INFECTIONS FOLLOWING HEMATOPOIETIC STEM CELL TRANSPLANTATION

Helen L. Leather, B. Pharm, BCPS, and John R. Wingard, MD

Hematopoietic stem cell transplantation (HSCT) is a well-established treatment modality for a variety of bone marrow failure states (aplastic anemia, myelodysplastic syndrome, immunodeficiency syndromes, congenital disorders of metabolism), hematologic malignancies (leukemia, lymphoma, multiple myeloma), and solid tumors (sarcomas, neuroblastoma, breast cancer, testicular cancer). Numerous advances have taken place in the field of HSCT over the past 10 years to make the procedure safer. Perhaps the most significant change has been the use of peripheral blood stem cells (PBSCT) as an alternative source of hematopoietic stem cells. Peripheral blood stem cell transplantation (PBSCT) results in faster engraftment of both platelets and neutrophils, leading to a shorter length of stay, fewer days of fever, and less antibiotic use. Secondly, increased understanding of donor-host immunobiology has led to the implementation of nonmyeloablative stem cell transplant protocols associated with less gastrointestinal toxicity and less overall chemotherapy-induced toxicities. In addition, better supportive care measures have been incorporated into practice, such as growth factors to accelerate neutrophil recovery; new, more potent antimicrobial agents; and prophylaxis strategies to prevent infection. New technologic advances permit earlier detection of infective pathogens, especially cytomegalovirus (CMV) (by antigenemia and polymerase chain reaction [PCR] technology), a significant cause of mortality in HSCT patients.
These advances have resulted in better overall outcomes and have increased the safety of the procedure, that in turn enables more patients to be eligible for HSCT.

Despite these advances, infection remains a major cause of transplant related morbidity. There are several risk factors for infection that still exist in HSCT patients. First is the intensity of the conditioning regimen. The majority of chemotherapeutic agents used in traditional autologous and allogeneic HSCT conditioning regimens leads to significant gastrointestinal injury that then serves as a portal of entry of microorganisms into the bloodstream. Second, the type of HSCT plays an important role in infection. Patients who undergo allogeneic HLA-identical sibling or matched unrelated donor (MUD) HSCT are at greater risk for infective episodes as a consequence of receiving immunosuppressive medications to prevent graft-versus-host disease (GVHD). The severity and extent of GVHD also impacts rates of infection. The increasing use of indwelling catheters and implantable infusion devices has served as a focus for gram-positive infections. Finally, the occurrence of viral infections that can suppress responses to other opportunistic pathogens places patients at increased risk for infection.216

**BLOOD AND MARROW TRANSPLANTATION TODAY**

Infections following HSCT are expected, given the immunologic deficiencies that remain after myeloablative conditioning therapy.27 The types of immunodeficiency and the duration and depth of immunodeficiency can vary considerably from one type of transplant to another. Accordingly, the frequency and type of opportunistic infections can differ enormously (Table 1). There are three risk periods (phases) for opportunistic infections following HSCT, that is, pre-engraftment, early postengraftment, and late postengraftment.

**Pre-engraftment Phase**

This phase starts early after the transplant and lasts until engraftment (the first 2 to 4 weeks). During this phase the predominant impaired host defense is loss of effective phagocytosis. The HSCT conditioning regimen intended to destroy neoplastic cells also destroys normal hematopoiesis including neutrophils, monocytes, and macrophages. In addition, damage to mucosal progenitor cells leads to a temporary compromise in the integrity of the mucosal barrier, another important first line of defense. The effect of chemotherapy intensity on mucosal damage and infection has been well described, with the more intense chemotherapy regimens leading to greater infection, particularly fungal infections.19, 20

During the pre-engraftment phase, patients typically develop neutropenic fever. The most common causes are bacterial pathogens, al-
though the rate of positive cultures remains low even with serial blood cultures. Neutropenic fever should be treated empirically with broad-spectrum antibiotics at the onset of fever and antibiotics should be continued for the duration of neutropenia (see treatment of bacterial infection for details).

Prolonged neutropenia also is associated with an increased risk of fungal infections (i.e., the longer the duration of neutropenia, the greater the chance of developing a fungal infection). The most common fungal infections during this phase are caused by *Candida* spp. When neutropenia is prolonged, *Aspergillus* spp. also are problematic.

The final type of infective process that occurs during the pre-engraftment phase of HSCT is viral reactivation. Reactivation of latent herpesviruses is common and herpes simplex virus (HSV) IgG positive patients should routinely receive antiviral therapy throughout the period of neutropenia.176

The duration of the pre-engraftment phase varies according to the type of transplant, with autologous PBSC transplants (PBSCT) typically having the fastest neutrophil engraftment, followed by autologous bone marrow transplant (BMT), allogeneic PBSCT, allogeneic BMT, MUD PBSCT, and MUD BMT. There are, therefore, different risks for the different types of transplants. Prophylaxis and treatment strategies should be selected according to risk based on the type of HSCT. Today many HSCT centers use growth factors post HSCT to accelerate recovery and minimize the duration of neutropenia. The reduction in duration of neutropenia may eventually translate into a lower infection rate, but thus far this technology only has resulted in a reduction in the duration of neutropenia, days of fever, and the total amount of antibiotics used, with no effect on the actual overall incidence of infection.107, 141, 186

**Early Postengraftment Phase**

The duration of this phase ranges from the time of neutrophil engraftment until day 100 (second and third months). This phase is characterized by a period of impaired cell-mediated and humoral immunity. These immune deficiencies are seen in both autologous and allogeneic transplant recipients but to varying degrees. Restoration of effective phagocytic function occurs typically upon engraftment (in the absence of corticosteroid usage), and the risk for bacterial and fungal infections decreases. Cellular components of the immune system return to normal levels in 4 to 6 months following conventional bone marrow transplant, with the exception of CD4+ T-cell and B-cell reconstitution, which is often delayed. The duration of immune deficiency is dependent upon the development of GVHD, its severity, and the dose and number of immunosuppressive medications prescribed. Both the occurrence and the treatment of GVHD can lead to profound deficiencies of cell-mediated and humoral immunity, and dysregulated immune responses that may render the patient especially vulnerable to opportunistic viral and
### Table 1. FREQUENCY AND TYPES OF OPPORTUNISTIC INFECTIONS AT DIFFERENT TIMES AFTER HSCT

<table>
<thead>
<tr>
<th>Period of Risk</th>
<th>Autologous</th>
<th>Allogeneic Matched Sibling Without GVHD</th>
<th>Allogeneic Matched Sibling with GVHD</th>
<th>Allogeneic Matched Sibling T-Cell Depletion</th>
<th>Allogeneic Alternative Donor</th>
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<tr>
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<tr>
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Late postengraftment

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<th>Enteric viruses</th>
<th>Respiratory viruses</th>
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Any phase

Hepatitis viruses
- Hepatitis B: $+$
- Hepatitis C: $++$ $+$ $+$ $+$ $+$

Enteric viruses
- Coxsackie: $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$
- Rotavirus: $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$
- Calicivirus: $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$
- Norwalk agent: $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$
- Adenovirus: $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$

Respiratory viruses
- Influenza: $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$
- Parainfluenza: $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$
- RSV: $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$

(From Wingard JR: Opportunistic infections after blood and marrow transplantation. Transpl Infectious Disease 1:3–20, 1999; with permission.)

'The number of "+" signs indicates the relative frequency of infection.

For CMV, risk is greatest in seropositive patients, irrespective of donor serostatus.

Rare in seronegative patients.

Risk is greatest in patients who received ganciclovir during the early postengraftment period.

