Infections in Allogeneic Stem Cell Transplantation

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Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has become a widely used modality of therapy for a variety of malignant and nonmalignant diseases. While many advances have been made in the field, infection remains one of the most severe and frequently encountered complications of HSCT. In this chapter we review the defects in host defenses and important risk factors predisposing allo-HSCT recipients to infection, the major categories of infection and their time courses following transplantation, and preventive strategies.

Risk Factors for Infection Following Allo-HSCT

The severity of defects in host defenses and the subsequent risk of infection are influenced by a complex interaction between several factors. Particularly salient are (1) the underlying illness of the patient, (2) the conditioning regimen, (3) the graft and the closeness of the match, (4) the type of transplant, and (5) the presence of graft-versus-host disease (GVHD). Immediate local and remote epidemiological factors are also important. The timing of impaired host defenses and infectious risk in allo-HSCT recipients are outlined in Fig. 11.1.

Underlying Host Disease

Infection risk is very much impacted by the disease for which the patient is being transplanted and also by the presence of preceding infections. Acute leukemia, for example, predisposes to neutropenia and other defects of innate immunity. Profound neutropenia (<500 cells/mm^3) of greater than 10-day duration is considered a strong risk factor for bacterial and invasive fungal infection [1]. In addition to neutropenia, other factors that increase risk for invasive aspergillosis include advanced or refractory acute myelogenous leukemia, high-risk myelodysplastic syndrome, chronic neutropenia prior to chemotherapy, iron overload secondary to repeated peripheral blood transfusions, and prior fungal infection [2–6]. Further, antileukemic agents have been shown to diminish antibody response to primary antigens, thereby increasing susceptibility to bacterial pathogens even in the absence of neutropenia [7]. Other underlying diseases such as primary immunodeficiency, for example, may predispose to progression or reactivation of antecedent infections, and individuals with myelodysplastic syndrome who are neutropenic at the time of transplant are at an increased risk of infection and mortality. In addition to innate immune defects, increasing age, waning cellular immunity, organ dysfunction, fragile skin, and prior antibiotic exposure may all contribute to the progression of preexisting infection, including aspergillosis, as well as to the risk for new infections during the posttransplant period [8–11].

The presence of infection immediately preceding allo-HSCT also impacts infectious risk during the posttransplant period. In individuals scheduled to undergo allo-HSCT, active infections should be treated prior to transplantation whenever possible. The timing of allo-HSCT following the initiation of antibiotics for active infection should be made on a case by case basis by an experienced practitioner.

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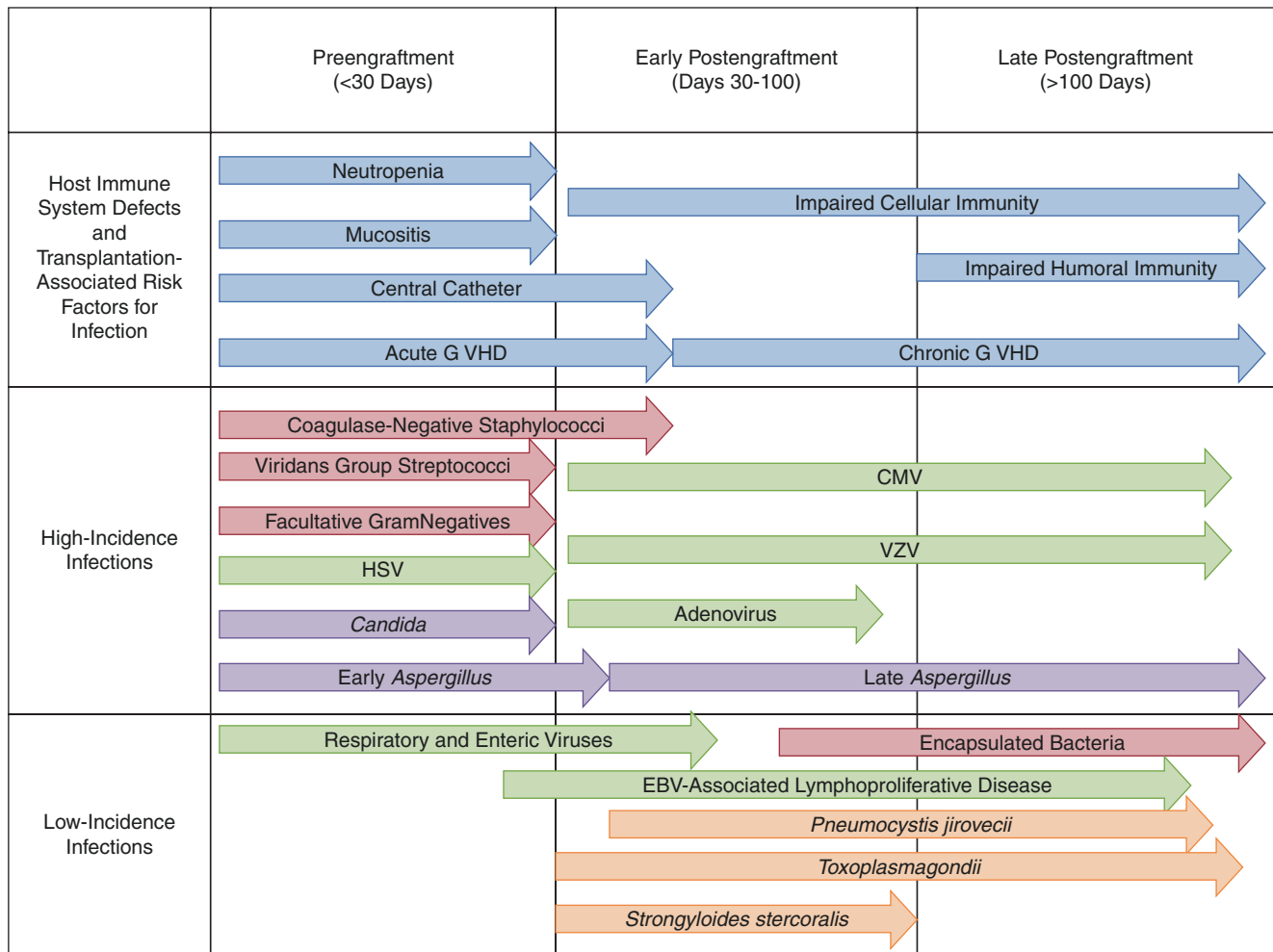e-mail: spouch@emory.edu

