6 Risks and Epidemiology of Infections After Hematopoietic Stem Cell Transplantation

Juan Gea-Banacloche

6.1 Introduction

Understanding the epidemiology of infections after allogeneic hematopoietic stem cell transplantation (HCT) is important to implement appropriate preventive strategies as well as to effectively diagnose and treat individual patients.

Several groups of experts and professional organizations publish guidelines that provide specific recommendations for prophylaxis and management of infections after HCT [1–8], including vaccinations [1, 9, 10]. Many of these recommendations are necessarily based on low-quality evidence and rely heavily on expert opinion. Guidelines should not be followed blindly, but understood as tools that may help to provide the best possible care.

Risk factors for infection include individual characteristics (e.g., indication for HCT, prior infections, CMV serostatus, particular genetic traits) and type of transplant (based on conditioning regimen, stem cell source, degree of HLA homology, and immunosuppression). The development of graft-versus-host disease (GVHD) is frequently the decisive contributor to infectious morbidity and mortality.

6.2 Individual Characteristics and the Risk of Infection

Different indications for HCT are associated with their own infectious risks. Primary immunodeficiencies (PID), hemoglobinopathies, and hematologic malignancies present different challenges. Even in hematologic malignancies, the risk may vary depending on the specific condition: patients with chronic myelogenous leukemia (CML), acute myeloid leukemia (AML), and chronic lymphocytic leukemia (CLL) present different risks based on both the biology of the disease and prior treatment. These factors should be considered when assessing individual patients.

Prior infections must be considered. A history of infection or colonization with a multidrug-resistant organism (MDRO) like carbapenem-resistant enterobacteria (CRE), extended-spectrum beta-lactamase (ESBL)-producing Gram-negative bacteria, vancomycin-resistant enterococcus (VRE), or methicillin-resistant Staphylococcus aureus (MRSA) has implications regarding optimal management of fever during neutropenia [6, 11, 12], which is a common complication of HCT. Transplant candidates are routinely screened for serologic evidence of latent infections that may reactivate (HSV, VZV, CMV, EBV, hepatitis B and C, toxoplasmosis); some of these will be discussed later in this chapter. Some transplant centers will perform screening for tuberculosis with tuberculin skin test (TST) or interferon-gamma release assay (IGRA), at least for patients who are considered at significant risk for the disease. Prior invasive fungal infections may reactivate following transplant, and secondary prophylaxis is required [13–15]. Even active fungal infection has been reported to be controllable. There are, however, cases of progression of prior aspergillosis after transplant; myeloablative conditioning, prolonged neutropenia, cytomegalovirus (CMV) disease, and graft-versus-host disease (GVHD) are risk factors [15, 16].

As the correlates of native and adaptive immunity are better understood, genetic associations are coming to light. There is evidence that some donor haplotypes of TLR4, the gene that encodes the toll-like receptor protein 4 (TLR4) are associated with increased risk of invasive aspergillosis after HCT [17]. Recipient’s mutations in MBL2, the gene that encodes mannose-binding lectin (MBL), have been associated with increased risk of infection after neutrophil recovery following myeloablative transplant [18]. Other polymorphisms of MBL2 may be important for infection through a direct influence on the risk of developing GVHD [19, 20]. Different genotypes of activated killer immunoglobulin-like receptors (aKIR) in the donor have been found to protect from CMV reactivation [21]. Many of these associations are preliminary and require more data to be confirmed, but they hold the promise of a more individualized approach to infectious prophylaxis.
6.3 Time Course of Infections After Allogeneic Stem Cell Transplantation

From a practical standpoint, it is helpful to consider three distinct periods during transplant: pre-engraftment (until neutrophil recovery), early post-engraftment (from engraftment until day 100), and late post-engraftment (after day 100). This framework originated with myeloablative transplants, and is eminently pragmatic. The pre-engraftment phase may be accompanied by profound neutropenia and significant mucositis, which results in increased risk of bacterial infections from the resident gastrointestinal flora, candidiasis, aspergillosis (in cases of prolonged neutropenia) and herpes simplex virus reactivation. After engraftment, with neutropenia no longer being a factor, many infections are related to the profound defect in cellular immunity caused by the conditioning regimen and the immunosuppression administered to prevent GVHD. CMV reactivation and the development of acute GVHD and its treatment play a central role during this time. The day 100 landmark derives from the standard time at which immunosuppression (e.g., cyclosporine A or tacrolimus) is frequently tapered. Infections after this point would be primarily related to lack of immune reconstitution and, in the absence of GVHD, become progressively less common.

6.4 Types of Allogeneic Hematopoietic Stem Cell Transplantation (HCT)

Not all allogeneic stem cell transplantations are the same. Several characteristics of the transplant influence the risk of infection: the conditioning preparative regimen, the source of stem cells, the degree of HLA identity between donor and recipient, and the prophylactic strategy adopted to prevent GVHD (use of T cell depletion or immunosuppressive medications). Table 6-1 summarizes the impact of these factors on infections.

| Factor                | Type of transplant                        | Risk of infection                                                                 |
|-----------------------|-------------------------------------------|-----------------------------------------------------------------------------------|
| Conditioning regimen  | Myeloablative                              | In general, there are less early infections (mainly bacterial) with nonmyeloablative transplants, but different regimens may have very different risks |
|                       | Reduced intensity                          | Nonmyeloablative regimens do not seem to result in less late infections           |
|                       | Nonmyeloablative                           |                                                                                   |
| HLA match             | HLA-matched sibling                        | With higher degree of mismatch, more immunosuppression is required, immortal reconstitution is delayed, and the risk of infection is higher. Haploidentical and partially matched transplants often incorporate T cell depletion |
|                       | HLA-matched unrelated (URD or MUD)         |                                                                                   |
|                       | Haploidentical                             | Haploidentical transplants using posttransplant cyclophosphamide seem to have good immune reconstitution |
|                       | Partially matched                          |                                                                                   |
| Source of stem cells  | Bone marrow                                | G-CSF-mobilized peripheral blood stem cells often result in shorter neutropenia, but may be associated with higher risk of chronic GVHD. Conflicting data on CMV risk |
|                       | G-CSF-mobilized peripheral blood stem cells| UCD transplants result in long-lasting neutropenia and prolonged immunodeficiency, with higher risk of infection |
|                       | Cord blood (UCD)                           | High risk of viral infections with cord transplants                                 |
| GVHD prophylaxis      | T cell depletion (in vitro via CD34+ cell selection or in vivo with ATG or alemtuzumab) | T cell depletion results in increased risk for infections. ATG and alemtuzumab may result in prolonged lymphopenia and immunodeficiency, depending on the dose used. Viral infections, EBV-related PTLD, and toxoplasmosis seem to be more common after T cell depletion |
| (posttransplant       | Immunosuppressive agents                   | Differences between pharmacological immunosuppressive regimens are not well defined; sirolimus may be associated with less CMV reactivation |
| immunosuppression)    |                                            |                                                                                   |

G-CSF granulocyte-colony-stimulating factor, GVHD graft-versus-host disease, CMV cytomegalovirus, ATG anti-thymocyte immunoglobulin, EBV-related PTLD Epstein–Barr virus-related posttransplant lymphoproliferative disorder.

J. Gea-Banacloche
6.4.1 Preparative (Conditioning) Regimen

The conditioning regimen administered before the infusion of stem cells has some influence on the risk of infection through its effect on neutropenia, mucosal damage, and GVHD. The conditioning regimen has several goals: reduction of the malignancy (when there is one), creation of space in the bone marrow to provide a selective advantage to the infused stem cells, and elimination of the recipient’s immune system to minimize the risk of rejection. Different conditioning regimens may be more appropriate depending on the disease and the general status of the recipient [22]. Myeloablative, reduced intensity, and nonmyeloablative are the general categories, but within each one there are substantial differences that may be relevant. In general, fully myeloablative regimens result in more prolonged neutropenia and more severe mucosal barrier damage, which may impact the infectious risk during the pre-engraftment period [23].

6.4.2 Degree of HLA Similarity Between Donor and Recipient

Data from the Center for International Blood and Marrow Transplant Research (CIBMTR) indicate that there is a direct association between the number of donor–recipient HLA mismatches and the risk for mortality [24]. The current standard aims for high-resolution matching at HLA-A, HLA-B, HLA-C, and HLA-DRB1 (i.e., an “8 out of 8” match), but only about 30% of transplant candidates will have a perfectly matched sibling or unrelated donor (MUD). If a mismatch is unavoidable, a single-locus mismatched donor can be used [24]. Other alternatives include haploidentical and umbilical cord blood (UCB) transplants.

Haploidentical transplants are one special type of mismatched transplant, where the donor shares at least one complete haplotype with the recipient. Most candidates for transplant have a potential haploidentical donor. The successful use of a regimen of posttransplant cyclophosphamide to prevent GVHD in the haploidentical setting has resulted in an increasing number of this type of transplant being performed during the last decade [25]. Interestingly, early data suggest haploidentical transplants do not result in delayed immune reconstitution or increased infections [26].

Matching for UCB transplants focuses on three loci (HLA-A, HLA-B, and HLA-DRB1). The majority of UCB transplants are mismatched by at least one loci (often two). Among transplants mismatched at two loci, mismatching at HLA-C and HLA-DRB1 was associated with the highest risk of mortality [24].

The degree of mismatch between the donor and the recipient affects the infectious risk mainly through the likelihood of GVHD. More GVHD usually results in more infections. To prevent GVHD in a mismatched transplant, more potent immunosuppression may be required, increasing the risk of infection. It is also possible that immune reconstitution proceeds more slowly (even with the same immunosuppressive regimen) after a URD HCT. These factors may result in increased risk of infections associated with T cell immunodeficiency, like CMV, *Pneumocystis jirovecii* pneumonia (PCP), and Epstein–Barr virus (EBV)-related posttransplant lymphoproliferative disorder (PTLD).

However, provided the number of stem cells administered is the usual (>3×10^6 kg^-1), neutrophil recovery proceeds at the standard pace and there is no increased risk of neutropenia-related infections.

The problems with UCB transplants include a markedly decreased stem cell dose (often <1×10^6 kg^-1) which results in prolonged neutropenia (up to 6 weeks), with the attendant risk of bacterial and fungal infections [27]. In addition, the cord blood does not have antigen-specific memory T cells that can expand in a thymus-independent fashion to provide protection against viruses and opportunistic pathogens. This results in high frequency of late severe infections following cord transplantation, even when the neutropenic period is shortened by coadministration of stem cells from a third-party donor [28].

