

Chapter 12

Infections in Leukemia and Hematopoietic Stem Cell Transplantation

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Abstract Infections are one of the most common complications in patients diagnosed with leukemia and serve as a major obstacle to treatment. Through the early 1970s, infections were the most common cause of death in patients diagnosed with acute leukemia, but improvement in treatment and supportive care over the past few decades, coupled with expanded prophylaxis and prevention regimens, have led to reduction in both the frequency and severity of infections. Regardless, due in part to an aging cancer population and the diversity of cancer treatments and procedures, infectious diseases remain a major cause of morbidity and mortality in patients with leukemia.

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Introduction

Infections are one of the most common complications in patients diagnosed with leukemia and serve as a major obstacle to treatment [1]. Through the early 1970s, infections were the most common cause of death in patients diagnosed with acute leukemia [2, 3], but improvement in treatment and supportive care over the past few decades, coupled with expanded prophylaxis and prevention regimens, have led to reduction in both the frequency and severity of infections [4–6]. Regardless, due in part to an aging cancer population and the diversity of cancer treatments and procedures, infectious diseases remain a major cause of morbidity and mortality in patients with leukemia.

Leukemia is associated with marked alterations in humoral and cellular immunity which enhance the ability of microorganisms to evade detection and destruction. As the bone marrow is replaced with malignant cells, myeloid and lymphoid cell production fall, and those available have weakened responses to pathogens. Peripheral leukocytes in patients with acute leukemia have impaired phagocytosis [7, 8] which can lead to increased risk of bacterial and fungal infections, while chronic leukemias demonstrate reduced immunoglobulin production [9, 10]. Due to these immune deficits, it is not uncommon for infections to be a primary reason for patients to seek care, and uncontrolled or uncommon infections are known to portend an undiagnosed hematologic malignancy [11].

In addition to direct effects, treatment leads to further decrements in the ability of patients to fight infection. Chemotherapy-associated marrow toxicity is unavoidable, and neutropenia and/or lymphopenia is nearly universal during therapy for acute leukemia. Protracted periods of agranulocytosis and delayed recovery of adaptive immunity are more common following aggressive therapy for relapsed disease and/or conditioning prior to hematopoietic cell transplantation (HCT) [12–14]. Furthermore, alterations in normal gut flora [15], destruction of mucosal barriers [16, 17], transfusion-associated iron overload [18], and loss of skin integrity further increase the risk of infection. All told, the multiple negative effects of therapy further compromise the immune response, placing these patients at added risk for severe and life-threatening infections.

The development of prophylactic strategies for viral [6, 19, 20] and bacterial infections [4], as well as broad-spectrum antifungals [21, 22], has improved prevention and treatment options for these high-risk patients. Novel laboratory techniques, such as molecular diagnostics for viral infections [23], have also allowed for earlier detection of major infections [24]. Hematologic support through the use of colony-stimulating factors has helped to shorten neutropenia and further limit infectious complications [25]. However, even as diagnostic and therapeutic options have evolved, novel treatment options for leukemia, biologic immune-modulating

therapies, expanded transplant protocols for high-risk patients, and alternate stem cell donor sources have led to additional immune dysfunction and infectious risk. Not surprisingly, prevention regimens have also led to the emergence of drug-resistant pathogens [26–30], many of which are associated with increased infection-related mortality.

In this chapter, we review the most prevalent infections seen in leukemia, but we will focus primarily on transplant-associated infections. We review timing of infections and then common infections by organ systems. We also discuss the management of neutropenic fever and assess important prevention strategies. This chapter should serve as a reference for clinicians on common infectious complications; however, the sheer number of potential infections is too large to allow for a comprehensive review. In addition, when addressing this topic, there is a large variation on the strength of clinical evidence in the literature. Randomized clinical trials evaluating treatment and prevention of infections, for example, are the strongest for cytomegalovirus (CMV) and fungal infections, but the majority of data are based either on retrospective clinical studies or on expert opinion. In this overview, we do not address the strength of evidence and instead refer you to more comprehensive guidelines and reviews whenever possible throughout the chapter [31, 32]. Finally, when providing care for these complex patients, we recommend close collaboration with colleagues in Infectious Diseases, Pulmonary/Critical Care, Surgery, and with local Clinical Microbiology and Virology laboratories.

Timing of Infections (Reviewed in Reference [31])

Pretransplant/Preinduction

Patients with underlying leukemia are at high risk for infections, and many present to primary care providers with infections as the first sign of their underlying hematologic malignancy. Prolonged neutropenia prior to transplant has also been shown to be a predictor of posttransplant infectious risk and mortality [33]. Providers must assess patients at presentation for infection symptoms such as recurrent fevers, chronic cough, skin nodules, or upper respiratory symptoms prior to starting treatment, and all patients with infectious symptoms should undergo pretransplant evaluation. Some infections may even require delay in transplant conditioning (e.g., respiratory syncytial virus [RSV]) [34–36]. All patients should also have standard pretransplant serologic testing as recommended in updated guidelines [31].

Preengraftment (Days 0–15)

During the early period postchemotherapy and conditioning, patients have abnormalities in barrier and innate responses which dramatically increase the risk of

infection. Significant mucositis, long-term catheters, and prolonged periods of hospitalization all increase risk. Early bacterial infections are typically associated with mucositis, such as *Streptococcus* species and enteric gram-negative rods (GNRs), or related to central catheters. Viral infections are infrequent in the early preengraftment phase, except for HSV and HHV-6, which commonly occur in this time frame. Respiratory pathogens are less frequent during this period due to the more limited outpatient exposure. Patients are at high risk for *Candida* and invasive moulds during this period [31].

Postengraftment (Days 16–100)

In this period after neutrophil recovery, adaptive and humoral immune responses remain impaired [31]. Patients continue to be at risk for bacteremia with gram-positive and GNR organisms, but viral and fungal infections become more prominent. Cytomegalovirus (CMV) usually occurs in weeks 3–4, and EBV in the second and third months posttransplant [37]. Respiratory viral infections increase in frequency with the move to more outpatient therapy. *Aspergillus*, *Candida*, and other fungal infections continue through the postengraftment phase due to the development of graft-versus-host disease (GVHD) and associated treatments.

Late Period (Days 100–1 Year)

After day 100, patients more commonly develop infections with encapsulated (e.g., *Streptococcus pneumoniae*) and community-acquired bacterial infections. Respiratory viruses remain major pathogens. Late T-cell recovery and lymphopenia also allow for continued development of CMV and other viral-related complications. Varicella-zoster virus (VZV) reactivation primarily occurs as a late complication [37]. Late fungal infections occur in patients with ongoing GVHD issues. *Pneumocystis jiroveci* (PCP) occurs in posttransplant patients not receiving appropriate PCP prophylaxis.

Infections by Organ System

Empiric therapy for neutropenic fever during leukemia treatment and transplantation is reviewed in detail in other sources [31, 32, 39]. In order to address the multiple possible infections that can occur during treatment for leukemia, we have divided infections into specific organ systems (Fig. 12.1). In this section, we focus on clinical signs/symptoms, differential diagnosis, and diagnostic strategies, followed by a brief review of treatment options.

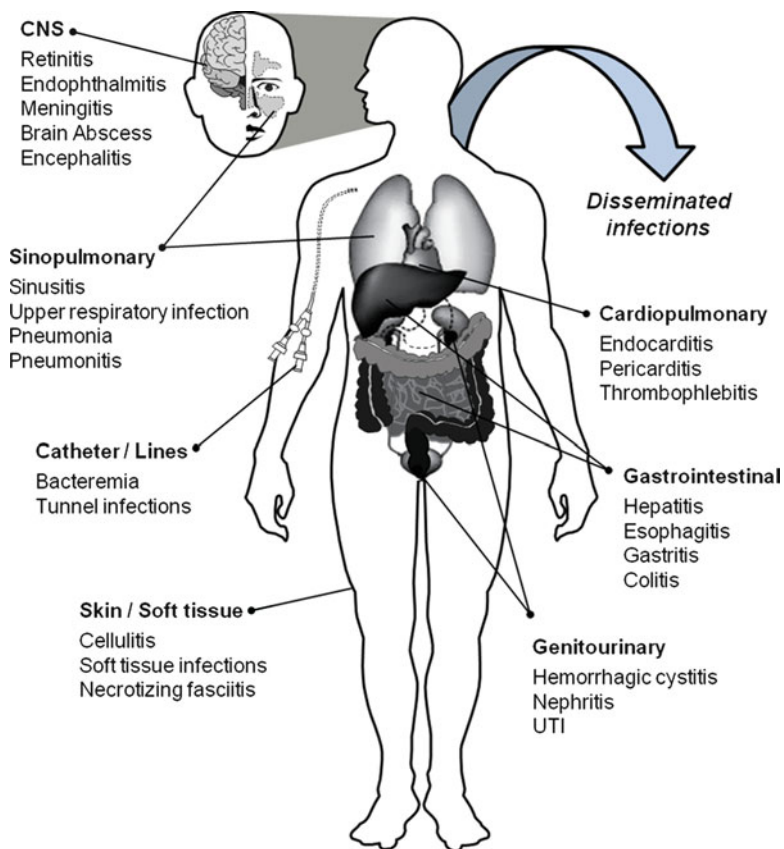


Fig. 12.1 Locations and types of common infections in leukemia and transplant recipients (*Figure drawn by Kyoko Kurosawa*)

Line-Associated and Bloodstream Infections

Signs and Symptoms

Patients who develop bloodstream infections present with a wide spectrum of symptoms which vary from asymptomatic (usually detected by surveillance cultures) [40] to fulminant septic shock. Patients with bloodstream infections are usually febrile, but fever may be masked in some patients on immunosuppression, particularly those on high-dose steroids. Hypothermia is an infrequent presentation. Careful examination of the central venous catheter (CVC) may provide visual clues that suggest infection, such as erythema or purulence around the line or exit site; some patients may complain of chest wall pain or numbness at sites of catheter placement. A thorough skin exam is also important, as some patients develop skin

nodules, ecthyma gangrenosum, or other lesions during episodes of bacteremia [41, 42] or fungemia [43, 44]. The development of hypoxia, renal insufficiency, and liver function abnormalities are ominous signs of developing septic shock and multiorgan failure.

Differential Diagnosis

Bacterial

Central lines can be a source for infection for leukemia patients, but more frequently, patients can develop infections due to the breakdown of mucosal barriers. Once bacteria gain access to the bloodstream, either through mucosal breakdown or through central catheters, they adhere to synthetic material by developing complex biofilms. These foreign bodies can thus become foci for infections and allow bacteria to escape immune control [45] without altering their pathogenicity [46]. Neutropenia and innate immune dysfunction following postinduction therapy and transplantation may also help facilitate biofilm formation [47–49]. The development of mucositis and GVHD facilitates bacterial translocation and increases the risk for bloodstream infections [50].

Guidelines for line-associated infections and specific recommendations for transplant recipients are reviewed in greater detail in other sources [31, 51]. Line-site and bloodstream infections occur during therapy for leukemia; they occur most commonly during the first week after line placement and during neutropenia and in patients with GVHD [52]. The majority of cases are due to chemotherapy-associated bacterial translocation from mucosal sites. Most early infections in these patients are caused by gram-positive organisms; however, GNRs are not infrequent in patients with severe mucositis or lower gastrointestinal GVHD. GNR resistance to prophylactic antibiotics is increasing [43, 54]. Nontuberculous mycobacteria (NTM) are a rare cause of tunnel- and line-associated infections; line removal is required for cure [55].

