INTRODUCTION — Hematopoietic cell transplant (HCT) recipients, especially those who have received allogeneic transplants, are at substantial risk for a variety of infections depending upon the degree of immunodeficiency, exposure to pathogens, and the time elapsed since transplantation. HCT patients are at risk for infectious diseases resulting from bacteria, fungi, viruses, and/or parasites, all of which are associated with higher morbidity and mortality than in immunocompetent individuals.

The term "hematopoietic cell transplantation" will be used throughout this topic as a general term to cover transplantation of progenitor cells from any source (eg, bone marrow, peripheral blood, umbilical cord blood). Possible sources for these cells include the patient's own cells (autologous); an identical twin (syngeneic, human leukocyte antigen [HLA] identical); a sibling, a related, or an unrelated donor (allogeneic; HLA identical, haploidentical, or mismatched); or umbilical cord blood (UCB; HLA identical, haploidentical, or mismatched). (See "Sources of hematopoietic stem cells".)

An overview of infections following HCT will be presented here and will be organized by risk period and clinical syndrome; the syndromes discussed are often infectious in nature but may also have noninfectious etiologies. The evaluation for infection and prevention of infection in HCT recipients is discussed separately. (See "Evaluation for infection before hematopoietic cell transplantation" and "Prevention of infections in hematopoietic cell transplant recipients" and "Prophylaxis of invasive fungal infections in adult hematopoietic cell transplant recipients" and "Prevention of viral infections in hematopoietic cell transplant recipients" and "Immunizations in hematopoietic cell transplant candidates and recipients".)

RISK OF INFECTION — It is important to identify the population at high risk for infections and also the magnitude of and period of highest risk in order to predict which patients are most likely to benefit from targeted prophylaxis, diagnostic procedures, and/or preemptive therapy. The risk of infection results from the interaction of at least three factors (figure 1):

- The intensity of exposure to and the relative virulence of the offending microorganisms
- The patient's specific immune effectors and the patient's net state of immunosuppression (type, degree, pace, and duration)
- The presence of tissue and/or organ damage (eg, mucositis, renal failure, lung damage) and/or the use of central venous catheters

Depending on these interactions, patients can be stratified as being at high or low risk for infection (table 1). This risk decreases with hematologic reconstitution, specifically with reconstitution of innate and adaptive cellular immune effectors. Immune reconstitution is typically faster in autologous hematopoietic cell transplantation (HCT) recipients than in allogeneic HCT recipients. In the allogeneic HCT recipients, immune reconstitution can be delayed by various factors, which are discussed below. Immune
reconstitution following HCT is discussed in detail separately. (See "Strategies for immune reconstitution following allogeneic hematopoietic cell transplantation", section on 'Overview of immune reconstitution'.)

Among allogeneic HCT recipients, the most important risk factors for infection include [1]:

- **Patient factors:**
  - Older age
  - High HCT comorbidity index (see "Determining eligibility for allogeneic hematopoietic cell transplantation", section on 'Risk assessment scoring systems')

- **Disease and prior therapy-related factors:**
  - The underlying disease, particularly in the setting of extensive prior therapy (eg, multiple myeloma after prolonged therapy with glucocorticoids [2]; chronic lymphocytic leukemia after therapy with a purine analog [3]) (see "Risk of infections in patients with chronic lymphocytic leukemia")
  - Prior HCT
  - Prior infections of the donor and/or recipient (see "Evaluation for infection before hematopoietic cell transplantation")
  - Presence of pretransplant-specific immunity to cytomegalovirus (CMV), herpes simplex virus (HSV), varicella-zoster virus (VZV), and/or Epstein-Barr virus (EBV)
  - Iron overload

- **Transplant-related factors (table 2):**
  - Myeloablative conditioning regimens (see "Preparative regimens for hematopoietic cell transplantation", section on 'Myeloablative preparative regimens')
  - Degree of donor/recipient human leukocyte antigen (HLA) mismatch, with higher infectious risk with use of mismatched or partially matched (haploidalidentical) allografts (see "Donor selection for hematopoietic cell transplantation")
  - Graft source – Peripheral blood stem cells are associated with faster neutrophil engraftment than marrow or cord blood but more chronic graft-versus-host disease (GVHD); umbilical cord blood is associated with slower neutrophil engraftment and slower B and T cell immune reconstitution but less GVHD compared with marrow or peripheral blood (see "Sources of hematopoietic stem cells")
  - T cell depletion is associated with greater risk for graft rejection, slower B and T cell immune reconstitution, greater risk for neutropenic infections, lower risk for GVHD and infections associated with GVHD, and greater and longer risk for herpesvirus and invasive fungal infections (see "Sources of hematopoietic stem cells", section on 'T cell manipulation' and "Prevention of acute graft-versus-host disease", section on 'T cell depletion-based therapy')
  - Immunosuppressive regimen – More profound deficiency of T cell immunity with antithymocyte globulin; more mucosal injury and longer time to neutrophil engraftment with methotrexate

- **Immunogenetics – Examples of polymorphisms that confer increased or decreased risk of infection include:**
Polymorphisms in recipient mannose-binding lectin mutations have been associated with increased infections after engraftment following myeloablative sibling allogeneic HCT [4]. Various gene polymorphisms (in HCT donors, HCT recipients, or patients with hematologic malignancies) have been associated with an increased risk of invasive aspergillosis in HCT recipients and/or patients with hematologic malignancies. Examples include polymorphisms in genes involved in the innate immune response, such as the toll-like receptor 4 gene [5]; the soluble pattern recognition receptor, long pentraxin 3 (PTX3) [6]; dectin-1 [7,8]; and others [9]. Protection from CMV reactivation was shown to be related to different genotypes of donor-activated killer-immunoglobulin receptors [10].

• Protection from CMV reactivation was shown to be related to different genotypes of donor-activated killer-immunoglobulin receptors [10].

Prolonged and severe neutropenia – The Multinational Association for Supportive Care in Cancer (MASCC) risk index is a validated tool for measuring the risk for neutropenic fever-related medical complications (calculator 1) [11-14]; this risk index and other methods for assessing risk of complications in neutropenic patients are discussed in detail separately (see "Risk assessment of adults with chemotherapy-induced neutropenia")

Severe acute and extensive chronic GVHD and its therapy (particularly with high-dose glucocorticoids and novel immunosuppressants) leading to delayed immune reconstitution (see "Pathogenesis of graft-versus-host disease" and "Clinical manifestations, diagnosis, and grading of acute graft-versus-host disease" and "Clinical manifestations, diagnosis, and grading of chronic graft-versus-host disease" and "Overview of immunosuppressive agents used for prevention and treatment of graft-versus-host disease")

• Infection with immunomodulating viruses, particularly CMV [15]

• Graft failure

• Respiratory complications, such as airflow decline [16]

Many of the risk factors for infection are interrelated. As an example, duration of neutropenia is related to patient and transplant variables including underlying disease, extensive prior therapy, stem cell source (cord) and cell dose (low), conditioning regimen (myeloablative), graft failure or rejection, and others. Similarly, many risk factors increase the risk for GVHD, including stem cell source (peripheral stem cell more than bone marrow) and HLA relatedness (mismatched or unrelated donor more than matched related).

A careful pretransplant screening of donor and recipient to evaluate the risk of posttransplant infection is one of the most important steps in the management of HCT recipients. (See "Evaluation for infection before hematopoietic cell transplantation" and "Donor selection for hematopoietic cell transplantation").

TIMELINE FOR INFECTIONS — The types of infections to which hematopoietic cell transplantation (HCT) recipients are most vulnerable can be roughly divided based upon the time elapsed since transplantation [1,17]. The three periods are:

• Preengraftment – From transplantation to neutrophil recovery, approximately day 20 to 30
• Early postengraftment – From engraftment to day 100
Late postengraftment – After day 100

It is useful to think of the most likely infectious disease manifestations during each period among allogeneic and autologous HCT recipients and also to think of the clinical syndromes that occur during each period (table 3). Both perspectives offer complementary information. Knowledge of likely pathogens during each period facilitates decisions about the need for and potential benefit of prophylaxis and to allow the clinician to construct a differential diagnosis for clinical syndromes that occur. For many clinical syndromes that occur after HCT, there are possible infectious and noninfectious etiologies.

This division into time periods is artificial, but it is helpful in the management of HCT recipients. The timing and length of interval of each of these phases may vary according to the source of stem cells, degree of human leukocyte antigen (HLA) and minor histocompatibility antigen match, the type and intensity of conditioning regimen used, and any manipulation of the graft to remove T cells or other cell populations, the type of post-transplant immnosuppressive therapy (especially glucocorticoids), and the presence of graft-versus-host disease (GVHD). In general, allogeneic HCT recipients are at risk for infection during all three periods (figure 2), whereas autologous HCT recipients are typically only vulnerable to infection during the pre- and immediate postengraftment periods (figure 3). During each of these time periods, patients can develop bacterial, fungal, viral, and/or parasitic infections, although certain pathogens tend to cause disease during some of these periods more frequently than others (table 3).

In HCT recipients, the general risk of infectious complications is not limited to the period of granulocytopenia but persists for 6 to 12 months after autologous HCT and 12 to 24 months after allogeneic HCT, until B and T cell immune recovery occurs. The period of increased risk for infection includes the period during which the patient is profoundly neutropenic (absolute neutrophil count ≤100 cells/microL) and/or lymphopenic (absolute lymphocyte count ≤300 cells/microL) [1]. Receipt of T cell suppressive therapies (high-dose glucocorticoids, anti–T cell antibodies, purine analogs, others), the occurrence of GVHD, and/or receipt of a T cell–depleted hematopoietic cell graft may delay T cell recovery, and use of agents such as rituximab may delay B cell recovery [18]. The risk for infection usually decreases six months after the last dose of T cell suppressive therapies or when the absolute lymphocyte count is ≥500 cells/microL (or the absolute CD4 count is ≥200 cells/microL), whichever is longer. (See "Strategies for immune reconstitution following allogeneic hematopoietic cell transplantation", section on 'Overview of immune reconstitution'.)

PREENGRAFTMENT PERIOD — The major risk factors for infection during the preengraftment period after hematopoietic cell transplantation (HCT) are mucocutaneous damage, which disrupts the natural barriers of the skin and mucous membranes, and neutropenia, with resulting loss of phagocytic abilities (figure 2 and figure 3) [1].

