6

Risks and Epidemiology of Infections After Hematopoietic Stem Cell Transplantation

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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.

TABLE 6-1. Type of transplant and infectious disease risk

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, immune 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 (posttransplant immunosuppression)	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
	Immunosuppressive agents	Differences between pharmacological immunosuppressive regimens are not well defined; sirolimus may be associated with less CMV reactivation

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.

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 locus (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 ($>3 \times 10^6$ 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 $<1 \times 10^5$ 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, Immunosuppressive 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 12.5×10^3 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 is 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 hyposplenism [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.

TABLE 6-2. Risk factors and epidemiology of fungal infections after HCT

| Pathogen	Risk factors	Comment
Candida spp.	Neutropenia, mucositis, indwelling catheter, heavy colonization, TBI	Non-*albican*s *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
	Type of transplant: cord blood, T cell depletion, partially matched transplant	Not all species of *Aspergillu*s are equally invasive or equally susceptible to antifungal agents
	GVHD, acute GVHD and chronic extensive GVHD; systemic corticosteroids	
	CMV disease	
Other molds		
Mucormycosis (formerly zygomycosis)	Prophylaxis with voriconazole	Simultaneous disease of sinuses and the lung was identified as suggestive of mucormycosis in a case–control study
Fusarium spp.	HLA-mismatched transplant	Paronychia and positive blood cultures common
	Prolonged neutropenia	
	Smoking	
Scedosporium spp.	Neutropenia, GVHD, environmental exposure, voriconazole	*Scedosporium prolificans* more invasive and refractory to treatment than *S. apiospermum*
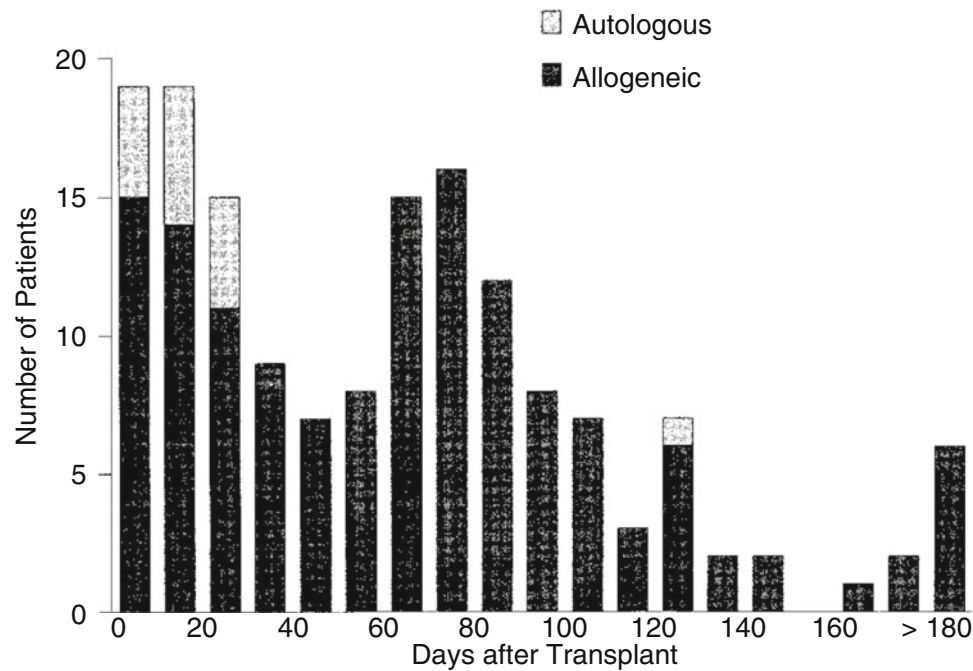
FIGURE 6-1. Time from transplant to diagnosis of aspergillosis in days (From Wald A, Leisenring W, van Burik JA, Bowden RA. Epidemiology of aspergillus infections in a large cohort of patients undergoing bone marrow transplantation. J Infect Dis 1997, Jun;175(6):1459–66, with permission).