	Preengraftment (<30 Days)	Early Postengraftment (Days 30-100)	Late Postengraftment (>100 Days)
Host Immune System Defects and Transplantation-Associated Risk Factors for Infection	Neutropenia	Impaired Cellular Immunity	
	Mucositis		Impaired Humoral Immunity
	Central Catheter		
	Acute G VHD	Chronic G VHD	
High-Incidence Infections	Coagulase-Negative Staphylococci		
	Viridans Group Streptococci	CMV	
	Facultative GramNegatives		
	HSV	VZV	
	Candida	Adenovirus	
	Early *Aspergillus*	Late *Aspergillus*	
Low-Incidence Infections	Respiratory and Enteric Viruses	Encapsulated Bacteria	
		EBV-Associated Lymphoproliferative Disease	
		Pneumocystis jirovecii	
		Toxoplasma gondii	
		Strongyloides stercoralis	

Fig. 11.1 Timeline of host immune defects and infections in Allo-HSCT recipients. Predictable opportunistic infections encountered following allo-HSCT. Immune defects and transplant-associated risk factors are shaded in blue, bacterial infections in pink, viral infections in green, fungal infections in purple, and parasitic infections in orange

The Conditioning Regimen

Prior to transplantation, the prospective recipient must be conditioned so as to allow engraftment of the transplant. The goals of conditioning are twofold: (1) to suppress the recipient's immune system, particularly the T-cell arm, in order to prevent rejection of the graft, and (2) to eliminate the tumor. Many regimens are myeloablative, employing total body irradiation and cytotoxic chemotherapy, with resultant profound and prolonged neutropenia, mucositis, and potential organ toxicities. Recipients of such conditioning are highly susceptible to early infection and sepsis. Less intense regimens increasingly used in some of the more vulnerable older patients may result in minimal neutropenia and mucositis and a correspondingly lower risk of infection [12]. However, recipients of reduced-intensity conditioning regimens may experience prolonged neutropenia should engraftment fail.

The Graft

The closeness of the human leukocyte antigen (HLA) match dictates the likelihood and severity of GVHD as well as the intensity of the immunosuppressive regimen. The various degrees of match include the following: the donor may be an HLA-matched sibling or twin, HLA-matched but unrelated, haploidentical such that donor and recipient share one complete haplotype, or partially matched. The latter two categories often necessitate more intense immunosuppressive regimens to prevent GVHD.

The source of the stem cells also impacts the risk of infection. Bone marrow transplant recipients have more prolonged periods of neutropenia and a higher risk for early infection, but lower risk of GVHD than peripheral stem cells mobilized by granulocyte colony-stimulating factor [13, 14]. Cord blood cells, in contrast, are typically obtained from unrelated donors and confer a much lower

stem cell dose than in the other transplants. Cord blood stem cell transplant recipients have delayed engraftment, such that neutropenia may extend for 6 weeks or longer and T-cell immune dysfunction may persist for months to years [15].

Graft-Versus-Host Disease

GVHD occurs when donor T-cells attack the recipient's tissues as a consequence of either T-cell ablation of the graft prior to transplant or by the administration of immunosuppressive drugs after transplantation. When unmanipulated bone marrow or peripheral stem cells are used, $24–300 \times 10^6$/kg CD3 cells are administered. Ex vivo pretreatment of the graft may produce up to a 3-log reduction in cells transplanted and decrease the potential risk and severity of GVHD. However, there is a resultant prolonged T-cell immunodeficiency, and the patient must then walk an immunological-infection tightrope for many months. If an untreated graft is transplanted, then any one of a variety of immunosuppressive regimens may be given. Examples are sirolimus and a calcineurin inhibitor, such as tacrolimus. It appears that these regimens pose a lower infection risk than pretransplant T-cell ablation [16]. Sirolimus therapy has also been associated with a reduced risk of cytomegalovirus (CMV) infection [17, 18].

GVHD is classified as acute when the onset is prior to posttransplant day 100 and chronic when the onset is after day 100. Acute disease may persist into the chronic period, in which case it is termed progressive. While GVHD may respond to treatment and go into remission, it may also reactivate at a later date.

Acute disease, characterized by secretory diarrhea, hepatitis, and skin rash, is categorized according to severity with grades 3 and 4 posing an increased risk of mortality. Corticosteroids are the mainstay of therapy. The intense immunosuppression associated with the condition itself and enhanced by its treatment, combined with disrupted barrier defenses, especially in the intestine, place patients at great risk of infection. CMV infection is common as are other viral, bacterial, and fungal infections such as aspergillosis [19].

In chronic GVHD, humoral defects and functional hyposplenism markedly suppress cellular immunity. Severe pneumococcal, disseminated fungal, and CMV infections are frequently seen in this context [20, 21]. Infections are even more problematic when steroid-refractory disease necessitates the use of potent immunosuppressive regimens such as cyclophosphamide, alemtuzumab, or anti-thymocyte globulin. In this situation, human herpesvirus-6 (HHV6), adenovirus, disseminated fungal and nocardial infections, as well as posttransplant lymphoproliferative disease (PTLD) may occur [22].

Timing of Opportunistic Infections in Allo-HSCT Recipients

Three periods of immunodeficiency occur following hematopoietic stem cell transplantation: pre-engraftment (days 0–30), early post-engraftment (days 30–100), and late post-engraftment (until day 100). The immune suppression that takes place during each of the periods conveys a particular risk for infection and drives the use of standard prophylaxis following transplantation (Figs. 11.1) [23, 24].

Pre-engraftment

The pre-engraftment period is associated with three major risk factors for infection: (1) prolonged neutropenia, (2) disruption of the mucosal barrier related to preparative chemotherapeutic regimens, and (3) the presence and frequent utilization of central venous access [24, 25]. The combined effect of neutropenia and mucositis contributes to high risk of reactivation of HSV in seropositive patients, prompting standard use of acyclovir during this period [26, 27]. These factors also predispose to candidemia and early-onset aspergillosis [24]. While prophylactic antifungals are used in the pre-engraftment period, fluconazole prophylaxis has been linked to an increased risk of non-albicans candidal infections, particularly due to *C. glabrata* and *C. krusei* [28–30]. Voriconazole prophylaxis has also been associated with an increased risk of zygomycosis in this setting [31–34]. Additionally, mechanical disruption of the skin and the use of prophylactic antibiotics targeted toward gut flora increase the risk for bloodstream infections with Gram-positive flora, particularly viridians group streptococci and coagulase-negative staphylococci [25, 35].