Neutropenic fever — Neutropenic fever occurs in most HCT patients during the preengraftment period. An infectious source is identified in only 20 to 30 percent of febrile neutropenic episodes [19,20]. Often, fever is the only evidence of infection. Bacteremia is documented by blood cultures in 10 to 25 percent of patients
with neutropenic fever [19]. Aerobic gram-positive and gram-negative bacteria account for most neutropenic fevers during this period.

In addition to fever, infectious complications present as pneumonia and lower gastrointestinal tract infection (neutropenic enterocolitis or *Clostridium difficile* colitis). Less frequent manifestations include septic shock, ecthyma gangrenosum, and perirectal cellulitis.

Antibacterial prophylaxis reduces the risk of bacterial infections, mainly bacteremias, during neutropenia. The evaluation and management approaches are similar to those used for neutropenic fever in nontransplant high-risk patients. (See "Overview of neutropenic fever syndromes" and "Diagnostic approach to the adult presenting with neutropenic fever" and "Treatment of neutropenic fever syndromes in adults with hematologic malignancies and hematopoietic cell transplant recipients (high-risk patients)" and "Prevention of infections in hematopoietic cell transplant recipients" and "Prophylaxis of infection during chemotherapy-induced neutropenia in high-risk adults".)

The greatest risk for infection during neutropenia is in HCT patients who receive myeloablative conditioning, which produces more mucosal injury and longer durations of neutropenia compared with nonmyeloablative conditioning. Antibiotic prophylaxis is generally recommended in such high-risk patients (see "Prophylaxis of infection during chemotherapy-induced neutropenia in high-risk adults", section on 'Antibacterial prophylaxis').

Persistent fever has a wide differential diagnosis, including antibiotic-resistant bacteria, fungi (especially *Candida*, less commonly *Aspergillus*), occult infection, inflammatory response to tissue damage, and drug fever (see "Treatment of neutropenic fever syndromes in adults with hematologic malignancies and hematopoietic cell transplant recipients (high-risk patients)"). Antifungal prophylaxis is recommended in such high-risk patients [21,22]. (See "Prophylaxis of invasive fungal infections in adult hematopoietic cell transplant recipients".)

**Mucositis** — Mucositis of the oral cavity, oropharynx, and esophagus is most common in patients receiving myeloablative conditioning regimens and is principally due to mucosal toxicity. However, herpes simplex virus (HSV) reactivation occurs in two-thirds of HSV-seropositive patients not receiving specific antiviral prophylaxis. HSV can exacerbate mucositis [23,24] and occasionally cause esophagitis. Antiviral prophylaxis is highly effective in preventing HSV reactivation. Rarely, deep punched-out localized oral ulcers can be caused by the agents of mucormycosis, *Fusarium* spp, or other pathogenic molds. (See "Prevention of viral infections in hematopoietic cell transplant recipients" and "Mucormycosis (zygomycosis)".)

**Diarrhea** — Diarrhea is common and can have both infectious and noninfectious etiologies. Mucosal injury due to the conditioning regimen is a frequent cause of diarrhea during the first week after HCT and is most common after myeloablative conditioning regimens. Multiple medications, particularly oral magnesium supplements given to counter the hypomagnesemia often seen with calcineurin inhibitors, are frequent causes of diarrhea.
One of the most common causes of infectious diarrhea in patients undergoing HCT is *C. difficile*-associated diarrhea (CDAD), with incidences as high as 10 to 20 percent in some studies [25-27]. Of particular concern is the increasing worldwide prevalence of CDAD caused by a hypervirulent strain of *C. difficile*. Clinicians should remain vigilant about the possibility of CDAD in any patient with significant diarrhea and/or abdominal pain. (See "Clostridium difficile in adults: Epidemiology, microbiology, and pathophysiology").

Another frequent cause of diarrhea is neutropenic enterocolitis (or typhlitis). Fever, diarrhea, abdominal pain or distention, and tenderness are often present. This is covered in detail separately. (See "Neutropenic enterocolitis (typhlitis)").

Multiple other enteric pathogens can also cause diarrhea and should be excluded. (See 'Diarrhea' below and "Approach to the adult with acute diarrhea in resource-rich settings").

Pneumonia — Pneumonia can be caused by both infectious and noninfectious etiologies. The differential diagnosis is highly influenced by the type of infiltrate. Pulmonary infiltrates can be divided into nodular (or localized) or diffuse infiltrates.

- **Nodular lesions** — Most nodular lesions are caused by infectious etiologies during the preengraftment period [28]. Both bacterial (gram positive and gram negative) and, less commonly, mold pathogens predominate.

- **Diffuse infiltrates** — Diffuse infiltrates during this period are more common due to noninfectious causes such as pulmonary edema or lung damage resulting from the conditioning regimen (table 4). However, respiratory viruses may be causes of both upper and lower respiratory tract infections, with the latter manifesting commonly as diffuse or patchy infiltrates.

It is important to note that pulmonary infiltrates (typically a diffuse pattern) that coincide with engraftment are often not infectious but, rather, are due to hemorrhagic alveolitis or to a cytokine-driven inflammatory process known as engraftment syndrome. The engraftment syndrome has been reported in 7 to 10 percent of autologous HCT recipients but less commonly following allogeneic HCT. (See "Pulmonary complications after autologous hematopoietic cell transplantation", section on 'Engraftment syndrome and PERDS' and "Pulmonary complications after allogeneic hematopoietic cell transplantation", section on 'Engraftment syndrome'.)

**Vascular catheter-associated cellulitis** — Erythema, pain, swelling, and/or tenderness on palpation at the insertion site of the catheter or along the catheter subcutaneous track are common manifestations of vascular catheter-associated cellulitis. Cultures of secretions at the exit site or bloodstream may be helpful and should be done, but cultures are often negative; accordingly, presumptive therapy is justified and agents chosen to cover the most likely pathogens. Blood cultures should also be performed since bacteremia may occur. At least half of the pathogens are staphylococci (especially *Staphylococcus epidermidis*). Evaluation and management are discussed separately. (See "Epidemiology, pathogenesis, and microbiology of intravascular catheter infections" and "Treatment of intravascular catheter-related infections").
Bloodstream infection — Bloodstream infections are common in HCT recipients, often related to the central venous line (CVL) or mucosal injury. Gram-positive bacteria (S. epidermidis, Staphylococcus aureus) are most common, but gram-negative bacteria and Candida spp bloodstream infections also occur. Possible sources other than the CVL include the gastrointestinal tract and, for bacterial infections, the lungs. (See "Overview of neutropenic fever syndromes", section on 'Bacterial pathogens' and "Overview of neutropenic fever syndromes", section on 'Fungal pathogens' and "Epidemiology, pathogenesis, and microbiology of intravascular catheter infections" and "Clinical manifestations and diagnosis of candidemia and invasive candidiasis in adults".)

Hepatitis — Infectious causes of hepatocellular injury are uncommon during this period. Hepatic sinusoidal obstruction syndrome (formerly known as venoocclusive disease) generally first manifests during the preengraftment period and its onset is rare after day 30. Occasionally, acute cholecystitis may occur and should be considered in patients with a syndrome that involves cholestasis.

Hemorrhagic cystitis — Preengraftment hemorrhagic cystitis is typically caused by toxicity to the bladder mucosa from the conditioning regimen (eg, cyclophosphamide, ifosfamide, busulfan, total body irradiation) [29,30]. In contrast, postengraftment hemorrhagic cystitis is often caused by a virus, such as BK polyomavirus or adenovirus. (See 'Hemorrhagic cystitis' below.)

EARLY POSTENGRAFTMENT PERIOD — The major risk factors for infection during the early postengraftment period (days 30 to 100 after hematopoietic cell transplantation [HCT]) are acute graft-versus-host disease (GVHD) and its therapy as well as residual mucositis and cutaneous damage (similar to preengraftment) and recurrent or ongoing neutropenia (figure 2 and figure 3) [31]. Various pathogens cause infection during this period.

Pneumonia — Pneumonia is a common complication during the early postengraftment period. The radiologic pattern (nodular versus diffuse), as in the preengraftment period, drives the differential diagnostic considerations.

- Nodular lesions – Nodular pneumonias are most likely infectious, with both bacterial (gram positive and gram negative) and molds being most likely [28].

In contrast with the preengraftment period, invasive aspergillosis (and less commonly other molds) is a more frequent cause of nodular infiltrates, causing 40 to 50 percent of nodular pneumonias and aggressive therapy, and diagnostic assessment is recommended [28]. Invasive aspergillosis can occur among both allogeneic and autologous HCT recipients, although the incidence is higher among the former group (5 to 30 percent versus 1 to 5 percent) [32-35]. (See "Epidemiology and clinical manifestations of invasive aspergillosis".)

Although various risk factors for postengraftment invasive aspergillosis have been identified, GVHD (acute and chronic) and cytomegalovirus (CMV) disease have been the most consistently identified [36]. Aspergillus accounts for approximately 90 percent of pulmonary fungal infections. However, there has been increasing recognition of the less common but potentially fatal opportunistic mycoses in HCT recipients, including those caused by the agents of mucormycosis (accounting for 5 to 10 percent of
pulmonary fungal infections) and, less frequently, *Fusarium* spp, *Pseudallescheria boydii* (*Scedosporium apiospermum*), and others [32,37]. The clinical features of these infections often mimic aspergillosis, although fusariosis has some unique manifestations, which include skin lesions and bloodstream infections [37,38]. (See "Clinical manifestations and diagnosis of *Fusarium* infection" and "Mucormycosis (zygomycosis)" and "Epidemiology, clinical manifestations, and diagnosis of *Scedosporium* infection".)

**Diffuse infiltrates** – For diffuse infiltrates, infectious causes are much more frequent during the early postengraftment period than during the preengraftment period (table 5). CMV, respiratory viruses, and *Pneumocystis* pneumonia (PCP) are more likely causes, whereas they are infrequent prior to engraftment. Idiopathic pneumonitis due to toxicity from the conditioning regimen is also a common cause of diffuse infiltrates in this period, especially in allogeneic HCT recipients who receive ablative conditioning regimens. (See "Pulmonary complications after allogeneic hematopoietic cell transplantation", section on 'Idiopathic pneumonia syndrome'.)