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 another azole 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
	CD4+ 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
	Refractory GVHD	
	GVHD on corticosteroids	
Others (metapneumovirus rhinovirus, coronavirus, enterovirus, bocavirus)	Risk factors not well defined	
Herpesvirus		
HSV	HSV + serology in the recipient	
Acyclovir-resistant HSV	Low-dose prophylaxis	
	Intermittent treatment	
	HSV-seronegative donors	
Varicella zoster virus (VZV)	VZV + serology	Clinical reactivation of 25% in the first year after stopping acyclovir prophylaxis
		HCT recipients with multidermatomal zoster should be on airborne and contact precautions
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 $D-/R+ > D+/R+ \gg D+/R- > D-/R-$, 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 up to day 100 or a preemptive strategy of weekly monitoring and 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 more cases of late CMV disease [97, 102]. Late CMV disease has emerged as a significant problem, as it occurs when patients are not being under close monitoring by the transplant center. Risk factors include lymphopenia and chronic GVHD [103]. Preventing late CMV disease may be accomplished by either prophylaxis with valganciclovir or the preemptive approach with weekly CMV PCR monitoring [104]. The effect of CMV serostatus of donor and recipient on overall survival is complex (for a review, see [105] and Chap. 24).

6.8.1.4 Epstein–Barr Virus and Posttransplant Lymphoproliferative Disorder

PTLD is a spectrum of lymphoid proliferations that may happen after solid organ or allogeneic stem cell transplantation, usually (but not always) driven by EBV [106]. Pathologically the spectrum goes from polymorphic, polyclonal tissue infiltration of lymphocytes to monomorphic involvement with high-grade B cell lymphoma. After allogeneic HCT, the proliferating cells may be from donor (most commonly) or recipient origin. This disorder is typically related to insufficient or abnormal T cell responses against EBV [107], and accordingly it is more common in the setting of HLA-mismatched transplants, T cell depletion, or intense immunosuppression for the treatment of GVHD [108–110]. Some cases have followed the use of alemtuzumab for in vivo T cell depletion or GVHD prophylaxis [110], despite the fact that anti-CD52 also results in depletion of B cells 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
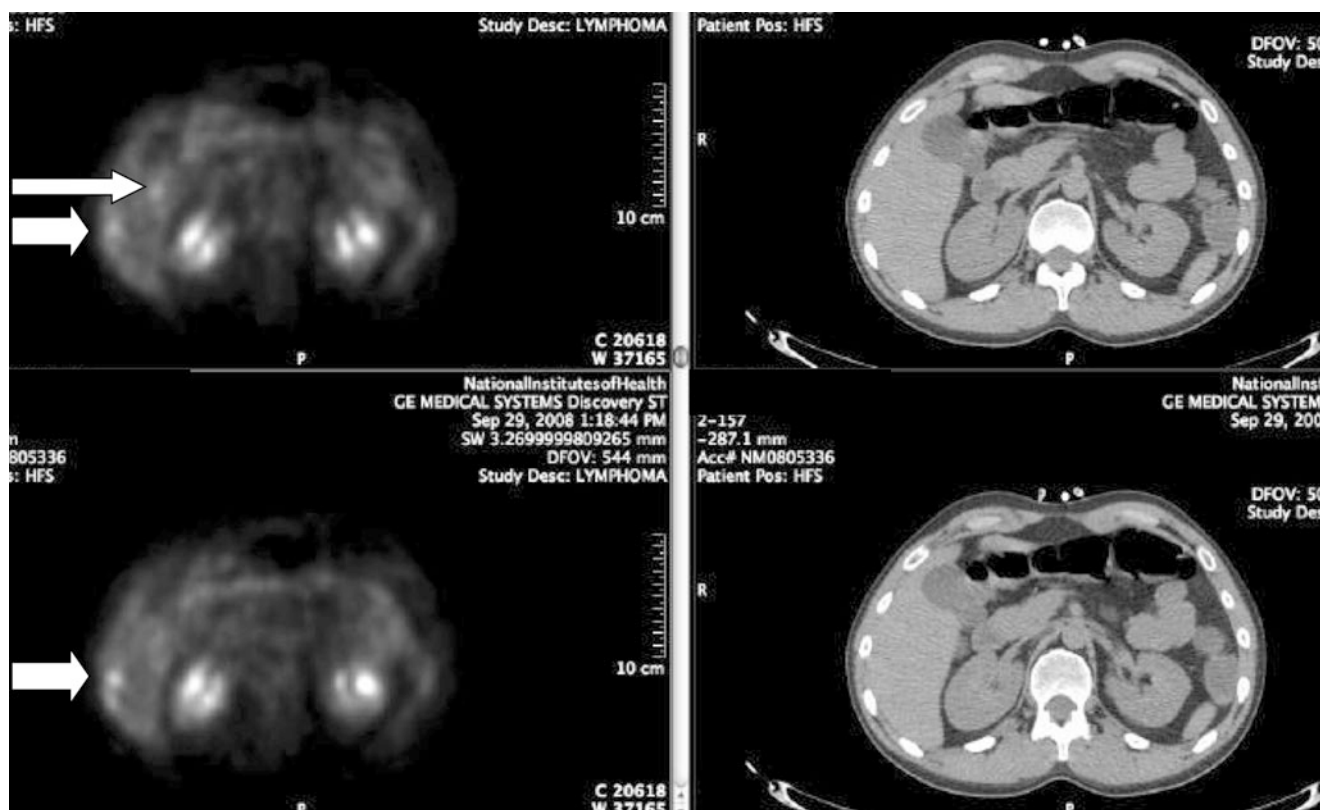
FIGURE 6-2. EBV-related lymphoproliferative disorder after a matched unrelated donor transplant. A 24-year-old man with Hodgkin lymphoma underwent a syngeneic HCT followed by MUD HCT (cyclophosphamide + fludarabine followed by alemtuzumab and cyclosporine). His day-28 CT/PET showed a mixed response: improvement in the intrathoracic lesions and cervical lymph nodes but appearance of new PET+ lesions in the liver, pharynx, and stomach. EBV viral load had been increasing slowly. Biopsies of the PET+ liver and stomach lesions showed a polyclonal EBV+ B cell infiltrate. The disease responded to rituximab and cyclosporine taper.

