not confirm these findings [2, 48].

Ceftazidime. Despite its activity against *Pseudomonas aeruginosa*, ceftazidime is not included in the list of preferred empirical treatments for neutropenic fever, due to its lack of activity against gram-positive pathogens.

7.3. Antibacterial empirical treatment - Persistent neutropenic fever

Persistent neutropenic fever, defined as neutropenic fever after 3-5 days of empirical antibiotic treatment, is a frequent occurrence in allogeneic HCT recipients. 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 [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 [2]. The following antibiotic adjustments may be considered in select patients with persistent neutropenic fever (**Table 3**):

(a) 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 or meropenem, to include coverage against ESBL-producing pathogens.

- (b) In case of MRSA and/or VRE or penicillin-resistant *Streptococcus viridans* colonization/infection, treatment with vancomycin (daptomycin or linezolid) should be instituted.
- (c) In case of CPE-producing gram-negative organism colonization, antibiotic treatment should be adjusted based on already existing antibiogram results and after consultation with the Infectious Disease consultation team.
- (d) In patients with persistent neutropenic fever despite broad-spectrum antibacterial treatment, less common bacterial pathogens should be considered, including *Stenotrophomonas maltophilia* or *Nocardia* species.
- (e) In patients with a definitive diagnosis of a specific infection, antibiotic treatment should be tailored based on culture and antibiotic susceptibility results.
- (f) In patients with hemodynamic instability, addition of an aminoglycoside (i.e. amikacin) should be considered.

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 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.

7.4. 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, 49]. This approach has been recently questioned, 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 [50, 51]. Nevertheless, current guidelines endorse broad-spectrum empirical antibiotic therapy continuation until resolution of fever and neutropenia [2]. De-escalation to a fluoroquinolone has been suggested in 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 stable and afebrile for ≥ 48 hours [50]. Secondary prophylaxis with a narrower-spectrum agent, such as a fluoroquinolone, may be used, depending on local epidemiology [50, 51]. 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 [52]. 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.

7.5. 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 [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 [53]. 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, 54-56]. 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 (**7.6. Antifungal preemptive treatment**).

7.6. 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 [57-59]. In addition, fungal biomarkers, such as the GM EIA and b-D glucan have been introduced in clinical practice in the last two decades for the diagnosis of IA and IFI, respectively, with variable sensitivity and specificity depending on multiple variables [60]. Maertens et al were the first to assess the feasibility of a preemptive antifungal approach in a cohort of neutropenic patients receiving fluconazole prophylaxis [59]. 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 >0.5) and/or positive bronchoalveolar lavage culture. A 78% reduction in antifungal treatment administration was observed, when compared to the number of patients who would require empirical antifungal treatment based on pre-defined criteria and there were no missed cases of IA. 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 [61]. Preemptive treatment was defined as initiation of antifungal therapy in patients with clinical, imaging or microbiological evidence of an IFI, including a positive GM EIA (optical density index ≥ 1.5). Overall survival 14 days after 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% and 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. While several additional questions remained unanswered, preemptive antifungal treatment in patients with persistent neutropenic fever appears to be a safe and effective approach in high-risk hematologic patients. Although not studied in allogeneic HCT recipients, most centers follow a preemptive antifungal treatment approach in the preengraftment period in cases of persistent neutropenic fever.

8. DISCUSSION

De nombreux progrès ont été réalisés dans la gestion des complications infectieuses chez les patients avec des hémopathies malignes et des receveurs d'une greffe allogénique de cellules hématopoïétiques. L'introduction sur le terrain de prophylaxies antibactériennes, antifongiques, antivirales et antiparasitaires de routine a permis une diminution significative des maladies infectieuses observées chez ces patients [1-4, 34]. Dans de nombreux cas, cela a permis de réduire significativement la mortalité associée à ces infections.

De même, l'introduction rapide d'une thérapie empirique et préventive a eu pour résultat une amélioration de la survie et des résultats cliniques de ces patients. Cependant, la grande majorité de ces interventions - avec quelques exceptions - reposent sur des données observationnelles rétrospectives et non contrôlées [1-4, 34]. Par conséquent, de nombreuses questions, qui pourraient améliorer la qualité des résultats observés, restent sans réponse. Cette brève discussion a pour but de présenter les principales questions qui nécessiteraient des recherches supplémentaires pour permettre un impact favorable sur la survie et la qualité de vie de nos patients (**Table 4**).