6.4.3 Source of Stem Cells

Stem cells may be given using the bone marrow, G-CSF-mobilized peripheral blood stem cells (PBSCs), or UCB. Frequently bone marrow will result in more prolonged neutropenia compared with PBSC, and increased infections during neutropenia should be expected. However, a multicenter randomized trial comparing peripheral blood stem cells with the bone marrow from unrelated donors showed no difference in the relapse or infectious mortality between both groups, but confirmed that chronic GVHD is more common with mobilized PBSC [29]. The particular features of UCD transplants were discussed on the preceding paragraph.

6.4.4 Strategy to Prevent GVHD:

Manipulation of the Stem Cells, Imunosuppressive Drugs,

or a Combination

GVHD may be prevented by decreasing the amount donor T cells or by limiting T cell function with immunosuppressive agents. The stem cells, whether from the bone marrow or the periphery, may be administered unmanipulated (sometimes called “T cell replete”) or enriched by CD34 selection (also called “T cell depleted”). If unmanipulated bone marrow or PBSCs are used, the dose of CD3+ T cells administered with the graft varies between 24×10^6 kg^-1 when bone marrow is used and 300×10^6 kg^-1 when PBSCs are used [30]. Reductions in the amount of T cells of 2–3 log_{10} are possible,
and in some haploidentical transplant regimens, as few as $12.5 \times 10^3$ CD3+ cells are given, which still results in detectable immune reconstitution starting 2–3 months after transplant [31]. T cell depletion may minimize or altogether prevent GVHD but may result in prolonged immunodeficiency, depending on the degree of depletion. If an unmanipulated product is used, T cell depletion may be attained in vivo by using alemtuzumab or ATG. These agents produce a profound depletion of T cells in vivo, and their long half-life makes them still be present and active in the recipient when the stem cell product is administered.

If no in vitro or in vivo T cell depletion is used, one of a variety of immunosuppressive regimens will be given to prevent GVHD (e.g., tacrolimus + methotrexate, tacrolimus plus mycophenolate mofetil, cyclosporine A, sirolimus, posttransplant cyclophosphamide). A randomized controlled trial documented more infections in patients randomized to (moderate) T cell depletion than in the group who received pharmacologic immunosuppression [32]. T cell depletion in vivo with alemtuzumab has been associated with increased risk of infection [33]. It is possible that different pharmacological regimens may result in different infectious risks, but this has not been adequately studied. Preliminary evidence suggests that a sirolimus-based regimen may result in less CMV reactivation [34] and that posttransplant cyclophosphamide result in relatively decreased risk of PTLD [35].

The above categories may combine in several ways, compounding the risk of infection. These variations should be considered both when designing a regimen of anti-infective prophylaxis and when considering an individual patient who may have an infection.

### 6.5 Graft-Versus-Host Disease

GVHD is the most important cause of non-relapse mortality following HCT, and it is frequently complicated by infection. GVHD is categorized as acute or chronic based on its time of onset. Acute GVHD develops before day 100 and is characterized by gastrointestinal disease (secretory diarrhea, nausea, vomiting), liver dysfunction, and skin rash. Stages of GVHD in the skin, gut, and liver combine to give a grade (I–IV) of the severity of the disease. Acute GVHD grades III–IV is associated with significant mortality. The treatment of choice is high-dose systemic corticosteroids. GVHD is associated with significant immune dysregulation [36, 37] and is frequently accompanied by CMV reactivation [38]. The combination of disruption of the GI mucosa (and sometimes skin) and high-dose corticosteroids (in addition to the immunosuppressive agents concurrently given, like tacrolimus and MMF) constitute a high-risk setting for infection. Bacterial, fungal, and viral infections are common under these circumstances.

Chronic graft-versus-host disease (cGVHD) has been traditionally defined chronologically: GVHD starting after day 100. It has been classified based on its relation to prior GVHD (progressive when acute GVHD continues after day 100, quiescent when there is a period of time during which the patient is free of GVHD, or de novo when chronic GVHD is the first manifestation of GVHD) and its extension (limited or extensive, reformulated as clinical limited, or clinical extensive). The clinical syndrome of typical chronic GVHD is quite distinct from the acute form, and a new classification focusing on the clinical characteristics of the disease as well as on the timing is being increasingly used [39]. From the standpoint of infectious diseases, the important consideration is that the presence of chronic GVHD is associated with high risk of infection [40, 41]. Multiple immune defects have been described during chronic GVHD, involving humoral and cellular immunity [42, 43] as well as functional hyposplenism [44, 45]. Besides these abnormalities, that result in delayed immune reconstitution and poor response to immunizations, the risk of infection is increased by the treatment of extensive cGVHD [41], which typically includes systemic corticosteroids and a variety of steroid-sparing agents. Notably, cGVHD is a well-documented risk for pneumococcal infections [45, 46], fungal infections, and late CMV disease. However, all types of infections are more common during cGVHD, particularly during the first few months [47].

When GVHD is not controlled by corticosteroids, it is called “steroid refractory,” and there is currently no universally accepted standard treatment. This situation is important from the infectious disease standpoint because patients are usually treated with a variety of highly immunosuppressive regimens (e.g., ATG, cyclophosphamide, MMF, infliximab, daclizumab, alefacept, alemtuzumab, sirolimus, visilizumab, denileukin diftitox, and others) [48] that result in a wide array of infectious complications. Reactivation of CMV is very common, as are fungal infections [49, 50], Epstein–Barr virus-related PTLD [51], as well as human herpesvirus 6 (HHV-6) [52] and adenovirus [53]. There are no controlled studies to support any particular infection prevention strategy during this period of increased immunosuppression, but some authors have emphasized that early use of prophylactic antibiotics and antifungals is an essential part of a successful approach to this problem [54]. Unfortunately, this is a condition for which controlled trials are unlikely to be performed, and different centers will have to decide on a particular approach of close monitoring versus prophylaxis based on local experience and published case series.

In the following sections, the epidemiology of bacterial, fungal, viral, and parasitic diseases will be discussed. The implications for prophylaxis and management will be mentioned. Immunizations for transplant recipients, (as well as their caregivers and immediate contacts) are discussed in Chap. 48.
6.6 Risks and Epidemiology of Bacterial Infections After Allogeneic HCT

6.6.1 Early Bacterial Infections: Pre-engraftment

Approximately 20% of HCT recipients will experience at least one episode of bacteremia during the first few weeks, and a similar proportion after engraftment [55]. These infections are usually related to either neutropenia with subsequent bacterial translocation through the GI mucosa (mucosal barrier injury laboratory-confirmed bloodstream infection or MBI-LCBI) or the intravascular catheter (central line-associated bloodstream infections or CLABSIs) [56].

The relative frequency of Gram-positive and Gram-negative infections during neutropenia varies in different series and with the use of prophylactic antibiotics. In some centers, the most frequent Gram-positive isolates are viridans group Streptococcus [55]; this may be a function of the conditioning regimen or the patient population. Enterococcus faecium, frequently VRE, is another Gram-positive organism that tends to cause bloodstream infection relatively early, although this seems to be rather institution dependent [57]. The Gram-negative bacteria are commonly Enterobacteriaceae. These infections are generally related to the disruption of the GI mucosa due to the preparative regimen. The role of reduced diversity of the microbiota with subsequent bacterial domination and ultimately bacteremia is an area of intense study [58]. The risk of bacteremia during neutropenia may be decreased by the use of prophylactic antibiotics [59, 60]. This had been shown in multiple studies over the years, but the recommendation of using antibiotics did not become part of practice guidelines until recently. It is not clear whether this recommendation will continue amidst the increasing concern over the role of antibiotic-induced decreased microbiome diversity on the outcome of HCT [61]. In this regard it is of interest that fluoroquinolones seem to have less detrimental effects on biodiversity of the fecal flora than beta-lactams. Levofloxacin at a dose of 500 mg/d for patients who are going to be profoundly neutropenic for longer than 1 week is the current recommendation of the IDSA [11].

6.6.2 Early Bacterial Infections Following Engraftment

In a large study from the Sloan Kettering Cancer Center, the risk factors for post-engraftment bacteremia included acute GVHD, renal dysfunction, hepatic dysfunction, and neutropenia [55]. Enterococcus (VRE) and coagulase-negative Staphylococcus were the most common Gram-positive isolates. Enterobacteriaceae and non-fermentative Gram-negative bacteria (including Pseudomonas, Stenotrophomonas, and Acinetobacter, possibly related to the indwelling catheter) were the most common Gram-negative isolates. Bacteremia following engraftment often happens in the setting of patients with a complicated clinical course, acute GVHD, and multiple medical problems or else is catheter related.

Daily bathing with chlorhexidine-impregnated washcloths decreased the risk of acquisition of MDROs and development of hospital-acquired bloodstream infections in transplant recipients in a randomized trial [62], and this practice should be considered by every transplant program.

The advantages and disadvantages of active screening for colonization by resistant pathogens have not been adequately studied in HCT recipients. It is likely that local epidemiology determines whether screening is an efficacious and cost-effective approach to either prevent infection or improve outcomes. A retrospective study on VRE bacteremia from the Sloan Kettering Cancer Center showed that VRE carriage was predictive of subsequent VRE bacteremia, but failed to detect the pathogen in many patients [63]. Performing surveillance cultures for resistant organisms in vulnerable patient populations is part of the CDC recommendations “Management of Multidrug-Resistant Organisms in Healthcare Settings, 2006” [64], and has been vigorously advocated by some experts [65].

6.6.3 Late Infections: Streptococcus pneumoniae and Others

HCT recipients are at high risk for Streptococcus pneumoniae infections (2–8.6/1000 patients transplanted) [66, 67]. Both early and late (beyond day 100) pneumococcal disease has been reported, with late infections strongly associated with active cGVHD [46]. These have been attributed to inadequate antibody production and functional hypogammaglobulinemia [44, 67]. Vaccination against S. pneumoniae should be given to all HCT recipients, starting 3–6 months after transplant and using the 13-valent conjugate vaccine [9] (see Chap. 48 for details). Four doses of the vaccine result in enhanced antibody response and tolerable side effects [68]. Antibiotic prophylaxis against S. pneumoniae prophylaxis for adults with active cGVHD has been recommended [69], although there is only weak evidence supporting its efficacy. Penicillin V-K is safe and well tolerated, but the local patterns of penicillin resistance may make other antibiotics (e.g., trimethoprim, sulfamethoxazole, azithromycin, or levofloxacin) preferable, although their long-term safety is not well established.

