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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.



**Contents**



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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)<br>• Unrelated or mismatched donor (delayed recovery of cellular and humoral immune response) | All agents including herpes virus, fungal, bacterial |
| Source of stem cell graft<br>• Peripheral blood (fast engraftment, but higher risk of chronic GVHD)<br>• Bone marrow (slow engraftment, but lower risk of chronic GVHD) | Different agents in case of prominent neutropenia or GvHD |
| Conditioning regimens<br>• Myeloablative (higher mucosal damage and longer period of neutropenia)<br>• TBI (functional asplenia) | Increased risk of neutropenic infections such as typhlitis, fungal and bacterial |
| Manipulation on stem cell graft<br>• 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<br>• ATG (disruption of T-cell immunity)<br>• 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 |