L'administration d'une prophylaxie antibactérienne systématique post-conditionnement pendant les épisodes de neutropénie est de nos jours considérée comme le «standard of care» [1-4, 34]. Cependant dans de nombreux centres, y compris tous les centres de transplantation allogénique en Suisse, la prophylaxie bactérienne primaire de routine n'est pas encore usuellement administrée chez les patients neutropéniques [62]. L'administration de routine de la prophylaxie bactérienne présente de nombreux problèmes potentiels, notamment la sélection d'agents pathogènes bactériens résistants, la préservation de la flore GIT et ses effets sur le développement de la GvHD, ainsi que le développement de complications telles que la colite à *Clostridium difficile* [9-11, 63-69]. Malgré le fait qu'un grand nombre d'essais cliniques prospectifs randomisés et de méta-analyses systématiques aient été effectués par le passé, la plupart de ces données se révèlent de nos jours obsolètes [69]. À l'ère des schémas de conditionnement non ablatifs avec une incidence et gravité moindre de mucite, il est pertinent de s'attarder sur le sujet, afin d'évaluer l'effet global potentiel que pourrait montrer la

prophylaxie antibactérienne primaire chez les receveurs d'une greffe allogénique de cellules hématopoïétiques. Il s'avère nécessaire de réaliser de nouvelles études prospectives en tenant compte non seulement de l'incidence des infections bactériennes démontrées, mais également de l'effet sur la mortalité, ainsi que de la colonisation avec des germes multi-résistants et la variabilité de la flore normale du GIT de ces patients.

Table 4. Les questions pertinentes dans les traitements antibiotiques chez les transplantés allogéniques.

Question	
Prophylaxie antibactérienne	Une prophylaxie antibactérienne primaire avant la prise de greffe est-elle toujours nécessaire?
	Combien de temps faut-il poursuivre la prophylaxie contre les organismes encapsulés?
	Comment mesurer l'immunité humorale afin d'évaluer le besoin d'une prophylaxie antibactérienne?
Prophylaxie antifongique	La prophylaxie au fluconazole doit-elle être poursuivie après la prise de greffe?
	Tous les patients atteints de GvHD devraient-ils recevoir une prophylaxie primaire contre les champignons filamenteux?
	Pouvons-nous identifier certaines catégories de patients à haut risque après la prise de greffe qui bénéficieraient le plus d'une prophylaxie active contre les champignons filamenteux?
	Quel est l'effet de facteurs de risque génétiques sur le risque pour les infections aux champignons filamenteux?
	Quel est le meilleur moment pour introduire une prophylaxie contre <i>Pneumocystis</i> ?
Prophylaxie antivirale	Combien de temps faut-il administrer une prophylaxie contre VZV après HCT?
	Tous les patients doivent-ils recevoir une prophylaxie au letermovir et pour combien de temps post-HCT?
	Quels sont les effets à long terme de la prophylaxie de routine par letermovir?
	Quels patients et pendant combien de temps devrait recevoir une prophylaxie contre la réactivation HBV?
Traitement antibactérienne empirique	Pendant combien de temps le traitement antibactérien empirique doit-il être poursuivi en cas de neutropénie profonde prolongée?
	Comment est-ce que les tests de diagnostic précis plus sensibles peuvent-ils limiter les traitements prolongés de traitement antibactérien empirique et comment?

Traitement antifongique empirique	Comment pouvons-nous mieux identifier les patients atteints d'infections fongiques invasives?
	Comment pouvons-nous augmenter les taux d'infections fongiques prouvées et probables par rapport aux infections fongiques possibles?

Après la prise de greffe, l'introduction d'une prophylaxie contre les organismes encapsulés pendant un à deux ans après la greffe de cellules hématopoïétiques est également considérée comme «standard of care», selon plusieurs guidelines [1]. Cependant, des données de meilleure qualité sont nécessaires concernant la chronologie de l'arrêt de la prophylaxie, avec des mesures potentiellement plus précises de l'immunité humorale de ces hôtes et l'introduction de la vaccination anti-pneumococcique précoce. Une meilleure compréhension de la cinétique de l'immunité humorale efficace contre le pneumocoque pourrait nous aider afin de mieux décrire les périodes à haut risque pour l'administration d'une prophylaxie comme telle.