Late bacterial infections often involve the respiratory tract. Pneumonia is the most common cause of fatal late infection [40, 70]. Chronic GVHD is the risk factor most commonly identified. Besides S. pneumoniae, multiple other pathogens have been reported. Nocardia also tends to occur...
late and in patients with cGVHD [71, 72]. Mycobacterial infections are uncommon and difficult to diagnose [73]. Risk factors for the development of active TB include GVHD, corticosteroid treatment, and total body irradiation (TBI) [74]. The need for universal testing for tuberculosis is controversial, given the unknown sensitivity and specificity of the tests in this population and the fact that tuberculosis is a relatively uncommon complication after HCT (albeit still approximately three times higher than in the general population) [74].

### 6.7 Risks and Epidemiology of Fungal Infections After Allogeneic HCT

It is necessary to separate invasive candidiasis and candidemia (often related to neutropenia or to the intravenous catheter) from invasive mold infection (of which invasive aspergillosis (IA) is by far the most frequent) [75] (Table 6-2). When deciding on a prophylaxis strategy, it is recommended to consider what kind of fungal infection one is trying to prevent.

Invasive candidiasis follows prior colonization and favorable conditions for the yeast: disruption of the GI mucosa during chemotherapy or acute GVHD, overgrowth in the presence of broad-spectrum antibiotics, and/or presence of indwelling catheters (the catheter seems to be the main risk factor in the case of *C. parapsilosis*). Early studies showed that fluconazole during the pre-engraftment period could decrease the incidence of invasive candidiasis [76, 77]. Accordingly, fluconazole is recommended as part of the standard prophylactic regimen during the pre-engraftment period. The prevalent use of fluconazole has resulted in substantial decrease in the incidence of infections caused by *C. albicans* with relative increases in the incidence of other species of Candida with decreased susceptibility to this agent (e.g., *C. glabrata*, *C. krusei*) [78].

Invasive aspergillosis occurs during specific “at risk” periods following HCT, with a first peak around the time of neutropenia pre-engraftment, a second peak between days 40 and 70 (the time of acute GVHD and its treatment), and a third peak late after transplant, usually in the midst of actively treated cGVHD [79] (Figure 6-1). A variety of risk factors for invasive aspergillosis have been identified over the years, but the most consistently found to be significant in multivariate analyses are acute GVHD, chronic extensive GVHD, and CMV disease [80-82]. Systemic corticosteroids are almost always present as part of the treatment of acute and chronic GVHD.

Non-aspergillus mold infections (e.g., fusariosis, mucormycosis, scedosporiosis), sometimes referred to as emerging mold infections, have been reported with increasing frequency [83]. The increased use of prophylaxis with activity against *Aspergillus* would be expected to result in a relative increase of other opportunistic mycoses like mucormycosis [84].

Considering the diversity of fungal infections after transplant and the current antifungal armamentarium, it is controversial which antifungal prophylaxis is appropriate at what point during transplant. For instance, although fluconazole is a safe and well-established intervention during the pre-engraftment period of myeloablative transplants [76, 77], it is reasonable to question how necessary it is in transplants with conditioning regimens that result in shorter neutropenia.

| Pathogen                | Risk factors                                      | Comment                                                                 |
|-------------------------|--------------------------------------------------|--------------------------------------------------------------------------|
| *Candida* spp.          | Neutropenia, mucositis, indwelling catheter, heavy colonization, TBI | Non-*albicans* Candida is increasing; *Candida albicans* breakthrough is usually associated with fluconazole resistance |
| *Aspergillus* spp.      | Prolonged neutropenia                            | Aspergillus is the most common mold infection in a proportion 7:1 to 9:1 in most series. Antifungal prophylaxis with voriconazole or echinocandins increases the likelihood of non-aspergillus molds |
| **Other molds**         |                                                  |                                                                          |
| *Mucomycosis* (formerly zygomycosis) | Prophylaxis with voriconazole                      | Simultaneous disease of sinuses and the lung was identified as suggestive of mucomycosis in a case–control study |
| *Fusarium* spp.         | HLA-mismatched transplant                         | Paronychia and positive blood cultures common                             |
| *Scedosporium* spp.     | Neutropenia, GVHD, environmental exposure, voriconazole | *Scedosporium prolificans* more invasive and refractory to treatment than *S. apiospermum* |
Micafungin showed to be equivalent to fluconazole in a randomized controlled trial [85], and the same question (what kind of transplant patient would benefit most) applies. Regarding the duration of antifungal prophylaxis, fluconazole up to day 75 posttransplant was associated with improved survival mainly due to decreased incidence of systemic candidiasis [86], but it is uncertain whether this strategy should be used for all patients or should be received for some selected subgroups considered at higher risk. Similarly, it is reasonable to question the indication for fluconazole during periods when the main fungal infection is aspergillosis. Several randomized controlled trials have compared fluconazole with anotherazole with activity against molds (itraconazole [87, 88], voriconazole [89], or posaconazole [90]) either as standard posttransplant prophylaxis or during periods of increased risk. The general conclusion of these trials is that the aspergillus-active drugs are, indeed, more effective than fluconazole in preventing IA, but the benefit in survival in the context of a clinical trial with careful monitoring of galactomannan antigen is hard to demonstrate [91]. The 2009 ASBMT/EBMT Guidelines recommend posaconazole or voriconazole as antifungal prophylaxis in the setting of GVHD and micafungin in the setting of prolonged neutropenia [1]. Of note, posaconazole prophylaxis was superior to fluconazole or itraconazole and improved survival in prolonged neutropenia in non-transplant patients [92]. Now, there are even more options of mold-active prophylaxis with posaconazole delayed-release tablets, intravenous posaconazole, and the new agent isavuconazole.

### 6.8 Risks and Epidemiology of Viral Infections After Allogeneic HCT

Viral infections remain a challenge because newer transplant modalities result in severe prolonged T cell immunodeficiency and because the current antiviral armamentarium is very limited. Multiple latent viruses may reactivate following HCT [93]. The role of monitoring by PCR is well defined mainly for CMV. Latent viral reactivation is of particular concern in recipients of cord [94] or T cell-depleted transplants. Table 6-3 presents a summary of this section.

#### 6.8.1 Herpesviruses

Members of the herpesvirus family that have caused significant disease after transplant include HSV-1, HSV-2, VZV, EBV, CMV, and HHV-6. Posttransplant complications of HHV-7 are not well defined, although multiple associations have been described. HHV-8 infection and disease (primary effusion lymphoma and Kaposi’s sarcoma) occur only infrequently after HCT.

##### 6.8.1.1 Herpes Simplex Virus

HSV-1 and HSV-2 may reactivate following the preparative regimen and complicate chemotherapy-induced mucositis, so it is customary to administer prophylaxis with acyclovir or valacyclovir at least until engraftment. In patients with common recurrences, long-term suppression may be appropriate.
### Table 6-3. Risk factors and epidemiology of viral infections after HCT

| Pathogen                          | Risk factors                                                                 | Comment                                                                                                                                 |
|-----------------------------------|------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| **Respiratory virus**             |                                                                              |                                                                                                                                        |
| Respiratory syncytial virus (RSV) | Pre-engraftment                                                              | Progression to pneumonia is associated with older age and lymphopenia                                                                 |
|                                   | Lymphopenia                                                                  | It may be less common in nonmyeloablative or reduced intensity transplants                                                             |
|                                   | Preexisting obstructive airway disease                                      |                                                                                                                                        |
| Parainfluenza                     | Unrelated donor (URD) transplant                                             | Progression to pneumonia (less common than in RSV) is associated with corticosteroid use and lymphopenia                                |
| Influenza                         | Advanced disease                                                             | Progression to pneumonia seems less in patients who are receiving corticosteroids                                                      |
|                                   | Female sex                                                                   |                                                                                                                                        |
|                                   | Transplantation during influenza season                                       |                                                                                                                                        |
| Adenovirus                        | Lymphopenia (T cell depletion), anti-T cell antibodies, umbilical cord blood transplants, mismatched transplants (other than DRB1), haploidentical transplants | Both reactivation of latent adenovirus and new infections occur. Plasma viremia is an important predictor of disease                    |
| Others (metapneumovirus rhinovirus, coronavirus, enterovirus, bocavirus) | Risk factors not well defined                                                |                                                                                                                                        |
| **Herpesvirus**                   |                                                                              |                                                                                                                                        |
| HSV                               | HSV + serology in the recipient                                              | Clinical reactivation of 25% in the first year after stopping acyclovir prophylaxis                                                    |
| Acyclovir-resistant HSV           | Low-dose prophylaxis                                                          | HCT recipients with multidermatomal zoster should be on airborne and contact precautions                                               |
|                                   | Intermittent treatment                                                       |                                                                                                                                        |
|                                   | HSV-seronegative donors                                                      |                                                                                                                                        |
| Varicella zoster virus (VZV)      | VZV + serology                                                               |                                                                                                                                        |
| CMV (early disease)              | CMV + serology in recipient                                                  | Rate of CMV infection in seronegative recipients of seropositive donor (R−/D+) is very low if leucodepleted products are used          |
|                                   | URD transplants and mismatched transplants (in some studies)                 |                                                                                                                                        |
|                                   | T cell depletion (Holmberg, 1999 #131)                                        |                                                                                                                                        |
| CMV (late disease)               | Chronic GVHD                                                                 |                                                                                                                                        |
|                                   | Corticosteroids                                                              |                                                                                                                                        |
|                                   | CD4+ lymphopenia (<50)                                                       |                                                                                                                                        |
|                                   | Unrelated transplants                                                        |                                                                                                                                        |
|                                   | Haploidentical transplants                                                   |                                                                                                                                        |
|                                   | Umbilical cord blood transplants                                             |                                                                                                                                        |
|                                   | T cell-depleted transplants                                                  |                                                                                                                                        |
| Epstein–Barr virus (EBV)-related posttransplant lymphoproliferative disorder (PTLD) | Profound T cell cytopenia                                                   |                                                                                                                                        |
|                                   | T cell depletion                                                             |                                                                                                                                        |
|                                   | Anti-T cell antibodies                                                       |                                                                                                                                        |
|                                   | UCB transplants                                                              |                                                                                                                                        |
|                                   | Haploidentical transplants                                                   |                                                                                                                                        |
| Human herpesvirus 6 (HHV-6)       | UCB                                                                          | Reactivation after transplant is very common; disease is rare; multiple disease associations described                                 |
|                                   | Unrelated donor transplant                                                   |                                                                                                                                        |
|                                   | Mismatched transplant                                                        |                                                                                                                                        |
|                                   | GVHD                                                                         |                                                                                                                                        |
| BK virus                          | Reactivation almost universal after allo-HCT                                  | High-level viremia associated with disease                                                                                           |

### 6.8.1.2 Varicella Zoster Virus

VZV predictably reactivates following transplant (approximately 25% in the first year), either as shingles, multidermatomal, disseminated, or even without a rash (“zoster sine herpete”). In patients who are at risk for VZV reactivation, the use of long-term acyclovir safely prevents the occurrence of VZV disease [95, 96], and currently it is recommended for at least 1 year following HCT.
6.8.1.3 Cytomegalovirus (CMV)

CMV remains latent in a variety of human cells. CMV-seropositive HCT recipients are at risk for CMV reactivation and disease after transplant. The term “CMV infection” is used to denote the presence of CMV in the blood detected by PCR or pp65 antigenemia [97]. Following reactivation, CMV may cause disease typically in the form of pneumonia and/or gastrointestinal disease (most commonly colitis). Other CMV diseases like retinitis or CNS involvement are rare after HCT but have been described: retinitis has been associated with high CMV viral load [98] sometimes in the context of chronic GVHD and CNS disease (encephalitis and ventriculitis), sometimes with resistant virus in the CNS [99, 100].

