1.1 Introduction

Patients with acute leukemia are at increased risk of developing infections both as a result of the leukemia and its treatment [1]. Neutropenia is the primary risk factor associated with the development of infection, with the severity and frequency of infection increasing as the absolute neutrophil count drops below 500 cells/mm³, as initially described by Bodey and colleagues [2]. Other risk factors may be present including impaired cellular or humoral immunity, breakdown of normal barriers such as the skin and mucosal surfaces, and vascular access catheters and other...
foreign medical devices. Multiple risk factors are often present in the same patient. Additionally, the frequent use of antimicrobial agents for various indications (prophylaxis, empiric therapy, pre-emptive administration, specific or targeted therapy, and occasionally maintenance or suppressive therapy) has an impact on the nature and spectrum of infections, with the emergence/selection of multidrug-resistant (MDR) organisms being of particular concern [3–7]. Bacterial infections tend to occur early on in a neutropenic episode, with fungal infections being uncommon at this stage. If neutropenia persists, the risk for fungal infections increases. There are periodic changes in the epidemiology/spectrum of infection in patients with leukemia. It is important to conduct periodic epidemiologic and susceptibility/resistance surveys, especially at institutions dealing with large numbers of such patients, in order to detect these shifts and changes in susceptibility/resistance patterns, since empiric therapy is largely based on this information [8, 9]. Such surveys are conducted every 3–5 years at our institution.

Fever (defined by the Infectious Diseases Society of America as a single oral temperature of 38.3 °C (101 °F) or a temperature of >38.0 °C (100.4 °F) sustained over a 1 h period) is the most consistent sign of infection and occurs with or without focal signs or symptoms [10]. Greater than 90% of episodes of fever in neutropenic patients with acute leukemia are likely to be caused by an infection. Noninfectious causes include drug fever, fever related to the underlying malignancy, transfusion reactions, or allergic reactions. This chapter will focus on the current epidemiology of infections in patients with acute leukemias. Infections that occur in patients with malignant lymphomas and those that occur as a consequence of treatment with specific modalities (e.g., monoclonal antibodies and nucleoside analogs) will be dealt with separately.

1.2 Nature of Febrile Episodes

Febrile episodes in neutropenic patients have been classified into three distinct categories:

- Clinically documented infections (presence of clinical or radiographic features of infection such as cellulitis or pneumonia, without microbiologic confirmation)
- Microbiologically documented infections (positive cultures from any significant site)
- Unexplained fever – formerly fever of unexplained origin (FUO) – (fever, but no positive cultures or clinical/radiographic features of infection)
**Clinically Documented Infections**

Clinically documented infections account for 25–30 % of febrile episodes in neutropenic patients (Fig. 1.1). They are defined by the presence of a site suggestive of an infection such as cellulitis, pneumonia, esophagitis, or enterocolitis, without microbiological documentation of the causative pathogen for the infection. This may be due to various reasons including the use of antimicrobial prophylaxis, which can render microbiologic cultures negative and/or a blunted inflammatory response resulting in lack of specimens (e.g., sputum) to culture. The vast majority of these episodes respond to empiric antimicrobial therapy, providing indirect evidence that they are due to an infectious process.

**Microbiologically Documented Infections**

Microbiologically documented infections also account for 25–30 % of febrile episodes in neutropenic patients (Fig. 1.1). The majority of these are monomicrobial (i.e., caused by a single pathogen), but polymicrobial infections are being documented with increasing frequency. Recent data show that ~15–25 % of bacteremias in neutropenic patients, including catheter-related infections, are polymicrobial [11–13]. Infections involving deep tissue sites are predominantly polymicrobial [14]. These include neutropenic enterocolitis, perirectal infections, complicated skin/skin structure infections, and pneumonia. The majority of polymicrobial infections are caused by multiple bacterial pathogens (gram-positive, gram-negative, and occasionally anaerobic organisms) although bacterial and fungal or bacterial and viral infections can also co-exist.
1.5 Sites of Infection

