Hematopoietic Stem Cell Transplantation: An Overview of Infection Risks and Epidemiology

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KEYWORDS

- Hematopoietic stem cell transplantation
- Opportunistic infections • GVHD

Hematopoietic stem cell transplantation (HSCT) (also known as ''bone marrow transplantation'') is associated with a variety of infectious complications that pose serious threats to transplant recipients. The risk of infectious complications, type of pathogens, and timing of infectious threats varies substantially according to type of HSCT and the manner in which it is performed. In recent years there have been a number of changes in transplant practices that have altered the epidemiology of infectious complications.

HSCT is used to treat two categories of medical conditions. The first category consists of nonmalignant diseases that result in failure of bone marrow function or bone marrow–derived cells including aplastic anemia; myelodysplastic syndromes; immunodeficiency syndromes, such as severe combined immunodeficiency or chronic granulomatous disease; genetic diseases, such as the mucopolysaccharidoses or glycogen storage diseases; or the hemoglobinopathies of thalassemia and sickle cell anemia. The second category is far more prevalent and consists of neoplastic diseases, particularly hematopoietic malignancies, such as acute or chronic leukemia, lymphomas, multiple myeloma, and myeloproliferative diseases. In the first category of diseases, the transplant serves to replace a defective tissue, much in the same way kidney transplantation is performed for kidney failure. In the second category of diseases, the transplant serves two functions. The first function is to facilitate the safe use of cytotoxic therapies (intensive chemotherapy with or without total body irradiation) by reversing the myelosuppressive or myeloablative

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effects of the cytotoxic therapy; the second function is to provide immune cells to directly attack neoplastic cells that express tumor-specific or tumor-associated antigens.

There are two major types of HSCT: autologous and allogeneic. Autologous refers to the patient serving as his or her own donor. Allogeneic refers to someone else serving as the donor. The hematopoietic stem cells are collected from the autologous patient before the transplant procedure and cryopreserved. The allogeneic hematopoietic stem cells are collected from the donor (a family member, a volunteer donor, or banked cord blood cells) either before or synchronously with the transplant procedure and are infused into the recipient after receiving a pretransplant conditioning regimen. For allogeneic transplantation, stringent HLA matching between donor and recipient is required to minimize the risk for graft rejection; reduce the risk for graft-versus-host disease (GVHD), which can be viewed as the donor immunity attempting to ''reject'' the recipient; and to facilitate the development of robust donor protective immunity. When cord blood is used as the source of hematopoietic stem cells, less stringent HLA matching is required because of the naive state of the newborn's immunity, in which case greater donor and recipient HLA disparity is tolerated. Rarely, individuals may have an identical twin, allowing for ''syngeneic'' HSCT. Although this may be the most optimal source of stem cells for many patients with nonmalignant marrow disorders, the lack of an allogeneic graft versus tumor effect makes this less desirable for patients with malignant disorders, particularly the leukemias and some lymphoproliferative disorders. Autologous transplantation is most commonly used in the treatment of malignant diseases to facilitate intensive antineoplastic cytotoxic therapy.

The hematopoietic stem cell graft may be obtained either from harvesting of bone marrow or by apheresis of the peripheral blood. Bone marrow is the traditional source of stem cells used in HSCT, and is collected by needle aspirations of 1 to 1.5 L of bone marrow obtained from the posterior iliac crests. Ordinarily, hematopoietic stem cells rarely traffic in the circulation, but after chemotherapy, or after administration of granulocyte colony–stimulating factor or plerixafor, large numbers of stem cells are ''mobilized'' from the bone marrow into the circulation and can be collected from peripheral or central veins by apheresis. Peripheral blood grafts contain more lymphocytes and a greater risk for GVHD when this donor source is used. Bone marrow and peripheral blood grafts consist of a mixture of immature hematopoietic cells, mature hematopoietic cells, and immune cells. Hematopoietic potency of the graft is generally measured by enumeration of the cells expressing the CD34 antigen, an antigen expressed on the cell surface of primitive hematopoietic progenitors. The larger the CD34 count, the faster the neutrophil recovery. Immune potency is measured by enumeration of the lymphocytes (the CD3 count). The larger numbers of $CD3^+$ cells, natural killer cells, and dendritic cells, the more rapid is posttransplant immune reconstitution and greater adoptive immunotherapeutic potency. In some cases the graft may be manipulated ex vivo before administration to the recipient. The most common manipulation of allogeneic grafts is T-cell depletion, which is done to reduce the risk of GVHD. An unintended consequence of T-cell depletion is a greater risk of graft rejection, a higher risk for relapse of the cancer being treated, and slower T-cell reconstitution after transplant.

