Infectious Complications of Stem Cell Transplantation

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Abstract

Hematopoietic stem cell transplantation (HSCT) is an accepted treatment for a variety of hematologic malignancies. The profound immunosuppression these patients experience adversely affects their risk of infection. This risk is much higher than in the general population and requires aggressive diagnostic and therapeutic interventions. The chapter will outline the major infections after HSCT.

Keywords

Hematopoietic stem cell transplantation · Immunocompression · Myeloablative conditioning · Non-myeloablative conditioning · Scleraderma · Multiple sclerosis · Hypogammaglobulinemia

Contents

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1 Introduction/Overview

Hematopoietic stem cell transplantation (HSCT) is an accepted therapeutic modality for a variety of life-threatening hematologic and lymphoid malignancies, cancers, and congenital disorders. This intense therapy is also being utilized more recently in the management of non-malignant and severe autoimmune processes such as scleroderma and multiple sclerosis. Nearly 50,000 stem cell transplants are performed annually worldwide (>30,000 autologous transplants and >15,000 allogeneic transplants) [1, 2]. The source of the transplanted cells may be from bone marrow, peripherally harvested stem cells, or umbilical cord blood. Infectious complications are more frequent in recipients of HLA-mismatched transplants and HLA-matched unrelated donor (MUD) transplants compared to HLA-matched related donors. This is largely the result of a higher incidence of graft-versus-host disease (GVHD) associated with these donor sources. Progenitor cells are transfused following a conditioning regimen (either myeloablative or non-myeloablative) that prepares the recipients' marrow. The conditioning regimen 'prepares' the recipient's marrow by eradicating malignant disease, creating physical space in the recipient's marrow to allow engraftment and virtually completely eradicates the recipient's immune system to prevent rejection of the graft. Conditioning regimens are broadly categorized into 'myeloablative' and 'non-myeloablative' (reduced intensity) and have major implications on the time until engraftment, transplant-related morbidity and mortality, and risk of infection. Infections are a major complication of this process that results in profound defects in several arms of the immune system. Following stem cell transplantation, there is an evolving reconstitution of donor-derived immune functions that remain poor for a prolonged period of time [3–5]. Innate immunity is the first to recover following transplantation (epithelial barriers and neutrophils) occurring within 2–3 weeks after infusion of donor cells. It takes months for the recipient to demonstrate adequate numbers of CD8 T-cells and B-cells; however, CD4 T-cells may remain low for

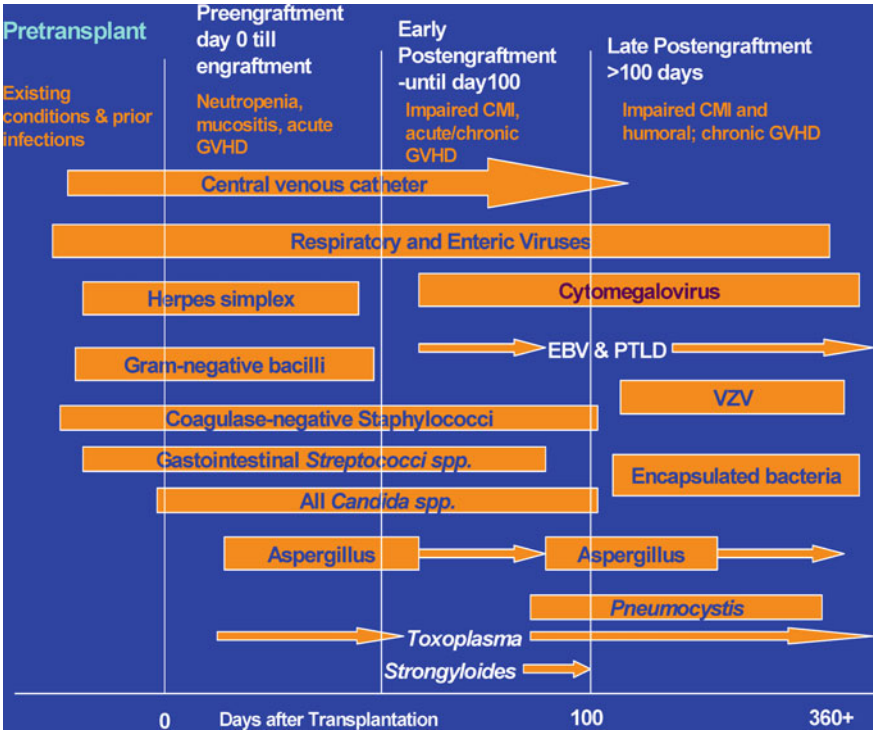

Fig. 1 General time course of immune defects and infectious complications following hematopoietic stem cell transplantation. *GVHD* graft-versus-host disease; *CMI* cell-mediated immunity; *EBV* Epstein–Barr virus; *PTLD* Post-transplant lymphoproliferative disorder; *VZV* varicella zoster virus

years particularly in the elderly recipient with less thymic reserve. Consequently, B-cell functions and humoral immunity, which is dependent on intact CD4-cell interactions, are depressed for an extended period manifest by hypogammaglobulinemia and infections from encapsulated organisms. In addition, the frequent development of GVHD and the treatment regimens (immunosuppression) used to control this complication significantly increases the risk of infection at all points following transplantation. By convention, the sequential re-acquisition of immune function and the associated immune defects and infectious risks have been demarcated into four general time periods or phases (Fig. 1) [6–10].

1. Pre-transplant Period.
2. Pre-engraftment Period (day 0 until engraftment).
3. Early Post-engraftment Period (engraftment to day +100).
4. Late Post-engraftment Period (>day +100 following engraftment).

2 Pre-transplant Period

The patient's underlying disease, the treatments they have received, the amount of immune suppression, and the infectious complications and exposures all contribute to infectious risk during this time frame. The risk of infectious complications in the pre-transplant period is generally low (<20 % of infectious complications), however is quite variable. Localized infections of the skin, oral cavity, and urinary tract are the most common infections. Severe invasive infections and fatalities are very uncommon during this time period [8]. Pre-transplant infectious complications do not negatively influence the transplant or delay engraftment. It should be remembered that certain infections once felt to be contraindications to proceeding with transplantation, particularly aspergillosis, can now be managed appropriately so that successful transplantation is possible [11].

