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Review article

An overview of infectious complications after allogeneic hematopoietic stem cell transplantation

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ABSTRACT

Infections are the most common and significant cause of mortality and morbidity after allogeneic hematopoietic stem cell transplantation (allo-HSCT). The presence of neutropenia and mucosal damage are the leading risk factors in the early pre-engraftment phase. In the early post-engraftment phase, graft versus host disease (GvHD) induced infection risk is increased in addition to catheter related infections. In the late phase, in which reconstitution of cellular and humoral immunity continues, as well as the pathogens seen during the early post-engraftment phase, *varicella–zoster virus* and encapsulated bacterial infections due to impaired opsonization are observed. An appropriate vaccination schedule following the cessation of immunosuppressive treatment after transplantation, intravenous immunoglobulin administration, and antimicrobial prophylaxis with penicillin or macrolide antibiotics during immunosuppressive treatment for GvHD might decrease the risk of bacterial infections. Older age, severe mucositis due to toxicity of chemotherapy, gastrointestinal tract colonization, prolonged neutropenia, unrelated donor and cord blood originated transplantations, acute and chronic GvHD are among the most indicative clinical risk factors for invasive fungal infections. Mold-active anti-fungal prophylaxis is suggested regardless of the period of transplantation among high risk patients. The novel serological methods, including *Aspergillus* galactomannan antigen and beta-D-glucan detection and computed tomography are useful in surveillance. Infections due to *adenovirus*, *influenza* and *respiratory syncytial virus* are encountered in all phases after allo-HSCT, including pre-engraftment, early post-engraftment and late phases. Infections due to *herpes simplex virus-1* and *-2* are mostly seen during the pre-engraftment phase, whereas, infections due to *cytomegalovirus* and *human herpes virus-6* are seen in the early post-engraftment phase and *Epstein–Barr virus* and *varicella–zoster virus* infections often after +100th day. In order to prevent mortality and morbidity of infections after allo-HSCT, the recipients should be carefully followed-up with appropriate prophylactic measures in the post-transplant period.

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1. Introduction

Infections are the most common and significant cause of mortality and morbidity after allogeneic hematopoietic stem cell transplantation (allo-HSCT). Allo-HSCT is a more complicated and multifactorial process when compared to autologous hematopoietic stem cell transplantation (auto-HSCT), in which the standard risks are mainly related to neutropenia, mucositis and catheter use, provided that immunosuppressive drugs are not used. The presence of myeloablation, the reconstitution of a new immune system, the use of immunosuppressive drugs and graft versus host disease (GvHD) are independent risk factors for complications [1–5]. Other factors, such as the type of the conditioning regimen, HLA compatibility between the patient and the donor and the type of infectious agents detected during the course of pre-HSCT treatment also modify the risk [6–9]. Transplantation related factors affecting the risk of infection are presented in Table 1 [10].

The transplantation process and additional immunosuppressive therapy for GvHD treatment might deepen and prolong the existing deficiencies in humoral and cellular immune functions [11]. At least two to three years are needed for a complete immune reconstitution after adult allo-HSCT.

In general, three different phases for infection risk are described for the post-HSCT:

1. The early pre-engraftment phase involves 2–4 weeks after the stem cell infusion
2. The early post-engraftment phase involves 2–3 months after the HSCT
3. The late phase involves beyond the third month after engraftment [10]

The leading risk factors in the early pre-engraftment phase are the presence of neutropenia and mucosal damage. As known, neutropenia lasts approximately 5–7 days or 15–30 days depending on the type of the conditioning regimen, being either reduced intensity or myeloablative, respectively [12]. The management of infectious agents commonly encountered during this phase is similar to the febrile neutropenic episodes seen after various chemotherapy regimens. Bacteria are the leading responsible pathogens, whereas fungal pathogens (i.e., *Candida* spp.) and *herpes simplex virus* (*HSV*) are less frequent. Bacteremia/sepsis, pneumonia, oropharyngitis, sinusitis, proctitis and cellulitis are frequent.

In the early post-engraftment phase, GvHD induced infection risk is increased in addition to catheter related infections. Enteric bacteria may lead to life-threatening situations, especially in the presence of gastrointestinal system GvHD. In this period *adenovirus*, *BK virus*, respiratory viruses, *Pneumocystis jirovecii*, *Candida* spp., *Aspergillus* spp. and other fungi are also frequently encountered and they might easily cause serious infections among patients on immunosuppressive therapy for GvHD [10]. Symptomatic *cytomegalovirus* (*CMV*) infection usually presents with either life-threatening pneumonia or enterocolitis among patients with pre-transplantation seropositivity and GvHD.

In the late phase in which reconstitution of cellular and humoral immunity continues, as well as the pathogens seen during the early post-engraftment phase, *Varicella zoster virus* (VZV) and encapsulated bacterial infections due to impaired opsonization are observed. The presence of chronic GvHD not only prevents immune recovery, but also results in predisposition to infections due to prolonged immunosuppressive treatments. In this late phase, a very close relationship is observed between cellular immune recovery and infections. Examples are *Toxoplasma gondii* reactivation in seropositive patients and *P. jirovecii* pneumonia seen as a result of early discontinuation of trimethoprim/sulfamethoxazole (TMP–SMX) prophylaxis. After cessation of immunosuppressive treatment the patients should be administered a vaccination schedule.

