

Chapter 2

Infections in Hematopoietic Stem Cell Transplant Recipients

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Abstract The risk of infection among allogeneic hematopoietic stem cell transplant (aHSCT) recipients is determined by patient age, underlying disease, the complications that occurred during preceding treatment regimens, the selected transplantation modality, and the severity of graft-versus-host disease. Immunological reconstitution after hematopoietic recovery has an impact on the type of posttransplant infectious complications, and infection-related mortality is significantly higher postengraftment than during the short posttransplant neutropenia. As different pathogenetic and epidemiological backgrounds of infections occur following aHSCT, three consecutive time periods posttransplant are separately described: the early posttransplant period (preengraftment, comprising 3 weeks), the intermediate posttransplant period (3 weeks to 3 months), and the late posttransplant period (later than day +90).

Keywords Allogeneic • Hematopoietic stem cell transplant • Early infection • CMV • Late infections • Graft-versus-host disease

Introduction

Fever and Infection After Allogeneic Hematopoietic Stem Cell Transplant

The risk of infection among allogeneic hematopoietic stem cell transplant (aHSCT) recipients is determined by patient age, underlying disease, the complications that occurred

during preceding treatment regimens, the selected transplantation modality, and the severity of graft-versus-host disease (GvHD) [1, 2]. In comparison with patients undergoing high-dose chemotherapy and autologous stem cell transplantation, recipients of aHSCT are at a much higher risk of infection also after hematopoietic reconstitution, due to delayed recovery of T-cell and B-cell functions. Immunological reconstitution after hematopoietic recovery has an impact on the type of posttransplant infectious complications [3, 4], and infection-related mortality is significantly higher postengraftment than during the short posttransplant neutropenia. After nonmyeloablative conditioning, there is a lower risk of severe and fatal infections in the early posttransplant period [5–9]. Because of different pathogenetic and epidemiological backgrounds of infections, three consecutive time periods posttransplant are separately described: the early posttransplant period (preengraftment, comprising 3 weeks), the intermediate posttransplant period (3 weeks to 3 months), and the late posttransplant period (later than day +90) (Fig. 2.1).

Early Posttransplant Period (Preengraftment; Earlier than Day +21)

Epidemiology of Infections During Neutropenia Posttransplant

Almost all patients receiving myeloablative conditioning regimens develop fever during neutropenia, and most of these febrile episodes are due to infections. The risk of severe bacterial or fungal infection in the early posttransplant period is markedly reduced when nonmyeloablative conditioning has been used. Clinical signs of infection apart from fever may be absent or discrete, and an infectious focus frequently will not be identified by clinical examination, microbiological, or imaging techniques. The differential diagnosis of non-infectious causes of fever, such as transfusion reactions,