CMV = Cytomegalovirus, HSV = herpes simplex virus; VZV = varicella zoster virus; EBV = Epstein-Barr virus; RSV = respiratory syncytial virus.
fungal pathogens. Those patients who develop acute GVHD and require therapy with systemic corticosteroids are at great risk of infection and typically develop fungal (*Candida* spp. and *Aspergillus* spp.) and viral (cytomegalovirus [CMV], varicella zoster) infections. Corticosteroids, in addition to effects on cell-mediated immunity, also impair effective functioning of phagocytic cells (especially pulmonary alveolar macrophages), that prevents the host from effectively destroying colonizing fungal opportunists. The burden of organisms may increase, encouraging tissue invasion and the potential for systemic infection.

Typically during this phase bacterial infections are less common, with the exception of those patients who still have indwelling vascular access devices. This population is at continued risk of developing gram-positive catheter-associated infections with *Staphylococcus* spp., although line sepsis with less common gram-negative pathogens such as *Acinetobacter baumannii* and *Stenotrophomonas maltophilia*, and gram-positive rods such as *Corynebacterium* can and do occur.

**Late Postengraftment Phase**

The late postengraftment phase ranges from day 100 until the patient regains normal immunity. Patients at greatest risk during this phase are allogeneic HSCT recipients (HLA-matched sibling or MUD) and recipients of T-cell depleted marrows that develop GVHD. Patients developing chronic GVHD (cGVHD) have significant T-lymphocyte dysfunction that may be prolonged. In addition, humoral and macrophage dysfunction may still persist during this phase. Patients are therefore at risk of developing bacterial, viral, and fungal infections during this phase.

Bacterial infections during this phase are caused predominantly by encapsulated bacteria, namely *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae*. Fungal infections can be either *Candida* spp. or *Aspergillus* spp., although *Aspergillus* spp. are more likely. Viral infections are the most frequent pathogens during this period, especially in those patients with ongoing GVHD. The most common viral pathogen is CMV. Prior to the advent of prophylactic and preemptive ganciclovir strategies, CMV infections were unlikely past 100 days, but the widespread implementation of such treatment strategies has led to late CMV infections. HSCT programs must therefore ensure that CMV surveillance practices are continued for the duration of GVHD, if necessary. The other viral infection of concern during this period is varicella zoster.

From this summary of the different phases of HSCT, it is apparent that different forms of infection may occur at different time points post-transplant, reflecting the dominant host defense defects that are present and operative. A timetable therefore can be defined that delineates the prominent infections that occur (Figure 1). The utility of such a time-
INFECTIONS FOLLOWING HEMATOPOIETIC STEM CELL TRANSPLANTATION

The predominant pathogens during the pre-engraftment phase are gram-negative bacteria, namely *Escherichia coli*, *Klebsiella* spp., and *Pseudomonas* spp., but over time less common isolates are increasingly being identified. These include *Acinetobacter* spp., \(^{202}\) *Stenotrophomonas maltophilia*, \(^{105}\) \(^{137}\) \(^{153}\) \(^{192}\) *Alcaligenes xylosoxidans*, \(^{124}\) *Bacillus* spp., *Listeria monocytogenes*, \(^{32}\) \(^{123}\) \(^{145}\) *Corynebacterium* spp., and *Bacteroides fragilis*. Many of these organisms are not susceptible to standard empiric broad-spectrum antibiotics and hence will lead to empiric therapy treatment failures before the identification of the organisms is made and appropriate antibiotic changes occur. In a review of bacteremias in the BMT unit at Shands at the University of Florida (UF) over the period 1991 through 1997, such uncommon organisms as those previously listed accounted for 5% of all isolates.\(^{108}\)

Despite the increase in uncommon isolates, the backbone of empiric antibacterial therapy should be directed against those organisms known to be most likely. When selecting an antibacterial agent, the following must be considered: the most likely site of infection (are there any localizing signs); the local antibacterial susceptibility patterns; duration of neutropenia; prior and current antibacterial usage; prophylactic antibacterial therapy; and the type and frequency of bacterial isolates found in the particular institution over time.\(^{95}\) Empiric antibacterial treatment in the hemodynamically stable, febrile neutropenic patient early post-transplant should, therefore, include either a third- or fourth-generation cephalosporin or extended-spectrum penicillin as a single agent (monotherapy). Agents that have been studied and are recommended include ceftazidime, \(^{139}\) \(^{165}\) \(^{174}\) imipenem, \(^{69}\) \(^{85}\) \(^{104}\) \(^{115}\) cefepime, \(^{49}\) \(^{100}\) \(^{149}\) \(^{164}\) \(^{222}\) and meropenem.\(^{86}\) There also are data supporting the use of piperacillin/tazobactam\(^{86}\) and ciprofloxacin as monotherapy, but there has been variability in the outcomes seen with the latter.\(^{94}\) \(^{95}\) \(^{129}\) In those institutions
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where there is high-level resistance to the beta-lactams, carbapenems, monobactams, and cephalosporins, or where *Pseudomonas* infections are common, double-coverage with another antibiotic with good gram-negative coverage should be considered. The most common combinations are a third-generation antipseudomonal cephalosporin plus an aminoglycoside or antipseudomonal carboxypenicillin or ureidopenicillin plus an aminoglycoside. In general, two-drug combinations have been shown to produce results similar to monotherapy. Combination therapy brings with it additional costs, increased likelihood of toxicity (especially among allogeneic HSCT patients receiving cyclosporine or tacrolimus), and still lacks gram-positive coverage, so unless absolutely indicated, monotherapy is the preferred treatment option.

One of the most controversial questions in the management of infection in neutropenic HSCT patients is the role of vancomycin. Should vancomycin be included as part of the routine empiric management of fever and neutropenia, or should it be reserved for documented infection, or infections where there is a high index of suspicion of gram-positive origin? Over the last 20 years there has been a significant change in the types of bacteremia seen in neutropenic patients. In 1973 the EORTC trials demonstrated that gram-positive bacteria were responsible for bacteremia in 29% of cases and gram-negative organisms in 71% of cases. Over the next 20 years the pattern of infection changed drastically with 69% of bacteremias caused by gram-positive organisms versus 31% due to gram-negative organisms. The major organisms contributing to these changing patterns are the coagulase-negative staphylococci and the viridans group streptococci, and more recently the enterococci. These changes in infection patterns are attributable in part to the routine use of prophylactic fluoroquinolones (although some centers who have never used prophylaxis are also seeing changing patterns of infection), increasingly intensive chemotherapy regimens that cause greater mucosal injury (conditioning regimens that contain cytosine arabinoside have been shown to have a statistically higher incidence of *Streptococcus viridans* septicemia), and the use of indwelling venous access devices. Indwelling central venous catheters provide a surface that bacteria can adhere to and the formation of biofilms may serve as a source of persistent septic foci.

The Infectious Diseases Society of America (IDSA) recommendations for inclusion of vancomycin in the empiric antibiotic regimen are dependent upon the relative risk of *Staphylococcus aureus* sepsis to the patient. Patients at high risk (ANC < 100/mm³, mucositis, hypotensive or other evidence of cardiovascular impairment) should receive empiric vancomycin, with regular reassessment and discontinuation once the patient stabilizes or if all blood cultures are negative. Those patients

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**Figure 1.** Risk periods for opportunistic infections with standard prophylaxis after marrow transplant. (From Bowden RA: Blood and Marrow Transplantation. In Armstrong D, Cohen J (eds): Infectious Disease: Fungal Infections, ed 1. London, Mosby-Wolff, 1999; with permission.)
already on broad-spectrum antibiotics but who have an indwelling catheter that is likely to be contributing to fever (i.e., erythematous exit site, pain and tenderness to touch surrounding catheter placement) should have vancomycin added to therapy, again until resolution of clinical signs if improvement occurs or until exclusion of a gram-positive infection.