2. Bacterial infections

In the early pre-engraftment phase after allo-HSCT two main sources of bacterial infections exist: the first one is the normal endogenous gastrointestinal system flora, being especially responsible from gram negative bacterial infections and the other is

Table 1
Effect of transplantation parameters on infection.

Factor	Infection/Agents
• Allo-HSCT (delayed recovery of cellular and humoral immune response) • Unrelated or mismatched donor (delayed recovery of cellular and humoral immune response)	All agents including herpes virus, fungal, bacterial
Source of stem cell graft • Peripheral blood (fast engraftment, but higher risk of chronic GVHD) • Bone marrow (slow engraftment, but lower risk of chronic GVHD)	Different agents in case of prominent neutropenia or GvHD
Conditioning regimens • Myeloablative (higher mucosal damage and longer period of neutropenia) • TBI (functional asplenia)	Increased risk of neutropenic infections such as typhlitis, fungal and bacterial
Manipulation on stem cell graft • T cell depletion (graft failure risk, delayed recovery of cellular and humoral immune response)	Infectious risk related with chronic GVHD is low; however, increased risk of neutropenic and fungal infections with herpes virus
Immunosuppressive drugs • ATG (disruption of T-cell immunity) • Methotrexate (higher risk of mucosal damage and disruption in neutrophil recovery)	Increased fungal and herpes virus infections
• Central venous catheters (disruption in skin barrier)	Increased risk of especially bacterial and less frequently fungal infections

indwelling vascular catheters, most gram positive bacterial infections occur from. Under normal circumstances, only 30–40% of febrile neutropenic episodes can be microbiologically documented [13]. The frequency of gram-positive bacterial infections has been increasing since 1980s [14]. Historically, gram-negative bacilli, especially *Pseudomonas aeruginosa* were the most commonly seen pathogens [15]. However, gram-negative bacterial infections are still associated with a high mortality rate and the frequency of infections with multi-drug resistant strains has been increasing within the last decade [16].

In the early phases, antibacterial prophylaxis plays a quite important role. Hand washing, oral hygiene, low bacterial diet, oral fluoroquinolones and gastrointestinal decontamination have been described as important precautions [17,18]. Prophylaxis with oral fluoroquinolones has been shown to reduce the frequency of febrile neutropenic episodes and mortality among neutropenic patients [19]. In a meta-analysis, quinolone prophylaxis has also been linked to a one-third decrease in the relative risk of mortality among allo-HSCT patients with acute leukemia [20]. According to guidelines of the Infectious Diseases Society of America (IDSA) levofloxacin and ciprofloxacin have equivalent prophylactic efficacy; however, levofloxacin might be preferred in the presence of oral mucositis due to its broader coverage against viridans streptococci [13]. Although the development of resistance and emergence of quinolone-resistant strains, such as extended-spectrum b-lactamase (ESBL) and carbapenemase-producing gram-negative bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) are major concerns of quinolone prophylaxis, prophylaxis still offers a greater clinical benefit and there is no evidence for an increase in adverse outcomes due to prophylaxis [20]. However, some recent studies suggest an increased risk for acute gastrointestinal GvHD among allo-HSCT recipients receiving levofloxacin prophylaxis due to alterations in intestinal microbiota [21].

In the presence of fever or suspected infection, cultures of blood, urine, feces and other specimens from possible sources of infection, antigen screening, polymerase chain reaction (PCR) studies, blood gases analysis, biochemical analyses including C-reactive protein (CRP) and procalcitonin, as well as various imaging techniques should be ordered immediately in consideration with the most probable exposed infectious agents, medical history and previously encountered pathogens during the past treatments [22]. Antibiotic treatment should be administered immediately to a patient diagnosed with a febrile neutropenic episode. In the absence of an apparent specific infection, the standard treatment approach is monotherapy with a broad spectrum beta lactam antibiotic such as piperacillin/tazobactam, ceftazidime, cefepime or a carbapenem providing coverage against gram positive and gram negative bacteria including *P. aeruginosa*, after evaluating the patient and facility specific factors. In the presence of a catheter related infection, cellulitis, pneumonia, mucositis or MRSA colonization a glycopeptide antibiotic should be added to this regimen. If pneumonia, typhlitis or cellulitis is present or a gram negative bacterial colonization is detected, it is suitable to add an aminoglycoside. The presence of dominant abdominal complaints or suspected *Clostridium difficile* infection warrants the addition of metronidazole [13]. Fever might last up to one week upon initiation of therapy and clinical recovery occurs with normalization of temperature, serum CRP and procalcitonin levels [22]. However, there are some key points to be considered while interpreting serum CRP and procalcitonin levels. The production of CRP, which is an acute phase reactant, is dependent on the release of pro-inflammatory cytokines in response to inflammatory/infectious processes. Thus, its specificity for infections is very low. Serum CRP rises within 24 h of infection and it can predict the development of fever and severe sepsis in neutropenic patients [23]. However, it may not allow for reliable discrimination of bacteremic and non-bacteremic febrile episodes [24]. Procalcitonin is more specific for the diagnosis of bacterial infections in febrile neutropenia and has a higher negative predictive value for the presence of bacteremia [25]. However, it has limited value in the decision of antibiotic cessation in the high-risk populations [25]. The presence of deep leukopenia and immunosuppression has also been linked to a blunted procalcitonin response [26]. Serum procalcitonin rise may be delayed up to three days after the onset of fever and thus, may not allow for early detection and proper risk stratification [24].