The risk for reactivation may be related to the presence of CMV-specific immunity in the donor. The rate of CMV infection in the donor–recipient (D/R) pairs often follows the progression D−/R+ > D+/R+ > D+/R− > D−/R−, suggesting that CMV-specific memory T cells administered with the stem cells may play a role in preventing reactivation and disease. CMV infection or disease in CMV-seronegative recipients of seronegative donors (R−/D−) is rare when leucodepleted or CMV-negative blood products are used [101].

Every transplant program must decide on a strategy to monitor CMV and prevent disease. Depending on a variety of factors, either universal prophylaxis with ganciclovir or foscarnet early therapy may be used. Both approaches resulted in similar overall mortality when compared in a randomized controlled trial, but universal prophylaxis was followed by higher viral loads of HHV-6 in plasma [102] and earlier had been reported to be associated with relatively less risk. Interestingly, the use of posttransplant cyclophosphamide to prevent GVHD seems to be associated with lower risk of PTLD [35]. Monitoring of EBV viral load by quantitative PCR is now recommended in those transplants considered at high risk. Preemptive management of increasing EBV viral load in patients at risk has been associated with good outcomes [111], although it is not clear when exactly this treatment should be given. A CT/PET may be useful to localize areas amenable to biopsy (Figure 6-2).

6.8.1.5 Human Herpesvirus 6

HHV-6 is acquired early in life, when it may cause roseola infantum and nonspecific febrile illnesses. It frequently reactivates following HCT. Using quantitative PCR, HHV-6 can often be detected in peripheral blood 2–5 weeks after transplant. Most of the time the reactivation seems to be asymptomatic [112], but a number of associations (rash, delayed engraftment, GVHD, thrombocytopenia, increased overall mortality) as well as actual clinicopathological entities (hepatitis, pneumonitis, encephalitis) have been described [113–115]. HHV-6 is possibly the most common cause of infectious encephalitis after HCT [116]. It seems to be particularly frequent after cord blood transplant. Cases of encephalitis tend to be accompanied by higher viral loads of HHV-6 in plasma [117], but the role of systematic monitoring of HHV-6 in plasma is unknown at this time, as reactivation seems much more common than disease [118] and attempts to use a preemptive strategy using foscarnet have not been successful [119]. The European Conference on Infections in Leukemia has proposed evidence-based guidelines to address the diagnostic and therapeutic uncertainties related to this infection [120].

6.8.2 Respiratory Viruses

Respiratory viruses, a heterogeneous group of virus that is responsible for most upper acute respiratory infections in normal hosts, result in significant morbidity and mortality after HCT, particularly during the first 3 months following transplant [121]. Even asymptomatic carriage of respiratory viruses at the time of transplant has been reported to result in increased risk of unfavorable outcomes [122]. Besides respiratory syncytial virus (RSV) [123], influenza, parainfluenza virus (PIV) [124], rhinovirus [125], and adenovirus, newly identified viruses including metapneumovirus [126], coronavirus [127], and bocavirus [128] have emerged as significant pathogens. These infections present significant risks both acutely and in the long term. During the acute infection, HCT recipients are at risk of developing viral pneumonia.
that sometimes progresses to respiratory insufficiency, mechanical ventilation and death, and also at risk of concomitant or secondary bacterial or fungal infections that are associated with increased mortality [124, 129, 130]. Long-term, there seems to be an association between early infection (pre-day 100) with some of these viruses (most notably PIV and RSV) and later development of chronic airflow obstruction [131]. The most significant risk factor overall for progression of these infections from the upper respiratory tract to the lungs seems to be lymphopenia [132]. Corticosteroid use seems to contribute to progression to pneumonia in RSV and parainfluenza infections but not so in influenza [129, 130] (see Table 6-3).

6.8.3 Adenovirus
Besides its role among the community-acquired respiratory virus, adenovirus may cause disease in transplant recipients following reactivation in the gastrointestinal tract followed by dissemination and end-organ damage [133]. De novo acquisition of adenovirus may also result in disseminated disease. There are more than 60 types of human adenovirus, with different tropisms and possibly varying susceptibilities to antiviral agents. They can cause a variety of diseases, including upper and lower respiratory tract infection, colitis, hemorrhagic cystitis (HC), nephropathy, and CNS disease. Systemic adenovirus disease seems to be more common in children, particularly in recipients of cord blood or T cell-depleted transplants [134–136]. Patients with GVHD on treatment with high-dose corticosteroids are also at risk (Figure 6-3). Some studies have documented that sustained high levels of adenoviremia are associated with disease [137]. It is not known yet whether a preemptive approach with cidofovir can successfully prevent disseminated disease and death [133, 138].

6.8.4 Polyomavirus: BK and JC Virus
6.8.4.1 BK Virus
BK virus infects 90% of humans by age 12. It predictably reactivates in most patients following HCT and causes hemorrhagic cystitis (HC) in a minority of them [139]. Detection of high levels of BK in the peripheral blood seems to correlate with the presence of BK-induced HC [140, 141]. In a
large study from the Fred Hutchinson Cancer Research Center (FHCRC), no association was found between BK virus-associated HC and lymphopenia, corticosteroid use, and GVHD—the typical risk factors for viral infections after HCT [140]. In contrast, other smaller studies have found an association with GVHD. The pathogenesis of this disease remains unexplained. BK-induced nephropathy, a common problem after kidney transplant, remains infrequent after HCT and does seem to be related to profound immunosuppression [142]. BK pneumonitis has also been described, but it is distinctly rare [143].

6.8.4.2 JC Virus

JC virus is also acquired by most people during childhood. In immunocompromised hosts, it may cause encephalitis (JC encephalitis, previously called progressive multifocal leukoencephalopathy (PML)) with multiple areas of demyelination without edema detectable by MRI. Some studies have suggested that detectable viral load after HCT may be more common than currently thought [144]. Ascertaining risk factors for this disease is difficult because some transplant recipients may have conditions known to be associated with it and also received medications like MMF, rituximab, or brentuximab, which have been associated with PML even in the absence of allo-HCT.

6.9 Risks and Epidemiology of Pneumocystis After Allogeneic HCT

PCP is an opportunistic infection of patients with profound cellular immunodeficiency, and prophylaxis is recommended after HCT. It is now relatively uncommon: 1.3–2.4% of
patients transplanted from several series [145, 146] Most cases seem to occur relatively late, after discontinuing prophylaxis or during periods of intensive immunosuppression for the treatment of GVHD [147]. Hypoxemia is characteristic at presentation. Atypical radiological manifestations, including nodular infiltrates and pleural effusions (in contrast to typical interstitial pneumonitis), are described frequently, as is the presence of co-pathogens [148]. The preferred prophylaxis is trimethoprim/sulfamethoxazole (TMP/SMX), and several dosing regimens are effective (one single-strength tablet daily, one double-strength tablet daily, or one double-strength tablet three times/week) [149]. TMP/SMX may be poorly tolerated because of hematologic toxicity, skin rash and/or gastrointestinal toxicity [150].

It is unclear which is the prophylaxis of choice if TMP/SMX cannot be used. Aerosolized pentamidine is convenient, obviates the problem of compliance, and is less toxic than dapsone and better tolerated than atovaquone. However, it has been reportedly associated with more failures than dapsone [150]. Dapsone seemed to be effective and well tolerated in one study [151] but not in another when it was given only three times per week [152]. Dapsone should not be given to patients with G6PD deficiency. Methemoglobinemia is a well-known complication of dapsone [153] that should be considered in the presence of unexplained shortness of breath. Atovaquone suspension 1500 mg/d may be used, but published experience in HSCT recipients is limited [154, 155]. Atovaquone is expensive and poor tolerance has made compliance for some patients difficult. Absorption is better in the presence of significant amount of fat, and breakthroughs are well documented.

FIGURE 6-4. Pneumocystis pneumonia. A 23-year-old man with Ph+ALL s/p matched sibling allo-HCT presented for his 1-year post-transplant visit complaining of worsening fever and cough over the last 2 weeks, despite oral levofloxacin. He was in complete remission. A month earlier, abnormal liver enzymes had prompted the initiation of sirolimus for suspected chronic GVHD. He was on prophylaxis with acyclovir and atovaquone. The CT showed multifocal infiltrates. The bronchoalveolar lavage showed abundant Pneumocystis. After 1 week of treatment with trimethoprim/sulfamethoxazole, the radiographic pattern became characteristic of pneumocystis pneumonia. Atovaquone failures are well documented. The radiographic features of PCP after allogeneic transplant may be atypical.

