

# Chapter 19

## Infection in the Hematopoietic Stem Cell Transplant Recipient

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### Introduction

A number of factors interact to determine the risk of infection following HSCT: the underlying disease that led to the need for transplantation; the conditioning regimen employed; the source of the stem cells and preinfusion manipulations such as T cell depletion; the degree of histocompatibility mismatch between donor and recipient; the presence of latent recipient infections; the severity of GVHD that develops and the nature of the immunosuppressive program needed to prevent or treat GVHD; and the environmental exposures to which the recipient has been and will be subjected [1–4].

Environmental exposures of importance include both those experienced in the community and those encountered within the hospital (Table 19-1). Of particular concern are potential hospital exposures to opportunistic molds, *Legionella species*, and resistant gram-negative bacilli. Hospital exposures are further divided into domiciliary and nondomiciliary. Domiciliary exposures are those that occur in the room or on the ward where the patient is housed within the hospital – often there is clustering of cases in time and space [3–5]. Nondomiciliary nosocomial exposures occur when patients are taken to other sites in the hospital environment for procedures and are exposed to contaminated air and/or potable water at those times. Nondomiciliary exposures are more difficult to identify due to the lack of clear-cut clustering of cases, but are actually more common than domiciliary exposures, particularly with the widespread use of HEPA filters on transplant wards. In addition, HSCT recipients are at risk for person-to-person spread of such organisms as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, beta-lactamase producing gram-negative bacilli and azole-resistant yeast on the hands of medical personnel. Finally, as will be discussed subsequently, person-to-person spread of respiratory virus infection (e.g., influenza, respiratory syncytial virus (RSV), parainfluenza, and others) can have a major effect on HSCT patients [6].

**Table 19-1.** Infections in HSCT patients due to excessive environmental hazards.

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| Infections related to excessive nosocomial hazard   |
| <i>Aspergillus</i> species  |
| <i>Legionella</i> species   |
| <i>Pseudomonas aeruginosa</i> and other gram-negative bacilli                                       |
| <i>Nocardia asteroides</i>  |
| Infections related to particular exposures within the community                                     |
| Systemic mycotic infections in certain geographic areas   |
| <i>Histoplasma capsulatum</i>   |
| <i>Coccidioides immitis</i>   |
| <i>Blastomyces dermatidis</i>   |
| <i>Strongyloides stercoralis</i>  |
| Community-acquired opportunistic infection resulting from ubiquitous saprophytes in the environment |
| <i>Cryptococcus neoformans</i>  |
| <i>Aspergillus</i> species  |
| <i>Nocardia asteroides</i>  |
| <i>Pneumocystis jiroveci</i> (formerly <i>carinii</i> )   |
| Respiratory infections circulating in the community   |
| <i>Mycobacterium tuberculosis</i>   |
| Influenza   |
| Adenoviruses  |
| Parainfluenza   |
| Respiratory syncytial virus   |
| Infections acquired by the ingestion of contaminated food/water                                     |
| <i>Salmonella</i> species   |
| <i>Listeria monocytogenes</i>   |
| Enteric viruses (Rotavirus, Adenovirus, Norovirus, etc.)  |

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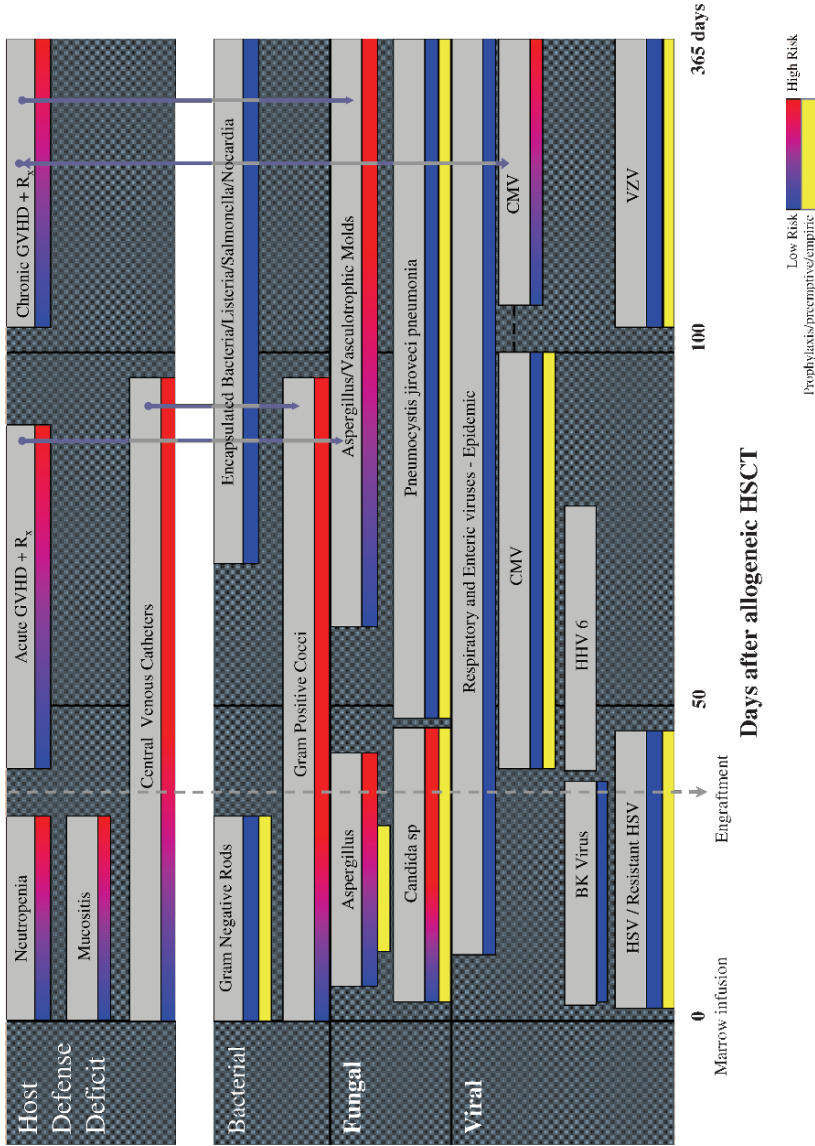
### Temporal Course of Infection Post-HSCT

There are three key elements of the HSCT procedure that determine the type and timing of the infectious risk profile after transplantation [1, 7]:<sup>1, 7</sup>

- a. The duration of neutropenia and mucosal injury which is a function of the conditioning regimen selected (myeloablative or not) and the stem cells' procurement (cord or adult; peripheral or bone marrow acquisition among adult donors).
- b. The strategy chosen to prevent GVHD among allogeneic recipients. T cell depletion and other T cell manipulation procedures lead to delayed recovery of lymphocyte function and provide a specific immune deficiency profile.
- c. The occurrence and severity of acute and chronic GVHD and its treatment [1, 7].

The temporal course of infection following HSCT can be divided into three time periods (Fig. 19-1) [1, 3, 4, 7]:

1. **Conditioning to Engraftment** The duration of this period has become dynamic and depends on the conditioning regimen itself, the source and



**Fig. 19-1.** Timetable of infection for allogeneic HSCT patients receiving antimicrobial prophylaxis. This table outlines the time period of the major host deficits and infections which occur during allogeneic HSCT in relation to when targeted pathogen-specific prophylaxis, preemptive and empiric therapies are deployed. Risk for infectious complications are temporally dependent and are significantly decreased in the setting of prophylactic, preemptive or empiric therapy. The risk of certain infections after transplantation is highly associated with ongoing immunologic manipulation as seen with the therapy for GVHD (linkages noted by vertical arrows).