2.1 Pre-engraftment Period

This period begins with infusion of the cells, conventionally labeled 'day 0' and extends until marrow engraftment. The primary immune defects occurring during this phase are neutropenia and breaches in primary barriers due to mucositis and the routine use of central venous catheters. The duration of neutropenia/aplasia is usually in the range of 2–3 weeks. The source of the donor cells (peripheral blood vs. bone marrow, related vs. unrelated, matched vs. mismatched) and the absolute number of cells infused are major determinants in hematopoietic recovery. Other factors that can delay engraftment and extend the period of neutropenia (Table 1) include GVHD prophylaxis method (T-cell depleted graft, methotrexate), the development of GVHD, infectious syndromes particularly viral infections, and antimicrobial prophylaxis [e.g., trimethoprim–sulfamethoxazole for PCP prophylaxis and ganciclovir for cytomegalovirus (CMV) prevention]. Bacterial infections dominate this period of neutropenia with most organisms isolated derived from the recipient's gut (enteric gram-negative and gram-positive) and/or skin commensals (gram-positive) which include hospital-acquired skin organisms with increased antimicrobial resistance, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). As mentioned, central venous catheters are almost universally employed, which can lead to more unusual bacterial isolates in blood cultures if these vascular devices become infected. Herpes simplex virus (HSV) commonly reactivates during this time period prompting the routine use of acyclovir prophylaxis in patients with serologic evidence of past infection. Patients with delay in engraftment and a prolonged duration of neutropenia are susceptible to opportunistic fungal infections, particularly from *Candida* and *Aspergillus*. *Candida* infections typically present as bloodstream infections arising from contamination of central venous catheters while *Aspergillus* infections most often manifest as nodular pulmonary infiltrates with or without surrounding hypoattenuation on CT scanning. During this phase of transplantation, there have been reports of up to a 20 % incidence of *Clostridium*

Table 1 Factors influencing marrow recovery/engraftment

Source of cells
Related versus unrelated
Matched versus mismatched
Marrow versus peripheral stem cells versus cord
Absolute number of stem cells transfused
Type of GVHD prophylaxis
Methotrexate
T-cell depletion
Viral infections
CMV
HHV-6
Antimicrobial prophylaxis
Trimethoprim–sulfamethoxazole
Ganciclovir/valganciclovir

difficile associated diarrhea (CDAD) as a complication of the ubiquitous application of broad-spectrum antibiotics [12]. Recent outbreaks in North America and Western Europe of hypersecreting variants of *C. difficile* (BI/NAP1/027 strain) with elaboration of high levels of toxin A and toxin B leading to more severe disease and complications raise serious concern of spread to this susceptible patient population [13] (see Chapter Enteric Infections).

2.2 Early Post-engraftment Period

Following engraftment and resolution of neutropenia comes a roughly 4–6-month period of early immune reconstitution. Impaired T-cell functions leading to defective cell-mediated immunity (CMI) are the hallmark immune defect of this phase of transplantation. This is the period where CMV typically reactivates and when prophylactic/preemptive strategies need to be targeted to manage this potentially fatal complication. These strategies include serial monitoring for the emergence of CMV viremia (e.g., CMV PCR analysis) and rapid employment of effective antiviral treatment (e.g., valganciclovir, foscarnet) to suppress viral replication and prevent progression to end-organ disease. The major event contributing to continued increased infectious risk is the development of GVHD. Both the pathophysiology of GVHD and the therapeutic management of this complication combine to render the transplant recipient susceptible to numerous infectious complications. Invasive aspergillosis, which historically has been a complication of the prolonged neutropenia of the pre-engraftment phase, is now more commonly encountered during this phase of transplantation. Also, there is an increasing emergence of non-*Aspergillus* mold infections

as well, particularly the Zygomycetes. Central venous catheters tend to remain in place during this phase and bacteremia and fungemia due to *Candida* spp. continue to be encountered. At our institution, the majority of central venous catheter infections in this patient population occur outside the hospital setting (unpublished). Other opportunistic infections that take advantage of the marked CMI defects include *Pneumocystis jirovecii* (PCP) and respiratory and gastrointestinal viral infections.

2.3 Late Post-engraftment Period

This phase of transplantation occurs around 100 days after infusion of donor cells. This time frame corresponds to the recognition of chronic GVHD, if it is present. The transplant recipient who does not develop chronic GVHD can expect to restore reasonable immune function in 1–2 years. Chronic GVHD may prolong immune recovery by years and lead to combined deficiencies in CMI and humoral immunity with hypogammaglobulinemia. Infectious complications including bacteremia, aspergillosis, pneumonia, and adenoviral infections are much more frequently seen in patients being treated for chronic GVHD, especially when higher doses of corticosteroids are used [14]. The humoral defects predispose the patient to infections with encapsulated organisms (*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*) especially of the respiratory tract. Prophylaxis with penicillin is routinely used at our institution in patients with chronic GVHD (quinolones are used in the penicillin allergic patient). Invasive mold infections have become a major infectious complication during this time frame in patients with severe GVHD receiving aggressive immunosuppressive management. As noted above, invasive *Aspergillus* infections are now more commonly diagnosed in these later phases of transplantation because of the emergence of GVHD. Dermatomal reactivation of varicella zoster virus (VZV) occurs in up to 50 % of patients and can progress to life-threatening disseminated infections. Of note, with the continued augmented immunosuppression attendant with chronic GVHD, there is an increasing incidence of 'late' reactivation of CMV. CMV reactivation historically has occurred in the early phase of immune reactivation; however, it is now being seen at much later periods owing to the continued immunosuppression associated with GVHD and effective preemptive anti-viral prophylaxis [15]. The inability to mount specific anti-CMV T-cell responses is associated with the development of late CMV disease [16, 17].

3 Infectious Syndromes Following Stem Cell Transplantation

Stem cell transplant recipients may present with one of numerous infectious syndromes after transplantation. These include febrile neutropenia, infected vascular catheters, pneumonia, sinusitis, hemorrhagic cystitis, rash, diarrhea, and

meningitis/encephalitis. Several principles apply to the care of these patients. First, knowledge of time from transplant, type of transplant, graft-versus-host disease, immunosuppression, and antimicrobial prophylaxis are critical to generating a differential diagnosis. Second, the social and personal histories of transplant recipients, including travel history, occupation, and hobbies, are essential. Finally, diagnostic procedures, when safe and feasible, should be aggressively pursued, given the broad spectrum of infectious pathogens to which these patients are susceptible, the high attributable morbidity and mortality of these infections, and the complications that arise from their therapies.

3.1 Febrile Neutropenia

Febrile neutropenia frequently complicates stem cell transplantation. For example, in one study of autologous stem cell transplant recipients not receiving anti-bacterial prophylaxis, neutropenic fever was seen in 83 % of patients. In this same study, 5 % of patients suffered from severe sepsis [18]. The high attributable mortality in patients with febrile neutropenia mandates prompt therapy with broad-spectrum anti-bacterial medications with an anti-pseudomonal B-lactam. Cefepime and carbapenems and/or piperacillin–tazobactam are frequently used [19–24]. The prevalence of extended spectrum B-lactamase and AmpC producing organisms, as well as local resistance data, should be taken into consideration when deciding upon an empirical antimicrobial therapy. A glycopeptide should be added if there is suspicion for a resistant gram-positive infection or the presence of mucositis. After the prompt administration of anti-bacterial therapy, a thorough search for an infectious source should be undertaken. In patients with febrile neutropenia unresponsive to anti-bacterial therapy after 72 h, empirical anti-mold therapy is recommended [19, 25] (see Chapter Neutropenic Fever and Sepsis: Evaluation and Management).

