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## SHORT VIEW SUMMARY

### TYPES OF DONORS OF STEM CELLS FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

- Syngeneic: donor is an identical twin sibling
- Autologous: the recipient donates to self
- Allogeneic: the donated material comes from a different individual than the recipient

### SPECIFIC TYPES OF ALLOGENEIC DONORS

- Matched related or partially matched related donor, such as a sibling with the same or similar human leukocyte antigen (HLA) type
- Unrelated donor or matched unrelated donor
- Haploidentical: parent, cousin, sibling, or child is the donor; one HLA haplotype matched
- Cord: umbilical cord blood usually partially HLA matched, not matched for blood type; sometimes two cords used to provide blood with sufficient cells
- Haplo-cord: haploidentical peripheral blood stem cells plus cord blood cells; haplo-cord engrafts rapidly but may not be sustained yet provides neutrophil production until the cord engrafts

### TYPES OF CELLS USED IN HSCT

- Peripheral blood stem cells, usually filgrastim (granulocyte colony-stimulating factor) mobilized; may be CD34 selected for T-cell depletion
- Umbilical cord blood: usually associated with delayed engraftment but less graft-versus-host disease (GVHD)
- Bone marrow: collected by aspiration harvest from matched related or matched unrelated donor; associated with less chronic GVHD
- Donor lymphocyte infusion: donor cells sorted for lymphocytes; given after engraftment or after relapse for antitumor or antiviral effect but can stimulate GVHD

### PREPARATION OF PATIENT FOR CELL INFUSION ("CONDITIONING REGIMEN")

- Myeloablative: total-body irradiation plus cyclophosphamide or busulfan; can be without irradiation
- Nonmyeloablative (reduced intensity): using lower-dose total-body irradiation or with antithymocyte globulin, most often with fludarabine

### OUTCOMES

- Engraftment: absolute neutrophil count rises to more than 500 cells/ $\mu$ L by day 42
- Primary graft failure: no engraftment by day 42
- Mixed chimerism: persistence of host and donor hematopoiesis

- Relapse: return of the underlying malignant condition

### COMPLICATIONS

- Mucositis: mucosal inflammation that serves as a portal of entry for oral or intestinal infections; common with methotrexate-containing regimens. Palifermin may reduce mucositis.
- Hemorrhagic cystitis: often occurs in conjunction with cyclophosphamide early after transplant, despite the use of mesna and forced diuresis; viral causes more common later after transplant, including adenovirus or BK virus
- Engraftment syndrome (immune reconstitution syndrome): fever with or without rash and/or pulmonary infiltrates at engraftment
- Veno-occlusive disease, also called sinusoidal obstruction syndrome: triad of jaundice, weight gain, and ascites leading to multiorgan failure, usually occurring in the first 3 to 4 weeks after transplantation
- Diffuse alveolar hemorrhage: bleeding into alveoli, usually during the second or third week after transplant; diagnosed by progressive bloody returns on lung lavage and treated with corticosteroids
- Graft-versus-host disease: inflammation and cell death (apoptosis) in skin, liver, gut, or lung. Acute form usually occurs until day 100. Chronic form generally occurs later and has features resembling but distinct from scleroderma. The risk is higher in the elderly and with grafts from partially matched donors. Calcineurin inhibitors (cyclosporine, tacrolimus), less often sirolimus, and mycophenolate mofetil are started soon after transplant to decrease the incidence and severity of GVHD. High-dose corticosteroids (and other agents) are used to treat GVHD.
- Posterior reversible encephalopathy syndrome: neurotoxicity from hypertension, calcineurin inhibitors, or fludarabine
- Bronchiolitis obliterans organizing pneumonia and obliterative bronchiolitis: pneumonitis associated with small airway injury, sometimes associated with chronic GVHD

### ANTIMICROBIAL AGENTS FOR PROPHYLAXIS

- Acyclovir: low dose for herpes simplex virus, high dose for cytomegalovirus (see Table 312-3)
- Levofloxacin: used for prevention of bacterial infections, until fevers or infection develop
- Fluconazole: for prevention of candidiasis, starting with neutropenia

- Trimethoprim-sulfamethoxazole: agent of choice for *Pneumocystis*; also covers *Toxoplasma* and some bacteria, such as *Nocardia*. Alternatives include aerosolized pentamidine, atovaquone, and dapsone.
- Penicillin VK: prevention against *Streptococcus pneumoniae* during active chronic GVHD. Regional penicillin resistance may lead to the use of levofloxacin for this indication.
- Voriconazole or posaconazole: given in place of fluconazole to prevent mold infections
- Echinocandins (micafungin or caspofungin): intravenously administered agents that may be substituted for azoles
- Lamivudine: prevention of hepatitis B virus reactivation in anti-hepatitis B core antibody-positive, hepatitis B surface antigen-negative, and hepatitis B DNA-negative patient with hepatitis B-positive donors. Entecavir or tenofovir may be substituted for lamivudine.
- Entecavir or tenofovir: prevention of hepatitis B virus reactivation in hepatitis B surface antigen-positive patient
- Ivermectin: two doses for patients from countries with high risk for *Strongyloides* infestation

### PREEMPTIVE THERAPY

- Ganciclovir, valganciclovir, or foscarnet: given to patients with cytomegalovirus reactivation based on polymerase chain reaction assay of blood or pp65 neutrophil antigen (see Table 312-3)

### EMPIRICAL ANTIBACTERIAL THERAPY DURING FEVER AND NEUTROPENIA WITH NEGATIVE WORKUP

- Designated broad-spectrum agent such as ceftazidime, piperacillin-tazobactam, or cefepime
- Addition of an aminoglycoside possibly required for institutional antibiotic resistance patterns
- Vancomycin if any cellulitis, dysfunction with an indwelling catheter, or hemodynamic instability or colonized with methicillin-resistant *Staphylococcus aureus*.

### VIRAL DISEASES IN THE TRANSPLANT RECIPIENT

- Herpes simplex virus: oral, esophageal, vaginal ulcers; autoinoculation of other skin sites
- Varicella-zoster virus: dermatomal zoster; may disseminate; rarely severe hepatitis or visceral zoster
- Cytomegalovirus: fever, viremia, cytopenias, pneumonitis, gastrointestinal disorders (e.g., hepatitis, esophageal ulcers, mucosal changes in the duodenum or colon), retinitis

**KEYWORDS**

adenovirus; allogeneic; *Aspergillus*; autologous; BK virus; bronchiolitis obliterans organizing pneumonia; chimerism; cytomegalovirus; donor lymphocyte infusion; diffuse alveolar hemorrhage; graft-versus-host disease (GVHD); haploidentical; hematopoietic stem cell transplant (HSCT); hemorrhagic cystitis; matched unrelated donor; mold-active agent; parainfluenza virus; *Pneumocystis*; posterior reversible encephalopathy syndrome; post-transplant lymphoproliferative disorder (PTLD); preemptive; prophylaxis; respiratory syncytial virus; stem cell transplantation; syngeneic; toxoplasmosis; transplant; typhlitis; umbilical cord blood; veno-occlusive disease (VOD)

- Human herpesvirus 6: viremia, pneumonitis, encephalitis; may be associated with delayed neutrophil recovery or prolonged thrombocytopenia
  - Adenovirus: hemorrhagic cystitis, pneumonitis, hepatitis
  - BK polyomavirus: hemorrhagic cystitis
  - Hepatitis B and C: hepatitis
  - Major respiratory viruses: influenza, respiratory syncytial virus in the winter; parainfluenza virus and rhinovirus year-round.
  - JC polyomavirus: progressive multifocal leukoencephalopathy
  - Epstein-Barr virus: viremia or post-transplant lymphoproliferative disorder
- OTHER INFECTIONS**
- *Clostridium difficile* diarrhea: stool toxin polymerase chain reaction assay considered the best test
  - Intravascular central catheter-related bacteremia or tunnel infection
  - Typhlitis: abdominal pain and cecal edema during neutropenia
  - *Pneumocystis* infection: diffuse pneumonitis among those not taking prophylaxis
  - Candidiasis: candidemia originating from the gut
  - Infection with *Aspergillus* and other molds: lung field abnormalities, sinusitis
  - Toxoplasmosis: brain lesions

The clinical approach to infections in patients undergoing hematopoietic stem cell transplantation (HSCT) involves an understanding of basic transplantation techniques, clinical syndromes, host defense defects at different times after transplantation, the natural history of individual infections, and the mechanisms underlying reconstitution of the immune system after transplantation. In general, the dominant elements of infectious risks for bacterial, viral, fungal, and parasitic infections after HSCT depend on the pretransplantation exposure history (viral serostatus), whether the transplant is from an autologous or an allogeneic donor source, and the number of days after the transplant under consideration. The distinguishing determinant of infectious risk between autologous and allogeneic grafts is the associated risk incurred by ongoing immunosuppression from graft-versus-host disease (GVHD) and its therapy; differing tempos of humoral and cellular immune reconstitution also affect the risk. The time period after transplantation defines eras of differing transplantation complications and the evolution of the slowly resolving post-transplantation immunodeficiency: cutaneous and mucosal barrier breakdown, neutropenia, lymphopenia, hypogammaglobulinemia, or a combination of these. Many post-transplantation complications mimic infectious processes, and multiple infections may occur in the same patient at the same time. Therefore, the patient undergoing HSCT should be examined in the context of pretransplantation infections, serologic profiles to document infection latency, conditioning regimen, available culture data from mucosal surfaces, contemporaneous transplantation complications in the patient's institution, current antimicrobial prophylaxis, and the current degree and duration of neutropenia and lymphopenia.

## BASIC TRANSPLANTATION TECHNIQUES

HSCT involves the intravenous delivery of hematopoietic stem cells to a recipient whose hematopoietic and immune systems have been ablated or altered by a cytotoxic and immunosuppressive preparative regimen, commonly referred to as the "conditioning regimen," given over the 4 to 10 days before HSCT. Hematopoietic stem cells are obtained from bone marrow, filgrastim-stimulated peripheral blood, or umbilical cord blood.<sup>1,2</sup> Allogeneic donors can be related or unrelated and human leukocyte antigen (HLA) matched at loci of the major histocompatibility complex or mismatched. HSCT is an option in treatment of disorders of bone marrow failure (e.g., aplastic anemia, Fanconi anemia), malignancies (e.g., acute and chronic leukemias), lymphomas, multiple myeloma, hemoglobinopathies or thalassemias, severe immunodeficiency syndromes, inborn errors of metabolism (e.g., osteopetrosis, chronic granulomatous disease, Hurler's syndrome, inherited leukodystrophies, other lysosomal disorders), and high-risk solid tumors (e.g., neuroblastoma, germ cell tumors). It is currently used investigational in treatment of diseases such as epidermolysis bullosa and autoimmune disorders (scleroderma).<sup>3,4</sup> Allogeneic transplant has been feasible for selected human immunodeficiency virus (HIV)-positive patients with malignant and nonmalignant diseases since highly active antiretroviral therapy became standard treatment for HIV infection.<sup>5</sup>

Autologous HSCT is used in the treatment of multiple myeloma, neuroblastoma, and certain leukemias and lymphomas. Morbidity and mortality arise from regimen-related toxic effects and early infections. Allogeneic HSCT is used for these and for all the diseases listed previously, with the additional hazards of a higher risk of graft failure

(prolonging neutropenia) or GVHD. Substantial improvements in the supportive care of severely immunosuppressed patients have evolved since the 1980s, and survival has markedly improved over time.<sup>6</sup> As outcomes with transplantation improve, the utilization of transplantation as an option depends less on the availability of certain donor sources (i.e., whether there is an available matched donor) than in prior decades. Unrelated adult volunteer donors are available for more than half the general population, and unrelated umbilical cord blood is used increasingly as a source of stem cells for transplantation.<sup>7</sup> Umbilical cord blood has been shown to be an effective alternative for patients who lack a suitable adult donor, but its use is limited by finding an umbilical cord blood unit with an adequate cell dose for the recipient's size and weight. Strategies such as transplanting two closely matched or ex vivo expanded umbilical cord blood units have enabled transplantation for adults.<sup>7</sup>

The conditioning regimen used to prepare the host is a major determinant of outcome because of variable host tissue injury and the potential for induction of prolonged immunodeficiency. Conditioning regimens may include immunosuppressive and cytotoxic chemotherapy alone or in combination with wide-field or total-body irradiation. Conditioning can damage mucosal surfaces, facilitating transmucosal entry of bloodstream infections.<sup>8</sup> Indwelling intravenous catheters can also lead to disseminated bloodstream infections. Environmental exposure to airborne dusts and fungal spores can inoculate the sinuses or respiratory tree. Prophylactic antibiotic therapies and nutritional changes can deplete commensal and potentially protective elements of the cutaneous and intestinal microbiome. The infectious risks for the patient undergoing HSCT are affected by transplantation complications, including the direct effects of this high-dose conditioning, such as mucositis, hemorrhagic cystitis, diarrhea, and hepatic veno-occlusive disease (VOD); GVHD; and relapse of the underlying hematologic or oncologic disease.