A conditioning regimen is given before intravenous infusion of the hematopoietic stem cell graft. For patients with cancer, the conditioning regimen consists of intensive chemotherapy with or without total body irradiation, with agents chosen to destroy as much residual cancer as possible. For patients undergoing allogeneic HSCT, suppression of the recipient immunity is also a goal of the conditioning regimen. Agents are chosen to optimize therapeutic goals and minimize toxicities. For autologous transplants, the regimens consist of drugs found to be active against the type of cancer

being treated, whose toxicities spare as much as possible nonhematopoietic tissues, and where an antitumor dose-response association is demonstrable. There is a wide array of effective regimens used that vary from cancer to cancer and center to center. For allogeneic HSCT, similar antitumor considerations are also important, but even more important is the immunosuppressive properties of the agents selected. The most widely used agents in allogeneic HSCT are cyclophosphamide, total body irradiation, and antithymocyte globulin. In recent years purine analogs with potent immunosuppressive properties, such as fludarabine, pentostatin, and cladrabine, are increasingly used because they have been found to have less severe nonhematopoietic tissue toxicity. Many elderly individuals and patients with comorbid conditions unrelated to cancer are unable to tolerate intensive conditioning regimens because of high transplant-related morbidity and mortality. With the increasing recognition that much of the anticancer potency of allogeneic HSCT resides in the adoptive immunotherapeutic effects of the graft and the advent of less toxic immunosuppressive agents, a growing body of experience with reduced-intensity (nonablative) conditioning regimens has developed. Increasingly, reduced-intensity regimens are being used in allogeneic HSCT. To facilitate the development of robust anticancer effects, many such nonablative regimens are coupled with acceleration of the tapering of the posttransplant immunosuppressive regimen. Nonablative regimens are associated with shorter times of neutropenia and less injury to the mucosa because the regimens have less cytotoxicity to nonlymphohematopoietic tissues. This has allowed many such transplants to be performed in an outpatient setting with a less intense need for multiple transfusions of blood products, antibiotic support, parenteral analgesics, and fluid and electrolyte supplementation.

After transplantation, a variety of supportive care measures are provided. A tunneled central venous catheter is usually placed for administration of the chemotherapy, stem cell infusion, intravenous medications, electrolyte supplements, nutritional support, and blood products. An immunosuppressive regimen consisting most commonly of a calcineurin inhibitor (cyclosporine or tacrolimus) plus a short course of intravenous methotrexate is given after transplantation both to prevent graft rejection and to prevent GVHD. Other immunosuppressive regimens are sometimes used. After transplantation the immunosuppressive regimen is usually tapered over 4 to 6 months and eventually discontinued, unless GVHD develops and a more prolonged course of immunosuppressive therapy is required. Because no immunosuppressive therapy is given after autologous transplant, immune reconstitution occurs much faster, with humoral and T-cell responses recovering in 3 to 9 months. In contrast, immune reconstitution after allogeneic HSCT is much slower and may take a year or longer. Immune reconstitution may be even slower if GVHD occurs. Even in the absence of GVHD, immune reconstitution is slower if a cord blood, T-cell depleted graft, or graft from a mismatched donor is used as the source of hematopoietic stem cells.

THE DYNAMIC NATURE OF DAMAGE TO HOST DEFENSES AND RESTORATION OF HOST DEFENSES AND IMMUNITY AFTER HSCT

The risk for infection and the spectrum of infectious syndromes differs by type of transplant, type of conditioning regimen, type of stem cell graft, and type of posttransplant therapies and whether or not certain posttransplant complications occur, such as GVHD. **Table 1** illustrates some of these considerations. The risk of infection can be divided into three time intervals. The time periods and infectious risks are illustrated in **Table 2**.