Use of fluoroquinolones for prophylaxis in patients who are afebrile, neutropenic, and have hematologic malignancies has been shown to reduce all-cause mortality, infection-related death, and fever [26]. As multi-drug-resistant pathogens continue to emerge, continued vigilance for the presence of these organisms is needed given the high anti-microbial exposure in stem cell transplant patients. The administration of prophylactic granulocyte transfusion to prevent febrile neutropenia has also been evaluated, and although this practice did lower infection-related mortality, it had no impact on all-cause mortality [27]. A study of allogeneic stem cell transplant recipients showed a decrease in days of fever and days of intravenous antibiotics, but no impact on hospital days or day 100 survival [28]. Colony-stimulating factors decrease febrile neutropenia, infections, and hospital length. However, they do not confer a survival benefit, and concerns about their effects on residual leukemic cells remain [29, 30]. Several biomarkers, such as procalcitonin, C-reactive protein, and vascular endothelial growth factor, have been evaluated as prognostic indicators in febrile neutropenia, but are not routinely employed [31, 32]. Low citrulline, a marker of mucosal barrier injury, is seen in autologous transplant patients with bacteremia [33].

3.2 Infected Vascular Catheters

Patients undergoing stem cell transplant have increased risk of catheter-related blood stream infections [34]. Gram-positive, gram-negative, mycobacterial, and fungal pathogens have all been reported. Training of health care workers in the proper use of central venous catheters is of paramount importance and has been shown to significantly decrease risk of catheter-associated blood stream infections [35]. Patient education is similarly important as patients often go home after transplantation with a catheter in place. An outbreak in an outpatient stem cell transplant unit of gram-negative blood stream infections was associated with increased baths (in contrast to showers) and patient self-administration of intravenous infusions [36]. Several catheter-specific interventions have been tried to decrease infection rates. The use of chlorhexidine/silver sulfadiazine catheters reduces catheter colonization but not related blood stream infections or fever in stem cell transplant recipients [37]. Urokinase rinses, which dissolve fibrin, have been shown to decrease coagulate-negative staphylococcal catheter-related blood stream infections in patients undergoing intensive cytotoxic chemotherapy for hematologic malignancy [38]. Guidelines for the management of central venous catheter infections have recently been published [39].

3.3 Pneumonia

The differential diagnosis for post-stem cell transplant pneumonia is broad. Infectious pathogens can be bacterial, viral, fungal, or tuberculous, and risk varies according to time from transplant. In the pre-engraftment time period, bacterial, fungal (e.g., *Aspergillus fumigatus*, but increasingly other *Aspergillus* species and mold infections), and respiratory viruses predominate. Immediately post-engraftment, respiratory viruses, CMV, toxoplasmosis, *P. jirovecii*, and *Aspergillus* are prevalent. Late post-engraftment, the differential diagnosis includes respiratory viruses, encapsulated bacteria, toxoplasmosis, aspergillosis, and *P. jirovecii*. In general, the endemic mycoses such as histoplasmosis and blastomycosis are rare, but they have been reported [40–43]. The incidence of tuberculosis is variable (less than one to almost 10 %) and depends on the incidence of disease in the population. *Nocardia* is also seen [44] (see Chapter Respiratory Infections).

3.4 Sinusitis

Sinusitis, especially from fungal causes, can be invasive and rapidly fatal in stem cell transplant recipients. Any patient with symptoms of sinusitis, including facial pain, facial swelling, tooth pain, palate or nasal necrosis or pallor, should be emergently evaluated by otolaryngology. Broad-spectrum anti-bacterial and anti-mold coverage should be initiated immediately. GVHD host disease is a

predisposing factor to rhinosinusitis, as is total body irradiation [45–47]. The course of sinusitis in transplant patients can be complicated, and vigilance for related intracranial pathology, such as cavernous sinus thrombosis, should be high [48]. Gram-negative pathogens (especially *Pseudomonas*) are isolated in more than half of the cultures obtained, with gram-positive bacterial and fungal organisms recovered in a significant minority. Cultures are negative in almost 1/3 of samples obtained, largely due to empiric broad-spectrum antibiotic use at the time of sampling. The spectrum of fungal pathogens involved in sinusitis continues to broaden. The agents of mucormycosis and *Aspergillus* are common, although other pathogens such as *Scedosporium* are increasingly reported [49–51].

3.5 Hemorrhagic Cystitis

The causes of hemorrhagic cystitis can be infectious or non-infectious. Non-infectious causes include radiation and cyclophosphamide, and recently, genetic polymorphisms in cyclophosphamide metabolism genes have been associated with hemorrhagic cystitis [52]. Common causes of infectious hemorrhagic cystitis are BK virus, adenovirus, and CMV [53, 54]. Diagnosis is made using polymerase chain reaction testing on urine or by histopathology. Hemorrhagic cystitis can lead to life-threatening blood loss and ureteral obstruction from blood clots and is one of the several syndromes associated with BK reactivation in the uroepithelial tract [55]. Treatment options for BK virus and adenovirus are limited. Several therapeutic strategies are being investigated, including treatment of BK virus with low-dose cidofovir (1 mg/kg) or intravesicular cidofovir [56, 57]. Leflunomide, ciprofloxacin, and intravenous immune globulin are also being studied for BK virus [58]. Urologic consultation should be obtained in these patients. Several newer therapies to stop bleeding, including intravesicular hyaluronic acid for a child with CMV and likely BK virus grade III hemorrhagic cystitis [59], fibrin glue therapy in five patients with refractory BK virus or CMV hemorrhagic cystitis [60], and palifermin (a human keratinocyte growth factor), have all been used successfully [61].

3.6 Rash

There are both infectious and non-infectious etiologies of rash after stem cell transplant. GVHD and drug reactions are common non-infectious causes. Rarer causes, such as microangiopathy, have also been reported [62]. Bacteria or fungal endocarditis or catheter-related septic emboli should always be considered in a bacteremic or fungemic patient, and surveillance for extent of embolic disease is important. *Nocardia* has been reported to cause subcutaneous nodules [44, 63], as have atypical mycobacteria, such as *Mycobacterium szulgai* and *M. fortuitum* [64, 65]. Viral causes of rash include HSV (local or disseminated) and VZV

(primary disease or reactivation) [66]. These typically cause vesicular lesions, and acyclovir or its derivatives can be used for therapy. In patients who worsen or do not improve on acyclovir, resistance should be considered. CMV, which can cause ulcerative lesions, is treated with ganciclovir. If resistance is present, foscarnet, or cidofovir can be used. Human herpesvirus 6 (HHV-6) can cause a maculopapular rash [67]. Fungal pathogens can also result in rash. For example, disseminated candidiasis can result in macules, papules, or nodules, usually on the trunk and extremities [68], as can Fusarium [69]. *Cryptococcus* can result in nodules or a cellulitic appearance. Skin manifestations of all of these pathogens are frequently atypical. As such, culture and biopsy are crucial to establish a definitive diagnosis (see Chapter Dermatologic Infections in Cancer Patients).