Specific causes of pneumonia that are important to consider include:

**Pneumocystis** – PCP is uncommon (<1 percent) in HCT recipients receiving prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) [39-42]. The diagnosis of PCP should be considered in patients with high fever, dry cough, hypoxemia, and interstitial pneumonitis who are at risk but are not being given prophylaxis, who are being given suboptimal agents (aerosolized pentamidine or dapsone given on alternate days), or who are nonadherent to the prophylactic regimen. A significant risk for developing PCP has been reported when dapsone was given three times per week (7.2 versus 0.37 percent for TMP-SMX) [41] but not when daily doses of dapsone were given to patients. The efficacy of daily dapsone in preventing PCP appears to be similar with that observed in patients able to remain on TMP-SMX prophylaxis [43]. Prophylaxis with aerosolized pentamidine is less effective than with TMP-SMX or dapsone (when given daily) [44]. Risk factors for PCP include prolonged administration of immunosuppressive therapies (high-dose glucocorticoids), chronic GVHD, therapy with purine analogs or rituximab, a CD4+ T cell count <200 cells/µL, and relapse of hematologic malignancy [39]. (See "Prevention of infections in hematopoietic cell transplant recipients", section on 'Pneumocystis prophylaxis'.)

**Respiratory viruses** – Respiratory viruses may cause both upper and lower respiratory tract infections, with the latter typically manifesting radiologically as diffuse or patchy infiltrates. It is important to note that prolonged asymptomatic viral shedding may also occur in the absence of clinical illness and may be detected along with copathogens such as CMV, *Aspergillus* spp, or *Pneumocystis jiroveci*. These copathogens may cause or contribute to lower respiratory tract disease and require therapy. [45-48].

**CMV** — Before the routine use of prophylactic or preemptive anti-CMV regimens, CMV-seropositive allogeneic HCT recipients had a 70 to 80 percent risk of reactivation of this virus, and one-third of these patients developed CMV disease, mostly pneumonia [49]. By comparison, CMV reactivation occurred in only 40 percent of autologous or syngeneic HCT recipients; CMV disease, mainly pneumonia, developed in fewer than 5 percent of these patients [50-52].
Currently, CMV pneumonia is infrequent, occurring in fewer than 5 percent of allogeneic HCT recipients. However, since it is treatable and fatal if not treated, evaluation of pneumonia should include tests to exclude CMV as a possible etiology of diffuse pneumonia. The major risk factors for CMV reactivation and disease are GVHD, the use of high-dose glucocorticoids, and prior CMV viremia. The prophylaxis of CMV in HCT recipients is discussed in greater detail separately. (See "Prevention of viral infections in hematopoietic cell transplant recipients", section on 'Cytomegalovirus'.)

- **Disseminated strongyloidiasis** – A rapidly fatal hyperinfection syndrome with disseminated strongyloidiasis and acute respiratory distress syndrome has been reported rarely in HCT recipients [53,54]. The infection develops after cutaneous exposure to contaminated soil.

- **Disseminated toxoplasmosis** – Disseminated toxoplasmosis is rare but is often associated with lung involvement, typically with diffuse infiltrates on imaging [55,56].

**Diarrhea** — Diarrhea during the early postengraftment period can have any of several infectious or noninfectious causes, as outlined below:

- **Acute GVHD** – During the early postengraftment period, acute GVHD is the most important and a frequent cause of diarrhea. Diarrhea due to gastrointestinal tract GVHD usually occurs in the presence of other manifestations of GVHD, particularly a rash, but it may occur without other organ involvement; lower endoscopy with biopsy is therefore necessary to adequately evaluate this. (See "Clinical manifestations, diagnosis, and grading of acute graft-versus-host disease").

- **CMV colitis** – CMV colitis is another important consideration that should be investigated by colon biopsy. CMV colitis can occur by itself or can occur concomitantly with gastrointestinal GVHD. Biopsy specimens should be examined for both.

- **Medications** – Medications are frequent causes of diarrhea during this period. A common medication to cause diarrhea following HCT is oral magnesium, which is given to counter the hypomagnesemia that often occurs with calcineurin inhibitors.

- **Clostridium difficile** – An important observation is that C. difficile–associated disease (CDAD) in this population is not typically associated with the classic clinical findings, which include mucosal pseudomembranes and elevated leukocyte counts [27,57-59]. Likewise, direct morbidities, such as perforation necessitating surgical resection, are relatively low compared with other hospitalized patients [27]. However, there are reports that CDAD is associated with a significant association with gastrointestinal tract GVHD [27,59].

- **Adenovirus** – Adenovirus may reactivate following HCT or be acquired de novo. Reactivation of adenovirus infection is common following HCT but rarely causes severe disease [60]. Adenovirus infection may remain asymptomatic (viremia only) or evolve into various syndromes including upper respiratory tract infection, severe pneumonitis, diarrhea and hemorrhagic colitis, nephritis, and/or hemorrhagic cystitis. Less common manifestations include myocarditis, hepatitis [61], encephalitis, and disseminated disease with multiorgan failure; disseminated disease is rare, occurring in 1 to 7 percent of cases, with reported mortality rates of 8 to 26 percent [60]. The development of adenovirus disease is related to deficiency in adenovirus-specific T cells. Risk factors for adenovirus
include severe GVHD requiring high-dose glucocorticoids [62,63], T cell depletion [64,65], alemtuzumab or antithymocyte globulin [66], and transplantation with matched unrelated donor or haploidentical grafts or with umbilical cord [60]. Children are more commonly affected than adults [67]. (See "Epidemiology and clinical manifestations of adenovirus infection", section on 'Hematopoietic cell transplantation'.)

**Enteric pathogens** – Enteric virus infections among HCT recipients may cause gastroenteritis (coxsackie A [68], rotavirus, norovirus [69,70]), which may be prolonged and cause significant diarrhea [71] but may also involve other organ systems including the lungs, cardiovascular system, and central nervous system. Lymphopenia is thought to be a predisposing factor for these enteric infections [71]. Infection is usually transmitted by the fecal-oral route. Viral infections of the enteric system (eg, coxsackie, echo, and rotaviruses) are most prevalent during the summer and fall months, although rotavirus infections have also been reported during the winter and spring [71]. *Cryptosporidium parvum* has rarely been reported to cause gastroenteritis after allogeneic T cell–depleted bone marrow transplantation, CD34-positive selected autologous HCT, T cell depletion, or intensive immunosuppression to treat GVHD. The infection may mimic intestinal GVHD [72,73]. (See "Epidemiology and pathogenesis of viral gastroenteritis in adults" and "Epidemiology, clinical manifestations, and diagnosis of cryptosporidiosis".)

**Hepatitis** — Hepatic abnormalities have many potential causes, including toxicity from medications, acute GVHD, iron overload, hepatitis viruses, other viruses (eg, CMV, Epstein-Barr virus [EBV], human herpesvirus 6 [HHV-6], adenovirus), and chronic disseminated candidiasis (hepatosplenic candidiasis). Hepatic sinusoidal obstruction syndrome (formerly known as venoocclusive disease) generally first manifests during the preengraftment period and its onset is rare after day 30. (See "Diagnosis of hepatic sinusoidal obstruction syndrome (veno-occlusive disease) following hematopoietic cell transplantation".)

GVHD is the primary consideration for hepatic complications during this period. In general, GVHD tends to exhibit a cholestatic pattern rather than a hepatocellular injury pattern, but there is considerable overlap. A liver biopsy is helpful in establishing the diagnosis. If the full constellation typical of acute GVHD (characteristic rash, elevated bilirubin, and diarrhea) is present, biopsy of the most accessible site involved may suffice to establish the diagnosis and abrogate the need for liver biopsy to minimize the risk of biopsy complications.

Because hepatitis B virus (HBV) may persist as an occult infection among HBsAg-negative patients, it may reactivate following HCT. Intense immunosuppression may cause seroreversion of some patients who are HBsAb positive and HBcAb positive to an HBsAg-positive status, particularly patients with lymphoma [74]. In a study from Korea, 7 of 129 (6 percent) HBsAg-negative patients undergoing autologous HCT seroconverted to a HBsAg-positive status, and 5 (4 percent) developed acute hepatitis [75]. Multiple myeloma also appears to increase the risk of HBV reactivation after autologous HCT [76,77], with a suggested role for the myeloma-active immunomodulatory agents (thalidomide, bortezomib) [77].
The serologic profile of HBV infection may be altered by severe immunosuppression that affects both humoral and cell-mediated control of HBV infection; some HBsAg-positive patients may not develop HBcAb, even in the setting of high-grade HBV replication or in recipients of an HBcAb-positive graft.

Acute hepatitis after immune reconstitution is the most common manifestation (in approximately 60 percent), particularly with tapering of immunosuppression, although up to 20 percent of patients may not show any signs or symptoms of liver pathology. Long-lasting transaminitis may develop. Reactivation may resolve spontaneously in one-fourth of the cases, while fulminant hepatitis is very rare.

An important differential diagnosis of viral hepatitis is GVHD because glucocorticoids for a presumptive diagnosis of hepatic GVHD may alleviate the symptoms of both conditions only to lead to increasing viral replication and delayed effective antiviral therapy. Liver biopsy may be required to establish the diagnosis of GVHD.

With immune reconstitution, HBV may manifest as acute hepatitis with a major increase in HBV viral load. Glucocorticoids should be given if the liver enzymes increase to ≥10 times their upper limits of normal [78]. Such immune "flares" may occur during this period or much later after HCT.

Reactivation of hepatitis C virus (HCV) occurs in >50 percent of patients undergoing allogeneic HCT. Patients with HCV viremia (HCV RNA positive) and elevated liver function tests before HCT are at a higher risk for developing severe peritransplant complications. HCV seropositivity is a risk factor for nonrelapse mortality after allogeneic HCT even in patients with normal liver function tests [79,80] and is associated with transient hepatitis in the early posttransplant period; HCV is also a risk factor for hepatic sinusoidal syndrome (SOS) and early cirrhosis [80,81]. However, in one study, HCV infection did not appear to negatively impact 10-year survival [82]. HCV reactivation may manifest as acute hepatitis with a substantial increase in HCV viral load and may be fatal [78].

The prevention of HBV- and HCV-associated disease following HCT is discussed separately. (See "Prevention of viral infections in hematopoietic cell transplant recipients", section on 'Hepatitis B virus' and "Prevention of viral infections in hematopoietic cell transplant recipients", section on 'Hepatitis C virus'.)