## Chemotherapy

Busulfan and melphalan are commonly used alkylating agents that are toxic to myeloid stem cells and mucosal and epithelial cells. Cyclophosphamide-containing regimens predispose patients to hemorrhagic cystitis. Fludarabine is less cytotoxic but intensely immunosuppressive and is often included in reduced-intensity or nonmyeloablative conditioning regimens.<sup>9</sup> Antithymocyte globulin, which alters the function of or depletes T cells and other lymphocytes, can be used as conditioning regimen for aplastic anemia and, at times, for GVHD prevention or treatment.<sup>10</sup> Serum sickness—a syndrome of fever, arthralgia, and rash—can occur with antithymocyte globulin or other xenoprotein therapy; it is treated with corticosteroid therapy. Antilymphoid antibodies, including alemtuzumab or rituximab, can induce prolonged and profound lymphopenia. Some GVHD prevention strategies include ex vivo graft manipulation (CD34<sup>+</sup> or CD3<sup>-</sup> selection) for T-lymphocyte depletion. A new approach is post-HSCT cyclophosphamide (on days 3 and 4 after grafting) to lyse proliferating alloreactive lymphoid cells. Cyclosporine, tacrolimus, mycophenolate mofetil, methotrexate, or sirolimus (and other agents) are often used for weeks to months after allografting to lessen the risks and severity of GVHD. Although all these may reduce the risks for GVHD, these maneuvers also substantially delay immune recovery, particularly in haploidentical (one HLA haplotype matched) or HLA-mismatched HSCT.

## Irradiation

Total-body irradiation may be administered as a single dose or more often “fractionated” in multiple doses given over several days. Diarrhea occurs in virtually all treated patients in the first week after irradiation. It may be treated symptomatically while stool studies are pending to rule out infectious causes. Severe oral mucositis occurs in many irradiated patients and is aggravated by prolonged neutropenia and the use of methotrexate for GVHD prophylaxis.<sup>8</sup> As long as bleeding and oral inflammation do not compromise the patient’s airway, mucositis is treated symptomatically. Keratinocyte growth factor (delivered clinically as palifermin) has proven activity in the prevention of oral and intestinal mucositis.<sup>11,12</sup> Its use to limit mucositis may be of benefit in patients receiving highly toxic conditioning, including high-dose total-body irradiation, high-dose melphalan, or post-HSCT methotrexate.<sup>13</sup> Palifermin has not been shown to reduce GVHD, infections, or mortality.<sup>14,15</sup>

## Nonmyeloablative Transplantation

Reduced-intensity, or nonmyeloablative, regimens have been developed with the goal of permitting donor-derived hematopoietic and immunologic reconstitution.<sup>16,17</sup> These lesser-intensity regimens may provide a somewhat weaker anticancer effect and rely on the graft-versus-tumor effects to eradicate underlying malignancies. Doses of total-body irradiation are usually not more than 2 Gy, in comparison with 12 to 14 Gy in fully ablative transplants. Fludarabine, antithymocyte globulin, or lower doses of cytotoxic drugs may be used with induction of extended immune suppression.<sup>18</sup> This approach is often used for older patients or those with significant medical comorbid conditions. They are intensely immunosuppressive but less cytotoxic, resulting in less mucosal, enteric, and hepatic injury in the early weeks after transplantation, yet they are followed by similar risks for GVHD and prolonged immunoincompetence.

## Human Leukocyte Antigen Matching

In general, engraftment is most rapid, and thus neutropenia is briefest, when the patient and allogeneic donor are completely matched at all genetic HLA loci (most often considering only HLA-A, B, C, DRB1). Similarly, identical twin (syngeneic) transplantations or those in which hematopoietic stem cells collected from the recipient (autologous) are used lead to prompt neutrophil recovery. Allogeneic HSCT has the highest chance of prompt engraftment when fully HLA-matched sibling donor transplants are used, but fewer than 30% of intended recipients have a matched sibling donor available.<sup>19-21</sup> Well-matched unrelated donor or umbilical cord blood or partial matched related donor grafts are also suitable for some patients. Greater HLA mismatch augments risks for graft failure, acute and chronic GVHD, and consequent prolonged immunodeficiency.<sup>22</sup>

Killer immunoglobulin-like receptors (KIR) interact with HLA and other molecules (KIR ligands) that bind to and modulate the function of natural killer (NK) lymphoid cells. After HSCT, altered NK-cell function may modify risks for infection, GVHD, or malignant relapse. KIR ligands can be grouped based on their amino-acid sequence determining the KIR-binding epitopes primarily in HLA-C and HLA-B molecules but, owing to linkage disequilibrium, are not inherited coordinately with HLA. T-cell recovery and NK-cell proliferation and functional maturation are not altered by KIR ligand match or mismatch status.<sup>23</sup> However, recipients of stem cells from unrelated donors with an activating NK-cell immunoglobulin-like receptor (KIR) (B/x) genotype have decreased infectious complications believed to be due to enhanced NK-cell function.<sup>24</sup> The role of KIR genotype in donor selection before HSCT is of research interest at this time.

## Prevention of Infection

Preventive strategies include protective isolation for reduced exposure to pathogens, enhancement of host immune reconstitution with hematopoietic growth factors, prophylaxis during high-risk periods with targeted antimicrobial chemotherapy, and suppression of subclinical infection with preemptive therapy, which is best facilitated by scheduled periodic surveillance.<sup>25-27</sup> Prophylaxis or preemptive strategies are more effective than treatment after infection is established, and the mortality rate among patients with established infections continues

to be high despite appropriate therapy. After mucositis has cleared and oral alimentation has resumed, oral therapy is preferred for prophylaxis.

## CLINICAL SYNDROMES UNIQUE TO THE HEMATOPOIETIC STEM CELL RECIPIENT

### Hemorrhagic Cystitis

Hemorrhagic cystitis is a common complication that can lead to gross hematuria, clots, urinary retention, and impairment of renal function. Cystitis that occurs within the first weeks after marrow infusion usually is noninfectious in origin, caused instead by the administration of high-dose cyclophosphamide in the conditioning regimen.<sup>28</sup> Prophylactic measures include mesna (for binding and elimination of the alkylator metabolites of cyclophosphamide), forced diuresis, and continuous bladder irrigation. Supportive care for established cystitis may also necessitate large-bore catheter drainage or bladder irrigation and transfusions. Later in the post-transplantation period, GVHD and infection are contributing causes of cystitis.<sup>29</sup> The majority of infectious agents inducing cystitis are viral, usually either the polyomavirus BK virus or adenovirus. Infection with herpes simplex virus (HSV), cytomegalovirus (CMV), the polyomavirus JC virus, human herpesvirus type 6 (HHV-6), various bacteria, and *Strongyloides* occurs in lower frequencies.<sup>30-32</sup> Use of fluoroquinolone antibacterial prophylaxis may be preventive for BK viruria.<sup>33</sup> Polyomaviruses are shed in the urine in many HSCT patients without clinical symptoms (see Chapter 147).<sup>34</sup> Higher urine or detectable blood viral loads of BK virus may indicate a higher risk for hemorrhagic cystitis.<sup>35</sup> No standard antiviral treatment is currently available for viruria caused by BK virus or adenovirus, although intravesicular cidofovir or low-dose intravenous cidofovir has been administered when ongoing hemorrhage or large mucosal clots persist despite continuous bladder irrigation.<sup>36</sup>

### Veno-occlusive Disease (Sinusoidal Obstruction Syndrome)

VOD is a syndrome of liver toxicity that occurs at any time after the onset of the high-dose conditioning regimen, usually before days 20 to 30. It is characterized by painful hepatomegaly, 5% or more weight gain, and hyperbilirubinemia (bilirubin levels >2 mg/dL).<sup>37</sup> Severe VOD (sometimes called “sinusoidal obstruction syndrome”) with marked jaundice or ascites leads to multiorgan failure involving the kidneys, heart, and lungs.<sup>38</sup> Sometimes effective anticoagulant or anti-thrombotic therapy can be initiated before serious organ failure. Five to 10 percent of patients with severe VOD die. Defibrotide, which stabilizes endothelium and limits microvascular thrombosis, is effective in VOD, but definitive, controlled data are unavailable. Defibrotide has strong promise as a potent new treatment option.<sup>39,40</sup>

Clinical predictors of severe VOD include cytoreductive therapy at high doses, the presence of hepatitis before cytoreductive therapy, persistent fever during cytoreductive therapy, previous radiation therapy to the liver, and, rarely, the presence of schistosomal hepatic periportal fibrosis. Conditions that may mimic VOD include cholestasis in patients with septicemia, hepatic infiltration secondary to infection or tumor, pericardial tamponade, cytomegaloviral or other viral hepatitis, and intra-abdominal inflammatory diseases such as pancreatitis, peritonitis, or cholecystitis. In addition, early GVHD and cyclosporine-induced cholestasis are noninfectious causes of liver toxicity that may coexist with or mimic VOD. Diagnosis of VOD may be difficult, and ultrasonographic assessment of hepatic portal venous flow may not be definitive. On occasion, liver biopsy with immunohistochemical staining and culture to rule out infectious causes may be indicated, although risk for hemorrhage is markedly increased. Hepatotoxic and nephrotoxic drugs should be avoided in patients with VOD. Genetic polymorphisms in drug metabolism may modify risks for VOD, but their clinical predictive value is uncertain.

### Graft-versus-Host Disease

GVHD is a major, life-threatening complication, developing in 40% to 80% of patients after allogeneic transplantation.<sup>41</sup> The risk for developing GVHD is higher in older patients and with partially matched or unrelated donor HSCT and is associated with the higher doses of

donor T cells infused with filgrastim-mobilized peripheral blood grafts.<sup>42</sup> In acute GVHD, donor T lymphocytes mount an immune attack against the recipient's tissues that is amplified by proinflammatory cytokines. The favorable antineoplastic impact accompanying GVHD is called the graft-versus-leukemia (GVL) effect.<sup>43</sup> T cells and possibly NK and other lymphoid cells mediate GVL effects after allogeneic HSCT by the production of inflammatory cytokines and by direct target lysis.

Clinical manifestations of acute GVHD include rash, cholestatic hepatitis, nausea, vomiting, and diarrhea. Effective immunosuppressive agents for the prevention of GVHD include calcineurin inhibitors (cyclosporine or tacrolimus) with or without methotrexate, mycophenolate mofetil, and sirolimus; they are usually started before transplantation. GVHD itself can compound and prolong post-HSCT immunodeficiency. The corticosteroids or other immunosuppressive drugs used as treatment of GVHD may impair phagocytic function and directly worsen lymphopenia and cellular immune deficiency.<sup>44,45</sup> Patients with acute and chronic GVHD have splenic dysfunction and thus an added risk for infection with encapsulated bacteria such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*. T-cell depletion of the donor graft is less associated with GVHD, but more with CMV and *Aspergillus* infections<sup>46</sup> and sometimes with very delayed immune recovery.

## Hepatitis

Clinical hepatitis in HSCT recipients can range from fever accompanied by abdominal pain to fulminant illness. Infectious hepatitis must be distinguished from several common noninfectious causes, including liver dysfunction related to the "conditioning regimen" (VOD), acute GVHD, cholestatic liver injury related to sepsis, and chemical hepatitis related to either drugs or hyperalimentation.<sup>47</sup>

Clinically important viral hepatitis syndromes that occur after transplantation include acquisition or reactivation of infection with hepatitis B virus (HBV), hepatitis C virus (HCV), varicella-zoster virus (VZV), adenovirus, HSV, CMV, and HHV-6.<sup>48</sup> Reactivation of HBV is more likely than HCV to result in fulminant hepatitis, although this occurs in only a minority of infected patients. Disseminated VZV and adenovirus infections may manifest as elevations in serum aminotransferase levels; these elevations can precede the appearance of other disease manifestations by several days. In rare cases, liver biopsy with viral culture and polymerase chain reaction (PCR) assay are needed to establish a diagnosis of severe hepatitis in the early postengraftment period. Viruses such as hepatitis G virus and transfusion-transmitted viruses are not known to influence the outcome of HSCT.

HBV (surface antigen [HBsAg], surface antibody [HBsAb], and core antibody [HBcAb]) and HCV serologic profiles are tested in donor and recipient before HSCT. Pretransplantation imaging studies or liver biopsy may be needed to evaluate HCV-seropositive patients with abnormal liver enzyme levels or tender hepatomegaly. Donors and recipients with positivity for HBsAg should be tested for viral load with PCR studies for HBV DNA before transplantation, because the risk for HBV hepatitis can be reduced by treatment to lower a detectable viral load. Lamivudine, adefovir, and tenofovir are commonly used to suppress HBV replication (see Chapter 148).<sup>49</sup>

A transplant from an HBV-infected donor can be used if no alternative donor is available or if the intended recipient is already seropositive.<sup>50</sup> HBV can be transmitted from an HBsAg-positive (or, less likely, an HBcAb-positive) donor to a recipient who is either HBV naïve or HBsAb positive but HBcAb negative. The risk for transmission is low when an HBV-positive donor has an undetectable viral load. If the recipient is HBV naïve before transplantation, the subsequent infection is more likely to have clinical consequences. If the transplant can be delayed, then HBV vaccination of the recipient or use of HBV immune globulin or both may reduce the likelihood of hepatitis after transplantation. HBV immunity can be transferred from an HBsAb-positive donor to an HBV-naïve recipient. Through adoptive immune transfer, HBV infection can be cleared from an HBsAg-positive recipient by transplant from an HBsAb-positive (i.e., immune) donor.