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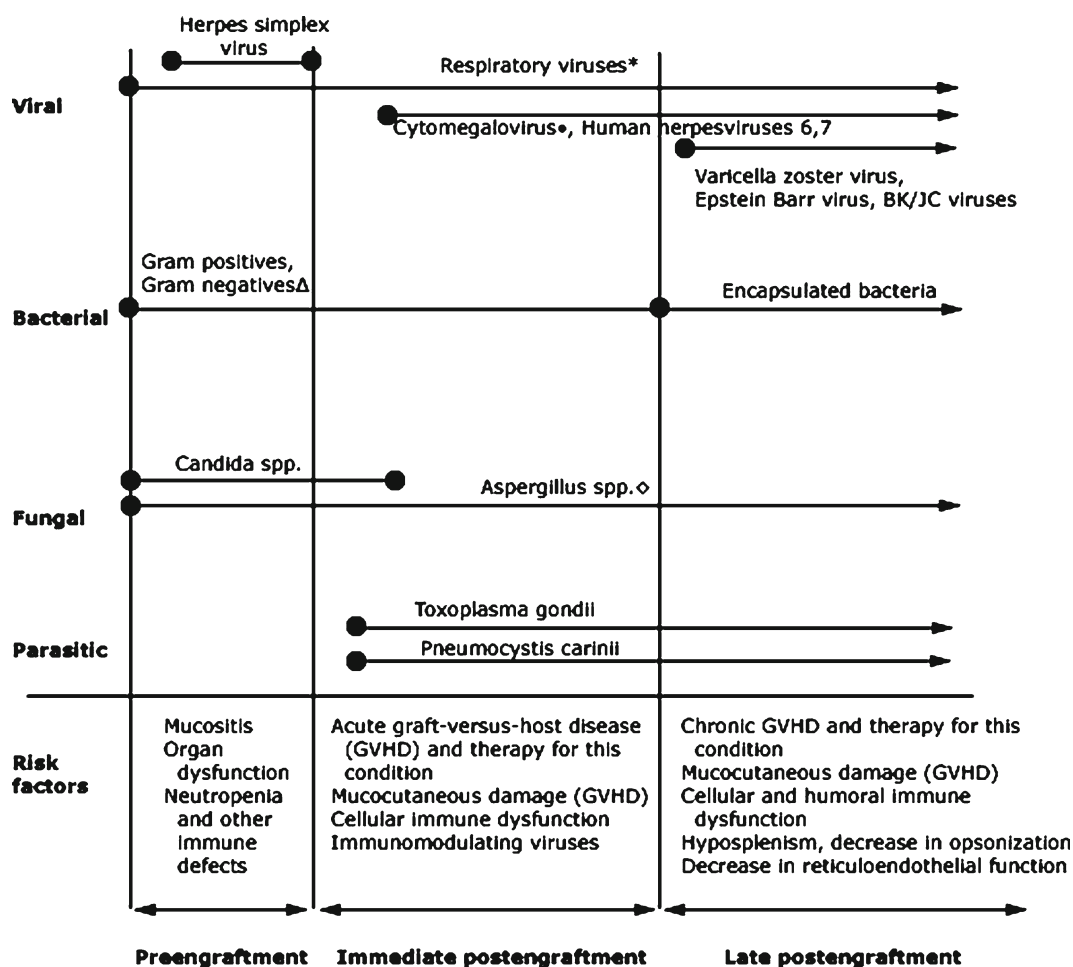


Fig. 2.1 Infections following allogeneic hematopoietic stem cell transplantation (from Up to Date v18.3, Anaissie E, Marr KA, Thorner AR, 2010)

drug-related adverse events, allergy, and acute GvHD, must be considered.

Infections in neutropenia after aHSCT may be life-threatening. Bacterial pathogens account for about 90% of infections during this phase. Epidemiological factors relevant for bacterial infections are shown in Table 2.1. Bacteremia, often related to central venous catheters (CVCs) and/or severe mucositis, occurs in up to 30% of patients after aHSCT, with the majority being caused by Gram-positive pathogens, predominantly coagulase-negative staphylococci, corynebacteria, and alpha-hemolytic streptococci [10–14]. Rarely, viridans streptococcal bacteremia may cause toxic shock and acute respiratory distress, potentially resulting in fatal outcome. Gram-negative infections are less frequent, but typically associated with higher morbidity and mortality. Gram-negative pathogens may enter the bloodstream via mucosal damage in the gastrointestinal tract of patients. Beyond that, fungal infection may occur in up to 15% of patients [15], and herpes simplex virus (HSV) infections emerge in this early posttransplant period unless acyclovir prophylaxis is given.

Table 2.1 Epidemiological aspects of bacterial infections after hematopoietic stem cell transplantation (HSCT)

- Similar spectrum as neutropenic patients after intensive chemotherapy
- Lower risk of severe and fatal infections early post-TxP after non-myeloablative conditioning
- Short neutropenia±mucositis after autologous HSCT: infections comparable to other patients with short-term neutropenia, but Gram-positive pathogens more frequent
- Allogeneic HSCT: critical role of immune reconstitution
 - Slow after T-cell depletion
 - Slow after mismatched donor
 - Slow/absent with significant graft-versus-host disease
 - Chronic GvHD: functional asplenia

Diagnostic Procedures

- Afebrile patient.
 - Daily clinical exam+body temperature at least three times daily.
- Note: antipyretic medication (steroids; analgesics such as metamizole).