Table 1
Effect of transplant characteristics on infectious risk

Transplant Parameter	Effect on Host Barriers and Immunity	Infectious Consequences
Type of transplant	Allogeneic: slower B- and T-cell immune reconstitution	Greater risk for infections of all types, but especially invasive fungal and herpesvirus infections; longer interval of risk
Type of allogeneic donor	Unrelated or mismatched donor: slower B- and T-cell immune reconstitution	Greater risk for infections of all types, but especially invasive fungal and herpesvirus infections; longer interval of risk
Type of stem cell graft	Peripheral blood: faster neutrophil engraftment, more chronic GVHD Cord blood: slower neutrophil engraftment, less GVHD, slower B- and T-cell immune reconstitution	Different risks for infections associated with neutropenia and GVHD
Stem cell graft manipulation	T-cell depletion: greater risk for graft rejection, slower B- and T-cell immune reconstitution	Greater risk for neutropenic infections, lower risk for infections associated with chronic GVHD, greater and longer risk for herpesvirus and invasive fungal infections
Conditioning regimen	Intensive regimens: more mucosal injury, shorter time to neutropenia and longer neutropenia	Greater risk for neutropenic infections, especially typhlitis
Immunosuppressive regimen (allogeneic)	ATG: more profound deficiency of T-cell immunity Methotrexate: more mucosal injury, longer time to neutrophil recovery	Greater risk for invasive fungal and herpesvirus infections
Central venous catheter	Breach in skin barrier	Greater risk for bacterial and (less frequently) fungal infections

Abbreviations: ATG, antithymocyte globulin; GVHD, graft-versus-host disease.

Early, before engraftment, the major compromises in host defenses are neutropenia and mucosal injury. The duration of neutropenia is 10 to 14 days after autologous HSCT, 15 to 30 days after allogeneic HSCT using an ablative conditioning regimen, and only 5 to 7 days using a nonablative conditioning regimen. The infectious threats are principally the same bacterial and (less commonly) fungal pathogens (eg, *Candida* species and molds) as seen in neutropenic cancer patients who are not transplant recipients. The evaluation and management strategies of these infectious complications are similar to the ones that have been developed for chemotherapy-induced

Table 2
Types of infections encountered at various times after HSCT

Type of Infectious Pathogen	Early Preengraftment (First 2–4 wk)	Early Postengraftment (Second and Third Month)	Late Postengraftment (After Second or Third Month)	Time Independent
Bacteria	Gram-negative bacteria (related to mucosal injury and neutropenia) Gram-positive bacteria (related to venous catheters) *Clostridium difficile* (related to neutropenia, antibiotics, antiacid medications)	Gram-positive bacteria (related to venous catheters) Gram-negative bacteria (related to enteric involvement of GVHD, venous catheters)	Encapsulated bacteria (related to poor opsonization with chronic GVHD) *Nocardia* (related to chronic GVHD)	
Fungi	*Candida* (related to mucosal injury and neutropenia)	*Aspergillus*, other molds and *Pneumocystis jirovecii* (related to GVHD)	*Aspergillus*, other molds and *P jirovecii* (related to GVHD)	
Herpesviruses	HSV	CMV (related to GVHD and impaired cellular immunity) EBV (in patients who have T-cell depleted grafts, receive ATG, or whose donor is mismatched)	CMV and VZV (related to GVHD and impaired cellular immunity and viral latency before transplant) EBV (in patients who have T-cell depleted grafts, receive ATG, or whose donor is mismatched)	
Other viruses		BK virus (related to GVHD and cyclophosphamide in conditioning regimen)		Respiratory viruses (temporally tracks with community outbreaks) Adenoviruses

Abbreviations: ATG, antithymocyte globulin; CMV, cytomegalovirus; EBV, Epstein-Barr virus; GVHD, graft-versus-host disease; HSV, herpes simplex virus; VZV, varicella-zoster virus.

neutropenic fever. Herpes simplex virus (HSV) reactivates in most HSV-seropositive patients during this time period between 1 and 2 weeks after transplantation. Engraftment demarcates the transition to the second time interval.