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]. Longterm, 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 dif-

ferent 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
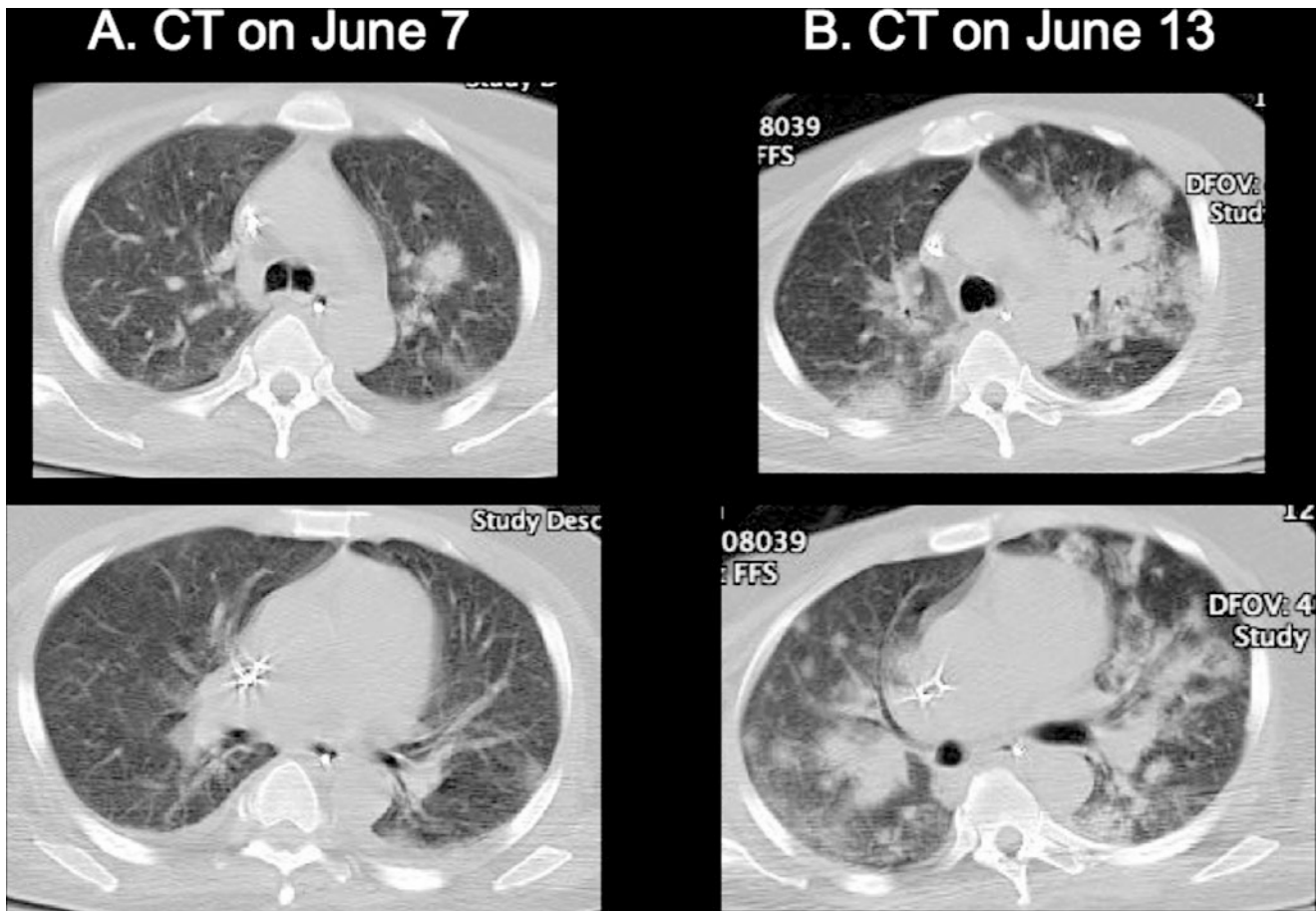
FIGURE 6-3. Adenovirus pneumonia in the setting of disseminated disease. A 48-year-old man received HLA-matched sibling donor non-myeloablative HCT for myelodysplastic syndrome in transformation. Leukemia recurred immediately after transplant. He received several donor lymphocyte infusions/stem cell boosts and then induction treatment for AML with FLAG (fludarabine + cytarabine + G-CSF) followed by donor stem cells. Graft-versus-host disease involving the skin and gut had been documented being treated with methylprednisolone 1 mg/kg/day. After the patient recovered from neutropenia, he developed spiking fever and progressive shortness of breath. Adenovirus was isolated from tears, respiratory secretions, and urine. PCR in the blood was positive for adenovirus, and the autopsy showed only disseminated adenovirus disease.