Post-HSCT administration of granulocyte colony stimulation factors (G-CSF) may shorten the time to neutrophil engraftment 1–4 days and reduce complications related to prolonged neutropenia [27]. However, it neither affects the length of hospitalization, nor the number of days with febrile neutropenia. In the presence of bone marrow harvested cell infusions, it might increase the frequency of acute GvHD [27,28]. In a recent prospective multicenter randomized trial, granulocyte–macrophage colony stimulating factor (GM-CSF) has been reported to have a lower transplantation related, overall and invasive fungal infection related mortality, when compared to G-CSF [29].

Infections seen in the late phase after allo-HSCT are rather due to GvHD and its treatment, functional asplenia as well as hypogammaglobulinemia. The leading causes are encapsulated bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseriae meningitidis*. As mentioned previously, an appropriate vaccination schedule following the cessation of immunosuppressive treatment after transplantation, intravenous immunoglobulin (IVIg) administration, if necessary, and antimicrobial prophylaxis with penicillin or macrolide antibiotics during immunosuppressive treatment for GvHD might decrease the risk of infection. Although rare, *Mycobacterium, Nocardia* and *Listeria* might also be mentioned among the bacterial pathogens.

3. Fungal infections

Fungal pathogens, one of the leading causes of mortality and morbidity after allo-HSCT also present with a certain chronological frequency distribution. In the early pre-engraftment phase, *Candida* spp. are seen more frequent. However, the vast majority of fungal infections are observed during the early post-engraftment period and the late phase, especially due to GvHD and its treatment [30]. As opposed to yeasts, which generally enter the body via translocation through indwelling catheters or impaired intestinal mucosa, molds are taken into the body via inhalation of airborne spores. Due to suppression of cellular immunity, phagocytosis of those pathogens by macrophages is impaired, which allows for their proliferation.

A prospective study including 23 transplantation centers in United States analyzed the epidemiology and risk factors of invasive fungal infections and reported invasive aspergillosis as the leading infection; whereas, invasive candidiasis and non-*Aspergillus* mold infections was less frequent [31]. A multi-center prospective study from Brasil reported that invasive fungal infections detected at a rate of 9.2% after allo-HSCT [32]. While the incidences of aspergillosis and invasive candidiasis were similar, the incidence of *Fusarium* infections was found as high as 5.2%. In another prospective study from Italy, the rate of invasive fungal infections detected after +40th and +100th days after allo-HSCT was reported as 5.1% and 6.7%, respectively [33]. Invasive aspergillosis (81.1%) took the first place, while invasive candidiasis (11%), zygomycosis (3.7%) and fusariosis (1.8%) were observed less frequently. In this study, apart from expected, invasive fungal infections were observed in very early phases of the allo-HSCT period. The reasons for this were given as the increased frequency of unrelated donor and the cord

blood originated transplantations and the presence of active disease before the transplantation. Unmanipulated haploidentical hematopoietic stem cell transplantation (haplo-HSCT) has not yet been linked to an increased invasive fungal infection risk [34].

Older age, severe mucositis due to toxicity of chemotherapy, gastrointestinal tract colonization, prolonged neutropenia, unrelated donor and cord blood originated transplantations, acute and chronic GvHD are among the most indicative clinical risk factors for invasive fungal infections [34–37]. Additionally, the presence of *CMV* infections, iron overload, mismatched-related donor and acute leukemia with active disease before the transplantation also may facilitate the development of fungal infections [33]. The prevalence of fungal infections increases after haplo-HSCT, in which *ex vivo* or *in vivo* T-cell depletion is performed in order to prevent GvHD, while the infusion of more CD34+ cells were reported to overwhelm this risk [38].

When classified in terms of invasive fungal infection risk, the allo-HSCT cases with an expectancy of <14 days of neutropenia are considered in the moderate risk-standard group, whereas all the other allo-HSCT cases with an expectancy of >14 days of neutropenia or the presence extensive chronic GvHD and steroid depended or refractory or grade 3/4 severe GvHD are classified as the high risk group. According to this risk stratification, the suggested approach is the administration of mold-active prophylaxis in the high risk group, which has almost higher than 10% incidence of invasive fungal infection, and an anti-*Candida* prophylaxis in the moderate risk group [39]. However, the choice of using prophylaxis or not may also depend on institutional factors, such as overall incidence of invasive aspergillosis and availability and effective utilization of diagnostic-driven anti-fungal treatment (DDAT) strategies [40,41].