Guidelines for further modification of the empiric antibacterial regimen are outside the scope of this article and can be found in the IDSA practice guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever.9z

Anaerobic infections are uncommon in HSCT recipients. Patients who receive high doses of cytarabine are at risk of developing typhlitis and in this population it would be prudent to add metronidazole or clindamycin in the presence of any abdominal symptoms.

_Mycobacterium_ infections are common in patients with deficiencies in cell-mediated immunity such as the HIV-positive population. Following allogeneic HSCT, recipients have impaired cell-mediated and humoral immunity and it would be expected that there would be a high incidence of _Mycobacterium_ infections. To date, this has not been seen in the HSCT population and is thought to be because the majority of transplant procedures are performed in developed countries where the number of new cases of _Mycobacterium_ infections in the general population remain low. In developing countries, the frequency of infection is higher and is proportional to the incidence of tuberculosis in the general population. In general, those countries with a high rate of tuberculosis are likely to have higher infection rates in the HSCT patient population.91

A 20-year retrospective review of mycobacterial infections following HSCT was conducted at the University of Minnesota, and found that mycobacterial infections were diagnosed in only 11 of 2241 (0.5%) patients.172 Infections seen included _M. tuberculosis_, but also the atypical _Mycobacterium_ species such as _M. avium-intracellulare, M. fortuitum, and M. chelonae_. Atypical mycobacterial infections are being increasingly reported in the HSCT literature.71, 91, 199 A recent review from the Fred Hutchinson Cancer Research Center found that over 20 years (1977-1997) there were 40 cases of nontuberculous mycobacteria isolated from 6259 HSCT recipients (0.6%).71 Of these cases, the majority were either pulmonary in origin (15 cases) or catheter-related infections (23 cases). All patients responded to antibiotic treatment. Pulmonary cases were treated with triple therapy combinations including three of the following: isoniazid, rifampin, pyrazinamide, azithromycin, ethambutol, rifabutin, clarithromycin, or ciprofloxacin for 2 to 6 months. Catheter-related infections were treated initially with two antimicrobial agents administered intravenously (e.g., amikacin, imipenem-cilastatin, cefoxitin, tobramycin) for 2 to 4 weeks followed by two antimicrobials administered orally (e.g., clarithromycin, ciprofloxacin, doxycycline) for 4 to 6 weeks.71 Patients who have tunnel infections should undergo surgical debridement of the soft tissues around the tunnel tract. As with all infections, susceptibility testing should be performed on all isolates that are identified and used
to guide therapy. Although the diagnosis of mycobacterial infections can be difficult, the HSCT practitioner must maintain a high index of suspicion for mycobacterial infections when treating fever of unknown origin, particularly in high-risk patients such as those with prior tuberculosis exposure, ethnic origin, or positive PPD skin test.72

Another opportunistic infection rarely described in HSCT recipients is nocardiosis. Nocardia spp. are gram-positive aerobic actinomycetes that are found in soil and decaying organic matter.191 Van Burick and colleagues evaluated 27 cases of Nocardia in HSCT recipients. Nocardia was isolated from blood, brain abscess, sputum, bronchoalveolar lavage (BAL) fluid/washings, open lung biopsy, and skin (catheter exit sites and abscesses). Pulmonary signs were common, including nodules with or without infiltrates. Abnormal chest radiographs were documented in 56% of patients. The overall survival rate was 34% at 6 years, with 84% survival from the infection itself. Treatment of choice is a sulfonamide-containing regimen, but it is important to note that in this series 40% of patients developed Nocardia while on sulfamethoxazole-trimethoprim (SMX-TMP) prophylaxis (four double-strength tablets per week) for Pneumocystis carinii pneumonia. The majority of patients required addition of another antimicrobial agent. Alternative agents include amikacin, imipenem, minocycline, and ceftriaxone.191 Adjunctive treatment includes surgical debridement if there is cutaneous involvement.

Prophylaxis Against Bacterial Infections

Early infection: Infectious complications that occur in the early pre-engraftment HSCT phase are often caused by bacteria that comprise the endogenous flora of the alimentary tract. When the patient becomes neutropenic and has impaired mucosal defense barriers, these bacteria disseminate and become pathogenic, causing fever and infection. In an attempt to minimize the risk of infection in neutropenic hosts, several groups have implemented prophylactic antibiotic strategies.7, 21, 22, 28, 44, 47, 73, 80, 99, 111, 128, 219 Initial strategies used oral nonabsorbable antibiotics (polymyxin or neomycin)178, 190 in combination with low bacteria or sterile diets and patients were placed in protective isolation.110 Later, absorbable oral agents such as SMX-TMP were used as prophylaxis with success,43, 79 and finally the advent of the broad-spectrum fluoroquinolones led to another era in gut decontamination. Much of the data with the fluoroquinolones were generated from patients with hematologic malignancies who were expected to be neutropenic. Limited data in the HSCT population are available112, 179 so the benefit of these agents was extrapolated to these patients, as they have a similar duration of neutropenia.

The majority of bone marrow transplant centers start patients undergoing HSCT on oral prophylactic antibiotics at the time of chemotherapy or on the day of HSC infusion. Typically agents used include ciprofloxacin,44, 47, 111 norfloxacin,22, 99, 128, 179, 219 ofloxacin, SMX-TMP, penicillin,62 and
Prophylactic antibiotics are continued until the first fever spike; at that time intravenous broad-spectrum antibiotics are commenced and prophylactic antibiotics discontinued. Fluoroquinolones have been shown to be safe, are well tolerated, and are effective in reducing the number of gram-negative infections. In spite of effective suppression of gram-negative bacteria, most patients still develop fever and become bacteremic, and none of the studies with fluoroquinolones in HSCT patients has been able to show a survival advantage.

One of the major concerns of widespread use of fluoroquinolones is the emergence of resistant strains of common gut bacteria, and overgrowth of other organisms including fungi. This concern was realized with most studies of fluoroquinolone prophylaxis demonstrating increased infections with gram-positive organisms. The most common pathogens are the viridans streptococci and coagulase-negative staphylococci. DePauw noted that fever developed in 91% of patients receiving ciprofloxacin prophylaxis. Positive blood cultures occurred in 42 cases (59%), of which viridans streptococci were responsible for 35 episodes. In all but one case the streptococcal infection was associated with reduced in vitro susceptibility to ciprofloxacin.

As a consequence of increasing gram-positive infections, many centers modified their prophylactic strategy to include antibiotics with gram-positive coverage. Broun conducted a randomized trial examining the effectiveness of adding streptococcal prophylaxis to standard antibacterial, antifungal, and antiviral prophylaxis in 43 HSCT recipients. Penicillin G (1 million units) intravenously every 6 hours started on day 7 and continued until the ANC was greater than 500/μL. The total number of infections was statistically different between the groups, with 14% of the gram-positive prophylaxis group and 49% of the standard prophylaxis group developing documented infection. The main difference in infection patterns was streptococcal infections. Penicillin use significantly reduced these infections with only one patient in this treatment arm developing streptococcal infection compared to nine patients in the standard prophylaxis arm. Unfortunately, the emergence of resistance to penicillin limits its utility.

