

# Chapter 8

## Stem Cell Transplantation

John R. Wingard

**Abstract** Hematopoietic cell transplantation (HCT) is associated with profound compromises in host defenses. The patterns of immune compromise change over time. Infections are an important cause of serious morbidity and pose substantial threats to life. Thus, the challenges of infection facing the transplant clinician are both myriad and dynamic. Early after transplant, neutropenic infections are most important. Later herpesvirus and invasive fungal infections predominate. Even late after transplant, patients with chronic graft versus host disease remain susceptible to encapsulated bacterial, varicella zoster virus, and invasive fungal infections. Over time, with robust engraftment and control of GVHD, the risk of serious infections recedes with immune reconstitution.

**Keywords** Hematopoietic cell transplant • Antifungal prophylaxis • Antibiotic prophylaxis • Pneumonia • Diarrhea • Neutropenic fever • Cytomegalovirus • Respiratory viral infections • Varicella zoster virus infection

### 1. Hematopoietic Cell Transplantation

Hematopoietic cell transplant (HCT) is variously known as bone marrow transplant, stem cell transplant, or hematopoietic stem cell transplant. It is used to treat conditions that result in bone marrow failure (such as aplastic anemia or myelodysplastic syndromes), immunodeficiencies (such as severe combined immunodeficiency or chronic granulomatous disease), or congenital disorders that result in enzyme deficiencies in cells derived from hematopoietic precursors that result in metabolic disorders (such as mucopolysaccharidoses or glycogen storage diseases). These disorders are relatively rare in the general population. More commonly, HCT is used as a cancer therapy, primarily for hematologic malignancies (such as lymphomas, leukemias, and multiple myeloma). In this latter type of application, HCT is used to facilitate administration of intensive chemoradiotherapy. The intensive conditioning regimen suppresses and sometimes ablates the normal hematopoietic precursors. The graft is given to rescue the hematopoietic injury. In the case of allogeneic

HCT, the graft also provides adoptive immunotherapy targeting cancer cells that express novel antigens.

Autologous transplants do not require prolonged immunosuppressive therapy after the transplant and robust immune recovery typically occurs within 3–9 months. Allogeneic HCT necessitates stringent HLA matching to optimize engraftment and minimize the risk of graft versus host disease (GVHD). Immunosuppressive therapy is typically given posttransplant for 4–6 months and then tapered gradually and finally stopped after approximately 6 months. The occurrence of GVHD may necessitate a more prolonged course of immunotherapy and slow immune recovery. Immunodeficiency is more prolonged after allogeneic HCT (typically a year, sometimes longer) than after autologous transplant and the risk of infection is greater.

Each of the basic components of the transplant (the conditioning regimen, the graft, the posttransplant immunosuppressive therapy, and other supportive care regimens) influence the risk for infection and types of infectious syndromes that occur after transplant (Table 8-1).

Ablative conditioning regimens consisting of intensive chemotherapy or chemoradiotherapy have been the standard regimens used for decades. Ablative regimens have been associated with a number of toxicities to normal tissues (including mucosal injury) that are natural barriers against potential microbial pathogens. Mucosal injury allows easier entry of organisms that ordinarily colonize mucosal surfaces, leading to susceptibility to streptococcal organisms, enteric Gram negative organisms, anaerobes, and Candida.

In the past decade, transplant clinicians are increasingly using reduced intensity conditioning regimens in allogeneic HCT. Potent immunosuppressive

**Table 8-1.** Elements of the transplant procedure and their effects on infectious risk.

<b>Component</b>	<b>Transplant role</b>	<b>Influence on infectious risk</b>
Conditioning regimen	<ul style="list-style-type: none"> <li>• Anticancer activity</li> <li>• Immunosuppression to facilitate engraftment</li> </ul>	<ul style="list-style-type: none"> <li>• Intensive conditioning regimens cause mucosal injury that increases susceptibility to bacteria and Candida infections</li> <li>• Myelosuppression poses risk for bacterial and Candida infections</li> </ul>
Graft	<ul style="list-style-type: none"> <li>• Hematopoietic reconstitution</li> <li>• B &amp; T cell recovery</li> </ul>	<ul style="list-style-type: none"> <li>• Higher numbers of CD34+ cells associated with shorter neutropenia, fewer and less severe neutropenic infection</li> <li>• T cell depletion slows T cell reconstitution increasing susceptibility to viral and fungal infections</li> <li>• High T cell content increases risk for GVHD and susceptibility for viral and fungal infections</li> <li>• Histocompatibility differences between donor and recipient increases the risk for GVHD and susceptibility for viral and fungal infections</li> </ul>
Immuno-suppressive regimen	<ul style="list-style-type: none"> <li>• Prevents graft rejection</li> <li>• Prevents GVHD</li> </ul>	<ul style="list-style-type: none"> <li>• Deficiency of T cell protective responses increases the risk for herpesvirus and fungal infections</li> </ul>
Supportive care	<ul style="list-style-type: none"> <li>• Central venous catheters permit administration of medications, transfusions, and blood sampling</li> <li>• HEPA filters in rooms</li> </ul>	<ul style="list-style-type: none"> <li>• Catheters breach the integument and increase risk for skin colonizing bacteria</li> <li>• Air filters reduce the exposure to air-borne mold pathogens</li> </ul>

agents are used in the place of intensive chemoradiotherapy. Such regimens produce less acute toxicity sparing mucosal injury. In addition, myelosuppression is less and times to engraftment are typically shorter. With reduced intensity transplants, there is less susceptibility for neutropenia-associated bacterial and fungal infections. However, there still are substantial risks for later viral and fungal infections typically seen with GVHD and immunosuppressive therapy.