After transplantation, the following recipients should be monitored periodically with PCR testing of HBV DNA viral load: (1) those with liver enzyme elevation suggestive of activation of HBV from latency;

(2) those with transplants from HBV-infected donors; and (3) those with known infection before transplantation. High HBV viral load (>10<sup>5</sup> copies/mL) is the most important risk factor for clinically apparent reactivation in recipients positive for HBsAg.<sup>51</sup> Among recipients in whom PCR studies of HBV DNA yield positive results persistently after transplantation despite treatment, the risk for fatal liver disease may be up to 12%.<sup>51</sup>

HCV-positive donors and recipients should undergo RNA viral load testing. Although best avoided, but if there are no other options, an HCV-infected individual can serve as a donor. In contrast to HBV, however, the rate of transmission of HCV from an HCV RNA-positive donor approaches 100%. Interferon can be used to suppress HCV replication in donors,<sup>52</sup> but its limited efficacy, systemic and hematologic toxicity, and delayed response may not contain active HCV to render a donor suitable for donation. Expanded treatment options, including protease inhibitor therapies, may be useful, but drug interactions with calcineurin inhibitors may be an issue (see Chapter 156).

Because the cellular immune system must be functioning for HCV to produce hepatitis, few clinical consequences are recognizable in the recipient early after HSCT. HCV infection does not increase the incidence of VOD. Beyond 10 years, the long-term complication of HCV infection is cirrhosis.<sup>53</sup> No data have demonstrated a correlation between hepatitis C genotype and type or severity of liver disease after transplantation. Because of the myelosuppressive effects of interferon and other antiviral agents, their use in the treatment of hepatitis C after HSCT is limited.

## Pneumonia Syndromes

Infectious pneumonias must be distinguished from noninfectious pulmonary complications after HSCT, which can include pulmonary edema, pleural effusion, alveolar hemorrhage, radiation injury (pneumonitis or fibrosis), drug reactions, adult respiratory distress syndrome, idiopathic pneumonia syndrome, cytolytic thrombi (causing multiple peripheral lung nodules), obliterative bronchiolitis, bronchiolitis obliterans with organizing pneumonia, and chronic GVHD.<sup>54</sup> Management of noninfectious pneumonias requires that lower respiratory tract infection be ruled out or recognition of its coexistence. Their pathophysiologic processes may be distinct: some syndromes may be more likely to respond therapeutically to high-dose corticosteroid therapy.

Diffuse alveolar hemorrhage begins with dyspnea and alveolar infiltrates and is distinguished from other noninfectious pneumonias by progressively bloody return during bronchoscopic examination and alveolar lavage.<sup>55</sup> The syndrome usually occurs in the second and third weeks after HSCT. Thrombocytopenia, rapid neutrophil recovery, infection, toxic effects of drugs and of radiation, intensely cytotoxic regimens, and solid malignancy have been implicated as risk factors. Corticosteroids are recommended but improve chances of survival only infrequently.

Idiopathic pneumonia syndrome is a process of widespread alveolar epithelial injury that is characterized clinically by diffuse interstitial infiltrates and varying degrees of respiratory failure in the absence of active lower respiratory tract infection.<sup>56</sup> It is believed to be related to the chemotherapy or total-body irradiation, or both, used as part of the "conditioning regimen," which induces proinflammatory cytokine release and increasing alveolar capillary permeability. Idiopathic pneumonia syndrome occurs in 8% to 17% of patients but may be more frequent after allogeneic than autologous transplantation and thus has been implicated, at least in animal models, as a component of the graft-versus-host reaction. Mortality rates are 60% to 80%. Idiopathic pneumonia syndrome occurs classically during two peaks: one in the first few weeks and the other in the second and third month after transplantation. Corticosteroids and etanercept may yield a clinical response.<sup>57</sup>

## Diarrhea

Diarrhea after transplantation is primarily a result of noninfectious causes such as regimen-related gut mucosal toxicity and GVHD. Diarrhea is associated with infection in fewer than 20% of cases.<sup>58,59</sup> The list of infectious agents responsible for diarrhea includes *Clostridium difficile*, adenovirus, rotavirus, norovirus, enterovirus, coxsackievirus,

HHV-6, *Escherichia coli*, *Salmonella*, *Giardia*, *Strongyloides*, *Cryptosporidium*, and *Campylobacter* spp. Infection with *C. difficile* occurs with increasing frequency.<sup>60,60a</sup> Outbreaks of diarrhea have been reported for *Cryptosporidium* and enterovirus. From other countries, reports of diarrhea have been associated with *Trichostrongylus* spp.

Typhlitis, or neutropenic enterocolitis, is an anaerobic infectious syndrome that is relatively common and may be associated with diarrhea during neutropenia.<sup>61</sup> Typhlitis is preceded by fever, abdominal pain, and right lower quadrant tenderness that may be accompanied by rebound tenderness. Appendicitis can mimic typhlitis. Computed tomography of the abdomen reveals right-sided colonic enlargement and inflammation with thickening of the mucosa. Therapy against anaerobic bacteria should be added to the medical regimen.

## Rash

Skin eruptions are often noninfectious, occurring as a direct result of radiation effect from conditioning therapy or secondary to GVHD or drug allergy.<sup>62</sup> Rashes from “conditioning regimens” can result in the sudden onset of marked erythema over large areas of the body and blistering on the hands and feet. A skin biopsy can assist in distinguishing infectious from noninfectious causes of rash. For all lesions suspected to be infectious, samples should be submitted for culture or biopsy. The most common infectious causes are VZV, catheter-related exit site or tunnel infections, and cutaneous manifestations of disseminated bacterial or fungal infections.<sup>63</sup> Focal areas of bacterial cellulitis may occur on the lower extremities in the setting of edema from heart failure, VOD, lymphedema, and impaired venous return.

## Osteomyelitis

Osteomyelitis is uncommon after HSCT. The spectrum of organisms can include atypical mycobacteria, yeasts, and molds, in addition to bacteria.<sup>64,65</sup> In rare instances, osteomyelitis follows marrow aspiration from the sternum or marrow harvest from the iliac crest.<sup>65,66</sup> When prolonged pain and fever occur after bone marrow harvest, osteomyelitis caused by *Staphylococcus aureus* should be considered.

## PATTERNS OF IMMUNOSUPPRESSION AT DIFFERENT TIMES AFTER MYELOABLATIVE HSCT

Historically, three risk periods of immunologic deficiency occur predictably in graft recipients after HSCT (Fig. 312-1). They are the preengraftment period, the early postengraftment period (until day 100), and the late postengraftment period (after day 100). An understanding of the immune deficiencies in each risk period and the period of peak risk for individual infections that are observed with standard infection prophylaxis helps the clinician recognize uncommon manifestations of these infectious pathogens (Table 312-1).

## Preengraftment Risk Period

The preengraftment risk period begins with the onset of conditioning therapy and continues until approximately days 20 to 40 after transplantation. By definition, graft failure is declared if there is no neutrophil recovery by day 42. Pretransplantation neutropenia is associated with increased infection-related mortality.<sup>67</sup> Bacterial infections are common during this time of profound neutropenia and lymphopenia, necessitating prophylactic and promptly administered empirical systemic antibiotic therapy (see Chapter 310).<sup>68</sup> Prophylactic systemic antibiotics (often a fluoroquinolone such as levofloxacin) can be administered when the neutrophil count drops to less than 500/mm<sup>3</sup> and continued until the neutrophil count recovers to prevent bacterial infection (see Chapter 311). Gastrointestinal decontamination with nonabsorbable antibiotics was used in the past but is now rarely performed.

Prophylactic antibiotic use has shifted the spectrum of gastrointestinal microbiota to potentially pathogenic organisms such as *C. difficile* and enterococci.<sup>60,69</sup> The etiologic agents of bacteremia have shifted to more gram-positive organisms; in particular, coagulase-negative staphylococci, enterococci, and viridans-group streptococci are often isolated from bloodstream cultures of febrile neutropenic HSCT recipients.<sup>70</sup> Mechanical barrier defects caused by mucositis and central catheters predispose patients to bloodstream infections by allowing

access for skin-colonizing organisms and gastrointestinal mucosal flora to otherwise sterile body sites.<sup>71</sup> Colonization with vancomycin-resistant enterococci or other multidrug-resistant pathogens may predispose patients to bacteremia.<sup>69,72</sup> Recipients of autologous-syngeneic and allogeneic grafts may develop a similar spectrum of infections during the preengraftment period; the major transplantation-related complications occurring in this risk period (mucositis, severe neutropenia, and VOD) are similarly frequent with all types of transplantations. However, the less frequent use of total-body irradiation and methotrexate and the more rapid neutrophil recovery after autologous transplantation of peripheral blood stem cells have markedly decreased the risks for mucositis and serious bacteremia in this subpopulation of patients. Similarly, the use of reduced-intensity conditioning regimens before nonmyeloablative allografting has lessened the risks for early bacteremia.

During this risk period, HSV is predictably reactivated in 80% of patients who are HSV seropositive. Most such infections occur before week 4 after transplantation. Prophylactic acyclovir, 400 mg twice daily (5 mg/kg twice daily for children), has minimized this clinical infection.<sup>73,74</sup>

Candidemia and early-onset aspergillosis occur in fewer than 5% of patients with neutropenia. The risk is greater in patients with slow engraftment or extended neutropenia before transplantation. With fluconazole (200 to 400 mg/day),<sup>75-77</sup> voriconazole,<sup>78</sup> or micafungin<sup>79</sup> (50 mg IV once daily) prophylaxis, *Candida albicans* infections have been mostly eliminated during this risk period; however, *Candida krusei* and *Candida glabrata* have emerged as fluconazole-resistant pathogens.<sup>80</sup>

Some allogeneic transplantation candidates are at higher risk for mold infections during the preengraftment period than others; their transplantation course begins with mold prophylaxis, possibly beginning even 2 to 4 weeks before HSCT.<sup>81</sup> These patients can include those with extended pre-HSCT neutropenia such as acute leukemia who have undergone serial chemotherapy before transplantation; those with myelodysplastic syndrome; those with aplastic or Fanconi anemia; and others. Fungal infection that occurred within 6 to 9 months before transplantation may not be cured and could reactivate. Patients with more remote fungal infections can receive a standard regimen of fungal prophylaxis. If patients have a history of aspergillosis within 4 months of transplantation or have suspect pulmonary nodules without a specific diagnosis,<sup>82</sup> they should receive secondary fungal chemoprophylaxis (i.e., ongoing maintenance antifungal therapy) and undergo rescanning before and after transplantation.

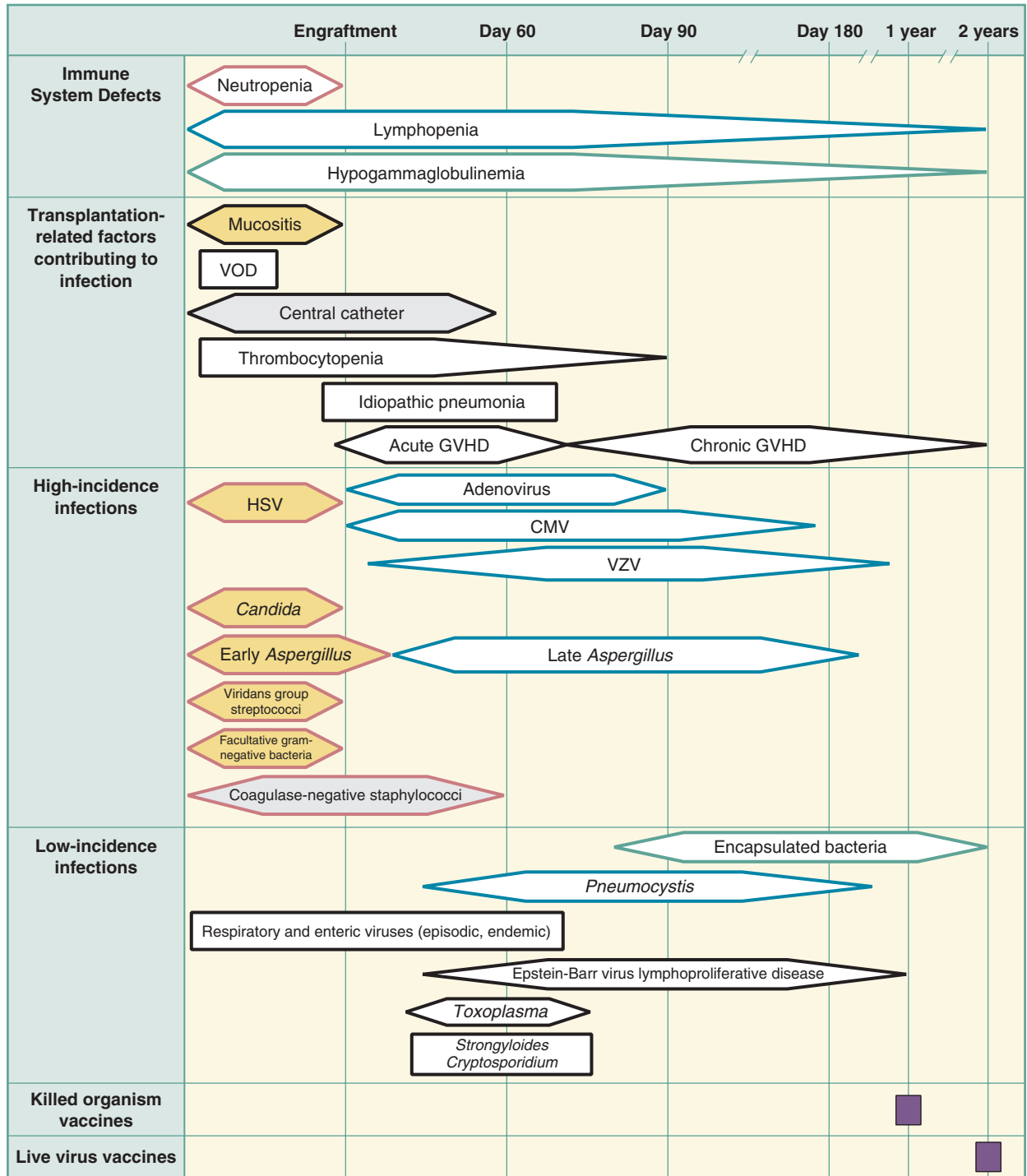
Use of hematopoietic growth factors has reduced the incidence of bacteremia by shortening the duration of neutropenia, but these agents have not been shown to improve outcome in established infections.