Several other groups took a much more controversial approach and studied the effect of adding vancomycin to the prophylactic regimen to prevent gram-positive infections after HSCT. Vancomycin, as would be expected, was highly effective in reducing the frequency of gram-positive infections. Arns da Cunha and colleagues from the University of Minnesota studied three different approaches to the reduction of gram-positive bacteremia (GPB) in HSCT recipients. Patients received vancomycin, penicillin/cefazolin, or no specific prophylaxis, in a sequential cohort study. Vancomycin prophylaxis reduced the incidence of GPB (11%) compared to penicillin/cefazolin (27%) or no prophylaxis (40%) (all $P < 0.03$). The incidence of fungemia, gram-negative bacteremia, and most importantly, infection-associated mortality was not affected by GPB prophylaxis, however. This indicates that vancomycin does not need to be a part of the empiric antibacterial regimen, and
more importantly that omission of gram-positive coverage from the empiric treatment regimen does not affect overall mortality. Attal et al studied the addition of vancomycin to the empiric antibacterial treatment and demonstrated a reduction in gram-positive infections in the vancomycin group compared to the control group (infections occurred in 11 of 30 control patients versus zero of 30 in the treatment group; $p < 0.002$). All gram-positive infections in the control group were symptomatic (nine septicemia and two local infections), and one patient with *Streptococcus* septicemia died with pneumonia.\(^7\) Despite the success of this treatment modality in the mid-1990s, the emergence of vancomycin-resistant enterococci (VRE) in many HSCT centers\(^97,101,103\) caused concern and resulted in the Centers for Disease Control and Prophylaxis (CDC) formulating a list of recommendations for use of vancomycin, that included limiting indiscriminate use in nondocumented infections.\(^89\)

While the addition of vancomycin to the prophylaxis regimen was able to decrease gram-positive infections in the Attal study, follow-up studies were not able to detect any difference in clinical parameters such as the number of days to first fever, total number of febrile days, or length of stay.\(^67\) Vancomycin cannot therefore be routinely recommended as a component of the initial antimicrobial prophylaxis regimen (DIII).\(^31,92\)

The issue of gram-positive prophylaxis did not disappear, and alternatives were studied. Several centers adopted rifampin as the preferred agent.\(^75,87\) A recent randomized study assessed the effect of adding of rifampin 300 mg PO twice daily to ciprofloxacin as antibacterial prophylaxis in 130 patients undergoing PBSC. Rifampin reduced the overall incidence of bacteremia, with 12 episodes in the control group compared to four in the rifampin-treated group ($p = 0.05$). The proportion of patients developing neutropenia and fever was similar in both groups (87 vs. 78%, $p = 0.25$), and the duration of fever and time to fever were similar between the two groups.\(^75\) Based on these data, the routine use of rifampin as part of the prophylactic antibiotic regimen does not seem to be useful and cannot be recommended.

Although prophylactic antibiotics have been shown to reduce bacteremia rates, overall survival is not improved as a consequence of this treatment strategy. The CDC/IDSA/ and the American Society of Blood and Marrow Transplantation (CDC/IDSA/ASBMT) therefore derived a set of guidelines for the prevention of opportunistic infections in HSCT recipients.\(^31\) These organizations do not recommend the routine use of prophylactic antibiotics based on the lack of convincing benefits (DIII recommendation).

**Prophylaxis Against Late Infection**

In the late postengraftment phase (>100 days post-HSCT) allogeneic HSCT patients with cGVHD are at great risk of infection from the encapsulated organisms. These organisms are common causes of sinopulmonary infections and occasionally may cause fever of unknown origin and overwhelming sepsis. Following allogeneic HSCT, patients
may have deficiencies in IgG subclasses, especially subclass two. Humoral responses to bacterial polysaccharide antigens reside mainly in subclass two, thus placing some HSCT patients at particular risk.\textsuperscript{214} Opsonization of bacteria is also impaired in patients with cGVHD, that when coupled with poor reticuloendothelial function of the liver and spleen, renders the patients especially susceptible to these pathogens.\textsuperscript{214}

The CDC/IDSA/ASBMT guidelines for the prevention of opportunistic infections after HSCT recommend antibiotic prophylaxis in postallogeic HSCT patients with cGVHD for as long as active cGVHD therapy is administered (BIII).\textsuperscript{31} Commonly employed agents include SMX/TMP and oral penicillin. If SMX/TMP is being used for \textit{P. carinii} prophylaxis it may provide protection against pneumococcal infection, although no data exist to support the use of SMX/TMP prophylaxis in HSCT recipients solely for the purpose of preventing \textit{Streptococcus pneumoniae} disease.\textsuperscript{31} In our own BMT unit at Shands at UF, \textit{S. pneumoniae} resistance to penicillin increased from 7\% in 1991–1993 to 20\% in 1994–1995 and to 58\% in 1996/1997,\textsuperscript{108} necessitating a change in treatment options. The choice of a particular antibiotic should therefore be guided by local susceptibility data, and should always be reassessed based on changing susceptibility patterns.

Another method of minimizing the risk of infection post-HSCT is to revaccinate high-risk individuals. Following HSCT, antibody titers decline slowly over 1 to 4 years if the patient is not revaccinated. Suggested vaccination schedules against the encapsulated organisms can be seen in Table 2.\textsuperscript{31}

**VIRAL INFECTIONS FOLLOWING HEMATOPOIETIC STEM CELL TRANSPLANTATION**

Viral infections are one of the major causes of morbidity and mortality following HSCT. The most common viruses isolated from HSCT patients are herpesviruses, with infections also caused by papovaviruses and enteroviruses. The herpesvirus family includes cytomegalovirus (CMV), herpes simplex virus (HSV), varicella zoster virus (VZV), and Epstein-Barr virus (EBV). Viral infections with HHV-6, a newer member of the herpesvirus family, have recently been increasingly described in BMT recipients.\textsuperscript{4, 37, 119, 198}

**Herpes viruses**

**Herpes Simplex Virus (HSV) Infections Prophylaxis and Treatment**

HSV remains dormant in HSV-seropositive patients for life. Reactivation following HSCT occurs in 70\% to 80\% of seropositive individuals, and this can lead to severe stomatitis.\textsuperscript{130} Extension along the esophageal mucosa can result in significant morbidity from painful mucositis and increases the risk for bacterial superinfections and bacteremia.

Several studies have suggested that antiviral prophylaxis effectively
prevents reactivation, reduces morbidity, and is associated with a lower potential for emergence of drug resistance than treating symptomatic cases as they occur.\textsuperscript{2, 175, 176, 196} If herpesvirus infections do develop, the treatment of choice is acyclovir (or valacyclovir if the oral route is possible), unless there is a suspicion that the patient may have acyclovir-resistant disease. Even with widespread use of prophylactic acyclovir there have been few reports of acyclovir-resistant HSV infections causing clinical problems in HSCT recipients. In contrast, with treatment of established infection the risk for resistance to emerge is greater, especially if repeated treatments are needed. Resistance is typically caused by loss of thymidine kinase (TK) expression, although it may also be caused by changes in viral DNA polymerase or altered TK-substrate specificities.\textsuperscript{39, 88} In the event of a poor response to therapy or suspicion of an acyclovir-resistant strain, treatment with foscarnet should be implemented; if that fails, cidofovir may be tried.\textsuperscript{42, 140}

All HSCT patients who are HSV IgG positive before transplant should receive HSV prophylaxis with either acyclovir (A1 grade of evidence) or valacyclovir (CIII grade of evidence). Treatment should be started at the onset of chemotherapy or on the day of marrow infusion and continued for the duration of neutropenia until engraftment. Currently at the Shands at UF HSCT program the authors routinely administer valacyclovir 500 mg once daily to all HSV IgG seropositive patients, and this is continued until the ANC is greater than 500/mm\textsuperscript{3}.

**Cytomegalovirus Infections**

One of the most problematic pathogens in the second and third month following HSCT is CMV. Infection rates in seropositive patients are high. Active infection can occur from reactivation of endogenous virus, reinfection from the donor graft, or from virus introduced through blood products from normal donors who may be seropositive.\textsuperscript{24} Even among seronegative patients, there is a potential risk for infection from either the marrow donor or blood product donors.\textsuperscript{209} Provision of blood products from only seronegative donors can be highly effective in prevention of infection in seronegative recipients whose donor also is seronegative.\textsuperscript{218} Alternatively, blood products from seropositive donors can be filtered to deplete leukocytes that harbor latent CMV and reduce the risk for viral transmission.\textsuperscript{35} These strategies have reduced the incidence of CMV infection from 40% to approximately 3% in seronegative patients with seronegative HSCT donors.