CVL = central venous line, GVHD = Graft-versus-Host disease, GNR = gram-negative rods, GPC = gram-positive cocci, PCP = *Pneumocystis jiroveci* pneumonia, CMV = cytomegalovirus, HHV-6 = human herpes virus 6, HSV = herpes simplex virus, and VZV = varicella zoster virus.

Standard prophylactic considerations in this context include: GNR= fluoroquinolone or trimethoprim/sulfamethoxazole; *Candida* sp = fluconazole; PCP = trimethoprim/ sulfamethoxazole, atovaquone, dapsone, or pentamidine; and HSV/VZV = acyclovir. Standard empiric therapeutic considerations in this setting include: GNR = ceftazidime, piperacillin/gentamicin, or imipenem; aspergillus/molds/candida = amphotericin preparations or extended spectrum azoles, and CMV = IV ganciclovir, valganciclovir or preemptive monitoring (by antigenemia or PCR).

dose of stem cells infused and whether growth factors are used. It usually ranges from five (with nonmyeloablative transplants) to 30 days (with bone marrow or umbilical cord blood transplants). The combination of profound granulocytopenia and mucositis with myeloablative conditioning makes the patient particularly vulnerable to bacterial and candidal infections. In addition, infection present in the transplant recipient pre-transplant may be amplified by the granulocytopenic state and deficiencies of T and B-cell numbers and function. Thus, control of pre-transplant infection is needed before initiating the conditioning regimen. Prior to engraftment (both with autologous and allogeneic transplants), approximately 50 percent of patients will have fever of unknown origin, with bloodstream infection in ~12.5 percent and pneumonia in ~10 percent. The risk of an invasive mold infection is related to the duration of neutropenia and the environmental strategy used in a transplant center.

2. **Engraftment to Post-Transplant Day 100** During this time period viral infections, particularly cytomegalovirus (CMV) and the other herpes group viruses, are the major concerns. The occurrence, severity and treatment modalities selected for acute GVHD further modulates and increases the risk of herpesvirus infections, especially CMV and Epstein-Barr virus (EBV), and invasive mold infections [8–11].
3. **More than 100 Days Post-Transplant** In the absence of GVHD, the incidence of infection decreases significantly, with varicella zoster virus (VZV), *Pneumocystis jiroveci* (formerly *carinii*) pneumonia (PCP) and pneumococcal infection being the primary problems of this time period. Routine use of prophylaxis, such as with trimethoprim/sulfamethoxazole and acyclovir, significantly decreases the occurrence of PCP and herpesvirus infections, respectively. In addition, late or relapsing CMV infection may manifest during this time. If GVHD is present, it is typically treated with significant augmentation of immunosuppressive therapy such as with high-dose corticosteroids and monoclonal antibodies. Patients in this last category (GVHD under treatment) are at particular risk for invasive mold infection, CMV reactivation, PCP and other common and opportunistic pathogens.

## Principles of Antimicrobial Therapy in the HSCT Recipient

There are four modes in which antimicrobial therapy can be administered to the HSCT patient [4]:

1. A **therapeutic** mode, in which antimicrobial therapy is prescribed for the treatment and eradication of identified microbes causing clinical illness.
2. A **prophylactic** mode, in which antimicrobial therapy is prescribed to an entire population before an event to prevent clinically important infection. For such a strategy to be successful, the infection(s) being targeted must be important enough to justify the intervention, and the antimicrobial therapy prescribed must be nontoxic and inexpensive enough to justify the intervention. By far the most effective antimicrobial prophylactic strategy is low-dose trimethoprim-sulfamethoxazole, which has virtually eliminated the occurrence of *Pneumocystis jiroveci*, *Listeria monocytogenes*, *Nocardia sp*, and

*Toxoplasma gondii* in patients who adhere to the regimen. Other prophylactic strategies commonly utilized in HSCT patients include acyclovir to prevent herpes simplex virus (HSV) and VZV reactivation, fluoroquinolones [5] to prevent gram-negative sepsis and fluconazole to prevent yeast infection.

3. An **empiric** mode, in which antimicrobial therapy is administered in response to a symptom complex. In this context, empiric antimicrobial therapy is initiated during the period of profound granulocytopenia in response to fever +/- rigors or subtle signs of sepsis (unexplained hypotension, tachypnea, an ongoing volume requirement, or acidosis). In the patient deemed not to be a therapeutic emergency, initial therapy is usually aimed at aerobic gram-negative bacilli (e.g., the Enterobacteriaceae and *Pseudomonas aeruginosa*). A variety of drugs have been utilized for this purpose, depending in part on the nature of particular problem organisms found at a given medical center. Advanced spectrum beta-lactams (e.g., ceftazidime, piperacillin or imipenem), either alone or together with an aminoglycoside or a fluoroquinolone, are the mainstays of this approach. Thus, empiric therapy is based on an algorithm rather than on microbiologic or other studies.
4. A **preemptive** mode, in which antimicrobial therapy is prescribed to a proportion of patients deemed to be at particularly high risk because of clinical/epidemiologic information or the isolation of microbial pathogens. Examples of preemptive therapy in HSCT are the molecular surveillance of CMV linked to deployment of ganciclovir or, more recently, the use of galactomannan monitoring for initiation of anti-*Aspergillus* antifungal treatment [12].

## Bacterial Infections

Given the nature, duration and severity of host defense defects present in HSCT patients, it is not surprising that bacterial infection is a regular feature of the post-transplant course. The most common involved sites include blood stream (often catheter-related), lung, gastrointestinal tract and skin/soft tissue. The greatest rate of bacterial infections occur during the period prior to engraftment; this rate is a product of granulocytopenia, mucositis that permits the translocation of bacteria and yeast from the oral cavity and gut into circulation, and the presence of vascular access devices that traverse the skin and serve as direct conduits into the systemic circulation. Thus, the primary mucocutaneous barriers to infection are compromised, and the absence of granulocytes only amplifies the susceptibility of the patient [1, 4, 7].

In an attempt to decrease bacterial infections during the neutropenic period, especially those due to gram-negative bacilli, strategies of prophylactic antimicrobial use have been studied, including the use of trimethoprim-sulfamethoxazole and fluoroquinolones. Some studies, most recently with levofloxacin, have demonstrated benefit in decreasing the occurrence of fever and microbiologically-confirmed bacterial infections [13–15]. However, significant concerns regarding this approach have been raised given that no mortality benefit has been demonstrated, the emergence of resistant organisms, and the impairment this widespread antimicrobial approach has on the use of quinolones in future oral outpatient management. Thus, in many transplant centers, an empiric antibacterial regimen targeting *Pseudomonas*

and other *Enterobacteriaceae* in response to fever or other infectious syndromes remains a preferred approach.

Whereas gram-negative bacteremia was the major cause of blood stream infection 15 to 30 years ago, today gram-positive organisms are the most frequent cause of positive blood cultures. The possible reasons for this shift are many: the widespread use of fluoroquinolones, with their potent activity against gram-negative bacteria, as prophylaxis during this period; the presence of indwelling central venous catheters for prolonged periods; and the widespread use of systemic anti-gram-negative therapy all contribute to the gram-positive predominance. The bacteria isolated during the preengraftment period, then, include staphylococci (especially coagulase-negative *Staphylococcus*), viridans streptococci, enterococci and corynebacteria, with fewer isolates of *Enterobacteriaceae* or *Pseudomonas aeruginosa* being identified. An increasing problem in the HSCT population is antibiotic resistant organisms, particularly vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, and resistant gram-negative bacilli (such as extended spectrum  $\beta$ -lactamase producing *Klebsiella* and chromosomal inducible  $\beta$ -lactamase producing *Enterobacter species*) [1, 4, 6, 7, 16–20].