Adjunctive therapy with granulocyte transfusions has been used in some centers for treatment of serious infections that develop in patients with neutropenia.<sup>83</sup> Use of colony-stimulating factors with dexamethasone to prime granulocyte donors and increase the collection yield is being evaluated. Evidence of efficacy and, therefore, the indications for use of this expensive and labor-intensive supportive measure are uncertain and still under study.

Routine culture of hematopoietic progenitor cell products yields low rates of recovery of bacterial organisms, most often *Corynebacterium* spp. or staphylococci. Appropriate testing of collections of graft products includes routine culture of hematopoietic progenitor cells before HSCT, but patients receiving culture-positive harvests usually do so without clinically adverse outcomes.<sup>84,85</sup>

## Postengraftment Risk Period

The postengraftment period begins with neutrophil recovery and continues until day 100, when early B- and T-lymphocyte functional recovery may be apparent. Reconstituting T lymphocytes have abnormal function for approximately 18 months, as evidenced by CD4 deficiency and by in vitro antigen and mitogen proliferative responses. However, T-lymphocyte reconstitution may be blunted by the effects of GVHD or CMV and their attendant treatments (corticosteroids, calcineurin inhibitors, anti-T-lymphocyte therapy, and ganciclovir products). As a result, the rate of infection during this risk period is higher in recipients of allogeneic grafts, who are more likely to develop



**FIGURE 312-1** Phases of predictable opportunistic infections among patients undergoing hematopoietic stem cell transplantation. Immune defects predisposing to infection are bordered by color (pink, neutropenia; blue, lymphopenia; green, hypogammaglobulinemia). Barrier defects predisposing to infection are shaded in color (gold, mucosal breakdown; gray, skin breakdown). Contribution of defects to infections occurring with high incidence are designated by border color (for immune defects) or shading (for barrier defects) or both. CMV, cytomegalovirus; GVHD, graft-versus-host disease; HSV, herpes simplex virus; VOD, veno-occlusive disease; VZV, varicella-zoster virus. (Modified from Van Burik JA, Freifeld AG. Infection in the severely immunocompromised host. In: Abeloff MD, Armitage JO, Niederhuber JE, et al, eds. Clinical Oncology. 3rd ed. Philadelphia: Churchill Livingstone; 2004:942.)

GVHD or CMV, than in recipients of autologous-syngeneic grafts. Another consequence of GVHD during this risk period is disruption of the gastrointestinal mucosa, which can permit transmural entry of pathogens and lead to bacteremia or fungemia.

Late-onset aspergillosis may also occur during this risk period in up to 10% of patients, especially those with continuing GVHD, those receiving high-dose corticosteroids, and those with poor graft function.<sup>86</sup> Advanced-generation azoles that have activity against

filamentous molds are effective prophylaxis against deep mycoses in patients at high risk.<sup>78,87</sup> Careful surveillance is required for these high-risk groups; serum galactomannan screening is insufficiently sensitive for reliable early detection of *Aspergillus* infections.<sup>25</sup> Although infrequent, infection with agents of mucormycosis may occur as they are resistant to the advanced azoles (e.g., voriconazole).

Prophylaxis of *Pneumocystis jirovecii* infection with trimethoprim-sulfamethoxazole (TMP-SMX), dapsone, atovaquone, or aerosolized



**TABLE 312-1 Infections after Hematopoietic HSCT in Order of Occurrence**

ORGANISM	PEAK TIME PERIOD OF RISK (WEEKS AFTER HSCT)	USUAL PROPHYLAXIS	INCIDENCE
<b>Preengraftment Risk Period (1-4 Weeks)</b>			
Herpes simplex virus (seropositive) <sup>73,146-148</sup>	1-2	Acyclovir or valacyclovir	5%-9%
Gram-positive bacteremia (most commonly coagulase-negative staphylococci, viridans group streptococci, and enterococci) <sup>59,108,111,112,119-121,123</sup>	1-4	Prophylactic broad-spectrum antibiotics	20%-30%
Gram-negative bacteremia <sup>68,69,70,113</sup>	1-4	Prophylactic broad-spectrum antibiotics	5%-10%
<i>Clostridium difficile</i> diarrhea <sup>60</sup>	1-5	—	5%-10%
<i>Candida</i> <sup>75-79,226,235,238,239</sup>	1-4	Fluconazole, micafungin, voriconazole	Systemic infection: <5% colonization: 30%
<i>Aspergillus</i> and other molds <sup>78,79,86,227,228,242</sup>	1-4	HEPA air filtration Itraconazole, voriconazole, posaconazole, micafungin, or low-dose amphotericin	<5%
Respiratory viruses <sup>191,193,195,197-201,203,204</sup>	2-5	Isolation, hand washing	15%
Idiopathic pneumonia syndrome <sup>54</sup>	2-4	—	8%-17%
<b>Early Postengraftment (4-26 Weeks) and Late Postengraftment (26-52 Weeks) Risk Periods</b>			
Cytomegalovirus (seropositive) <sup>46,96,98,104,152-155</sup>	7-26	Ganciclovir or foscarnet	<5% (end-organ disease), up to 40% (antigenemia/viremia)
Varicella-zoster virus (seropositive) <sup>171,172</sup>	4-52	—*	≤50%
<i>Aspergillus</i> and other molds <sup>86,87,318,228,242</sup>	4-26	Itraconazole, posaconazole, or voriconazole	10%-15%
BK virus <sup>34</sup>	—	—	≤50% (shedding)
Adenovirus <sup>183-187</sup>	—	—	1%-5%
<i>Pneumocystis jirovecii</i> <sup>88,90,231</sup>	4-104	Trimethoprim-sulfamethoxazole	<1%
<i>Toxoplasma gondii</i> (seropositive) <sup>288,290,291</sup>	2-8	— <sup>††</sup>	2%-7%
<b>Infrequent Infections (May Span Multiple Risk Periods)</b>			
Herpes simplex virus (seronegative)	—	—	<2%
Cytomegalovirus (seronegative) <sup>144,149,150</sup>	—	Blood product screening or filtration	1%-4%
Varicella-zoster virus (seronegative)	—	—	<3%
<i>Streptococcus pneumoniae</i> <sup>1155</sup>	—	Vaccination, penicillin <sup>¶¶</sup>	<1%
<i>Haemophilus influenzae</i> <sup>302,3035</sup>	—	Vaccination, penicillin <sup>¶¶</sup>	—
<i>Neisseria meningitidis</i> <sup>302,3035</sup>	—	Penicillin <sup>¶¶</sup>	—
Human herpesvirus 6 <sup>214-219,220</sup>	—	Ganciclovir or foscarnet	5%-60%, few treated
Epstein-Barr virus <sup>209-211</sup>	—	—	<1% (disease)
<i>Nocardia</i> spp. <sup>140</sup>	—	— <sup>§</sup>	<1%
<i>Legionella</i> spp. <sup>136-138,139</sup>	—	—	<1%
<i>Mycobacterium</i> spp. <sup>124,125,133,134</sup>	—	Screening, then prophylaxis	<1%
<i>Listeria monocytogenes</i> <sup>141-143</sup>	—	—	<1%

\*Antiviral medications used to prevent other viral infections may be acting as prophylaxis against reactivation of varicella-zoster virus.

<sup>†</sup>Prophylaxis with pyrimethamine-sulfadoxine may be used for seropositive patients in countries with a high rate of seroprevalence.<sup>203</sup>

<sup>††</sup>The sulfa component of *Pneumocystis* prophylaxis may be acting as prophylaxis against *Toxoplasma* or *Nocardia* infection.

<sup>§</sup>Risk is increased in patients with chronic graft-versus-host disease.

<sup>¶¶</sup>Efficacy in transplant recipients is undetermined.

<sup>¶¶¶</sup>Increasing penicillin resistance may indicate a need for macrolides or extended-spectrum quinolones.

HEPA, high-efficiency particulate air (filter); HSCT, hematopoietic stem cell transplantation.

pentamidine is required for 6 to 12 months or, if chronic GVHD is continuing, longer.<sup>88-92</sup>

Reactivation of CMV predictably occurs in 20% to 40% of patients who are CMV seropositive. Transmission to seronegative recipients from seropositive donors is uncommon.<sup>46</sup> Surveillance for reactivation of CMV has been improved by the use of scheduled CMV testing with either pp65 antigenemia assay or PCR testing for serum DNA.<sup>93</sup> Ganciclovir or other antiviral therapy initiated preemptively at subclinical indications of reactivation has reduced the incidence of end-organ disease caused by CMV to only 5% to 10% of seropositive recipients.<sup>94-96</sup> Continuing GVHD or delayed immune recovery after partially matched- or unrelated-donor HSCT can lead to later-onset CMV infection and may indicate a need for prolonged CMV surveillance.

### Late Risk Period

The late post-transplantation risk period begins at approximately day 100 and ends when the patient regains normal immunity, 18 to 36 months after HSCT.<sup>97-99,100-102</sup> In general, clinical immune recovery is demonstrable by the end of the first year after transplantation as long

as the patient is no longer taking immunosuppressive medication and remains free from GVHD. For patients with continuing chronic GVHD, this period persists as long as therapy for chronic GVHD is required and includes dysfunction of lymphocyte, macrophage, and humoral immunity. VZV reactivation, infections with encapsulated bacteria (*S. pneumoniae*, *N. meningitidis*, and *H. influenzae*), and invasive aspergillosis or other invasive tissue mold infections may develop in this late risk period. Malignant disease relapse, regardless of its tempo or the choice of therapy, impairs the restoration of immunocompetence. Survival after relapse may be lengthy for some more indolent malignancies (e.g., chronic myelogenous leukemia, chronic lymphocytic leukemia, follicular lymphomas), but their post-HSCT immunodeficiency will persist. Therefore, even after relapse, ongoing surveillance and therapy, as in post-HSCT patients in remission, is still required.

The most common clinical infection syndromes include sinusitis, bronchitis, pneumonia, and otitis media caused by respiratory viruses or bacteria. CMV disease may develop; therefore, CMV surveillance must be continued in seropositive recipients with chronic GVHD.<sup>98,99</sup>

Late infections may be more common among patients with unrelated donors than among patients whose donors were family members, even in the absence of GVHD. Approximately 50% of late pneumonias in patients with ongoing chronic GVHD are caused by noninfectious interstitial pneumonitis. Lung histopathologic studies reveal organizing obliterative bronchitis that may respond to corticosteroid therapy.

### IMMUNODEFICIENCY AFTER NONMYELOABLATIVE HSCT

Nonmyeloablative HSCT is associated with less disruption of mucosal barriers, shorter periods of severe neutropenia, fewer episodes of bacteremia in the first 30 days, and a trend toward fewer episodes of bacteremia during the first 100 days after HSCT.<sup>103</sup> However, this type of transplantation can still be associated with severe GVHD, often necessitating high-dose corticosteroid treatment. It is often used for older patients and those with compromised organ function and poor performance status. GVHD, CMV disease, and invasive fungal infection may be delayed 1 to 2 months, but the overall incidences of these conditions are similar to those with conventional myeloablative HSCT during the first year after HSCT.<sup>103,104,105</sup> Patients undergoing nonmyeloablative HSCT may need surveillance for CMV and fungal infections well beyond day 100, as well as preemptive or prophylactic treatment similar to that for myeloablative HSCT recipients between day 100 and 1 year after HSCT.