The most common and important sites of infection in patients with acute leukemia are listed in Table 1.1. Overall, the respiratory tract is the most common site of infection. Approximately 25% of patients with acute leukemia will develop a pulmonary infiltrate during an episode of neutropenia lasting 10 days or longer. Other parts of the respiratory tract including the oropharynx, upper airways, and the paranasal sinuses are also frequent sites of infection. Most pulmonary infiltrates are secondary to an infectious process (bacterial and fungal organisms predominate) although it is often quite difficult to establish a specific microbiologic diagnosis. Noninfectious causes of pulmonary infiltrates such as alveolar hemorrhage and drug toxicity are much less common. Consequently, empiric therapy directed against anticipated pathogens is generally administered in such patients and can be modified if confirmatory microbiologic data become available. The management of patients with pulmonary infections/complications is discussed in detail elsewhere.

Approximately 15–20% of patients with acute leukemia and neutropenia will develop a bloodstream infection. These include primary bacteremias and central line-associated infections. Gram-positive bacteria are isolated most often (~75–80% of the time) with organisms colonizing the skin (e.g., Staphylococcus species, Bacillus species, Corynebacterium species) being predominant [13–16]. In patients with oral or intestinal mucositis, viridans group streptococci (VGS), enterococci (including VRE), and enteric gram-negative organisms are common pathogens [17, 18]. The frequency of gram-negative bacteremia is lower in patients receiving antibacterial prophylaxis with agents such as the fluoroquinolones, than in patients not receiving prophylaxis [19, 20]. Fungemias occur ~4–6% of the time, are caused most often by Candida species, and are often associated with indwelling central venous catheters [21–24]. With the exception of Fusarium species, invasive mold

| Site of infection | Frequency (%) |
|------------------|---------------|
| Respiratory tract | 30–40         |
| Bloodstream      | 15–20         |
| Urinary tract    | 10–15         |
| Skin and skin structure | 8–10 |
| Intestinal tract  | 5–8           |
| Other sites      | 10–15         |

*Approximately 15–20% of patients will have multiple sites of infection (data from survey conducted at MD Anderson Cancer Center – 2012)

*Includes paranasal sinuses, upper respiratory tract, lungs, and infections such as empyema

*Includes primary and catheter-related bacteremia

*Includes neutropenic enterocolitis, perianal infections, cholangitis

*Includes meningitis, brain abscess, septic arthritis, and other uncommon sites
infections seldom cause fungemia [25, 26]. A small proportion of bacteremic infections are caused by nontuberculous mycobacteria [27].

Urinary tract infections are documented in 10–15% of patients with acute leukemia, especially in patients requiring the placement of short-term or long-term urinary drainage catheters. Gram-negative bacterial pathogens such as *Escherichia coli* predominate although *Candida* species are not uncommon in patients with urinary catheters, stents, or other devices and in those that have received multiple courses of broad-spectrum antibacterial therapy for previous episode of neutropenic fever.

Common skin and skin structure infections include cellulitis, infections at phlebotomy or other puncture wounds, and surgical site infections in patients who have undergone recent surgery. Uncommon, but more serious infections include pyomyositis (occasionally caused by *E. coli*) and necrotizing fasciitis [28]. These conditions usually require surgical intervention in addition to antimicrobial therapy. Even less common are primary cutaneous mold infections [29, 30].

Infections along the gastrointestinal tract are not uncommon. Prior to the frequent use of antifungal prophylaxis, thrush and esophagitis caused mainly by *Candida* species (occasionally by herpes viruses) were commonplace. Azole and echinocandin prophylaxis has rendered these infections largely of historical interest. Neutropenic enterocolitis (typhlitis) occurs primarily in patients with acute leukemia who receive therapy with agents (e.g., cytosine arabinoside, in combination with idarubicin or another anthracycline) that cause high-grade intestinal mucositis although it is being described with increasing frequency in patients receiving other mucotoxic antineoplastic agents such as the taxanes and vinorelbine [31–33]. Perirectal infections occur more often in patients with preexisting local lesions such as fissures and hemorrhoids [34]. True abscess formation is uncommon in patients with severe and prolonged neutropenia, but surgical drainage is almost always beneficial [35, 36].