The graft used in HCT consists of a mixture of hematopoietic stem cells, more differentiated hematopoietic precursors, and mature immune cells. The grafts differ in several respects: peripheral blood grafts typically have higher numbers of hematopoietic precursors and also more lymphoid cells. Peripheral blood grafts are associated with faster neutrophil engraftment and more chronic GVHD. Cord blood grafts have fewer hematopoietic precursors and the lymphoid cells are more naïve immunophenotypically and functionally. Such cord blood grafts are associated with slower neutrophil recovery and less GVHD.

T lymphocytes in the donor graft are responsible for GVHD. The various immunosuppressive regimens used after transplant to prevent and treat GVHD suppress T cell function and increase the patient's vulnerability for infection. Fungal and herpesvirus infections are especially problematic. T cell depletion of the donor graft is sometimes used to reduce the risk for GVHD but T cell depletion increases the risk for graft rejection and slows B and T cell immune reconstitution, rendering the recipient vulnerable to opportunistic infections for a longer time after transplant. Several polymorphisms in immune response genes that affect the likelihood for both GVHD and infection have been identified.

## 2. Effects of HCT on Host Defenses: A Dynamic Scenario

There are three phases after HCT: early, mid, and late recovery. Each period is characterized by different kinds of deficits of host defenses and these differences account for varying susceptibilities to different kinds of infectious risks.

The early recovery phase is the interval from the start of the conditioning regimen to the time of engraftment, generally 3–4 weeks in duration. Compromises in host defenses during this interval are characterized by gut mucosal injury due to the cytotoxic effects of chemoradiotherapy and myelosuppression from the conditioning regimen. Tunneled central venous catheters are routinely used and these foreign bodies breach the integument, allowing invasion by skin colonizing organisms. The types of infectious syndromes commonly seen during the early phase are neutropenic infections due to enteric bacteria and *Candida* (discussed in more detail elsewhere), catheter-related infections, primarily due to skin colonizing bacteria, especially *Staphylococcus epidermidis* or less commonly *Staphylococcus aureus*, and organisms that colonize the oral mucosa, such as alpha streptococci. Reactivation of herpes simplex virus occurs in most patients treated with intensive conditioning regimens, with an average onset between 2 and 3 weeks after initiation of the conditioning regimen in the absence of prophylaxis.

Patients treated with a nonablative conditioning regimen have shorter times of neutropenia and also less mucosal injury. Typically, neutrophil counts do not fall until 7–10 days after graft infusion and the neutrophil count may not fall below 100 cells/ $\mu\text{L}$ . Thus, such patients are much less susceptible to early infections of all types. For that reason, nonablative transplant patients are generally managed in the outpatient clinic.

Upon engraftment, the transplant recipient enters the mid recovery phase. This phase spans the second and third month after transplant. With the restoration of neutrophils and healing of the damaged mucosal barriers, the overall risk for infection is less. The central venous catheter still poses a breach in the skin barrier and catheter-related infections remain a concern.

The mid recovery phase is characterized by a profound immunodeficiency of both B and T cell functions, which eventually recover later over a period of several months (after autologous HCT) or up to a year (for allogeneic HCT). *Pneumocystis jiroveci* (PCP), *Aspergillus*, and cytomegalovirus (CMV) infections can occur during this period. The risk for serious infection is greater after allogeneic HCT since GVHD or the use of high dose corticosteroids can intensify T cell immunodeficiency [1–4]. The use of anti-thymocyte globulin (or alemtuzumab) to prevent or treat GVHD or promote engraftment can have enduring effects on T cells (and NK cells in the case of alemtuzumab) and may render the patient vulnerable for a longer period of time. T cell depletion of the graft and HLA disparity between the donor and recipient delay T cell recovery. With nonablative transplants, the immunosuppressive regimen is frequently tapered more quickly (to provoke a graft-versus-tumor effect); this may increase the risk for GVHD. Various single center reports have suggested either an increase or decrease in infectious risk with nonablative transplants; as yet, the difference in conditioning regimens, case mix, and immunosuppressive regimens prevent a clear understanding of whether the risk of infection or timing of infection and epidemiology of infection is truly similar or different. Further study is needed.

The late recovery phase follows after the third month. The overall risk for infection recedes greatly as B and T cell immunity gradually improves. There remains some risk for PCP. There is also a risk for reactivation of varicella zoster virus (VZV) that occurs in approximately 40% of VZV seropositive patients. Patients who develop chronic GVHD require prolonged immunosuppressive therapy and are susceptible to fungal and viral infections due to T cell immunodeficiency. The need for prednisone at daily doses of 1 mg/kg/day for extended periods of time has been associated with a particularly high risk for aspergillosis. The use of infliximab renders the patient at even higher risk for aspergillosis. In patients with chronic GVHD, there is also a risk for infections by encapsulated bacteria (e.g., *S. pneumoniae*, *N. meningitidis*, and *H. influenzae*) due to poor opsonization.