### MEASURES TO REDUCE RISKS FOR INFECTION

Protective measures that should be discussed before HSCT and reinforced during the recovery period involve travel, crowds, and pets.<sup>106</sup> With regard to travel, there are no particular restrictions, but strategies to minimize transmission of infectious diseases have been summarized.<sup>25</sup> Some social situations, such as sitting in a crowded movie theater or classroom, may increase the risk for acquiring a viral respiratory illness. Turning away from individuals who are coughing or sneezing, or even quickly donning a mask, may be helpful in preventing transmission of airborne, droplet-based infection. Patients need instruction to remember to augment infection prevention by washing their hands as soon as possible after being close to someone with a cold. Because outbreaks of noroviruses have involved cruise ships, and because other types of outbreaks (e.g., *Staphylococcus*) are commonly associated with the close living quarters of this type of vacation, cruise ships may be unwise vacation choices.

Healthy dogs and cats are considered acceptable pets. However, immunosuppressed patients should not get a new pet or be responsible for scooping cat litter because of potential *Toxoplasma* cyst exposure. Similarly, such patients should not play in sandboxes because these areas are concentrated sites that outdoor cats may use as litter boxes. Because reptiles of many sorts have been reported to be infected with *Salmonella*, such patients should not touch these animals or their aquarium homes. The water of tropical fish tanks may carry *Mycobacterium marinum*. *Chlamydia psittaci* can be transmitted from psittacine birds.

Hand washing or the use of alcohol-based hand rub disinfectant is the mainstay of infection prevention in the hospital or clinic.<sup>107</sup> Persons entering the patient's room to perform examination or touch the patient (including visitors, as well as health care workers) should wash or disinfect their hands outside the room. During respiratory virus season, infection control personnel will often add extra signage to doorways and other places on the wards to remind visitors of the importance of hand washing. Staff and visitors with respiratory viral infections should not be permitted to have direct contact with the patient. Routine use of gown, gloves, or masks, or a combination of these, is not required in the presence of a neutropenic transplant recipient, but ongoing caution to prevent interperson or nosocomial transmission is essential.

### NATURAL HISTORY OF INDIVIDUAL INFECTIONS AFTER HSCT

With advances in infection prevention strategies, the risk periods for some infections are changing. It is important to understand the

natural history of individual infections as they occur in the HSCT recipient and how it may be distinct from that in other immunocompromised patient populations. Infections that occur with a high incidence among HSCT recipients justify prophylaxis during the applicable risk period or empirical treatment during the course of infection (see Table 312-1).

### Bacterial Infections

Gram-positive organisms account for half of bacteremias occurring after HSCT.<sup>69,108-110</sup> Although the skin has been believed to be the primary reservoir for these organisms, colonization of the gastrointestinal tract may be an additional source. *Staphylococcus epidermidis* (i.e., coagulase-negative *Staphylococcus*) is the species most commonly recovered in culture from the skin and nose. Oropharyngeal organisms include *Streptococcus pyogenes*, *Streptococcus mitis*, and *Enterococcus* spp. (both vancomycin-sensitive and vancomycin-resistant species).<sup>110</sup> Unlike catheter-associated infections with *S. aureus*, *Candida* spp., or some gram-negative bacilli, most gram-positive bacteremias can be managed successfully without removal of the intravascular device.<sup>111,112</sup> Methicillin-resistant *S. aureus* (MRSA), which had been rare in neutropenic infections, is becoming more frequent. If the patient does not respond to initial antibiotic management, or if there is tenderness or erythema along a catheter tunnel tract, the catheter should be removed. In rare cases, adjunctive surgical débridement of the skin tunnel is needed. Catheter removal and surgical débridement are often required when a tunnel infection is caused by rapidly growing mycobacteria.

Gram-negative organisms are the second most frequent cause of bloodstream infection. The incidence of infection with *Pseudomonas* spp. is low, in part because of the use of antipseudomonal antibiotics for prophylaxis against, and initial empirical therapy for, neutropenic fever.<sup>69</sup> However, the virulence and potential for sepsis syndrome remain high for gram-negative organisms, including *E. coli*, *Klebsiella* spp., *Enterobacter* spp., and *Pseudomonas* spp. Although bacteremias have historically occurred during the neutropenic period, bacteremias continue to develop in patients with long-term central intravenous catheters, in patients with ongoing immunosuppression resulting from GVHD or its therapy, and in those with neutropenia secondary to graft failure or drug-related marrow suppression (e.g., ganciclovir).<sup>113,114</sup>

### Encapsulated Bacteria

For patients who experience chronic GVHD or are otherwise asplenic, the risk for life-threatening bacterial sepsis with encapsulated organisms is increased. Invasive pneumococcal infection may occur months to years after HSCT. The annual incidence is 8 per 1000 allogeneic HSCT recipients and is higher (21 per 1000) among those with chronic GVHD.<sup>115</sup> Penicillin or macrolide prophylaxis may be indicated until immunosuppression is discontinued.<sup>101,116</sup> Reports of frequent penicillin-resistant pneumococcal infections in the general population have prompted a change in prophylaxis from penicillin to a quinolone in some centers.<sup>117,118</sup>

### Viridans-Group Streptococci

Viridans-group streptococcal bacteremias, mostly caused by *S. mitis*, may carry a high mortality rate early after HSCT.<sup>119-121,122</sup> Poor dental hygiene is a risk factor for *S. mitis* bacteremia in HSCT patients.<sup>123</sup> Normally antibiotic sensitive, these organisms may be resistant to norfloxacin, ciprofloxacin, and penicillin in patients receiving prophylactic antibiotics. Vancomycin is the drug of choice for HSCT patients. Oral ulcerations caused by HSV reactivation during conditioning are believed to be an entry point, corroborated by a decreased incidence of viridans-group streptococcal septicemia after active prophylaxis of HSV infections with acyclovir.<sup>120</sup>

### Mycobacteria

Mycobacteria are an infrequent cause of infection after HSCT, but it is important to identify them because treatment requires medication that would not be used empirically. The rapidly growing nontuberculous mycobacteria are responsible for catheter exit site infections, tunnel infections, bacteremia (with waterborne *Mycobacterium mucogenicum*), or pneumonia.<sup>124,125</sup> Infection with *Mycobacterium tuberculosis* occurs predominantly in countries with high endemic rates;

the number of cases may be increasing worldwide as transplantation becomes available globally.<sup>126-130</sup> Transplantation candidates and donors who are at risk for reactivation of latent tuberculosis can be readily identified during the pretransplantation evaluation on the basis of residence in endemic areas or close contact with another person with known or suspected tuberculosis. For these transplantation candidates, screening is recommended with tuberculin skin testing or an *ex vivo* interferon- $\gamma$  release assay, such as QuantiFERON-TB Gold.<sup>131-134</sup> Clinically significant infection can be prevented by extended-duration antituberculous prophylaxis when QuantiFERON-TB Gold assays or reactive tuberculin skin testing yields positive results. Potential transplantation patients and donors should also receive screening if they have a history of abnormal chest radiographic findings before HSCT, have recently traveled to a foreign country for longer than 3 months, have been employed in an institution with tuberculous clients, have a history of alcoholism or intravenous drug use, or are seropositive for human immunodeficiency virus (HIV). QuantiFERON-TB Gold has 96% to 99% specificity that is unaffected by the vaccine for bacillus Calmette-Guérin.<sup>135</sup> For patients with a positive result of a screening test but no signs of active tuberculosis and no previous antituberculous therapy, a chest radiograph and liver function studies should be obtained, in addition to peritransplantation and 9-month post-transplantation therapy with isoniazid and pyridoxine.

### Intracellular Bacteria

Legionellosis<sup>136-138,139</sup> and nocardiosis<sup>140</sup> are uncommon, but both can manifest as pneumonia or lung nodules in the HSCT patient. Detection of *Legionella* by direct fluorescent antibody (DFA) assays has proved unreliable in the HSCT setting because of false-positive results and because it does not detect a high proportion of disease caused by *Legionella* species. These species include *Legionella feeleii*, *Legionella micdadei*, and *Legionella bozemanii*.<sup>139</sup> Infection can persist or relapse after 3 weeks of appropriate antimicrobial therapy, which suggests that prolonged antibiotic treatment is indicated for HSCT recipients with legionellosis.<sup>138</sup> Medical therapies for nocardiosis often consist of administration of sulfonamide in combination with a synergistic agent such as ceftazidime or imipenem-cilastatin; adjunctive surgical débridement may be useful for catheter-related infections with this organism. The role of other intracellular bacterial agents as pathogens has not been well defined, but *Listeria monocytogenes* infection may manifest as bacteremia or meningitis.<sup>141-143</sup>

### Viral Infections

Certain viral infections are preventable. Administration of acyclovir for HSV-seropositive patients during the preengraftment period is widely accepted. CMV-safe (serologically screened or filtered) blood product transfusions for CMV-seronegative patients have proved very effective in preventing transfusion-acquired CMV infections.<sup>144,145</sup> Periodic (e.g., weekly) CMV diagnostic surveillance for CMV-seropositive patients during the postengraftment period and prompt institution of antiviral therapy are essential. CMV-seronegative patients (with seronegative allogeneic donors) are at comparatively low risk; therefore, diagnostic monitoring continues for only 6 to 10 weeks. Scrupulous hand washing and avoidance of crowds to prevent transmission of respiratory viral and other infections (in the hospital or ambulatory clinic) remain the mainstay of effective infection control practice for the HSCT recipient.

### Herpes Simplex Virus

Among HSV-seropositive recipients during the first month after transplantation, the incidence of HSV reactivation can be reduced from 80% to less than 5% through the use of acyclovir or valacyclovir, initiated at the time of conditioning and continued until mucositis has healed.<sup>73,146,147</sup> The majority of postengraftment HSV infections are confined to the oropharynx, although the infection occasionally extends directly to squamous epithelial surfaces in the upper esophagus, larynx, or skin in the perioral or perianal areas. Patients who do not respond to acyclovir after engraftment, and particularly those who have received prolonged or repeated courses of acyclovir, may have acyclovir-resistant HSV. Foscarnet or cidofovir may be beneficial in that setting. In uncommon cases, HSV infection causes Bell's palsy, hepatitis, or encephalitis. Valacyclovir achieves predictably higher drug levels than does acyclovir after oral administration.<sup>147,148</sup>

### Cytomegalovirus

The historical incidence rate of primary CMV infection among the CMV-seronegative HSCT recipient can be reduced from 40% down to 4% or less by use of CMV-safe blood products during transfusions.<sup>149,150</sup> A cellular graft is associated with CMV transmission when a CMV-seronegative recipient receives a CMV-seropositive donor graft.<sup>151</sup> The incidence of CMV reactivation and viremia, traditionally 70% in CMV-seropositive patients with allogeneic transplants and 45% among patients with autologous transplants, can be reduced down to between 20% and 40% by the use of preemptive or prophylactic antiviral therapy.<sup>94,152-158,159</sup> With the most common approach, prophylactic acyclovir combined with preemptive early ganciclovir product therapy, the median time of onset of CMV end-organ disease has been delayed from 1 to 2 months toward 4 to 6 months after HSCT; this indicates that CMV surveillance must be longer in groups at high risk (see Chapter 140).<sup>98,99</sup>

Weekly screening enables identification of patients who might benefit most from preemptive therapy with ganciclovir products (Table 312-2). CMV pp65 leukocyte antigen and quantitative DNA PCR testing are excellent methods for early CMV detection, although antigen testing is unreliable during neutropenia. Once CMV is identified by an early detection method, most patients are treated with 7 to 14 days of induction ganciclovir therapy (5 mg/kg intravenously twice daily), followed by maintenance therapy (ganciclovir, 5 mg/kg intravenously once daily, or valganciclovir, 900 mg orally once daily), for several weeks beyond negative CMV test results (Table 312-3). Maintenance therapy may need to be continued for patients with persistent detection of virus or those with profound immunosuppression caused by active GVHD.

Oral valganciclovir is a safe and effective ganciclovir prodrug, with the valine ester cleaved during the first pass through the liver, and it can be considered for the patient who needs induction and/or long-term maintenance and is otherwise taking oral medications without difficulty. A valganciclovir dosage of 900 mg once per day produces blood-level drug exposure similar to those produced by an intravenous 5 mg/kg dose of ganciclovir.

Foscarnet can be used empirically for patients who have marrow suppression from ganciclovir, who fail to respond to ganciclovir, or who have concurrent HHV-6 viremia. Foscarnet is administered in doses of 90 mg/kg intravenously every 12 hours for induction and 90 mg/kg intravenously every 24 hours for maintenance. Good urine

**TABLE 312-2 Weekly Screening Schedule for Initiation of Preemptive Cytomegalovirus (CMV) Therapy after Hematopoietic Stem Cell Transplantation**

CMV SEROSTATUS OF RECIPIENT	CMV SEROSTATUS OF DONOR	BLOOD PRODUCTS	DURATION OF WEEKLY SURVEILLANCE
Seronegative	Seronegative	CMV safe*	Weeks 2-12
Seronegative	Seropositive	CMV safe*	Weeks 2-12
Seronegative	None (autologous)	CMV safe*	Weeks 2-5
Seropositive	Seronegative or seropositive	CMV untested	Weeks 2-12, then every 2-4 weeks until week 26 <sup>†</sup>
Seropositive	None (autologous)	CMV untested	Weeks 2-5

\*Blood filtered to remove neutrophils or from seronegative donor.