Specific gram-positive bacterial species are commonly associated with leukemia therapy and transplantation. Coagulase-negative *Staphylococcus* species (CoNS) are the most common cause of bacteremia in most studies [54, 56–59]. *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]) is associated with the development and treatment of GVHD and with significantly more morbidity than CoNS [60]. *Streptococcus viridans* bacteremia often occurs following conditioning and can be associated with the development of septic shock, multiorgan failure, and death [61–63]. Leukemic patients are at high risk for *S. pneumoniae* and may be more likely to develop invasive complications [64–66]. *Enterococcal* species, particularly vancomycin-resistant *Enterococcus* (VRE), are a major problem in patients with leukemia and transplantation and are an increasing cause of bacteremia [67, 68]. Risk is increased with prolonged hospitalization, high-dose steroids, gut GVHD, prior cephalosporin therapy, and prior VRE colonization [68, 69].

Less frequent gram-positive species such as *Corynebacterium jeikeium* can also cause disease in this population [70].

A variety of GNR organisms cause bloodstream infections, but *Pseudomonas aeruginosa* remains one of the most important GNRs. *P. aeruginosa*'s intrinsic virulence leads to additional mortality, and it is often associated with high-level resistance [71, 72]. *Stenotrophomonas maltophilia* is resistant to carbapenems and other standard neutropenic treatment options and is often preferentially selected in this population [73–75]. With the continued emergence of multidrug-resistant GNR pathogens, providers need to be cautious in choosing empiric regimens [52, 72] as these organisms are associated with prolonged bacteremia and increased morbidity and mortality [76]. Due to bacterial translocation during episodes of severe mucositis and gut GVHD, enteric GNRs and gram-positive clostridial species are more frequent. In particular, *C. perfringens* bacteremia can lead to severe life-threatening intravascular hemolysis [77], and *C. septicum* bacteremia is associated with gastrointestinal complications [78].

Fungal

Candida species can also lead to bloodstream infections, particularly in patients who either are receiving broad-spectrum antibiotics or have clinically significant mucositis [79]. *Candida* species that are detected in patients receiving antifungal prophylaxis are more likely to be resistant species, particularly *C. krusei* and *C. glabrata* [79, 80]. Data suggest that rates of candidemia may be decreasing [81]. Other yeasts, such as *Rhodotorula* [78], are a less frequent cause of bloodstream infections.

Although moulds can spread hematogenously, they are rare causes of bloodstream infections [82, 83]. *Fusarium*, however, are the one mould species that routinely can present with fungemia [84]. Typical “banana-shaped” conidia seen on gram stain from blood cultures are pathognomonic for fusariosis. At sites of skin breakdown, fungal infections can invade damaged tissue, so exit infections can sometimes be caused by fungal pathogens [85, 86].

Diagnostics

Blood cultures are the mainstay of any work-up for patients suspected of having an infection. It is recommended that patients with central catheters have cultures drawn from their lines; peripheral cultures should also be drawn if possible [51]. A meta-analysis found that line cultures were a better diagnostic test for bacteremia with better sensitivity and negative predictive value when compared to a peripheral culture [87]. Current guidelines suggest that if a peripheral culture is not possible, it is recommended that ≥ 2 blood samples should be drawn from each catheter lumen [51, 88]. Differential time to positivity and quantitative blood cultures are other

techniques to help identify catheter-associated infections that are beyond the scope of this chapter but are reviewed elsewhere [89–91].

Line tips should be sent for culture at the time of removal if at all possible [51]. Skin biopsies can also be helpful in patients with suspicious skin lesions in some infections [70].

Treatment

Treatment options vary by pathogen and site (see Table 12.1). Tunnel infections require line removal [51], but exit-site infections can sometimes be managed with antibiotic therapy, particularly if they are not associated with bacteremia. Exit-site infections that do not improve with systemic antibiotic therapy should lead to line removal [51]. Antibiotic therapy for any bloodstream infections should be based on culture and sensitivity testing, and patients should have repeat cultures to assure that the organism has cleared. Most bacterial infections require at least 2 weeks of IV therapy, but some pathogens (e.g., *Listeria monocytogenes*) may need more prolonged courses. Patients with NTM should be treated for at least 3 months with a combination of at least 2–3 agents [55]. Patients with candidemia should be treated with fluconazole, lipid amphotericin B formulations, or an echinocandin, and any central catheter should be removed [92]. All patients with candidemia should undergo an ophthalmologic evaluation. Recommendations regarding the management of *Candida* infections are reviewed in reference by Pappas et al. [92]. Decisions regarding tunneled line or port removal should be done in collaboration with Infectious Diseases, Interventional Radiology, or Surgery and are reviewed by Mermel [51].

Central Nervous System

Signs and Symptoms

Patients undergoing HCT and those who are receiving leukemia therapy are more likely to have neurologic complications [93]. Up to 30% of patients undergoing HCT can develop delirium during follow-up, with the nearly half occurring in the first 4 weeks posttransplant [94]. Infections may present with symptoms that are subtle (e.g., mild confusion) and rarely may be asymptomatic [95]. More common manifestations are headache, memory loss, focal weakness, or imbalance. Patients with eye infections can present with visual loss, eye pain, proptosis, changes in ocular movements (e.g., cranial nerve dysfunction), pupillary changes, or periorbital edema, all of which should lead to urgent ophthalmologic evaluation.

While certain symptoms such as anterograde amnesia [96] and personality changes [97] are classically associated with specific infections (HHV-6 and HSV, respectively), symptoms are not diagnostic of the underlying disorder. Patients with

Table 12.1 Treatment options for selected pathogens*

Pathogen	Treatment		Prevention	Notes
	First line	Second line		
Bacterial				
<i>S. epidermidis</i>	IV vancomycin	IV daptomycin or linezolid	–	–
<i>S. aureus</i>				
Methicillin sensitive	IV nafcillin	IV ceftazolin	• Nares swab for MRSA	• Infection control
MRSA	IV vancomycin	IV daptomycin or linezolid	• Nares swab for MRSA screening	
<i>Enterococcus</i> species				
Non-VRE†	IV ampicillin +/- gent		–	–
VRE	or IV vancomycin			
	IV daptomycin or linezolid	IV quinupristin/dalfopristin‡	• Pretransplant rectal screening	• Infection control
<i>Viridans strep.</i>	IV vancomycin	IV penicillin	• Penicillin or vancomycin preemptively during periods of high risk	• Caution for resistance to fluorquinolones in centers that use as prophylaxis for neutropenia
<i>C. jeikeium</i>	IV vancomycin	–	–	–
<i>L. monocytogenes</i>	IV ampicillin	–	• Avoid high-risk foods	–
<i>S. maltophilia</i>	IV TMP/S	Varies	–	–
<i>P. aeruginosa</i> and other GNR	Varies	Varies	• Fluoroquinolone prophylaxis for neutropenic fever	• Empiric treatment should be based on institutional antimicrobial rate of resistance
<i>Nocardia</i> species	IV TMP/S	IV imipenem	• TMP/S prophylaxis	• Patients with CNS disease should likely receive dual therapy initially
<i>C. difficile</i>	Metronidazole (IV or oral [preferred])	Vancomycin (oral)	–	• Treatment should be based on sensitivity testing
				• Oral vancomycin may have better outcomes in severe infections
				• Infection control

(continued)

Table 12.1 (continued)

Pathogen	Treatment		Prevention	Notes
	First line	Second line		
Fungal				
<i>Aspergillus</i> species	Voriconazole (IV or oral) or IV amphotericin B ^s	Posaconazole (oral)	• Posaconazole prophylaxis	• Benefits of combination therapy are not clear
<i>Mucorales</i> species	IV Amphotericin B ^s or posaconazole (oral)	–	–	• Benefits of combination therapy are not clear • Treatment should be based on sensitivity testing when possible • Unclear if posaconazole or IV amphotericin is the best first choice
<i>Candida</i> species				
Azole sensitive	IV fluconazole	IV echinocandins	• Fluconazole prophylaxis	• Azole-resistant strains are more likely in patients receiving fluconazole or other azole prophylaxis
Azole resistant	IV echinocandins	IV amphotericin B ^s	–	–
<i>P. jiroveci</i>	IV TMP/S	IV clarithromycin/ primaquine (oral) or IV pentamidine	• Oral TMP/S, dapsone, or atovaquone prophylaxis	–
Viral				
Cytomegalovirus	IV ganciclovir	IV foscarnet or cidofovir	• Surveillance and preemptive therapy • High-dose acyclovir prophylaxis	• Patients with ganciclovir-resistant strains should receive foscarnet
EBV	IV rituximab	–	• Preemptive screening in high-risk patients	–
HSV/NZV	IV acyclovir	IV foscarnet	• Oral acyclovir/ valacyclovir prophylaxis	–
HHV-6	IV foscarnet or IV ganciclovir	–	–	–

Adenovirus	IV cidofovir	Ribavirin (oral or IV)	<ul style="list-style-type: none"> • Preemptive screening in high-risk patients 	<ul style="list-style-type: none"> • IV ribavirin only available through FDA EIND • T-cell immunotherapy can be considered if available • Developing resistance has been reported to oseltamivir • Combination therapy can be considered in high-risk patients • Infection control • Use of palivizumab in adults is unclear but may provide benefits in severely ill patients IVIG may also be considered in high-risk cases. • Infection control
Influenza A and B	Oseltamivir (oral)	Zanamivir (inhaled)	<ul style="list-style-type: none"> • Vaccination 	
RSV	Ribavirin (inhaled) +/- IV palivizumab for treatment of lower tract disease	–	<ul style="list-style-type: none"> • Seasonal palivizumab prophylaxis in high-risk children • Inhaled ribavirin is thought to prevent development of lower tract disease (prophylaxis) in high-risk patients 	
Other infections				
<i>T. gondii</i>	Pyrimethamine (oral) + IV sulfadiazine + folic acid	TMP/S(oral or IV) or clindamycin (oral of IV) w/pyrimethamine (oral) + folic acid	<ul style="list-style-type: none"> • TMP/S prophylaxis • Dapsone prophylaxis +/- pyrimethamine • Consider surveillance in high-risk patients 	<ul style="list-style-type: none"> • Other PCP prevention agents and low-dose TMP/S are not as effective at preventing
<i>Strongyloidiasis</i>	Ivermectin (oral)	Albendazole (oral)	<ul style="list-style-type: none"> • Pretransplant serology and evaluation • Consider pretransplant empiric treatment if patient considered from high-risk area 	–

Abbreviations: IV, intravenous; MRSA, Methicillin-resistant *Staphylococcus aureus*; VRE, Vancomycin-resistant Enterococcus; TMP/S, Trimethoprim/Sulfamethoxazole; GNR, Gram negative rods; CNS, Central Nervous System; EBV, Epstein-Barr virus; HSV, Herpes simplex virus; VZV, Varicella zoster virus; HHV-6, Human herpesvirus-6; FDA, Federal Drug Administration; EIND, Emergency Investigational Drug Authorization; RSV, Respiratory syncytial virus; IVIG, intravenous immunoglobulin. *These are based on standard recommendations. All decision regarding therapy should be developed based on current clinical practice, resistance testing and institutional policies. † non-VRE Enterococcus are not always sensitive to Ampicillin, so decisions regarding first line therapy should be based on sensitivity testing. ‡ Only effective against *E. faecium* (*E. faecalis* intrinsically resistant). §Typically use lipid formulations of Amphotericin B to reduce side effects. ¶Includes caspofungin, micafungin, and anidulafungin.

more severe infections can present with more ominous symptoms such as seizures, encephalitis, or focal weakness. Perhaps most importantly, fever may not always be present to suggest an infectious etiology [98, 99]. Since these patients have numerous noninfectious etiologies that can lead to CNS dysfunction, it is even more important to aggressively pursue a diagnosis.