According to GITMO (Italian Group for Bone Marrow Transplantation) the risk stratification and management of allo-HSCT patients [42] should be as given in Table 2.

For primary prevention, high efficiency particulate air (HEPA) filtered transplantation rooms might be a rational choice. Fluconazole prophylaxis is effective against yeasts; however, its protection against molds is relatively lower. Prophylactic voriconazole decreases the frequency of *Aspergillus* infections and posaconazole prophylaxis provides a survival advantage especially among GvHD developed patients [43,44]. The choice of prophylactic agent, as well as the duration of treatment – at least until +75th day, or longer – varies among transplant centers. It was reported that fluconazole use decreased GvHD incidence in addition to preventing the development of candidiasis [45]. In the presence of GvHD anti-fungal prophylaxis should continue for at least 16 weeks or until when the corticosteroid dose is tapered below 10 mg daily prednisolone or equivalent dose [39].

Oral posaconazole possesses a broad anti-mold activity and low breakthrough of invasive fungal infections [39,44]. However, its bioavailability in gastrointestinal GvHD cases is low due to absorption problems. It is originally prescribed as forms of injection, delayed-release tablets, and oral suspension for use in the prophylaxis of invasive *Aspergillus* and *Candida* infections among patients at high risk such as HSCT recipients with GvHD or those with hematologic malignancies with prolonged neutropenia from chemotherapy [46]. For prophylaxis it is given parenterally as 300 mg injections intravenously twice a day on the first day as a loading dose and 300 mg injection intravenously once a day thereafter as maintenance. Duration of therapy is based on recovery from neutropenia or immunosuppression. The tablet formulation has a more common use and given as a dose of 300 mg twice daily in the first day as a loading dose followed by 300 mg once daily use and continued until recovery from neutropenia or immunosuppression. The dosing of oral suspension is suggested as 200 mg thrice daily.

Voriconazole is an important anti-fungal agent for high risk patients given through parenteral administration with proven anti-mold activity. In a randomized, double-blind study comparing voriconazole and fluconazole among allo-HSCT patients, less frequent use of empirical anti-fungal therapy in patients who received voriconazole compared to those received fluconazole has been detected, although this was not statistically significant [43]. In a study including 72 allo-HSCT patients, voriconazole prophylaxis was administered starting from −2nd day until the cessation of immunosuppressive treatment and resulted with fungal infection in only 2 patients during the early phase (<120 days) and no fungal infection in the late phase [47]. Voriconazole had to be discontinued due to various side effects including liver toxicity seen as high as 14%. Another prospective randomized study compared the efficacy and safety of voriconazole and itraconazole [48]. The success of prophylaxis was significantly higher with voriconazole than itraconazole, as well as drug tolerance during prophylaxis for 100 days. There were no differences in the incidence of proven/probable invasive fungal disease (1.3% vs. 2.1%) or survival to day +180 (81.9% versus 80.9%) between voriconazole and itraconazole, respectively. Both posaconazole and voriconazole have pharmacokinetic limitations such as drug interaction, variable absorption and toxicity in long term use [42]. The possible drug interactions might alter the efficacy and toxicity profiles of immunosuppressive, anticonvulsant and antimicrobial treatments, which are mandatorily used after allo-HSCT.

In a prospective randomized study comparing fluconazole and itraconazole, itraconazole was more effective against invasive mold infections; however, both were similarly effective against candidiasis [49]. A study comparing prophylaxis with thrice daily doses of

Table 2
The risk stratification and management of allo-HSCT patients.

1) In the early phase of allo-HSCT; for a patient to be characterized as high risk and therefore needs an anti-mold active treatment has to have at least one of the following criteria;
   a) acute leukemia with active disease before allo-HSCT
   b) cord blood transplantation
   c) grade III or IV acute GvHD developed after any type of transplantation
   d) the presence of one or more of the following additional factors if a mismatched related donor or unrelated donor is used; grade II acute GvHD, a steroid dose ≥2 mg/kg/day for at least 1 week, recurrent *CMV* infection, *CMV* disease, prolonged neutropenia, iron overload.
   e) steroid refractory/dependent acute GvHD developing after any type of transplantation.
2) In the early phase of allo-HSCT all other patients who are not included in high risk category mentioned above – standard risk – require a *Candida*-active primary anti-fungal prophylaxis.
3) Although suggestions for an anti-fungal prophylaxis for the late phase of allo-HSCT are similar with the ones in early phase, additional high risk factors for the very late phase are persistent or late-onset grade III–IV acute GvHD, persistent or late-onset steroid refractory/dependent acute GvHD, persistent or late-onset grade II acute GvHD after transplantation from mismatched related or unrelated donor and presence of an extensive chronic GvHD.

oral posaconazole to weekly administered high dose intravenous amphotericin B lipid complex reported that amphotericin B was as effective as posaconazole for the prevention of invasive fungal infections among allo-HSCT recipients [50]. However, renal toxicity was a concern for amphotericin B, as 43% of the patients in this group had to discontinue treatment due to toxicity. Another study using liposomal amphotericin B at a dose of 7.5 mg/kg once weekly reported lower rates of fungal infections during the first year of transplantation and a lower rate of fungal infection related mortality [51]. In this study, the tolerance to amphotericin B was better with only 12% of patients experienced a reversible nephrotoxicity leading to temporary treatment discontinuation of treatment.