The early postengraftment period is categorized by progressive recovery in cell-mediated immunity. This occurs much more rapidly after autologous than allogeneic transplant. The infectious threat then recedes dramatically. After autologous HSCT, many early posttransplant infections are associated with the presence of the central venous catheter. Although the venous catheter is generally removed as early as possible, this may be technically challenging in this group of patients and the catheter may need to remain in place if the patient continues to require transfusion support, supplemental medications, nutrition, intravenous fluid, or electrolyte supplements. Gram-positive bacteria are frequent causes of central venous catheter–associated infections, with gram-negative and mixed bacterial infections less common but occasionally seen. After allogeneic HSCT, there is a similar risk for catheter-associated infections, but GVHD also poses an additional risk for bacterial infections. Bacteremias from enteric organisms are especially problematic in patients with GVHD of the intestinal tract. Infections caused by *Candida* species occasionally occur in patients with GVHD, and are often associated with indwelling venous catheters especially in the presence of intravenous administration of nutritional supplementation. *Aspergillus* species and other mold infections and *Pneumocystis jirovecii* pneumonia (PCP) occur in patients with GVHD and in those on high doses of steroids for GVHD treatment. Cytomegalovirus (CMV) viremia occurs chiefly in patients who were seropositive before transplantation and who develop GVHD. Untreated, CMV viremia often is followed by pneumonia or enterocolitis after allogeneic HSCT, which can be associated with substantial morbidity and mortality.

Beyond 3 months, the risk for opportunistic infection in autologous HSCT patients is small. After allogeneic HSCT, there is gradual reconstitution of humoral and cellular immunity, which approaches normality by 1 year if GVHD does not occur. Immunization of the recipient with the childhood vaccines is recommended at that time.[1,2] The development of chronic GVHD leads to delays in immune reconstitution and necessitates prolonged courses of immunosuppressive therapy that compounds the immunodeficiency caused by the GVHD. Late infections in patients are caused by similar pathogens as those in the early posttransplant period (*Candida* species, *Aspergillus* species and other molds, PCP, and CMV) but also include encapsulated bacteria because of poor opsonization and varicella zoster virus (VZV) infections.

COMMON INFECTIOUS SYNDROMES AFTER HSCT AND THEIR ETIOLOGIES

Neutropenic Fever

Fever occurring in the neutropenic transplant recipient is frequent during the preengraftment period. Neutropenic fever is less frequent in patients receiving reduced-intensity conditioning regimens. Fever typically occurs 3 to 5 days after the onset of neutropenia and may be the sole manifestation of infection. Bacterial infections are by far the most common infectious causes of the first fever during neutropenia, but in most cases no microbiologic etiology is documented with the prompt initiation of broad-spectrum empiric antibiotic therapy. Likely sites of infection are lungs; skin (especially catheter insertion sites and the perianal area); and genitourinary tract. In addition, the oral cavity and intestinal tract are also possible sites of infection. Gram-positive bacteria are the most frequently isolated bacterial pathogens, with *Staphylococcus epidermidis* making up approximately half, viridians streptococci making up approximately one third, and *Staphylococcus aureus* and several other

species making up the remainder of episodes. Gram-negative bacteria make up about 30% to 45% of bacterial infections and include *Enterobacter* spp, *Escherichia coli*, *Klebsiella* spp, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia*. Cultures of blood and from suspected sites of infection should be obtained and empiric antibiotics instituted promptly.

Persistent fever is more problematic. Possible explanations included a delayed response to the initial antibiotic regimen, presence of a gram-positive organism not adequately treated with the initial antibiotic regimen, or antibiotic-resistant gram-negative bacteria. In addition, other types of pathogens are also possible explanations, especially invasive fungal infections by *Candida* spp, *Aspergillus* spp, or other molds. A detailed discussion of the evaluation and approaches to management of neutropenic fever is beyond the scope of this article but is discussed in detail in several authoritative guidelines.[3,4]

Nonneutropenic Fever

Most fevers in the neutropenic transplant recipient resolve at the time of neutrophil recovery. Fever may sometimes occur, however, at the time of engraftment. Although an infectious etiology is possible and should be vigorously pursued, fever often is caused by what has been referred to as the ''engraftment syndrome,'' a noninfectious syndrome of uncertain etiology that consists of fever alone or with rash, pneumonitis, hyperbilirubinemia, or diarrhea. Cultures should be obtained and CT scans of the chest and abdomen should be performed as part of the investigation to assess for a possible infectious focus. If the investigation does not reveal an infectious source, a short course of high-dose corticosteroids may be considered and is often very effective.