The typical approach for the severely granulocytopenic patient at present is the initiation of empiric antibacterial therapy in response to an unexplained fever or other signs of sepsis. What remains controversial is what the regimen should be. Since clinical deterioration can occur rapidly with untreated gram-negative sepsis in the granulocytopenic patient, anti-gram-negative therapy is always employed. The traditional approach of a  $\beta$ -lactam (e.g., piperacillin) plus an aminoglycoside is still favored by some experts, although nephrotoxicity from the aminoglycoside has led to the trial of other approaches, including the substitution of a fluoroquinolone for the aminoglycoside, or the prescription of a single advanced spectrum drug such as ceftazidime, cefepime, imipenem or meropenem. If fluoroquinolone prophylaxis has been utilized, then its use as a therapeutic agent may be diminished. Empiric fluoroquinolone monotherapy is inferior to other regimens, and if pure aerobic gram-negative agents are utilized, (e.g., aztreonam, aminoglycosides) due to confirmed severe beta-lactam hypersensitivity, then the addition of empiric gram-positive coverage that targets aerobic and anaerobic streptococci of the gastrointestinal tract should be considered. Use of extended interval (once-daily dosing) aminoglycoside administration may be safer and as effective.

The second area of controversy is whether empiric gram-positive treatment should be initiated at the same time, given the preponderance of gram-positive infection. As there is typically time to evaluate culture data and deploy targeted gram-positive antimicrobial therapy rather than empiricism, vancomycin should rarely be required empirically. Furthermore, empiric gram-positive coverage is not associated with better outcomes [21]. Indications for the immediate initiation of vancomycin as part of the empiric therapy regimen include the following [6, 16, 18–21]: catheter-related sepsis is likely because of evidence of infection at the insertion site (or within the tunnel), severe illness such as shock and/or respiratory distress are present, the patient is at particular risk for seeding of a prosthetic device (e.g., a prosthetic valve, a hip prosthesis, etc.), or the empiric gram-negative coverage exclusively covers aerobic gram-negative rods – such as the combination of

aztreonam and gentamicin. Vancomycin or other anti-staphylococcal agents should be started if cultures become positive for gram-positive cocci. In our experience, vancomycin can be discontinued safely in patients in whom vancomycin was started empirically, but in whom blood cultures remain negative after 48 to 72 hours and there is no specific syndrome, such as cellulitis, that requires treatment with vancomycin. On the other hand, empirical treatment against gram-negative organisms should be continued until resolution of neutropenia, whether fevers resolve or not [22]. The emergence and persistence of multidrug-resistant organisms should guide local practice in a dynamic fashion.

Indwelling long-term catheters remain a feature of the early post-transplant period to provide chemotherapy, nutritional and blood product support until stable engraftment. Routine anti-gram-positive antimicrobial therapy is not required just because a central catheter is in place for the prevention and management of catheter-related infections [21, 23]. The use of antimicrobial-coated catheters should be studied in this population, especially when non-tunneled catheters need to be used. Nonantimicrobial-based strategies to prevent bacterial infections during the neutropenic period include the systematic use of hand hygiene and the use of mask and gloves by health care personnel and family members. Other nonantimicrobial strategies which may be beneficial in preventing infections, but have not been tested in HSCT, include the use of palifermin to prevent mucositis [24] in patients undergoing myeloablative conditioning.

After engraftment, the risk of bacterial infections depend on the community exposures to common and opportunistic bacteria (e.g., *Nocardia*, *Rhodococcus*, *Listeria*), the presence of acute and chronic GVHD, the degree of B-cell reconstitution and the use of trimethoprim-sulfamethoxazole prophylaxis. Patients with chronic GVHD are at risk for invasive infection from encapsulated organisms, particularly *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis*. It is postulated that the combination of B lymphocyte dysfunction secondary to the conditioning regimen and the effects of GVHD and its treatment have resulted in the loss and failure to develop an opsonizing antibody to these organisms, particularly *Streptococcus pneumoniae*. In addition, for at least one to two years post-transplant, HSCT patients have an inadequate response to pneumococcal vaccine. As IgG levels are often low for some time after HSCT, they should be routinely monitored, with replacement being considered when the IgG level falls below 500mg/ml [25, 26]. In addition, antimicrobial prophylaxis, such as with low-dose trimethoprim-sulfamethoxazole (one single strength tablet daily for PCP prophylaxis), may afford further protection against this problem [1, 3].

## Viral Infections in HSCT Recipients

There are several classes of viral infection of particular importance in the HSCT recipient: those due to herpesviruses (CMV, EBV, HSV, VZV and human herpesvirus-6 [HHV-6]); those due to hepatitis viruses (e.g., hepatitis B [HBV]); those due to respiratory viruses (e.g., influenza, RSV, parainfluenza, adenoviruses, and others), and those due to polyoma viruses.

## Herpesvirus

The human herpesviruses share a number of characteristics that make them particularly successful pathogens in HSCT recipients [1, 4, 27]:

1. **Latency** Once infected with a herpesvirus, one is infected for life, with a circulating antibody (seropositivity) in the absence of active viral replication being the classic marker for latent infection. Reactivation from latency may be triggered by tumor necrosis factor (TNF), with the catecholamines epinephrine and norepinephrine and proinflammatory prostaglandins also playing a role. Thus, the virus may be reactivated by such processes as sepsis, GVHD, allogeneic reactions, OKT3 and antilymphocyte globulin. Once a replicating virus is present, medications such as cyclosporine, tacrolimus and prednisone may significantly amplify the viral replication.
2. **Cell Association** These viruses are highly cell-associated, meaning that transmission occurs through intimate person-to-person contact, or transfusion or transplantation of latently or actively replicating cells from a seropositive donor. Humoral immunity is, hence, less important than cell-mediated immunity. Indeed, the key host defense is accomplished by major histocompatibility complex (MHC)-restricted, virus-specific, cytotoxic T cells, just that component of host defense most affected by GVHD and its treatment.
3. **Oncogenesis** Herpesviruses, such as EBV and HHV-8, play a direct role in oncogenesis-causing post-transplant lymphoproliferative disease (PTLD) and Kaposi's sarcoma, respectively. Herpesviruses may also play an indirect role in oncogenesis with symptomatic CMV disease, increasing the incidence of EBV-associated PTLT severalfold.
4. **Indirect Effects** In addition to the direct causation of infectious disease syndromes, human herpesviruses, particularly CMV, have indirect effects that are clinically important. It is believed that cytokines, chemokines and growth factors produced in response to viral replication may be responsible for these effects. They include, in addition to the modulation of oncogenesis, increasing the net state of immunosuppression so that the risk of opportunistic infection is increased. This last point is particularly important, as a variety of experiments have shown that GVHD and infection are closely linked by the production of these mediators. That is, there is a bidirectional trafficking of mediators between these two processes.