<sup>†</sup>Possible indications for testing beyond week 26 include high risk for late CMV disease (e.g., in patients treated with corticosteroids for graft-versus-host disease).

**TABLE 312-3 Suggestions for Management of Possible CMV Infection after HSCT**

INDICATION	STRATEGY*	COMMENT
<b>Prevention</b>		
<b>Allogeneic Transplant</b>		
Seropositive recipient	Preemptive ganciclovir <sup>†</sup> induction for subclinical viremia, 5 mg/kg bid for 7-14 days, followed by 5 mg/kg daily until the end of maintenance or Ganciclovir prophylaxis <sup>‡</sup> at engraftment	Some cases of CMV disease may occur shortly after ganciclovir discontinuation.  CMV reactivation might be delayed, occurring later after HSCT.
Seronegative recipient with seropositive donor	Preemptive ganciclovir induction for subclinical viremia, 5 mg/kg bid for 7-14 days, followed by 5 mg/kg daily until the end of maintenance and Seronegative or filtered blood products	Prophylaxis at engraftment is not recommended because of the low incidence of post-transplantation infection.
Seronegative recipient with seronegative donor	Seronegative or filtered blood products	
<b>Autologous Transplant</b>		
Seropositive recipient	Early ganciclovir induction of subclinical viremia, 5 mg/kg ganciclovir bid for 7 days, followed by 5 mg/kg daily for 14 days of maintenance	Because of the very low risk in some settings, monitoring is not uniformly advocated.
Seronegative recipient	Seronegative or filtered blood products	
<b>Treatment of Disease</b>		
CMV pneumonitis	Ganciclovir induction, 5 mg/kg bid for 14-21 days, followed by 5 mg/kg daily for at least 3-4 wk of maintenance plus IVIG every other day for the duration of induction	Extended maintenance throughout periods of severe immunosuppression (i.e., GVHD treatment) may be considered.
Gastrointestinal disease	Ganciclovir induction, 5 mg/kg bid for 14-21 days, followed by 5 mg/kg daily for at least 3-4 wk of maintenance	If deep ulcerations are present, maintenance may be required for a longer time.
Marrow failure	Foscarnet, 90 mg/kg bid for 14 days, followed by 90 mg/kg daily for 2 wk plus G-CSF	Ganciclovir plus IVIG has also been used.
Retinitis	Ganciclovir, 5 mg/kg bid for 14-21 days, followed by 5 mg/kg daily for at least 3-4 wk	Extended maintenance may be required.

\*Regimens should be accompanied by weekly monitoring with antigenemia or PCR-based nucleic acid testing.

<sup>†</sup>Oral 900-mg doses of valganciclovir produce blood levels that are similar to those for the standard intravenous dose (5 mg/kg) of ganciclovir. Foscarnet and cidofovir are acceptable alternatives. Renal dose adjustment is required for all antiviral agents.

<sup>‡</sup>Foscarnet, high-dose acyclovir, or valacyclovir are acceptable alternatives. Renal dose adjustment required for all antiviral agents.

CMV, cytomegalovirus; G-CSF, granulocyte colony-stimulating factor; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; IVIG, intravenous immune globulin; PCR, polymerase chain reaction.

flow can minimize irritation of the urethra and labia by foscarnet. The serum biochemical abnormalities (chelation of calcium and phosphate) accompanying foscarnet therapy necessitates hospital observation and very careful electrolyte monitoring at least through the initial days of its use.

End-organ manifestations of CMV disease include pneumonitis (63%), enteritis (26%), and, in rare cases, retinitis (5%).<sup>95</sup> CMV pneumonitis occurs in fewer than 5% of CMV-seropositive allogeneic

patients who receive ganciclovir preemptive therapy during the first 100 days.<sup>95</sup> Among patients with CMV pneumonitis, the mortality rate is as high as 50%, even when prompt antiviral treatment is combined with intravenous immune globulin (IVIG) or CMV-specific immune globulin.<sup>160</sup> CMV viremia and pneumonitis are rare before engraftment.<sup>161,162</sup> Anorexia, nausea, vomiting, and sometimes diarrhea characterize CMV gastroenteritis; the diagnosis is made by endoscopy and biopsy with immunoperoxidase staining of CMV-infected cells.<sup>163,164</sup> CMV disease of the gastrointestinal tract is often associated with GVHD of the specific organ.<sup>164</sup> Response to therapy is not ensured, even with ganciclovir, but CMV gastrointestinal disease is not strongly associated with increased nonrelapse mortality.<sup>165</sup> Although CMV retinitis is common among patients infected with HIV, it is quite uncommon among HSCT recipients.<sup>166</sup>

Once an end organ has established disease from CMV, the infection is difficult to treat. CMV pneumonitis is treated with a combination of ganciclovir at induction doses for 14 to 21 days and IVIG (500 mg/kg every other day for the duration of induction, 14 to 21 days) and then with maintenance ganciclovir. Standard IVIG is generally used because CMV-specific immune globulin is scarce and costly and has not been shown to improve outcome. CMV enteritis is treated with ganciclovir at induction doses for 3 weeks or longer.<sup>167</sup> Treatment of protracted CMV enteritis might include ganciclovir and a longer duration of ganciclovir maintenance therapy to facilitate gastrointestinal healing.<sup>164</sup>

Development of a CMV-specific cytotoxic T-lymphocyte response is critical for the reconstitution of normal immunity and protection from late CMV disease.<sup>168</sup> Long-term IVIG delays recovery of CMV immunity. For patients who remain at risk for late disease, CMV monitoring should be continued beyond day 100. Patients who are treated with acyclovir followed by ganciclovir or those treated with serial ganciclovir courses may be at increased risk for developing genotypic resistance. Clinical resistance episodes should be treated with foscarnet (or cidofovir) until genotype assays for mutations in the UL97 or UL54 gene are able to confirm virologic resistance.<sup>169</sup> Extended ganciclovir therapy appears to delay recovery of cytotoxic T-lymphocyte activity, either by a direct effect on lymphocytes or by limitation of the amount of antigen exposure to lymphocytes. This immunodeficiency can be reversed when cytotoxic T lymphocytes are given adoptively, but this technology is available only at some tertiary centers.<sup>168,170</sup>

### Varicella-Zoster Virus

VZV infection is a primary occurrence (5% of occurrences) or a reactivation (95%) in 40% of patients at any time in the first year after transplantation.<sup>171,172</sup> VZV can be effectively prevented with acyclovir prophylaxis,<sup>173</sup> but VZV prophylaxis is not employed at all transplantation centers because only 30% to 50% of adult patients and 25% of pediatric patients develop this infection during the first year after transplantation. The median time of onset is 5 months after transplantation. Prolonged antiviral prophylaxis may delay the onset of VZV but is not associated with rebound VZV.<sup>173</sup> Localized zoster may manifest atypically with a few vesicles, or skin lesions may appear as atypical vesicles; therefore, laboratory confirmation of VZV reactivation is recommended.

Manifestations of VZV disease are most often dermatomal shingles but may include hemorrhagic pneumonia, hepatitis, abdominal pain, central nervous system disease, thrombocytopenia, and retinal necrosis.<sup>174-178</sup> Disseminated or visceral varicelliform zoster may manifest as low back pain or acute abdominal pain before the appearance of skin lesions. GVHD is a strong predisposing factor for VZV dissemination, which involves visceral organs in 20% to 40% of patients.<sup>174,179</sup> Most fatal cases of disseminated or abdominal zoster occur in patients who were treated with suboptimal doses of acyclovir or for whom therapy was initiated relatively late in the course of infection. High-dose acyclovir (10 mg/kg IV every 8 hours) has been the treatment of choice for disseminated VZV infection. Valacyclovir and famciclovir can be used as stepdown treatment after intravenous acyclovir or as initial treatment of localized infection. Although uncommon, patients who are already seropositive may acquire a second primary VZV infection. VZV vaccination is recommended at the 2-year anniversary visit for patients who have been free of immunosuppressive medications for

several months, unless the underlying hematologic or oncologic disease is in remission.<sup>180,181</sup> The vaccine used should be the lower-plaque-forming unit version (Varivax) used for prevention of chickenpox among children, not the higher-titer (Zostavax) vaccine used for immunocompetent older adults.

VZV is a fastidious virus and may not withstand the time required to transport the specimen to the diagnostic laboratory. By scraping the base of a vesicle and examining the cells by DFA with VZV-specific monoclonal antibodies, clinicians can best diagnose lesions of herpes zoster and chickenpox. The Tzanck smear is less sensitive and is no longer recommended. Tissue diagnosis can be made through histologic examination, immunohistochemical techniques, or culture. PCR assay, if available, is the laboratory technique of choice.

When a VZV-seronegative patient receives a significant exposure to a person with active or incubating chickenpox, a course of acyclovir with or without varicella-zoster immune globulin (VariZIG) is recommended to prevent chickenpox (see Chapter 308).<sup>182</sup> Acyclovir in the usual treatment doses of 10 mg/kg intravenously every 8 hours for 3 to 22 days after exposure seems appropriate. For a VZV-seropositive patient living in the same dwelling as someone with an index case of active chickenpox or shingles, acyclovir is reported to be useful in preventing new infection. VariZIG is usually not given to exposed seropositive patients, but antiviral prophylaxis is often recommended, depending on the exposure, the length of time since the transplantation, and the level of immunosuppression. For lower-risk patients, valacyclovir, 1 g orally three times daily, may be appropriate, although the efficacy in this situation is unknown. Patients already receiving empirical ganciclovir for CMV reactivation do not need further antiviral agents.

### Adenovirus

Adenovirus infection reactivates in approximately 12% of allogeneic and approximately 6% of autologous adult HSCT patients.<sup>183,184</sup> Chronic shedding can occur in the absence of clinical disease, but adenovirus can also be acquired from respiratory droplet transmission. In its most common clinical manifestation in this setting, adenovirus is a cause of hemorrhagic cystitis.<sup>30</sup> Systemic infection in the lungs, liver, gastrointestinal tract, and kidneys occurs in 18% to 20% of infected patients. GVHD is a risk factor for the occurrence of clinically apparent adenovirus infection after HSCT.<sup>185</sup> In addition, allogeneic patients who do not receive ganciclovir (seronegative for CMV or seropositive without need for ganciclovir) are at higher risk for developing adenovirus infection than are patients who did receive ganciclovir, even though ganciclovir has no activity against adenovirus.<sup>183</sup> Immunofluorescence, shell vial, or conventional tube culture of blood, urine, stool, or tissue can be used to diagnose adenovirus. PCR testing is helpful in diagnosis of infection, but in general is not cost-effective for surveillance because many patients are asymptomatic.<sup>186,187</sup> Some centers use quantitative viral load monitoring followed by preemptive treatment with low-dose (1 mg/kg) cidofovir three times a week.<sup>188</sup> Other centers may have access to adenovirus-specific cytotoxic T cells. No effective therapy is available for adenoviral infections, although cidofovir or the lipid-conjugated derivative (CMX001) has been used in patients able to tolerate the potential toxicities.<sup>189,190</sup>

### Respiratory Viruses

Patients who have undergone HSCT and develop a respiratory viral infection typically present with rhinorrhea and nasal congestion and may also have fever, cough, throat pain, headache, or myalgias.<sup>191</sup> The common pathogens in such patients include respiratory syncytial virus, parainfluenza virus, and, to a lesser extent, influenza virus, rhinovirus, human metapneumovirus, and coronavirus.<sup>191-202</sup> Current rapid test methods allow detection of respiratory syncytial virus, parainfluenza, influenza, and other viruses in respiratory specimens within 48 hours (see Chapter 16). Respiratory virus infections commonly occur during the winter season and cause pneumonia in up to 50% of patients, although progression to lower tract infection is less common with nonmyeloablative “conditioning regimens.”<sup>195</sup> In contrast, parainfluenza virus type 3 infections may occur throughout the year<sup>199</sup> and nosocomial outbreaks of respiratory syncytial virus have occurred at other times than the established winter season. Influenza, most often

type A, infrequently progresses to pneumonia. Prophylactic or early initiation of oseltamivir therapy for upper respiratory tract disease may prevent progression to lower respiratory tract disease.<sup>200</sup>

Respiratory syncytial virus and parainfluenza are associated with a high incidence of progression from upper to lower tract disease among infected patients. Upper respiratory tract illness with parainfluenza usually resolves without serious sequelae. Lower tract infection has a mortality rate of 80% for respiratory syncytial virus and 30% to 35% for parainfluenza virus.<sup>193,203,204</sup> Therapy with aerosolized ribavirin or a combination of ribavirin and IVIG has been used for respiratory syncytial virus, although rigorous trials to determine its efficacy are not available.<sup>191,205</sup> The survival rate appears to be higher when treatment is initiated before significant hypoxia is present, and aerosolized ribavirin may help to decrease the viral burden.<sup>205,206</sup> There are only anecdotal case reports regarding the effectiveness of ribavirin for treatment of other respiratory viruses, including parainfluenza, adenovirus, and influenza. Preemptive therapy with aerosolized ribavirin in patients with positive nasopharyngeal cultures for respiratory syncytial virus appears promising. Patients who develop respiratory viral pneumonia before engraftment have poorer outcomes. Aerosolized ribavirin (Virazole) is administered by a face mask to adults through a small-particle aerosol generator. This device can be used for patients on a ventilator. Although there are no data on what dose may be effective, 6 g (one vial) per 12 hours once daily is a schedule that has been used. Contamination of the patient's room with this possibly teratogenic agent is of concern to pregnant hospital staff (see Chapter 44).