En termes de prophylaxie antifongique, l'introduction du post-conditionnement du fluconazole et jusqu'à 75 à 100 jours a été approuvée par plusieurs études prospectives et appliquée de manière similaire dans la plupart des centres [1-4, 34]. La nécessité de poursuivre la prophylaxie antifongique après la prise de greffe en l'absence de GvHD et l'administration de corticostéroïdes à fortes doses reste discutable. Bien qu'une seule étude ait démontré un bénéfice supplémentaire en termes de survie à long terme chez les patients ayant reçu une prophylaxie au fluconazole au cours des 75 premiers jours suivant une greffe de cellules hématopoïétiques, on ne sait toujours pas si le fluconazole est toujours nécessaire après la prise de greffe [13]. En effet, le principal facteur de risque de candidémie (principal agent pathogène couvert par l'administration de fluconazole), à savoir la mucite, n'est plus un problème post-greffe. Donc, l'administration de fluconazole pourrait être obsolète dans ce contexte comme la candidémie n'est plus l'infection fongique la plus fréquente chez les patients post prise de greffe. Des données supplémentaires dans ce domaine sont nécessaires de toute urgence.

De plus, l'administration d'une prophylaxie active contre les champignons filamenteux après la prise de greffe en cas de GvHD sévère est devenue usuelle dans la plupart des centres [1-4, 34]. Cependant, le nombre de patients à traiter pour prévenir une infection par les champignons filamenteux pourrait atteindre 16-20 [20-22, 70]. Il est donc urgent de déployer davantage d'efforts pour identifier un groupe spécifique de patients atteints de GvHD qui bénéficieraient le plus de ce type de prophylaxie. De nouveaux développements dans le domaine, notamment l'identification de facteurs génétiques en tant que facteurs de risque importants pour les infections par les champignons filamenteux, pourraient nous éclairer davantage et conduire à d'autres études qui nous aideront à cibler un groupe spécifique à haut risque de receveurs de

greffe allogénique de cellules souches hématopoïétiques pour recevoir une prophylaxie active contre les champignons filamenteux.

Il est recommandé d'administrer une prophylaxie contre la PCP à base de TMP-SMX après la prise de greffe. Un certain nombre de centres, y compris tous les centres de greffe de cellules hématopoïétiques de Suisse, administrent en routine une prophylaxie par TMP-SMX dès le premier jour post une greffe de cellules hématopoïétiques [1, 3, 62]. Cette approche pourrait-elle conduire à de meilleurs résultats, avec moins d'épisodes de PCP observés au cours des 2-3 premières semaines post une greffe de cellules hématopoïétiques? Ou au contraire, une telle approche pourrait-elle avoir un effet potentiellement néfaste sur la chronologie et l'efficacité de prise de greffe, compte tenu de l'effet suppressif sur la moelle osseuse de cet agent? Davantage de données sont nécessaires pour pouvoir répondre à cette question qui est pertinente d'un point de vue clinique.

La prophylaxie contre le HSV et le VZV par acyclovir ou valacyclovir est également administrée en routine [1-4, 34]. La prophylaxie contre le VZV est poursuivie - parfois - jusqu'à deux ans après une greffe de cellules hématopoïétiques. La nécessité absolue de cette mesure reste encore incertaine. La plupart des données sur le terrain viennent d'études rétrospectives observationnelles menées par un seul centre [24, 71]. Une approche systématique par des études prospectives dédiées sur le sujet pourrait clarifier cette question spécifique qui reste sans réponse.