Early Post-engraftment

The early post-engraftment period extends from the time of neutrophil recovery (approximately day 30 posttransplantation) until day 100 and is notable for B- and T-lymphocyte dysfunction. In the setting of allo-HSCT recipients, the impact of this immunodeficiency is further mediated by GVHD and CMV infection, as well as their treatments. Such cell-mediated immune dysfunction contributes to increased risk for viral infections, including CMV, adenovirus, varicella zoster virus (VZV), and Epstein-Barr virus (EBV)-related PTLD, as well as late-onset aspergillosis and *Pneumocystis jirovecii* [24].

Late Post-engraftment

The late post-engraftment period extends from day 100 until normal immune function is regained. While immune func-

tion generally returns within 18–36 months of transplant, the duration of the late post-engraftment period may be extended in allo-HSCT recipients owing to chronic GVHD and its management. During this time, ongoing humeral and cell-mediated immune dysfunction contributes to the risk for infections with VZV, CMV, late-onset aspergillosis, and infections with encapsulated bacteria [24, 36, 37].

Bacterial Infections

The microbiology of bacterial infections in allo-HSCT patients has evolved over time. In the past decade or so, it has been greatly influenced by the widespread use of fluoroquinolone prophylaxis, the increased prevalence of *Clostridium difficile* infection, and the evolution of conditioning regimens. Once transplanted, patients are at increased risk for bacterial infections for the remainder of their lifetime.

Infection During the Pre-engraftment Period

During the pre-engraftment period, bacteremia occurs in up to 20% of patients [38]. Table 11.1 lists some common infecting pathogens, their particular risks, and their clinical manifestations. The main sources for bacteremia are the oral or gastrointestinal mucositis, the respiratory tract, and the presence of central venous catheters. Infecting organisms are commonly Gram-positive cocci such as *Streptococcus viridans* and enterococci or a variety of fermenting and non-fermenting Gram-negative rods. Enterococci are increasingly resistant to vancomycin, and these strains have been associated with a worse prognosis than vancomycin-sensitive strains [39]. Some recent studies also report an increase in infections due to multidrug resistant (MDR) Gram-negative rods such as *Pseudomonas aeruginosa and* carbapenemase-producing *Klebsiella pneumoniae* [40–43]. The isolation of such resistant bacteria has been associated with the use of fluoroquinolone prophylaxis and third-generation cephalosporins in several reports. These infections carry a high mortality and often relapse.

Gastrointestinal infections are prominent during this period. Necrotizing enterocolitis and typhlitis may occur in any severely neutropenic patient and can serve as a source of bacteremia and sepsis. *Clostridium difficile* colitis is very common, occurring in about 12% of allogeneic transplant patients versus 9% of autologous patients during the pre-engraftment period [44–46]. Extensive antibiotic exposures, mucosal damage from intense chemotherapy, and multiple prior hospitalizations are all contributory [47]. *Clostridium difficile* has been linked to levofloxacin, which is frequently given for bacterial prophylaxis in these patients [48]. Hypervirulent strains of *Clostridium difficile*, including the

Table 11.1 Bacterial infections following allo-HSCT

Bacterial pathogens	Predisposing risks	Clinical manifestations
Streptococcus viridans	Neutropenia, oral mucositis	Bacteremia
Streptococcus pneumoniae	Graft-versus-host disease (GVHD), lack of immunization	Pneumonia, meningitis, sepsis
Enterococcus species	Cephalosporin use, *C. difficile* infection	Bacteremia
Staphylococcus aureus	Central venous lines (CVL), colonization	Bacteremia, pneumonia, soft tissue infection
Coagulase-negative staphylococcus	CVL	Bacteremia
Escherichia coli	Neutropenia, mucositis	Bacteremia, pneumonia
Klebsiella pneumoniae	Neutropenia, mucositis	Bacteremia, pneumonia
Pseudomonas aeruginosa	Neutropenia, mucositis	Bacteremia, pneumonia, ecthyma
Stenotrophomonas maltophilia	CVL, prior broad-spectrum antibiotic exposure	Bacteremia
Acinetobacter species	CVL, prior broad-spectrum antibiotic exposure	Bacteremia, pneumonia
Achromobacter species	CVL, prior broad-spectrum antibiotic exposure	Bacteremia
Anaerobic bacteria (e.g., *Clostridium septicum*, *Bacteroides* species)	Neutropenia, mucositis	Bacteremia, necrotizing enterocolitis, typhlitis
Clostridium difficile	Antibiotic exposure, GVHD, local epidemiology, previous *C. difficile* infection	Colitis, megacolon, secondary bacteremia

epidemic North American pulse-field gel electrophoresis type 1 (NAP1) and ribotype 027/toxinotype III strains, have specifically been associated with moxifloxacin and other members of the fluoroquinolone class [49, 50]. An association between *Clostridium difficile* colitis and subsequent GVHD has also been reported [46]. The colitis may be severe, often relapses, and may also serve as a source for secondary bloodstream infections.

The risk of infection and bacteremia during this neutropenic pre-engraftment period is reduced by the use of prophylactic antibiotics. In general fluoroquinolones, usually levofloxacin, are the preferred agents [51]. Prophylaxis should start with the stem cell infusion and should continue until the resolution of the neutropenia or the initiation of antibiotic therapy for neutropenic fever. Several meta-analyses have demonstrated decreased infection-associated morbidity, mortality, as well as cost benefit, with the use of

prophylactic antibacterials [52–54]. These agents do, however, increase the risk for selection of resistant bacteria and *Clostridium difficile*-associated disease [55].

Infection During the Early Post-engraftment Period

During the early period after engraftment, the risk of bacterial infections and bacteremia is reduced but ongoing. Risk is increased by general debility, by the presence of renal or hepatic dysfunction, and by the presence of GVHD. Central venous lines are often the source. Most of the patients by this time will have received antibiotic courses making them more likely to be infected with resistant pathogens. Staphylococci, enterococci (often vancomycin resistant), and non-fermenting Gram-negatives such as *Stenotrophomonas maltophilia* and *Acinetobacter* are frequent pathogens [38]. By virtue of their T-cell immunosuppression, these patients are also particularly susceptible to *Listeria* and *Legionella* if exposed [56, 57].