Generally, by 1 year posttransplant, patients will recover their immune competence and will be no longer at risk for opportunistic infections except for patients who have developed chronic GVHD and who may have prolonged immunodeficiency extending for many months or years. At 1 year posttransplant, immunizations with the childhood vaccines should be given (see Chap. 13).

### 3. Major Infectious Syndromes: Clinical Manifestations and Diagnostic Approaches

#### 3.1 Neutropenic Fever

Prior to engraftment, neutropenia lasts for a variable duration according to the transplant type: 10–14 days after autologous transplant, 17–21 days after myeloablative allogeneic transplant, and only 4–7 days after nonablative

allogeneic transplant. Cord blood transplants often have longer durations of neutropenia that may extend up to 28–35 days. Neutropenic fever is common in the pre-engraftment period but is less problematic in nonablative transplants. Fever may be generally the only manifestation of infection and, operationally, infection should be approached as the likely cause since serious morbidity may ensue if untreated. Evaluation should include elicitation of symptoms suggestive of an infectious site and examination to look for an infectious site (especially skin, oral mucosa, lungs, catheter site, abdomen, and perianal area). Blood cultures should be obtained and cultures of any site suspected to be infected. A chest radiograph is generally done, but if the lungs are highly suspected from history or examination, then a CT scan is preferred since it would be more likely to yield useful information [6]. Persistent or recrudescent fever may be due to antibiotic-resistant Gram negative bacteria, Gram positive bacteria (especially *S. epidermidis*, less commonly an alpha streptococcus, or *S. aureus*), or fungus (especially *Candida* or *Aspergillus*). Evaluation and more specific diagnostic considerations for infections in the neutropenic host are addressed in Chap. 5 and have been delineated in consensus guidelines [7, 8].

### 3.2 Pneumonia

Pneumonia commonly occurs after HCT during all three phases of the postHCT period and may have both infectious and non-infectious etiologies (Table 8-2) [9]. In the early recovery phase, bacterial and mold infections may be etiologic, and adult respiratory distress syndrome due to toxicity from the conditioning regimen may also occur. In the mid recovery phase, interstitial pneumonitis due to conditioning regimen toxicity or due to CMV may occur. Also, bacterial and fungal pneumonia due to *Aspergillus* or other molds may occur. During the late recovery phase, late-onset CMV pneumonia may occur, especially in patients with early CMV infection or a history of acute GVHD [10]. Late-onset *Aspergillus* pneumonia may also occur, especially in patients with chronic GVHD. In recent years, increasing instances of very late onset *Aspergillus* pneumonias occurring 6–12 months after HCT have been noted in

**Table 8-2.** Various etiologies of pneumonia after HCT.

Radiographic pattern	Early recovery	Mid recovery	Late recovery
Diffuse infiltrates	<ul style="list-style-type: none"> <li>• ARDS</li> <li>• Hemorrhagic alveolitis</li> <li>• Respiratory virus</li> </ul>	<ul style="list-style-type: none"> <li>• Idiopathic interstitial pneumonitis</li> <li>• Hemorrhagic alveolitis</li> <li>• CMV</li> <li>• Respiratory virus</li> <li>• PCP</li> </ul>	<ul style="list-style-type: none"> <li>• Bronchiolitis obliterans or bronchiolitis obliterans with organizing pneumonia</li> <li>• CMV</li> <li>• Respiratory virus</li> <li>• PCP</li> </ul>
Localized infiltrates	<ul style="list-style-type: none"> <li>• Bacterial</li> <li>• <i>Aspergillus</i></li> <li>• Zygomycete or other mold</li> </ul>	<ul style="list-style-type: none"> <li>• Bacterial</li> <li>• <i>Aspergillus</i></li> <li>• Zygomycete or other mold</li> <li>• <i>Nocardia</i></li> </ul>	<ul style="list-style-type: none"> <li>• Bacterial</li> <li>• <i>Aspergillus</i></li> <li>• Zygomycete or other mold</li> <li>• <i>Nocardia</i></li> </ul>

patients with chronic persistent GVHD. PCP may occur during any of the 3 phases if prophylaxis is not given.

Respiratory viruses may occur during any of the 3 recovery phases. Influenza and respiratory syncytial virus (RSV) generally occur seasonally during the winter months [11–14]. Parainfluenza may occur at any time during the year. Adenovirus is an occasional pulmonary pathogen [15]. Upper respiratory symptoms generally precede lower tract involvement with respiratory viral infections, but not always.

Pneumonias may be caused by more than one pathogen; for example CMV may be accompanied by bacterial or *Aspergillus* infections. Thus, isolation of one pathogen may be an inadequate explanation for cause of pneumonia when the clinical syndrome suggests another etiology and further investigation is warranted.