- Serum C-reactive protein (CRP) twice weekly.
- *Aspergillus* antigen (GM) \geq twice weekly.
- First fever.
 - Update physical exam, blood cultures, clinical chemistry, CRP, interleukin-6 (IL-6), and thoracic computed tomography (CT) scan; other measures according to clinical findings (see below).
- Persistent fever.
 - Update physical exam, blood cultures, clinical chemistry, CRP, IL-6, and thoracic CT scan; consider abdominal ultrasound or magnetic resonance imaging (MRI).
 - Check results of antigen testings.
- Fever + pulmonary infiltrates.
 - Bronchoscopy + bronchoalveolar lavage (BAL) \Rightarrow microscopy + culture for bacteria; test for *Mycobacterium tuberculosis* (MTB), *Pneumocystis*, cytomegalovirus (CMV), respiratory viruses, adenovirus, *Aspergillus* + other fungi; check for *Aspergillus* GM; optional: *Aspergillus*-PCR and MTB-/*Pneumocystis*-PCR.
- Fever + signs of inflammation at CVC.
 - Blood cultures from peripheral vein and from CVC.
 - Follow-up cultures in case of cultures positive for *Staphylococcus aureus* and *Candida* spp.
- Fever accompanied by skin lesions.
 - Blood cultures.
 - Biopsy (\Rightarrow histopathology and *nonfixated* \Rightarrow microbiology).
- Neurological symptoms \pm fever.
 - Cerebrospinal fluid (CSF) \Rightarrow human herpes virus-6 (HHV-6); *Aspergillus* GM; CMV; HSV, VZV.
 - Fundoscopy.
 - Cranial MRI.
- Fever + abdominal symptoms.
 - *Clostridium difficile* toxins; noro-/rotaviruses; CMV; adenovirus; Epstein–Barr virus (EBV).
- Perianal infiltrate/abscess.
 - Beware of results from inappropriate microbiological diagnostics suggesting monomicrobial etiology.
- Fever + increasing “liver function tests” \Rightarrow viral (hepatitis B virus (HBV), varicella zoster virus (VZV); CMV, etc.), *Candida*?
 - Liver ultrasound or CT or MRI (preferred) [16].
NB: *Pneumocystis jiroveci* typically accompanied by lactate dehydrogenase rise

If causative microorganisms have been isolated from blood, urine, or CSF culture, follow-up cultures should be obtained to document microbiological eradication, whenever possible.

Since conventional chest radiography is insensitive and has a low negative predictive value for detecting pulmonary infiltrates in neutropenic patients, multislice or high-resolution CT of the lungs should be obtained early in neutropenic patients and particularly in those not responding to initial

Table 2.2 Pulmonary infections and noninfectious complications following allogeneic HSCT

	Early <90 days	Late (>90 days)
Infectious (pneumonia)	Bacterial, fungal, viral, protozoal pathogens	Bacterial, fungal, viral pathogens
Noninfectious	Pulmonary edema	Restrictive lung disease
	Idiopathic pneumonia syndrome	Constrictive bronchiolitis
	Diffuse alveolar hemorrhage	Lymphocytic interstitial pneumonitis
	Engraftment syndrome	
	Delayed pulmonary toxicity syndrome	
	Secondary pulmonary alveolar proteinosis, pulmonary veno-occlusive disease	

antimicrobial therapy [17]. Differential diagnoses to pulmonary infiltrates posttransplant are shown in Table 2.2.

Antimicrobial Therapy in Patients with Neutropenic Fever After Allogeneic Stem Cell Transplantation

Fever of more than 38.2°C, or fever of 38.0°C lasting for an hour or longer, or that recurs within 24 h should give reason for immediate broad-spectrum antibacterial treatment. Microbiological identification of an underlying pathogen is achievable in about one third of all patients. Therefore, it has become an accepted clinical practice to initiate broad-spectrum antimicrobial treatment empirically, or preemptively in the presence of specific clinical or radiological signs or symptoms. For selection of empiric antibacterial therapy in patients with febrile neutropenia, local antimicrobial resistance pattern must be taken into account.

Initial empirical regimens should be active against enterobacteriaceae, *Pseudomonas aeruginosa*, *S. aureus*, and streptococci. Clinical trials that investigated single-agent regimens in patients with neutropenic fever included only few patients after allogeneic stem cell transplantation. Patients with severe mucositis should not be given single-agent cef-tazidime because of the risk of bacteremia due to viridans streptococci, whereas piperacillin-tazobactam, imipenem, or meropenem appear appropriate.

In the case of skin infections or venous catheter infections, prompt addition of a glycopeptide antibiotic to the initial empiric regimen should be considered. Stopping the administration of glycopeptides should be considered, if no multiresistant Gram-positive bacteria have been identified.

In febrile neutropenic patients with pulmonary infiltrates, prompt preemptive addition of a systemic antifungal active against *Aspergillus* spp. is recommended [16].