Other potential causes of hepatitis are discussed below. (See 'Hepatitis' below.)

**Hemorrhagic cystitis** — BK polyomavirus (BKPyV) is a common cause of hemorrhagic cystitis during the early postengraftment period. Adenovirus is a less common cause. Even less frequent causes include infectious (eg, cytomegalovirus, JC polyomavirus [JCPyV]) and hematologic (bleeding disorders, thrombocytopenia) causes as well as damage from the conditioning regimen [30,63,83,84]. (See "Epidemiology and clinical manifestations of adenovirus infection", section on 'Genitourinary tract'.)

BKPyV-induced hemorrhagic cystitis occurs most commonly at three to six weeks following HCT [29,85]. Hemorrhagic cystitis due to toxicity from the conditioning regimen usually occurs during the preengraftment period. (See 'Hemorrhagic cystitis' above.)
BKPyV persistently infects renal tubular epithelial cells and also replicates in urothelial cells. Risk factors for BKPyV-associated hemorrhagic cystitis include a myeloablative conditioning regimen in the setting of human leukocyte antigen (HLA) mismatch, particularly from unrelated donor or umbilical cord blood HCT [86,87]. Conditioning with alemtuzumab has also been reported as a risk factor [88]. The complex interaction between BKPyV replication, the intensity of the conditioning regimen, and donor type was illustrated in a study in which recipients of haploidentical or umbilical cord blood grafts with myeloablative conditioning who had a positive urine BKPyV polymerase chain reaction (PCR) pretransplant had a significantly higher risk of developing hemorrhagic cystitis (58 percent) than all other recipients (7 percent) [87]. The possible role of GVHD as a risk factor has been suggested but is not clearly established [86,87].

BK viruria (BKPyV replication detected in urine) occurs in approximately half of allogeneic and fewer than 10 percent of autologous HCT recipients and has been associated with hemorrhagic cystitis [83,85,89-91]. However, the detection of BK viruria is not sufficient to establish the diagnosis of BKPyV-associated hemorrhagic cystitis. Detection of BKPyV DNA in plasma also appears to be a marker of BKPyV-associated hemorrhagic cystitis in HCT recipients. Levels of BK viremia >10,000 copies/mL are thought to predict renal and urologic outcomes in HCT recipients [92]. In a case-control study, 30 cases of hemorrhagic cystitis with documented BK viruria were compared with matched controls and weekly plasma samples were tested for BKPyV DNA by PCR [91]. BK viremia detected before or during the disease was independently associated with hemorrhagic cystitis. Cases of BKPyV-associated hemorrhagic cystitis had a significantly higher peak of BK plasma viral load and long-lasting BK viremia. (See "Overview of JC polyomavirus, BK polyomavirus, and other polyomavirus infections", section on 'Hemorrhagic cystitis'.)

The clinical manifestations of BKPyV-associated hemorrhagic cystitis after HCT range in severity and may include cystitis (dysuria, urinary urgency, lower abdominal discomfort), macrohematuria with or without clots, renal failure due to obstruction, and, rarely, life-threatening bleeding requiring urologic interventions including cystectomy.

Ureteral stenosis due to BKPyV has been reported rarely in HCT recipients [93,94]. In one report, an HCT recipient with BKPyV infection developed hemorrhagic cystitis followed by bilateral ureteral stenosis, suggesting that BKPyV can cause an ascending infection [93]. BKPyV viruria has been associated with a higher risk of renal failure, which has been proven by biopsy in occasional cases [95].

**Encephalitis** — Several pathogens can cause encephalitis, particularly viruses such as HHV-6, but also other pathogens such as *Toxoplasma gondii*:

- **Human herpesvirus 6** – HHV-6 reactivation occurs in 30 to 50 percent of patients undergoing allogeneic HCT [96-99], with encephalitis occurring in only a small subset of these patients. HHV-6 reactivation often manifests as HHV-6 viremia and typically occurs between two and four weeks after transplantation. HHV-6 infection in HCT recipients is discussed in greater detail separately. (See "Human herpesvirus 6 infection in hematopoietic cell transplant recipients".)
- **Herpes simplex virus (HSV)** – HSV infections should be considered in patients presenting with encephalitis [100,101], although today it would be a rare cause. HSV reactivation is usually prevented
with acyclovir or valacyclovir prophylaxis, but it can occur following discontinuation of antiviral prophylaxis or in patients infected with resistant isolates. (See "Herpes simplex virus type 1 encephalitis" and "Clinical manifestations of varicella-zoster virus infection: Herpes zoster" and "Prevention of viral infections in hematopoietic cell transplant recipients", section on 'Herpes simplex virus' and "Prevention of viral infections in hematopoietic cell transplant recipients", section on 'Varicella-zoster virus'.)

● **Varicella-zoster virus (VZV)** – VZV reactivation usually occurs during the late postengraftment period, but it should be considered in patients presenting with encephalitis even during the early postengraftment period. (See 'Encephalitis and meningitis' below and "Clinical manifestations of varicella-zoster virus infection: Herpes zoster", section on 'Encephalitis' and "Prevention of viral infections in hematopoietic cell transplant recipients", section on 'Varicella-zoster virus'.)

● **Cytomegalovirus** – CMV has been reported rarely as a cause of encephalitis in HCT recipients [100,102,103]. Risk factors for CMV disease of the central nervous system include severe and prolonged T cell immunodeficiency (T cell depletion, antithymocyte globulin, umbilical cord blood transplant), a history of recurrent CMV viremia treated with multiple courses of preemptive antiviral therapy, and ganciclovir-resistant CMV infection [102]. (See "Prevention of viral infections in hematopoietic cell transplant recipients", section on 'Cytomegalovirus'.)

● **Epstein-Barr virus** – Disease caused by EBV most commonly occurs in the late postengraftment phase, although the infection can be detected prior to day 100 among patients treated with T cell-depleted grafts or anti-T cell monoclonal antibodies such as alemtuzumab [104]. Posttransplant lymphoproliferative disorder (PTLD) can manifest as fever, lymphadenopathy, and/or extranodal lymphomatous proliferation in various organs (liver, gastrointestinal tract, lungs, central nervous system, and bone marrow) and is characterized by monoclonal B cell proliferation with malignant cytogenetic abnormalities and immunoglobulin gene rearrangements. (See "Epidemiology, clinical manifestations, and diagnosis of post-transplant lymphoproliferative disorders".)

● **JC polyomavirus** – JCPyV can replicate in the central nervous system, where it can lead to severe demyelination in subcortical areas (called progressive multifocal leukoencephalopathy [PML]) or in the cerebellum (called granule cell neuronopathy). PML usually presents with subacute neurologic deficits including seizures, altered mental status, visual symptoms related to visual field defects (hemianopia and diplopia), weakness, hemiparesis or monoparesis, and/or ataxia [105]. The diagnosis should be suspected when neuroimaging reveals a multifocal process limited to the white matter that does not exhibit pronounced contrast enhancement or a mass effect nor conform to vascular territories. Although brain biopsy is the gold standard for diagnosis of PML, it is associated with significant morbidity and even mortality. In most cases, a laboratory-confirmed diagnosis can be made using PCR for JCPyV DNA in the cerebrospinal fluid (CSF) in patients who exhibit characteristic neurologic and neuroimaging features [106]. The median time to the first symptoms of PML following HCT is 11 months, with a median survival of approximately 20 months following symptom onset [107]. Risk factors for PML in HCT recipients include therapy with fludarabine [108,109] or rituximab [110,111], particularly in patients with very low CD4+ T cell counts [111]. PML is discussed in greater detail
separately. (See "Progressive multifocal leukoencephalopathy: Epidemiology, clinical manifestations, and diagnosis").

**West Nile virus** – West Nile virus infections have been reported among HCT recipients and occur during late summer and fall [112,113]. The infection is acquired from mosquito bites (median incubation of two weeks) and rarely from transfusion of a blood product or from an infected graft (within four weeks of transfusion or receipt of the graft). The presentation of West Nile virus infection in HCT recipients includes fever, lethargy, and rapidly progressive bilateral extremity weakness leading to acute flaccid paralysis (severe quadriplegia or quadriplegia with hypotonia and loss of reflexes). Meningitis and/or encephalitis are other presentations of West Nile virus infection in HCT recipients. Most patients develop an encephalopathy. The diagnosis is made by the combination of the clinical findings and detection of West Nile virus from blood, tissue, or cerebrospinal fluid samples using PCR or rarely with viral culture [113]. Detection of West Nile virus immunoglobulin (Ig)M antibodies in CSF is not a sensitive test in HCT recipients because of their severe immunodeficiency [113]. West Nile virus is discussed in greater detail separately. (See "Epidemiology and pathogenesis of West Nile virus infection" and "Clinical manifestations and diagnosis of West Nile virus infection").

**Adenovirus** – Adenovirus has been reported as a rare cause of encephalitis in HCT recipients [101]. (See 'Diarrhea' above and "Epidemiology and clinical manifestations of adenovirus infection", section on 'Nervous system'.)

**Toxoplasmosis** – Cerebral toxoplasmosis typically develops between days 60 and 150 after allogeneic HCT. Patients may have manifestations of increased intracranial pressure, neurologic deficits, and/or seizures, all of which are caused by an intracerebral abscess that can be identified by magnetic resonance imaging of the brain. Other manifestations of toxoplasmosis in HCT recipients include Guillain-Barré syndrome, cutaneous infections, hematologic complications such as graft failure [114] or hemophagocytic syndrome [115], chorioretinitis [116], or disseminated disease [55]. Risk factors include positive serology, no trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis, severe GVHD, ablative conditioning regimen, T cell depletion, or use of antithymocyte globulin (ATG) [117-120].

Viral encephalitis (including causes not discussed above, such as Eastern equine encephalitis and other arboviruses) is discussed in greater detail separately. (See "Viral encephalitis in adults" and "Acute viral encephalitis in children: Clinical manifestations and diagnosis").

In addition to infectious causes, the following noninfectious causes can result in encephalopathy:

- **Fludarabine toxicity** – Delayed cortical damage from fludarabine may be a cause of encephalopathy. This may be seen in the early or late postengraftment period and typically progresses over time. (See "Overview of neurologic complications of non-platinum cancer chemotherapy", section on 'Purine analogs'.)