6.10 Risks and Epidemiology of Toxoplasmosis After Allogeneic HCT

Most cases of toxoplasmosis after HCT represent reactivation, although rare cases of transmission with bone marrow transplant have been suspected [157]. Recipients should be tested for anti-toxoplasma IgG antibody, and if they are found to be positive, prophylaxis is recommended. Rare cases of toxoplasmosis after HCT have occurred in seronegative recipients [158, 159]. The disease tends to occur within the first 6 months after transplant, but it can happen later in the presence of persistent immunosuppression [160–162]. The risk of toxoplasmosis varies with the type of transplant and the immunosuppression: cord blood and use of ATG were found to be risk factors for disease in a prospective study [162]; most cases in another series occurred in URD or mismatched transplants [107]. TMP/SMX as given for PCP prophylaxis is considered adequate to prevent toxoplasmosis, although there have been cases on HCT recipients who were receiving it [162]. The best alternative for patients who are intolerant to TMP/SMX is unknown. Dapsone and atovaquone showed some efficacy in HIV-infected patients and there is increasing experience after HCT [163], although failures have been reported. Other
regimens include clindamycin with pyrimethamine and leucovorin, pyrimethamine with sulfadiazine, or pyrimethamine and sulfadoxine and leucovorin [107]. If a reliable quantitative PCR assay is available, frequent monitoring and preemptive treatment may be appropriate, since PCR-detected reactivation seems to precede symptoms by 4–16 days [162]. Retrospective data suggest this strategy may result in improved outcome [164].

6.11 Summary

In summary, infections following HCT are frequently related to risk factors caused by the procedure itself. Neutropenia and mucositis predispose to bacterial infections. Prolonged neutropenia increases the likelihood of invasive fungal infection. GVHD and its treatment create the most important easily identifiable risk period for a variety of infectious complications, particularly mold infections. Profound, prolonged T cell immunodeficiency, present after T cell-depleted or cord blood transplants, is the main risk factor for viral problems like disseminated adenovirus disease or EBV-related PTLD.

Besides all these “procedure-related” risk factors, there are individual characteristics that only now are starting to be investigated and understood. Future epidemiological and basic studies will likely result in truly personalized prophylactic regimens that will increase the unquestionable benefits of antimicrobial prophylaxis and reduce the cost, both direct and indirect, associated with this life-saving practice.

References

1. Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant. 2009;15(10):1143–238.
2. Groll AH, Castagnola E, Cesaro S, Dalle JH, Engelhard D, Hope W, et al. Fourth European conference on infections in leukaemia (ECIL-4): guidelines for diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or allogeneic haemopoietic stem-cell transplantation. Lancet Oncol. 2014;15(8):e327–40.
3. Maertens J, Marchetti O, Herbrecht R, Cornely OA, Flückiger U, Frère P, et al. European guidelines for antifungal management in leukaemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3—2009 update. Bone Marrow Transplant. 2011;46(5):709–18.
4. Engelhard D, Mohty B, de la Camara R, Cordonnier C, Ljungman P. European guidelines for prevention and management of influenza in hematopoietic stem cell transplantation and leukemia patients: summary of ECIL-4 (2011), on behalf of ECIL, a joint venture of EBMRT, EORTC, ICHS, and ELN. Transpl Infect Dis. 2013;15(3):219–32.
5. Averbuch D, Cordonnier C, Livermore DM, Mikulska M, Orasch C, Viscoli C, et al. Targeted therapy against multi-resistant bacteria in leukemic and hematopoietic stem cell transplant recipients: guidelines of the 4th European conference on infections in leukemia (ECIL-4, 2011). Haematologica. 2013;98(12):1836–47.
6. Averbuch D, Orasch C, Cordonnier C, Livermore DM, Mikulska M, Viscoli C, et al. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European conference on infections in leukemia. Haematologica. 2013;98(12):1826–35.
7. Styczynski J, Reusser P, Einsele H, de la Camara R, Cordonnier C, Ward KN, et al. Management of HSV, VZV and EBV infections in patients with haematological malignancies and after SCT: guidelines from the second European conference on infections in leukemia. Bone Marrow Transplant. 2009;43(10):757–70.
8. Matthes-Martin S, Feuchtinger T, Shaw PJ, Engelhard D, Hirsch HH, Cordonnier C, et al. European guidelines for diagnosis and treatment of adenovirus infection in leukemia and stem cell transplantation: summary of ECIL-4 (2011). Transpl Infect Dis. 2012;14(6):555–63.
9. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58(3):e44–100.
10. Hilgendorf I, Freund M, Jilg W, Einsele H, Gea-Banacloche J, Greinix H, et al. Vaccination of allogeneic hematopoietic stem cell transplant recipients: report from the international consensus conference on clinical practice in chronic GVHD. Vaccine. 2011;29(16):2825–33.
11. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of America. Clin Infect Dis. 2011;52(4):e56–93.
12. Lehrnbecher T, Phillips R, Alexander S, Alvaro F, Carlesse F, Fisher B, et al. Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem-cell transplantation. J Clin Oncol. 2012;30(35):4427–38.
13. Cordonnier C, Maury S, Pautas C, Bastiè JN, Chehata S, Castaigne S, et al. Secondary antifungal prophylaxis with voriconazole to adhere to scheduled treatment in leukemic patients and stem cell transplant recipients. Bone Marrow Transplant. 2004;33(9):943–8.
14. Aki ZS, Sucak GT, Yeğin ZA, Güzel O, Erbaş G, Senol E. Hematopoietic stem cell transplantation in patients with active fungal infection: not a contraindication for transplantation. Transplant Proc. 2008;40(5):1579–85.
15. Liu F, Wu T, Wang JB, Cao XY, Yin YM, Zhao YL, Lu DP. Risk factors for recurrence of invasive fungal infection during secondary antifungal prophylaxis in allogeneic hematopoietic stem cell transplant recipients. Transpl Infect Dis. 2013;15(3):243–50.
16. Martino R, Parody R, Fukuda T, Maertens J, Theunissen K, Ho A, et al. Impact of the intensity of the pretransplantation conditioning regimen in patients with prior invasive aspergillosis undergoing allogeneic hematopoietic stem cell transplantation: a retrospective survey of the infectious diseases working party of the European group for blood and marrow transplantation. Blood. 2006;108(9):2928–36.
17. Bochud PY, Eggiman P, Calandra T, Van Melle G, Saghaﬁ L, Francioli P. Bacteremia due to viridans streptococcus in neutropenic patients with cancer: clinical spectrum and risk factors. Clin Infect Dis. 1994;18(1):25–31.
18. Mullighan CG, Healey SL, Danner S, Dean MM, Doherty K, Hahn U, et al. Mannose-binding lectin status is associated with risk of major infection following myeloablative sibling allogeneic hematopoietic stem cell transplantation. Blood. 2008;112(5):2120–8.
19. Harkensee C, Oka A, Onizuka M, Middleton PG, Inoko H, Nakaoka H, et al. Microsatellite scanning of the immunogenome associates MAPK14 and ELTD1 with graft-versus-host disease in hematopoietic stem cell transplantation. Immunogenetics. 2013;65(6):417–27.
20. Dickinson AM, Charron D. Non-HLA immunogenetics in hematopoietic stem cell transplantation. Curr Opin Immunol. 2005;17(5):517–25.
21. Zaia JA, Sun JY, Gallez-Hawkins GM, Thao L, Oki A, Lacey SF, et al. The effect of single and combined activating killer immunoglobulin-like receptor genotypes on cytomegalovirus infection and immunity after hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2009;15(3):315–25.
22. Gyurkoza B, Sandmaier BM. Conditioning regimens for hematopoietic cell transplantation: one size does not ﬁ t all. Blood. 2014;124(3):344–53.
23. Junghanss C, Marr KA, Carter RA, Sandmaier BM, Maris MB, Maloney DG, et al. Incidence and outcome of bacterial and fungal infections following nonmyeloablative compared with myeloablative allogeneic hematopoietic stem cell transplantation: a matched control study. Blood Marrow Transplant. 2002;8(9):512–20.
24. Spellman SR, Eapen M, Logan BR, Mueller C, Rubinstein P, Setterholm MI, et al. A perspective on the selection of unrelated donors and cord blood units for transplantation. Blood. 2012;120(2):259–65.
25. Luznik L, O’Donnell PV, Symons HI, Chen AR, Leffell MS, Zahurak M, et al. HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. Biol Blood Marrow Transplant. 2008;14(6):641–50.
26. Cieri N, Peccatori J. Tracking T cell dynamics in the ﬁ rst month after haplo-HSCT with post-transplant cyclophosphamide reveals a predominant contribution of memory stem T cells to the early phase of immune reconstitution. Blood. 2013;121(11):4615.
27. Safdar A, Rodriguez GH, De Lima MJ, Petropoulos D, Chemaly RF, Worth LL, et al. Infections in 100 cord blood transplantations: spectrum of early and late posttransplant infections in adult and pediatric patients 1996-2005. Medicine (Baltimore). 2007;86(6):324–33.
28. Martino R, Bautista G, Parody R, García I, Esquirol A, Rovira M, et al. Severe infections after single umbilical cord blood transplantation in adults with or without the co-infusion of CD34(+) cells from a third-party donor: results of a multicenter study from the grupo español de trasplante hematopoetico (GETH). Transpl Infect Dis. 2015;17(2):221–33.
29. Anasetti C, Logan BR, Lee SJ, Waller EK, Weisdorf DJ, Wingard JR, et al. Peripheral-blood stem cells versus bone marrow from unrelated donors. N Engl J Med. 2012;367(16):1487–96.
30. Kübler M, Anderlini P. Peripheral blood stem cell versus bone marrow allotransplantation: does the source of hematopoietic stem cells matter? Blood. 2001;98(10):2900–8.
31. Eyrieh M, Lang P, Lal S, Bader P, Handgretinger R, Klingebiel T, et al. A prospective analysis of the pattern of immune reconstitution in a paediatric cohort following transplantation of positively selected human leucocyte antigen-disparate haematopoietic stem cells from parental donors. Br J Haematol. 2001;114(2):422–32.
32. van Burik JA, Carter SL, Freifeld AG, High KP, Godder KT, Papanicolaou GA, et al. Higher risk of cytomegalovirus and aspergillus infections in recipients of T cell-depleted unrelated bone marrow: analysis of infectious complications in patients treated with T cell depletion versus immunosuppressive therapy to prevent graft-versus-host disease. Biol Blood Marrow Transplant. 2007;13(12):1487–98.
33. Pérez-Simon JA, Kottaridis PD, Martino R, Craddock C, Caballero D, Chopra R, et al. Nonmyeloablative transplantation with or without alemtuzumab: comparison between 2 prospective studies in patients with lymphoproliferative disorders. Blood. 2002;100(9):3121–7.
34. Marty FM, Bryar J, Browne SK, Schwarzbach T, Ho VT, Bassett IV, et al. Sirolimus-based graft-versus-host disease prophylaxis protects against cytomegalovirus reactivation after allogeneic hematopoietic stem cell transplantation: a cohort analysis. Blood. 2007;110(2):490–500.
35. Kanakry JA, Kasamon YL, Bolaños-Meade J, Borrello IM, Brodsky RA, Fuchs EJ, et al. Absence of post-transplantation lymphoproliferative disorder after allogeneic blood or marrow transplantation using post-transplantation cyclophosphamide as graft-versus-host disease prophylaxis. Biol Blood Marrow Transplant. 2013;19(10):1514–7.
36. Ferrara JL, Levy R, Chao NJ. Pathophysiological mechanisms of acute graft-versus-host disease. Biol Blood Marrow Transplant. 1999;5(6):347–56.
37. Chu YW, Gress RE. Murine models of chronic graft-versus-host disease: insights and unresolved issues. Biol Blood Marrow Transplant. 2008;14(4):365–78.
38. Boehm M, Nichols WG, Papanicolaou G, Rubin R, Wingard JR, Zaia J. Cytomegalovirus in hematopoietic stem cell transplant recipients: current status, known challenges, and future strategies. Biol Blood Marrow Transplant. 2003;9(9):543–58.
39. Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, et al. National institutes of health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant. 2005;11(12):945–56.
40. Bjorklund A, Aschan J, Labopin M, Remmerber M, Ringdén O, Wiiniarski J, Ljungman P. Risk factors for fatal infectious complications developing late after allogeneic stem cell transplantation. Bone Marrow Transplant. 2007;40(11):1055–62.
41. Yamasaki S, Heike Y, Mori S, Fukuda T, Maruyama D, Kato R, et al. 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. 2008;10(4):252–9.
42. Storek J, Witherspoon RP, Webb D, Storb R. Lack of B cells precursors in marrow transplant recipients with chronic graft-versus-host disease. Am J Hematol. 1996;52(2):82–9.
43. Storek J, Gooley T, Witherspoon RP, Sullivan KM, Storb R. Infectious morbidity in long-term survivors of allogeneic marrow transplantation is associated with low CD4 T cell counts. Am J Hematol. 1997;54(2):131–8.
44. Kalhs F, Panzer S, Kletterm M, Mayr E, Stain-Kos M, Walter R, et al. Functional asplenia after bone marrow transplantation. A late complication related to extensive chronic graft-versus-host disease. Ann Intern Med. 1988;109(6):461–4.
45. Dahut W, Georgiadis M. Pneumococcal arthriitis and functional asplenia after allogeneic bone marrow transplantation. Bone Marrow Transplant. 1995;15(1):161.
46. Kulkarni S, Powles R, Treleaven J, Riley U, Singhal S, Horton C, et al. Chronic graft versus host disease is associated with long-term risk for pneumococcal infections in recipients of bone marrow transplant. Blood. 2000;95(12):3683–6.
47. Arora M, Burns LJ, Davies SM, Macmillan ML, Defor TE, Miller WJ, Weisdorf DJ. Chronic graft-versus-host disease: a prospective cohort study. Biol Blood Marrow Transplant. 2003;9(1):38–45.
48. Martin PJ, Inamoto Y, Flowers ME, Carpenter PA. Secondary treatment of acute graft-versus-host disease: a critical review. Biol Blood Marrow Transplant. 2012;18(7):982–8.
49. Couriel D, Saliba R, Hicks K, Ippoliti C, de Lima M, Hosing C, et al. Tumor necrosis factor-alpha blockade for the treatment of acute GVHD. Blood. 2004;104(3):649–54.
50. Marty FM, Lee SJ, Fahey MM, Alyea EP, Soiffer RJ, Antin JH, Baden LR. Infliximab in use in patients with severe graft-versus-host disease and other emerging risk factors of non-candida invasive fungal infections in allogeneic hematopoietic stem cell transplant recipients: a cohort study. Blood. 2003;102(8):2768–76.
51. Carpenter PA, Appelbaum FR, Corey L, Deeg HJ, Doney K, Gooley T, et al. A humanized non-FcR-binding anti-CD3 antibody, visilizumab, for treatment of steroid-refractory acute graft-versus-host disease. Blood. 2002;99(8):2712–9.
52. Seeley WW, Marty FM, Holmes TM, Upchurch K, Soiffer RJ, Antin JH, et al. Post-transplant acute limbic encephalitis: clinical features and relationship to HHV6. Neurology. 2007;69(2):156–65.
53. Khandelwal P, Lawrence J, Filipovich AH, Davies SM, Blessing JJ, Jordan MB, et al. The successful use of alemtuzumab for treatment of steroid-refractory acute graft-versus-host disease in pediatric patients. Pediatr Transplant. 2014;18(1):94–102.
54. Srinivasan R, Chakrabarti S, Walsh T, Igarashi T, Takahashi Y, Kleiner D, et al. Improved survival in steroid-refractory acute graft versus host disease after non-myeloablative allogeneic transplantation using a daclizumab-based strategy with comprehensive infection prophylaxis. Br J Haematol. 2004;124(6):777–86.
55. Almyroudis NG, Fuller A, Jakubowski A, Sepkowitz K, Jaffe D, Small TN, et al. Pre- and post-engraftment bloodstream infection rates and associated mortality in allogeneic hematopoietic stem cell transplant recipients. Transpl Infect Dis. 2005;7(1):11–7.
56. Metzger KE, Rucker Y, Callaghan M, Churchill M, Jovanovic BD, Zembower TR, Bolon MK. The burden of mucosal barrier injury laboratory-confirmed bloodstream infection among hematology, oncology, and stem cell transplant patients. Infect Control Hosp Epidemiol. 2015;36(2):119–24.
57. Weinstock DM, Conlon M, Iovino C, Aubrey T, Gudiol C, Riedel E, et al. Colonization, bloodstream infection, and mortality caused by vancomycin-resistant enterococcus early after allogeneic hematopoietic stem cell transplant. Biol Blood Marrow Transplant. 2007;13(5):615–21.
58. Taur Y, Xavier JB, Lipuma L, Ubeda C, Goldberg J, Gobourne A, et al. Intestinal domination and the risk of bacteremia in patients undergoing allogeneic hematopoietic stem cell transplantation. Clin Infect Dis. 2012;55(7):905–14.
59. Bucanove G, Micozzi A, Menichetti F, Martino P, Dionisi MS, Martineili G, et al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. N Engl J Med. 2005;353(10):977–87.
development project on criteria for clinical trials in chronic graft-versus-host disease: V. The 2014 ancillary therapy and supportive care working group report. Biol Blood Marrow Transplant. 2015;21(7):1167–87.