Active CMV infection may be asymptomatic, but it can lead to life-threatening illness. The most common manifestation is interstitial pneumonitis (IP). Historically, 90% of CMV IP occurs within the first 100 days after transplant. Late-onset CMV IP, however, is being seen increasingly among unrelated donor transplant recipients and in individuals who are receiving CMV antiviral prophylaxis\textsuperscript{14, 70, 143} or pre-emptive therapy with ganciclovir (GCV) during the first 3 months following HSCT.\textsuperscript{16} A less common manifestation of CMV infection is gastroenteritis. CMV enteritis typically manifests as diarrhea, abdominal pain, or
nausea and vomiting. Other manifestations of CMV infection include chorioretinitis, fever, hepatitis, anorexia, wasting, and a reduction in blood counts, particularly white cells and platelets. Recovery from symptomatic CMV infection requires the development of robust anti-CMV cytotoxic responses.162

CMV disease as a sequela of infection occurs much more frequently in allogeneic HSCT recipients compared to autologous or syngeneic HSCT recipients. In allograft recipients, risk factors for CMV disease include recipients' seropositivity, histocompatibility differences between donor and recipient, T-cell depletion of the stem cell product, graft source from an unrelated donor, older age, more intensive GVHD prophylaxis regimens, and the intensity of the cytoreductive conditioning regimen. Recovery of virus from culture of a specific specimen of blood, urine, or throat secretions indicates also patients at risk for CMV disease.134, 209 Recovery of virus from BAL fluid from an asymptomatic patient 4 to 8 weeks following the transplant is highly predictive of subsequent development of CMV pneumonia.180, 183

Without treatment, CMV pneumonia is fatal in about 80% to 90% cases. GCV therapy resulted in improved survival rates, with 38% to 45% patients being alive longer than 90 days after CMV pneumonia.40, 63 The treatment of greatest benefit appears to be the combination of GCV and high-dose intravenous immunoglobulin (IVIG).9, 54, 166, 194 Combination therapy has resulted in survival rates of 52% to 85%. In a further effort to reduce the morbidity and mortality from CMV symptomatic infection, an emphasis has shifted to either prophylaxis with GCV begun at the time of engraftment or pre-emptive therapy with GCV in patients who have positive surveillance cultures of blood or bronchoalveolar fluid. Both strategies, either prophylaxis or pre-emptive therapy, have been shown in randomized studies to reduce CMV disease.77, 78, 160, 217

Although CMV infection rates after autologous HSCT are frequently as high as those after allogeneic HSCT, CMV disease is much less common. Accordingly, most centers do not employ prophylactic or pre-emptive strategies in autograft patients. The risk of CMV disease is greatest in the allogeneic population and all allogeneic CMV-seropositive HSCT recipients or CMV-seronegative recipients with a CMV-seropositive donor should be offered prophylactic or pre-emptive therapy with GCV.

The prophylactic approach using GCV is highly effective in preventing CMV disease before day 100 in CMV-seropositive patients (29% placebo vs. 0% GCV arm, \( p < 0.001 \)).77 although there was no difference in mortality between the two groups. The disadvantage of this approach is that 100% of patients are treated, resulting in unnecessary therapy in up to 65% of cases. In addition, there is the disadvantage of myelosuppression (30% GVC recipients vs. 0% placebo, \( p < 0.001 \)) and an increased risk for fungal infection (16% with GCV prophylaxis).

Surveillance technology has improved significantly over the last two decades, such that routine weekly CMV antigenemia screening, or CMV PCR screening (in those patients who are CMV seropositive prior to transplant or who have seropositive donors) enables implementation
of a pre-emptive treatment strategy leading to a targeted approach with less toxicity. Detection of CMV pp65 antigen in leukocytes (antigenemia)\textsuperscript{13,17} and detection of CMV-DNA by PCR\textsuperscript{30,83,52,116} is able to provide semiquantitative assessments of viral burdens and has the advantage of producing results approximately 7 to 10 days earlier than traditional shell vial culture techniques. Patients should be started on antiviral therapy upon isolation of CMV using either of these techniques. What level of antigenemia positivity to start treatment at is highly variable and depends on a risk assessment of the patient. Allogeneic and MUD HSCT patients with GVHD should be considered high risk and there should be a lower threshold for starting antiviral therapy. Randomized trials have shown pre-emptive GCV to be effective.\textsuperscript{15} The pre-emptive strategy compared to GCV prophylaxis at engraftment significantly reduced invasive fungal disease (6\% vs. 16\% respectively, \( p < 0.03 \)) and has the advantage of exposing fewer patients to a toxic and expensive therapy.

If the prophylactic approach is adopted in allogeneic patients, GCV should be administered at a dose of 5 mg/kg every 12 hours for 5 to 7 days followed by 5 to 6 mg/kg daily for 5 days a week from engraftment until day 100 (AI level of evidence).\textsuperscript{31} Those patients intolerant to GCV can be changed to foscarnet at a dose of 60 mg/kg every 12 hours for 7 days followed by 90 to 120 mg/kg daily until day 100 (CIII level of evidence).\textsuperscript{31} Data are emerging on less frequent administration of GCV (5 mg/kg IV daily for 21 days), but at this point it cannot be recommended outside the context of a clinical trial.\textsuperscript{6,195}

If the pre-emptive approach is adopted, the current CDC recommendations for allogeneic HSCT recipients is to start therapy with GCV when the patient develops any level of CMV antigenemia or viremia or has two or more consecutive CMV DNA PCR tests.\textsuperscript{31} In autologous recipients the recommendations are to start GCV when antigenemia is more than 5 cells/slide, but to have a lower threshold in CD34-selected patients and to initiate treatment in this population at any level of antigenemia.\textsuperscript{31}

Cidofovir, a new antiviral agent, has also been used extensively in Europe to treat those patients that are CMV antigenemia positive. This strategy has been successful, and has the advantage of being able to be administered less frequently.\textsuperscript{115} Judicious use is important, as the agent requires good renal function, along with extensive prehydration and adjunctive therapies.

**Varicella Zoster Virus Infections**

Recurrences of VZV infections occur in up to 50\% of patients following both allogeneic and autologous HSCT.\textsuperscript{6,82,118,181} The risk is increased in patients in whom GVHD occurs. Onset is approximately 5 months after transplantation, but may be much earlier or later. In a majority of patients, VZV infection may be disseminated at presentation; even in patients in whom the infection begins localized, dissemination may occur in a substantial proportion of patients.\textsuperscript{169,177,221} Atypical presentations of herpes zoster are also relatively common in the HSCT popula-
tion, including diffuse abdominal tenderness without the characteristic
telltale vesicles and lesions. Accordingly, patients and primary
care providers must be vigilant during the first year, since acyclovir or
valacyclovir can readily control this potentially life-threatening infection.
Prophylaxis against VZV is not justified or recommended. Prevention of
VZV infection following exposure should be attempted in all HSCT
recipients who are less than 24 months post-HSCT, or are more than 24
months post-HSCT and on immunosuppressive therapy or have chronic
GVHD. Varicella zoster immunoglobulin should be administered
within 96 hours (preferably 48 hours) after close contact with a person
with either chickenpox or shingles. The dose for adults more than 40 kg
is 625 units administered intramuscularly.