- **Posterior reversible encephalopathy syndrome (PRES)** – Calcineurin inhibitors are associated with PRES [121]. PRES may present as seizures, altered sensorium, visual symptoms or other
manifestation, and can present in either the early or late postengraftment periods. (See “Reversible posterior leukoencephalopathy syndrome”.)

**LATE POSTENGRAFTMENT PERIOD** — Patients remain at high risk for infections even late after transplantation and may require prolonged follow-up. Late infectious complications are typically only seen among allogeneic recipients with specific risk factors including [122]:

- Extensive chronic graft-versus-host disease (GVHD) and intensive therapy for GVHD, resulting in delayed immune reconstitution (eg, cellular and humoral immune dysfunction, hyposplenism, and decrease in opsonization)
- Cytomegalovirus (CMV)-seronegative donor status and -seropositive recipient status (CMV D-/R+)
- High-dose (myeloablative) and radiation-based conditioning regimens

Sinusitis, upper respiratory tract infections, pneumonia, and meningitis are frequently caused by the encapsulated bacteria (*Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis*) during the late postengraftment period [122-125]. Late bacteremia is also common after allogeneic HCT and is typically caused by encapsulated bacteria [123-125], staphylococci, and gram-negative bacteria such as *Pseudomonas* spp [126]. Patients with chronic GVHD are particularly vulnerable due to poor opsonization, hypogammaglobulinemia, and hyposplenism.

In a study of 196 long-term survivors after human leukocyte antigen (HLA)-matched related hematopoietic cell transplantation (HCT; median follow-up of eight years), infection was the cause of death of 19 of the 30 patients who died beyond the first year [122]. Late bacterial infections (mostly sepsis and pneumonia) occurred in 30 patients, yielding an eight-year cumulative incidence of 15 percent. Eighteen pathogens were identified, including *S. pneumoniae* (six infections, of which three were meningitis), *Salmonella* spp (three infections), *S. aureus* (two infections), *H. influenzae, C. difficile*, and others. Most infections developed during the second year after HCT while patients were receiving amoxicillin prophylaxis. Patients were vaccinated according to the European recommendations, including against *S. pneumoniae* [127]. Extensive chronic GVHD (hazard ratio [HR] 2.9), CMV D-/R+ serostatus (HR 2.5), and an irradiation-based conditioning regimen (HR 3.1) were independent predictors of late bacterial infections [122].

**Pneumonia** — The spectrum of infectious and noninfectious etiologies for pneumonia is mostly similar to the spectrum during the early postengraftment period. Diffuse pneumonias are evenly divided between noninfectious (cryptogenic organizing pneumonia) and infectious (CMV, respiratory viruses, *Pneumocystis* pneumonia [PCP]). Nodular pneumonias are mostly infectious, most commonly due to gram-positive or gram-negative bacteria but occasionally due to *Aspergillus* spp, other molds, or *Nocardia*.

- **Bronchiolitis obliterans/bronchiolitis obliterans syndrome and cryptogenic organizing pneumonia** — Idiopathic pneumonia due to toxicity from the conditioning regimen is no longer a major concern during the late postengraftment period. However, bronchiolitis obliterans/bronchiolitis obliterans syndrome (BO/BOS) and cryptogenic organizing pneumonia (COP; formerly known as bronchiolitis obliterans with organizing pneumonia [BOOP]),
which are associated with chronic GVHD, are major concerns. BO and COP manifest clinically by progressive dyspnea and cough; each entity has characteristic radiographic findings. Aggressive diagnosis and prompt treatment are necessary to reduce the threat of progressive respiratory insufficiency. When these diagnoses are being considered, infections should be searched for as they can present in a similar way and may also precipitate both processes. BO/BOS and COP are discussed in more detail separately. (See "Pulmonary complications after allogeneic hematopoietic cell transplantation", section on 'Airflow obstruction and bronchiolitis obliterans' and "Bronchiolitis in adults" and "Pulmonary complications after allogeneic hematopoietic cell transplantation", section on 'Organizing pneumonia' and "Cryptogenic organizing pneumonia").

● **Pneumococcus** – The risk of pneumococcal infection is greater among patients undergoing therapy for extensive chronic GVHD [125,128] and is attributed to immunoglobulin (Ig) deficiency (usually in subclasses IgG2 and IgG4) [129] and hyposplenism [130,131]. In a review of 47 HCT recipients who developed 54 pneumococcal infections, 50 infections occurred late at a mean of 473 days after transplantation [125]. Bacteremic pneumonia was the most common manifestation, but either isolated pneumonia or bacteremia also occurred. Infection occurred in five patients despite pneumococcal vaccination. (See "Pneumococcal pneumonia in adults").

● **Cytomegalovirus** – With the use of preemptive anti-CMV therapy, late CMV infection and disease (after day 100) has become a more significant problem following allogeneic HCT and is associated with nonrelapse mortality [132]. Overall, 15 to 30 percent and 6 to 18 percent of allogeneic HCT recipients develop late CMV infection and disease, respectively [132-135]. Factors predictive of late CMV disease include CMV-seronegative donor graft, delayed or no reconstitution of CMV-specific T cell responses as a result of mismatched/unrelated transplant, use of anti-CMV prophylaxis, and/or early CMV reactivation (before day 100) [132,135-137]. (See "Prevention of viral infections in hematopoietic cell transplant recipients", section on 'Cytomegalovirus'.)

● **Nocardia** – *Nocardia* can cause nodular pulmonary infiltrates during this period (and sometimes additionally skin nodules and cerebral infarcts) and can be indistinguishable from invasive pulmonary aspergillosis [138]. (See "Clinical manifestations and diagnosis of nocardiosis").

● **Fungal pneumonia** – Causes of fungal pneumonia include *Aspergillus* spp and the agents of mucormycosis. During this period, fungal pneumonia is most common in those receiving glucocorticoids for GVHD [1,35]. (See "Epidemiology and clinical manifestations of invasive aspergillosis" and "Mucormycosis (zygomycosis)").

● **Pneumocystis** – Late *Pneumocystis* pneumonia may occur among patients who are no longer receiving trimethoprim-sulfamethoxazole prophylaxis [39]. This is most common in patients receiving prolonged corticosteroids for chronic GVHD. (See "Epidemiology, clinical manifestations, and diagnosis of Pneumocystis pneumonia in HIV-uninfected patients").

● **Posttransplant lymphoproliferative disease** – Epstein-Barr virus (EBV)-associated posttransplant lymphoproliferative disease (PTLD) can present as pulmonary nodules. The median time to onset is between three to five months following transplantation, although it has occurred prior to day 100 among patients at high risk for PTLD [104]. (See "Epidemiology, clinical manifestations, and diagnosis of post-transplant lymphoproliferative disorders").
**Mycobacteria** — Mycobacterial infections in transplant recipients are rare, occurring in 1 to 3 percent of allogeneic and 0.2 percent of autologous HCT recipients [139-143]. Infection can arise due to reactivation or new exposure. Tuberculosis (TB) typically occurs late after engraftment (>100 days with a few cases diagnosed four years after HCT) and manifests with fever, cough, weight loss, and various types of pulmonary infiltrates. Extrapulmonary TB occurs in approximately 15 percent of patients and may involve the kidneys, bone marrow, central nervous system, and joints [144].

Nontuberculous mycobacteria (NTM) are more common causes of mycobacterial infections in HCT recipients in developed countries. Extrapulmonary disease, such as bloodstream, catheter-related, soft tissue, bone, and joint infections, is more common with NTM [139-141]. In a review of infections among HCT recipients, the incidence of NTM infection ranged from 0.4 to 4.9 percent with a median time of onset of 4.6 months [145]. GVHD appears to be a predisposing factor for NTM infections.

More than one-third of patients with NTM disease have a central venous catheter-related infection (bacteremia, exit site, or tunnel infection), most of which are caused by the rapidly growing NTM (eg, *Mycobacterium fortuitum*, *M. abscessus*, *M. chelonae*) [145]. Infection with the rapidly growing NTM is generally diagnosed using routine blood cultures. Pneumonia and disseminated disease are usually caused by *Mycobacterium avium* complex or *M. haemophilum*, whereas cutaneous lesions are seen with *M. haemophilum*, which may also cause disseminated, osteoarticular, and catheter-related infections. (See "Overview of nontuberculous mycobacterial infections in HIV-negative patients" and "Rapidly growing mycobacterial infections in HIV-negative patients".)

**Hepatitis** — Hepatic abnormalities may occur from multiple causes similar with those in the early postengraftment period, including toxicity from medications, chronic GVHD, iron overload, hepatitis viruses, other viruses (eg, CMV, EBV, human herpesvirus 6 [HHV-6], adenovirus), and chronic disseminated candidiasis (hepatosplenic candidiasis). As immune reconstitution progresses with tapering of the immunosuppressive regimen, hepatic injury from reactivation of hepatitis viruses may manifest. (See 'Hepatitis' above.)

Among the hepatitis viruses, not only hepatitis A, B, and C but also hepatitis E, can cause hepatitis in HCT recipients and has been reported to cause both acute and chronic disease in these hosts [146]. (See "Hepatitis E virus infection".)

Isolated varicella-zoster virus (VZV) reactivation in the absence of skin lesions involving liver, pancreas, or serosa of the bowel wall can present as severe hepatocellular injury, abdominal pain, or ileus in patients not receiving acyclovir prophylaxis [147]. This can lead to severe hepatocellular injury, bowel perforation or obstruction, or acute abdomen, and one should presumptively treat for VZV while the diagnostic evaluation proceeds.

Herpes simplex virus (HSV) can also be a rare cause of hepatitis. (See "Clinical manifestations and diagnosis of herpes simplex virus type 1 infection", section on 'Hepatitis'.)
Skin lesions — A variety of skin rashes and lesions are seen in patients with chronic GVHD. Cutaneous and subcutaneous nodules can result from disseminated fungal or bacterial infections. Labial and genital ulcers and vesicles can occur from recurrent HSV infections.