3.7 Diarrhea

Non-infectious causes of diarrhea include GVHD, chemotherapy-induced mucosal injury, and immunosuppression [70]. Common infectious causes include CMV and *C. difficile* [12, 71]. Rarer causes include diphyllobothriasis (in patients with a history of eating raw or undercooked fish) [72] and cryptosporidiosis [73]. Travel and social history are important to the differential diagnosis. Suspect strongyloidiasis in patients from an endemic area or unexplained eosinophilia during the pre-transplant evaluation, as post-transplant immunosuppression can lead to hyperinfection syndrome [74]. *Shigella* and *Salmonella* are more common in the developing world [75].

Neutropenic enterocolitis is characterized by fever and abdominal pain. Its pathogenesis not well understood, but likely arises from a combination of mucosal injury, lack of host defenses, and neutropenia. The incidence is as high as 5 %, with a high attributable mortality. Broad-spectrum antibiotics should be initiated and urgent surgical consult obtained [76] (see Chapter Enteric Infections).

3.8 Neurologic Syndromes

An infectious etiology is responsible for a minority of post-HSCT neurologic syndromes [77]. Infectious neurologic complications can have bacterial, fungal, or viral etiologies. Neurologic imaging and lumbar puncture (when safe) should always be performed. Bacterial meningitis can arise from typical pathogens such as pneumococcus, meningococcus, or *Listeria*. Drug resistance should be considered given the high antibiotic exposure in these patients [78–81]. Viral causes of encephalitis include HHV-6 [82], VZV (which has been reported in the absence of skin lesions) [83], West Nile virus [84, 85], HSV, and JC virus. Fungal etiologies include *Cryptococcus*, which is more common after allogeneic than autologous transplant [86]. Toxoplasmosis should be considered, and pre-transplant donor and recipient serologies should obtained (see Chapter Central Nervous System Infections in Cancer Patients and Hematopoietic Stem Cell Transplant Recipients).

4 Major Infectious Pathogens After SCT

In addition to infectious syndromes, there are several major infectious pathogens than warrant discussion.

4.1 Bacteria

Pneumococcus Several large studies have quantified the risk of invasive pneumococcal disease after stem cell transplantation. HSCT patients have more than 25 times the risk of the general population for pneumococcal infection. It is more commonly seen in the late post-transplant phase owing to persistent humoral immunity defects. Trimethoprim–sulfamethoxazole resistance rates are high (almost 50 %) [87]. GVHD is risk factor for disease. Overall mortality approaches 20 % [88].

Staphylococcus Coagulase-negative *Staphylococcus* is the most common cause of central venous catheter infections. Vancomycin is traditionally used as therapy; isolates are also sensitive to daptomycin [89]. *S. aureus*, including methicillin-resistant isolates, can be treated with vancomycin, daptomycin, or linezolid, although a B-lactam should be used if the isolate is sensitive. GVHD and length of hospital stay are the main risk factors for late staphylococcal infection after transplant [90]. The attributable mortality for *S. aureus* bacteremia in particular is high, and metastatic disease is common. If *S. aureus* is known or suspected, methicillin resistance should be covered until susceptibilities are known. Bacteremia should always be treated with intravenous antibiotics.

Pseudomonas The problem of emerging drug resistance seen in gram-positive organisms such as *S. aureus* is also present in numerous gram-negative pathogens, including *P. aeruginosa*. A recent study of gram-negative bacteremia found that *P. aeruginosa* constituted 22 % of all gram-negative bacteremia in stem cell transplant recipients (*Klebsiella pneumoniae* and *Escherichia coli* were 19 and 17 %, respectively). Thirty seven percentage of gram-negative isolated were multi-drug resistant (resistant to at least two of the following: a 3rd or 4th generation cephalosporin, a carbapenem, or piperacillin–tazobactam). This has profound implications for the selection of empirical gram-negative therapy [91]. In critical ill patients, dual coverage until susceptibilities are known should be considered.

4.2 Fungi

Candida Risk factors for *Candida albicans* infection include use of broad-spectrum antibiotics, breakdown of mucosal membranes, central venous catheterization, and neutropenia. The widespread use of fluconazole as *Candida* prophylaxis during neutropenia has decreased morbidity and mortality from invasive *Candida* infections considerably. This has also resulted in the increased

prevalence of non-*albicans Candida* such as *C. kruseii* (which is intrinsically resistant to fluconazole) and fluconazole-resistant *C. glabrata.* Other *Candida* species, such as *C. parapsilosis*, are seen in the setting of parenteral nutrition [92].

Aspergillus and other angioinvasive molds With the use of fluconazole prophylaxis, invasive mold infections, particularly invasive aspergillosis, have become dominant fungal pathogens in the stem cell transplant population. Disease prevalence ranges from 5 to 15 % [93, 94]. Risk factors include advanced age, allogeneic transplant, GVHD, neutropenia, and viral infections. The emergence of viral infections as risk factors for invasive aspergillosis has been a significant and relatively recent development, with hazard ratios for lower respiratory tract viral infection and CMV 4.2 and 2.8, respectively [95]. The increasing prevalence of non-*fumigatus Aspergillus* species, zygomycetes (especially in those patients on voriconazole prophylaxis), and *Scedosporium apiospermum* [50], combined with the toxicities of several of the anti-mold therapies, makes aggressive pursuit of diagnosis with biopsy, culture, or non-culture based means essential [96–103].

4.3 Viruses

Cytomegalovirus CMV seropositive recipients of grafts from seronegative donors represent those at highest risk for disease. With increasing and successful use of prophylaxis and preemptive strategies after HSCT, CMV reactivation is now being seen at later time points. Lack of CMV-specific T-cell-mediated immunity after transplant increases risk of CMV, particularly late disease [10, 104]. High-dose acyclovir and valacyclovir can be used as prophylactic agents. Intravenous ganciclovir and oral valganciclovir are also active and could be used as prophylaxis, but marrow toxicity limits long-term use [104, 105]. If acyclovir or valacyclovir is used as prophylactic medications, they must be combined with preemptive monitoring strategies with weekly CMV monitoring (pp65 antigen or CMV PCR).

Early detection of viremia and associated end-organ disease is essential for preventing severe CMV-associated complications. End-organ disease usually manifests as gastroenteritis or pneumonitis, with retinitis and encephalitis less frequently described in this population. Retinitis, when it is seen, is often present in the late post-transplant course. Viremia and end-organ disease are both treated with intravenous ganciclovir. Intravenous immune globulin has been used as adjuvant therapy for pneumonitis [104]. Mortality is high, even with appropriate therapy. Standardized therapy recommendations for gastrointestinal CMV disease are lacking, although most would agree that longer therapy and maintenance with ganciclovir is necessary. IVIG is not usually given for gastrointestinal disease. Additionally, it is critical to distinguish this manifestation from GVHD. Colonoscopy should be pursued if safe. Recurrence rates of invasive disease are high in the HSCT population, necessitating ongoing surveillance [10].