Later after engraftment, fever sometimes occurs in the absence of other symptoms. CMV infection, occult sinusitis, central venous catheter–associated infection, or occult fungal infection are frequent causes. Evaluation should include elicitation of infectious symptoms and physical signs; blood cultures for bacteria, fungi, and mycobacteria; urine analysis; and blood samples for CMV polymerase chain reaction (PCR) or antigen. Imaging studies with CT scans of the chest, sinuses, and abdomen should also be considered. Medications can cause fever, so discontinuation of discretionary medications is advisable. If fever persists and no etiology can be discerned, one should consider removal of the venous catheter.

Pneumonia and Pulmonary Infiltrates

Pneumonia is a common complication after HSCT.[5] There are both infectious and noninfectious causes of pneumonia and pulmonary infiltrates in the HSCT recipient, and the likely etiologies vary over time (**Table 3**).

The types of pneumonias can be categorized according to their radiologic appearance into diffuse and localized infiltrates. High-resolution CT scans are the most sensitive radiologic procedure[6,7] because standard radiographs are less sensitive. Diffuse infiltrates can be alveolar, interstitial, mixed alveolar interstitial, or diffuse micronodular. Localized infiltrates may present as lobar consolidation; macronodules (>1 cm); cavities; or wedge-shaped infiltrates.

Before engraftment, most episodes of pneumonia and pulmonary infiltrates are not related to infection. Volume overload may occur during this time period. Congestive heart failure from cardiotoxic drugs or the acute respiratory distress syndrome caused by pulmonary toxicity from the pretransplant conditioning regimen, other antecedent therapy, or prior medical conditions are frequent. Hemorrhagic alveolitis may also occur because of toxicity from the conditioning regimen or inflammatory cytokines

Table 3
Infectious and noninfectious causes of pneumonia after HSCT

Type of Pulmonary Infiltrate		Preengraftment	Early Postengraftment	Late
Diffuse	Noninfectious	Adult respiratory distress syndrome	Idiopathic interstitial pneumonitis	Bronchiolitis obliterans or bronchiolitis obliterans with organizing pneumonia
		Congestive heart failure Fluid overload Hemorrhagic alveolitis	Hemorrhagic alveolitis	
	Infectious	Respiratory virus	CMV Respiratory virus PCP Adenovirus	CMV Respiratory virus PCP Adenovirus
Localized	Noninfectious	Aspiration Pulmonary thromboembolism Micronodules caused by chemotherapy		
	Infectious	Bacterial pneumonia *Aspergillus* or other mold pneumonia	Bacterial pneumonia *Aspergillus* or other mold pneumonia *Nocardia*	Bacterial pneumonia *Aspergillus* or other mold pneumonia *Nocardia*

Abbreviations: CMV, cytomegalovirus; PCP, *Pneumocystis jirovecii* pneumonia.

released as a consequence of the transplant procedure. These noninfectious pulmonary syndromes typically produce diffuse infiltrates. Aspiration pneumonia or bacterial or mold pneumonia also occur but are less frequent and typically produce localized infiltrates. Mold pneumonias are characterized by macronodules, some with halo signs, which later become cavitary. *Aspergillus* spp are by far the most common mold pathogens, with Zygomycetes accounting for 10% to 20% of mold pneumonias, and *Scedosporium* spp, *Fusarium* spp, and other genera accounting for a small percent of mold pneumonias.

Early after engraftment, diffuse pneumonias are evenly divided between infectious and noninfectious causes. Idiopathic pneumonia accounts for half of diffuse pneumonias.[8] The risk for idiopathic pneumonia is associated with higher-intensity conditioning regimens. CMV accounts for approximately 40% of diffuse pneumonias and is most commonly seen in patients with acute GVHD.[9] PCP (if the patient is not taking PCP prophylaxis), legionella, adenovirus, or various respiratory viruses are other possible causes of diffuse pneumonia. Increasingly, respiratory virus infections are being recognized as important causes of diffuse pneumonias.[10–17] Bacterial or mold pneumonias are the most common causes of localized pulmonary infiltrates. The most important risk factor for pulmonary aspergillosis and other mold pneumonias is GVHD.[18,19] Pulmonary aspergillosis most frequently presents as macronodules on CT imaging of the chest. In a large series, 94% of patients had at least one nodule and 79% had multiple nodules.[20] Halo signs, which occur early in infection, were present in 61% of patients with pulmonary aspergillosis. In another single-center series, pulmonary infection with Zygomycetes was observed to have more nodules on CT imaging than commonly occurs in pulmonary aspergillosis.[21]