## Cytomegalovirus

The clinically most important direct effects of CMV in the HSCT recipient are pneumonia and gastrointestinal disease. Before effective antiviral treatment became available, CMV pneumonia occurred in 20 to 30 percent of seropositive recipients and had an associated mortality around 80 percent [28]. CMV commonly causes fever in the absence of preemptive treatment, and end-organ disease (hepatitis, bone marrow dysfunction, retinitis, and encephalitis) may occur. Among allogeneic HSCT recipients, the risk of CMV reactivation (60–80%) and end-organ disease is greatest in the seropositive recipient who receives a graft from a CMV seronegative donor (CMV D–/R+), likely due to the loss of native immunity during the transplant process and immune reconstitution with a CMV naïve allograft [29, 30]. Patients who are CMV



D+/R+ have CMV reactivation (50–60%) and disease risk that is similar to or slightly lower than that of the CMV D–/R+ patient. Patients who are CMV D+/R– have a lower risk of CMV infection (10–30%) and disease, but higher than CMV D–/R– patients (<5%). The risk of CMV infection in this latter group has been greatly decreased by use of leukoreduced blood products or by exclusive use of CMV negative products when available [31]. The risks of CMV reactivation and disease among autologous HSCT recipients is minimal (<1%) [1, 4]. Another major risk factor for the development of CMV reactivation and disease is the occurrence, severity and treatment of acute GVHD [29, 30]. Other potential factors associated with an increased risk of CMV reactivation and disease are reception of T cell-depleted or cord blood allograft, whether the donor is unrelated or mismatched, or donated bone marrow (instead of peripheral stem cells), and whether the conditioning regimen was myeloablative [29, 32].

The most widely used therapy for clinical CMV disease is ganciclovir, which can be administered either intravenously or orally in the form of a prodrug, valganciclovir, with an acceptable bioavailability profile (~50–60%). Typically, the parenteral form is administered until the patient is able to tolerate oral therapy. Gastrointestinal absorption of valganciclovir, even in the setting of mild to moderate GI GVHD, has been demonstrated to be adequate [33, 34]. Duration of treatment depends on the clinical response and the nature of the recovery of native immune function. In the case of serious illness, particularly pneumonia, anti-CMV hyperimmune globulin can be considered as adjunctive therapy. Despite these efforts, the mortality from CMV pneumonia remains high. The major toxicity of ganciclovir is myelosuppression, so that great effort is placed in monitoring these patients closely and adjusting doses appropriately [1, 4]. Occasionally, G-CSF support may be required to preserve an acceptable neutrophil count and to allow adequate therapy of a serious CMV infection. While certain medications, such as ATG and OKT3, are likely to induce CMV reactivation, others like sirolimus may inhibit this [29].

Current strategies are based on preventing CMV disease through prophylaxis or preemption. Prophylaxis with ganciclovir from the time of engraftment until at least day 100 post-transplant has been studied in randomized trials [35, 36]. Although CMV viremia and disease were prevented, there was no overall benefit of this strategy due to secondary bacterial and fungal infections related to ganciclovir-induced neutropenia. Alternatively, a preemptive strategy is employed in which patients are monitored weekly for viremia through either a PCR assay for CMV DNA or an antigenemia assay. Positive results are linked to initiating ganciclovir or other antiviral drugs active against CMV. Typically, these assays turn positive several days to weeks prior to the onset of clinical disease, permitting the use of effective preemptive therapy [1, 4, 29, 33, 37–41]. A preemptive approach significantly decreases the amount of prophylactic medication used, thus minimizing medication-associated toxicity.

In the pre-ganciclovir era, CMV disease typically occurred during the first three months post-transplant. Increasingly, with the widespread use of a prophylactic or preemptive antiviral strategy, breakthrough occurs much later, typically one to three months after the cessation of the antiviral therapy. Risk factors for late CMV disease include chronic GVHD, low CD4-T cell counts, and CMV infection before day 100. Relapse or the emergence of ganciclovir-resistant virus also can occur, particularly in the face of high viral loads and

inadequate courses or dosing of ganciclovir. Foscarnet is the preferred drug in this setting or when further potential myelosuppression with ganciclovir is not advisable. The experience with cidofovir use in the HSCT population is limited. Both foscarnet and cidofovir are potentially nephrotoxic and should be administered with caution [1, 4]. Studies are examining the emerging strategies for the management of CMV infection and the use of CMV vaccines in donors and recipients, adoptive immunotherapy for patients with refractory or relapsing CMV infection and the use of maribavir for prophylaxis.

## Epstein-Barr Virus

The major recognizable clinical effect of EBV in the HSCT patient is in the pathogenesis of PTLD. Following the recovery from primary EBV infection (>95% of the adult population), ongoing lytic infection of B-cells occurs in the oropharynx, with latent infection of B-cells in the peripheral blood and lymphoid tissues. These latently infected cells can be transformed and immortalized, resulting in polyclonal proliferation. In the normal seropositive individual, these cells are kept in check by a specific cytotoxic T cell response. In the presence of immunosuppressive therapy, this surveillance system is inhibited in a dose-related fashion, thus permitting continued B-cell proliferation. Such ongoing proliferation results in particular clones being favored and the potential for developing cytogenetic abnormalities, which leads to the development of a truly malignant process- PTLD [1, 4, 27, 42].

The spectrum of clinical disease seen with PTLD is quite broad, ranging from a mononucleosis-like process or a polyclonal proliferation of lymphocytes that usually responds to decreasing immunosuppressive therapy, to a monoclonal, highly malignant B-cell lymphoma. The mononucleosis-like process is seen particularly in children with primary post-transplant EBV infection. The clinical presentation is one of fever, sore throat, cervical adenopathy and tonsillar hypertrophy and inflammation. Unlike B-cell lymphoma in the normal host, in the transplant patient, particularly the adult, the process can be extranodal. Thus, presentations may include central nervous system (CNS) invasion (from involvement of the meninges to focal cerebral lesions), liver, lung and bone marrow diseases. Not uncommonly, involvement of the gut (particularly the small bowel) may lead to recognition of the PTLD, with a clinical presentation of small bowel obstruction, perforation, or occult gastrointestinal bleeding. Disseminated, multi-organ disease is quite common in the HSCT patient [1, 4, 41, 42].

Risk factors for developing PTLD include: primary EBV infection in association with high-dose immunosuppression; interventions such as T cell depletion, umbilical cord blood transplant and the systemic administration of anti-thymocyte globulin increase the risk significantly; and intensive immunosuppression that results in suppression of the key host defense against EBV-transformed cells (MHC-restricted, EBV-specific, cytotoxic T cells) significantly increases the risk of PTLD. In addition to the host characteristics mentioned, high EBV viral loads correlate with an increased risk of PTLD. It has been suggested that EBV viral load surveillance in peripheral blood be carried out in high risk patients (those with primary

EBV infection, anti-T cell antibody therapy for GVHD, HLA-mismatched or T cell-depleted HSCT recipients), with decreased immunosuppression +/- antiviral therapy (acyclovir or ganciclovir) carried out in the setting of high viral loads [1, 4, 41, 42].

Treatment of PTLD remains controversial. All patients with diagnosed PTLD should have a significant decrease in immunosuppressive medications. Many centers also prescribe antiviral therapy. Patients not responding to these measures are usually treated with an anti-B-cell monoclonal antibody (rituximab, an anti-CD20 monoclonal antibody) [43, 44]. After that, therapies have ranged from anti-lymphoma chemotherapy to alpha-interferon and intravenous gamma globulin.

## Herpes Simplex Virus

HSV infection prior to the introduction of acyclovir was a major problem in the HSCT recipient. Occurring in the preengraftment period, HSV infection greatly exacerbated the severity of mucositis. Not only were ulcers observed in the oral cavity and anogenital areas, ulcerations of the esophagus, stomach and intestine were also observed. HSV pneumonia was also noted, with rare cases of cutaneous dissemination and encephalitis. The current standard of care is to test all candidates for HSCT for an antibody to HSV, with seropositive individuals then placed on antiviral prophylaxis, beginning prior to HSCT. Effective agents for HSV prophylaxis include acyclovir (intravenous or oral), valacyclovir or famciclovir. Recurrence of HSV may occur later in the course, and should again be treated with an acyclovir regimen, with repeated episodes justifying long-term prophylaxis. Acyclovir resistance is uncommon in this situation, but can occur, and requires treatment with foscarnet [1, 4].