70. Ochs L, Shu XO, Miller J, Enright H, Wagner J, Filipovich A, et al. Late infections after allogeneic bone marrow transplantations: comparison of incidence in related and unrelated donor transplant recipients. Blood. 1995;86(10):3979–86.

71. van Burik JA, Hackman RC, Nadeem SQ, Hiemzen JW, White MH, Flowers ME, Bowden RA. Nocardiosis after bone marrow transplantation: a retrospective study. Clin Infect Dis. 1997;24(6):1154–60.

72. Daly AS, McGeer A, Lipton JH. Systemic nocardiosis following allogeneic bone marrow transplantation. Transpl Infect Dis. 2003;5(1):16–20.

73. Cordonnier C, Martino R, Trabasso P, Held TK, Akan H, Ward MS, et al. Mycobacterial infection: a difficult and late diagnosis in stem cell transplant recipients. Clin Infect Dis. 2004;38(9):1229–36.

74. de la Cámara R, Martino R, Granados E, Rodriguez-Salvanés FJ, Rovira M, Cabrera R, et al. Tuberculosis after hematopoietic stem cell transplantation: incidence, clinical characteristics and outcome. Spanish group on infectious complications in hematopoietic transplantation. Bone Marrow Transplant. 2000;26(3):291–8.

75. Camps IR. Risk factors for invasive fungal infections in hematopoietic stem cell transplantation. Int J Antimicrob Agents. 2008;32 Suppl 2:S119–23.

76. Goodman JL, Winston DJ, Greenfield RA, Chandrasekar PH, Fox B, Kaizer H, et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. N Engl J Med. 1992;326(13):845–51.

77. Slavin MA, Osborne B, Adams R, Levenstein MJ, Schoch HG, Feldman AR, et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation—a prospective, randomized, double-blind study. J Infect Dis. 1995;171(6):1545–52.

78. Marr KA, Seidel K, White TC, Bowden RA. Candidemia in allogeneic blood and marrow transplant recipients: evolution of risk factors after the adoption of prophylactic fluconazole. J Infect Dis. 2000;181(1):309–16.

79. Wald A, Leisenring W, van Burik JA, Bowden RA. Epidemiology of aspergillus infections in a large cohort of patients undergoing bone marrow transplantation. J Infect Dis. 1997;175(6):1459–66.

80. Marr KA, Carter RA, Boechk M, Martin P, Corey L. Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. Blood. 2002;100(13):4358–66.

81. Fukuda T, Boechk M, Carter RA, Sandmaier BM, Maris MB, Maloney DG, et al. Invasive fungal infections in recipients of allogeneic hematopoietic stem cell transplantation after non-myeloablative conditioning: risks and outcomes. Blood. 2003;10:10.

82. Barnes PD, Marr KA. Risks, diagnosis and outcomes of invasive fungal infections in haematopoietic stem cell transplant recipients. Br J Haematol. 2007;139(4):519–31.

83. Corzo-León DE, Satlin MJ, Souve R, Shore TB, Schuetz AN, Jacobs SE, Walsh TJ. Epidemiology and outcomes of invasive fungal infections in allogeneic haematopoietic stem cell transplant recipients in the era of antifungal prophylaxis: a single-centre study with focus on emerging pathogens. Mycoses. 2015;58(6):325–36.

84. Kontoyiannis DP, Lionakis MS, Lewis RE, Chamilos G, Healy M, Perego C, et al. 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. 2005;191(8):1350–60.

85. van Burik JA, Ratanatharathorn V, Stepan DE, Miller CB, Lipton JH, Vesole DH, et al. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. Clin Infect Dis. 2004;39(10):1407–16.

86. Marr KA, Seidel K, Slavin MA, Bowden RA, Schoch HG, Flowers ME, et al. Prolonged fluconazole prophylaxis is associated with persistent protection against candidiasis-related death in allogeneic marrow transplant recipients: long-term follow-up of a randomized, placebo-controlled trial. Blood. 2000;96(6):2055–61.