Infection During the Late Post-engraftment Period

During the late period following engraftment, the main predisposing factor for infection is the presence of GVHD. Many patients have B-cell dysfunction and are functionally asplenic [58, 59]. They are thus vulnerable to serious infections with encapsulated bacteria, most notably *Streptococcus pneumoniae*, with pneumonia as the usual source [36, 60, 61]. Some patients are hypogammaglobulinemic, further increasing their risk. Less common are infections due to mycobacteria and *Nocardia.* Case reports suggest a global incidence of nontuberculous mycobacterial infections in allo-HSCT recipients ranging from 0.4% to 4.9% [37, 62–66]. Tuberculosis in this patient population, however, ranges from 0.0014% to 3% in the United States to as high as 8.5% in Taiwan [67–70]. Systemic nocardiosis is rare, and one center reported a cumulative incidence of 1.75%; cases were all observed in patients with extensive chronic GVHD [71].

Preventive strategies include vaccination with the heptavalent conjugate pneumococcal vaccine at 3–6 months post-engraftment for all patients [51]. Immunogenicity of this vaccine, however, appears to be related to immune reconstitution, particularly in allo-HSCT recipients aged 50 and over. In this population, improved vaccine response has been associated with CD4 >200 cells/µL, IgG >500 mg/dL, and phytohemagglutinin within 60% of the lower limit of normal [72]. Patients with active GVHD should also receive antibiotic prophylaxis aimed at pneumococcus. Penicillin V usually suffices, but trimethoprim/sulfamethoxazole or dox-ycycline may also be considered depending on local resistance patterns. For patients who are severely hypogammaglobulinemic (<400 mg IgG), regular infusions of intravenous immunoglobulin (IVIG) can be considered. Meticulous care of central venous catheters is mandatory [51, 73].

Clostridium Difficile

Clostridium difficile can occur at any time, though the risk is greatest during periods of hospitalization. Risk is increased in proportion to antibiotic exposure, especially perhaps to fluoroquinolones, by the presence of GVHD and of course by nosocomial risks, e.g., during an outbreak. Relapses are common after treatment.

Viral Infections

Viral pathogens are a significant source of morbidity and mortality after allo-HSCT [74]. Allo-HSCT recipients are affected by a wide range of viruses, either through primary infection, donor-derived infection, or reactivation of latent virus.

Cytomegalovirus

CMV continues to be one of the most important pathogens in this group. It is estimated that about 50% of the population in the United States is latently infected with CMV [75]. In other places in the world, including developing nations, the prevalence is even higher [76, 77].

Prior to widespread use of anti-CMV prophylaxis, approximately 80% of seropositive allo-HSCT recipients developed CMV reactivation, usually in the first 3 months after transplantation [78]. Despite prophylaxis with either ganciclovir or valganciclovir, the incidence of CMV reactivation ranges between 20% and 50%, with episodes increasingly occurring after prophylaxis is finished (late CMV) [79–83]. Approximately 6–18% of allo-HSCT recipients with CMV reactivation develop disease [79, 80, 83]. Clinical manifestations of CMV disease are variable and include interstitial pneumonia, enteritis, hepatitis, retinitis, encephalitis, and a CMV syndrome that includes cytopenia and fevers. CMV-related mortality is on average 40–50%, but can be as high as 86% in cases of severe pneumonia [83]. In addition to its direct end-organ effects, CMV disease is also associated with increased bacterial, fungal, and other viral infections [84].

The classic and most important risk factor for CMV reactivation is the serostatus of the recipient and donor, with a CMV-infected (seropositive) patient receiving a graft from a CMV-naïve (seronegative) donor considered the highest risk.

Additional risk factors include total body radiation in the conditioning phase, development of acute and chronic GVHD, T-cell-depleting therapies, steroids at doses greater than 1 mg/kg per day, and the use of mismatched or unrelated donors [78, 79].

Diagnosis of CMV disease remains clinically challenging given the varied and nonspecific presentations. Although PCR analysis of CMV DNA in the serum has become the mainstay of diagnosis, no absolute cutoff in viremia exists for differentiation between infection and disease. The presence of viremia does not automatically indicate disease although studies have shown that the likelihood of disease is high when levels above 10,000 copies/mL are found [85]. Conversely, disease does not always correlate with viremia, especially in cases of gastrointestinal involvement. With the introduction of international units, better studies to correlate disease and viremia will be possible in the future.

Intravenous ganciclovir is first-line therapy for CMV disease in allo-HSCT recipients. In non-severe cases, including asymptomatic viremia, oral valganciclovir can be used. Due to toxicities, foscarnet and cidofovir are considered second-line drugs and reserved for treatment failure due to GCV resistance or in situations where GCV is not tolerated. It is recommended that continuing treatment for 14–21 days after CMV DNA is no longer detectable in serum, followed by 1–3 months of maintenance therapy [86]. CMV immunoglobulins have been studied and in general are reserved for severe cases, especially pneumonia, or lack of response to antiviral therapy [87]. Recent studies have suggested that CMV-specific T-cell administration can be effective in the prophylaxis and treatment of CMV [88].

Although risk-stratified prophylaxis with oral valganciclovir can be effective, problems with toxicity, especially bone marrow suppression, preclude it from being a standard approach. An alternative approach involves frequent serum CMV PCR monitoring and initiation of treatment if viremia is detected. This preemptive approach is usually more logistically difficult and leads to higher rates of CMV reactivation [51]. An elusive goal for many decades, the search for a vaccine has recently shown promising results around glycoprotein B and phosphoprotein 65 epitopes [89, 90].

Epstein-Barr Virus (EBV)

In the United States and worldwide, it is estimated that almost 95% of adults demonstrate past infection with EBV. The spectrum of EBV-related diseases includes asymptomatic viremia, a viral syndrome with fevers and neutropenia, oral hairy leukoplakia, and rarely meningoencephalitis. More importantly, EBV is also associated with 50–70% of cases of PTLD in allo-HSCT recipients [91].

PTLD usually occurs in the first year after transplant and arises when EBV-specific T-lymphocytes are depleted, allowing for unchecked proliferation of donor-derived monoclonal or polyclonal B cells [92]. The spectrum of PTLD includes extranodal lymphocyte infiltration to high-grade B-cell lymphoma and varies from an indolent to fulminant presentation. Although the overall incidence of EBV-related PTLD in this population is approximately 1% (up to 2.8% in children), mortality can be as high as 50–90% [93]. Risk factors include age >50; recipients of mismatched, matched unrelated, or T-cell-depleted transplants; acute and chronic GVHD; and use of T-cell-depleting agents such as thymoglobulin and alemtuzumab [92].