## Varicella Zoster Virus

All patients and donors should have serologic testing for VZV prior to transplant. Seronegative individuals post-transplant should avoid exposures to VZV, but if such an exposure occurs, valacyclovir or varicella hyperimmune globulin should be promptly initiated. Before universal prophylaxis with acyclovir became standard, an estimated 40 percent of HSCT patients developed active VZV, with a median time of onset being five months post-transplant. The great majority of these patients had zoster, but approximately 20 percent had a more generalized process resembling primary varicella. A significant concern was visceral involvement in the setting of disseminated disease as well as neurologic complications such as myelitis or encephalitis [1, 45–48]. Prophylaxis with acyclovir in the early period post-transplantation substantially decreases the occurrence of herpesvirus infections, including VZV, and is rarely, if ever, seen during acyclovir prophylaxis. Prophylaxis is typically given for the first year post-allogeneic transplantation. VZV reactivation is often seen three months post-discontinuation of prophylaxis. As the VZV vaccine is a live attenuated viral vaccine, its use is contraindicated for at least two years post-transplantation, and unless a research study or close follow-up is involved, should be omitted.

## Human Herpesvirus-6

HHV-6 is a  $\beta$ -herpesvirus (as is CMV) whose role in post-transplant complications is being defined. In the great majority of instances, HHV-6 primary infection occurs by the third year of life, with a seroprevalence rate of 90 percent at one year, and close to 100 percent at three years [49, 50]. The clinical effects associated with primary HHV-6 infection include exanthem subitum (roseola), and a form of encephalitis. In HSCT patients, bone marrow suppression, especially delayed platelet engraftment, and encephalitis have been associated with HHV-6 type B. The encephalitis typically occurs one to two months after transplantation and is associated with profound memory loss, especially short-term memory, and MRI changes in the mesial temporal lobes (limbic encephalitis) [51, 52]. The highest risk patients for this complication are male, umbilical cord blood recipients for whom the attack rate may be as high as 10 to 20 percent. Detecting HHV-6 DNA in the blood of allogeneic HSCT recipients is a common phenomenon occurring transiently in 40 to 60 percent of patients, yet encephalitis is a rather infrequent occurrence (1–2%). As obtaining brain biopsies is not usually feasible early after transplantation, the diagnosis of HHV-6 encephalitis is currently achieved by developing an acute limbic encephalitis syndrome, confirmed with MRI imaging of the brain and by the detection of HHV-6 in the CSF [52]. It remains unclear what the treatment of choice for this virus is. One approach that we currently favor is to use foscarnet. It is possible that anti-CMV preventative strategies with ganciclovir may have a beneficial effect on this virus as well [1, 53].

## Respiratory Viruses

HSCT recipients are at significant risk for infection with respiratory viruses circulating in the community. These infections can occur at any time in the post-transplant course, and can be acquired in the community or during hospitalization from infected staff, family and friends. Overall, an estimated 10 to 20 percent of HSCT patients will become infected in the first year post-transplant, with the potential for this figure to rise significantly in the setting of a community-wide outbreak [54]. The dilemma for the clinician is how to prevent these infections, as there is a far higher rate of progression to pneumonia (viral and/or bacterial or fungal superinfection), which carries a far higher morbidity and mortality than what is observed in the general population. In addition, antiviral therapy for these agents is in its infancy. It is important to attempt to make an etiologic diagnosis. Avoiding exposure to infected individuals by systematic infection control measures in both family members and friends, but most importantly in health care workers, is the best preventative strategy available [55–58].

## Respiratory Syncytial Virus

Although RSV can be acquired by inhaling an aerosol, direct contact with infected secretions is the usual mode of spread between individuals. In the HSCT patient, both adult and pediatric, RSV is a cause of significant morbidity and mortality. The illness begins with the signs and symptoms of a viral upper

respiratory tract infection (rhinorrhea, sinus congestion, sore throat and/or otitis media), that may progress to pneumonia, especially if the virus is acquired in the preengraftment phase. As with influenza, pneumonic syndromes can be due to RSV itself, but in our experience it is more frequently due to secondary bacterial and fungal infections. The advent of rapid RSV diagnosis by antigen detection in nasopharyngeal swabs has resulted in the recognition that RSV is a significant pathogen for both adults and children, particularly in immunosuppressed patients. Optimal antiviral management, however, remains unclear. There are reports that aerosolized ribavirin +/- anti-RSV polyclonal or monoclonal antibody may have therapeutic benefit, but this remains unproven. There is also interest in prophylaxis with an anti-RSV antibody, although there have been no trials in HSCT patients [55–59].

## **Influenza**

As with RSV, the incidence of influenza infection in HSCT patients reflects the level of influenza activity in the community. The impact of this virus on infected HSCT recipients is demonstrated by the following statistics: ~60 percent of the patients with influenza develop pneumonia and ~25 percent of patients with influenza pneumonia die of progressive respiratory failure. When influenza is identified as a pathogen, use of a neuraminidase inhibitor (oseltamvir or zanamavir) or an amantadate (amantadine or rimantadine) should be considered. The neuraminidase inhibitors are attractive in this setting as they are effective against both influenza A and B and antiviral resistance occurs more slowly compared with amantadine use. Annual influenza vaccination should be considered, but its benefit is attenuated; indeed, it is probably fair to say that maximal benefit from vaccination occurs when the vaccine is administered to health care workers, family, friends and other contacts of the patient. When an infection is diagnosed, early treatment should be considered [58, 60].

## **Adenovirus**

There are more than 50 serotypes of adenovirus and nearly all have been described to cause human disease. Adenovirus disease post-transplantation is likely due to both a newly acquired virus and viral reactivation. The most common adenovirus-associated illness post-transplantation is hemorrhagic cystitis which has been described in a recent report to occur in up to 42 percent of patients in the first year post-transplantation [61]. The overwhelming majority of cases are asymptomatic and require no intervention [62]. Occasionally the severity of hemorrhage or bladder-associated pain is so great that intervention is required. Other important adenovirus-associated syndromes include hepatitis and pneumonitis which may be fatal in the early post-transplant period. In the late post-transplant period adenovirus gastroenteritis may occur which is often a self-limited illness; however, severe disease has been described especially in patients requiring significant levels of immunosuppression for GVHD. Therapeutic options for adenovirus are limited. The role of the antiviral cidofovir is controversial with mixed results having been reported [63]. Decreasing immunosuppression and attempting reconstitution of the native

host immune response is critical. The role for other adjunctive therapies, such as IVIg, is unproven, but can be considered in severe cases. Avoiding exposure to new infection, as with all community-acquired pathogens, is central to optimal care.

### **Other Respiratory Viruses**

Parainfluenza, rhinoviruses, metapneumovirus and coronaviruses are all capable of causing lower respiratory tract infection in HSCT recipients. Of these many viruses, parainfluenza virus type III is especially associated with a high mortality [64, 65]. Again, specific therapy is not available, emphasizing infection control strategies in the hospital setting and avoiding individuals with respiratory tract complaints at home. When upper respiratory tract complaints occur in HSCT patients, a diagnosis should be made, utilizing rapid diagnostic techniques (e.g., antigen detection assays or nucleic acid testing). Preemptive therapy, when available, should be initiated, while immunosuppressive therapy diminished and isolation from other HSCT patients should be accomplished.