Second-Line Empiric Antimicrobial Regimens in Patients with Neutropenic Fever After Allogeneic Stem Cell Transplantation

If a causative infectious agent has been identified, modification of the empirically started antibacterial therapy according to the in vitro susceptibility pattern should be considered. In case of clinical nonresponse after 72–96 h of full-dose antibacterial treatment, modification of the antimicrobial regimen must be discussed and diagnostic procedures be repeated. Particularly in patients given a prednisone equivalent at a dose of >2 mg/kg/day, broad-spectrum systemic antifungal treatment should be part of the second-line treatment.

Duration of Antimicrobial Treatment

Antimicrobial treatment may be discontinued if all of the following conditions are met: defervescence for at least 48 h, negative cultures, no clinical or radiological evidence of an infection, and neutrophil recovery to above 1,000/ μ L.

If infections have been microbiologically proven, it is advisable to repeat the initial diagnostic procedures, in order to document the microbiological response (e.g., blood cultures, CSF cultures, urine cultures, stool cultures, bronchial secretions in case of ventilated patients, smears). In some cases, narrowing the antimicrobial spectrum can be acceptable.

Early Fungal Infections After Allogeneic Stem Cell Transplantation

Epidemiological aspects of invasive fungal infections in transplant patients are listed in Table 2.3. In this patient population, the incidence rate of systemic mycoses can be as high as 15%, or higher under certain circumstances [15]. Increased risk is expected in patients with a previous history of invasive fungal infection, long-lasting severe neutropenia, previous episodes of prolonged neutropenia, severe skin and mucosal damages due to conditioning treatment, transplantation outside of a laminar air flow unit, age >45 years, intensive immunosuppression as part of the conditioning regimen or for prophylaxis, and/or treatment of GvHD [18]. Apart from specific local epidemiological conditions, *Candida* and *Aspergillus* species are predominant pathogens.

Fever unresponsive to broad-spectrum antibiotic treatment may be the only early symptom of a systemic fungal infection. In patients with pulmonary *Aspergillus* infection, pleuritic chest pain, cough, or hemoptysis may occur. Blood cultures may occasionally grow *Candida* species. *Aspergillus*

Table 2.3 Risk factors of invasive fungal infection in patients after allogeneic SCT

Early fungal infection (<40 days after SCT)
• Previous history of invasive fungal infection
• Long-lasting neutropenia
• Advanced malignancy/previous neutropenia
• Severe skin and mucosal damages due to conditioning treatment
• Transplantation outside of LAF unit
• Age >45 years
Intensive immunosuppression as part of the conditioning regimen
• Immunosuppression as prophylaxis and/or treatment of GvHD
Late fungal infection (>40 days after SCT)
• Immunosuppression due to GvHD and its treatment (corticosteroid or other more intensive immunosuppressive treatments)
• Transplants from unrelated donors or family donors mismatched for HLA class I and/or class II antigens
• Cytomegalovirus infections and antiviral therapy
• Age >45 years

spp. detected in clinical specimens (such as saliva or throat swabs) from neutropenic patients are likely to indicate incipient invasive infection. At the same time, even if moulds have been isolated from BAL specimens, it may be difficult to distinguish between contamination and true invasive pulmonary infection, whereas in cases of documented invasive pulmonary aspergillosis, cultures from BAL are often negative. Serial screening of blood samples for *Aspergillus* galactomannan or beta-D-glucan as well as for fungal DNA by polymerase chain reaction (PCR) may be helpful for early initiation of broad-spectrum systemic antifungal treatment.

Antifungal agents frequently used in this situation are liposomal amphotericin B and caspofungin, both being licensed for empirical treatment of refractory neutropenic fever. If, however, thoracic CT scan shows typical findings indicative of invasive aspergillosis, voriconazole might be the first choice, as in case of probable or proven aspergillosis. Antifungal treatment is continued at least until neutrophil recovery and resolution of clinical and radiological signs of infection.

Other mould infections such as zygomycosis and fusariosis are rare, but increasingly reported in patients post-aHSCT, and in case of suspected zygomycosis, liposomal amphotericin B would be the preferred choice.