VZV typically presents with a characteristic dermatomal distribution of vesicular lesions. The incidence of VZV reactivation is approximately equal among allogeneic and autologous HCT recipients (20 to 40 percent). VZV infection tends to be more common among children (up to 90 percent by year 1) and to occur earlier posttransplantation (median 100 days) [148]. In one study, VZV accounted for the majority of late infections (>1 year) following allogeneic HCT with an eight-year cumulative incidence of 27 percent [122]. Infection typically occurs during the first six to nine months (80 percent during the first year) and may be associated with complications including:

- Cutaneous dissemination – 25 percent
- Postherpetic neuralgia – 25 percent
- Scarring – 20 percent
- Bacterial superinfection – 15 percent
- Death – 5 percent
- Central nervous system manifestations – <2 percent

Dissemination following allogeneic HCT is more common than after autologous HCT (45 versus 25 percent) [149]. In addition to the skin, dissemination may involve the lungs, liver, and the central nervous system manifesting as meningoencephalitis [150,151]. In HCT recipients, VZV lesions last longer (10 to 14 days) and heal more slowly (3 to 4 weeks) than in healthy adults [152].

Immunocompromised patients uncommonly develop varicella-like skin lesions without a primary dermatomal eruption, a syndrome termed atypical generalized zoster [152]. VZV infection without a skin rash occurs rarely after HCT [153,154]. Thrombocytopenia and disseminated intravascular coagulation have also been reported. Durable immunity seems to develop following this type of infection, since fewer than 5 percent of patients have a second episode [152].

The risk factors for VZV reactivation include VZV seropositivity, VZV infection prior to HCT, extensive therapy for the underlying cancer before HCT, hematologic cancer other than chronic myelogenous leukemia, intensive immunosuppression (pretransplant irradiation, posttransplant use of antithymocyte globulin), and severe and extensive chronic GVHD requiring intensive immunosuppression [150,151,155]. VZV may also occur in patients without GVHD (typically after discontinuation of acyclovir). VZV-specific cell-mediated immune responses (usually suppressed after HCT) inversely correlate with the risk of VZV infection. By contrast, no correlation exists between pretransplant VZV IgG antibodies and posttransplant reactivation [156].

Encephalitis and meningitis — The same causes of these syndromes seen in the early postengraftment period may occur during the late postengraftment period. (See 'Encephalitis' above.)
In addition, listeriosis, although uncommon after HCT, usually develops during the late postengraftment phase [157]. Infection with *Listeria monocytogenes* almost always involves the bloodstream with a high incidence of meningitis (two-thirds of patients) and other forms of parenchymal brain infection including encephalitis, cerebritis, and brain abscess and very rarely brainstem infection (rhombencephalitis) [158]. The use of *trimethoprim-sulfamethoxazole* prophylaxis for *Pneumocystis* prophylaxis and adherence to food safety guidelines usually protect against listeriosis. (See "Clinical manifestations and diagnosis of *Listeria monocytogenes* infection", section on 'CNS infection'.)

*Cryptococcus* is an infrequent cause of leptomeningitis during the late postengraftment period. (See "Clinical manifestations and diagnosis of *Cryptococcus neoformans* meningoencephalitis in HIV-seronegative patients", section on 'Clinical manifestations'.)

*VZV* has been reported to cause meningoencephalitis rarely during the late postengraftment period in patients with chronic GVHD [101,159,160]. (See "Clinical manifestations of varicella-zoster virus infection: *Herpes zoster*, section on 'Encephalitis'.")

**Diarrhea** — The causes are similar with those in the early postengraftment period. Of note, diarrhea is much less commonly a manifestation of chronic GVHD compared with acute GVHD; infectious etiologies should therefore be vigorously pursued, and the spectrum of infectious agents is similar with the earlier period. In addition, late manifestations of EBV may include gastrointestinal tract involvement with a risk for bleeding and perforation. (See 'Diarrhea' above.)

**Fever** — There are multiple possible causes of fever during the late postengraftment period, including GVHD, sinopulmonary infection, central venous line–associated infection, fungal infection, and mycobacterial infection. One-third of patients with NTM disease have a central venous catheter–related infection (bacteremia, exit site or tunnel infection), most of which are caused by the rapidly growing NTM (eg, *M. fortuitum*, *M. abscessus*, *M. chelonae*) [145].

A variety of viruses may cause fever, including CMV, EBV, HHV-6, adenovirus, West Nile virus, adenovirus, and others.

EBV reactivation may involve episomal, lytic, or both modes of genome replication [161] and may originate from B cells from the donor and/or recipient. Most patients with EBV reactivation remain asymptomatic. Three types of EBV-related lymphoproliferative disease occur in HCT recipients [104]:

- An infectious mononucleosis–type acute illness that develops two to eight weeks after induction, characterized by polyclonal B cell proliferation without features of malignant transformation
- A similar clinical disorder but with features of early malignant transformation, such as cytogenetic abnormalities and immunoglobulin gene rearrangements
- Posttransplant lymphoproliferative disease – A more severe clinical presentation with fever, lymphadenopathy, and/or extranodal lymphomatous proliferation in various organs (liver, gastrointestinal tract, lungs, central nervous system, bone marrow), which is characterized by
monoclonal B cell proliferation with malignant cytogenetic abnormalities and immunoglobulin gene rearrangements.

The rate of PTLD varies greatly according to the type of HCT. The risk is greatest in patients with profound T cell cytopenia (eg, after T cell depletion, use of anti-T cell antibodies, umbilical cord blood transplants, HLA-mismatched transplants) [17,162-164]. Donor/recipient EBV serologic mismatch, prior EBV reactivation, and splenectomy are additional risk factors for PTLD, and the number of risk factors present incrementally increases the risk [104,165].

The pace of PTLD ranges from indolent to fulminant, and the extent of disease varies from localized nodular lesions to widely disseminated disease [104,166]. PTLD is discussed in greater detail elsewhere. (See "Epidemiology, clinical manifestations, and diagnosis of post-transplant lymphoproliferative disorders" and "Treatment and prevention of post-transplant lymphoproliferative disorders".)

SUMMARY

● For most complications following hematopoietic cell transplantation (HCT), there are multiple potential infectious and noninfectious etiologies (table 3). (See 'Introduction' above.)

● Infectious pathogens and infectious syndromes vary during the different phases following HCT; the risk of infection is higher following allogeneic HCT (figure 2) compared with autologous HCT (figure 3). (See 'Timeline for infections' above.)

● Evaluation for infection before HCT and prevention of infection in HCT recipients are discussed separately. (See "Evaluation for infection before hematopoietic cell transplantation" and "Prevention of infections in hematopoietic cell transplant recipients" and "Prophylaxis of invasive fungal infections in adults with hematologic malignancies" and "Prevention of viral infections in hematopoietic cell transplant recipients" and "Immunizations in hematopoietic cell transplant candidates and recipients".)

Preengraftment period

● During the preengraftment period, neutropenic fever is frequent, and the causes, evaluation, and management strategies are the same as with high-risk non-HCT patients. (See 'Neutropenic fever' above and "Overview of neutropenic fever syndromes" and "Diagnostic approach to the adult presenting with neutropenic fever" and "Treatment of neutropenic fever syndromes in adults with hematologic malignancies and hematopoietic cell transplant recipients (high-risk patients)".)

● Diarrhea is commonly caused by Clostridium difficile or by neutropenic enterocolitis (typhlitis), but it may also be due to noninfectious causes such as mucosal injury due to the conditioning regimen or medication effects. (See 'Diarrhea' above and "Clostridium difficile in adults: Epidemiology, microbiology, and pathophysiology" and "Clostridium difficile infection in adults: Clinical manifestations and diagnosis" and "Neutropenic enterocolitis (typhlitis)".)

● Diffuse infiltrates during the preengraftment period are mostly due to noninfectious causes, such as pulmonary edema or lung damage resulting from the conditioning regimen, but respiratory viral infections can occasionally occur. Nodular pneumonias are mostly infectious, most commonly due to
gram-positive or gram-negative bacteria but occasionally due to *Aspergillus* spp. (See 'Pneumonia' above.)

**Early postengraftment period**

- During the early postengraftment period, diffuse pneumonias are evenly divided between noninfectious (conditioning regimen toxicity) and infectious (cytomegalovirus [CMV], respiratory viruses, *Pneumocystis* pneumonia [PCP]). Nodular pneumonias are mostly infectious, evenly divided between bacteria (gram positive and gram negative) and *Aspergillus* spp (or, less commonly, other molds). (See 'Pneumonia' above.)

- Diarrhea may be due to medication effects, graft-versus-host disease (GVHD), *C. difficile*, or CMV. (See 'Diarrhea' above.)

- Hepatocellular injury may be due to medication toxicity, GVHD, or reactivation of hepatitis for patients with prior hepatitis. (See 'Hepatitis' above.)

- Encephalitis may be due to drug toxicity or several viral pathogens, including human herpes virus 6, CMV, varicella-zoster virus (VZV), herpes simplex virus, JC polyomavirus, West Nile virus, or Epstein-Barr virus. (See 'Encephalitis' above.)

- Hemorrhagic cystitis is most commonly due to BK polyomavirus. Adenovirus is a less common cause. Even less frequent causes include infectious (other viruses [CMV, JC polyomavirus] and hematologic causes (bleeding disorders, thrombocytopenia, possibly GVHD) as well as damage from the conditioning regimen. (See 'Hemorrhagic cystitis' above.)

**Late postengraftment period**

- During the late postengraftment period, sinopulmonary infections, especially in patients with chronic GVHD, are frequently caused by encapsulated bacteria. (See 'Late postengraftment period' above.)

- Diffuse pneumonias are evenly divided between noninfectious (cryptogenic organizing pneumonia) and infectious (CMV, respiratory viruses, PCP). Nodular pneumonias are mostly infectious, most commonly due to gram-positive or gram-negative bacteria but occasionally due to *Aspergillus* spp, other molds, or *Nocardia*. (See 'Pneumonia' above.)

- VZV infection frequently occurs late after HCT. (See 'Skin lesions' above.)

**ACKNOWLEDGMENT** — The editorial staff at UpToDate would like to acknowledge Dr. Elias Anaissie, who contributed to earlier versions of this topic review.

Use of UpToDate is subject to the Subscription and License Agreement.

**REFERENCES**


44. Vasconcelles MJ, Bernardo MV, King C, et al. Aerosolized pentamidine as pneumocystis prophylaxis after bone marrow transplantation is inferior to other regimens and is associated with decreased survival and an increased risk of other infections. Biol Blood Marrow Transplant 2000; 6:35.