### **Polyomaviruses**

BK and JC viruses are the two important species in this family of viruses with a genitourinary and CNS predilection, respectively. Approximately 60 to 80 percent of adults have been infected with one or both of these viruses, typically in childhood. With immunosuppression, reactivation occurs which may lead to disease. BK virus is associated with hemorrhagic cystitis in the early post-transplant period. This virus is commonly found in the urine and rarely requires any therapeutic intervention. JC virus is the etiologic agent of progressive multifocal leukoencephalopathy (PML) which is a rare, but severe post-transplant complication. PML involves the white matter and presents with focal neurologic symptoms associated with the specific area of the CNS where the lesion(s) occur. Diagnosis requires correlating the clinical presentation, radiographic findings (typically by contrast-enhanced MRI imaging) and CSF PCR results for JC virus. Control of JC virus is associated with an intact cell-mediated immune response. Therapy for polyomavirus infection is quite limited with minimizing immunosuppression, when possible, being critical. The role of cidofovir is controversial with mixed results being reported. The use of quinolones for BK viruria is controversial at best and we do not recommend this practice [66]. Although the use of gatifloxacin was advocated by some authors, this drug is no longer available. Leflunomide administration has been used by some for treatment of BK in renal transplant patients, but no randomized trial data exists to support or recommend its use in either kidney or HSCT recipients at this time.

### **Hepatitis Viruses**

Hepatitis B and C viruses may cause chronic infection which often leads to eventual significant liver dysfunction. Given the high global prevalence of these viruses, it is prudent to screen for past or current infection prior to transplantation. When ongoing infection is found, careful assessment of liver function and a pre-transplant liver biopsy should be considered to assess for occult cirrhosis, as this may influence peri-transplant management [67].

HBV infects approximately 350 million people worldwide chronically, and substantially more have had prior resolved infection. The use of the HBV vaccine as a routine childhood immunization will likely decrease the number of chronically infected individuals over the next several decades. The advent of nucleic acid detection technology has allowed a more precise mechanism to detect active HBV replication compared with antigen- (for surface and e) only methods. For patients with evidence of prior HBV exposure (HBV core antibody positive), it is important to consider HBV reactivation in the setting of post-transplant liver dysfunction and to differentiate this from other causes such as hepatic GVHD or medication toxicity, although reactivation initially occurs in the setting of normal liver tests. The best strategy for surveillance post-transplantation remains to be defined. Some recommend routine surveillance for HBV reactivation post-transplantation, whereas others would suggest antiviral prophylaxis. It is important to be aware that old resolved infections, including those with hepatitis core and surface antibody, but without antigen or HBV DNA detected, are at risk for reactivation (seroreversion) post-transplantation, especially in the setting of high levels of immunosuppression [68, 69]. Several therapeutic options have become available over the last several years and include lamivudine [70–72], adefovir [73], entecavir [71, 72] and telbivudine. Other agents such as tenofovir and emtricitabine also have excellent anti-HBV activity. Use of these agents requires careful consideration to minimize the risk for the emergence of resistant virus, which may be as high as 10 percent per year for lamivudine, but is less than 1 percent for adefovir and entecavir.

Epidemiologic studies suggest that more than 170 million people worldwide have been infected with hepatitis C virus (HCV) and the majority (approximately 85%) are chronically infected [67]. Over several decades, chronic HCV infection is associated with progressive hepatic fibrosis, liver failure, and hepatoma. This process is accelerated in certain immunocompromised patients including HSCT recipients [74, 75]. It is important to assess patients for seropositivity to HCV prior to transplantation and in those who are found seropositive, to assess the HCV viral load, genotype and liver pathology. The presence of elevated liver enzymes in the setting of HCV before allogeneic HSCT has been associated with an increased incidence of VOD [76]. A more precise profiling of the HCV-infected patient, including liver biopsy, should be considered to better define the extent of the HCV-induced liver disease, and to optimize the conditioning regimen and frequency of surveillance post-transplantation. Treatment of HCV is limited and typically requires use of an interferon and ribavirin which are likely to be poorly tolerated in the early post-transplant setting. In patients who are infected, it is prudent to counsel them to avoid hepatotoxins, receive the hepatitis A and B vaccines, and minimize the risk of transmission to close contacts.

## Fungal Infections in the HSCT Recipient

There are three categories of fungal pathogens that can infect the HSCT patient: a) the classic opportunistic fungi, which cause >90 percent of the invasive fungal infections that occur in the HSCT patient – *Candida*, *Aspergillus* and *Cryptococcus* being the most important of these infections; b) the geographically restricted systemic mycoses caused by *Blastomyces dermatitidis*, *Coccidioides immitis* and *Histoplasma capsulatum*; and c) invasive

infection due to the so-called “newly emerging fungi” – *Fusarium*, the zygomycetes and such dematiaceous fungi as *Scedosporium*, *Scopulariopsis* and *Dactylaria* [4].

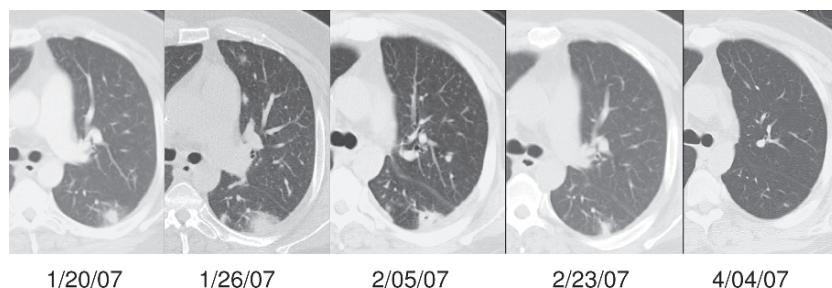
*Candida* is a major cause of fungal bloodstream infection during the preengraftment phase of HSCT. Although there is the possibility that the portal of entry can be vascular access catheters, it is believed that translocation of *Candida species* across gut mucosa damaged by the pre-transplant conditioning regimen is the major route of access to the bloodstream in the granulocytopenic patient [77, 78]. In the past, *C. albicans* and *C. tropicalis* accounted for virtually all of the *Candida* bloodstream infections. The incidence of candidemia was ~11 to 16 percent (with a median time to onset of two weeks post-transplant), resulting in a high rate of tissue invasion and an attributable mortality of nearly 40 percent [79, 80]. With the introduction of empirical antifungal therapy or fluconazole prophylaxis (400 mg/day) during the preengraftment period, the incidence of candidemia has been significantly decreased, hepatosplenic candidiasis has become quite rare, and the attributable mortality has been significantly decreased. Fluconazole-resistant *Candida sp.*, *C. krusei* and *C. glabrata*, have emerged as not uncommon causes of candidemia in HSCT patients, as have the other non-*albicans Candida species* [1, 4, 81–87].

It is also important to recognize that other species of yeast (e.g., *Trichosporon sp.*, *Blastoschizomyces capitatus*, *Saccharomyces cerevisiae* and *Rhodotorula sp.*) can cause clinical syndromes identical to those observed with invasive candidiasis (bloodstream infection, infection metastatic to the skin and subcutaneous tissues, as well as other sites, including hepatosplenic disease identical to that caused by *Candida species*) [88]. In an era of increased use of echinocandins for prophylaxis [89] and empirical antifungal treatment [90], these organisms [88, 91] and echinocandin-resistant *Candida sp.*, especially *C. parapsilopsis*, have become emerging causes of fungemia in the HSCT units [1, 4, 82].