Early Viral Infections After Allogeneic Stem Cell Transplantation

Virus infections can occur during the period before hematopoietic engraftment. HSV reactivates frequently in this early period unless acyclovir prophylaxis is given, and the clinical symptoms are frequently uncharacteristic [19]. Acyclovir-resistant viruses have been reported in different

patient series to occur in up to 10% and should be suspected if mucositis is prolonged in patients on acyclovir prophylaxis [20, 21]. Respiratory viral infections especially caused by RSV, parainfluenza, and influenza can occur early and are frequently due to nosocomial transmission within the transplant unit and therefore infection control procedures should be in place during times due to community outbreaks of these viruses [22–27]. Lower respiratory tract infection due to RSV and parainfluenza are associated with significant mortality. Patients, who are HBV DNA positive or HBsAg positive, before aHSCT are at risk for severe hepatitis and should be given prolonged antiviral prophylaxis [28–30].

Intermediate Posttransplant Period (3 Weeks to 3 Months)

Specific Epidemiology of Infections in the Intermediate Posttransplant Period

In the majority of allogeneic stem cell transplant recipients, infections emerge later than day +50 posttransplant. After hematopoietic reconstitution, a severe combined quantitative and functional deficiency in the T and B lymphocyte compartment persists. If T-cell depletion has been used, or if HLA-incompatibility between recipient and donor had to be accepted, immunodeficiency will be prolonged after transplantation. Immunodeficiency comprises impaired T helper cell function, immunoglobulin synthesis, and cytotoxic T cell response. Despite normalization of white blood cell counts, compromised granulocyte functions, primarily impairment of chemotaxis and phagocytosis, may persist.

Bacterial and Fungal Infections in the Intermediate Posttransplantation Period

In 14% of patients, bacteremia occurs after hematopoietic engraftment, with a mortality rate comparable to that before and after engraftment. Among blood culture isolates, Gram-positive pathogens (staphylococci in particular) are predominant, with the focus being identified in more than 50% of patients. Venous catheter infections are the cause for more than 30% of bacteremias, and fever and chills within the first hour after start of fluid infusion typically are indicating a catheter-related bacteremia. Other more frequent infections during the intermediate posttransplant period are pneumonias, preferably caused by *Streptococcus pneumoniae*, *Klebsiella* species, and *P. aeruginosa*, or by filamentous fungi such as *Aspergillus*. Among less frequent bacterial

pathogens relevant during this period are *Listeria monocytogenes* and *Legionella pneumophila*. While listeriosis may origin from products made from unpasteurized milk, the latter typically is related to the use of showers or jacuzzis after the water has been resting in the pipes for a longer period of time. In patients who are treated with tumor necrosis factor antagonists such as infliximab, a dramatic increase in the risk of invasive fungal infections must be considered [31, 32]. Apart from aspergillosis, some rare forms of invasive mycosis caused by *Fusarium* spp., zygomycetes, resistant *Candida* spp., *Pseudallescheria boydii* (or its asexual form, *Scedosporium apiospermum*), and others may occur during this time period [33]. Typically, patients with fusariosis have skin lesions and positive blood cultures, while zygomycetes cause clinical syndromes resembling aspergillosis.

Viral Infections

Viruses are common causes of infections during the period from engraftment to day +90 after HSCT. The classic viral pathogen during this period is CMV called “the troll of transplantation.” CMV reactivates in 60–70% of pretransplant seropositive patients and primary infections occur in up to one third of seronegative patients with seropositive donors [34]. Established end-organ CMV disease is still associated with significant morbidity and mortality. Therefore, preventive strategies either by antiviral prophylaxis or preemptive therapy should be used [35, 36]. Antiviral prophylaxis has been less used, but new antiviral agents might make this strategy more attractive. Monitoring with sensitive assays such as pp65 antigenemia or quantitative PCR in blood is indicated in all aHSCT recipients to allow early initiation of antiviral therapy with ganciclovir or valganciclovir [35].

Epstein-Barr Virus (EBV) also reactivates very frequently after aHSCT, but rarely causes end-organ disease [37]. However, EBV-driven posttransplant lymphoproliferative disease (PTLD) is a complication with high mortality unless treated [38–41]. This complication is more commonly seen in EBV seronegative patients receiving grafts from EBV seropositive donors and in patients having delayed immune reconstitution such as after a T-cell-depleted or HLA-mismatched stem cell transplantation. PTLD frequently causes unspecific symptoms frequently with fever and lymphadenopathy and is associated with high levels of EBV in blood [39, 40, 42–44]. Rituximab (anti CD20 antibody) given either as preemptive therapy or as therapy for established PTLD is most likely effective, although no controlled trial has been performed [45–49].