Radiologic assessment by high resolution CT scan is key to the assessment of pneumonia [6, 16]. Pneumonias can generally be categorized radiographically into either diffuse infiltrates or localized infiltrates (Table 8-2). The diffuse infiltrates can be either non-specific alveolar ground glass, interstitial, mixed alveolar/interstitial, or diffuse micronodular patterns. The localized infiltrates may be macronodules ( $\geq 1$  cm in diameter), consolidation, cavitary, or wedge-shaped.

The etiologies differ according to both the radiographic pattern and timing after transplant and evaluation and management strategies differ for each radiographic category and timepoint (Table 8-2). In the early recovery phase, diffuse infiltrates are most commonly due to noninfectious causes such as pulmonary edema, ARDS, or idiopathic interstitial pneumonitis. These are thought to be due mostly to toxicity related to the conditioning regimen and fluid balance. Occasionally, respiratory viruses may also be causative. Localized infiltrates during the early recovery period are usually due to bacterial pneumonia or mold pathogens (*Aspergillus* most commonly, or *Zygomycetes*, *Fusarium*, or *Scedosporium* less commonly).

During the mid recovery period, diffuse infiltrates are divided evenly between noninfectious and infectious etiologies. The potential etiologies are the same as in the early recovery period, but in addition, CMV becomes the major infectious etiology during this time interval. PCP assumes an important consideration but is effectively prevented by prophylaxis, which should be routinely given (see below). The diagnostic considerations for localized infiltrates are also the same as during the early period, but mold infections are more prominent concerns. In a large series of IA, macronodules with or without halos were present in 94% of cases of IA and 79% had multiple nodules [17]. Halo signs were present in 61%. In another small series, more than ten nodules or a pleural effusion tended to more likely in Zygomycosis compared to IA [18].

In the late recovery period, diffuse infiltrates have a more varied spectrum of etiologies [19]. CMV still is an important consideration as are PCP and respiratory viruses. Also important noninfectious considerations are bronchiolitis obliterans or bronchiolitis obliterans with organizing pneumonia. As for localized infiltrates, the same potential causes as during the earlier period are possible. Encapsulated bacteria are particularly important pathogens since opsonization is impaired in chronic GVHD. Also important is *Nocardia*, which can present in a similar manner as mold infections.

Prompt and thorough evaluation is crucial to treatment success. Elicitation of lower tract symptoms and evidence of consolidation on physical exam

should alert the clinician to the possibility of pneumonia. However, even in the absence of any of these, fever of uncertain etiology may warrant investigation of pneumonia as the source of fever. Hemoptysis may occur with diffuse alveolar hemorrhage early after transplant. Hemoptysis, pleuritic pain, and the presence of pleural rub may suggest Aspergillosis. Upper respiratory tract symptoms suggest a respiratory viral infection. Lack of sputum is typical of respiratory virus, CMV, and PCP pneumonias. However, these manifestations are too insensitive and not sufficiently specific to indicate firmly the etiology. CT scans to determine the character of infiltrate is more useful. Prior to the onset of pneumonia symptoms, a number of tests may identify those at risk for or with incipient lower respiratory tract infection. Nasal viral cultures, shell vial centrifugation cultures using RSV-specific monoclonal antibodies, or rapid diagnostics using DFA or ELISA assays are important for diagnostic assessment of the respiratory viruses, and may be useful in the assessment of patients with symptoms of upper respiratory tract infection. CMV antigen assays or PCR assays of blood samples should be performed and often are positive 1–2 weeks in advance of CMV pneumonia. Serum galactomannan can be useful as an adjunct in the diagnosis of *Aspergillus* pneumonia [20–32].

For patients suspected to have pneumonia, CT examination, as noted above, is essential and should be done promptly. Bronchoscopic examination with bronchoalveolar lavage should be performed early in the assessment of pneumonia wherever feasible [33, 34]. The yield is high for agents that cause diffuse infiltrates (e.g., PCP, CMV, respiratory viruses), but tends to be low with agents that cause localized infiltrates, especially *Aspergillus*. Even in localized pneumonias where the yield is suboptimal, performance of bronchoscopy is advisable to exclude certain pathogens in order to narrow the use of agents in presumptive therapy and to identify co-infecting pathogens.

In many cases, treatment should be initiated presumptively for the most likely pathogen(s) while evaluation is proceeding since early initiation of therapy is crucial to optimize treatment success. Presumptive therapy, however, should not be given in order to justify the failure to perform a careful and thorough evaluation, since the spectrum of pathogens is large and the toxicities of prolonged “shot-gun” anti-infective therapies is considerable. Once the evaluation is complete, elimination of the presumptive therapies no longer justified is appropriate. In the case of a suspected mold infection, even with an extensive negative evaluation, continued therapy may be justified if the clinical suspicion remains high. If the etiology is not clear and the patient does not improve clinically and radiographically, further investigation should be undertaken. Typically, infiltrates may get worse early even in the face of clinical improvement and even though pneumonia ultimately responds. It generally requires 2 weeks at a minimum to see radiographic improvement. If a patient clinically deteriorates with empirical antimicrobial therapy, then additional evaluation should be considered, including a lung biopsy if the patient’s condition permits.