Invasive fungal disease has been most commonly caused by *Aspergillus sp.*, with *A. fumigatus*, *A. flavus*, *A. terreus*, *A. niger* and *A. nidulans* being the most common causes of invasive aspergillosis. The portal of entry for 90 percent of cases of invasive aspergillosis is the lungs, with the nasal sinuses and the skin accounting for virtually all of the remaining cases. There are two major host defenses that are mobilized in response to inhalation of the *Aspergillus* spores – granulocytes and cell-mediated immunity, specifically cytotoxic T cells. The importance of these mechanisms is demonstrated by the clustering of cases of invasive aspergillosis at two timepoints in the post-transplant course: preengraftment when profound granulocytopenia is present, with the incidence of invasive aspergillosis increasing steadily as the period of granulocytopenia is extended, and after the diagnosis of GVHD and the treatment of this adverse event. Indeed, these late cases of invasive aspergillosis have become more common than the preengraftment cases. Mortality rates have traditionally been high in patients who developed invasive aspergillosis in either time period [1, 4, 92, 93].

The clinical syndromes caused by *Aspergillus* invasion reflect the pathologic consequences of the vasculotropic nature of this mold. The three major consequences of the vascular invasion that characterizes *Aspergillus* invasion include hemorrhage, infarction and metastatic disease. Initial clinical complaints include persistent fever, chest pain, tachypnea, hypoxemia and





**Fig. 19-2.** Computerized tomographic scan of the chest in a patient with a “halo sign” due to invasive aspergillosis.

Note that halo signs most commonly occur in granulocytopenic HSCT recipients with invasive aspergillosis. However, it must be emphasized that a halo sign is occasionally seen in patients with *Nocardia*, *Scedosporium*, *Fusarium* and other forms of pneumonia. The patient was treated with voriconazole monotherapy during neutropenia during consolidation chemotherapy for AML and his treatment was continued through allogeneic transplantation.

hemoptysis, as well as symptoms related to metastases. Before the availability of noninvasive fungal markers (galactomannan and  $\beta$ -glucan) and aggressive imaging with spiral chest computerized tomographic (CT) scanning, 50 percent or more of patients experience disseminated infection at the time of first diagnosis, accounting for the high mortality observed in allogeneic HSCT recipients. A particular problem is infection in the CNS, where mortality historically has approached 100 percent. Metastases can present any site, but particularly important is the skin, as innocent appearing skin lesions can lead to early recognition of the disease, and should be aggressively biopsied [4].

Definitive diagnosis of invasive mold infections, including invasive aspergillosis, is usually accomplished by biopsying the site of abnormality. Early diagnosis is the key to effective therapy [94]. Sputum or bronchoscopic samples rarely yield mold on culture. In recent years, considerable effort has been made to find other technology that will lead to an earlier and timely diagnosis. The ones that have been incorporated into practice are the systematic measurement of *Aspergillus* antigens and serial chest CT imaging. Monitoring the serum of HSCT patients for galactomannan or  $\beta$ -glucan is now commercially available and has been incorporated into the current diagnosis guidelines [95, 96]. The detection of circulating fungal DNA in the blood by PCR [97] remains experimental. Findings on chest CT, in particular the halo sign (Fig. 19-2), are associated in the neutropenic patient with invasive aspergillosis (although other pathogens can cause the same radiologic finding: *Fusarium* and other vasculotropic molds and *Nocardia asteroides* being examples of this). European groups have been advocating protocol serial chest CT scans to find such pathology as a guide to early diagnosis [98]. If prevention fails, then early diagnosis is the key to the patient’s survival [4, 92, 93].

Given the limitations of current diagnostic techniques and the significant morbidity associated with invasive fungal infection, two strategies of antimicrobial use are commonly deployed in the HSCT patient. The first is **prophylactic** fluconazole use during the initial transplant period, which has been shown to decrease fungal infections [80] in one study, and overall mortality

[79] in another, when started on day 0 until engraftment [80] or day +75 [79]. It is important to note that a high background rate of *Candida* infections was noted in both of these reports and may not represent the experience of other transplant centers. Echinocandins may be an alternative to fluconazole prophylaxis during this risk period [89]. The second common strategy is **empiric** antifungal therapy in neutropenic patients with persistent fever without a source, despite broad-spectrum antimicrobial therapy for >96 hours [99, 100]. In this setting the primary concern is both *Candida* and invasive mold infection, especially *Aspergillus* [2]. The traditional antifungal therapy utilized as empiric therapy is an amphotericin product [101, 102]. Caspofungin use in this setting has become common because of the favorable side effect profile of this class of agents, but at the expense of a more limited fungal spectrum [90]. Other echinocandins (micafungin, anidulafungin) are likely to be similarly effective, but no randomized comparisons with these latest drugs have been performed. The role of voriconazole in this setting is controversial [102].

When treating invasive aspergillosis several approaches should be considered simultaneously: 1) antifungal therapy, 2) reverse or minimize the host immune defects (decrease corticosteroids, increase neutrophils), 3) control permissive viral infections (e.g., CMV) and 4) consider surgical excision, if possible. Voriconazole has become a cornerstone of therapy for invasive *Aspergillus* infections, though the management of potential side effects is substantial [103–105]. Whether the combination of therapeutic agents (polyenes, azoles and echinocandins) increases the therapeutic benefit has yet to be determined [106]. Increasing experience suggests that voriconazole alone is sufficient in most cases for a successful outcome in invasive aspergillosis and has decreased the morbidity and mortality of this infection [11, 106].

Another significant risk period for invasive fungal infections (IFI) is in the setting of significant GVHD, such as grade III or IV, and its therapy [9]. In this setting, posaconazole (versus fluconazole) prophylaxis has recently demonstrated some benefit in preventing IFI compared to fluconazole (5.3% versus 9.0%,  $p = 0.07$ ) and in preventing probable or proven invasive aspergillosis (2.3% versus 7.0%,  $p = 0.006$  – interestingly, these results were largely driven by results from galactomannan assay testing) [107–109]. Posaconazole has activity against the Zygomycetes as well as *Aspergillus* sp [110–112]. When an azole is used in this patient population, careful assessment of drug interactions, both with the initiation and cessation of therapy, is critical.

Therapy for the emerging fungi *Fusarium* and *Scedosporium* should be guided by *in vitro* sensitivity testing done locally or at regional reference laboratories, but voriconazole use should be considered. When therapy for the endemic mycoses is indicated, initial treatment (induction therapy) with an amphotericin preparation should be considered, followed by a prolonged course of consolidative therapy with an oral azole. Cryptococcal disease should be treated initially with an amphotericin preparation, CNS involvement should be excluded by cerebrospinal fluid sampling, and the use of flucytosine should be considered if present.

## **Pneumocystis jiroveci**

*Pneumocystis jiroveci*, formerly *carinii*, is a ubiquitous environmental organism which is an important cause of pneumonia in patients who are immunosuppressed, such as those who have undergone an HSCT, on chronic prednisone

(typically >20mg per day) or with advanced HIV infection. PCP infection typically presents as an interstitial pneumonitis with marked hypoxemia. Severe infection can be life threatening. Fortunately, universal prophylaxis of high risk patients during the high risk periods with trimethoprim-sulfamethoxazole has markedly decreased this complication. However, intolerance to prophylaxis, use of second line prophylaxis agents (e.g., dapsone, pentamidine, or atovaquone), poor medication compliance or failure to re-institute prophylaxis in the setting of augmented immunosuppression (e.g., treatment of GVHD) are common reasons why cases still occur.