During the late postengraftment period, there is a more heterogeneous spectrum of infectious causes of pneumonia.[22] Patients with chronic GVHD are particularly susceptible to sinopulmonary infections caused by encapsulated bacteria and increasingly susceptible to mold pneumonias.[23,24] *Nocardia* is an occasional pathogen that can cause pneumonia with similar clinical and radiographic features as infection with *Aspergillus* spp.[25] Bronchiolitis obliterans with organizing pneumonia (cryptogenic organizing pneumonia) is a manifestation of chronic GVHD. PCP may also occur (if the patient is not taking PCP prophylaxis). In the past, CMV pneumonia rarely occurred late, but increasingly, late CMV pneumonia is becoming more common.[26] GVHD and early CMV viremia are risk factors for late CMV pneumonia.

In some cases pneumonias may be caused by multiple pathogens. For example, CMV may be accompanied by superinfection with bacterial pathogens or *Aspergillus* spp. Infection with *Aspergillus* species may similarly be accompanied by bacterial, CMV, or Zygomycetes coinfections. Accordingly, assessment should be thorough and one should not ignore cultures or other tests indicating more than one pathogen.

Although radiology is essential in the assessment of pneumonia, some clinical features suggest certain etiologies. Hemoptysis is suggestive of hemorrhagic alveolitis or thromboembolism. Hemoptysis with pleuritic pain or pleural friction rub is suggestive of infection with *Aspergillus* spp or another mold. Cough is usually nonproductive of sputum with CMV, respiratory virus, PCP, and most noninfectious pneumonias. Although useful, these findings are not sufficiently specific to be diagnostic.

Assessment of diffuse infiltrates should include nasal and throat swabs for viral diagnostic assays with culture or direct fluorescence assay, enzyme-linked immunosorbent assay, or PCR assays for the respiratory viruses. After engraftment, blood should be collected for CMV PCR or antigen assay. Bronchoscopy with bronchoalveolar lavage (BAL) can be quite useful in further assessment.[27,28] The sensitivity and

specificity of testing of BAL fluid for infectious etiologies causing diffuse infiltrates (eg, PCP, CMV, or respiratory viruses) are quite good.

Assessment of localized infiltrates should include blood cultures for bacteria and fungi. Sputum, if available, should be cultured. When infection with *Aspergillus* species is suspected, serum for galactomannan[29–31] can be helpful. One should consider bronchoscopic evaluation with cultures and stains in this setting, although the yield in the investigation of nodular infiltrates is lower. Bronchoscopy with BAL can still be useful because it may detect or exclude certain coinfecting pathogens and allow a more focused antimicrobial therapy. For peripheral nodules or infiltrates, CT-guided needle, video-assisted thoracoscopy guided, or even open lung biopsies may be useful if the patient is not significantly thrombocytopenic.

While evaluation of pneumonia proceeds, one should presumptively initiate therapy for the most likely etiologies because delay in initiating therapy may compromise the prospects for a successful outcome. Presumptive therapy should not be used in lieu of a proper assessment, because the spectrum of possible pathogens is large and toxicities of multiple therapies can lead to harm. Once the etiology is established it is important to discontinue the unneeded therapies. If the etiology has not been definitively established, evaluation should be continued.

Diarrhea

Diarrhea may have multiple etiologies (**Table 4**). Shortly after the conditioning regimen, cytotoxic mucosal injury may result in noninfectious diarrhea. During the pre-engraftment period, typhlitis and *Clostridium difficile* enterocolitis are potentially serious complications. Both infections are typically accompanied by fever, abdominal discomfort, and distention. Guarding and ileus may also be present. CT scan shows bowel wall thickening and may also demonstrate bowel distention. With typhlitis, the ascending colon is often involved but other portions of the large and small intestine may also be involved.[32–34] The microbiologic etiology of typhlitis is rarely determined, but is presumed to be caused mostly by gram-negative and anaerobic bacteria. Invasion of the compromised bowel wall by *Candida* species has been noted.[35,36] Toxic megacolon, perforation, and septic shock may result from severe typhlitis and can result in death.

Enteritis caused by *C difficile* is one of the most common nosocomial infections. Strains that produce highly potent toxins have been noted to cause outbreaks and such infections may result in perforation, shock, and death.[37–41] The use of fluoroquinolones and the use of gastric acid suppressants are risk factors for overgrowth in the bowel and infection with *C difficile*.