86. Dalianis T, Ljungman P. Full myeloablative conditioning and an unrelated HLA mismatched donor increase the risk for BK virus-positive hemorrhagic cystitis in allogeneic hematopoietic stem cell transplanted patients. Anticancer Res 2011; 31:939.


118. Hoyle C, Goldman JM. Life-threatening infections occurring more than 3 months after BMT. 18 UK Bone Marrow Transplant Teams. Bone Marrow Transplant 1994; 14:247.


Topic 1403 Version 8.0

GRAPHICS

Risk of infection following hematopoietic cell transplantation
Factors affecting risk of infection following hematopoietic cell transplantation

<table>
<thead>
<tr>
<th>Net state of immunosuppression</th>
<th>High risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underlying disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute myelogenous leukemia/aplastic anemia*</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Non-first remission malignancy*</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Chronic myelogenous leukemia, chronic phase</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Neutropenia³</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Graft failure</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>CD4 cytopenia &lt;200 cells/mcL³</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Glucocorticoids ≥1 mg/kg/day⁴</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Immunomodulating viruses³</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Age (in years)⁵</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>&gt;40°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;19</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Graft characteristics**

**HLA relatedness**

| Allogeneic matched unrelated | +         |
| Allogeneic mismatched related| +         |
| Allogeneic matched related   | +         |
| Autologous                   | +         |

**T cell depletion**

| Yes                           | +         |
| No                            |           |

**CD34 infused (autologous) X 10⁶/kg**

| <2.0                          | +         |
| >2.5                          | +         |

**Conditioning regimen, allogenic**

| Ablative                      | +         |
| Reduced intensity             | +         |

**Organ dysfunction**

<p>| Severe mucositis⁰             | +         |
| Renal failureα                | +         |
| Graft failureα                | +         |
| Graft-versus-host disease¹, grades II-IVα | + |
| Skin breakdown, breech in skin due to central venous catheter | + |
| Liver insufficiency           | +         |</p>
<table>
<thead>
<tr>
<th>Pathogen exposure</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endogeneous:</strong> reactivation of latent infection</td>
<td>+</td>
</tr>
<tr>
<td><strong>Exogeneous:</strong></td>
<td></td>
</tr>
<tr>
<td>Water/food/inanimate objects</td>
<td>+</td>
</tr>
<tr>
<td>Healthcare worker</td>
<td>+</td>
</tr>
<tr>
<td>Air</td>
<td>+</td>
</tr>
<tr>
<td>Donor infection</td>
<td>+</td>
</tr>
</tbody>
</table>

* Most important risk factors pre-engraftment.
¶ Most important risk factors post-engraftment.
◊ Risk is intermediate if age is between 19 and 40 years. Lowest risk is among children.
§ Graft-versus-host disease (especially chronic) and its therapy are major contributors to risk of infection.

_Courtesy of Elias J Anaissie, MD._
Graphic 70011 Version 5.0

**Effect of transplant characteristics on infectious risk in hematopoietic cell transplant recipients**

<table>
<thead>
<tr>
<th>Transplant parameter</th>
<th>Effect on host barriers and immunity</th>
<th>Infectious consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of transplant</td>
<td>Allogeneic: slower B and T cell immune reconstitution</td>
<td>Greater risk for infections of all types, but especially invasive fungal and herpesvirus infections; longer interval of risk</td>
</tr>
<tr>
<td>Type of allogeneic donor</td>
<td>Unrelated or mismatched donor: slower B and T cell immune reconstitution</td>
<td>Greater risk for infections of all types, but especially invasive fungal and herpesvirus infections; longer interval of risk</td>
</tr>
<tr>
<td>Type of stem cell graft</td>
<td>Peripheral blood: faster neutrophil engraftment, more chronic GVHD Cord blood: slower neutrophil engraftment, less GVHD, slower B and T cell immune reconstitution</td>
<td>Different risks for infections associated with neutropenia and GVHD</td>
</tr>
<tr>
<td>Stem cell graft manipulation</td>
<td>T cell depletion: greater risk for graft rejection, slower B and T cell immune reconstitution</td>
<td>Greater risk for neutropenic infections, lower risk for infections associated with chronic GVHD, greater and longer risk for herpesvirus and invasive fungal infections</td>
</tr>
<tr>
<td>Conditioning regimen</td>
<td>Intensive regimens: more mucosal injury, shorter time to neutropenia and longer period of neutropenia</td>
<td>Greater risk for neutropenic infections, especially neutropenic enterocolitis (typhlitis)</td>
</tr>
</tbody>
</table>
**Differential diagnosis of specific clinical syndromes after allogeneic hematopoietic cell transplantation**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Preengraftment, &lt;3 weeks</th>
<th>Immediate postengraftment, 3 weeks to 3 months</th>
<th>Late postengraftment, &gt;3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CNS manifestations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized</td>
<td>Bacteria, molds, <em>Candida</em> spp, stroke, drug toxicity</td>
<td>Bacteria, toxoplasmosis, molds, tumor relapse, drug toxicity</td>
<td>Bacteria, molds, PML, tumor relapse, drug toxicity, PRES</td>
</tr>
<tr>
<td>Diffuse</td>
<td>Bacteria, <em>HSV, Candida</em> spp, drug toxicity</td>
<td><em>HHV-6, CMV, Cryptococcus</em> spp, drug toxicity</td>
<td>VZV, drug toxicity</td>
</tr>
<tr>
<td>Ocular manifestations</td>
<td><em>Candida</em> spp, molds</td>
<td>CMV, <em>Pneumocystis jirovecii</em> (formerly <em>P. carinii</em>), toxoplasmosis</td>
<td>VZV, CMV</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>Bacteria, molds, respiratory viruses</td>
<td>Bacteria, molds, respiratory viruses</td>
<td>Bacteria, molds, respiratory viruses</td>
</tr>
<tr>
<td><strong>Mucositis, mucosal ulcerations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectious</td>
<td><em>HSV, Candida</em> spp, agents of mucormycosis</td>
<td><em>HSV, Candida</em> spp, agents of mucormycosis, CMV (esophagitis), <em>Aspergillus</em> spp (small or large intestine)</td>
<td><em>HSV, Candida</em> spp, agents of mucormycosis, CMV (esophagitis), <em>Aspergillus</em> spp (small or large intestine)</td>
</tr>
<tr>
<td>Other</td>
<td>GVHD, drug toxicity</td>
<td>GVHD, drug toxicity</td>
<td>GVHD, drug toxicity</td>
</tr>
<tr>
<td><strong>Pneumonia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

*Reproduced from: Wingard JR, Hsu J, Hiemenz JW. Hematopoietic stem cell transplantation: an overview of infection risks and epidemiology. Infect Dis Clin North Am 2010; 24:257. Table used with the permission of Elsevier Inc. All rights reserved.*

Graphic 98314 Version 1.0
<table>
<thead>
<tr>
<th>Condition</th>
<th>Microorganisms or Events</th>
<th>Diagnosis</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage, ARDS, hypersensitivity drug reaction, idiopathic interstitial pneumonitis, leukoagglutinin reaction, fluid overload, congestive heart failure</td>
<td>radiation pneumonitis, idiopathic interstitial pneumonitis, ARDS, hypersensitivity drug reaction, pulmonary VOD, congestive heart failure</td>
<td>CNS: central nervous system; PML: progressive multifocal leukoencephalopathy; PRES: posterior reversible encephalopathy syndrome; HSV: herpes simplex virus; HHV-6: human herpesvirus 6; VZV:</td>
<td></td>
</tr>
</tbody>
</table>

Graphic 50318 Version 5.0

**Phases of opportunistic infections among allogeneic hematopoietic cell transplant recipients**

<table>
<thead>
<tr>
<th>Phase I: Pre-engraftment</th>
<th>Phase II: Post-engraftment</th>
<th>Phase III: Late phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graft-versus-host-disease: Acute Chronic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia, barrier breakdown (mucositis, central venous access devices)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired cellular and humoral immunity; NK cells recover first, CD8 T cell numbers increasing but restricted T cell repertoire</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired cellular and humoral immunity; B cell &amp; CD4 T cell numbers recover slowly and repertoire diversifies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Bacterial**
- Gram-negative bacilli
- Gram-positive organisms
- Gastrointestinal *Streptococcus* species
- Encapsulated bacteria

**Viral**
- Herpes simplex virus
- Respiratory and enteric viruses (Seasonal/intermittent)
- Other viruses eg, HHV6
- EBV PTLD
- Varicella zoster virus

**Fungal**
- *Aspergillus* species
- *Candida* species
- *Pneumocystis*

Day 0

Day 15-45

Day 100

Day 365 and beyond

More common

Less common

EBV: Epstein-Barr virus; HHV6: human herpesvirus 6; PTLD: posttransplant lymphoproliferative disease.


Graphic 52716 Version 2.0

**Typical timing of infections among autologous hematopoietic cell recipients receiving antimicrobial prophylaxis**
# Pulmonary complications of allogeneic hematopoietic cell transplantation: Preengraftment

<table>
<thead>
<tr>
<th>Disease process</th>
<th>Risk factors</th>
<th>Associated manifestations</th>
<th>Radiographic findings</th>
<th>Useful diagnostic tests</th>
<th>Lung biopsy needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial pneumonia</td>
<td>Mucositis, neutropenia</td>
<td>Fever, cough, sputum</td>
<td>Usually focal consolidation; becomes diffuse in acute lung injury</td>
<td>Broad microbiologic testing; response to empiric antibiotics</td>
<td>Generally not</td>
</tr>
<tr>
<td>Fungal pneumonia</td>
<td>Prolonged neutropenia; exposure to endemic fungi; prior treatment for invasive fungus</td>
<td>Fever</td>
<td>Focal nodular and consolidative opacities, “halo sign,” “reverse halo sign”</td>
<td>Broad microbiologic testing including BAL; β-D-glucan of the blood; Aspergillus galactomannan EIA of the blood and BAL fluid; response to empiric antifungal therapy</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td>Impaired swallowing due to mucositis; opiate</td>
<td>Fever, dyspnea</td>
<td>Diffuse or focal ground glass or consolidative opacities</td>
<td>Cultures are often negative</td>
<td>No</td>
</tr>
</tbody>
</table>