Differential Diagnosis

Bacterial

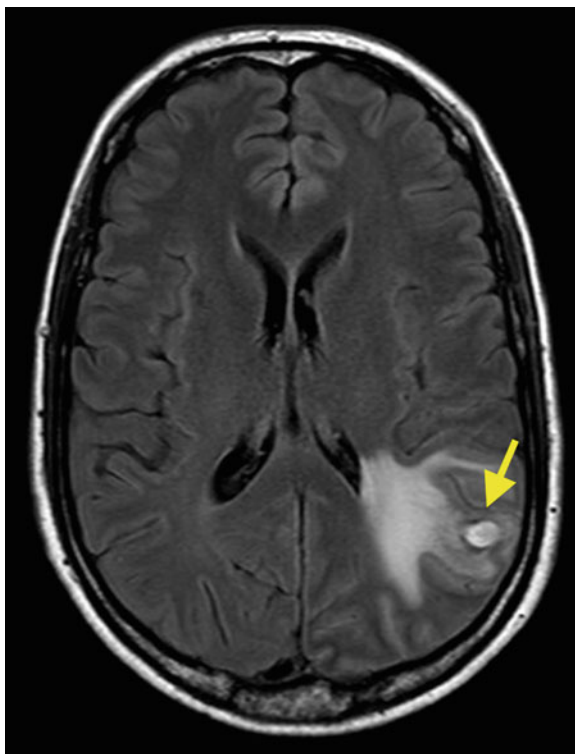
Bacterial infections are a relatively uncommon cause of CNS infections in an age where prophylactic antibiotics are standard practice. Gram-negative and gram-positive organisms can get into the CNS and lead to meningitis during treatment, and although rare, resistant bacteria may be more common due to prior antibiotic exposure. Community-acquired meningitis caused by bacteria such as *S. pneumoniae* is infrequent, but due to alterations in humoral immunity, emerging microbial resistance and a move to more outpatient care can occur late posttransplant and during periods of treatment for GHVD [100, 101]. *Rothia mucilaginosa*, a gram-positive organism that is a commensal organism in oral flora, is associated with a rare, but severe, meningitis that occurs almost exclusively during periods of severe mucositis [102]. Central line-associated bacteremia rarely leads to ophthalmic infection causing sight-threatening endophthalmitis or brain involvement [103, 104], and even less frequently, bacteria can gain access through intracranial interventions such as Ommaya port placement [105].

Some bacteria have a known predilection for the CNS and may not be addressed by standard prophylaxis strategies. *Listeria monocytogenes* is a non-spore-forming gram-positive rod that is most commonly acquired as a food-borne illness with a particular penchant for involving the CNS [106]. Nearly 50% of immunocompromised patients who develop listeriosis develop CNS disease [107], which can present as acute cerebritis or brain abscesses (Fig. 12.2). *Nocardia* species are filamentous bacteria that usually lead to pulmonary infections, of which over 30% develop CNS lesions; most commonly single or multiple abscesses. Many with CNS involvement are asymptomatic at the time of diagnosis, so routine brain imaging is recommended in all patients diagnosed with *Nocardia* [108].

Fungal

Cryptococcus neoformans is a cause of meningitis in immunocompromised hosts and leads to occasional infections in leukemic patients [109]. Fluconazole prophylaxis has limited this infection, but late disease can occur in transplant recipients. Similarly, *Candida* species ophthalmic infections (endophthalmitis or retinitis) can occur in leukemia patients undergoing chemotherapy or transplant, but CNS infections are almost universally associated with systemic fungemia. Resistant species, such as *C. krusei* and *C. glabrata*, should be considered in patients who develop CNS involvement while on prophylactic therapy [110].

Fig. 12.2 Patient presented with fever, seizures, dysarthria, and right-sided weakness. An MRI of the brain demonstrated an abscess (yellow arrow) with surrounding edema. Blood cultures were positive for gram-positive rods which were later identified to be *Listeria monocytogenes*. Symptoms improved after institution of ampicillin and gentamicin therapy. The patient improved after a prolonged course of antibiotics



Mould infections, particularly *Aspergillus* species, can also lead to serious and life-threatening CNS infections. Involvement of the CNS usually develops from a primary pulmonary source, through hematogenous spread or through direct invasion from involved sinuses. Mould infections primarily lead to space-occupying lesions, but can also present as cerebral infarctions or meningitis [111, 112]. Retrospective reviews of brain abscesses in transplant patients suggest that *Aspergillus* is the most common cause [99, 113, 114] and that fungal etiologies make up close to 90% of episodes [113, 114]. While *Aspergillus* may be the most common fungus, CNS infection can also be caused by other opportunistic moulds such as the *Mucorales* (*zygomycetes*) species [115, 116] and *Scedosporium* [117]. Rhinocerebral involvement and cavernous sinus involvement are unique presentations nearly always associated with the *Mucorales* [118]. Endemic moulds, such as *Histoplasma capsulatum* [119] and *Coccidioidomycosis immitis* [120], are infrequent and develop only in patients with travel or residence in areas of endemicity [121–123].

Viral

Latent viruses can cause CNS-related disease, particularly in patients undergoing HCT [124]. During the early posttransplant period, HHV-6 is the most common viral cause of CNS infection [94, 124]. HHV-6 reactivation usually occurs between 2 and

4 weeks posttransplant, and symptoms can range from mild delirium and cognitive dysfunction to seizures and encephalitis [125]. Varicella-zoster virus (VZV) is another neurotropic virus primarily associated with encephalitis, though vasculopathy can also be associated with CNS involvement [126]. Interestingly, although VZV reactivation usually presents with prominent skin involvement (herpes zoster), patients with CNS disease may present without rash [127, 128]. Herpes simplex (HSV) encephalitis can also occur in leukemia and transplant recipients, though patients are more likely to present with personality changes and focal abnormalities [129]. Additionally, both HSV and VZV can present with involvement in the otic branch presenting with unilateral facial paralysis, ear pain, and vesicles in the auditory canal and auricle (Ramsay Hunt syndrome) [130, 131]. CNS involvement of both VZV and HSV usually occurs only after the discontinuation of prophylactic acyclovir; such prophylaxis has not been shown to prevent HHV-6. Other latent herpesvirus infections, such as Epstein-Barr virus (EBV) [132] and cytomegalovirus (CMV) [133, 134], can also cause CNS disease and, in EBV's case, can be associated with both encephalitis and posttransplant lymphoproliferative disorder (PTLD) [37, 135].

The polyomaviruses, particularly JC virus, are less frequent CNS pathogens in this population. JC virus is the causative agent of progressive multifocal leukoencephalopathy (PML), which occurs late in the posttransplant period and presents with focal neurologic findings and altered mental status as a result of white matter demyelination [136–138]. Other viral pathogens such as West Nile virus [139, 140] and enteroviruses [141] cause sporadic cases of CNS disease.

Other Infections

Toxoplasmosis is most commonly found in patients who are seropositive prior to starting therapy [142], but has been rarely reported in patients who were seronegative [143, 144]. When toxoplasmosis does develop in the posttransplant period, nearly all cases are associated with CNS involvement [144]. Symptoms are varied, diagnosis is difficult, and outcomes are very poor [144, 145]. *Strongyloides stercoralis* hyperinfection, which occurs from a reactivation of a clinically silent infection, can lead to a polymicrobial meningitis and direct parasite invasion into the CNS [146, 147]. Patients with prior exposure to areas of high endemicity of *Strongyloides* are at risk, but this is a rare complication.

Diagnostics

The mainstay of any work-up for CNS-related symptoms is first and foremost a thorough neurologic exam. Early findings can be subtle and missed on cursory review, but a focal neurologic exam can identify subtle cranial nerve abnormalities, unsuspected confusion, and/or focal weakness. It is important to pay special attention

to the oropharynx, sinuses, auditory canals, and nasal passageways, as lesions in these locations (e.g., a black eschar or vesicles) can suggest either a route of infection and/or a specific pathogen. Patients with nuchal rigidity, mental status changes, fever, and other classic signs for bacterial meningitis should be considered for urgent lumbar puncture and empiric antibiotics to avoid major delays in treatment.

Radiologic imaging is critical to assessing high-risk immunocompromised patients, as clinical symptoms vary in these patients. Both computed tomography (CT) and magnetic resonance imaging (MRI) provide important diagnostic data; an MRI provides better resolution, but CT scans are often more readily available. Radiologic imaging can evaluate for space-occupying lesions or evidence of increased intracranial pressure which would preclude cerebrospinal fluid (CSF) analyses. Specific radiologic manifestations of certain infections, such as herpes simplex (temporal lobe involvement), HHV-6 (mesial temporal lobes, limbic encephalitis) [148], and JC virus (single or multifocal white matter lesions without mass effect) [149], can be suggestive of the underlying diagnosis. These patients may also present with atypical findings on imaging. Toxoplasmosis for example, may not present with classic ring-enhancing lesions [150, 151]. Additionally, imaging can suggest other noninfectious etiologies which can lead to CNS symptoms. An excellent review of radiologic findings associated with hematopoietic transplantation is reviewed by Nishiguchi [151].

CSF analyses are critically important for a diagnosis. Standard cell counts, glucose, total protein as well as gram stain, cultures, polymerase chain reaction (PCR) testing, and molecular analyses can potentially lead to a diagnosis. Specific tests that can be considered during CSF analysis are listed in Table 12.3. Serologic tests can be beneficial in patients who are considered to be at risk for endemic mycoses or parasitic disease, and blood cultures can provide additional data for potential bacterial and fungal processes. Patients with symptoms at other locations (e.g., cough) should undergo additional imaging to help complete a diagnostic work-up. Other data to rule out other noninfectious etiologies should also be considered, such as drug levels to assess for CNS drug toxicity and CSF cytologic review and flow cytometry to assess for CNS involvement of leukemia if appropriate. Toxoplasmosis PCR from serum should be assessed in patients who are known to be seropositive for toxoplasmosis [152]. Finally, brain biopsy may be necessary in some rare cases to make the diagnosis.