Prevention of exposure is critical because treatment is not very effective. Protection involves the use of frequent hand washing by hospital staff and droplet isolation of patients with colds or respiratory tract symptoms. In addition, family members and health care workers with upper respiratory tract symptoms should be separated from patients. Vaccination of family members, health care workers, and other close contacts against influenza may help control exposures. Amantadine or rimantadine prophylaxis has limited usefulness because of the widespread development of resistance. Oseltamivir provides useful prophylaxis against both influenza A and B and appeared useful when used in a housing facility for HSCT recipients.<sup>207</sup> Immune globulin prophylaxis with respiratory syncytial virus-specific polyclonal or monoclonal antibody, which is useful in infants at high risk, has not been sufficiently evaluated in the HSCT setting.<sup>208</sup> During the respiratory virus season, all patients with respiratory symptoms should have a sample taken from the nasopharynx to be evaluated for respiratory viruses.

### Epstein-Barr Virus

The majority of Epstein-Barr virus (EBV) reactivation is subclinical and requires no therapy. The incidence of EBV-related complications may be higher (7%) among recipients of umbilical cord blood transplants or those receiving anti-T-cell serotherapy (antithymocyte globulin or alemtuzumab) (21%) than among recipients of HLA-matched, unrelated-donor marrow myeloablative transplants (3%).<sup>209</sup> HLA-mismatched (especially haploidentical) or T-cell-depleted grafts may lead to prolonged T-cell lymphopenia and augment the risk for EBV reactivation. Quantitative diagnostic monitoring of EBV viral load accompanied by preemptive therapy may reduce the risk for progression to life-threatening post-transplantation lymphoproliferative disorder (PTLD).<sup>210</sup> In most cases, high viral loads are associated with progression to PTLD.<sup>211</sup> Infusions of rituximab or nonirradiated donor leukocytes may be effective treatment for allograft recipients with high-titer EBV viremia or PTLD.<sup>209,212,213</sup>

### Human Herpesvirus 6

HHV-6 has been implicated as a possible cause of bone marrow suppression, fatal meningoencephalitis, and interstitial pneumonitis in fewer than 2% of HSCT patients.<sup>214</sup> Recipients of umbilical cord blood may have more viremia than do other populations.<sup>215,216</sup> HHV-6 appears to reactivate commonly, occurring in 46% of HSCT patients according to culture diagnosis and as many as 100% of patients according to PCR assay of blood.<sup>217</sup> Many episodes of reactivation detected by DNA PCR may be asymptomatic, and the value of therapy for subclinical viremia and hence surveillance is unknown.<sup>218</sup> High-level

HHV-6 viremia is associated with acute GVHD and nonrelapse mortality.<sup>219</sup> Most strains of HHV-6 identified after HSCT appear to be caused by the B variant in blood or urine, although the A variant has been correlated with pneumonitis.<sup>220</sup> HHV-6 has greater than 60% DNA homology with CMV, and treatment of documented infection is usually initiated with induction doses of foscarnet. Responses to antiviral therapy are not universal, and benefits of antiviral therapy have not been rigorously determined.<sup>221</sup>

### Parvovirus

Parvovirus B19 (HPV B19) is a rare cause of refractory anemia with erythroid hypoplasia after HSCT.<sup>222-225</sup> Antibody or PCR tests detect parvovirus, although PCR assay may yield positive findings for months after the acute infection. Use of single-patient rooms on HSCT wards may be preventing transmission of this contagious virus to other patients undergoing HSCT, and the administration of IVIG for other reasons may be treating subclinical infections (see Chapter 149).

### Fungal Infections

Invasive fungal infections are important causes of morbidity and mortality. The major causes of invasive fungal disease include *Candida* spp., *Aspergillus* spp., and, less frequently, the non-*Aspergillus* filamentous molds. Patients undergoing allogeneic transplantation are at 10-fold increased risk for invasive fungal infection in comparison with patients receiving an autologous graft. Systemic fluconazole prophylaxis or low-dose amphotericin B (0.1 to 0.3 mg/kg daily) can decrease the incidence of systemic candidiasis.<sup>75-77,226,227</sup> Advanced-generation azoles and micafungin prophylaxis extend the spectrum of organisms covered to include molds, but their general value or cost-effectiveness for all allograft recipients has not been shown.<sup>228</sup> Empirical therapy for febrile neutropenic patients is discussed in Chapter 311.

### Pneumocystis

*P. jirovecii* infection<sup>229</sup> usually manifests as pneumonia with dyspnea, cough, fever, and bilateral infiltrates in the majority of infected patients.<sup>88</sup> It can occur after both autologous and allogeneic transplantation, although the frequency is lower for the former. Before the use of routine prophylaxis, *Pneumocystis* infection occurred in approximately 7% of patients who underwent allogeneic HSCT, at a median of 1 to 3 months after transplantation, and was associated with a 5% risk for death.<sup>230,231</sup> Prophylaxis with TMP-SMX has resulted in negligible rates of infection. For patients who do not tolerate medications containing sulfa, prophylaxis options include desensitization with TMP-SMX and use of dapsone,<sup>92,232</sup> atovaquone,<sup>233</sup> and inhaled pentamidine.<sup>89,234</sup> The treatment of choice for *P. jirovecii* infection is TMP-SMX.<sup>88,90</sup>

### Candida

Candidiasis is an infection acquired from endogenous organisms colonizing the gastrointestinal tract; it usually manifests as fungemia or visceral candidiasis (see Chapter 258). Before fluconazole prophylaxis, the onset of candidiasis occurred at a median of 2 to 3 weeks after transplantation and *Candida* spp. were second in frequency to *Aspergillus* spp. as the cause of brain abscess after HSCT.<sup>235,236</sup> The current cumulative incidence rate of invasive candidiasis during the first year after HSCT is probably less than 5%.<sup>237</sup> Risk factors for invasive candidiasis include neutropenia, breakdown of the normal mucosal barriers, and the use of broad-spectrum antibiotics or corticosteroids. *C. albicans* infections are successfully prevented when fluconazole is given as prophylaxis from the time of conditioning until either engraftment or day 75 after HSCT. The strategy of prolonged fluconazole therapy has been associated with improved survival rates, although the mechanism of the observed benefits is uncertain.<sup>77,238,239</sup> The benefit of fluconazole prophylaxis is less clear for autologous transplants, for which the degree of mucositis is less.

With the use of fluconazole since the 1990s, the number of *Candida* infections has decreased.<sup>226</sup> The spectrum of colonizing and infecting *Candida* organisms has shifted from *C. albicans* and *Candida tropicalis* to include *C. krusei*, *C. glabrata*, and *Candida parapsilosis*.<sup>80</sup> *C. krusei* is innately resistant to fluconazole.

### Aspergillus

*Aspergillus* and other mold infections are acquired exogenously, by inhalation of spores into the respiratory tract from the environment, and in some localities may occur with higher frequency during the summer.<sup>86</sup> Common sites of initial infection include the lung and sinuses, although contiguous or hematogenous extension to the central nervous system or other internal organs may occur. With the use of fluconazole prophylaxis during the preengraftment period, invasive aspergillosis emerged as the leading fungal infection found at autopsy among patients who underwent HSCT.<sup>226</sup> Preengraftment prophylaxis with mold-active therapy is now being used for patients who may have *Aspergillus* incubating at the time of transplantation owing to prior infection or prolonged neutropenia.<sup>78,79</sup> Postengraftment prophylaxis with posaconazole or voriconazole has led to a decrease in mortality among patients with a high risk for invasive aspergillosis.<sup>78,87,240</sup>

The incidence of invasive aspergillosis among patients undergoing HSCT ranges from 4% to 15%.<sup>86,241,242</sup> The onset of *Aspergillus* infection after HSCT occurs in a bimodal distribution, with the first peak at 2 to 3 weeks (during neutropenia) and the second at 3 to 4 months after HSCT, usually in conjunction with persisting GVHD.<sup>86</sup> Postengraftment aspergillosis can occur after 6 months, again alongside chronic GVHD but also with CMV. Older age is associated with the acquisition of aspergillosis during either the preengraftment or postengraftment risk periods. Donor type, male gender, and summer season are recognized risk factors for preengraftment aspergillosis, whereas construction in the vicinity of the hospital, GVHD and attendant corticosteroid therapy, lymphopenia, CMV, respiratory virus infection, and multiple myeloma are significant risk factors for the development of postengraftment aspergillosis.<sup>86,243</sup> Early aspergillosis is temporally associated with neutropenia; therefore, infection among autologous HSCT patients is rare after engraftment. The estimated 1-year survival rate among patients with proven invasive aspergillosis is 7% to 30%, although more aggressive, prolonged, or combination antifungal therapies may be improving these outcomes.

Preventive strategies focus on reducing both environmental and host risk factors. The use of high-efficiency particulate air (HEPA)-filtered air systems or laminar airflow rooms during the preengraftment risk period aids in the prevention of infection, particularly for allograft recipients. HEPA filters are capable of removing particles greater than 0.2  $\mu\text{m}$  in diameter, such as mold spores. The patient's room is continuously maintained at positive pressure in relation to the corridor, which enhances the barrier effect. For transport out of HEPA-filtered rooms or after discharge, tight-fitting face masks reproduce this barrier and are sometimes used, at least for the early post-HSCT period.

Patients might ask whether portable HEPA filters should be purchased for use after the hospitalization. This extra measure can be implemented on an individual basis: units can be obtained for each of the rooms that the patient will occupy during the day and night, and each unit is sized for the room it will be placed in. There is no evidence of the clinical efficacy of these filters out of the hospital setting in preventing acquisition of airborne mold infections. For outpatients, they are probably of little value and of considerable expense.

Other prevention strategies, including nasal and aerosolized amphotericin B, have not been studied in controlled trials.

The availability of accurate early diagnostic tests for invasive fungal infections lags behind those for other types of infections. The *Aspergillus* galactomannan test is most useful for patients not already taking antifungal therapy that includes coverage for molds, which is a minority of high-risk allogeneic recipients.<sup>244</sup> Other antigen- and nucleic acid-based diagnostic tests have been studied for early diagnosis of invasive tissue mold infection, but they have not demonstrated usefulness in clinical practice. Most have not been tested in large numbers of clinical samples from HSCT recipients. Blood cultures for molds rarely yield positive findings of mold organisms, except in the case of *Fusarium*.

A high index of suspicion in persistently febrile neutropenic patients and timely computed tomography of the chest to detect new infiltrates are important for early detection of invasive pulmonary aspergillosis. A small "ground-glass" halo around the lung lesion or pleura-based or nodular infiltrates on computed tomographic scans

are highly suggestive of aspergillosis or other mold infection in a neutropenic host.<sup>82</sup> Bronchoscopy with cytologic examination and culture of lavage fluid for fungi, as well as other organisms common to immunocompromised hosts, is important. Galactomannan assay of the bronchoalveolar lavage fluid may have augmented diagnostic value. A lack of clinical or radiographic response during empirical antifungal therapy may necessitate tissue sampling. Minimally invasive surgery (video-assisted thoracoscopic surgery) is associated with less morbidity than is open-lung biopsy.

Patients who have undergone HSCT and have suspected invasive mold infections should promptly begin taking a mold-active antifungal agent while diagnostic procedures are being arranged. Advanced-generation azole agents and echinocandins have less nephrotoxicity than do lipid preparations of amphotericin B. A lack of clinical or radiographic response during proven infection may necessitate a switch to an agent from a different class or to combination therapy. Combination treatment of fungal infections with echinocandins, azoles, and polyene agents is common, whereas results of a large randomized clinical trial failed to show a benefit. Echinocandin agents may be fungistatic rather than fungicidal in the case of mold infections because their interruption of cell wall synthesis is limited to actively growing hyphae.

For documented invasive tissue mold infection, therapy is usually continued until some weeks (4 to 6) after lesions are resolved or stable, immunocompetence has improved, and the patient is afebrile. Although amphotericin B had been the gold standard antifungal agent since the 1960s, voriconazole produced superior outcomes in treatment for aspergillosis in 53% of patients, in contrast to 32% of patients treated with amphotericin B (followed by other antifungal therapy).<sup>245</sup> Treatment of central nervous system mold infections should include voriconazole, which (on the basis of a few patients studied) attains cerebrospinal fluid levels approximately 50% of plasma levels and central nervous system tissue levels approximately 200% of plasma levels (see Chapter 39).