Epstein-Barr Virus Infections

Epstein-Barr Virus (EBV) infections have been less well-studied in
HSCT recipients than the other herpesviruses (HSV, CMV, VZV). It is
clear, however, that viral replication can occur frequently and transmis-
sion from the stem cell donor, blood products, or reactivation of endoge-
nous virus also may occur. EBV-associated lymphoproliferative diseases
have been noted in solid organ and marrow transplant recipients and
the risk is dependent on the interplay between viral burden and effective
immune responses. Patients whose immunity is highly
suppressed are at greater risk. Recipients of T-cell depleted marrow, for
example, are at greatest risk and if antithymocyte globulin is added the
risk is even greater.

For EBV, as with each of the herpesviruses, the development of
virus-specific cytotoxic responses (especially T-lymphocyte–mediated re-
sponses) is crucial for the control of the viral infection. For EBV-associ-
ated lymphoproliferative diseases, a reduction in the immunosuppres-
sive medications is a useful intervention (if possible). Buffy-coat
lymphocyte infusions from the marrow donor may also be effective. Recent data suggest that rituximab (anti-CD 20 monoclonal antibody) at
the conventional dose of 375 mg/m² weekly for four doses is highly
effective in post-transplant lymphoproliferative disease (PTLD).

RESPIRATORY VIRUSES

Respiratory Syncytial Virus Infections

The frequency of infection with respiratory syncytial virus (RSV) in
the immunocompromised patient population is increasing. RSV infec-
tions in HSCT patients were first described in 1988, and since that time
have become almost commonplace with several outbreaks reported in
large HSCT centers. The incidence of RSV infections in hospital-
ized HSCT patients ranges from 7% to 20%, with the majority of infec-
tions occurring in the winter months. RSV infection typically presents
as an upper respiratory tract (URT) illness (cough, fever, sinus/nasal
congestion, rhinorrhea, dyspnea, and increased sputum), but rapidly progresses to severe and often-fatal lower respiratory tract (LRT) viral pneumonia with marked radiographic changes. Risk factors for progression of RSV URT infections to pneumonia in HSCT recipients include older age and HLA-mismatched or unrelated donor transplants.

The development of pneumonia is associated with a high mortality rate (66% to 100%); therefore, treatment should be implemented rapidly to prevent progression. The speed of diagnosis and implementation of treatment have been shown to affect the outcome of HSCT patients with RSV infections. In a recent series, those patients treated early (<1 day from symptoms) had an overall mortality rate of 22% versus 100% in those patients in whom treatment was delayed greater than 3 days or not given. Engraftment status is another predictor of whether a HSCT recipient will develop pneumonia, with patients who have not engrafted being at greater risk for developing pneumonia than those who have engrafted (79% vs. 41%).

Currently available treatment options for RSV pneumonia are limited and associated with variable success. The most commonly employed agent is ribavirin, although the efficacy in HSCT recipients is poor, with high mortality rates and frequent recurrence with subsequent death. For ribavirin to be effective, therapy should be implemented before the development of pneumonia because the response rates once pneumonia develops are significantly reduced. The combination of ribavirin with IVIG or respiratory syncytial virus immunoglobulin (RSVIG) has been studied and is associated with survival rates of 78% to 86%. These results appear to be more favorable than ribavirin alone, although the majority of studies were retrospective reviews. Because no randomized studies comparing ribavirin alone to ribavirin plus IVIG have been conducted, it is not possible to make definite conclusions. There is data available supporting the use of RSVIG in HSCT recipients. DeVincenzo studied 11 patients with RSV LRT infection. RSVIG 1500 mg/kg was administered intravenously as salvage treatment, with some patients receiving both RSVIG and ribavirin. In this cohort 54% of patients had resolution of RSV LRT infections and the mortality rate was only 9%, a promising result in a group of patients who have a traditionally poor outcome. The final agent that has been studied in HSCT patients is palivizumab (Synagis, MedImmune, Gaithersburg, MA), a humanized RSV monoclonal antibody that is highly active against RSV types A and B. Palivizumab was studied in 15 HSCT patients who had proven RSV infections. At enrollment, 80% of patients had LRT involvement and 20% were mechanically ventilated. The standard dose (15 mg/kg) was administered in conjunction with ribavirin therapy. Eighty-seven percent of patients survived, a result similar to those seen with RSVIG. A randomized phase II study evaluating the efficacy of palivizumab combined with aerosolized ribavirin compared to ribavirin alone to treat RSV pneumonia in patients undergoing HSCT is currently being conducted, and the results are much awaited.

It is clear that the best treatment is prevention of exposure. This is
important because despite treatment the mortality rate is high, particularly once there is LRT involvement. At this point, there is no prophylactic strategy that has been studied well in this population and therefore prevention of exposure is of paramount importance. Preventing exposure to community respiratory viruses (CRV) is critical to preventing all community respiratory virus disease. Appropriate precautions and infection control measures should be instituted in HSCT recipients and candidates undergoing conditioning therapy, especially during community or nosocomial CRV outbreaks. In addition, patients with URT or LRT infections should be placed under contact precautions to avoid transmission to other HSCT patients. The CDC has published guidelines for the prevention of opportunistic infections in recipients of HSCT, with an entire section devoted to appropriate hospital infection control. The reader is referred to this document for all precautionary measures that should be taken when dealing with CRV infections.

Parainfluenza Infections

Parainfluenza infection (PIV) also is common in the immunocompromised HSCT recipient. In contrast to RSV, which typically occurs in the winter months, PIV can occur at any time during the year. PIV commonly progresses from an URT infection to a LRT infection, with up to 50% of adult HSCT recipients developing pneumonia as a consequence of an URT infection. Patients who develop PIV infections are also at higher risk for the development of secondary fungal, viral, and bacterial infections. Unfortunately no well-documented treatment is available for the management of PIV infection, and again prevention of exposure is of utmost importance.

OTHER VIRUSES

Adenovirus infections have been reported to occur in 5% to 21% of HSCT recipients. Recipients of allogeneic HSCT are more likely to develop adenovirus infections than autologous recipients. Adenovirus infections can present in several different ways, including gastrointestinal infections (diarrhea, hemorrhagic colitis or hepatitis), pulmonary infections (resulting in interstitial pneumonitis), and urinary tract infections such as hemorrhagic cystitis and subsequent renal failure. The most common manifestation in HSCT recipients is hemorrhagic cystitis. Infections in HSCT patients typically are disseminated in nature and result in multiorgan failure. The risk of dissemination is greater in recipients of matched unrelated donor transplants. Mortality rates approaching 60% have been reported.

Treatment options remain limited. Agents successfully used in limited number of patients include ribavirin, ganciclovir, vidarabine, and cidofovir. Success rates with the majority of these agents are low, although results seen with cidofovir appear promising.
**Fungal Infections**

**Treatment of Fungal Infections**

Fungal infections in HSCT recipients are the most difficult to manage and remain the leading cause of infectious mortality after HSCT.\(^{215}\) The main risk factor for the development of fungal infections is neutropenia, and more specifically, the depth and duration of neutropenia. This risk is directly proportional to the duration of neutropenia, increasing incrementally into the second and third weeks of the neutropenic episode.\(^{72, 215}\) Recipients of allogeneic HSCT who fail to engraft or recipients who receive stem cell grafts containing low number of hematopoietic progenitors are at greatest risk of developing a fungal infection. Fungal infections largely occur in allogeneic HSCT recipients and are much less common in autologous HSCT patients.