### 1.6 Spectrum of Bacterial Infection

Recent epidemiologic data document a predominance of gram-positive pathogens from microbiologically documented infections [13–16]. Unfortunately, these data focus on monomicrobial bacteremic infections, and do not provide details from most other sites of infection, or from polymicrobial infections. This gives an incomplete and skewed view about the microbiology of these infections since bacteremias are caused most often by gram-positive organisms that colonize the skin, whereas infections at most other sites (lung, intestinal tract, urinary tract) have a predominance of gram-negative pathogens [14]. Additionally ~80% of polymicrobial infections have a gram-negative component, and ~33% are caused by multiple gram-negative species [11]. When all sites of infection and polymicrobial infections are taken into consideration, a substantially different picture emerges, with gram-negative pathogens being almost as frequent as gram-positive pathogens [14]. Indeed, some institutions are now reporting a predominance of gram-negative
pathogens [37]. Knowledge of local epidemiologic patterns is critical as empiric regimens need to be designed with this information in mind.

1.6.1 Gram-Positive Organisms

The microorganisms isolated most often from neutropenic patients are listed in Table 1.2. The most commonly isolated organisms isolated overall are the coagulase-negative staphylococci (CoNS) [38]. These organisms are generally of low virulence and seldom cause serious or life-threatening infections. Catheter-related bacteremias are the most common infections caused by CoNS. These can often be treated with antimicrobial agents without removal of the offending catheter, although some infections may recur if the catheter is retained [39]. The one exception is *Staphylococcus lugdunensis*, which resembles *S. aureus* in virulence, and infections caused by this species need to be managed like those caused by *S. aureus* [40–42]. Other gram-positive organisms that frequently colonize human skin and often cause infections in patients with leukemia include *Bacillus* species, *Corynebacterium* species, and *Micrococcus* species [43–49]. Like CoNS, the most common infection caused by these organisms is catheter-related bacteremia. Occasionally more
serious infections such as pneumonia, endocarditis, endophthalmitis, and meningitis develop. The organisms are uniformly susceptible to vancomycin, linezolid, and daptomycin, whereas susceptibility to other agents is variable. Most patients respond to appropriate antimicrobial therapy, and infection-related mortality is low. It is not clear whether removal of the infected catheter is always necessary for response; however, recurrent infections seem to be more frequent if the catheter is retained [45, 48, 50]. As mentioned earlier, infections caused by S. aureus are more virulent and are associated with substantial morbidity and mortality [51]. In some cancer treatment centers, ~40–60% of these organisms may be methicillin resistant, although institutional and regional differences do occur, with resistance rates <10% in the Netherlands or Scandinavian countries. Some of these isolates have also developed tolerance or reduced susceptibility to vancomycin (the so-called MIC creep), and slow response to, or overt failure of vancomycin therapy has been reported especially in infections caused by organisms with vancomycin MICs of >1.0/ml [51–56]. In a recent study of MRSA bacteremia in cancer patients from a comprehensive cancer center, a high treatment failure rate for vancomycin (52%) was demonstrated, and a vancomycin MIC of >2/ml was found to be an independent factor for vancomycin failure [57]. Based on this and similar reports, the current recommendation is to consider therapy with alternative agents such as linezolid or daptomycin for infections caused by organisms with reduced susceptibility to vancomycin [58–60].