Treatment options range from reduced immunosuppression to chemotherapeutic agents such as rituximab or CHOP. Antiviral agents have a limited role in the treatment or prevention of EBV-PTLD. Given that persistent or increasing EBV viremia usually precedes PTLD, preemptive treatment with rituximab may reduce the risk of progression to PTLD [94, 95].

Herpes Simplex Virus (HSV)

More than 50% of US adults are latently infected with HSV-1 [96]. In allo-HSCT recipients who do not received antiviral prophylaxis, the rate of reactivation can be as high as 80% and often occurs earlier, 2–3 weeks post-engraftment, than other herpesviruses [97, 98]. Clinical manifestations most commonly include oral-labial lesions and esophagitis, but can be varied and cause bone marrow suppression, keratitis, pneumonia, hepatitis, as well as meningoencephalitis [99–104]. HSV-2, on the other hand, is less frequent and is usually involved with perineal lesions only. Recurrent episodes of either HSV-1 or 2 infections may warrant suppressive therapy [51].

Varicella Zoster Virus (VZV)

Similar to HSV, reactivation is the most common cause of VZV-related disease after allo-HSCT, occurring in about 16% of patients in the first year after transplant [105]. Since anti-HSV or CMV prophylaxis is effective against VZV, reactivation usually occurs after prophylaxis has stopped, although breakthrough can also occur [105, 106]. GVHD is a major risk factor for VZV reactivation [107]. Clinical manifestations include either classic or multi-dermatomal shingles with lesions usually taking longer to heal that in immunocompetent patients. Disseminated VZV is a rare but severe occurrence, which can involve the lungs, liver, and CNS [108].

Human Herpesvirus (HHV) 6, 7, and 8

HHV-6 reactivation is common early post allo-HSCT, ranging from 36% to 47% of patients in the first month [109, 110]. The vast majority of cases range from asymptomatic viremia to fevers and transient marrow suppression, but patients can infrequently develop severe disease, including encephalitis, hepatitis, and pneumonitis. Posttransplant acute

limbic encephalitis [111] is a form of CNS disease in allo-HSCT recipients that is related to HHV-6 reactivation [112]. In addition to its direct effects, HHV-6 viremia has been found to increase delayed engraftment and GVHD as well as predispose patients to CMV and EBV reactivation [109]. Risk factors for HHV-6 reactivation include cord blood transplantation as well HLA mismatch [113]. Ganciclovir has activity against HHV-6 and is used for treatment [114]. Screening and preventative measures have not been developed.

HHV-7 viremia is also a common occurrence, but its association with post-HSCT disease is not well documented at this time. Reports of CNS disease associated with this virus have been reported [115].

HHV-8 can be transmitted to seronegative recipients, but clinical manifestations of viremia are also not well documented at this time, although it may possibly be related to fever, rash, mild hepatitis, and bone marrow aplasia. Unlike solid organ transplantation, cases of Kaposi's sarcoma are very rare [116].

Adenovirus (ADV)

Besides reactivation of latent infection, allo-HSCT recipients are susceptible to transmission of ADV via the stem cell graft as well as primary acquisition of any of the other >50 serotypes. About 12% of allo-HSCT recipients are affected by ADV reactivation, most of which are children under 5 years of age [117]. Reactivation usually occurs between 30 and 90 days posttransplant. Besides young age, risk factors for reactivation include severe GVHD, high-dose steroids, as well as use of unrelated cord blood [74]. In recipients with ADV viremia, approximately 40–50% develop disease, which ranges from a viral syndrome (fever, elevated liver enzymes, and pancytopenia) to pneumonitis, nephropathy, hemorrhagic cystitis, colitis, myocarditis, and CNS disease. Mortality in the setting of ADV disease is estimated to be around 22% [117].

Diagnosis is usually a combination of high clinical suspicion, serum ADV quantitative PCR, and histology. Treatment is not well defined but usually consists of reduced immunosuppression and cidofovir, which has a high incidence of nephrotoxicity [118]. Preventative measures are also not well defined.

Respiratory Viruses

With continuously improving detection techniques, respiratory viral pathogens have been increasingly recognized as significant sources of morbidity and mortality among recipients of allo-HSCT. These include, among others, influenza [119], parainfluenza [120], RSV [121], human metapneumovirus [122], as well as multiple strains of rhinoviruses, coronaviruses, and bocaviruses [123, 124]. Both community and nosocomial outbreaks are responsible for majority of infections, and rates of respiratory viral infections among allo-HSCT recipients undergo seasonal variation, much like the general population [125]. Estimates vary, but studies have shown that influenza (both A and B), parainfluenza, and RSV are the most common causes of viral respiratory infections [125]. Risk factors include GVHD, lymphopenia, and the presence of children younger than 12 years of age at home. Diagnosis involves clinical suspicion and RT-PCR. Mortality is variable and is usually associated with complications such as respiratory failure and bacterial or fungal superinfection. Preventative measures include vaccination, hand washing, and isolation measures in the setting of outbreaks. Besides anti-influenza drugs, antiviral therapy for most other respiratory viruses remains largely unproven [119, 120].

Hepatitis B Virus

The main risk with hepatitis B virus is reactivation of previously resolved infection, which can occur in up to 20% of cases if prophylaxis is not instituted [126]. Among those who reactivate, liver failure can be a rare complication. It is recommended that both recipients and donors be checked for hepatitis B serologies prior to HSCT and appropriate therapeutic or prophylactic measures taken [127].

Polyoma Viruses (BK and JC)

Although more commonly affecting renal transplant recipients, BK virus reactivation has also been described to cause both hemorrhagic cystitis and nephropathy in allo-HSCT recipients [128–131]. JCV-related progressive multifocal leukoencephalopathy (PML) is a rare but well-described complication in allo-HSCT recipients with dismal prognosis [132].

Fungal Infections

Invasive fungal infections (IFIs) are a major cause of morbidity and mortality among HSCT recipients. Individuals undergoing allo-HSCT are at higher risk for developing IFIs compared to recipients of autologous grafts, largely owing to delayed engraftment and GVHD. The epidemiology of IFIs in HSCT recipients remains dynamic. Since the 1990s, there has been a decrease in the incidence of invasive candidiasis among HSCT recipients due to the more widespread use of fluconazole prophylaxis; however, IFIs due to *Aspergillus* and other filamentous molds remain a significant concern.

Candida

Candida species commonly inhabit the skin and mucosa of the gastrointestinal tract, and disruption of the integrity of either mucosal barrier can lead to invasive candidiasis. In the

setting of allo-HSCT, invasive candidiasis typically results from mucositis of the gastrointestinal tract incurred during conditioning. Additional risk factors for invasive candidiasis include HLA mismatch, recipient age, prolonged neutropenia, GVHD, gastrointestinal tract colonization, and CMV disease [133, 134].