Commonly *Candida* infections involve the mucosal surfaces causing thrush, esophagitis, vaginitis, or intertriginitis, but tissue invasion may result in fungemia. The portal of entry for systemic *Candida* infections is the damaged mucosa of the gastrointestinal tract. The suppression of bacterial flora by the widespread use of broad-spectrum antibiotics leads to proliferation of *Candida* spp. These organisms can then cross the mucosal barrier into the bloodstream. One of the main risk factors for *Candida* infections is the use of a conditioning regimen that causes significant mucosal damage. Studies have shown that different chemotherapeutic regimens lead to different rates of invasive fungal infections, and infection rates have correlated well with mucosal injury.\(^{19, 20}\)

Before the advent of fluconazole prophylaxis, *Candida* spp. were the most common cause of fungal infection in the HSCT patient; however fluconazole prophylaxis has significantly reduced the number of systemic fungal infections\(^{76, 170}\) and has been shown to improve overall survival in allogeneic HSCT patients when therapy is continued until at least 75 days post-transplant.\(^{184}\) As a consequence of the widespread implementation of this successful strategy other *Candida* spp. have evolved as important pathogens. Species of most concern today include *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis*, *Candida krusei*, and *Candida lusitania*, which represent approximately half of all bloodstream *Candida* isolates.\(^{142, 156, 157, 213}\) Emergence of resistant species (C. krusei and C. glabrata) is increasing and has been shown to be associated with the widespread use of fluconazole.\(^{120, 207, 208, 213}\) C. krusei is universally resistant to fluconazole and therefore should be treated with amphotericin. Infections of other non-*albicans* *Candida* spp. detected while a patient is receiving azole prophylaxis should be treated with alternative agents until susceptibility results are available. Vigilant surveillance techniques should be employed in institutions using prophylactic strategies, and alternative treatments should be implemented if resistant organisms are isolated.

As *Candida* infection rates have declined with the widespread use of fluconazole, other fungal pathogens such as *Aspergillus* spp., *Fusarium* spp., and members of the Mucorales family have emerged as the leading
cause of infectious mortality. The portal of entry for *Aspergillus*, an airborne pathogen, is the nasal passages and respiratory tract. The usual manifestations of *Aspergillus* infection are fever, sinus symptomatology, or respiratory symptoms, especially those suggestive of pulmonary infarction. The portal of entry for *Fusarium* spp. is typically onychomycosis or trauma, but the sino-pulmonary tract also is a potential portal of entry. The usual manifestations of *Fusarium* spp. are fever, nodular or cavitary lesions, and metastatic skin lesions. All of these fungi are extremely difficult to treat and are difficult to diagnose. Fungal infections are frequently only found at autopsy,\textsuperscript{10} with the exception of *Fusarium* spp., in which identification in the bloodstream is reported in 50% to 70% of cases.\textsuperscript{18}

Whenever one of these organisms is isolated in a neutropenic patient or a patient with impaired cellular and humoral immune responses, the treatment of choice is conventional amphotericin B (cAmB) at a dose of 1 to 1.5 mg/kg/day.\textsuperscript{18} In the case of intolerance to or organ dysfunction as a consequence of cAmB therapy, one of the lipid amphotericin B products such as Amphotericin B lipid complex (ABLC) [Abelcet, Liposome Company Inc., Princeton, NJ], Liposomal Amphotericin B (LAMB) [Ambisome, Fujisawa Healthcare Inc., Deerfield, IL] and Amphotericin B Colloidal Dispersion (ABCD) [Amphotec, Alza Corp., Palo Alto, CA] should be considered. There are many reports in the literature supporting the use of LAMB,\textsuperscript{53, 109, 161} ABLC,\textsuperscript{126, 197, 212} and ABCD\textsuperscript{146} in the treatment of fungal infections in the HSCT recipient. The most common debate among BMT and infectious diseases practitioners is when a lipid formulation should be used in place of conventional amphotericin B. Are the lipid amphotericin B products superior to cAmB in terms of efficacy? This is a difficult question, and much of the available literature is flawed with poor study design or inclusion of small numbers of documented invasive fungal infections according to strict criteria (such as the criteria of the Mycosis Study Group). There is limited data on the comparative efficacy of the lipid products versus cAmB, but of the data available it can be concluded that the lipid products are as efficacious as cAmB, and do have the advantage of a safer side effect profile.\textsuperscript{3, 23, 81, 109}

Lipid amphotericin B products cause less nephrotoxicity than cAmB.\textsuperscript{161} LAMB is the only lipid product also to have less infusion-related toxicity. The choice of which lipid amphotericin B product to use is controversial. There are no comparative studies of ABCD versus the other lipid-based products, although two studies comparing the side effect profiles of ABLC and LAMB recently have been completed. Wingard et al conducted a randomized comparative trial evaluating the safety of ABLC (5 mg/kg/day) versus LAMB (3 mg/kg/day and 5 mg/kg/day) in the empirical treatment of febrile neutropenia. LAMB demonstrated a superior side effect profile with significantly less fever, chills/rigors, and nephrotoxicity. The frequency of toxicity-related discontinuations of therapy also were less in the LAMB treated group.\textsuperscript{211} Therapeutic success was similar in all three groups, although the study was not powered to detect differences in efficacy.

There should be a lower threshold for starting a lipid amphotericin
B product in allogeneic HSCT patients. The risk for developing renal dysfunction requiring dialysis is increased significantly in allogeneic HSCT patients on CAmB and receiving concomitant immunosuppressive medications and nephrotoxins\textsuperscript{204} (see Table 2).

In those patients with documented systemic mycoses who are intolerant to both CAmB and the lipid-based amphotericin B products, itraconazole is an alternative\textsuperscript{45, 46, 188} Itraconazole was limited in the past by a capsule formulation that was poorly absorbed and the lack of an intravenous preparation. The oral preparation since has been reformulated into a cyclodextrin base that has overcome the limitations of the capsule formulation in that both adequate plasma concentrations are reliably reached and it can be administered with or without food.\textsuperscript{83, 127, 189} In addition, an intravenous preparation is now commercially available, making treatment of patients with severe mucositis possible. The role of itraconazole in the treatment of systemic mycoses is currently reserved for those patients who have responded to amphotericin B and require ongoing treatment in the outpatient setting. In this population regular blood level monitoring should be performed to ensure adequate absorption of the oral solution. The minimally effective trough required for treatment is 250 ng/mL, although recent data suggest that 500 ng/mL is more efficacious.\textsuperscript{74, 160} The role of itraconazole in the treatment of invasive Aspergillus infections in HSCT is unclear and there is a lack of data to support this indication at present. The current primary role of itraconazole in HSCT is as prophylaxis against the development of systemic mycoses.

**Table 2. Vaccination of Hematopoietic Stem Cell Transplant Recipients**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>12 Months</th>
<th>14 Months</th>
<th>24 Months</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Haemophilus influenzae</em> Type b (Hib) Conjugate\textsuperscript{a}</td>
<td>Hib</td>
<td>Hib</td>
<td>Hib</td>
<td>B II</td>
</tr>
<tr>
<td>23-Valent Pneumococcal Polysaccharide Vaccine\textsuperscript{b} (Pneumo)</td>
<td>Pneumo</td>
<td>Pneumo</td>
<td></td>
<td>B III</td>
</tr>
<tr>
<td>Meningococcal Vaccine</td>
<td>Routine administration is not indicated</td>
<td>Not rated—limited data</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Haemophilus influenzae type b (Hib)-conjugate vaccine is recommended for HSCT recipients of any age.