Alpha-hemolytic or viridans group streptococci are major components of human oral microflora. For many years, they were considered contaminants or organisms of low virulence, even in neutropenic patients. However, subsequent clinical experience has shown that they are responsible for serious, life-threatening infections in this patient population [61, 62]. The most consistent predisposing factor for infection by these organisms appears to be high-dose chemotherapy with agents such as cytosine arabinoside that induce severe mucosal damage, thereby facilitating entry of these organisms into the bloodstream [63]. Other probable predisposing factors include antimicrobial prophylaxis with fluoroquinolones that might encourage selection and overgrowth of these organisms and treatment of chemotherapy-induced gastritis with antacids or histamine type 2 (H2) antagonists [64–66]. Streptococcus mitis, S. sanguis, and S. salivarius are the predominant species [18, 67]. Bacteremia is the most common manifestation. In some patients, a rapidly progressive and disseminated infection (sometimes referred to as the streptococcal toxic shock syndrome) occurs involving the bloodstream, lungs, central nervous system, and skin [68]. Despite prompt and aggressive antimicrobial therapy, the mortality associated with this syndrome is 25–35%. Of increasing concern are reports that 20–60% of VGS are non-susceptible or overtly resistant to penicillin [18, 68]. This has limited the utility of penicillin G and other penicillins for the prevention and treatment of these infections. All isolates are currently susceptible to vancomycin, although tolerance has been described [18, 69–72]. The use of antibiotic combinations may be necessary, especially against tolerant organisms. These organisms are also susceptible to the newer-generation quinolones (e.g., moxifloxacin), daptomycin, and linezolid, but clinical experience with these agents is limited.
The enterococci reside primarily in the intestinal tract and cause a variety of infections such as bacteremia, urinary tract infection, endocarditis, intra-abdominal/pelvic infections, biliary tract infections, and occasionally pneumonia and meningitis. They are seldom primary pathogens but are seen most often following prolonged therapy with broad-spectrum cephalosporins or carbapenems to which they are intrinsically resistant. Increased use of vancomycin especially in neutropenic cancer patients was at least in part responsible for the emergence of vancomycin-resistant enterococci (VRE) globally, and these organisms now account for 15–30% of all enterococcal isolates [4]. Fecal colonization with VRE is not uncommon in patients with acute leukemia and recipients of stem cell transplantation [73, 74]. Approximately 30% of patients with VRE fecal colonization will go on to develop bacteremia or other significant infections with these organisms following chemotherapy, and some experts recommend the empiric use of agents with activity against VRE when such patients develop fever during an episode of neutropenia [10, 75]. Attempts at eradicating fecal colonization with VRE have been singularly unsuccessful. Consequently, infection control measures to reduce transmission of VRE are of overriding importance.

1.6.2 Gram-Negative Bacilli

The gastrointestinal tract serves as an important source of infection in neutropenic patients, with the predominant pathogens being enteric gram-negative bacilli. The use of antibacterial prophylaxis in high-risk patients including those with acute leukemia has led to a reduction in the frequency of documented gram-negative infections, although some centers are reporting a reversal of this trend [19, 20]. Nevertheless, gram-negative infections, when they do occur, are generally associated with greater morbidity and mortality than infections caused by their gram-positive counterparts. Multiple surveillance studies have shown that *E. coli*, *Klebsiella* spp., and *P. aeruginosa* remain the three most commonly isolated gram-negative organisms from neutropenic patients and collectively cause 65–75% of microbiologically documented gram-negative infections [76–79]. Other Enterobacteriaceae such as *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp., and *Proteus* spp. are less common, although institutional differences do exist. Despite the overall decline in the frequency of gram-negative infections in neutropenic patients, there has been an increase in the proportion of such infections caused by non-fermentative gram-negative bacilli (NFGNB) such as *Acinetobacter* spp., non-aeruginosa *Pseudomonas* spp., and *Stenotrophomonas maltophilia* [80]. Collectively, NFGNB now cause ~38% of documented gram-negative infections, a proportion that has gradually increased over the years. The overall spectrum of infections caused by gram-negative bacilli is wide, with pneumonia, primary and catheter-related bacteremia, and urinary tract infection being common – Table 1.3.