Herpes simplex viruses After primary HSV infection, latency is established, with reactivation occurring during periods of immunosuppression. HSV-1 and HSV-2 frequently reactivate and can cause disease after HSCT, although disease attributable to HSV-1 is more common [106]. Reactivation of HSV was common prior to routine anti-viral prophylaxis (around 80 %), which is now given routinely to seropositive patients. Cutaneous and mucosal lesions (including oropharyngeal and esophageal) are the most common manifestations, although dissemination to the brain, lungs, and liver can occur. Intravenous acyclovir therapy should be used for visceral disease or severe mucocutaneous disease, while oral acyclovir, valacyclovir, or famciclovir can be used for less serious disease. Diagnosis can be made by culture, immunofluorescence, or PCR.

Varicella zoster virus After primary infection, VZV establishes latency in the dorsal root ganglia and reactivates during periods of immunosuppression as herpes zoster [106]. Prior to the use of prophylaxis, 50 % of those HSCT patients surviving 6 months developed herpes zoster, with high attributable morbidity and mortality. VZV manifests locally as a vesicular rash, with serious risk of dissemination to brain, lungs, and liver. Prophylaxis of seropositive allogeneic recipients is recommended for 1 year. Initial treatment of disease should be with intravenous acyclovir, although oral therapy can be used to finish therapy. Diagnosis can be made by culture, immunofluorescence, or PCR.

Epstein–Barr Virus (EBV) Primary infection with EBV occurs in childhood or adolescence. Reactivation after transplantation is usually subclinical; however, numerous EBV-related tumors can arise after transplant. Unlike previously noted viral infections, prophylaxis against EBV reactivation is not recommended as it has no impact on prevention of EBV-related post-transplant lymphoproliferative disorders (PTLD). Monitoring by PCR is recommended in high-risk patients, and preemptive therapy with agents such as rituximab can be considered [106]. Serial monitoring of EBV DNA levels by PCR may be useful is ascertaining which patients may progress to EBV-associated PTLD [107].

Human herpesvirus 6 HHV-6 exposure usually occurs during childhood. It reactivates frequently after HSCT; therefore, its detection in the blood alone is of unclear clinical significance. Encephalitis is the most common clinical manifestation but still remains quite rare—there are approximately 40 reported cases in the literature. Prophylaxis against HHV-6 reactivation is not recommended. Encephalitis can be treated with foscarnet or ganciclovir [108]. PCR can detect viral DNA in peripheral blood or CSF. Interesting, HHV-6 has the ability to integrate into the host's chromosome, although this happens in the vast minority of cases.

Adenovirus The incidence of adenovirus infection is between 5 and 21 % after HSCT [54]. Cystitis and enteritis results in low mortality, but adenovirus pneumonia and hepatitis are often fatal. Cidofovir has in vitro activity and has been used at both low and high doses though despite treatment, mortality from invasive disease is very high. Of 687 patients who received allogeneic stem cell transplants, adenovirus was isolated from 64 patients. It was most commonly found in stool (49 patients), respiratory specimens (22 patients), and urine. Eleven of these patients met the criteria for invasive disease (3 had pneumonia, 1 had hepatitis, 4 had

hemorrhagic colitis, and 3 had hemorrhagic cystitis). Eight of the 11 patients received T-cell-depleted grafts, and all 3 with pneumonia died despite therapy.

Respiratory Viruses Respiratory syncytial virus (RSV) causes typical upper respiratory tract infection symptoms [109]. It progresses to pneumonia in 30–40 % patients and in this form may be fatal. Co-pathogens are identified 30 % of the time. Ribavirin has been use for treatment with mixed results. Lymphopenia is a major risk factor for progression to lower tract disease within the first 3 months of HSCT.

Parainfluenza also presents initially as an upper tract infection. It has four serotypes, with serotype three being the most common. Lymphopenia and use of corticosteroids are the risk factors for progression to lower tract disease, and like RSV, it is often isolated with a co-pathogen. Mortality from parainfluenza pneumonia is around 35 %. The data on aerosolized ribavirin and IVIG in parainfluenza are retrospective in nature and it is unclear whether their use is beneficial.

Influenza has a lower incidence than RSV and parainfluenza and importantly can be prevented and attenuated with vaccination although response rates to vaccines are low in the HSCT population. Anti-viral treatment is generally instituted in all HSCT patients who test positive, and chemoprophylaxis in immunocompromised hosts can be considered in the setting of an outbreak. Yearly information about circulating strains and their susceptibility should be incorporated into treatment decisions, given the recent issues with resistance and the emergence of the novel H1N1 strain during 2009.

Finally, human metapneumovirus was recently discovered. It is structurally similar to RSV. Risk factors for disease acquisition and progression are unclear. There are no established treatment guidelines, although ribavirin has in vitro activity.

References

1. Tabbara IA, Zimmerman K, Morgan C, Nahleh Z (2002) Allogeneic hematopoietic stem cell transplantation: complications and results. Arch Intern Med 162:1558–1566
2. Copelan EA (2006) Hematopoietic stem-cell transplantation. N Engl J Med 354:1813–1826
3. Storek J, Geddes M, Khan F et al (2008) Reconstitution of the immune system after hematopoietic stem cell transplantation in humans. Semin Immunopathol 30:425–437
4. Storek J, Dawson MA, Storer B et al (2001) Immune reconstitution after allogeneic marrow transplantation compared with blood stem cell transplantation. Blood 97:3380–3389
5. Geddes M, Storek J (2007) Immune reconstitution following hematopoietic stem-cell transplantation. Best Pract Res Clin Haematol 20:329–348
6. Meyers JD (1986) Infection in bone marrow transplant recipients. Am J Med 81:27–38
7. Wingard JR (1999) Opportunistic infections after blood and marrow transplantation. Transpl Infect Dis 1:3–20
8. Sable CA, Donowitz GR (1994) Infections in bone marrow transplant recipients. Clin Infect Dis 18:273–281 (quiz 82–84)
9. LaRocco MT, Burgert SJ (1997) Infection in the bone marrow transplant recipient and role of the microbiology laboratory in clinical transplantation. Clin Microbiol Rev 10:277–297
10. Hiemenz JW (2009) Management of infections complicating allogeneic hematopoietic stem cell transplantation. Semin Hematol 46:289–312
11. Hill BT, Kondapalli L, Artz A et al (2007) Successful allogeneic transplantation of patients with suspected prior invasive mold infection. Leuk Lymphoma 48:1799–1805