Table 4
Infectious and noninfectious causes of diarrhea after HSCT

Preengraftment	Early Postengraftment	Late
Mucosal injury from conditioning regimen	GVHD	GVHD
Neutropenic enterocolitis (typhlitis)	*C difficile* enterocolitis	*C difficile* enterocolitis
Clostridium difficile enterocolitis	CMV	CMV
Enteric viruses	Adenovirus	Adenovirus
	Enteric viruses	Enteric viruses

Abbreviations: CMV, cytomegalovirus; GVHD, graft-versus-host disease.

Enteric viruses, including enteroviruses, caliciviruses, and astroviruses, are potential causes of diarrhea[42–45] in the patient undergoing HSCT. Generally, HSCT patients become vulnerable to such pathogens as viral outbreaks occur in the community. Adenoviruses and CMV also can cause diarrhea.[46–48] Infrequently, enteropathic bacteria, such as *Shigella* spp and *Salmonella* spp, protozoa, and helminthic infections can cause enterocolitis.

After engraftment, GVHD is a major noninfectious cause of diarrhea in addition to the previously noted infectious causes. GVHD of the gastrointestinal tract is most commonly associated with the presence of cutaneous GVHD, but occasionally it may occur in the absence of other manifestations of GVHD. GVHD of the gut typically occurs in the early postengraftment period as part of acute GVHD (rather than chronic GVHD). With changing transplant practices, however, which have included the increasing use of peripheral blood as a source of stem cells, donor lymphocyte infusions, and reduced intensity transplant regimens, the spectrum of clinical manifestations of acute and chronic GVHD are blending over time.

Evaluation should include stool samples for assays for *C difficile* antigen or toxin, viral cultures or enzyme-linked immunosorbent assays, CMV antigen or PCR testing, and examination of stool for presence of ova and parasites. For more severe episodes of diarrhea, abdominal CT provides assessment of bowel wall thickening or the development of intra-abdominal abscesses. In patients with typhlitis or severe *C difficile* enterocolitis, serial kidneys-ureter-bladder radiographs can be useful to monitor for evidence of toxic megacolon. For cases where the etiology remains uncertain, colonoscopy should be considered for visual inspection to determine if there are pseudomembranes and to obtain biopsy for histologic examination to assess for GVHD and presence of CMV or other infections by immunostaining, culture, or PCR.

CMV

Decades ago, CMV pneumonia was the predominant infectious life-threatening complication after HSCT. Although pneumonia is the most common CMV syndrome, esophagitis, gastritis, or enterocolitis are other infections that may be caused by CMV. Unlike the patient with severe immunodeficiency caused by infection with HIV, CMV chorioretinitis rarely occurs in patients undergoing HSCT. Although CMV infection occurs after both autologous and allogeneic HSCT, CMV disease is uncommon after autologous HSCT. In allogeneic HSCT patients, seropositivity and GVHD are the major risk factors for CMV reactivation and disease.[49,50] CMV viremia generally precedes pneumonia by 1 to 2 weeks. Because of the adoption of close monitoring for reactivation of CMV and antiviral management strategies routinely used after allogeneic HSCT, CMV disease has receded as a serious threat early after HSCT. In the past, CMV disease most commonly occurred during the early postengraftment period. Recently, however, late-onset CMV disease has been increasing in occurrence.[26] Risk factors for late CMV disease include early viremia posttransplantation and the development of GVHD.

Clinical presentation of CMV pneumonia is low-grade fever, nonproductive cough, and dyspnea. Progressive hypoxia ensues over several days. Examination of the chest may be unrevealing or demonstrate scattered rales. Chest radiographic examination demonstrates alveolar, interstitial, or mixed alveolar-interstitial diffuse infiltrates. Bronchoscopy with BAL specimens for immunostaining or PCR assays is diagnostic with sensitivity and specificity of 90% or higher. Bronchoscopy may also reveal coinfection by bacteria, PCP, or *Aspergillus* spp. For gastrointestinal CMV syndromes, endoscopic examination of the gastrointestinal tract with biopsy should be performed.