Treatment

Due to the poor outcome of infections that occur in the CNS, it is important to consider early antimicrobial therapy while awaiting the results of diagnostic testing, as delay can lead to major morbidity with severe infections. Bacterial infections need aggressive IV therapy with duration dependent on the diagnosis (see Table 12.1). Dual therapy for CNS *Nocardia* species infections should be considered initially (e.g., trimethoprim/sulfamethoxazole and imipenem) and long-term therapy based on sensitivity testing

Table 12.2 Tests for patients with potential CNS infections^a

	Primary	Secondary
Radiologic imaging	CT/MRI of the brain	Chest imaging Sinus imaging PET scans
Cerebrospinal fluid	Opening pressure ^b CBC with differential Glucose Total protein Gram stain Bacterial and fungal cultures Viral PCR HHV-6 HSV ^c VZV ^c Cytology and flow cytometry <i>Save a tube for later testing</i>	Viral PCR Adenovirus CMV EBV Enteroviral JC virus West Nile virus Molecular bacterial DNA analysis AFB cultures/MTB-specific PCR CSF cryptococcal antigen Toxoplasma PCR
Antigen testing	–	Serum cryptococcal antigen Serum galactomannan VDRL
Serologic testing	Toxoplasma serology	Coccidioides immunofixation Histoplasma urinary antigen Strongyloides antibody
Additional testing	Blood and urine cultures Neurologic exam HHV-6 PCR from serum Drug levels ^d	Electroencephalogram (EEG) Ophthalmologic exam Brain biopsy ^e

Abbreviations: *CNS* central nervous system, *CT* computed tomography, *MRI* magnetic resonance imaging, *PET* positron emission tomography, *CBC* complete blood count, *PCR* polymerase chain reaction, *HHV-6* human herpesvirus-6, *HSV* herpes simplex virus, *VZV* varicella-zoster virus, *CMV* cytomegalovirus, *EBV* Epstein-Barr virus, *AFB* acid-fast bacilli, *MTB* mycobacterium tuberculosis, *VDRL* venereal disease research laboratory test for syphilis

^aThis list is *not* completely inclusive, and decisions should be made based on clinical symptoms and history. Primary and secondary options may be different depending on presentation

^bOpening pressure should be determined at the time of lumbar puncture whenever possible

^cMay not be necessary in patients taking prophylactic acyclovir

^dDrug levels will depend on patients' current medications

^eBrain biopsy may be necessary in some cases to make the diagnosis, but this should be reserved for patients with severe and life-threatening symptoms when possible

once available. Length of therapy is dependent on CT resolution, but most feel that at least a year of therapy is needed [153]. Usual antimicrobial coverage for bacterial meningitis (vancomycin, cephalosporins, and aminoglycosides) will not treat *Listeria monocytogenes*. All immunosuppressed patients with presumed meningitis should have IV ampicillin added to the underlying empiric regimen. Patients with proven listeriosis require prolonged IV ampicillin therapy. *Aspergillus* CNS infections should be guided by sensitivity testing when possible, but usual treatment includes either voriconazole or lipid amphotericin B formulations; treatment guidelines are reviewed by Walsh et al. [154]. Voriconazole, in particular, is known to get excellent CNS penetra-

tion [155, 156]. Patients with CNS infection with any of the *Mucorales* species should be treated with either lipid amphotericin B formulations or posaconazole, but overall outcomes are poor [116]. Endemic fungal CNS infections' treatment options are reviewed in references by Wheat et al. [119], Galgiani et al. [120], and Perfect et al. [109]. HSV and VZV CNS infections require high-dose IV acyclovir, and patients with HHV-6 encephalitis should receive either IV foscarnet or IV ganciclovir [157]. Patients with toxoplasmosis should receive intensive therapy with pyrimethamine, sulfadiazine, and folinic acid or high-dose trimethoprim/sulfamethoxazole [158].

Sinopulmonary Infections

Signs and Symptoms

The sinopulmonary system is one of the most frequent sites of infection during leukemia therapy. Symptoms vary depending on the involved site, particularly since both upper and lower tract infections can occur. Classic symptom presentations, however, normally seen in immunocompetent patients are uncommon in this population. Upper tract infection symptoms often involve the sinuses and nasopharynx, including: rhinorrhea, sore throat, facial pain/pressure, headaches, cough, disturbances in taste and smell, among others. Classic symptoms that are consistent with the common cold or sinusitis are not infrequent in mild cases, but the development of bloody/black nasal discharge, lesions on the palate, facial weakness, periorbital erythema, or proptosis are signs of severe invasive disease.

With lower tract parenchymal involvement, symptoms may include cough, sputum production, shortness of breath, and wheezing. Focal chest pain or hemoptysis are more ominous signs of an invasive fungal infection, and hypoxia can be a harbinger of the development of acute respiratory distress. Still, specific symptoms in transplant are not always pathognomonic for a specific infectious etiology, and patients receiving corticosteroids may have less prominent symptoms. Occasional patients may be asymptomatic with lesions found only on imaging. Noninfectious etiologies such as diffuse alveolar hemorrhage, idiopathic pneumonia syndrome, cryptogenic organizing pneumonia, and drug toxicity can cause symptoms and even radiographic changes that mimic infections, making a prompt diagnosis even more challenging [159, 160].

Differential Diagnosis

Bacterial

Numerous bacterial pathogens can lead to sinusitis. In immunocompetent hosts, sinusitis is caused by predominantly respiratory pathogens such as *S. pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, but in transplantation, other

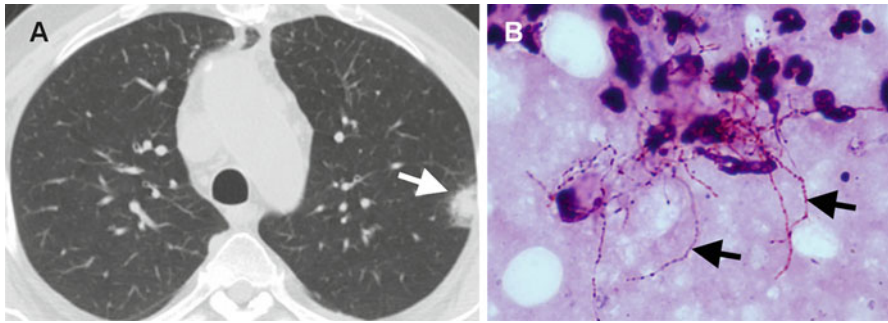


Fig. 12.3 (a) A patient found to have a 2-cm pulmonary nodule on a routine CT of the chest (*white arrow*). Standard infectious work-up, including bronchoalveolar lavage, was negative. (b) Video-assisted thoracic surgical (VATS) biopsy of nodule demonstrated weakly staining gram-positive branching filaments that were partially acid-fast on Kinyoun staining (*black arrows*) consistent with *Nocardia* species, and cultures from lesion grew *Nocardia nova*

GNR, resistant organisms, and polymicrobial infections are more frequent etiologies [75, 161]. Patients with preexisting disease or those with a history of chronic sinus infections prior to transplant are likely at higher risk [162]. Specific pathogens cannot always be identified, and most patients are treated empirically with broad-spectrum antibiotics.

Pneumonia can be caused by a variety of bacterial organisms in leukemic patients, although after transplant, bacterial pneumonias are less frequent [163]. Patients with prolonged neutropenia or undergoing salvage chemotherapy are not surprisingly at higher risk for developing this complication. There are a wide variety of gram-positive and GNR species that can lead to pneumonia in this immunocompromised population, but providers should be aware of specific bacterial pathogens that are more specific to these patients. The gram-positive filamentous bacteria *Nocardia* is an opportunistic infection that after inhalation can develop into pulmonary disease. *Nocardia* are usually resistant to standard antimicrobial prophylaxis regimens, are more frequent in patients not on trimethoprim/sulfamethoxazole prophylaxis [164] and those receiving steroids [165]. *Nocardia* species can have varied presentations in transplantation, but most frequently appear as nodular pulmonary disease; some patients may have asymptomatic nodules found only on imaging (Fig. 12.3) [165]. *Legionella* species can also occur in posttransplant recipients, though nonpneumophila species, particularly *L. micdadei*, are more frequent [166–168]. *Legionella* species can present with lung nodules, mimicking fungal infections, or as pulmonary infiltrates. *Mycoplasma* and other atypical organisms are rare [169, 170]. *Mycobacterium avium-intracellulare* (MAI) is the most frequently isolated mycobacteria from pulmonary specimens in HCT patients, but since many have colonization, not all warrant treatment [55].

Fungal

Fungal infections are one of the most common and vexing problems in patients with leukemia and HCT, and most lead to sinopulmonary infections. Fungal sinusitis can particularly be troubling due to the proximity of the infection and risk for invasion into the CNS and can present initially with similar features to bacterial cases. A high index of suspicion is needed to prevent life-threatening complications particularly in patients who worsen after treatment for bacterial sinusitis or in patients on steroids. *Aspergillus* species are the most common cause of fungal sinusitis [171, 172], but less frequent fungal organisms, such as *Scopulariopsis* [173] and *Paecilomyces* [174], among others, can also lead to sinus disease. The Mucorales are notorious for leading to life-threatening sinus disease [115, 116, 118, 175].

Pulmonary fungal infections are even more common in this patient population, where invasive *Aspergillus* remains the most common etiology [176–178]. Patients with known GVHD, high-dose steroids, iron overload, CMV infection, and prolonged neutropenia are at increased risk for fungal infections [179–184]. Iron overload is particularly associated with the Mucorales, which may also be more prevalent in patients who are treated or undergo prophylaxis with voriconazole [185, 186]. Because of the severity of immunosuppression, multiple other fungal species manifest as pulmonary disease in hematopoietic transplant recipients [187, 188]. Yeast less commonly causes pulmonary disease, with the exception of *Cryptococcus* species, which can lead to pulmonary nodules [189]. Although resistant *Candida* species can be isolated from bronchoalveolar lavage (BAL) cultures, *Candida* pneumonia is a rare complication, even more so with the addition of standardized antifungal prophylaxis [190].

The other unique pulmonary fungal pathogen in these patients is PCP. PCP is more common in patients on high-dose steroids and in those who do not receive or discontinue trimethoprim/sulfamethoxazole prophylaxis [191, 192]. Disease usually occurs as a late complication due to current prevention strategies [191]. Even with appropriate treatment and diagnostics, patients who develop PCP can develop major complications [193].

Viral

Multiple viral pathogens lead to sinopulmonary complications during therapy for leukemia. These break down into two main categories: reactivation from latency and community acquisition. Latent herpesviruses, particularly CMV, can lead to invasive pulmonary disease in transplant recipients. Patients typically present with shortness of breath and hypoxia, and most have evidence of CMV reactivation from other sites. Risk factors for the development of CMV pneumonia include: lymphopenia, GVHD, and high-dose steroids, among others [194]. Patients who undergo umbilical cord blood transplant or T-cell depletion are at significantly higher risk [195, 196]. Early CMV pneumonia/pneumonitis is seen within the first 3 months posttransplantation during the period of greatest immunosuppression. Late CMV disease occurs more than 3 months after HSCT, and likely as a result of residual deficits in cell-mediated immunity [194,

197, 198]. HSV, VZV, and other herpesviruses can also rarely lead to pulmonary complications in patients [199]. EBV-associated posttransplant related lymphoproliferative disease (PTLD) can manifest in the lungs as pulmonary nodules [200]. Adenovirus can be latent in the lung and reactivate during the posttransplant period [201], leading to severe pulmonary complications and dissemination [202, 203].

Respiratory viral pathogens are the most frequent sinopulmonary infection in these patients, with up to 30% of patients developing at least one infection (mostly upper respiratory events) during follow-up [204, 205]. These viruses can cause a spectrum of disease, including upper respiratory infection, pneumonia, and/or even late airflow obstruction [206], and are a cause of significant morbidity and mortality [205]. Influenza A and B, parainfluenza virus, metapneumovirus, and RSV can all be associated with both upper and severe lower tract disease. Influenza viruses and RSV are seasonal, while parainfluenza can occur year round. Community-acquired adenovirus can also be associated with high rates of mortality when associated with lower tract disease [207]. Rhinovirus and coronavirus are the most common respiratory viral infections, often limited to only upper respiratory disease [204]. They have been rarely associated with pulmonary complications in transplant recipients [208]. Other novel and emerging respiratory pathogens' (e.g., human bocavirus, WU and KI polyomaviruses) epidemiology in this population has not been well described to date [209].