12. Bobak D, Arfons LM, Creger RJ, Lazarus HM (2008) *Clostridium difficile*-associated disease in human stem cell transplant recipients: coming epidemic or false alarm? Bone Marrow Transplant 42:705–713
13. Blossom DB, McDonald LC (2007) The challenges posed by reemerging *Clostridium difficile* infection. Clin Infect Dis 45:222–227
14. Yamasaki S, Heike Y, Mori S et al (2008) Infectious complications in chronic graft-versus-host disease: a retrospective study of 145 recipients of allogeneic hematopoietic stem cell transplantation with reduced- and conventional-intensity conditioning regimens. Transpl Infect Dis 10:252–259
15. Hebart H, Einsele H (2004) Clinical aspects of CMV infection after stem cell transplantation. Hum Immunol 65:432–436
16. Boeckh M, Leisenring W, Riddell SR et al (2003) Late *Cytomegalovirus* disease and mortality in recipients of allogeneic hematopoietic stem cell transplants: importance of viral load and T-cell immunity. Blood 101:407–414
17. Moins-Teisserenc H, Busson M, Scieux C et al (2008) Patterns of *Cytomegalovirus* reactivation are associated with distinct evolutive profiles of immune reconstitution after allogeneic hematopoietic stem cell transplantation. J Infect Dis 198:818–826
18. Hamalainen S, Kuittinen T, Matinlauri I, Nousiainen T, Koivula I, Jantunen E (2009) Severe sepsis in autologous stem cell transplant recipients: microbiological aetiology, risk factors and outcome. Scand J Infect Dis 41:14–20
19. Freifeld AG, Bow EJ, Sepkowitz KA et al (2011) Clinical practice guidelines for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infections Diseases Society of America. Clin Infect Dis 52:e56–e93
20. Harter C, Schulze B, Goldschmidt H et al (2006) Piperacillin/tazobactam vs ceftazidime in the treatment of neutropenic fever in patients with acute leukemia or following autologous peripheral blood stem cell transplantation: a prospective randomized trial. Bone Marrow Transplant 37:373–379
21. Bow EJ, Rotstein C, Noskin GA et al (2006) A randomized, open-label, multicenter comparative study of the efficacy and safety of piperacillin-tazobactam and cefepime for the empirical treatment of febrile neutropenic episodes in patients with hematologic malignancies. Clin Infect Dis 43:447–459
22. Sanz MA, Bermudez A, Rovira M et al (2005) Imipenem/cilastatin versus piperacillin/tazobactam plus amikacin for empirical therapy in febrile neutropenic patients: results of the COSTINE study. Curr Med Res Opin 21:645–655
23. Cherif H, Bjorkholm M, Engervall P et al (2004) A prospective, randomized study comparing cefepime and imipenem-cilastatin in the empirical treatment of febrile neutropenia in patients treated for haematological malignancies. Scand J Infect Dis 36:593–600
24. Raad II, Escalante C, Hachem RY et al (2003) Treatment of febrile neutropenic patients with cancer who require hospitalization: a prospective randomized study comparing imipenem and cefepime. Cancer 98:1039–1047
25. Neuburger S, Maschmeyer G (2006) Update on management of infections in cancer and stem cell transplant patients. Ann Hematol 85:345–356
26. Gafter-Gvili A, Paul M, Fraser A, Leibovici L (2007) Effect of quinolone prophylaxis in afebrile neutropenic patients on microbial resistance: systematic review and meta-analysis. J Antimicrob Chemother 59:5–22
27. Massey E, Paulus U, Doree C, Stanworth S (2009) Granulocyte transfusions for preventing infections in patients with neutropenia or neutrophil dysfunction. Cochrane Database Syst Rev 1:CD005341
28. Oza A, Hallemeier C, Goodnough L et al (2006) Granulocyte-colony-stimulating factor-mobilized prophylactic granulocyte transfusions given after allogeneic peripheral blood progenitor cell transplantation result in a modest reduction of febrile days and intravenous antibiotic usage. Transfusion 46:14–23

29. Levenga TH, Timmer-Bonte JN (2007) Review of the value of colony stimulating factors for prophylaxis of febrile neutropenic episodes in adult patients treated for haematological malignancies. Br J Haematol 138:146–152
30. Battiwalla M, McCarthy PL (2009) Filgrastim support in allogeneic HSCT for myeloid malignancies: a review of the role of G-CSF and the implications for current practice. Bone Marrow Transplant 43:351–356
31. Hamalainen S, Juutilainen A, Matinlauri I et al (2009) Serum vascular endothelial growth factor in adult haematological patients with neutropenic fever: a comparison with C-reactive protein. Eur J Haematol 83(3):251–257
32. Prat C, Sancho JM, Dominguez J et al (2008) Evaluation of procalcitonin, neopterin, C-reactive protein, IL-6 and IL-8 as a diagnostic marker of infection in patients with febrile neutropenia. Leuk Lymphoma 49:1752–1761
33. Herbers AH, Blijlevens NM, Donnelly JP, de Witte TJ (2008) Bacteraemia coincides with low citrulline concentrations after high-dose melphalan in autologous HSCT recipients. Bone Marrow Transplant 42:345–349
34. Sariosmanoglu N, Ugurlu B, Turgut NH et al (2008) Use of tunnelled catheters in haematological malignancy patients with neutropenia. J Int Med Res 36:1103–1111
35. Chaberny IF, Ruseva E, Sohr D et al (2009) Surveillance with successful reduction of central line-associated bloodstream infections among neutropenic patients with hematologic or oncologic malignancies. Ann Hematol 88:907–912
36. Toscano CM, Bell M, Zukerman C et al (2009) Gram-negative bloodstream infections in hematopoietic stem cell transplant patients: the roles of needleless device use, bathing practices, and catheter care. Am J Infect Control 37:327–334
37. Maaskant JM, De Boer JP, Dalesio O, Holtkamp MJ, Lucas C (2009) The effectiveness of chlorhexidine-silver sulfadiazine impregnated central venous catheters in patients receiving high-dose chemotherapy followed by peripheral stem cell transplantation. Eur J Cancer Care (Engl) 18:477–482
38. van Rooden CJ, Schippers EF, Guiot HF et al (2008) Prevention of coagulase-negative staphylococcal central venous catheter-related infection using urokinase rinses: a randomized double-blind controlled trial in patients with hematologic malignancies. J Clin Oncol 26:428–433
39. Mermel LA, Allon M, Bouza E et al (2009) Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis 49:1–45
40. Vail GM, Young RS, Wheat LJ, Filo RS, Cornetta K, Goldman M (2002) Incidence of histoplasmosis following allogeneic bone marrow transplant or solid organ transplant in a hyperendemic area. Transpl Infect Dis 4:148–151
41. Jones O, Cleveland KO, Gelfand MS (2009) A case of disseminated histoplasmosis following autologous stem cell transplantation for Hodgkin's lymphoma: an initial misdiagnosis with a false-positive serum galactomannan assay. Transpl Infect Dis 11:281–283
42. Peterson MW, Pratt AD, Nugent KM (1987) Pneumonia due to Histoplasma capsulatum in a bone marrow transplant recipient. Thorax 42:698–699
43. Serody JS, Mill MR, Detterbeck FC, Harris DT, Cohen MS (1993) Blastomycosis in transplant recipients: report of a case and review. Clin Infect Dis 16:54–58
44. Freites V, Sumoza A, Bisotti R et al (1995) Subcutaneous *Nocardia* asteroides abscess in a bone marrow transplant recipient. Bone Marrow Transplant 15:135–136
45. Ortiz E, Sakano E, De Souza CA, Vigorito A, Eid KA, Chronic GVHD (2006) Predictive factor for rhinosinusitis in bone marrow transplantation. Braz J Otorhinolaryngol 72:328–332
46. Thompson AM, Couch M, Zahurak ML, Johnson C, Vogelsang GB (2002) Risk factors for post-stem cell transplant sinusitis. Bone Marrow Transplant 29:257–261