### 3.3 Diarrhea

Diarrhea can occur at any time after HCT and there are a myriad of both infectious and noninfectious causes (Table 8-3). During or shortly after completion of the conditioning regimen, diarrhea may be caused by intestinal tract mucosal injury due to cytotoxicity from the conditioning regimen.

**Table 8-3.** Etiologies of diarrhea.

Early recovery	Mid recovery	Late recovery
• Chemotherapy	• GVHD	• GVHD
• Neutropenic enterocolitis	• <i>C. difficile</i> colitis	• <i>C. difficile</i>
• <i>C. difficile</i> colitis	• CMV	• CMV
• Enteric viruses	• Adenovirus	• Adenovirus
	• Enteric viruses	• Enteric viruses

Later during neutropenia, diarrhea is more likely to be infectious, due to either neutropenic enterocolitis or *C. difficile*. A highly virulent strain of *C. difficile* has been noted in outbreaks in Canada and northeastern US cities, and also in other locales in the US and Europe [35–39]. The use of fluoroquinolones (and other antibiotics as well) has been associated with predisposition to *C. difficile* infection. The use of gastric acid suppressants has also been implicated to add to the risk [40].

Neutropenic enterocolitis (typhlitis) is usually accompanied by abdominal pain [41–43]. Although there is a predilection for the ascending colon, other portions of the gut can also be involved. The microbiological etiology of neutropenic enterocolitis is rarely discerned but is presumed to be caused by gram-negative bacteria and anaerobic bacteria. In recent years, *Candida* has also been implicated as contributory [44, 45]. Toxic megacolon, perforation, and hypotension are complications of progressive enterocolitis and may result in death.

A variety of viruses are occasional causes of diarrhea in the HCT patient, such as the enteroviruses (including the coxsackieviruses), caliciviruses (including the Norwalk virus), and astroviruses [46–49]. These infections do not occur at specific times after HCT like the herpesviruses but rather may occur at different seasons of the year, tracking along with outbreaks in the general population of the local community. Also, adenovirus and CMV may be viral causes of diarrhea. Other infectious agents including enterobacteria, such as *Salmonella*, *Shigella*, *E. coli*, and protozoal and helminthic infections may also be rare causes of diarrhea.

GVHD may also present as diarrhea. Usually a skin rash is also present, but some cases of GVHD may present with gut involvement alone. This occurs mostly during the mid recovery phase, but in recent years late onset GVHD with features resembling acute GVHD have been noted with transplants performed with the use of peripheral blood as stem cell source, reduced intensity conditioning regimens, and donor lymphocyte infusions after transplant.

Evaluation should include stool assay for *C. difficile* antigen and toxin, viral cultures or ELISA assays, and CMV antigen or quantitative PCR testing. An abdominal CT scan should be performed to look for bowel thickening and/or dilatation. Serial KUB radiographs should be performed in patients with bowel wall thickening to screen for toxic megacolon. Colonoscopy should be performed for visual inspection, looking for pseudomembranes, and to perform biopsy for tissue examination and culture for the various infectious etiologies or GVHD.



### 3.4 Cytomegalovirus Infection

Historically, CMV was the most dangerous infectious pathogen and the cause of death in 15–20% of allogeneic HCT recipients. Although CMV infections (detected by detection of CMV pp65 antigen or quantitative PCR testing) occur frequently in autologous transplant recipients, CMV disease is generally infrequent. The chief risk factors identified for CMV symptomatic disease are allogeneic transplant type, older age, CMV seropositivity (of the recipient), and the occurrence of GVHD [4, 50]. Other factors that diminish T cell recovery also increase the risk for CMV disease, such as T cell depletion of the stem cell graft, HLA disparity between donor and recipient, and the use of certain immunosuppressive agents that produce profound and prolonged T cell deficiency such as antithymocyte globulin, alemtuzumab, or high doses of corticosteroids. Purine analogs, such as fludarabine, cladribine, and pentostatin, given in the posttransplant period may also have prolonged immunosuppressive effects, but whether or not their more common use in the pretransplant conditioning regimen has any lingering posttransplant effects has not been studied.

The most common manifestation of CMV disease is pneumonia, but gastroenteritis can also occur. Rarely does CMV ophthalmitis occur in HCT recipients in contrast to the situation with advanced HIV infection.

In past decades, most episodes of CMV pneumonia occurred during the mid recovery period, and only 10% occurred after 100 days. However, in recent years there has been a dramatic shift to later onset (beyond 100 days) [10]; this is particularly true in patients who develop acute GVHD or receive pre-emptive antiCMV therapy for CMV reactivation infection during the mid recovery period (see below).