The use of fluconazole (400 mg/day) for candidiasis prophylaxis among patients with a moderate-standard risk for invasive fungal infection is commonly accepted. It is continued for a minimum of 75 days or at least until the cessation of immunosuppressive treatment. In fact, itraconazole, micafungin and voriconazole are also as effective as fluconazole in candidiasis prophylaxis during the peri-engraftment period [42].

Voriconazole when compared to fluconazole causes liver toxicity more frequently and interacts especially with vinca alkaloid-based regimens, which has clinical importance. As a result, when the cost and the drug interactions are considered, fluconazole seems to be a more suitable agent for prophylaxis during the peri-engraftment period. On the other hand, mold-active anti-fungal prophylaxis is suggested regardless of the period of transplantation among high risk patients. The use of voriconazole is especially preferred in the early pre-engraftment phase, considering its apparent superiority to fluconazole and itraconazole and the moderate superiority to posaconazole [42]. However, anti-fungal prophylaxis with posaconazole oral solution (600 mg/day) is accepted in the presence of GvHD. In gut GvHD, in which gastrointestinal absorption might be a problem, parenteral voriconazole might be preferred. Mold active prophylaxis is favored until cessation of steroids or other immunosuppressive drugs and may be maintained even after. For the secondary prophylaxis, the first choice for candidiasis should be the agent previously used for treating candidiasis, whereas it is generally voriconazole in mold infections [39].

The diagnosis of fungal infections relies on histopathological and microbiological examinations and imaging methods. Microbiological methods are valuable. However, they are impractical, since their results take a long time. DDAT strategies involve the utilization of highly sensitive and specific diagnostic tests, such as serological and molecular methods for detecting *Aspergillus* and imaging modalities including computed tomography (CT) of thorax [41]. *Aspergillus* galactomannan antigen and beta-D-glucan detection are novel serological methods used in surveillance. Serum galactomannan is detected via commercial enzyme-linked immunosorbent assay (ELISA) kits and an optical density index (ODI) of $\geq$0.5 is considered as a positive test result [52]. The positive predictive value of this test is very low. In contrast, it has a high negative predictivity, which makes it a proper screening test. It is also validated for use in bronchoalveolar lavage (BAL). BAL is more sensitive than serum samples; however, the cut-off value for BAL samples has not been clarified. In a meta-analysis a cut-off value of >1.5 has been suggested [53]. Serum galactomannan antigen testing should be repeated twice weekly during neutropenia. The presence of a gradual increase in ODI in consequent tests has a prognostic importance [54]. False-positive results may be seen due to interference with some foods or enteral nutrition, administration of parenteral beta-lactam antibiotics, sodium gluconate, blood products, the presence of other fungal infections and multiple myeloma [55]. Among the imaging techniques, chest X-ray and CT are frequently used. Invasive fungal infections are generally classified as proven, probable and possible depending on the presence of tissue diagnosis, microbiological and/or imaging evidences [56].

Aspergillus species are the leading pathogens with a capability of developing severe fungal infections in almost all major organs among allo-HSCT patients [57]. The most frequently involved organs are lungs, followed by paranasal sinuses, central nervous system, skin and soft tissues, eyes and heart [58–61]. The most common pathogens are *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus niger* and *Aspergillus terreus* with the order of decreasing incidence [57,58].

A randomized study, comparing the efficacy of liposomal amphotericin B and voriconazole as a primary treatment for definite or probable invasive aspergillosis reported better response, improved survival and fewer severe side effects with voriconazole than initial therapy with amphotericin B [62]. Another study in which liposomal amphotericin B was compared in different doses for “possible” invasive fungal infection cases, the survival rate in 12th week with amphotericin B at a dose of 3 mg/kg/day was reported as 82% [63]. A study from the European Organization for Research and Treatment of Cancer (EORTC) evaluated caspofungin at standard dose as a first-line monotherapy for probable/proven invasive aspergillosis among allo-HSCT patients [64]. The use of caspofungin in the initial therapy for allo-HSCT patients having a mycologically documented invasive fungal infection was reported to be effective with a survival rate of 50% in 12th week without causing any severe adverse effects and treatment discontinuation due to a serious toxicity. In a randomized study comparing combination therapy to single agent voriconazole among allo-HSCT patients with hematological malignancies having suspected or documented aspergillosis, the mortality rates in 6th week were reported to be lower in the voriconazole + anidulafungin group. The incidence of adverse effects was similar between the groups [65].