Diagnosics

Radiologic imaging of the sinopulmonary system has become an important part of any diagnostic evaluation in this population. Bacterial, viral, and fungal infections can opacify sinus spaces on plain film or CT, but more invasive findings, such as bony erosion, suggest fungal sinusitis. Bacterial infections typically present as lobar consolidations or infiltrates. Fungal infections typically present on CT as solitary or multiple pulmonary nodules, and a classic "halo sign" on CT is very suggestive of an underlying fungal nodule (Fig. 12.4) [210, 211]. Lobar consolidation and cavitary disease are less frequent CT presentations [210]. International criteria for the diagnosis of fungal infections, which include radiologic findings, can help providers determine which patients should receive antifungal therapy [212]. Lower tract viral infections primarily present with diffuse interstitial disease or ground-glass infiltrates; other infections such as PCP can have a similar appearance. Pulmonary consolidation [213] and nodular disease [214] have also been described for viral infections (e.g., CMV, HMPV). Since multiple pathogens can occur in a single patient, radiologic findings are only suggestive and need confirmatory testing.

Noninvasive modalities are available for viral and fungal infections. Serum galactomannan (GM) testing has improved diagnostics specifically for *Aspergillus* species and has become an important tool for screening [215–217]. The serum (1→3)-beta-D-glucan assay has also been used for detecting fungal infections in transplant patients [218]. Similar to GM, this assay does not identify *Mucorales* species but may be useful in diagnosing PCP [219]. Serum cryptococcal antigen testing can be useful in patients where *Cryptococcus* is a diagnostic possibility.

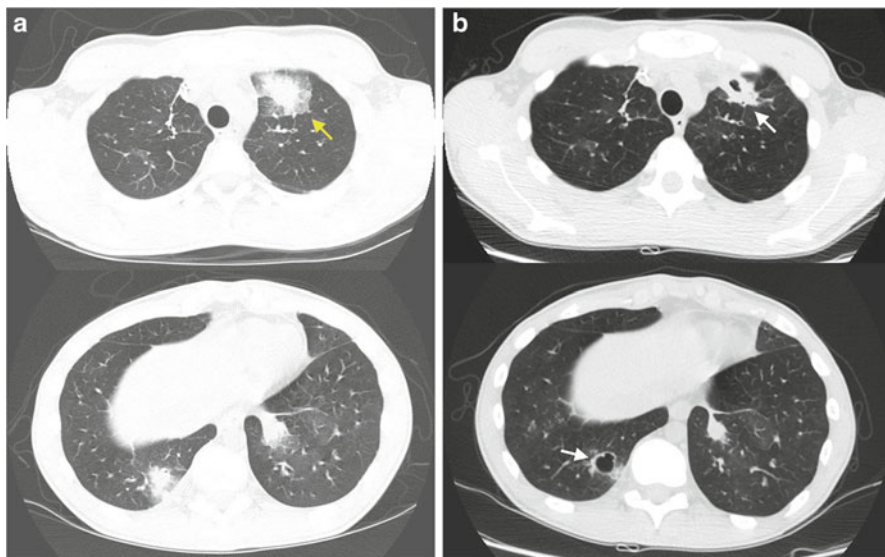


Fig. 12.4 Patient with acute myelogenous leukemia found to have pulmonary nodules during a work-up for neutropenic fever. (a) Upper panel demonstrates large nodule surrounded by white zone of ground glass which is reflective of a “halo sign” (yellow arrow). The patient was diagnosed with *Aspergillus fumigatus* pneumonia after bronchoalveolar lavage. (b) The same patient after 2 months of voriconazole therapy with the formation of posttherapy cavitation (white arrows)

CMV and adenovirus pneumonia are typically associated with dissemination, so viremia is often found during and before pulmonary infection. Upper respiratory viral infections can be detected by a number of laboratory modalities, including culture, direct fluorescent antigen (DFA) testing, and other rapid commercial antigen detection kits. Comprehensive or multiplex PCR panels are becoming increasingly utilized at many centers, including ours, since these techniques offer greater sensitivity than standard modalities and can detect coinfection [220, 221]. The fact that many of these patients develop prolonged shedding, particularly those on steroids [222], also suggest that PCR-based methods may enhance infection control practices.

Invasive diagnostic modalities are also needed to diagnose patients, and BAL should be considered in all patients with pulmonary findings [216]. Cultures, cytology, and antigen testing (e.g., GM from BAL) [215] can all provide additional microbiologic evidence to avoid the institution of empiric therapies (see Table 12.2). Additionally, this modality may help to evaluate other nonfungal infections, separate specific pathogens from each other, detect coinfections, and provide samples for antimicrobial resistance testing. While PCR-based strategies for specific fungal pathogens are still under development, PCR-based respiratory testing for viral pathogens from BAL samples is becoming standard at many centers [209, 220]. PCP is classically diagnosed from induced sputum samples in other immunocompromised populations (e.g., HIV); however, bronchoscopy may enhance diagnosis in transplant recipients due to the low burden of disease [223, 224]. CMV shell vial assays and cultures from BAL are also necessary criteria for the diagnosis of CMV pneumonia [225].

Table 12.3 Bronchoalveolar lavage infectious work-up^a

Bacterial	Gram stain
	Quantitative culture
	Special media for specific pathogens (<i>Legionella/Nocardia</i>)
	AFB stain and culture
Fungal	KOH preparation with calcofluor ^b
	Cytologic review
	Fungal specific cultures
	Galactomannan antigen by EIA
Viral	PCR for <i>Aspergillus</i> or other fungal species ^c
	CMV shell vial
	RSV shell vial
	Viral cultures
	Respiratory DFAs (<i>rapid</i>)
	– Adenovirus, influenza A and B, metapneumovirus, parainfluenza, and RSV
	Respiratory PCR testing
– Adenovirus, bocavirus, coronavirus ^d , influenza A and B, metapneumovirus, parainfluenza ^e , RSV, and rhinovirus	

Abbreviations: AFB acid-fast bacillus, KOH potassium hydroxide, EIA enzyme immunoassay, PCR polymerase chain reaction, CMV cytomegalovirus, RSV respiratory syncytial virus, DFA direct fluorescent antibody

^aThese are current strategies used at our center but may not be appropriate at all centers

^bThe KOH preparation dissolves keratin and other cellular in the specimen; calcofluor is a fluorescent dye that binds to polysaccharides in chitin of fungi

^cPCR for fungal pathogens are not standardized and not currently considered part of standard diagnostic testing for fungal diagnoses

^dSpecific coronavirus species associated with clinical disease

^eIncludes parainfluenza (1,2,3, and 4)

A microbiologic diagnosis is important to allow targeted treatment and can help determine the duration of therapy. When a diagnosis of a pulmonary process is not made by BAL, video-assisted thoracoscopic biopsy (VATS) or CT-guided biopsy may be necessary to determine the cause of the pulmonary symptoms. For sinus infections, Otolaryngology evaluation should be obtained in all high-risk patients with sinus symptoms, as early nasal/sinus endoscopy with visual inspection, and biopsy can allow for more prompt diagnosis.

Treatment

Bacterial pneumonias should be treated when possible as directed by cultures and sensitivities (Table 12.1). Treatment guidelines for community-acquired pneumonia are reviewed by Mandell [226], and recommendations for treatment of nosocomial or ventilator-associated pneumonia are reviewed by the American Thoracic Society and the Infectious Diseases Society of America [227]. In particular, *Pseudomonas* pneumonia may require prolonged treatment due to the high risk of fatal relapse [71]. Similar to CNS disease, *Nocardia* pulmonary disease should be treated with trimethoprim/sulfamethoxazole or based on microbiologic sensitivities for at least

6 months [108]. Patients with *Legionella* pneumonia should receive 3 weeks of a respiratory fluoroquinolone or azithromycin.

Aspergillus pulmonary infections are most frequently treated with voriconazole or lipid amphotericin B formulations; treatment guidelines are reviewed by Walsh [154]. There is a lack of randomized clinical trials comparing different agents, and the role of combination therapy is controversial; results from a future trial addressing combination therapy are forthcoming. Patients should typically undergo therapy until pulmonary nodules have completely resolved or stabilized for 2–3 months of immunosuppressive therapy. Patients with *Mucorales* pulmonary infections should be treated with either lipid amphotericin B formulations or posaconazole; when possible, sensitivity testing can help tailor therapy. Cardiothoracic surgery consultation should be considered in patients failing therapy and can be considered as adjunctive treatment for patients with solitary fungal nodules. Treatment of less frequent fungal infections (e.g., *Scedosporium* species) should be based on sensitivity testing. Endemic fungal CNS infections' treatment options are reviewed in references by Wheat et al. [119], Galgiani et al. [120], and Perfect et al. [109].

Patients who develop pulmonary CMV should receive IV ganciclovir or foscarnet, with the addition of intravenous immunoglobulin (IVIG) for at least 5 weeks; treatment options are reviewed by Boeckh [19]. Adenovirus pneumonia has no approved therapy, but many centers will attempt IV cidofovir and IVIG, although neither have been studied prospectively [228, 229]. Treatment options for patients with influenza are reviewed by Casper [230] but usually include oseltamivir or inhaled zanamivir as primary therapy. Alternate combination therapy can be considered in patients with life-threatening infections [230], particularly since the development of resistance can occur during therapy [29]. RSV is responsive to aerosolized ribavirin, which has been shown to reduce mortality from lower tract disease [231]. Survival may be improved when aerosolized ribavirin is used in combination therapy with intravenous immunoglobulin or palivizumab [29, 205]. Few options exist for treatment of other viral respiratory pathogens, so although no randomized data exist, oral or inhaled ribavirin can be considered in patients with parainfluenza [232] or metapneumovirus [233].

Cardiovascular

Signs and Symptoms

Cardiac infections are relatively infrequent in patients who undergo therapy for leukemia. A diagnostic clue for a cardiovascular infection is the development of persistently positive blood cultures. Patients who receive appropriate antimicrobial therapy and have continued positive cultures after removal of all hardware (e.g., central catheters) should be evaluated for a cardiac or vascular source of infection (e.g., endocarditis, aortitis, or infected thrombophlebitis). Additionally, patients with cardiovascular infections can present with tachycardia, arrhythmias, acute heart block, heart failure or myocardial infarction, painful phlebitis or limb swelling.

Bacterial and Fungal

The two most common infections associated with cardiopulmonary system are septic thrombophlebitis and endocarditis. Septic thrombophlebitis typically involves the development of bacteremia or fungemia that infects a preexisting thrombus, typically at sites of line placement. *Candida* species are commonly associated with this phenomenon, but any bacteria can lead to this complication [234]. Endocarditis in this population is an uncommon outcome following transplantation. These cases are often due to *Streptococcus*, *Staphylococcus*, or *Enterococcal* species, but other rare GNRs and atypical organisms have occasionally been reported [235, 236]; nearly all cases involve the right side of the heart unless patients have known underlying valvular pathology [235]. *Candida* or other fungal endocarditis is rare but associated with high rates of morbidity and mortality [237–239]. Interestingly, non-infectious etiologies of endocardial masses (thrombi or marantic changes) can lead to similar symptoms in this population [236, 240]. Invasive fungal infections of the myocardium can also occur, but most are associated with primary pulmonary involvement or dissemination [241, 242]. Rare bacterial and fungal processes can lead to purulent pericarditis [243, 244].

Viral

Viral cardiac complications are uncommon in patients being treated for leukemia. Rare cases of herpesviruses and sporadic community-acquired viral infections and pericarditis or myocarditis have been reported [128, 245–248]. Noninfectious etiologies and adverse drug side effects are significantly more likely as causes of inflammatory heart disease [249, 250].