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 demyelin-ation 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
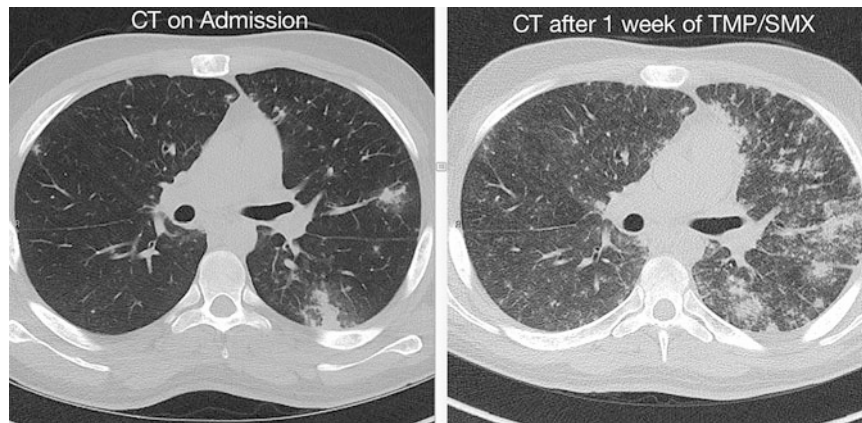
FIGURE 6-4. Pneumocystis pneumonia. A 23-year-old man with Ph+ALL s/p matched sibling allo-HCT presented for his 1-year post-transplant visit complaining of worsening fever and cough over the last 2 weeks, despite oral levofloxacin. He was in complete remission. A month earlier, abnormal liver enzymes 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.

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). PCP prophylaxis is recommended at least until all immunosuppression has been stopped but it is unclear how much longer to continue it [156].

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.

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