The usual presentation of CMV pneumonia is low grade fever, a nonproductive cough, and dyspnea. Progressive worsening of symptoms occurs if untreated and the mortality untreated has ranged 80–90%. Chest radiographs show a mixed interstitial/alveolar infiltrate. Bronchoscopy with immunofluorescent stains for pp65 antigen of cytologic samples and shell vial cultures of BAL samples has a high diagnostic yield with sensitivity and specificity of at least 90%. Bronchoscopic biopsies are somewhat less sensitive than the BAL for CMV. Blood pp65 antigen and the PCR assay are usually positive before and at the onset of pneumonia, but since CMV viremia may be present without pneumonia, bronchoscopy is still required to determine if the lung process is due to the viremia. Co-infections with bacteria or *Aspergillus* may be present. Diarrhea is the chief manifestation of CMV enterocolitis. Colonoscopy with tissue biopsy is the diagnostic test of choice with immunofluorescent stains

### 3.5 Other Viral Infections

Adenovirus infections occasionally occur (generally in less than 5% of allogeneic HCT recipients) [15, 51, 52] and case fatality rates of 30–50% have been reported. As with CMV infections, factors that result in more profound T cell immunodeficiency pose greater susceptibility for adenovirus infection; in contrast to CMV, younger patients are at greater risk. Pneumonia, hepatitis, and gastrointestinal disease are the most common manifestations, but less frequent presentations include nephritis and cystitis. Viremia can be detected with PCR assays. Detection of virus in BAL or tissue samples can be achieved using rapid culture techniques or immunofluorescent antibody staining of cytologic or tissue specimens.

Community acquired respiratory viruses have been increasingly recognized as important respiratory pathogens as noted above [13, 53–56]. RSV, influenza, rhinovirus, and metapneumovirus infections have a seasonal pattern, mirroring occurrences in the community, whereas parainfluenza virus infections occur during all seasons. Upper tract symptoms typically occur before lower tract disease and this offers an opportunity for early diagnosis and potential intervention, although no studies have shown definitively that treatment of upper tract infection prevents lower tract disease. Nasal swabs are excellent means of detecting the virus in patients with upper tract symptoms by culture, immunofluorescent antibody staining, or PCR assays of specimens. BAL or tissue specimens can be assessed with the same diagnostic assays.

Herpesvirus 6 persists lifelong (like HSV, CMV and VZV) in most individuals after primary infection during infancy. Active infection can be detected in about one-third of HCT recipients. In most cases, it is asymptomatic, but it can be a cause of rash, encephalitis, and possibly pneumonitis [57, 58]. PCR assays can be useful in the diagnosis [57].

BK virus is a polyoma virus that infects many individuals early in life and persists lifelong in urogenital epithelial tissues. Reactivation may occur after allogeneic HCT, especially in patients with GVHD and is a cause of hemorrhagic cystitis [59, 60]. Cystitis generally occurs during the mid recovery period, but may occur at any time after HCT. Diagnosis is made generally by the use of immunofluorescent antibody staining or PCR assays of urine specimens. BK virus can also be detected in blood samples but its correlation with hemorrhagic cystitis has been less well documented.

### 3.6 Nonneutropenic Fever

At time of engraftment, fever occasionally occurs in the absence of infection (sometimes known as “engraftment syndrome”). After cultures are obtained with no growth after 24–48 h and CT scans of chest and abdomen are negative, a noninfectious etiology should be considered. A short course of corticosteroids is highly efficacious with rapid taper. Rash, elevation of transaminases or bilirubin, or dyspnea with an ARDS-like syndrome may accompany the fever.

After engraftment fever may present occasionally in the absence of other symptoms. A systemic evaluation strategy is necessary. Continued monitoring to elicit symptoms that may provide clues is needed. Careful examination of sinuses, oral cavity, catheter site and tunnel, skin, lungs, and perineal area is important and should be ongoing. Blood cultures for bacteria, fungi, and mycobacteria should be obtained. Urinalysis is useful. Blood sampling for CMV assays, galactomannan, or glucan assays may be useful. CT scans of sinuses, chest, and abdomen should be considered. If these do not provide an explanation after several days, removal of the venous catheter should be considered. Since drug fever may occur, careful consideration of stopping any discretionary medications should be entertained.

### 3.7 Rash

Rashes are frequent and there are a myriad of causes. Erythema may be a prominent sign of GVHD. Involvement of palms, soles, and earlobes are especially seen in GVHD. Focal lesions may be seen with bacterial or fungal bloodstream infections. Paronychia should suggest the possibility of *Fusarium*. Vesicular lesions,

especially in a dermatomal distribution, should suggest VZV infection. In most cases a biopsy should be done. Cultures should be performed if an infection is suggested. For lesions where a fungal etiology is suspected, fungal stains are necessary.

### 3.8 Hepatitis

The hepatic transaminases may be elevated for a variety of reasons, both infectious and noninfectious. Most commonly, this is a result of some drug reaction. Viral hepatitis, iron overload, sepsis, and GVHD may also be etiologic. Hepatic veno-occlusive disease (VOD) and GVHD more commonly have a cholestatic predominance rather than transaminemia. In the case of VOD, the onset is almost always before day 30; in the case of GVHD, onset is usually after engraftment. Hepatitis serologies and PCR assays, ferritin measurement should be performed. A liver biopsy should be considered if the patient is able to tolerate it.

In patients with chronic GVHD, a rare manifestation of VZV infection is fulminant hepatitis (with or without concomitant pancreatitis) antecedent to the cutaneous rash and which can pursue a virulent course leading rapidly to shock and death. Prompt presumptive antiVZV therapy is warranted.

## 4. Management Strategies

Specific management of the individual infections described above is discussed in other chapters. Only anti-infective strategies that pertain to HCT will be discussed below.