Adenovirus infections can cause multiorgan disease including pneumonia, encephalitis, hepatitis, gastroenteritis, and hemorrhagic cystitis. Severe adenovirus disease is more frequently seen in children especially after transplant

procedures resulting in delayed reconstitution of the immune system such as haploidentical transplants or mismatched cord blood grafts and monitoring for adenovirus in blood might be indicated in such patients [50–57]. Cidofovir is a potentially effective antiviral agent, but is associated with nephrotoxicity [58–60].

Other viral pathogens potentially important during this period after HSCT are HHV-6 associated with encephalitis and bone marrow suppression [61–66], BK-virus infections associated with hemorrhagic cystitis [67, 68], and respiratory viruses.

Late Period After Allogeneic Stem Cell Transplantation (Later than Day +90)

Specific Epidemiology of Infections During the Late Posttransplant Period

In the late posttransplant period, immune reconstitution usually advances, particularly in patients who have received a transplant from an HLA-identical family donor. These patients often show full hematopoietic reconstitution and early immune reconstitution. If no relevant GVHD emerges, prophylactic immunosuppression will typically be discontinued. Patients with a CD4-count of $>200/\mu\text{L}$ blood and normalized serum immunoglobulin levels can be considered as immunocompetent without an increased risk of opportunistic infections. However, in the case of chronic GvHD, which may occur in more than 30% of patients, a severe combined cellular and humoral immunodeficiency will persist for a prolonged period of time. Mucosal damage, functional deficiencies of granulocytes (especially impaired chemotaxis), functional asplenia, and qualitative as well as quantitative T- and B-cell deficiencies pave the way to a significantly increased susceptibility to infections in these patients. In particular, bacterial infections of the respiratory tract constitute a major cause of death [69]. Life-threatening infections are typically caused by encapsulated bacteria such as *S. pneumoniae* or *Haemophilus influenzae*. Sinusitis, otitis media, and pharyngitis may indicate such infections in the late posttransplant period. Patients among this risk group presenting with signs of infection should receive immediate antibacterial treatment.

An important pathogen of interstitial pneumonia in the late phase after allogeneic stem cell transplantation is *P. jiroveci* [70]. Without specific prophylaxis, about 30% of patients with chronic GvHD develop *Pneumocystis pneumonia*, which can take a fatal course in up to 15% of patients and prophylaxis given for at least 6 months (and longer in patients with chronic GvHD) is recommended to all patients. In regions

with relatively high prevalence rates, mycobacterial infections should be taken into consideration as well [71, 72].

Late Viral Infections After Stem Cell Transplantation

Late-occurring CMV infection and disease have become more frequent during the last decade. These are associated with delayed and incomplete reconstitution of specific immunity, primarily of T-cells, and occur more commonly in patients experiencing severe GvHD [73, 74]. Prolonged monitoring and repeated antiviral therapy are needed in such patients, although toxicity from antiviral therapy and development of resistant CMV strains are important considerations [34, 36]. The possibility to reconstitute specific immunity by adoptive transfer of T-cells has been explored by several groups.

VZV is an important pathogen after HSCT. Primary varicella – chickenpox – occurring in seronegative patients is an important complication especially in children. Preventive measures should be taken after exposure and i.v. acyclovir therapy given if the infection develops. VZV can reactivate also early after aHSCT, but infections are more commonly seen during the late posttransplant period. The clinical manifestations vary from localized herpes zoster – shingles – to visceral disseminated disease associated with high mortality [75–77]. Visceral disease including CNS disease can occur without cutaneous manifestations and can therefore be difficult to diagnose. Early initiation of antiviral therapy with intravenous acyclovir is crucial when visceral or disseminated VZV disease is suspected. Localized shingles can often be treated with orally given valacyclovir or famciclovir [37]. In many centers, long-term prophylaxis given for at least one year after HSCT is used to prevent VZV reactivations [78, 79].

Respiratory viruses, especially influenza, can also be severe late after HSCT. Yearly vaccination against influenza is therefore recommended [80]. RSV and parainfluenza infections have been associated with late respiratory compromise presumably through immune-mediated mechanisms [81, 82].

HBV infection can reactivate in previously HBV-infected patients, especially during prolonged treatment for GvHD. Reactivation can result in a potentially severe acute hepatitis and patients should be carefully monitored, and if signs of HBV reactivation develop, be given antiviral therapy [28–30].

Late Fungal Infections After Stem Cell Transplant

Fungal infections during late transplant period are discussed in detail in Part III.

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