After initial control of an *Aspergillus* infection, subsequent maintenance therapy for the duration of immunosuppression has been advocated to reduce the risk for reactivation. Multiple drug-drug interactions occur with the azoles, and adjustments may be required for immunosuppressive agents. Transient visual disturbances or hallucinations can occur with voriconazole. Difficulty in achieving therapeutic plasma drug levels complicates the administration of itraconazole and posaconazole. Itraconazole solution has improved oral bioavailability over the capsule and can be used, although blood level monitoring may be needed to ensure adequate absorption. Posaconazole has good antimold activity, but its oral absorption requires high fat intake, which may not be feasible in patients with GVHD or other enteric complications.

### Other Yeasts

*Malassezia furfur* causes tinea versicolor, catheter-related fungemia, and sometimes pneumonia.<sup>246-248</sup> Response to either topical or systemic therapy is slow; recovery of granulocyte counts is usually associated with resolution.<sup>247</sup> Catheter removal and discontinuation of intravenous lipids are important for a successful outcome in cases of fungemia. Trichosporonosis has manifested as fungemia, skin lesions, pneumonitis, and arthritis.<sup>249,250</sup> Fungemia, usually acquired via an intravenous catheter, has been reported with *Trichosporon* and *Rhodotorula* spp., *Cryptococcus laurentii*, and *Hansenula anomala*. Meningitis with *Cryptococcus neoformans* is unusual, in contrast to its frequent occurrence among patients infected with HIV. Widespread anti-*Candida* prophylaxis with fluconazole may contribute to the low frequency of these infections.

### Other Molds

Non-*Aspergillus* molds such as *Alternaria*, *Pseudallescheria/Scedosporium*, *Paecilomyces*, *Fusarium*, and *Phialophora* spp. are infrequent causes of invasive tissue infections whose clinical appearance is similar to that of *Aspergillus* infection. They are indistinguishable from *Aspergillus* hyphae in tissue sections; thus, culture is required for identification. Disseminated fusariosis can be a fatal infection for patients who have undergone HSCT, manifesting as positive blood cultures, skin lesions, or endophthalmitis.<sup>251</sup> Successful resolution is usually

associated with neutrophil recovery in addition to antifungal therapy.<sup>252</sup> In the case of fusarial endophthalmitis, enucleation of the affected eye may be required.

Mucormycosis is uncommon after HSCT, but it mimics aspergillosis clinically and may occur long after HSCT.<sup>253,254</sup> The cause of one hepatic infection included over-the-counter herbal medication.<sup>255</sup> Patients receiving voriconazole prophylaxis are at risk for breakthrough infection with invasive mucormycosis, but the risk for such breakthrough infections appears low.<sup>256-259</sup> Posaconazole may be an effective maintenance treatment for infections caused by certain species of Mucorales after response to amphotericin B.<sup>260</sup> Clinically significant infections caused by the dimorphic fungi, including coccidioidomycosis, histoplasmosis, and blastomycosis, are unusual even in hyperendemic areas of the United States.

### Parasitic Infections

Parasitic infection after HSCT usually manifests as reactivation of toxoplasmosis,<sup>261</sup> although Chagas' disease,<sup>262-266</sup> malaria,<sup>267-272</sup> strongyloidiasis,<sup>273</sup> schistosomiasis,<sup>274</sup> *Clonorchis* infection,<sup>275</sup> giardiasis,<sup>276</sup> cryptosporidiosis,<sup>277-280</sup> pulmonary microsporidiosis,<sup>281-283</sup> and *Acanthamoeba* and *Trichomonas* meningoencephalitis<sup>284-287</sup> have also been reported. Routine blood smears before HSCT cannot be used to rule out malarial transmission. In Hong Kong, *Clonorchis sinensis* infection was identified in only 1% of screening stool examinations performed 7 days before HSCT.<sup>275</sup> None of the patients had symptoms related to clonorchiasis; patients received praziquantel (25 mg/kg orally three times for 1 day) before HSCT, and subsequent stool examinations did not reveal the presence of ova.

Toxoplasmosis is infrequent after HSCT, occurring in 2% to 7% of patients who are seropositive before transplantation.<sup>288-291</sup> Although the parasite can be transmitted as a primary infection through marrow, blood products, or donor solid organs, toxoplasmosis in patients who have undergone HSCT is almost always the result of reactivation of prior infection. GVHD is a risk factor for the suppression of cell-mediated immunity that is critical for host defense against *Toxoplasma gondii*.<sup>292</sup> The clinical presentation includes fever, encephalitis with focal cerebral lesions, pneumonitis, or myocarditis. One postmortem diagnosis of disseminated toxoplasmosis was associated with hemophagocytic syndrome.<sup>293</sup> Parasitemia is a feature of reactivation that may be identified in tissue culture, although many diagnoses are now made with PCR.<sup>294,295</sup> In countries where the prevalence of this infection is high, pretransplant detection of DNA using PCR may indicate those at highest risk for infection after transplant.<sup>296</sup> Stereotactic brain biopsy is also useful in diagnosis of the infection.<sup>297</sup> The identifiable risk period is 2 to 8 weeks after HSCT, and toxoplasmosis is more common among those receiving myeloablative conditioning.<sup>298</sup> Seropositive patients not receiving TMP-SMX are at risk for breakthrough toxoplasmosis.<sup>299</sup> For these patients, *Toxoplasma* reactivation can be monitored through PCR assay during the first 1 to 3 months after HSCT.<sup>300</sup> However, in countries where the prevalence is low, routine prophylaxis is not justified.

## METHODS OF IMMUNE SYSTEM RECONSTITUTION AFTER HSCT

### Vaccination

Patients undergoing autologous or allogeneic HSCT eventually lose immunity to the common childhood diseases and should be serially reimmunized 6 and 24 months after transplantation (Table 312-4; see Fig. 312-1).<sup>181,301</sup> The efficacy of vaccination is influenced by the time elapsed since transplantation, the nature of the hematopoietic graft, the presence of GVHD, and the use of serial immunization.<sup>302</sup> There have been no reports of exacerbation of GVHD after immunization of patients who underwent HSCT. A national survey of HSCT immunization practices revealed that vaccines were underutilized and schedules for revaccination varied.<sup>303</sup> To ensure compliance it is recommended that all transplant recipients should be immunized on the same schedule, regardless of cell source.<sup>304</sup>

All indicated nonlive vaccines should be administered to patients who have undergone HSCT, regardless of transplant type or presence of GVHD. Such patients should be revaccinated every 10 years with the combined tetanus-diphtheria-pertussis toxoid, absorbed.

TABLE 312-4 Suggested Schedule for Vaccination after HSCT

VACCINE	TIME PERIOD FOR IMMUNIZATION AFTER HSCT		
	6 to 12 Months	14 Months	24 Months
<b>Inactivated Vaccines</b>			
Diphtheria, tetanus, pertussis <sup>305</sup>	X	X	X
<i>Haemophilus influenzae</i> serotype B conjugate	X	X	X
Hepatitis B <sup>306</sup>	X	X	X
Pneumococcal	X (13-valent conjugated)		X* (13-valent conjugated)
Inactivated polio	X	X	X
Influenza <sup>307</sup>	Lifelong, seasonal administration of inactivated vaccine, beginning before HSCT and resuming $\geq 6$ mo after HSCT, is recommended		
Hepatitis A	Routine administration is not indicated If hepatitis A vaccination is given, two doses, given 6-12 mo apart, are required		
Meningococcal conjugate	Routine administration is not indicated		
Human papillomavirus <sup>308</sup>	Administration is recommended for men and women younger than 27 yr		
Rabies	Routine administration is not indicated; any decision to use should be individualized		
<b>Live Replication Competent Vaccines</b>			
Measles-mumps-rubella	Administration is not indicated		X* <sup>†</sup>
Varicella-zoster (Varivax) <sup>310</sup>	Administration is not indicated		X* <sup>†</sup>
Yellow fever virus	Routine administration is not indicated; any decision to use should be individualized		

\*Optional.

<sup>†</sup>In patients with no active graft-versus-host disease or immunosuppressive therapy. HSCT, hematopoietic stem cell transplantation.

Vaccination with acellular pertussis does not generate enough immunity, so vaccines with higher-dose pertussis toxoid should be used until transplant recipients are further studied.<sup>305</sup> At 6 months, they should also be immunized against polio by the inactivated intramuscular vaccine, *H. influenzae* type B, hepatitis B, and *S. pneumoniae*. If the patient was previously immunized, only one dose of hepatitis B vaccine should be given. Postvaccine titers of hepatitis B virus should be documented to ensure response and adequate protection, even when the vaccine is given at the specified time interval after HSCT.<sup>306</sup> At 2 years, a second dose of pneumococcal vaccine is optional; it provides a second opportunity to vaccinate persons who failed to respond to the first dose, especially patients with chronic GVHD. Lifelong, seasonal administration of influenza vaccine should begin before HSCT and resume by 2 to 6 months after HSCT. Children younger than 9 years who are receiving influenza vaccination for the first time require two doses yearly. Adults do not benefit from receiving two influenza vaccine doses.<sup>307</sup> Influenza vaccine for HSCT ward employees, clinical health care workers, and household contacts may be especially necessary within the first year or for patients with ongoing GVHD, in whom protective responses may be impaired. For health care workers directly caring for HSCT recipients, the live, attenuated intranasal vaccine should be avoided to limit inadvertent exposure to patients. Vaccination with the quadrivalent human papillomavirus vaccine has not been studied but may be appropriate for male and female long-term transplant recipients ages 9 to 26 years and perhaps for women older than age 26 who are at risk for squamous intraepithelial lesions.<sup>308,309</sup>

Live virus vaccines such as measles-mumps-rubella and varicella should not be given to transplant recipients with active GVHD or ongoing immunosuppressive therapy; the first doses are given to transplant recipients more than 24 months after HSCT who are taking no immunosuppressive medications and are presumed immunocompetent. A second measles-mumps-rubella dose should be given 6 to 12 months later; however, the benefit of a second dose in this population has not been evaluated.

Vaccination with live-attenuated VZV vaccine (Varivax, not Zostavax) is used for VZV-seronegative patients who no longer require immunosuppressive therapy and are free of GVHD.<sup>310</sup> When varicella vaccination is given to persons older than 13 years, two doses, given 4 to 8 weeks apart, are required. Vaccination of HSCT recipients who have developed reactivation shingles after transplant is not needed. Susceptible family members should receive VZV vaccine to minimize chickenpox exposure for VZV-seronegative transplant recipients.

Routine administration of hepatitis A, meningococcal, and rabies vaccines is not indicated. Hepatitis A vaccine is recommended for

transplant recipients with chronic liver disease, including hepatitis C infection or chronic GVHD, or who live in hepatitis A–endemic areas or in areas experiencing outbreaks. If given, hepatitis A vaccination requires two doses, given 6 to 12 months apart. For transplant recipients with potential occupational exposure to rabies, preexposure rabies vaccination should be delayed until at least 12 months, if not 24 months, after HSCT.

## Immunoglobulin Replacement

The major defect in humoral immunity is the absence of specific antibody production. Antibody levels in the first year after HSCT are affected primarily by pretransplantation levels in the recipient and, to a lesser degree, in the donor.<sup>311</sup> Among patients with chronic GVHD, reduced production of opsonizing antibody and of all classes of immunoglobulin G and immunoglobulin A antibodies is seen.<sup>312</sup> This immunodeficiency is further complicated by poor splenic function and is associated with risks for recurrent pneumococcal infections and episodes of bronchitis or pneumonia. IVIG does not prevent infections when given weekly during the preengraftment or late risk periods, but it does reduce rates of septicemia and localized infection when given in the postengraftment risk period after transplantation.<sup>313-315</sup> It may modulate the severity of GVHD.<sup>316</sup> Replacement IVIG (200 to 500 mg/kg every 1 to 2 weeks) may be beneficial for patients with immunoglobulin G levels lower than 400 mg/dL; however, in one prospective trial, routine use of IVIG delayed the recovery of antigen (viral)–specific immunity.<sup>314</sup>

The role of hyperimmune globulin for prevention of specific infections is less clear. High-titer CMV globulin for prevention of CMV infection and treatment of end-organ CMV disease has proved to be of clear benefit in comparison with IVIG. However, antiviral drugs are effective in providing protection against CMV disease. Therefore, because of its limited availability, as well as cost considerations, the use of CMV-specific globulin is minimal at most transplantation centers. Hyperimmune respiratory syncytial virus globulin provided only a very modest increase in neutralizing antibody when given in the first 6 weeks after HSCT.<sup>208</sup> Hepatitis B, human rabies, and tetanus immune globulin should be used as needed in the event of exposures. VariZIG is a human polyclonal immunoglobulin G available for intramuscular or intravenous administration under an expanded access program through Cangene Corporation for patients at high risk within the first 10 days of exposure.<sup>317</sup> VariZIG administration may extend the varicella incubation period from 10 days to as much as 28 days, is expensive, and is not uniformly effective in preventing chickenpox in patients who have undergone HSCT.



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The complete reference list is available online at Expert Consult.

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