### 4.1 Bacterial Prophylaxis

A variety of antibacterial regimens have been evaluated in the HCT setting over the past decades. Indeed, several decontamination regimens have been advocated more as a way to reduce the release of proinflammatory cytokines, key contributors to GVHD, in order to reduce the risk for severe GVHD, rather than to reduce bacterial infections. Such regimens were difficult for patients to tolerate and definite benefits could not be discerned; over time, they have largely been abandoned.

Today, the fluoroquinolones have largely replaced other antibiotic regimens for the purpose of preventing bacterial infection during the pre-engraftment phase. The benefits of antibiotic prophylaxis after HCT have been debated and no firm recommendation was given in the HCT consensus guidelines in 2000 [5]. However, they are widely used in the pre-engraftment phase, and more recent studies suggest such benefits as reductions in febrile episodes, bacterial infections, and death (from any cause) in patients with neutropenia. Such benefits have been seen in patients with acute leukemia and HCT [61–63]. Ciprofloxacin and levofloxacin are the most suitable agents. Drawbacks include cost, toxicities, and the risk of antibiotic resistance. If antibiotic prophylaxis is elected, surveillance of isolates for resistance is important since various centers have reported the emergence of fluoroquinolone resistance [64]. Although most infections that are prevented are from gram-negative bacteria, there seems to also be some protection against alpha streptococcal and methicillin-sensitive *Staphylococcus aureus* infections as well [61]. Another concern is an increased susceptibility for *C. difficile* infection. Accordingly, centers that choose to use

fluoroquinolone prophylaxis must monitor both resistance as well as *C. difficile* infection rates. The issues concerning antibiotic prophylaxis are discussed in greater detail in Chap. 10.

Severe infections by the encapsulated bacteria can occur in allogeneic HCT recipients with chronic GVHD. Although never tested in randomized trials, routine prophylaxis with antibiotics effective against this group of bacterial pathogens is advisable [5].

#### 4.2 Fungal Prophylaxis

Several studies have demonstrated that the fluconazole is highly effective in the prevention of invasive *Candida* infections [65–67]. The use of fluconazole prophylaxis has been embraced by consensus guidelines for HCT [5] and the subject has been discussed widely [68, 69]. There are two HCT scenarios in which its use may not be necessary. After nonablative allogeneic HCT, the duration of neutropenia is short and the risk for invasive *Candida* infection is low; the need for routine prophylaxis in this situation has not been studied. Also, in autologous transplantation for solid tumors, some conditioning regimens do not cause significant mucosal injury and the risk for invasive *Candida* infections may be sufficiently low to not warrant routine prophylaxis. This has not been well studied.

Micafungin has also been found to be effective in the prevention of *Candida* infections after HCT [70] and caspofungin has been found to be effective in patients with neutropenia after treatment for hematologic malignancies [71]. Although the echinocandins do act against *Aspergillus* and have been studied as a salvage therapy for invasive aspergillosis (IA), they have not been adequately evaluated as prophylaxis against *Aspergillus*.

The lipid formulations of amphotericin B have been evaluated only in a limited manner as prophylaxis but they do offer protective effects [72, 73]. Both the echinocandins and polyenes will likely have limited roles for prophylaxis since they require parenteral administration, a major shortcoming for the prolonged period of risk for mold infections.

Most interest for antimold prophylaxis has been in the extended spectrum azoles, since oral formulations make them suitable for prolonged administration necessary to cover the protected risk period. Itraconazole, posaconazole, and voriconazole have been shown to offer protection against IA during neutropenia in nontransplant oncology settings [74–77]. Two studies of itraconazole prophylaxis in the allogeneic HCT setting suggest a potential for benefit to prevent IA [78, 79], but limitations include poor tolerability and concerns about toxicity. Posaconazole has been evaluated in HCT patients with acute and chronic GVHD and compared to fluconazole [80]. This “targeted” approach seems sensible since GVHD and its therapy are the major risk factors for IA. Although there was a decrease in breakthrough IA, there was no improvement in clinical success (defined as survival without IFI or use of systemic antifungal therapy). Voriconazole prophylaxis has also been studied in standard-risk allogeneic BMT patients in a randomized double-blind multicenter trial and is not found to be superior to fluconazole in terms of survival at 6 months free of invasive fungal infection although there were fewer IA infections and voriconazole was not associated with greater toxicity [81]. One potential concern with voriconazole is its lack of activity against *Zygomycetes*; its routine use has been associated with an apparent increase in zygomycosis in several

single center studies [18, 82–84]. However, there were no increases in IA rates in the prospective randomized prophylaxis trial [81].

### 4.3 Neutropenic Fever

The management of neutropenic fever is a frequent challenge for the transplant clinician. The diagnostic considerations and approaches for evaluation and treatment in the HCT patient are similar to those in the nontransplant neutropenic patient and are discussed in detail elsewhere in Chap. 5.

### 4.4 CMV Management Strategies

The risks for serious morbidity and mortality from CMV disease are substantial. Technological advances have quelled this threat. Improvements in rapid diagnostics including the shell vial culture assay, pp65 antigen assay, and PCR assay, the validation of a high degree of accuracy in detection of CMV pneumonia by BAL to supplant the need for open lung biopsy [4, 10, 50]. The recognition that viremia generally precedes the onset of disease, the introduction of effective antiviral agents including ganciclovir, foscarnet, and cidofovir, and the testing of strategies to prevent or pre-empt CMV disease have all been major strides in reducing sequelae from CMV.