In the early 1990s, two large trials demonstrated a significant decrease in candidiasis with the use of fluconazole prophylaxis, and its administration through 75 days posttransplant was later shown to significantly reduce mortality among allo-HSCT recipients [135–137]. This prompted the widespread use of fluconazole prophylaxis in the early posttransplant period. More recent data from the Prospective Antifungal Therapy (PATH) Alliance registry, however, reported a 28% and 23% incidence of invasive candidiasis in allo-HSCT recipients from matched-related and matched-unrelated donors, respectively [138]. While *Candida albicans* accounted for over half of all episodes of invasive candidiasis in HSCT recipients in the 1980s, invasive candidiasis caused by azole-resistant *Candida* species such as *C. glabrata* and *C. krusei* has increased since the 1990s, which may reflect the routine use of fluconazole prophylaxis [28–30, 137, 138].

Invasive candidiasis in allo-HSCT recipients most commonly presents as fungemia or hepatosplenic candidiasis. Candidemia occurs in approximately 3% of HSCT recipients and may be accompanied by sepsis, a discreet palpable vasculitic rash, and/or end-organ involvement including but not limited to meningitis, endophthalmitis, and endocarditis [139]. In contrast, hepatosplenic candidiasis, or chronic disseminated candidiasis, results from invasion of *Candida* species into the portal vasculature with subsequent seeding of the liver and/or spleen during periods of neutropenia. While the exact incidence of hepatosplenic candidiasis remains unknown, one autopsy study identified hepatic candidal infection in 9% of HSCT recipients [140]. Patients typically present with fever and an elevated alkaline phosphatase level following neutrophil recovery. Blood cultures tend to be negative in this setting, but computed tomography of the abdomen demonstrates multiple lesions in the liver and spleen; such lesions decrease in size with recurrent neutropenia, indicating that hepatosplenic candidiasis results from a systemic inflammatory response. Biopsy is required for definitive diagnosis, especially because other IFIs and malignancy can result in a similar clinical syndrome.

The diagnosis of invasive candidiasis remains challenging, particularly because conventional blood cultures may only have a sensitivity of 50% in those with deep fungal infection [141]. Newer diagnostic assays, including the beta-D-glucan test, which detects beta-glucans in the cell wall of molds and yeasts except zygomycetes and cryptococci, may be valuable in the diagnosis of invasive candidiasis. One recent study demonstrated a sensitivity and specificity of 87.5% and 85.5%, respectively, of this assay. The mannan antigen and antibody and the Cand-Tec *Candida* antigen assays have demonstrated lower sensitivities than the beta-D-glucan assay (58.9%, 62.5%, and 13%, respectively) [142].

Given the prevalence of azole-resistant *Candida* species in neutropenic patients, particularly *C. glabrata* and *C. krusei*, management of invasive candidiasis in allo-HSCT recipients should include amphotericin B or an echinocandin such as caspofungin, micafungin, or anidulafungin. Several studies have demonstrated comparable efficacy between both antifungal classes; however, echinocandins have been associated with a more favorable toxicity profile [143, 144]. Voriconazole may be used in situations where additional mold coverage is desired; however, since voriconazole resistance has been seen in 3% of Candida infections in solid organ and HSCT recipients, this agent should not be used unless susceptibility of the isolate is confirmed [145, 146]. As the majority of cases of hepatosplenic candidiasis are caused by *C. albicans*, clinically stable patients may receive fluconazole. Those who are acutely ill or who have relapsed disease should receive 1–2 weeks of induction with liposomal amphotericin B or an echinocandin followed by fluconazole. Duration of therapy for hepatosplenic candidiasis is dependent upon resolution of visceral lesions, typically 3–6 months. Chronic suppressive therapy may be used in individuals at high risk for recurrence, including those with GVHD [146].

Invasive Mold Infections

Aspergillus and other molds are ubiquitous environmental pathogens. HSCT recipients are at high risk of infection with these organisms, which are largely acquired via inhalation of conidia that are inadequately cleared in the setting of immunosuppression. Less common routes of infection include invasion of the gastrointestinal tract or cutaneous inoculation.

Aspergillus

Invasive aspergillosis is the most frequent IFI encountered among allo-HSCT recipients. Data from the PATH Alliance demonstrated an incidence of invasive aspergillosis of 53.5% and 59.8% in recipients of matched-related donor and matched-unrelated donor transplants, respectively [138]. While both autologous and allo-HSCT recipients are at risk for the development of invasive aspergillosis, prolonged neutropenia, as well as GVHD, and its treatment contribute to higher incidences of invasive aspergillosis among allo-HSCT recipients [147, 148].

The onset of invasive aspergillosis following HSCT occurs in a bimodal fashion, with the first peak noted within the first 40 days of transplantation [149] and corresponding to the period of neutropenia. The second peak occurs post-

engraftment ("late period"), typically defined as 41+ days following transplant, and tends to arise in the setting of acute or chronic GVHD [147, 148, 150]. Age >40 has been associated with the development of invasive aspergillosis at any time following transplantation, as have donor and recipient polymorphisms in various Toll-like receptors and genes regulating interleukin-1, interleukin-10 promoter, and plasminogen [147, 151–155]. Specifically, donor haplotype 1363T/1063G, which contains two cosegregated single nucleotide polymorphisms in the Toll-like receptor 4 gene, has been associated with the development of invasive aspergillosis [151]. Single nucleotide polymorphisms in the chemokine ligand 10 (CXCL-10) gene have also been demonstrated to reduce dendritic cell CXCL-10 expression when exposed to *Aspergillus* germlings; these polymorphisms have also been associated with invasive aspergillosis following allo-HSCT [154]. Hematologic malignancies other than chronic myelogenous leukemia in the chronic phase, as well as aplastic anemia, myelodysplastic syndrome, mismatched donor, the use of cord blood, summer season, lack of laminar air flow, and local building construction, have been identified as risk factors for invasive aspergillosis in the early posttransplant period. The risk of invasive aspergillosis in the late posttransplant period increases in the setting of underlying multiple myeloma, use of T-cell-depleted or CD34-selected stem cell products, neutropenia, lymphopenia, use of corticosteroids, CMV disease, respiratory virus infection, and GVHD [147, 148]. GVHD and CMV disease are the major risk factors for the development of invasive aspergillosis >6 months after transplantation [148]. The contribution of GVHD to the risk of invasive aspergillosis is highlighted by the fact that conditioning regimens do not appear to impact the incidence of this invasive fungal infection. While the period of neutropenia is shorter and the incidence of early invasive aspergillosis is less in non-myeloablative HSCT recipients, this group remains at highest risk in the late posttransplant period in conjunction with GVHD [12, 156–158].