Hepatitis

Hepatocellular injury is common after HSCT. Two patterns are seen: cholestasis (elevations of bilirubin and alkaline phosphatase) and hepatitis (elevations of hepatic transaminases). Abnormalities of liver function tests after HSCT are most commonly of noninfectious causes that can give rise to either pattern. These abnormalities can be in the form of cholestasis from hepatic veno-occlusive disease (VOD) (sinusoidal obstruction syndrome) caused by the conditioning regimen, either cholestasis or hepatitis caused by various medications, or cholestasis caused by acute or chronic GVHD. VOD almost always occurs before day 30, GVHD almost always occurs after engraftment. Iron overload from red cell transfusions before the transplant often leads to a hepatocellular injury pattern that can occur at any time after HSCT. Exacerbation of viral hepatitis present before the transplant can produce a hepatitis pattern that may wax and wane periodically after HSCT. This can lead to serious and progressive hepatic injury with tapering of immunosuppressive therapy as immune reconstitution strengthens. In the late postengraftment period, fulminent hepatitis may occur from severe infection with VZV, which may occur even in the absence of vesicular skin lesions. In some cases of hepatic syndromes, the cause may be multifactorial because of multiple etiologies, both infectious and noninfectious. Biliary obstruction caused by a stone may give rise to a cholestatic pattern. Cholecystitis has also been reported to occasionally occur, with an association with busulfan in the conditioning regimen.

Evaluation of liver function abnormalities occurring in the HSCT recipient depends on the type of pattern and time posttransplant. A patient with a cholestatic picture should undergo ultrasonongraphy of the abdomen first to exclude biliary obstruction. A review of medications should be performed and discontinuation of any implicated medications should be considered. Before engraftment cholestasis is frequently caused by VOD. Biopsy is often not possible at this time because of significant thrombocytopenia. After engraftment, GVHD is a strong consideration and biopsy should be performed if possible to confirm the diagnosis. HSCT recipients with the hepatitis pattern should be evaluated with viral hepatitis PCR assays and serum iron studies. Although the latter may be difficult to interpret in the presence of ongoing inflammation, HSCT recipients with a history of multiple red cell transfusions and a serum ferritin in excess of 1000 ng/mL should be considered at risk for iron overload syndrome. Any medications that might be suspected should be discontinued if possible and if the etiology remains uncertain, liver biopsy should be considered.

Rash

Rashes frequently occur after HSCT from a variety of causes. The rash of acute GVHD typically presents as an erythematous maculopapular rash, especially of the palms, soles, and earlobes, but the entire body may be affected along with the mucosal surfaces. In the setting of chronic GVHD, lichenoid or sclerodermatoid changes of skin and mucosal surfaces predominate. Skin involvement by infections usually produces localized lesions. Common manifestations of disseminated infections may include subcutaneous nodules of the skin. These lesions may be macronodular erythematous lesions, sometimes with a necrotic center. Vesicular lesions are characteristic of VZV either in a dermatomal or widely disseminated distribution. Paronychia may be caused by bacteria or yeasts; however, they can commonly be caused by *Fusarium* spp or other molds in the severely immunocompromised HSCT recipient and can lead to life-threatening systemic fungal infection.

Punch biopsy of skin lesions can be diagnostic. If a fungal infection is suspected, special stains for fungal organisms, such as the Gomori methenamine silver stain, are necessary because routine histologic stains, such as hematoxylin and eosin, may not be sufficient to visualize the presence of fungi in the tissues. Where disseminated infection is suspected bacterial and fungal blood cultures should also be part of the evaluation. Vesicles found on the skin should be unroofed with a tuberculin-sized syringe and needle to collect fluid for viral cultures, immunostains, or PCR for VZV and HSV.

PREVENTION AND TREATMENT APPROACHES

Management strategies are beyond the scope of this article. Consensus guidelines for infection prevention for HSCT patients were first published in 2000[51] and recently have been updated.[1] Evaluation and management guidelines for neutropenic fever have been published.[3,4] Prevention and treatment guidelines for *Candida* and *Aspergillus* have been published.[52,53] Discussions of CMV treatment have been published.[49,54]

SUMMARY

HSCT has become a common treatment of bone marrow failure and certain malignancies. Types of transplant, including types of stem cells and conditioning regimens vary, impacting the magnitude and duration of primary risk periods. Risks for infections caused by numerous bacterial, viral, and fungal pathogens can extend over a long period of time, dictating preventative strategies and differential diagnoses.

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