## Post-Transplant Management

Several important issues must be addressed after successful HSCT to minimize infectious complications. First, it is important to avoid exposure to pathogens, especially when the immunosuppressive therapy to prevent GVHD is the highest. This includes avoiding gardening and soil exposures, mold exposures such as cleaning out damp basements or smoking marijuana, individuals with active respiratory infections, especially children, and avoiding enteric pathogens. Second, optimal treatment or monitoring for latent infections such as herpesviruses, hepatitis viruses and prior granulomatous diseases (e.g., *Mycobacterium tuberculosis*). Those patients with a positive test for latent tuberculosis should receive secondary prophylaxis, which typically is begun within one month post-transplantation, after the acute regimen toxicities associated with transplantation have subsided, when screening and preventive treatment have not occurred previous to HSCT. The first line therapy for secondary prophylaxis is isoniazid for nine months. However, in patients with significant hepatic dysfunction or peripheral neuropathy alternative regimens need to be considered. Rifamycin-based regimens are difficult given the potential hepatotoxicity, as well as the significant drug interactions, especially with concomitant use of a calcineurin or an azole. A quinolone, such as levofloxacin, with ethambutol may be considered. When a mycobateriologically static regimen is chosen, the duration of therapy often must be extended with some using this combination for 18 months as secondary prophylaxis (Table 19-2).

Third, optimizing vaccinations for routine pathogens such as diphtheria, tetanus, pertussis, influenza and pneumococcus (Table 19-3). This optimal timing of re-vaccination depends on the nature of the transplant, with earlier re-vaccination schedules being considered in the nonmyeloablative setting.

Fourth, prophylaxis for PCP, which is typically continued for approximately one year or until the immunosuppressive medications are tapered off. The optimal medication to use for PCP prophylaxis is trimethoprim-sulfamethoxazole which offers some protection for a variety of other important pathogens including *Pneumococcus*, *Hemophilus influenza*, *Nocardia sp.*, *Toxoplasma*, *Listeria*, *Salmonella sp.*, and other enteric bacterial pathogens. If trimethoprim-sulfamethoxazole is not tolerated due to significant renal dysfunction or bone marrow suppression, then alternative agents for PCP prophylaxis include dapsone, atovaquone or aerosolized pentamidine; however, none of these second line agents afford the broad microbial protection which trimethoprim-sulfamethoxazole affords. And lastly, herpes group viral prevention which should include acyclovir to prevent HSV and VZV and systematic monitoring for CMV, in the allogeneic setting, with early use of a CMV active antiviral if evidence for CMV activation or disease is observed.

**Table 19-2.** Prevention of infectious complications post-HSCT.

| Organism              | Primary Prevention or Prophylaxis  | Alternative Prevention or Prophylaxis  |
|-----------------------|--|--|
| PCP                   | Trimethoprim-sulfamethoxazole* either a double strength (DS) 3-times per week or as a single strength (SS) once a day for 1 year | Dapsone 50mg po BID, atovaquone 1,500 mg per day, pentamidine (aerosolized or intravenous)             |
| HSV/VZV               | Acyclovir 800 mg BID or 400mg TID for 1 year   | Valacyclovir 500 mg BID, famciclovir 250 mg BID  |
| CMV                   | Preemption is preferred, where available   | Valganciclovir** 900 mg po BID or QD post-engraftment to day 100<br>Intravenous ganciclovir, foscarnet |
| HBV***                | Monitor for reactivation   |  |
| MTb (positive ppd)    | Isoniazid 900 mg QD for 9 months**** with pyridoxine   | Levofloxacin and/or ethambutol   |
| Encapsulated bacteria | Monitor IgG level and consider replacement with IVIg when < 400–500 mg/dL<br>Trimethoprim-sulfamethoxazole                       | Amoxicillin 500 mg BID   |
| Candida/Aspergillus   | Fluconazole 400 mg QD<br>Posaconazole 200 mg TID*****  |  |

Prophylaxis must be re-assessed in the setting of persistent or augmented immunosuppression, such as in the setting of clinically significant GVHD, regardless of time since HSCT. Medication doses may need to be adjusted for renal dysfunction.

\* Trimethoprim-sulfamethoxazole affords modest protection for a broad array of potential environmental and community pathogens including: *Nocardia* sp, toxoplasmosis, pneumococci, H influenza, listeria, shigella, and salmonella sp.

\*\* Alternatively preemptive monitoring with serial viral antigen or viral load assays can be considered.

\*\*\* For those with evidence of prior HBV infection (e.g., Hepatitis B core antibody positive), consider monitoring HBV viral load for evidence of reactivation periodically. If reactivation is detected then consider treatment if persistent HBV viremia detected. Specific HBV antiviral therapy is discussed in the text.

\*\*\*\* Pre-transplant secondary prophylaxis for MTb is preferred.

\*\*\*\*\* Decision for systemic azole prophylaxis should be based on local epidemiology of invasive fungal infections. Consider posaconazole prophylaxis in the setting of significant GVHD (e.g., Grade 3 or 4) and its therapy. Drug interactions must be carefully managed both with initiation and cessation of azole therapy.

## Drug Interactions

An important aspect of antimicrobial therapy in the HSCT patient is the management of drug interactions, especially between antimicrobial agents (e.g., azoles, macrolides) and the immunosuppressive medications (e.g., calcineurin inhibitors, sirolimus) used to prevent and treat GVHD. There are three important categories of interaction to pay particular attention to, two of which are

**Table 19-3.** Vaccination considerations post-HSCT.

| Vaccine                      | Timing post-HSCT  |
|------------------------------|---|
| Tetanus/Diphtheria/Pertussis | 12, 14 and 24 months  |
| Pneumococcal                 | 12, 14, 24 months   |
| Haemophilus (HiB)            | 12, 14 and 24 months  |
| Hepatitis A                  | 12, 18 months   |
| Hepatitis B                  | 12, 14, 18 months   |
| Meningococcal                | 12 months   |
| Influenza                    | Annually: as available in the fall                                  |
| MMR (Live virus vaccine)     | At 24 months (if no significant GVHD and minimal immunosuppression) |
| Inactivated polio            | 3 doses   |

related to the major route of drug metabolism for the calcineurin inhibitors, hepatic cytochrome P450 enzymatic metabolism. These interactions are as follows: 1) certain antimicrobial agents (most notably the macrolides [erythromycin>clarithromycin>azithromycin] and the azoles [ketoconazole>itraconazole>voriconazole>fluconazole]) will downregulate the metabolism of the calcineurin inhibitors, resulting in elevated blood levels of active drug, and an increased risk of nephrotoxicity, as well as over-immunosuppression and an increased incidence of opportunistic infection; 2) certain antimicrobial agents (such as rifampin and rifabutin) upregulate metabolism of the calcineurin inhibitors, leading to a fall in blood levels and an increased risk of GvHD, and 3) therapeutic blood levels of the calcineurin inhibitors, when combined with such drugs as amphotericin B, aminoglycosides and vancomycin, can cause significant renal toxicity.

## Summary and Conclusions

HSCT has become one of the great success stories of modern medicine. It is the therapy of choice for an increasing number of conditions, including a variety of cancers, bone marrow failure states, congenital immunodeficiencies, metabolic disorders and even as a means for introducing new genes. The major hurdle in most of these attempts, however, remains infection. Bacterial and fungal sepsis, as well as herpes group viral infection and community-acquired respiratory virus infection threaten the well-being of these patients. There are two phases of the post-transplant course when the patient is at particular risk: preengraftment with profound granulocytopenia and mucositis, and post-engraftment when GVHD and its therapy render the patient vulnerable to both fungal and viral infection. New preventative strategies are being formulated involving both prophylaxis and preemptive therapy. Similarly, new non-culture diagnostic approaches that rely on antigen detection or PCR detection of microbial DNA are being developed. New therapies, both antiviral and antifungal, have emerged. These should prompt much more effective prevention and therapeutic strategies.

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