Aspergillus fumigatus is the most commonly isolated species associated with invasive aspergillosis in allogeneic HSCT recipients; infections with *A. niger*, *A. flavus*, and *A. terreus* are less frequently encountered [147, 159]. The lungs represent the most commonly involved site of infection, though patients may develop sinusitis, CNS disease, and tracheobronchitis. Clinical presentation may be variable, but frequently includes fever, cough, chest pain, hemoptysis, and/or respiratory failure, and the presence of these symptoms should prompt CT of the chest. Lung lesions, with surrounding ground-glass halos, nodular infiltrates, and cavitations, are highly suggestive of pulmonary aspergillosis; however, radiographic findings can be variable in allo-HSCT recipients with concomitant GVHD and include focal infiltrates and/or bronchopneumonia [160]. Given the lack of specificity of symptoms and radiographic findings, prompt microbiologic diagnosis via bronchoscopy should be pursued. Diagnosis of invasive aspergillosis may also be facilitated with use of the *Aspergillus* galactomannan assay, which employs a double-sandwich enzyme immunoassay to detect the galactomannan component of the *Aspergillus* cell wall. While the sensitivity of the serum galactomannan assay has varied between studies, it has proven clinically useful for the diagnosis of invasive aspergillosis and monitoring of clinical response during therapy [161, 162]. The galactomannan assay on bronchoalveolar lavage fluid in patients with hematologic malignancies and HSCT recipients has demonstrated higher sensitivity than bronchoalveolar lavage culture, cytology, and the serum galactomannan assay [163]. Important caveats for the use of galactomannan testing include false negative results in individuals receiving concomitant antifungals, false positive results in children and patients receiving beta-lactams, particularly piperacillin-tazobactam, and cross-reactivity with plasmalyte [164–166]. The beta-D-glucan test, which detects beta-glucans in the cell wall of molds and yeasts except zygomycetes and cryptococci, may also be a valuable adjunctive screening test for invasive aspergillosis particularly in conjunction with the galactomannan assay, though the performance characteristics of the beta-D-glucan assay in the HSCT population have not yet been evaluated.

Empiric therapy for suspected invasive aspergillosis should include a mold-active azole or amphotericin B. The use of an echinocandin can also be entertained, though these agents are fungistatic, rather than fungicidal. Once the diagnosis of invasive aspergillosis has been confirmed, primary therapy should include voriconazole in most patients, as this agent has been associated with improved clinical outcomes and survival rates and less toxicity compared with amphotericin B [167, 168]. Voriconazole is also the preferred therapy for *Aspergillus* tracheobronchitis [168]. Combination therapy with an echinocandin and either amphotericin B or a mold-active azole may be more efficacious than voriconazole alone, however, particularly for salvage therapy [169, 170]. The duration of therapy in allogeneic HSCT recipients should be prolonged and continue at least until immunosuppressives, particularly corticosteroids, are completed.

Prevention of invasive aspergillosis in allogeneic HSCT recipients should include the use of high-efficiency particulate air (HEPA) filtration and/or laminar flow rooms during the pre-engraftment period. In addition, two recent studies have suggested that voriconazole may be appropriate secondary prophylaxis prior to HSCT in patients with previous IA [171, 172].

Other Molds

Mucor and *Rhizopus* species are the most commonly encountered zygomycetes in clinical practice, with an incidence of 8.5% and 5.9% in recipients of matched-related and matched-

unrelated allo-HSCT, respectively [138]. Infection with these organisms results in mucormycosis, which can occur in the late posttransplant period and causes devastating sino-orbital, CNS, and gastrointestinal disease, as well as cutaneous lesions and fasciitis. Among HSCT recipients, risk factors for zygomycosis include HLA mismatch, prolonged neutropenia, corticosteroid use, iron overload, and GVHD [173, 174]. Additionally, several studies have noted increasing numbers of zygomycosis cases among patients receiving voriconazole as either prophylaxis or treatment of invasive aspergillosis [32, 111, 175]. Whether this reflects azole-related selective pressure remains unknown.

Fusarium species are environmental organisms, which cause infrequent but severe invasive fungal infection in HSCT recipients. Cases of fusariosis among HSCT recipients have been linked to contamination of central venous catheters and hospital water supply [176, 177]. Risk factors for fusariosis include underlying multiple myeloma and HLA mismatch. As with invasive aspergillosis, the onset of fusariosis occurs in a bimodal fashion; infection in the early posttransplant period is associated with prolonged neutropenia, and late infection is associated with T-cell depletion, corticosteroid use, and GVHD. Infection with *Fusarium* species can mimic invasive aspergillosis; however, patients with fusariosis are more likely to have positive blood cultures and multiple papular or ulcerated skin lesions compared to patients with invasive aspergillosis [176, 178].

Scedosporium apiospermum and *Scedosporium prolificans* have also been isolated in HSCT recipients; their disease spectrum is similar to invasive aspergillosis. Risk factors for *Scedosporium* infection include prolonged neutropenia and GVHD [159, 179, 180].

Miscellaneous Infections

Pneumocystis Jirovecii (PJP)

Due to effective prophylaxis, PCP has become a rare event among allo-HSCT recipients with retrospective studies showing incidence rates from 1.3% to 2.5% [181, 182]. PCP is usually a late occurrence, and risk factors include treatment for GVHD or cessation of PCP prophylaxis [183]. Despite effective treatment, mortality can be high if infection occurs early after transplant [184].

Toxoplasmosis

The majority of cases of toxoplasmosis in allo-HSCT recipients are due to reactivation of latent infection. In the United States, the incidence of toxoplasmosis has been reported to be as low as 0.25% [185], reflecting a low seroprevalence in the population [186]. In regions of the world with a higher seroprevalence, incidence rates of toxoplasmosis are predictably higher [187]. Disease usually occurs in the first 6 months after transplantation [185, 186]. Besides seropositivity, the main risk factor for reactivation is intensification of immunosuppression due to GVHD [186]. The most common clinical presentation is encephalitis, which usually presents with focal neurological deficits. Extra-CNS forms of toxoplasmosis include pneumonitis, chorioretinitis, and myocarditis. Diagnosis of toxoplasmosis in any of the above manifestations requires a high clinical suspicion. A toxoplasma PCR can be obtained in serum and tissue such as CSF and vitreous fluid [188, 189]. First-line treatment includes extensive treatment with pyrimethamine and sulfadiazine. Despite best efforts mortality in allo-HSCT recipients remains high [185, 190]. Prophylaxis is usually accomplished with trimethoprim/sulfamethoxazole [191].