Pneumocystis is a common microorganism identified approximately 100 years ago and categorized as a fungus depending on RNA sequence analysis [66]. The historical name *Pneumocystis carinii* has been currently modified as *P. jirovecii*. *P. jirovecii* pneumonia (PCP) is commonly seen and it has environmental and person-to-person transmission. Prophylaxis against *P. jirovecii* infections with TMP–SMX should definitely be administered after allo-HSCT. Before the prophylaxis era, PCP starting at median 9th week and leading to a mortality rate of up to 76% have been reported after allo-HSCT [67]. However, after the advent of prophylaxis with TMP–SMX in routine clinical practice PCP incidence after allo-HSCT decreased significantly [68]. The factors facilitating the development of PCP following allo-HSCT are immunosuppressive therapy, chronic GvHD, relapse of primary disease and low CD4+ cell count.

Early discontinuation of TMP–SMX prophylaxis before the post-transplantation 6th month has been linked to an increased risk of late onset PCP. In a retrospective study, all PCP episodes were reported to occur after 6 months post-transplantation due to the presence of facilitating factors and it was emphasized to prolong the TMP–SMX prophylaxis to at least 1 year or further in the presence of immunosuppressive treatment or primary disease relapse [69–71]. Many transplantation centers prefer once- or twice-daily regimens (single-strength or double-strength tablets) 2–7 days per week, all of which seem efficacious [72]. However, some adverse effects such as rash, bone marrow suppression, fever and liver, gastrointestinal and renal toxicity may necessitate discontinuation of treatment. Thus, low dose prophylaxis such as the administration of two single-strength tablets twice a week is preferred by some centers [68].

In general, although there are slight differences among centers, TMP–SMX prophylaxis should be started with the pre-transplant

conditioning regimen and continued for at least 6 months or further, as long as the risk factors persist. Due to its myelosuppressive effects, prophylaxis with TMP–SMX should be withheld starting from the day of stem cell infusion till engraftment in order to prevent distortion of engraftment kinetics.

Treatment refractoriness should be considered, if radiological, clinical or microbiological progression is detected after at least a seven days of anti-fungal therapy [57]. In a retrospective study of evaluating efficiency and safety of caspofungin + posaconazole for salvage therapy in immunocompromised patients resistant to first line anti-fungal treatment, 77% of the cases recovered with a combination of caspofungin 50 mg daily + posaconazole 200 mg four times daily and no treatment discontinuation due to adverse effects occurred [73]. Another study including patients resistant to amphotericin B or triazoles and the first line anti-fungal treatment, a favorable response in 45% of the patients were reported with the second line caspofungin treatment [74].

Although there is no consensus about the duration of the anti-fungal treatment in invasive aspergillosis, it is generally accepted that a treatment response occurs within the first 12 weeks. Thus, the treatment is continued for at least 6–12 weeks or until immune recovery or clinical and/or radiological evidences of recovery are evident [57,75]. Therapeutic drug monitoring during treatment would be a suitable approach, especially for the azoles.

Proper prospective randomized studies regarding the optimum treatment choices for mucormycosis is currently not available. Liposomal amphotericin B provides moderately successful responses if the treatment is started earlier on the grounds of clinical suspicion [76]. Actually, the successful management of mucormycosis depends on early diagnosis, emergent surgical debridement of devitalized tissues and proper management of underlying risk factors. Iron chelation has a clinical importance since iron overload is considered a risk factor [57]. However, the studies on iron chelation have controversial results. In a recent randomized placebo-controlled trial, deferasirox in combination with liposomal amphotericin-B, deferasirox arm had a higher mortality rate at 90 days due to progression of disease/infection [77].

Fusariosis is a serious fungal infection with mortality rates currently up to 40–50% in spite of the use of liposomal amphotericin B and new azoles [78]. Amphotericin B and voriconazole have been reported to provide responses up to 32–46% and 45–47%, respectively [57].

In conclusion, the administration of an empirical treatment with caspofungin or liposomal amphotericin B in cases when there is no response with 5–7 days daily antibacterial treatment is the general approach [79]. Similarly, IDSA guidelines suggest initiation of empirical anti-fungal therapy after a rapid re-evaluation for high-risk patients with fever unresponsive to four days of empirical antibiotics [13]. The use of voriconazole and amphotericin B is suggested for invasive candidiasis accompanied by sepsis. Invasive aspergillosis cases developed after allo-HSCT should be treated first line with voriconazole or amphotericin B [30]. When resistance develops to the first line treatment, as single agent therapy with amphotericin B, posaconazole or caspofungin are recommended; however, their combinations might also be considered [57].

4. Viral infections

Viral infections are among the most important causes of mortality and morbidity after allo-HSCT and their incidence follow a certain chronology [11]. Infections due to *adenovirus*, *influenza* and *respiratory syncytial virus* (*RSV*) are encountered in all phases after allo-HSCT, including pre-engraftment, early post-engraftment and late phases. Infections due to *HSV*-1 and -2 are mostly seen during the pre-engraftment phase, whereas, infections due to *CMV* and *human herpes virus-6* (*HHV-6*) are seen in the early post-engraftment phase (<3 months) and *Epstein–Barr virus* (*EBV*) and *varicella–zoster virus* (*VZV*) infections often after +100th day (late phase).