De plus, les stratégies prophylactiques contre le CMV sont en pleine évolution ces dernières années. L'introduction du letermovir, un antiviral bien toléré, sûr et spécifique contre le CMV au cours des 100 premiers jours post-HCT allogénique chez les patients à haut risque a été associé à une diminution significative du taux de réactivation de CMV et de mortalité globale [30, 34]. Cependant, il reste encore des questions sans réponse. Par exemple, est-ce que tous ou seulement certains patients à risque plus élevé devraient recevoir une prophylaxie au letermovir? Cette prophylaxie devrait-elle être administrée pendant plus de 3 mois après la HCT, par exemple pendant les 6, voire 12 premiers mois? Quels sont les effets à long terme de telles stratégies? Cette approche conduirait-elle à davantage d'infections virales autres que le CMV, telles que le HHV6 et l'adénovirus, associées toutes deux à des tableaux cliniques et à des

taux de mortalité significativement plus élevés? Jusqu'à ce que davantage de données soient disponibles, il convient de faire preuve de prudence lors de l'introduction universelle du letermovir en pratique clinique.

Les recommandations concernant la prophylaxie du HBV chez les patients présentant un risque modéré et élevé de réactivation du HBV sont principalement basées sur de petites études observationnelles rétrospectives [1-4, 34]. Cependant, la question de la prophylaxie active contre le HBV chez ce groupe des patients se pose fréquemment en pratique clinique. Les cliniciens sont confrontés à un grand nombre de patients qui pourraient nécessiter une administration prophylactique prolongée. Compte tenu de la piètre qualité des données disponibles, des études prospectives devraient être mis en place pour apporter des réponses définitives à cette question pertinente.

L'administration d'un traitement antibactérien empirique dans le contexte de la fièvre neutropénique hante le terrain depuis de nombreuses décennies [1-4, 34]. Certaines études récentes ont tenté de clarifier un peu plus le contexte [51]. Cependant, la grande majorité des centres continuent d'utiliser des approches datant des années 1980 et début des années 1990. Le maintien d'antibiotiques à large spectre jusqu'à la résolution de la neutropénie, même en l'absence de tout signe d'infection bactérienne, est appliqué de manière générale et globale. Il est absolument nécessaire de mener davantage d'essais cliniques randomisés prospectifs pour tenter de résoudre définitivement cette question. L'effet de ces approches sur la flore GIT de nos patients et la sélection d'agents pathogènes résistants aux médicaments doit être correctement évaluée. Cela reste l'un des principaux sujets de préoccupation sur le terrain et des efforts communs sont absolument nécessaires. Une solution à ce problème serait l'introduction de tests de diagnostic plus sensibles et plus précis qui pourraient nous aider à identifier les patients atteints de maladies infectieuses démontrées devant être traités avec un traitement antibiotique prolongé. Jusqu'à ce que davantage de données dans le domaine diagnostic, y compris moléculaire, soient disponibles, un grand nombre de patients continueront à recevoir des traitements prolongés d'antibiotiques à large spectre sans qu'il soit clairement démontré qu'ils en ont réellement besoin.

L'administration d'un traitement antifongique empirique est la méthode standard depuis plus de 4 décennies. Cependant, la grande majorité des patients traités avec des antifongiques à large spectre ne présentent pas d'infection fongique invasive sous-jacente. Cependant, les difficultés et les limites dans l'établissement du diagnostic d'une IFI ont nourri pendant des décennies l'approche de la thérapie empirique dans la perspective d'une éventuelle IFI. Il faudrait investir davantage dans le domaine du diagnostic fongique afin d'améliorer notre capacité à diagnostiquer ces infections avec un degré de certitude qui nous permettra de réduire l'administration de traitements antifongiques empiriques. Ceci est encore plus pertinent, à une époque où la pharmaco résistance surtout sur les espèces d'*Aspergillus* est plus fréquemment observées et les «breakthrough» IFI résistantes dans la plupart des agents antifongiques disponibles sont de plus en plus observées dans le monde entier [62, 72]. En outre, l'administration d'antifongiques à activité étendue, notamment les formulations d'amphotéricine B et des azoles à large spectre, est associée à des événements indésirables et des interactions médicamenteuses significatifs, qui affectent davantage le statut des receveurs de greffe allogénique, déjà fragiles, et les résultats cliniques.

En conclusion, bien que des progrès significatifs aient été réalisés sur le terrain, un grand nombre de questions sans réponse appelle des actions supplémentaires et des essais cliniques randomisés prospectifs pour aider à améliorer les soins cliniques et à réduire la morbidité et la mortalité associées.

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