Strongyloides

Strongyloides stercoralis can latently infect auto-HSCT recipients who previously lived or visited endemic areas (tropical and subtropical region worldwide), even many decades earlier. In the setting of immunosuppression, the parasite's life cycle is accelerated and cause hyperinfection and disseminated disease [192]. Clinical manifestations include intestinal obstruction, respiratory failure including alveolar hemorrhage, bacterial sepsis, or meningitis [193]. Because of delays in diagnosis, infections can be devastating and carry high mortality. Patients from endemic areas should be serologically screened and treated with ivermectin prior transplant [193].

Preventative Strategies

Like solid organ transplant recipients, allo-HSCT recipients can benefit from measures aimed to prevent infectious complications in the posttransplant period. These can include infection control practices in hospitals and outpatient clinics as well as guidelines for the prevention of opportunistic infections.

The CDC/IDSA and ASBMT have published extensive evidence-based infection control guidelines that include specific practices regarding room ventilation, isolation and barrier precautions, cleaning, hand hygiene, equipment disinfection, plants, patient skin and oral care, prevention of intravascular catheter-related infections, construction and renovations, as well as healthcare workers [194].

In terms of specific infections, guidelines from the CDC were published in 2000. Because many of these organisms not only involve reactivation of latent infection in the recipient but can also be donor-derived, both donors and recipients should be universally tested for CMV, EBV, HIV I/II, HTLV I/II (although this is not done in all centers), hepatitis B and C, syphilis, and *M. tuberculosis* (in donor only if from endemic country). Additionally, all recipients should be tested for HSV I/II, VZV, and *Toxoplasma*. Potential donors and recipients

Table 11.2 Pretransplant screening in candidate allo-HSCT donors and recipients

Donor screening	Recipient screening
Standard	
CMV IgG	CMV IgG
EBV VCA IgG	EBV VCA IgG
VZV IgG	HSV I/II IgG
HIV Ab and NAT	VZV IgG
HTLV I//II Ab	HIV Ab and NAT
Hepatitis B surface Ag and core Ab	HTLV I/II Ab
Hepatitis C Ab, NAT	Hepatitis B surface Ag and core Ab
Syphilis screening (RPR)	Hepatitis C Ab, NAT
	Syphilis screening (RPR)
	Latent Tb screening (PPD or IGRA)
Optional (if risk factors are present)	
Hepatitis B NAT	Hepatitis B NAT
West Nile virus Ab	West Nile virus Ab
Toxoplasma Ab	*Toxoplasma* Ab
Strongyloides Ab	*Strongyloides* Ab
Trypanosoma cruzi	*Trypanosoma cruzi*
Leishmania Ab/PCR	*Coccidioides* Ab
Babesia Ab	*Histoplasma* Ab
Rickettsia Ab	*Brucella* Ab
Coxiella burnetii Ab	

Table 11.3 Recommended and optional vaccination of allo-HSCT recipients [195]

Vaccine	Comments on use after allo-HSCT	Time post-HSCT to initiate vaccine
Recommended		
Pneumococcal conjugate (PCV)	3–4 doses, a fourth dose with PPSV23[a] may be beneficial	3–6 months
Tetanus, diphtheria, acellular pertussis	3 doses, DTaP preferred over Tdap	6–12 months
Haemophilus influenzae conjugate	3 doses	6–12 months
Meningococcal conjugate	1 dose, follow country recommendations for general population	6–12 months
Inactivated polio	3 doses	6–12 months
Recombinant hepatitis B	3 doses, follow country recommendations for general population	6–12 months
Inactivated influenza	Yearly	4–6 months
Measles, mumps, rubella (live)	1–2 doses, all children and measles seronegative adults, not recommended if active GVHD or on immunosuppression	>24 months
Optional		
Hepatitis A	Follow country recommendations for general population	12 months

Table 11.3 (continued)

Varicella (Varivax, live)	Limited data regarding safety and efficacy. Not recommended if active GVHD or on immunosuppression	>24 months
Human papillomavirus	Follow country recommendations for general population	No data
Yellow fever (live)	Limited data regarding safety and efficacy. The risk-benefit balance may favor use of the vaccine in patients residing in or traveling to endemic areas	>24 months
Rabies	Appropriate for use in HCT recipients with potential occupational exposures to rabies. Postexposure administration of rabies vaccine with human rabies Ig can be administered any time after HCT, as indicated	12–24 months
Tick-borne encephalitis	According to local policy in endemic areas	No data
Japanese B encephalitis	According to local policy when residing in or travelling to endemic areas	No data

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Contraindicated vaccines: BCG (live), oral polio (live), intranasal live influenza, cholera (live), typhoid (live and IM), *Rotavirus*, zoster vaccine (Zostavax, live)
[a]PPV23: 23-valent pneumococcal vaccine

should also be tested for *Strongyloides* and *Trypanosoma cruzi* if they have epidemiologic risks. Patients with evidence of syphilis, *Strongyloides*, or latent tuberculosis infection should be treated in the pretransplant period (see Table 11.2).

Vaccinations are an important component of disease prevention. Because of predictable decline in antibody titers posttransplant, it is recommended that recipients be revaccinated in the post-engraftment at the appropriate time (see Table 11.3) [195].

Prophylaxis in the posttransplant period is usually aimed at the most common and predictable organisms. A discussion of strategies to prevent CMV is beyond the scope of this chapter but includes either preemptive treatment in cases of CMV viremia or universal prophylaxis for those at risk for CMV reactivation. Recipients not at risk for CMV should receive acyclovir for HSV prophylaxis. PCP and *Toxoplasma* prophylaxis is accomplished with sulfamethoxazole/trimethoprim for 6–13 months, although this practice varies when taking into consideration the myelosuppressive effects of

this drug combination. Dapsone, atovaquone, and pentamidine are alternatives for PCP prophylaxis. Of those, only atovaquone has activity against *Toxoplasma* as well. Many centers also institute bacterial and fungal prophylaxis in the peri-transplant period until neutropenia resolves.

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