\textsuperscript{b}The 23-valent pneumococcal polysaccharide vaccine may not be protective against pneumococcal infection in HSCT recipients. The second dose of vaccine is not a booster dose, but provides a second chance for immunologic response for persons who failed to respond to the first dose. Adjunctive antibiotic prophylaxis against encapsulated organisms, including pneumococcal disease, is recommended for allogeneic HSCT with cGVHD. No data are available on safety and immunogenicity of the 7-valent conjugate pneumococcal vaccine in HSCT recipients, so no recommendation regarding the use of this vaccine can be made.
There are several other antifungal agents currently being evaluated in clinical trials, including the second-generation triazoles. Drugs of this class include posaconazole (SCH 59562, Schering Plough), voriconazole (Pfizer), and ravuconazole (BMS-207, 147, Bristol). All agents in this class have activity against resistant C. albicans, non-albicans Candida spp. (C. krusei, C. glabrata), and Aspergillus spp. There are limited data demonstrating that posaconazole is active against murine Fusarium spp. Concerns with these agents include either the lack of an intravenous formulation, the occurrence of cytochrome P450 drug interactions, or nonlinear kinetic profiles. Currently active areas of investigation with the majority of agents include the treatment of invasive fungal infections in patients who are resistant or refractory to standard antifungal therapies and in the prophylaxis of invasive fungal infections in high-risk recipients of allogeneic HSCT.

Another class of drugs of interest to the HSCT practitioner is the echinocandins. Agents of this class have a different mechanism of action to other known antifungals (inhibit cell wall synthesis by inhibiting (1,3)-beta-D-glucan synthase) and potentially may be synergistic with currently marketed agents. There are currently three agents under investigation, namely FK463 (Fujisawa), caspofungin (MK 0991, Cancidas; Merck), and LY-303, 366 (Lilly). All drugs in this class have been shown to be fungicidal against all species of Candida, and they are also being investigated for their activity against Aspergillus spp. Ongoing studies with FK463 are being conducted in HSCT patients. A dose finding study was published in 1999, and current trials are evaluating the efficacy of FK463 as prophylaxis in HSCT recipients. The echinocandin closest to marketing is caspofungin, and currently is in phase II and III clinical trials. Caspofungin has been shown to be effective in the HIV population and the product is now being studied in immunocompromised patient populations.

Choices of antifungal therapy are about to expand, offering the clinician a greater choice, potentially with less toxicity and drug interactions. Current data are limited with the newer agents, and only time will tell if the in vitro activity translates into clinical efficacy. Nevertheless, the future is bright and anticipated with much enthusiasm.

**Prophylaxis Against Fungal Infections**

Current CDC recommendations are that antifungal prophylaxis with fluconazole be administered to all allogeneic HSCT recipients and to autologous HSCT recipients with lymphoma or leukemia who have or will have prolonged neutropenia and mucosal damage from intensive conditioning regimens or graft manipulation. Patients who have received fludarabine or 2-chlorodeoxyadenosine close to HSCT should also receive antifungal prophylaxis. The aim of prophylaxis is to prevent infection with fluconazole-susceptible Candida spp. Prophylaxis should start on the day of transplantation and continue until engraftment, or
until 7 days after the ANC is greater than 1000 cells/mm\(^3\). The dose of fluconazole recommended by the CDC is 400 mg daily (AI grading), although there are data available in the literature supporting lower doses of fluconazole.\(^1\) It is important that local infection patterns and susceptibility data be considered when choosing a dose. A reproducible antifungal susceptibility testing method is now available for antifungal agents, and over time may be incorporated into clinical practice to guide the decision making process.\(^6\)

Fluconazole’s efficacy is limited by its spectrum of activity. Fluconazole provides adequate protection against most *Candida* spp., but is ineffective against *C. krusei*, some strains of *C. glabrata*, and the molds. Itraconazole also has limited activity against *C. krusei* and some strains of *C. glabrata* but has the advantage of efficacy against the molds. Several studies have been performed with itraconazole capsules as prophylaxis against fungal infections in patients with hematologic malignancies.\(^136, 147\) The most recent study published by Nucci et al demonstrated no overall difference in empirical use of amphotericin B or in the development of systemic fungal infections, although among patients with prolonged and profound neutropenia, less empirical amphotericin B was used and fewer systemic fungal infections developed (6% vs. 19%, \(p = 0.04\)). Studies using itraconazole solution also have been published, and these demonstrate that the incidence of superficial fungal infections is reduced by itraconazole solution. However, the incidence of proven fungal systemic fungal infections, the number of deaths caused by deep fungal infections, and the use of systemic antifungals while tending to be lower in the itraconazole treated arm were not statistically different to placebo or fluconazole.\(^6, 83, 136\) Additional studies using prophylactic itraconazole solution and injection in HSCT recipients are necessary before itraconazole can be recommended routinely.

The final well-described prophylactic strategy for the prevention of fungal infections in HSCT recipients is the administration of low-dose cAmB.\(^148, 154, 171, 220\) The administration of 0.1 to 0.2 mg/kg/day of cAmB before and during HSCT has been shown to reduce colonization and in the majority of studies there was a trend toward a reduction in fungal infections. A recent comparative study of low dose cAmB (0.2 mg/kg/day) versus fluconazole (400 mg/day) demonstrated similar outcomes in proven fungal infections, total number of days of fever over 38°C, and therapeutic cAmB usage. The only difference was in toxicity with 19% of cAmB recipients developing toxicity versus 0% in the fluconazole arm.\(^220\) This treatment strategy is reserved best for those patients who are unable to tolerate azole antifungals.

**Pneumocystis carinii pneumonia**

The treatment of choice for *Pneumocystis carinii* pneumonia (PCP) infection is SMX-TMP at doses of 15 to 20 mg/kg/day based on the TMP component. If drug levels are monitored, a range of 100 to 150
mg/L should be targeted (based on the SMX component). Second line agents include intravenous pentamidine (4 mg/kg/day); combination therapy dapsone (100 mg per day) plus TMP (15 to 20 mg/kg/day); or atovaquone, 750 mg orally three times daily. There are several treatment options for PCP prophylaxis in HSCT recipients. Well-studied agents include SMX-TMP, dapsone, and aerosolized pentamidine. The selection of a particular prophylactic strategy is institution dependent and until recently there were no data available comparing outcomes with the different agents in HSCT recipients. Two recent publications have proven that SMX-TMP is the agent of choice. Data from the Dana Faber Institute demonstrated SMX-TMP to be superior to aerosolized pentamidine (AP) as prophylaxis against PCP. A retrospective review of 327 patients revealed a total of 8 PCP cases (no cases in SMX-TMP recipients). The odds ratio of developing PCP in recipients of AP was 23.4 compared to SMX-TMP. Patients receiving AP had a lower probability of treatment-related toxicity than SMX-TMP, although the probability of developing other non-PCP infections was increased. The overall 1-year mortality was also higher in recipients of AP.

Souza and colleagues evaluated the efficacy of SMX-TMP (twice weekly, \(n = 535\)) and dapsone (50 mg bid 3 times per week, \(n = 111\)) in preventing PCP following allogeneic HSCT. Ten patients developed PCP (eight were receiving dapsone). The relative risk for developing PCP associated with dapsone was 18.8 \((p < 0.001)\), and could not be accounted for by standard risk factors. With the availability of these results, the prophylactic drug of choice in HSCT recipients should be SMX-TMP (AII grade of evidence). In the event of intolerance other agents can be used, but a high index of suspicion for PCP should be maintained in patients with pulmonary signs and symptoms.

**SUMMARY**

Numerous advances have been made in the management of infection in HSCT recipients. With increasing knowledge the authors are able to prevent several serious infections from occurring, and reduce the severity of infections once they occur. Despite these advances, several previously unrecognized pathogens have emerged and pose risks to this population. Ongoing surveillance and reporting of atypical infections are warranted. Transplant and infectious disease clinicians alike must be vigilant to the shifts in infectious syndromes as a consequence of various prophylaxis and preemptive strategies, and be ready to modify empiric strategies to meet the changing microbiologic milieu. As we increase our understanding of the HSCT process, and use the immune system rather than relying on high-dose chemotherapy, the authors are likely to reduce toxicities and improve patient outcomes.
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