47. Savage DG, Taylor P, Blackwell J et al (1997) Paranasal sinusitis following allogeneic bone marrow transplant. Bone Marrow Transplant 19:55–59
48. de Medeiros CR, Bleggi-Torres LF, Faoro LN et al (2001) Cavernous sinus thrombosis caused by zygomycosis after unrelated bone marrow transplantation. Transpl Infect Dis 3:231–234
49. Beltrame A, Sarmati L, Cudillo L et al (2009) A fatal case of invasive fungal sinusitis by Scopulariopsis acremonium in a bone marrow transplant recipient. Int J Infect Dis 13:e488–e492
50. Machado CM, Martins MA, Heins-Vaccari EM et al (1998) *Scedosporium apiospermum* sinusitis after bone marrow transplantation: report of a case. Rev Inst Med Trop Sao Paulo 40:321–323
51. Schlemmer F, Lagrange-Xelot M, Lacroix C, de La Tour R, Socie G, Molina JM (2008) Breakthrough Rhizopus infection on posaconazole prophylaxis following allogeneic stem cell transplantation. Bone Marrow Transplant 42:551–552
52. Rocha V, Porcher R, Fernandes JF et al (2009) Association of drug metabolism gene polymorphisms with toxicities, graft-versus-host disease and survival after HLA-identical sibling hematopoietic stem cell transplantation for patients with leukemia. Leukemia 23:545–556
53. Ison MG (2006) Adenovirus infections in transplant recipients. Clin Infect Dis 43:331–339
54. Symeonidis N, Jakubowski A, Pierre-Louis S et al (2007) Invasive adenoviral infections in T-cell-depleted allogeneic hematopoietic stem cell transplantation: high mortality in the era of cidofovir. Transpl Infect Dis 9:108–113
55. Rajpoot DK, Gomez A, Tsang W, Shanberg A (2007) Ureteric and urethral stenosis: a complication of BK virus infection in a pediatric renal transplant patient. Pediatr Transplant 11:433–435
56. Savona MR, Newton D, Frame D, Levine JE, Mineishi S, Kaul DR (2007) Low-dose cidofovir treatment of BK virus-associated hemorrhagic cystitis in recipients of hematopoietic stem cell transplant. Bone Marrow Transplant 39:783–787
57. Bridges B, Donegan S, Badros A (2006) Cidofovir bladder instillation for the treatment of BK hemorrhagic cystitis after allogeneic stem cell transplantation. Am J Hematol 81:535–537
58. Rinaldo CH, Hirsch HH (2007) Antivirals for the treatment of polyomavirus BK replication. Expert Rev Anti Infect Ther 5:105–115
59. Cipe FE, Soygur T, Dogu F, Erdogan O, Bozdogan G (2009) Ikinciogullari A. Treatment with intravesical hyaluronic acid. Pediatr Transplant, Late onset hemorrhagic cystitis in a hematopoietic stem cell recipient
60. Tirindelli MC, Flammia G, Sergi F et al (2009) Fibrin glue for refractory hemorrhagic cystitis after unrelated marrow, cord blood, and haploidentical hematopoietic stem cell transplantation. Transfusion 49:170–175
61. Czibere A, Bruns I, Graef T et al (2007) Treatment of severe hemorrhagic cystitis after allogeneic stem cell transplantation with palifermin, a recombinant human keratinocyte growth factor. Biol Blood Marrow Transplant 13:872–874
62. Choi CM, Schmaier AH, Snell MR, Lazarus HM (2009) Thrombotic microangiopathy in haematopoietic stem cell transplantation: diagnosis and treatment. Drugs 69:183–198
63. Hodohara K, Fujiyama Y, Hiramitu Y et al (1993) Disseminated subcutaneous *Nocardia* asteroides abscesses in a patient after bone marrow transplantation. Bone Marrow Transplant 11:341–343
64. Frisk P, Boman G, Pauksen K, Petrini B, Lonnerholm G (2003) Skin infection caused by *Mycobacterium szulgai* after allogeneic bone marrow transplantation. Bone Marrow Transplant 31:511–513
65. Okano A, Shimazaki C, Ochiai N et al (2001) Subcutaneous infection with *Mycobacterium fortuitum* after allogeneic bone marrow transplantation. Bone Marrow Transplant 28:709–711

66. Onozawa M, Hashino S, Haseyama Y et al (2009) Incidence and risk of postherpetic neuralgia after varicella zoster virus infection in hematopoietic cell transplantation recipients: hokkaido hematology study group. Biol Blood Marrow Transplant 15:724–729
67. Ljungman P, Singh N (2006) Human herpesvirus-6 infection in solid organ and stem cell transplant recipients. J Clin Virol 37(Suppl 1):S87–S91
68. Pedraz J, Delgado-Jimenez Y, Perez-Gala S, Nam-Cha S, Fernandez-Herrera J, Garcia-Diez A (2009) Cutaneous expression of systemic candidiasis. Clin Exp Dermatol 34:106–110
69. Busemann C, Kruger W, Schwesinger G et al (2009) Myocardial and aortal involvement in a case of disseminated infection with Fusarium solani after allogeneic stem cell transplantation: report of a case. Mycoses 52:372–376
70. Selbst MK, Ahrens WA, Robert ME, Friedman A, Proctor DD, Jain D (2009) Spectrum of histologic changes in colonic biopsies in patients treated with mycophenolate mofetil. Mod Pathol 22:737–743
71. Schulenburg A, Turetschek K, Wrba F et al (2004) Early and late gastrointestinal complications after myeloablative and nonmyeloablative allogeneic stem cell transplantation. Ann Hematol 83:101–106
72. Detrait M, Poirier L, Roy DC et al (2009) Diphyllobothriasis, a rare cause of profuse diarrhea following autologous transplantation. Bone Marrow Transplant 44:131–132
73. Manivel C, Filipovich A, Snover DC (1985) Cryptosporidiosis as a cause of diarrhea following bone marrow transplantation. Dis Colon Rectum 28:741–742
74. Wirk B, Wingard JR (2009) Strongyloides stercoralis hyperinfection in hematopoietic stem cell transplantation. Transpl Infect Dis 11:143–148
75. Kang G, Srivastava A, Pulimood AB, Dennison D, Chandy M (2002) Etiology of diarrhea in patients undergoing allogeneic bone marrow transplantation in South India. Transplantation 73:1247–1251
76. Davila ML (2006) Neutropenic enterocolitis. Curr Opin Gastroenterol 22:44–47
77. Batlle M, Oriol A, Ribera JM et al (2005) Neurologic complications following hematopoietic stem cell transplantation. Study of 14 patients. Med Clin (Barc) 125:697–699
78. Buxmann H, Soerensen J, Koehl U et al (2003) Meningitis due to multiple-resistant penicillin- and cefotaxime-intermediate *Streptococcus pneumoniae* in a German child after bone marrow transplantation. Infection 31:425–427
79. de Almeida SM, Teive HA, Brandi I et al (2003) Fatal Bacillus cereus meningitis without inflammatory reaction in cerebral spinal fluid after bone marrow transplantation. Transplantation 76:1533–1534
80. Matsubara H, Makimoto A, Higa T et al (2003) Successful treatment of meningoencephalitis caused by methicillin-resistant *Staphylococcus aureus* with intrathecal vancomycin in an allogeneic peripheral blood stem cell transplant recipient. Bone Marrow Transplant 31:65–67
81. Girmenia C, Iori AP, Bernasconi S et al (2000) Listeriosis in recipients of allogeneic bone marrow transplants from unrelated donors. Eur J Clin Microbiol Infect Dis 19:711–714
82. Yoshida H, Matsunaga K, Ueda T et al (2002) Human herpesvirus 6 meningoencephalitis successfully treated with ganciclovir in a patient who underwent allogeneic bone marrow transplantation from an HLA-identical sibling. Int J Hematol 75:421–425
83. Leveque N, Galambrun C, Najioullah F, Bleyzac N, Pages MP, Bertrand Y (2006) Two cases of varicella zoster virus meningitis found in pediatric patients after bone marrow transplantation despite valaciclovir prophylaxis and without skin lesions. J Med Virol 78:514–516
84. Robertson KB, Barron MA, Nieto Y (2004) West Nile virus infection in bone marrow transplant patients. Bone Marrow Transplant 34:823–824
85. Hiatt B, DesJardin L, Carter T, Gingrich R, Thompson C, de Magalhaes-Silverman M (2003) A fatal case of West Nile virus infection in a bone marrow transplant recipient. Clin Infect Dis 37:e129–e131