Diagnosis

Blood cultures remain a staple for the diagnosis of cardiovascular infections. Patients with recurrent bacteremia either during or immediately after completing their antibiotic therapy should be considered for imaging to rule out septic thrombophlebitis. Ultrasound evaluation of veins near either the site of a line placement or involving an edematous limb can help identify suspicious thrombi. Patients who have clinical symptoms concerning for endocarditis should undergo an electrocardiogram and echocardiography. Transthoracic echocardiography can be helpful in diagnosing right-sided endocarditis, but transesophageal echocardiography has higher sensitivity for left-sided lesions and should be pursued in those who are considered high risk [251]. Guidelines for the diagnosis, treatment, and management of infective endocarditis can be found in Baddour [251]. Cardiac MRI may be

useful in diagnosing invasive fungal infections [252], but biopsy is the gold standard for diagnosis. Many patients with invasive cardiac mould infections are only diagnosed at autopsy.

Treatment

Patients with infected thrombophlebitis should receive extended antibiotic therapy that is based on antimicrobial sensitivity testing of the organism. In addition to prolonged antibiotic therapy, anticoagulation or surgical thrombus removal may be necessary for cure. Patients with endocarditis need appropriate antibiotics for 4–6 weeks following bacterial clearance. Patients who develop additional complications such as heart failure, or who fail antibiotic therapy may need valve replacement. Patients with *Candida* or other fungal endocarditis need cardiothoracic surgical consultation as few, if any, recover without surgical valve replacement. Treatment and follow-up of patients with endocarditis are reviewed in detail by Baddour [251]. Patients with invasive cardiac fungal infections have a poor prognosis, but antifungal therapy should be attempted.

Gastrointestinal/Hepatobiliary

Signs and Symptoms

Gastrointestinal (GI) symptoms are frequent during the treatment for leukemia as a consequence of chemotherapy, adverse reactions, GVHD, and infections. Diarrhea, for example, occurs in nearly 80% of patients at some during the posttransplant period [253]. Not surprisingly, it can be difficult to separate infectious from noninfectious etiologies. Typical GI symptoms associated with infections are abdominal or perirectal pain, diarrhea, nausea vomiting, dysphagia, or GI bleeding. Signs of an infectious GI process can also include elevated temperature, tachycardia, jaundice, and liver enzyme abnormalities, but many of these are also seen in noninfectious etiologies such as GVHD or sinusoidal obstruction syndrome [254].

Bacterial

Bacterial GI complications can occur during treatment of leukemia and during the transplant process. Most community-acquired bacterial causes for diarrhea, such as *Salmonella* and *Shigella*, occur only sporadically due to limited oral intake, less frequent exposure, and to standard prophylactic antibiotic therapy [255]. A more frequent infectious etiology for diarrhea is *Clostridium difficile* infection.

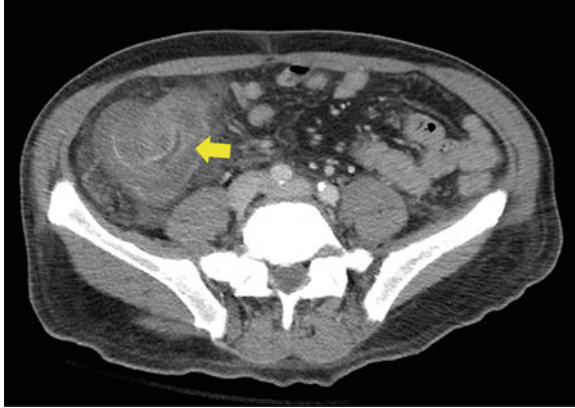


Fig. 12.5 Patient approximately 10 days following induction chemotherapy for acute myelogenous leukemia developed increasing right-sided abdominal pain, fever, and shortness of breath. Underwent CT scan of the abdomen which demonstrated bowel wall thickening and edema throughout the cecum and ascending colon with surrounding fat stranding (yellow arrow), consistent with neutropenic enterocolitis (typhlitis). Blood cultures from the day of admission were positive for *C. septicum*. The patient improved with broad-spectrum antibiotic therapy and did not need surgical intervention

The use of broad-spectrum antibiotic therapy and prolonged exposure to inpatient care increase the risk for *C. difficile*. Usually *C. difficile*-associated diarrhea occurs within the first 30–40 days posttransplant [253, 256], but patients are at risk through the transplant process. Episodes of *C. difficile* that occur during neutropenia can develop into life-threatening disease [257].

Neutropenic enterocolitis (typhlitis) presents with the triad of right lower quadrant pain, diarrhea, and fever; patients with severe disease may have rebound tenderness and signs of peritonitis (Fig. 12.5) [258]. This condition involves the cecum and is related to loss of integrity of the bowel wall and subsequent bacterial invasion [258]. Classically, this condition is associated with *Clostridium septicum* but likely involves other anaerobic organisms as well [259]. Perirectal abscesses can occur during early conditioning and mucositis, as neutropenic patients may present with minimal swelling or erythema, a high index of suspicion is needed in patients with rectal pain. Necrotizing fasciitis should be ruled out in patients with perineal involvement (see Skin and Soft Tissue section). Intra-abdominal and hepatic abscesses are infrequent.

Fungal

Oral candidiasis (thrush) was a frequent complication following transplantation, but is much less common with the addition of fluconazole to prevention strategies. Thrush can occur as a result of azole-resistant species. Candida esophagitis is less

frequent as it is primarily due to *C. albicans* [260] which is reliably sensitive to fluconazole [261]. *Candida* species, primarily *C. albicans*, can also present as involvement in the liver as hepatosplenic candidiasis. Patients with hepatosplenic candidiasis acquire the disease during periods of neutropenia but may develop fever, right upper quadrant pain, and increasing liver function tests only after neutrophil recovery [262]. Patients with hepatosplenic candidiasis do not normally have detectable candidemia, and nearly all cases are thought to be due to *C. albicans* [262]. Similar to other invasive *Candida* complications, hepatosplenic candidiasis has become less common since the addition of standardized fluconazole prophylaxis.

Mould involvement of the gut can be a devastating complication. Most mould infections in the GI tract are thought to be acquired from ingestion during periods of high risk. Unfortunately, these invasive infections are difficult to diagnosis pre-mortem, due to nonspecific symptoms and imaging (Fig. 12.6). Patients typically present with abdominal pain, but others can have only fever or nonspecific findings; GI bleeding or perforation can be late signs of invasive involvement. The most frequent GI moulds are *Aspergillus* species and the Mucorales which can both lead to disease throughout the GI tract [263, 264] including the liver [265]. Clinical diagnosis can be very challenging, and such a delay leads to high rates of mortality; many are diagnosed only at autopsy [263].

Viral

Herpesviruses, particularly CMV, can lead to invasive disease throughout the GI tract. CMV GI disease in transplant recipients resembles gut GVHD and, not infrequently, is found on biopsy in conjunction with a gut GVHD diagnosis. Patients typically present with abdominal pain, diarrhea (lower tract), nausea, and early satiety (upper tract); most patients are either on high-dose steroids or are T-cell-depleted transplant recipients [194]. The majority of patients have CMV detected in the blood at the time of diagnosis, but since a significant proportion have no blood dissemination, a negative plasma PCR does not preclude invasive CMV disease. GI disease is the most common site of late CMV disease [266]. CMV rarely leads to severe hepatitis [267]. HSV can cause erosive esophagitis [268] and hepatitis [269], but the routine use of acyclovir prophylaxis limits these complications.

VZV reactivation can lead to GI disease. Visceral varicella-zoster is unique to this population and is a life-threatening condition that necessitates treatment with high-dose IV acyclovir. This complication must be considered in any leukemic or transplant patient who presents with the triad of abdominal pain, increasing liver function tests, and hyponatremia [270, 271]. Patients with visceral involvement can also present with hepatitis and pancreatitis as a component of the diagnosis [271]. Importantly, unlike most episodes of VZV reactivation, this presentation is not always associated with the rash or skin lesions usually associated with herpes zoster [272]. Empiric therapy should be started immediately if this diagnosis is suspected.

EBV in posttransplant recipients can cause PTLD in high-risk patients and occurs in about 1% of all HCT patients [273]. PTLD can present anywhere but has a predilection for the gut and liver. Symptoms vary by location, but GI disease can be challenging to diagnose. Risk factors for the development of EBV-associated complications include T-cell depletion, EBV serologic mismatch, splenectomy [274], mismatched or unrelated transplantation, and the development of chronic GVHD. 200 PTLD peaks around 2–3 months posttransplant, and most are polymorphic disease [200]. Umbilical cord blood transplant recipients may be more likely to develop early malignant monomorphic disease [275]. Interestingly, patients over the age of 50 have an increased rate of PTLD [200].

Adenovirus most frequently leads to the development of diarrhea, and in more severe cases lower tract GI bleeding and dissemination [229, 276]. There is a strong correlation between the detection of viremia and the development of invasive disease [277]. Adenovirus reactivation occurs most frequently in patients with mismatched grafts and in those who have received T-cell-depleted transplants [278]. In children, adenovirus occurs more frequently, and earlier posttransplant; invasive disease is more prevalent [279]. Adenovirus can lead to hepatitis and fulminant hepatic failure [280, 281].

Norovirus (Norwalk agent) has been increasingly recognized as a major cause of morbidity and mortality in cancer patients [282, 283]. These patients are more likely to develop chronic diarrhea which has been associated with significant weight loss and need for parenteral nutrition [282, 284]. Patients who develop norovirus from the community are likely to shed the virus for extended periods of time [284], making infection control practices critical for prevention [285]. Rotavirus is also recognized as a potential pathogen [286, 287].

Finally, hepatitis B (HBV) can be a major problem in patients with prior exposure. During treatment for leukemia, patients with quiescent HBV (HBsAg positive or those with occult HBV) can develop reactivation with the development of hepatitis and even fulminant liver failure [288]. Prophylaxis and treatment for patients with a prior history of HBV have led to fewer complications related to the disease [289–291]. While, hepatitis C (HCV) is also known to cause long-term complications in transplant recipients [292], it may also be associated with the development of sinusoidal obstruction syndrome [293].

Diagnosis

Patients who develop GI symptoms, particularly diarrhea and abdominal pain, should be evaluated for infectious etiologies. Routine bacterial cultures and parasite examinations are rarely useful as these pathogens are uncommon [286]. Samples however should routinely be sent for *C. difficile* testing regardless of prior antibiotic exposure. Elevated liver transaminases and alkaline phosphatase, and rising bilirubin, can also suggest potential etiologies [294]. Viral testing including adenovirus PCR, norovirus PCR, and rotavirus EIA from stool can be considered

for patients. All patients with known HBV exposure should have a HBV PCR at baseline, and if they develop severe transaminitis, have it repeated. Additionally, although CMV, EBV, and adenovirus PCRs from serum can suggest an underlying diagnosis, VZV and HSV PCRs from serum/plasma in the face of symptoms consistent with visceral zoster or acute hepatitis are of critical importance for diagnosis. Serum GM can be sent in patients who are felt to be at risk for gut-related *Aspergillus* but may be falsely positive in patients with severe mucosal breakdown or in those receiving piperacillin-tazobactam therapy [295, 296]. All patients receiving intensive chemotherapy should have baseline serologic testing for viral hepatitis.