Life threatening serious mucocutaneous disease due to HSV is a well-known complication after allo-HSCT, unless *HSV* seropositive patients are given the standard low dose (200 mg/day) prophylaxis with acyclovir [80,81].

VZV is a late complication after allo-HSCT and generally occurs due to viral reactivation. Primary infection is rare and usually severe and may occur in seronegative patients. The risk of reactivation is higher in the first 24 months after allo-HSCT [22]. Risk factors include the presence of immunosuppressive therapy, chronic GVHD, pre-HSCT diagnosis of leukemia and other lymphoproliferative disorders, advanced age, HLA-mismatch between donor and recipient, myeloablative regimen and CD34 selection in the graft [81]. Anti-viral treatment stops disease progression, prevents dissemination and fulminant visceral involvement, decreases the risk of post-herpetic neuralgia. In the presence of disseminated skin involvement or possibility of encephalitis, pneumonitis or hepatitis parenteral therapy with acyclovir at a dose of 500 mg/m^2 every 8 h is required. Oral valacyclovir (3 × 1000 mg), famciclovir (3 × 500 mg), acyclovir (5 × 800 mg) or brivudin (125 mg once daily) for 7 days can be used in oral therapy. Parenteral foscarnet (60 mg/kg every 12 h) or cidofovir (5 mg/kg once a week combined with probenecid and hydration for 2 weeks, once every 2 weeks after then, if required) can be used in the presence of resistance to acyclovir [81].

CMV infections are probably in the first place among the causes of unsuccessful transplantation. Although there is a geographical variation, 40–80% of the world population are estimated to be infected with *CMV* during childhood. After the silent primary infection, *CMV* becomes latent (IgG positive serology) throughout the entire life. In case of immunosuppression, as in the allo-HSCT process, reactivation of *CMV* occurs.

Advanced age, positive *CMV* serology, allogeneic graft and acute GvHD are among the risk factors for the development of *CMV* infection. Actually, most of the *CMV* infections are triggered by viral reactivation; however, it might also be due to a primary exposure [11]. Prophylaxis has a vital importance for the *CMV* infections encountered during the early post-engraftment phase. As a result of the success of prophylaxis and empirical treatment, infections due to this agent have been deferred from early to later phases after allo-HSCT [10]. Currently, as a rule, anti-*CMV* IgG serology should be screened for all transplant candidates before the initiation of conditioning regimen in order to determine the risk of *CMV* infection. In case of *CMV* seronegativity, choosing a seronegative donor or purifying the blood products from leukocytes in order to decrease the *CMV* contamination risk have become standard nowadays. The prevention of *CMV* related infections in cases when the recipient is seropositive has been explored in various studies. A double-blind, placebo-controlled study from Fred Hutchinson Cancer Research Center, in which 93 *CMV* seropositive patients were included, reported that daily ganciclovir started after engraftment and continued until the +100th day decreased both *CMV* infection and the *CMV* disease when compared to placebo [82]. Similar results were also confirmed in other randomized and placebo-controlled studies [83,84].

Foscarnet sodium have been found effective in the prevention of the *CMV* infection/disease among *CMV* seropositive recipients in phase I-II studies [85]. In clinical practice, high dose acyclovir and valacyclovir might also be used for this purpose [86]. Concurrently, CMV viral load should be monitored during acyclovir or valacyclovir prophylaxis and pre-emptive treatment with ganciclovir or foscarnet should be started immediately when a breakthrough is

detected. Although acyclovir and valacyclovir have favorable adverse effect profiles, they exert weak activity against *CMV*.

Pre-emptive treatment approach has slowly replaced prophylaxis recently after the development of novel diagnostic methods. The routine use of PCR which allows for quantification of *CMV* DNA made it possible to detect *CMV* viremia earlier [11]. Regular monitorization of *CMV* DNA should routinely be performed up to +60 days after the transplantation. This interval should also be prolonged up to +180 days in seropositive recipients, unrelated and haplo-HSCT and when HLA incompatibility and/or GvHD are present. Although there is no consensus for the cut-off values of *CMV* DNA test results among centers, there is a tendency to evaluate <100–300 copy/mL as a low positive and >300–500 copy/mL as a positive test result. Generally, observation of two consecutive positive results is suggested before starting treatment at lower copy numbers. Parenteral ganciclovir or foscarnet are suggested at first place for the pre-emptive anti-viral treatment [86].

In clinical practice, foscarnet is generally used as a second step treatment for patients intolerant to ganciclovir. Ganciclovir may cause neutropenia and thrombocytopenia due to bone marrow suppression, while foscarnet may lead to a severe nephrotoxicity but it is generally well tolerated [87].