86. Mendpara SD, Ustun C, Kallab AM, Mazzella FM, Bilodeau PA, Jillella AP (2002) Cryptococcal meningitis following autologous stem cell transplantation in a patient with multiple myeloma. Bone Marrow Transplant 30:259–260
87. Kumar D, Humar A, Plevneshi A et al (2008) Invasive pneumococcal disease in adult hematopoietic stem cell transplant recipients: a decade of prospective population-based surveillance. Bone Marrow Transplant 41:743–747
88. Engelhard D, Cordonnier C, Shaw PJ et al (2002) Early and late invasive pneumococcal infection following stem cell transplantation: a European Bone Marrow Transplantation survey. Br J Haematol 117:444–450
89. Kratzer C, Rabitsch W, Hirschl AM, Graninger W, Presterl E (2007) In vitro activity of daptomycin and tigecycline against coagulase-negative *Staphylococcus* blood isolates from bone marrow transplant recipients. Eur J Haematol 79:405–409
90. Mihu CN, Schaub J, Kesh S et al (2008) Risk factors for late *Staphylococcus aureus* bacteremia after allogeneic hematopoietic stem cell transplantation: a single-institution, nested case-controlled study. Biol Blood Marrow Transplant 14:1429–1433
91. Oliveira AL, de Souza M, Carvalho-Dias VM et al (2007) Epidemiology of bacteremia and factors associated with multi-drug-resistant gram-negative bacteremia in hematopoietic stem cell transplant recipients. Bone Marrow Transplant 39:775–781
92. De La Rosa GR, Champlin RE, Kontoyiannis DP (2002) Risk factors for the development of invasive fungal infections in allogeneic blood and marrow transplant recipients. Transpl Infect Dis 4:3–9
93. Pagano L, Caira M, Nosari A et al (2007) Fungal infections in recipients of hematopoietic stem cell transplants: results of the SEIFEM B-2004 study–Sorveglianza Epidemiologica Infezioni Fungine Nelle Emopatie Maligne. Clin Infect Dis 45:1161–1170
94. Grow WB, Moreb JS, Roque D et al (2002) Late onset of invasive *Aspergillus* infection in bone marrow transplant patients at a university hospital. Bone Marrow Transplant 29:15–19
95. Martino R, Pinana JL, Parody R et al (2009) Lower respiratory tract respiratory virus infections increase the risk of invasive aspergillosis after a reduced-intensity allogeneic hematopoietic SCT. Bone Marrow Transplant 44:749–756
96. Ghiasian SA, Maghsood AH, Mirhendi SH (2006) Disseminated, fatal Trichosporon asahii infection in a bone marrow transplant recipient. J Microbiol Immunol Infect 39:426–429
97. Shi JM, Cai Z, Huang H et al (2009) Role of CT-guided percutaneous lung biopsy in diagnosis of pulmonary fungal infection in patients with hematologic diseases. Int J Hematol 89:624–627
98. Herbrecht R, Denning DW, Patterson TF et al (2002) Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 347:408–415
99. Lionakis MS, Kontoyiannis DP (2005) Sinus zygomycosis in a patient receiving voriconazole prophylaxis. Br J Haematol 129:2
100. Kontoyiannis DP, Lionakis MS, Lewis RE et al (2005) Zygomycosis in a tertiary-care cancer center in the era of *Aspergillus*-active antifungal therapy: a case-control observational study of 27 recent cases. J Infect Dis 191:1350–1360
101. Chamilos G, Marom EM, Lewis RE, Lionakis MS, Kontoyiannis DP (2005) Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer. Clin Infect Dis 41:60–66
102. Rachwalski EJ, Wieczorkiewicz JT, Scheetz MH (2008) Posaconazole: an oral triazole with an extended spectrum of activity. Ann Pharmacother 42:1429–1438
103. Schulenburg A, Sperr W, Rabitsch W, Knobl P, Thalhammer F (2005) Brief report: practicability and safety of amphotericin B deoxycholate as continuous infusion in neutropenic patients with hematological malignancies. Leuk Lymphoma 46:1163–1167
104. Ljungman P (2008) CMV infections after hematopoietic stem cell transplantation. Bone Marrow Transplant 42(Suppl 1):S70–S72

105. Kline J, Pollyea DA, Stock W et al (2006) Pre-transplant ganciclovir and post transplant high-dose valacyclovir reduce CMV infections after alemtuzumab-based conditioning. Bone Marrow Transplant 37:307–310
106. Styczynski J, Reusser P, Einsele H et al (2006) Management of HSV, VZV and EBV infections in patients with hematological malignancies and after SCT: guidelines from the second European Conference on Infections in Leukemia. Bone Marrow Transplant 43:757–770
107. Aalto SM, Juvonen E, Tarkkanen J et al (2007) Epstein-Barr viral load and disease prediction in a large cohort of allogeneic stem cell transplant recipients. Clin Infect Dis 45:1305–1309
108. Ljungman P, de la Camara R, Cordonnier C et al (2008) Management of CMV, HHV-6, HHV-7 and Kaposi-sarcoma herpesvirus (HHV-8) infections in patients with hematological malignancies and after SCT. Bone Marrow Transplant 42:227–240
109. Boeckh M (2008) The challenge of respiratory virus infections in hematopoietic cell transplant recipients. Br J Haematol 143:455–467