87. Winston DJ, Mazarit RT, Chandrasekar PH, Lazarus HM, Goldman M, Blumer JL, et al. Intravenous and oral itraconazole versus intravenous and oral fluconazole for long-term antifungal prophylaxis in allogeneic hematopoietic stem-cell transplant recipients. A multicenter, randomized trial. Ann Intern Med. 2003;138(9):705–13.

88. Marr KA, Crippa F, Leisenring W, Hoyle M, Boechk M, Balajee SA, et al. Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants. Blood. 2004;103(4):1527–33.

89. Wingard JR, Carter SL, Walsh TJ, Kurtzberg J, Small TN, Baden LR, et al. Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. Blood. 2010;116(24):5111–8.

90. Ullmann AJ, Lipton JH, Vesole DH, Chandrasekar P, Langston A, Tarantolo SR, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med. 2007;356(3):335–47.

91. Ping B, Zhu Y, Gao Y, Yue C, Wu B. Second- versus first-generation azoles for antifungal prophylaxis in hematology patients: a systematic review and meta-analysis. Ann Hematol. 2013;92(6):831–9.

92. Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, et al. Posaconazole vs. fluconazole oritraconazole prophylaxis in patients with neutropenia. N Engl J Med. 2007;356(4):348–59.

93. Inazawa N, Horii T, Hatakeyama N, Yamamoto M, Yoto Y, Nojima M, et al. Large-scale multiplex polymerase chain reaction assay for diagnosis of viral reactivations after allogeneic hematopoietic stem cell transplantation. J Med Virol. 2015;87(8):1427–35.

94. Milano F, Pergam SA, Xie H, Leisenring WM, Gutman JA, Riffkin I, et al. Intensive strategy to prevent cytomegalovirus disease in seropositive umbilical cord blood transplant recipients. Blood. 2011;118(20):5689–96.

95. Boechk M, Kim HW, Flowers ME, Meyers JD, Bowden RA. Long-term acyclovir for prevention of varicella zoster virus disease after allogeneic hematopoietic cell transplantation—a randomized double-blind placebo-controlled study. Blood. 2006;107(5):1800–5.
96. Erard V, Wald A, Corey L, Leisenring WM, Boeckh M. Use of long-term suppressive acyclovir after hematopoietic stem-cell transplantation: impact on herpes simplex virus (HSV) disease and drug-resistant HSV disease. J Infect Dis. 2007;196(2):266–70.

97. Boeckh M, Gooley TA, Myerson D, Cunningham T, Schoch G, Bowden RA. Cytomegalovirus pp 65 antigenemia-guided early treatment with ganciclovir versus ganciclovir at enrollment after allogeneic marrow transplantation: a randomized double-blind study. Blood. 1996;88(10):4063–71.

98. Jeon S, Lee WK, Lee Y, Lee DG, Lee JW. Risk factors for cytomegalovirus retinitis in patients with cytomegalovirus viremia after hematopoietic stem cell transplantation. Ophthalmology. 2012;119(9):1892–8.

99. Reddy SM, Winston DJ, Territo MC, Schiller GJ. CMV central nervous system disease in stem-cell transplant recipients: an increasing complication of drug-resistant CMV infection and protracted immunodeficiency. Bone Marrow Transplant. 2010;45(6):979–84.

100. Jeong TD, Sung H, Choi SH, Lee SO, Yoon HK, Kim MN, Im HJ. Cytomegalovirus ventriculocerebralitis with compartmentalization of antiviral-resistant cytomegalovirus in a T cell-depleted haploidentical peripheral blood stem cell transplant recipient. Diagn Microbiol Infect Dis. 2012;74(3):307–10.

101. Nichols WG, Price TH, Gooley T, Corey L, Boeckh M. Transfusion-transmitted cytomegalovirus infection after receipt of leukoreduced blood products. Blood. 2003;101(10):4195–200.

102. Boeckh M, Bowden RA, Gooley T, Myerson D, Corey L. Successful modification of a pp 65 antigenemia-based early treatment strategy for prevention of cytomegalovirus disease in allogeneic marrow transplant recipients [letter]. Blood. 1999;93(5):1781–2.

103. Boeckh M, Leisenring W, Riddell SR, Bowden RA, Huang ML, Myerson D, et al. Late cytomegalovirus disease and mortality in recipients of allogeneic hematopoietic stem cell transplants: importance of viral load and t-cell immunity. Blood. 2003;101(2):407–14.

104. Boeckh M, Nichols WG, Chemaly RF, Papanicolaou GA, Wingard JR, Xie H, et al. Valganciclovir for the prevention of complications of late cytomegalovirus infection after allogeneic hematopoietic cell transplantation: a randomized trial. Ann Intern Med. 2015;162(1):1–10.

105. Ljungman P. The role of cytomegalovirus serostatus on outcome of hematopoietic stem cell transplantation. Curr Opin Hematol. 2014;21(6):466–9.

106. Singavi AK, Harrington AM, Fenske TS. Post-transplant lymphoproliferative disorders. Cancer Treat Res. 2015;165:305–27.

107. Foot AB, Garin YJ, Ribaud P, Devergie A, Derouin F, Gluckman E. Prophylaxis of toxoplasmosis infection with pyrimethamine/sulfadoxine (Fansidar) in bone marrow transplant recipients. Bone Marrow Transplant. 1994;14(2):241–5.

108. Landgren O, Gilbert ES, Rizzo JD, Socié G, Banks PM, Sobocinski KA, et al. Risk factors for lymphoproliferative disorders after allogeneic hematopoietic cell transplantation. Blood. 2009;113(20):4992–5001.

109. Sanz J, Arango M, Senent L, Jarque I, Montesinos P, Sempere A, et al. EBV-associated post-transplant lymphoproliferative disorder after umbilical cord blood transplantation in adults with hematological diseases. Bone Marrow Transplant. 2013;49(3):397–402.

110. Fox CP, Burns D, Parker AN, Peggs KS, Harvey CM, Natarajan S, et al. EBV-associated post-transplant lymphoproliferative disorder following in vivo t-cell-depleted allogeneic transplantation: clinical features, viral load correlates and prognostic factors in the rituximab era. Bone Marrow Transplant. 2013;11.

111. García-Cadenas I, Castillo N, Martino R, Barba P, Esquirol A, Novelli S, et al. Impact of Epstein Barr virus-related complications after high-risk allo-SCT in the era of pre-emptive rituximab. Bone Marrow Transplant. 2015;50(4):579–84.

112. Cone RW, Huang ML, Corey L, Zeh J, Ashley R, Bowden R. Human herpesvirus 6 infections after bone marrow transplantation: clinical and virologic manifestations. J Infect Dis. 1999;179(2):311–8.

113. Ljungman P, Wang FZ, Clark DA, Emery VC, Remberger M, Ringdén O, Linde A. High levels of human herpesvirus 6 DNA in peripheral blood leucocytes are correlated to platelet engraftment and disease in allogeneic stem cell transplant patients. Br J Haematol. 2000;111(3):774–81.

114. Zerr DM, Corey L, Kim HW, Huang ML, Nguy L, Boeckh M. Clinical outcomes of human herpesvirus 6 reactivation after hematopoietic stem cell transplantation. Clin Infect Dis. 2005;40(7):932–40.

115. Gotoh M, Yoshizawa S, Katagiri S, Suguro T, Asamo M, Kitahara T, et al. Human herpesvirus 6 reactivation on the 30th day after allogeneic hematopoietic stem cell transplantation can predict grade 2–4 acute graft-versus-host disease. Transpl Infect Dis. 2014;16(3):440–9.

116. Ogata M, Fukuda T, Teshima T. Human herpesvirus-6 encephalitis after allogeneic hematopoietic cell transplantation: what we do and do not know. Bone Marrow Transplant. 2015;50(8):1030–6.

117. Ogata M, Satou T, Kadota J-I, Saito N, Yoshida T, Okumura H, et al. Human herpesvirus 6 (HHV-6) reactivation and HHV-6 encephalitis after allogeneic hematopoietic cell transplantation: a multicenter, prospective study. Clin Infect Dis. 2013;57(5):671–81.

118. Olson AL, Dahi PB, Zheng J, Devlin SM, Lubin M, Gonzales AM, et al. Frequent human herpesvirus-6 viremia but low incidence of encephalitis in double-unit cord blood recipients transplanted without antithymocyte globulin. Biol Blood Marrow Transplant. 2014;20(6):787–93.

119. Ogata M, Satou T, Inoue Y, Takano K, Ikebe T, Ando T, et al. EBV-associated post-transplant lymphoproliferative disorder following in vivo t-cell-depleted allogeneic transplantation: breakthrough HHV-6 encephalitis following antiviral prophylaxis. Bone Marrow Transplant. 2013;48(2):257–64.

120. Ljungman P, de la Camara R, Cordonnier C, Einsele H, Engellard D, Reusser P, et al. 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. 2008;42(4):227–40.

121. Boeckh M. The challenge of respiratory virus infections in hematopoietic cell transplant recipients. Br J Haematol. 2008;143(4):545–67.

122. Campbell AP, Guthrie KA, En gland J, Farney RM, Minerich EL, Kuypers J, et al. Clinical outcomes associated...
with respiratory virus detection before allogeneic hematopoietic stem cell transplantation. Clin Infect Dis. 2015;61(2):192–202.

123. Waghamre A, Campbell AP, Xie H, Seo S, Kuyers J, Leisenring W, et al. Respiratory syncytial virus lower respiratory disease in hematopoietic cell transplant recipients: viral RNA detection in blood, antiviral treatment, and clinical outcomes. Clin Infect Dis. 2013;57(12):1731–41.

124. Nichols WG, Corey L, Gooley T, Davis C, Boeckh M. Parainfluenza virus infections after hematopoietic stem cell transplantation: risk factors, response to antiviral therapy, and effect on transplant outcome. Blood. 2001;98(3):573–8.

125. Ison MG, Hayden FG, Kaiser L, Corey L, Boeckh M. Rhinovirus infections in hematopoietic stem cell transplant recipients with pneumonia. Clin Infect Dis. 2003;36(9):1139–43.

126. Renaud C, Xie H, Seo S, Kuyers J, Cent A, Corey L, et al. Mortality rates of human metapneumovirus and respiratory syncytial virus lower respiratory tract infections in hematopoietic stem cell transplantation recipients. Biol Blood Marrow Transplant. 2013;19(8):1220–6.