In patients with abdominal pain, CT scans of the abdomen and pelvis can help evaluate potential etiologies, assess for perforation or abscess, and may help to identify diseases with classic appearance on CT. Hepatosplenic candidiasis, for example, presents with multiple hypodense “bull’s eye” lesions in the liver and spleen which are indicative of *Candida* abscesses within the liver [294]. Neutropenic enterocolitis typically demonstrates inflammation and stranding around the cecum (Fig. 12.5). Unfortunately, GI mould infections may be difficult to diagnose from imaging [264], with many diagnosed following death (Fig. 12.6). Intervention may also be important in the work-up of patient’s symptoms. In patients at risk for GVHD, gastroenterology consultation is suggested to evaluate by endoscopy. Endoscopic visualization and biopsies can help differentiate between viral infections (CMV and adenovirus) and GVHD and may detect other infectious lesions [297]. It is important to stress that more than one diagnostic method for CMV detection is needed in the GI tract [298] and that CMV PCR still needs to be validated as a diagnostic entity for the diagnosis. Surgical intervention or liver biopsy may be necessary particularly in patients without a clear diagnosis or if CT findings are suspicious for a fungal process. Patients with severe neutropenic enterocolitis or those with severe abdominal pain may need emergent surgical consultation [258].

Treatment

Patients who develop *C. difficile* infections should be treated with either oral metronidazole or oral vancomycin (Table 12.1). Patients with severe infections may have better outcomes with oral vancomycin [299]. Patients with neutropenic enterocolitis and perirectal infections should receive broad-spectrum antibiotics covering anaerobic species (e.g., metronidazole) and GNRs. Surgical consultation should be pursued in all patients with these conditions, as some patients may need early surgical intervention [258]. Patients with invasive *Candida* infections should receive prolonged fluconazole or echinocandin therapy, and patients diagnosed with invasive moulds should receive mould-active therapy depending on the pathogen identified. Voriconazole, lipid amphotericin B formulations, or posaconazole are the most commonly used agents. All patients should also have a surgical consultation.

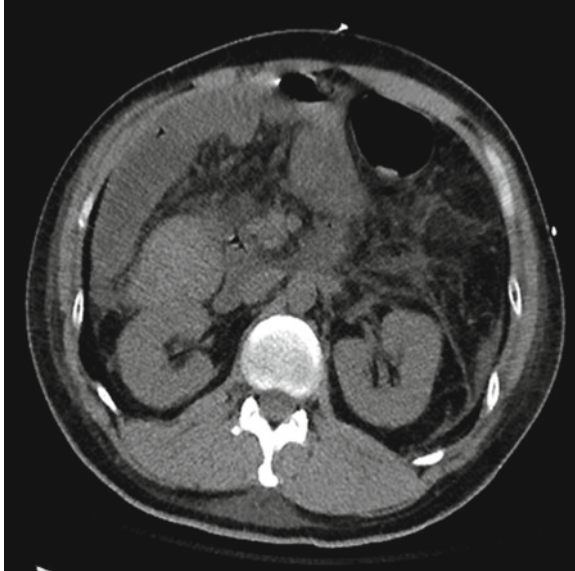


Fig. 12.6 Patient posttransplant presented with *Enterobacter* bacteremia. On broad-spectrum antibiotics, continued to be febrile with increasing abdominal distention and increasing bilirubin despite aggressive antibiotics. Underwent CT scan of the abdomen which demonstrated moderate ascites, but no pneumoperitoneum or obstruction was identified (*above*). The patient developed respiratory distress, anasarca, and dense pulmonary infiltrates. At autopsy found to have disseminated intra-abdominal *Rhizopus* species. Mould invaded into celiac axis (with thrombosis) and also involved liver, diaphragm, stomach, pancreas, spleen, and adrenal glands

CMV infections should be treated with ganciclovir or foscarnet and HSV/VZV infections with high-dose IV acyclovir. Patients who develop PTLD after HCT are often treated with rituximab but may need additional chemotherapy [300, 301]. Few options exist for norovirus therapy, but nitazoxanide may be an option [302]. Treatment of HBV is reviewed in detail by Lok [303] but typically entails lamivudine, entecavir, or adefovir.

Genitourinary

Signs and Symptoms

Patients with genitourinary (GU) infections during treatment for leukemia often present with symptoms that are similar to immunocompetent patients: urinary frequency, dysuria, flank pain, hematuria, and fevers. These patients are at risk for additional complications and are more likely to develop renal dysfunction and invasive infections. Additionally, side effects of numerous medications and chemother-

apy agents (e.g., cyclophosphamide and calcineurin inhibitors) can lead to additional GU toxicity. The need for urinary catheters in highly compromised patients may also increase risk. The combination of adverse drug toxicity, GVHD, sepsis, and subsequent multiorgan failure can lead to renal failure and the need for acute renal replacement therapy [304, 305].

Differential Diagnosis

Bacterial

Patients receiving standard therapy for leukemia and patients undergoing transplantation are at risk for developing urinary tract infections (UTI). The use of standard prophylactic antibiotics has limited UTIs, somewhat, but has led to the development of more resistant nosocomial infections particularly in patients who have prolonged hospitalizations and are catheterized [306, 307]. Patients undergoing leukemia therapy have *Escherichia coli* and *Klebsiella pneumonia* as the predominant species detected from urinary samples [307]. In patients with urinary catheters, it is important to separate colonization from symptomatic infection [308]. Patients can also develop complications in the kidney from septic emboli, and more invasive infections of the kidneys and bladder can occur but are infrequent.

Fungal

Fungal infections of pelvic organs are a relatively infrequent phenomenon. *Candida* is the most frequent organism to infect the GU tract, with urinary tract infections being the typical presentation, but invasive candidal abscesses can occur during episodes of candidemia [309]. Patients who develop candiduria typically have anatomic abnormalities of the GU tract, have been treated with broad-spectrum antibiotics, or have a urinary catheter [310]. Candidal organisms can also lead to asymptomatic colonization of urinary catheters and, in some cases, invasive disease.

GU tract infections are an uncommon manifestation of mould infections. Patients with *Aspergillus* infection will not infrequently develop parenchymal involvement with disseminated infections [242], but occasionally they can be seen as isolated infections in the bladder [311] or kidney [312, 313]. The Mucorales and other less common fungal species have also been rarely reported to cause invasive disease in the genitourinary tract [314, 315].

Viral

BK virus frequently reactivates in the genitourinary system during immunosuppression and can lead to the development of hemorrhagic cystitis (HC) [316].

Many patients who have detectable BK virus in the urine may be asymptomatic, but those that develop BK-associated HC present with frequent urination, flank pain, frank hematuria, and, in severe cases, the development of severe inflammation and clotting in the bladder that can lead to urinary obstruction [317, 318]. Rarely, BK can lead to nephritis in HCT recipients [319]. Interestingly, the immune response to BK may play an important role in the development of BK-associated symptoms [320]. Adenovirus also leads to HC [320, 321] but is a more common cause of nephritis than BK [322]. Unlike BK virus, risk factors for the development of invasive adenovirus include major changes in immune function, including T-cell depletion [202, 320]. Adenovirus genitourinary infections are also known to be more common in children and in patients with mismatched grafts [202, 229].

Diagnosis

Standard urinalysis and urine and blood cultures are important components of the work-up for patients with urinary symptoms. Urine culture results must be interpreted with caution in patients with urinary catheters, as separating colonization versus invasive disease can be challenging (reviewed by Nicolle) [308]. Viral PCRs for adenovirus and BK, from both blood and urine, can be helpful in evaluating patients with either HC and/or renal failure. A BK viral load in serum $\geq 10,000$ copies/mL may predict patients with BK-associated HC [323]. Ultrasound and CT imaging may also help in determining invasive fungal infections. If there is concern for possible nephritis or fungal infection, kidney biopsy or bladder cystoscopy may be necessary to make a definitive diagnosis.

Treatment

Bacterial infections typically require focused therapy based on sensitivity testing, but length of therapy depends on the severity of infection (Table 12.1). Patients with catheters should have them replaced prior to starting therapy if possible. Candida infections should be treated with fluconazole, echinocandin therapy, or lipid amphotericin B formulations, depending on sensitivity testing. Amphotericin bladder washes are used by some centers as adjunctive therapy or for patients with known colonization [324]. Patients with invasive mould infections should receive voriconazole, lipid amphotericin B formulations, or posaconazole, depending on the pathogen identified; all patients should also have a urology consultation.

BK-virus-related disease is difficult to treat, particularly since reductions in immunosuppression are not possible. In patients with severe disease, cidofovir, leflunomide, IVIG, and fluoroquinolones have all been suggested as possible therapeutic options, but no randomized trials exist [325–327]. Adenovirus HC and nephritis are difficult to treat, but IV cidofovir can be attempted [328].

Skin and Soft Tissue

Signs and Symptoms

Leukemia patients can present with a myriad of skin and soft tissue manifestations that can be clues to an underlying infectious etiology. When examining transplant patients and those receiving therapy for leukemia, it is important to do a good skin exam. Cutaneous infections can present in a wide variety of visual appearances as nodules, ulceration, eschars, petechiae, rash/erythema, and/or pustules. Most patients present with fever, but pain suggests a more invasive process. Depending on the appearance and distribution, cutaneous findings can be helpful in making a diagnosis (e.g., dermatomal herpes zoster). Many important noninfectious etiologies such as drug side effects, GVHD, leukemia cutis [329], and neutrophilic dermatosis (Sweet's syndrome) [330] can mimic infectious etiologies. Regardless, any notable lesions or rashes should be promptly evaluated.

Bacterial

Cellulitis is a common manifestation of bacterial infections. The majority of cellulitis cases are due to *Streptococcus* and *Staphylococcus* species, but more frequently, no bacterial etiology is identified. Certain bacterial species present with specific skin manifestations. *Pseudomonas* and other GNRs can present with ecthyma gangrenosum, which in the early stage appears as bullae and later slough to classically form a gangrenous ulcer with a black eschar [331]. *C. jeikeium* often presents with an erythematous papular eruption during episodes of bacteremia [332]. Nocardia and other uncommon organisms have also led to cutaneous manifestations in this population [333, 334]. Gangrenous or necrotizing fasciitis is a life-threatening skin infection and is characterized by necrosis of the deeper subcutaneous fat and fascia. Patients typically present with signs of overwhelming infection, and rates of mortality are very high [335]. In leukemia, necrotizing fasciitis can be either a polymicrobial process or caused by singular primarily GNR species [335]. Patients may present with bacteremia and minimal skin findings which may progress rapidly to a more fulminant course [336]. Clues to this diagnosis include a rapidly expanding cellulitis, black/dusky areas of involvement, pain out of proportion to the cutaneous findings, and laboratory alterations such as an elevated creatinine and lactic acidosis. Surgical consultation and immediate debridement of the affected area are mandatory. A specific form of necrotizing fasciitis that involves the perineum, Fournier's gangrene, can be particularly morbid [337].

Fungal

Fungal skin lesions in transplantation can be similar to their bacterial counterparts. *Candida* species are one of the most common fungal infections to have

dermatologic manifestations, and during candidemia, can present with <1 cm scattered erythematous papular nodules with pale centers [338]. *Cryptococcus* also can lead to skin nodules in those with disseminated disease [339]. Solitary nodules are more likely to be caused by moulds, typically *Aspergillus* and the Mucorales, and initially can be subtle in presentation. Mould infections can occur at sites of trauma, such as sites for bone marrow biopsy or IV placement [340]. Typically, lesions will progress rapidly without appropriate treatment. *Fusarium* is the one mould that presents frequently with dermatologic manifestations, usually appearing in greater than 60% of patients with disseminated fusariosis [341]. Typical lesions are erythematous macules and papules with gray necrotic or ulcerated centers [242]. Any patient with a cutaneous fungal infection should undergo further evaluation to identify others sites of infection.