Prophylaxis with acyclovir, ganciclovir, and foscarnet has been shown to be effective [85–89]. Although acyclovir and its prodrug, valacyclovir, are well tolerated the relatively poor in vitro activity against CMV has led most clinicians to rely on ganciclovir which has much greater intrinsic anti-CMV activity. Unfortunately, ganciclovir is associated with myelosuppression. This toxicity has led to evaluation of serial monitoring of HCT patients with weekly testing of blood by the pp65 antigen or PCR assay, and institution of pre-emptive antiCMV therapy with ganciclovir (or foscarnet) in patients who become viremic [87, 90]. In general, there are advantages and disadvantages to both approaches. Prophylaxis is generally associated with fewer episodes of breakthrough CMV pneumonia, but more toxicity. Pre-emptive therapy is associated with more episodes of late-onset CMV pneumonia. Oral valganciclovir has good bioavailability and has been used in limited studies to replace intravenous ganciclovir. Although the toxicities are the same, there are obvious advantages in convenience and cost.

Most centers use the pre-emptive antiCMV strategies. Some centers stratify patients by risk: standard risk patients receive the pre-emptive strategy, while patients at high risk for CMV disease receive prophylaxis. Typical risks to consider include the use of a T cell depleted graft, HLA disparity between donor and recipient, use of antithymocyte globulin or alemtuzumab after transplant, or the use of steroids as prophylaxis. There are no data that suggest that nonablative transplant recipients should be monitored differently from ablative transplants.

A phase 2 trial of maribavir as CMV prophylaxis appears promising and a phase 3 trial is underway. This agent has the potential advantages of oral formulation and excellent tolerability and safety profiles.

Monitoring of patients beyond 100 days has assumed greater importance today with rising rates of late onset CMV disease. This is a challenge since most HCT patients are no longer receiving routine follow-up care at the transplant center after the mid recovery period and the knowledge level of community

physicians of this threat is low and availability of the screening assays in the community setting is not good. A trial to evaluate the use of valganciclovir prophylaxis in patients at risk for late CMV disease is underway.

#### 4.5 VZV Prophylaxis

VZV reactivation occurs in approximately 40% of HCT patients with a median onset of 5 months. Although acyclovir (or valacyclovir) treatment is effective, some patients can present with a life-threatening visceral infection (involving serosal intestinal wall, liver, or pancreas) without cutaneous lesions with a high fatality rate. This condition should be suspected in any HCT patient presenting with excruciating abdominal pain, even with a benign abdominal exam. Moreover, sequelae of VZV can pose significant compromises in quality of life in HCT survivors. Accordingly, there has been considerable interest in prevention. Acyclovir prophylaxis given for 6 months was associated with fewer VZV infections while the patient was receiving acyclovir, but relapses occurred shortly after cessation of drug abrogating the benefit. However, more recently, prophylaxis for 1 year has been shown to offer durable protection [91] and preservation of viral T cell helper responses but without rebound relapses after stopping prophylaxis.

#### 4.6 Infection Control Measures

Infection control measures have not been well studied in HCT patients. Hospitalization in air filtered rooms with >12 air exchanges/hour is generally recommended [5]. This is particularly important during construction periods when air-borne pathogens (especially *Aspergillus*) pose threats to HCT patients [92]. Survival benefits of air filtration have been observed in allogeneic HCT patients given ablative conditioning regimens [93, 94]. Whether there is a demonstrable benefit for patients receiving nonablative conditioning regimens (whose treatment is mostly outpatient) or in patients undergoing autologous HCT is not known.

Handwashing has been recognized to be the single most important tool in infection prevention [95]. The use of alcohol-based rubs as a substitute for hand washing has become widely adopted. Although they have been shown to reduce the risk for antibiotic-resistant bacteria such as methicillin-resistant *S. aureus* and vancomycin-resistant enterococci [96], they lack activity against *C. difficile* and there is a potential for increased risk for nosocomial outbreaks from this organism. Guidelines for the prevention of nosocomial transmission of these infectious pathogens have been developed [97] and are discussed in detail in Chap. 12.

The occurrence of antibiotic resistance in bacteria continues to plague hospital environments and the HCT unit is no exception. HCT patients are at especially high risk due to immune compromise, the widespread use of multiple antibiotics, often for prolonged intervals, and the universal use of central venous catheters. Infections by methicillin-resistant *S. aureus* and vancomycin-resistant enterococci have been abundantly reported in HCT patients. Such resistant organisms are frequently associated with considerable morbidity and mortality. Handwashing and contact isolation of colonized patients is advocated to reduce the risk for nosocomial transmission [5].

Patients with respiratory viral infections should be placed under both contact and droplet precautions [5]. Prolonged shedding of virus can occur due to high viral burden and poor immune status and follow-up cultures are advisable to determine when isolation procedures may be discontinued. Infected health care workers (HCW) should avoid contact with patients until symptoms resolve.

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