127. Milano F, Campbell AP, Guthrie KA, Kuyers J, Englund JA, Corey L, Boeckh M. Human rhinovirus and coronavirus detection among allogeneic hematopoietic stem cell transplantation recipients. Blood. 2010;115(10):2088–94.

128. Schenk T, Strahm B, Kontny U, Hufnagel M, Neumann-Haefelin D, Falcone V. Disseminated bocavirus infection after stem cell transplant. Emerg Infect Dis. 2007;13(9):1425–7.

129. Nichols WG, Guthrie KA, Corey L, Boeckh M. Influenza infections after hematopoietic stem cell transplantation: risk factors, mortality, and the effect of antiviral therapy. Clin Infect Dis. 2004;39(9):1300–6.

130. Ustun C, Slabý J, Shanley RM, Vydra J, Smith AR, Wagner JE, et al. Human parainfluenza virus infection after hematopoietic stem cell transplantation: risk factors, management, mortality, and changes over time. Biol Blood Marrow Transplant. 2012;18(10):1580–8.

131. Erard V, Chien JW, Kim HW, Nichols WG, Flowers ME, Martin PJ, et al. Airflow decline after myeloablative allogeneic hematopoietic cell transplantation: the role of community respiratory viruses. J Infect Dis. 2006;193(12):1619–25.

132. Kim YJ, Guthrie KA, Waghamre A, Walsh EE, Falsey AR, Kuyers J, et al. Respiratory syncytial virus in hematopoietic cell transplant recipients: factors determining progression to lower respiratory tract disease. J Infect Dis. 2013;209(8):1195–204.

133. Feghoul L, Chevet S, Cuinet A, Dalle JH, Ouachée M, Yacouben K, et al. Adenovirus infection and disease in pediatric hematopoietic stem cell transplant patients: clues for antiviral preemptive treatment. Clin Microbiol Infect. 2015;21(7):701–19.

134. Myers GD, Krance RA, Weiss H, Kuehnle I, Demmler G, Heslop HE, Bollard CM. Adenovirus infection rates in pediatric recipients of alternate donor allogeneic bone marrow transplants receiving either antithymocyte globulin (ATG) or alemtuzumab (campath). Bone Marrow Transplant. 2005;36(11):1001–8.

135. Chakrabarti S, Mautner V, Osman H, Collingham KE, Fegan CD, Klapper PE, et al. Adenovirus infections following allogeneic stem cell transplantation: incidence and outcome in relation to graft manipulation, immunosuppression, and immune recovery. Blood. 2002;100(5):1619–27.

136. Symeonidis N, Jakubowski A, Pierre-Louis S, Jaffe D, Pamer E, Sepkowitz K, et al. Invasive adenoviral infections in t-cell-depleted allogeneic hematopoietic stem cell transplantation: high mortality in the era of cidofovir. Transpl Infect Dis. 2007;9(2):108–13.

137. Erard V, Huang ML, Ferrenberg J, Nguy L, Stevens-Ayers TL, Hackman RC, et al. Quantitative real-time polymerase chain reaction for detection of adenovirus after T cell-replete hematopoietic cell transplantation: viral load as a marker for invasive disease. Clin Infect Dis. 2007;45(8):958–65.

138. Ljungman P, Ribaud P, Eyrich M, Matthes-Martin S, Einsel H, Bleakley M, et al. Cidofovir for adenovirus infections after allogeneic hematopoietic stem cell transplantation: a survey by the infectious diseases working party of the European group for blood and marrow transplantation. Bone Marrow Transplant. 2003;31(6):481–6.

139. Dropulic LK, Jones RJ. Polymavirus BK infection in blood and marrow transplant recipients. Bone Marrow Transplant. 2008;41(1):11–8.

140. Erard V, Kim HW, Corey L, Limaye A, Huang ML, Myers D, et al. BK DNA viral load in plasma: evidence for an association with hemorrhagic cystitis in allogeneic hematopoietic cell transplant recipients. Blood. 2005;106(3):1130–2.

141. Oshrine B, Bunin N, Li Y, Furth S, Laskin BL, Kidney and bladder outcomes in children with hemorrhagic cystitis and BK virus infection after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2013;19(12):1702–7.

142. Verghese PS, Finn LS, Englund JA, Sanders JE, Hingorani SR. BK nephropathy in pediatric hematopoietic stem cell transplant recipients. Pediatr Transplant. 2009;13(7):913–8.

143. Yapa HM, McLornan DP, Raj K, Streetly M, Kazmí M, Cutthill K, et al. Pneumonitis post-haematopoietic stem cell transplant—cytopathology clinches diagnosis. J Clin Virol. 2012;55(3):278–81.

144. Wittmann T, Horowitz N, Benyamin N, Henig I, Zuckerman T, Rowe JM, et al. JC polyomavirus reactivation is common following allogeneic stem cell transplantation and its preemptive detection may prevent lethal complications. Bone Marrow Transplant. 2015;50(7):984–91.

145. Tuan IZ, Dennison D, Weisdorf DJ. Pneumocystis carinii pneumonitis following bone marrow transplantation. Blood. 2005;106(3):1130–2.

146. De Castro N, Neuville S, Sarfati C, Ribaud P, Derouin F, T, Rowe JM, et al. JC polyomavirus reactivation is common following allogeneic stem cell transplantation and its preemptive detection may prevent lethal complications. Bone Marrow Transplant. 2015;50(7):984–91.

147. Lyytikäinen O, Ruutu T, Volin L, Lautenschlager I, Jokipiö L, Tiittanen L, Ruutu P. Late onset pneumocystis carinii pneumonia following allogeneic bone marrow transplantation. Bone Marrow Transplant. 2003;31(6):481–6.

148. Torres HA, Chemaly RF, Storey R, Aiguëra EA, Nogueiras GM, Saldaña A, et al. Influence of type of cancer and hematopoietic stem cell transplantation on clinical presentation of pneumocystis jiroveci pneumonia in cancer patients. Eur J Clin Microbiol Infect Dis. 2006;25(6):382–8.

149. El-Sadr WM, Luskin-Hawk R, Yurik TM, Walker J, Abrams D, John SL, et al. A randomized trial of daily and thrice-weekly
trimethoprim-sulfamethoxazole for the prevention of pneumocystis carinii pneumonia in human immunodeficiency virus-infected persons. Terry beirn community programs for clinical research on AIDS (CPCRA). Clin Infect Dis. 1999;29(4):775–83.

150. Vasconcelles MJ, Bernardo MV, King C, Weller EA, Antin JH. Aerosolized pentamidine as pneumocystis prophylaxis after bone marrow transplantation is inferior to other regimens and is associated with decreased survival and an increased risk of other infections. Biol Blood Marrow Transplant. 2000;6(1):35–43.

151. Sangiolo D, Storl B, Nash R, Corey L, Davis C, Flowers M, et al. Toxicity and efficacy of daily dapsone as pneumocystis jiroveci prophylaxis after hematopoietic stem cell transplantation: a case-control study. Biol Blood Marrow Transplant. 2005;11(7):521–9.

152. Souza JP, Boeckh M, Gooley TA, Flowers ME, Crawford SW. High rates of pneumocystis carinii pneumonia in allogeneic blood and marrow transplant recipients receiving dapsone prophylaxis. Clin Infect Dis. 1999;29(6):1467–71.

153. Ash-Bernal R, Wise R, Wright SM. Acquired methemoglobinemia: a retrospective series of 138 cases at 2 teaching hospitals. Medicine (Baltimore). 2004;83(5):265–73.

154. Colby C, McAfee S, Sackstein R, Finkelstein D, Fishman J, Spitzer T. A prospective randomized trial comparing the toxicity and safety of atovaquone with trimethoprim/sulfamethoxazole as pneumocystis carinii pneumonia prophylaxis following autologous peripheral blood stem cell transplantation. Bone Marrow Transplant. 1999;24(8):897–902.

155. Chan C, Montaner J, Lefebvre EA, Morey G, Dohn M, McIvor RA, et al. Atovaquone suspension compared with aerosolized pentamidine for prevention of pneumocystis carinii pneumonia in human immunodeficiency virus-infected subjects intolerant of trimethoprim or sulfonamides. J Infect Dis. 1999;180(2):369–76.

156. Gea-Banacloche J, Masur H, Arns da Cunha C, Chiller T, Kirchhoff LV, et al. Regionally limited or rare infections: prevention after hematopoietic cell transplantation. Bone Marrow Transplant. 2009;44(8):489–94.

157. Jurges E, Young Y, Eltumi M, Holliman RE, Vellodi A, Rogers TR, Hobbs JR. Transmission of toxoplasmosis by bone marrow transplant associated with campath-1g. Bone Marrow Transplant. 1992;9(1):65–6.

158. Chandrasekar PH, Monin F. Disseminated toxoplasmosis in marrow recipients: a report of three cases and a review of the literature. Bone marrow transplant team. Bone Marrow Transplant. 1997;19(7):685–9.

159. Osthoff M, Chew E, Bajel A, Kelsey G, Panek-Hudson Y, Mason K, et al. Disseminated toxoplasmosis after allogeneic stem cell transplantation in a seronegative recipient. Transpl Infect Dis. 2013;15(1):E14–9.

160. Martino R, Maertens J, Bretagne S, Rovira M, Deconinck E, Ullmann AJ, et al. Toxoplasmosis after hematopoietic stem cell transplantation. Clin Infect Dis. 2000;31(5):1188–95.

161. Martino R, Bretagne S, Rovira M, Ullmann AJ, Maertens J, Held T, et al. Toxoplasmosis after hematopoietic stem transplantation. Report of a 5-year survey from the infectious diseases working party of the European group for blood and marrow transplantation. Bone Marrow Transplant. 2000;25(10):1111–4.

162. Martino R, Bretagne S, Einsele H, Maertens J, Ullmann AJ, Parody R, et al. Early detection of toxoplasma infection by molecular monitoring of toxoplasma gondii in peripheral blood samples after allogeneic stem cell transplantation. Clin Infect Dis. 2005;40(1):67–78.

163. Mendorf A, Klyuchnikov E, Langebrake C, Rohde H, Ayuk F, Regier M, et al. Atovaquone for prophylaxis of toxoplasmosis after allogeneic hematopoietic stem cell transplantation. Acta Haematol. 2015;134(3):146–54.

164. Robert-Gangneux F, Sterkers Y, Yera H, Accoceberry I, Menotti J, Cassaing S, et al. Molecular diagnosis of toxoplasmosis in immunocompromised patients: a three-year multicenter retrospective study. J Clin Microbiol. 2015;53(5):1677–84.