Viral

HSV is commonly associated with vesicular lesions either around the oropharynx (typically HSV-1) or around anogenital region (HSV-2). Lesions during periods of severe immunosuppression can be much more severe but typically present as erythematous vesicles (“dew drop on a rose petal”). With the standard use of acyclovir, prophylaxis episodes of HSV during transplant and leukemia therapy are less frequent, although acyclovir-resistant cases can occasionally occur, especially in low-dose regimens [38]. Similar to HSV, VZV can present as herpes zoster or disseminated disease. Typical dermatomal reactivations occur late after transplant, but during active chemotherapy and postconditioning, patients are at risk for dissemination which can have an appearance not unlike primary Varicella (chickenpox) [343]. Erythematous rashes can be seen in other viral infections [344].

Diagnosis

As with all infections blood cultures can be helpful in identifying an underlying etiology to skin infections. Dermatology consultation and biopsies can also help in making a diagnosis and may be necessary in some cases that have a large differential diagnosis. Any patient with lesions suspicious for an invasive fungal infection should undergo routine biopsy. In patients with increased concern for necrotizing fasciitis, a high lactate and abnormal chemistry panel (low CO₂ and elevated creatinine) can also be suggestive. Diagnosis must be confirmed by visual inspection of the fascia and on pathologic review, so an urgent surgical consultation is required. Patients with lesions consistent with HSV or VZV should have lesions unroofed and samples from the base of the lesion sent for DFA, shell vial, and PCR. HSV and VZV PCR levels from serum should also be sent in patients who appear to have disseminated disease.

Treatment

Bacterial cellulitis is often treated with empiric regimens, as patients rarely have a known causative organism. Vancomycin is often added gram-positive coverage, but GNR treatment should be added in cases of severe infection. Patients with identified pathogens should have therapy focused on the sensitivity patterns of that organism (Table 12.1). Patients with evidence of necrotizing fasciitis must undergo immediate surgical consultation and debridement; broad coverage is recommended for empiric therapy while awaiting the operating room. Fungal infections should be treated with fluconazole, echinocandin, voriconazole, lipid amphotericin B formulations, or posaconazole, depending on the species, sensitivities, and severity of disease. Patients with invasive *Aspergillus*, *Mucorales* species, or other mould need more extensive surgical debridement to cure the infection. Patients with localized HSV or VZV reactivation should be treated with high-dose acyclovir or valacyclovir.

Prevention Strategies

Bacterial Prophylaxis

(Guidelines reviewed in Freifeld [39], Tomblyn [31], and Baden [32])

Neutropenic fever is one of the most common complications following therapy for patients with leukemia occurring in greater than 80% of patients undergoing treatment [345]. Fever can be caused by numerous etiologies, and only about 20–30% of patients have documented infections during a neutropenic evaluation [39]. However, due to the high risk for morbidity and mortality associated with infections, most providers give standard prophylaxis during this period of risk. There are numerous risk categories that are reviewed in detail by Freifeld et al. and prevention strategies differ slightly between groups [39]. Patients receiving therapy for leukemia and transplant recipients are expected to have prolonged periods of neutropenia (>7–10 days) so are considered to be higher risk. Most centers and guidelines recommend the use of fluoroquinolone prophylaxis in this population, and this appears to be as effective as IV ceftazidime [31, 57]. Due to the emergence of fluoroquinolone-resistant *S. viridans* (particularly ciprofloxacin) [346], some centers add additional penicillin VK or amoxicillin to fluoroquinolones [347, 348] and others early vancomycin in patients at high risk for this organism [349]. Trimethoprim/sulfamethoxazole can be considered in patients who have an allergy to fluoroquinolones but is often not possible in patients with neutropenia [32]. Prophylaxis should be stopped after neutrophil recovery. Late strategies to prevent posttransplant *S. pneumoniae* and encapsulated bacteria in patients with chronic GVHD should be based on local resistance patterns [31].

Since VRE and MRSA can be major problems in the treatment phase of leukemia therapy, standard screening for VRE (rectal) and MRSA (nasal) are recommended prior to starting chemotherapy.

Fungal Prevention

Due to the increased risk and significant morbidity associated with fungal infections, most centers use standard antifungal prophylaxis [350]. Fluconazole prophylaxis has been shown to decrease the rates of major fungal infections [351, 352], but its major effect is on prevention of invasive *Candida* [22]. Breakthrough candidemia on prophylactic fluconazole can occur typically in the form of *C. glabrata* and *C. krusei* [353]. The echinocandins, particularly micafungin, have been shown to be useful alternative agents [354, 355].

Voriconazole prophylaxis has been shown to be equivalent to fluconazole in patients undergoing myeloablative HCT, but it did not significantly reduce the number of *Aspergillus* infections during follow-up in a randomized trial [355]; an increase in *Mucorales* species was not seen. Posaconazole prophylaxis has been shown to decrease the risk of invasive mould infections in high-risk patients with GVHD [356] and in patients with neutropenia [357]. Limitation of proton-pump inhibitor use, coadministration with food or acidic beverages, and increases in dosing may prevent the development of insufficient drug levels and subsequent breakthrough infections [358]. Drug levels should be considered in patients receiving voriconazole or posaconazole prophylaxis.

PCP prevention is also an important component of posttransplant prevention. The preferred agent for prevention is postengraftment trimethoprim/sulfamethoxazole [31]. Trimethoprim/sulfamethoxazole is preferred because of superiority to other preventative agents [359] and cross-protection for toxoplasmosis and *Nocardia*. If patients have a known allergy to sulfa drugs, an attempt at desensitization should be attempted. Second-line agents include dapsone, atovaquone, and aerosolized pentamidine, but pentamidine is clearly inferior [360], and atovaquone has not been studied prospectively.

Viral Prevention

Cytomegalovirus (CMV)

Two major prevention strategies are currently used in practice to prevent the development of CMV disease: primary antiviral prophylaxis and preemptive therapy (Fig. 12.7). Clinical trials of ganciclovir prophylaxis have been performed and shown to decrease CMV disease [361, 362], but prophylactic approaches with ganciclovir can cause neutropenia, and increase susceptibility to bacterial or fungal infections [363, 364]. Prolonged exposure to CMV-specific antiviral

agents, particularly with minimal immune pressure and subclinical reactivation, can lead to the selection of drug-resistant CMV [365].

At many transplant centers, preemptive therapy is used for CMV prevention in HCT [350]. Although preemptive strategies are similar at most centers, specific cutoffs for starting therapy vary between centers. At our institution, transplant recipients are monitored weekly for CMV viremia by quantitative real-time serum PCR for the first 100 days posttransplant [23]; other centers use the pp65 CMV antigenemia of whole blood PCR assay. Not all patients with detectable CMV will progress to disease, so centers need to develop viral load thresholds for PCR and antigenemia that will maximize effect and minimize toxicity. Alternatively, some centers use a combined strategy with primary prophylaxis with high-dose acyclovir in addition to preemptive therapy [366].

After 100 days posttransplant, PCR surveillance may be discontinued in low-risk patients [19]. High-risk patient, particularly those with ongoing GVHD therapy, should continue weekly surveillance for late CMV disease until they reach minimal immunosuppressant levels and have at least three consecutive negative weekly tests [19]. During late surveillance, our threshold for initiation of therapy is 1,000 copies/mL or greater than fivefold increase in viral load above the patient's established baseline [19].

Epstein-Barr Virus (EBV)

Some centers screen high-risk posttransplant patients (e.g., T-cell-depleted transplants) by weekly EBV PCR. Numerous testing strategies have been advocated, including whole blood, PBMCs, or cell-free plasma. In general, all of these specimens provide good sensitivity, although comparisons suggest that cell-free plasma may provide superior specificity for PTLD [367]. Most authors favor a preemptive therapy similar to what is seen in CMV, in which detection of EBV DNA levels above a certain threshold triggers a reduction in immunosuppression or rituximab therapy [368, 369]. There are no current guidelines for a threshold for EBV viremia due to variances in testing and in transplant populations [31]. Other groups use "prompt" therapy in which treatment is triggered only when detection of EBV DNA is accompanied by overt signs of EBV disease. Prompt therapy has shown similar efficacy to preemptive therapy [370]. Based on the concern that the delay in treatment may lead to increased complications, many groups still favor preemptive approaches [31, 301]. T-cell immunotherapeutic regimens are still experimental and not widely available.

HSV and VZV

Studies using both moderate- and low-dose acyclovir during the posttransplant period have demonstrated a marked decrease in both VZV and HSV complications [6, 371]. The use of acyclovir or valacyclovir is recommended for at least one year posttransplant and through 6 months after cessation of all immunosuppressive

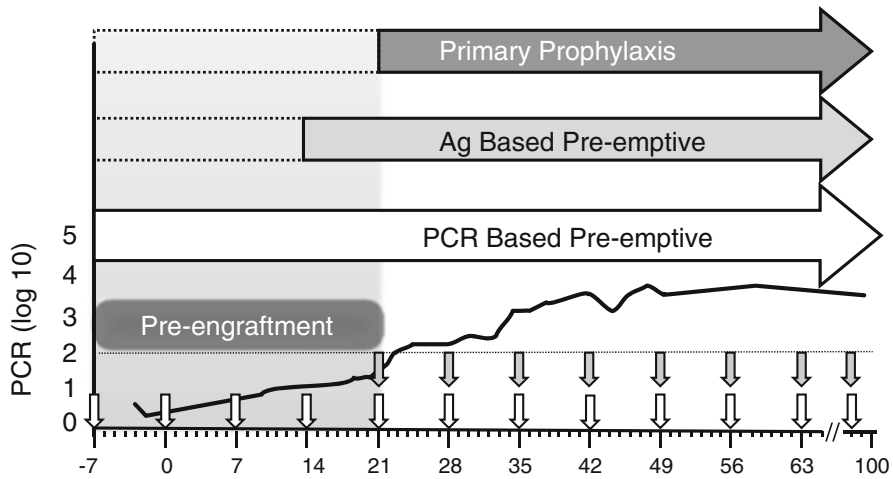


Fig. 12.7 CMV prevention strategies in the posthematopoietic cell transplant period. The X axis indicates the approximate CMV PCR level in serum (log₁₀ copies per mL), which is indicated by the *thick solid line*. The *thin solid line* indicates the typical level of PCR detection. The Y axis represents days pre- or posttransplant. Primary prophylaxis (*large dark-gray arrow*), with drugs such as ganciclovir (IV or oral), is usually given after the point at which patients engraft. Many centers use an antigenemia-based preemptive testing (pp65) strategy (*large medium-gray arrow*). This can be started earlier and has been shown to prevent CMV disease. PCR-based preemptive therapy (*large white arrow*) is the standard at many other centers, including our own, and allows for testing to begin immediately after conditioning. *Small white arrows* indicate weekly testing by PCR that we do at our center through at least day 100. *Small gray arrows* indicated weekly antigenemia testing that typically starts near engraftment

therapies [31]. Long-term prophylaxis also appears to prevent the emergence of acyclovir-resistant HSV [38]. Low-dose acyclovir has also shown the ability to prevent both HSV and VZV reactivation in smaller studies [371, 372].

Adenovirus

Generally, surveillance is not recommended in low-risk patients. Preemptive monitoring has been advocated for adenovirus [277, 373, 374], particularly in children undergoing transplantation and in other high-risk adults (e.g., T-cell-depleted transplant recipients). Most often, cidofovir is used as the agent of choice for preemptive therapy [374].

Respiratory Viruses

Several nonrandomized studies support the use of prophylactic palivizumab for children ≤ 2 years throughout RSV season [375, 376], but adults should not receive palivizumab as prophylaxis.

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