Valganciclovir, the oral prodrug form of ganciclovir, is highly effective and safe [88]. In the absence of serious gastrointestinal GvHD per oral use of valganciclovir is as effective and safe as ganciclovir and foscarnet in the first line pre-emptive therapy [87,89]. Cidofovir due to its prominent nephrotoxicity is generally the third choice. A retrospective study from the European Group for Blood and Marrow Transplantation (EBMT) Infectious Diseases Working Party, reported a 50% response rate in *CMV* disease, most of which included cases with *CMV* pneumonia, and a 66% response rate in pre-emptive treatment [90]. Moreover, in cases unresponsive to first line ganciclovir, foscarnet or both in combination, second line pre-emptive cidofovir treatment ended up with up to 66% response rate [90]. Recently, there is increasing data on maribavir, another oral anti-*CMV* agent. However, the preliminary results on its clinical utilization are disappointing [91].

Late *CMV* viremia, infection or disease occur after the 100th day despite prophylaxis or pre-emptive treatment and tend to be persistent and life-threatening. GvHD and T-cell depletion are among the risk factors. Having a CD4+ T-cell count of less than 50 cells/mcL and a total lymphocyte count of less than 100 cells/mcL 3 months after allo-HSCT together with the presence of accompanying GvHD strongly predict the development of a possible *CMV* infection [92].

Esophagitis, gastritis, and enterocolitis are encountered quite often, while the most severe infection related to *CMV* is pneumonia [10]. *CMV* pneumonia presents with a low-grade fever, non-productive cough and shortness of breath followed by hypoxia within days. The presence of alveolar–interstitial infiltrations on chest X-rays and analysis of BAL with PCR or immune-staining are very sensitive for *CMV* pneumonia. Similarly, biopsy with endoscopic examination is a rule in case of gastrointestinal *CMV* disease. Improved outcomes are observed with the addition of IVIg to treatment only in the presence of pneumonia. Maintenance treatment is suggested in all conditions [93].

Generally accepted practical approach includes a routine *CMV* surveillance at least for 180 days after allo-HSCT and pre-emptive treatment with parenteral ganciclovir, oral valganciclovir, parenteral foscarnet or cidofovir in case of a breakthrough. The drug of choice depends on the center; however, the first choice is usually parenteral ganciclovir for 14–21 days at a dose of 10 mg/kg/day in two divided doses. Maintenance treatment is given at a dose of 5 mg/kg/day for 7–14 days and discontinued after obtaining a negative PCR result. *CMV* surveillance should not be stopped in the presence of GvHD requiring immunosuppressive treatment, or until CD4+ T-cell count exceeds 100 cells/mcL.

Endogenous reactivation or graft originated contamination may cause *EBV* related disease among allo-HSCT recipients and the most significant clinical syndrome is post-transplant lymphoproliferative disease (PTLD) irrespective of acquisition route. Primary *EBV* infection, splenectomy, transplantation from a seropositive donor to a seronegative recipient, unrelated and/or mismatched allo-HSCT, the use of T-cell depletion and anti-thymocyte globulin (ATG) are the risk factors for PTLD [22]. In high risk patients, once weekly surveillance with *EBV*-DNA and immediate pre-emptive treatment in case of a viral breakthrough are suggested. Rapid tapering of immunosuppression is a common approach as an initial response. Rituximab (375 mg/m^2/week, one or two doses) and donor-originated *EBV* specific cytotoxic T-lymphocyte infusions are suggested; however, anti-viral therapy is not recommended [94,95]. After the development of PTLD, donor lymphocyte infusion (DLI) and chemotherapy are among the treatment options in addition to previously mentioned measures.

Infections due to *HHV-6* are generally encountered earlier than *CMV*. *HHV-6* may lead to engraftment delays or graft failure after allo-HSCT. It may also cause a prominent disease with a facial rash and confused with encephalitis or acute GvHD. Ganciclovir or foscarnet are recommended in treatment [22]. The risk factors for the development of encephalitis include higher plasma HHV-6 DNA levels and umbilical cord blood transplantation [96].

Viral hemorrhagic cystitis usually occurs more than 2 weeks post-HSCT [30]. BK polyomavirus and rarely other polyomaviruses, adenovirus or CMV are implicated in the etiology. It is more frequent in the presence of unrelated allo-HSCT, advanced age, GvHD, persistent thrombocytopenia, cord blood and haplo-HSCT [30,97,98]. Initial therapy is mainly supportive, including parenteral saline hydration, continuous bladder irrigation with saline, platelet support and aminocaproic acid. Systemic or intravesical cidofovir, ciprofloxacin and ribavirin are all effective against BK-virus and related hemorrhagic cystitis [30,99–102]. Leflunomide is an immunosuppressive drug with anti-viral properties and may be effectively and safely used in the treatment of viral hemorrhagic cystitis [101,103,104]. In refractory cases the treatment options are mainly surgical and include selective embolization of bladder arteries, bilateral nephrostomy and cystectomy. Hyperbaric oxygen therapy is also an option for refractory cases [105].

In conclusion, bacterial, fungal or viral infections are the most common and significant cause of mortality and morbidity after allo-HSCT. Recipients should be carefully followed-up with appropriate prophylactic measures in the post-transplant period. New treatment options should be considered in order to reduce the infection related mortality rates.

Conflict of interest

The authors have no conflict of interest to disclose.

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