### Risk factors

- **Herpes simplex virus**
- **Cytomegalovirus**
- **Varicella-zoster virus**
- **Gram-positive, gram-negative organisms**
- **Candida spp**
- **Pneumocystis jirovecii**

### Radiographic findings

- **Focal nodular and consolidative opacities, “halo sign,” “reverse halo sign”**
- **Diffuse or focal ground glass or consolidative opacities**

### Useful diagnostic tests

- **Broad microbiologic testing; response to empiric antibiotics**
- **Broad microbiologic testing including BAL; β-D-glucan of the blood; Aspergillus galactomannan EIA of the blood and BAL fluid; response to empiric antifungal therapy**
- **Cultures are often negative**
<table>
<thead>
<tr>
<th>Condition</th>
<th>Symptoms</th>
<th>Findings</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permeability pulmonary edema</td>
<td>Fever, dyspnea</td>
<td>Diffuse ground glass opacities</td>
<td>Normal BNP, normal LV function on echocardiogram</td>
</tr>
<tr>
<td>Cardiogenic pulmonary edema</td>
<td>Dyspnea, weight gain, peripheral edema</td>
<td>Perihilar opacities in butterfly distribution, septal thickening, pleural effusion, cardiomegaly</td>
<td>Elevated BNP; echocardiogram showing reduced LV function</td>
</tr>
<tr>
<td>Engraftment syndrome</td>
<td>Erythematous maculo-papular rash, fever &gt;38.3°C, weight gain</td>
<td>CT: bilateral ground-glass opacification, hilar or peribronchial consolidation, and thickening of interlobular septa</td>
<td>Skin biopsy; BAL to exclude infection</td>
</tr>
<tr>
<td>Hyperacute GVHD*</td>
<td>Rash, abdominal cramps, diarrhea, elevated bilirubin</td>
<td>Diffuse ground glass consistent with acute lung injury</td>
<td>Skin biopsy; BAL to exclude infection</td>
</tr>
<tr>
<td>Diffuse alveolar hemorrhage</td>
<td>CT: patchy or diffuse opacities, may have air bronchograms</td>
<td>BAL to exclude infection and to identify increasingly bloody return in sequential lavages and &gt;20 percent hemosiderin-laden macrophages</td>
<td>No</td>
</tr>
</tbody>
</table>

BAL: bronchoalveolar lavage; EIA: enzyme immunoassay; BNP: brain natriuretic protein; LV: left ventricular; CT: computed tomography; GVHD: graft-versus-host-disease; HLA: human leukocyte antigens; CTPA: computed tomography pulmonary angiogram.

* Hyperacute GVHD is very rare preengraftment, but may rarely occur at the time of engraftment and overlaps clinically with engraftment syndrome.

Graphic 83194 Version 2.0
<table>
<thead>
<tr>
<th>Disease process</th>
<th>Risk factors</th>
<th>Associated manifestations</th>
<th>Radiographic findings</th>
<th>Useful diagnostic tests</th>
<th>Lung biopsy needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial pneumonia</td>
<td></td>
<td></td>
<td>Focal or patchy consolidation, may be peribronchial Occasionally mass-like &quot;round-pneumonia&quot;</td>
<td>Blood cultures, Legionella and pneumococcal urinary antigens, BAL for Gram stain and aerobic and anaerobic cultures, Legionella culture, Mycoplasma PCR, and modified AFB stain and culture for Nocardia</td>
<td>Rarely</td>
</tr>
<tr>
<td>Mycobacterial pneumonia</td>
<td>Total body irradiation, chronic GVHD, M. haemophilum</td>
<td>M. haemophilum is associated with skin nodules and/or joint inflammation</td>
<td>Miliary pattern</td>
<td>TST after HCT not helpful; AFB staining and cultures of induced sputum and BAL are helpful</td>
<td>Rarely</td>
</tr>
<tr>
<td>CMV pneumonitis</td>
<td>Seropositive recipient with seronegative donor; delayed reconstitution, prior treatment for CMV</td>
<td>CT; patchy or diffuse ground-glass opacities, patchy consolidation, small nodular opacities; rarely tree-in-bud pattern</td>
<td></td>
<td>Serology, blood test for pp65 antigen or CMV PCR, BAL and endobronchial brush for cytologic examination for inclusion bodies and BAL shell vial cultures for CMV</td>
<td>Rarely</td>
</tr>
<tr>
<td>Respiratory viruses</td>
<td>Exposure to someone with active viral infection</td>
<td>URI symptoms prior to onset of lower respiratory tract symptoms</td>
<td>Diffuse ground glass opacities are the most common</td>
<td>PCR, culture, or rapid immunofluorescence of nasopharyngeal lavage or swab and BAL fluid</td>
<td>Sometimes to completely exclude other possibilities</td>
</tr>
<tr>
<td>Fungal infection (eg, invasive aspergillosis, Fusarium, agents of mucormycosis, Candida, Scedosporium, Pneumocystis)</td>
<td>Presence and severity of GVHD, older patient age, cytopenia, CMV infection</td>
<td></td>
<td>Focal nodular and consolidative opacities, &quot;halo sign,&quot; &quot;reverse halo sign,&quot; sometimes subpleural</td>
<td>Broad microbiologic testing of blood and BAL; blood tests for β-D-glucan and Aspergillus galactomannan EIA; BAL for Aspergillus galactomannan</td>
<td>Sometimes when cultures are negative and no response to initial therapy</td>
</tr>
<tr>
<td>Condition</td>
<td>Cause</td>
<td>Radiographic Findings</td>
<td>Laboratory Findings</td>
<td>Biopsy/Treatment</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>----------------------------------------------------------</td>
<td>-------------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Idiopathic pneumonia syndrome</td>
<td>Busulfan, high dose cyclophosphamide, radiation, nonmyeloablative conditioning regimen</td>
<td>Extensive opacities</td>
<td>Negative stains, cultures, antigen testing, and PCR of blood, sputum, urine, and BAL.</td>
<td>Yes, either transbronchial or surgical</td>
<td></td>
</tr>
<tr>
<td>Diffuse alveolar hemorrhage</td>
<td>Underlying mucopolysaccharidosis</td>
<td>CT: patchy or diffuse opacities, may have air bronchograms</td>
<td>BAL showing increasingly bloody return in sequential lavages and &gt;20 percent hemosiderin-laden macrophages</td>
<td>Not usually</td>
<td></td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>Myeloablative conditioning regimen</td>
<td>Extrapulmonary manifestations such as dry mouth/dry eyes, joint pain/swelling, muscle weakness</td>
<td>CT: subpleural, ground-glass opacities; septal thickening</td>
<td>Autoantibody tests positive; often to identify specific type of interstitial pneumonitis</td>
<td></td>
</tr>
<tr>
<td>Cryptogenic organizing pneumonia/organizing pneumonia (formerly known as bronchiolitis obliterans organizing pneumonia)</td>
<td>Irradiation, CMV infection, HCT associated connective tissue disease, chronic GVHD</td>
<td>CT: patchy airspace consolidation, ground-glass opacities, small nodular opacities, &quot;reverse halo sign&quot;</td>
<td>Lung biopsy</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Bronchiolitis obliterans</td>
<td>Chronic GVHD, postviral</td>
<td>CT initially clear; as progresses, CT may show mosaic ground glass opacities and bronchiectasis</td>
<td>Spirometry showing airflow limitation, Skin biopsy for GVHD</td>
<td>Sometimes, if diagnosis uncertain</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>Underlying lymphoma, EBV infection in posttransplant lymphoproliferative disorder</td>
<td>Nodular opacities, lymphangitic pattern</td>
<td>BAL cytology and flow cytometry, biopsy</td>
<td>Biopsy usually needed</td>
<td></td>
</tr>
<tr>
<td>Pulmonary alveolar proteinosis</td>
<td>HCT for myeloid disorder</td>
<td>Perihilar opacities in a &quot;bat-wing&quot; distribution often with air bronchograms</td>
<td>Bronchialveolar lavage showing characteristic milky appearance and positive stain for lipoproteins</td>
<td>Not usually</td>
<td></td>
</tr>
<tr>
<td>Pulmonary cytolytic thrombi</td>
<td>Chronic GVHD is a risk factor</td>
<td>Low grade fever, cough</td>
<td>CT: peripheral nodules</td>
<td>BAL to rule out infection; lung biopsy</td>
<td>Yes, findings are basophilic cytolytic thrombi in the small to medium distal pulmonary vessels with entrapped monocytes</td>
</tr>
<tr>
<td>Pulmonary veno-occlusive disease</td>
<td>Onset after first 100 days, chronic GVHD</td>
<td>Reduced DLCO</td>
<td>CXR: pleural effusion and Kerley B lines; CT chest: centrilobular ground glass opacities; no emboli on CTPA</td>
<td>Right heart catheterization; BAL showing occult hemorrhage</td>
<td>For definitive diagnosis</td>
</tr>
<tr>
<td>Drug toxicity</td>
<td>History of pneumotoxic drug use (eg, busulfan, cyclophosphamide)</td>
<td>May be associated with rash, peripheral eosinophilia</td>
<td>Varied</td>
<td>Increased BAL eosinophils may be seen; other processes excluded by negative blood and BAL stains and cultures, negative fungal studies</td>
<td>Sometimes to completely exclude other possibilities</td>
</tr>
<tr>
<td>Radiation pneumonitis</td>
<td>History of radiation therapy involving lungs</td>
<td>Acute: onset usually 4 to 12 weeks following irradiation Late: onset after 6 to 12 months</td>
<td>Acute CT: ground-glass attenuation within the area of irradiated lung Late CT: linear opacities (scarring) or an area of dense consolidation and</td>
<td>Other processes excluded by negative blood and BAL stains and cultures, negative fungal studies</td>
<td>Sometimes to completely exclude other possibilities</td>
</tr>
</tbody>
</table>
Selection of specific diagnostic tests is based on clinical features and results of prior testing. BAL: bronchoalveolar lavage; PCR: polymerase chain reaction; AFB: acid-fast bacillus; GVHD: graft-versus-host disease; TST: tuberculin skin test; HCT: hematopoietic cell transplantation; CMV: cytomegalovirus; CT: computed tomography; URI: upper respiratory infection; EIA: enzyme immunoassay; EBV: Epstein-Barr virus; DLCO: diffusing capacity for carbon monoxide; CXR: chest radiograph; CTPA: computed tomography pulmonary angiography.