*P. aeruginosa* is the most frequently isolated and the most important pathogenic NFGNB in this setting and causes between 15 and 20% of all gram-negative infections [13–16]. Additionally, it is the most common gram-negative organism isolated 
from polymicrobial infections [11, 12]. These organisms have the propensity for developing resistance to antimicrobial agents by multiple mechanisms [81, 82]. A recent study demonstrated that the risk factors associated with multidrug-resistant P. aeruginosa infections were the use of a carbapenem as monotherapy for >7 days, a history of P. aeruginosa infection in the preceding year, and a history of chronic obstructive pulmonary disease [83]. Consequently, the antimicrobial stewardship program at our institution has targeted the prolonged use of carbapenem monotherapy, with a resultant decrease in the frequency of infections with MDR P. aeruginosa [84]. Stenotrophomonas maltophilia colonization/infection rates in neutropenic patients, especially those with acute leukemia and recipients of HSC transplantation, have increased considerably over the past two to three decades. Surveillance studies conducted at the University of Texas MD Anderson Cancer Center have documented an increase in the proportion of S. maltophilia from 2 % of all gram-negative bacilli isolated in 1986 to 7 % in 2012. Patients with prolonged neutropenia, those exposed to broad-spectrum antibiotics, especially the carbapenems, and those requiring mechanical ventilation have a higher risk of infection, although these infections are also seen in patients without traditional risk factors [85, 86]. The shift from trimethoprim/sulfamethoxazole (TMP/SMX) which has potent activity against S. maltophilia to the fluoroquinolones (which are much less active against S. maltophilia) as the preferred agents for antimicrobial prophylaxis in high-risk neutropenic patients may also have contributed to the increase in infections caused by these organisms. TMP/SMX has been and remains the agent of choice for the treatment of infections caused by S. maltophilia, but in vitro resistance to it appears to be increasing [85, 87]. Ticarcillin/clavulanate also has reliable activity, whereas other beta-lactams such as ceftazidime, cefepime, and piperacillin/tazobactam have variable activity against these organisms. The newer quinolones such as moxifloxacin are more active than older agents such as ciprofloxacin and

| Table 1.3 | The spectrum of infections caused by Pseudomonas aeruginosa and other gram-negative bacilli |
|-----------|------------------------------------------------------------------------------------------|
| Bacteremia – primary and catheter related |
| Pneumonia, empyema, lung abscess |
| Urinary tract infection – primary and catheter related |
| Neutropenic enterocolitis (typhilitis) |
| Perirectal infection/abscess |
| Skin and skin structure infection (ecthyma) |
| Cholangitis/biliary tract infection |
| Abdominal/pelvic/hepatic abscess |
| Otitis externa/mastoiditis |
| Keratitis/endophthalmitis |
| Osteomyelitis/septic arthritis |
| Prostatitis |

Data from infectious diseases consultation records at MD Anderson Cancer Center

*Abscess formation is uncommon in patients with severe and prolonged neutropenia
levofloxacin [80]. Minocycline and the novel glycyicycline – tigecycline, are also active against many *S. maltophilia* isolates [88]. Clinical experience with agents other than TMP/SMX and ticarcillin/clavulanate is limited. Combination regimens based on the susceptibility of individual isolates are often employed [89].

Other less common but important NFGNB include *Acinetobacter* spp., *Achromobacter* and *Alcaligenes* spp., *Burkholderia* spp., *Chryseobacterium* spp., and non-aeruginosa *Pseudomonas* species such as *P. putida* and *P. fluorescens* [90–96]. The clinical importance of these organisms has increased in recent years as they frequently cause outbreaks and MDR infections. Many outbreaks can be traced to sources such as contaminated dialysis fluid, chlorhexidine solution, deionized water, and mechanical ventilators.

### 1.7 Fungal Infections

Whereas bacterial infections predominate during the first 7–10 days of severe neutropenia, invasive fungal infections start to develop as neutropenia persists. Prior to the availability of agents like fluconazole, invasive candidiasis with or without hematogenous dissemination was common, with *Candida albicans* being the predominant species isolated. The frequency of invasive candidiasis has been substantially reduced with the routine usage of antifungal prophylaxis (azoles, echinocandins) in high-risk patients, with manifestations like *Candida* esophagitis, and chronic disseminated (hepatosplenic) candidiasis becoming increasingly of historical interest [97]. The use of some of these agents also led to the emergence of *Candida* spp. other than *Candida albicans* as frequent pathogens in this setting, although *C. albicans* continues to be the single most common species isolated [98,99]. Regional differences have been documented with a preponderance of different *Candida* species at different centers [21, 22, 100–102]. These differences may represent divergent use of antifungal prophylaxis and/or geographic diversity. Consequently, local epidemiologic and susceptibility data should be used to guide empiric and targeted therapy. Other yeasts that are encountered in this setting include *Trichosporon beigelii*, *Malassezia furfur*, *Saccharomyces cerevisiae*, and occasionally *Hansenula anomala* [103, 104].

The risk of hematogenous dissemination with various yeasts is greater in patients who have indwelling vascular catheters and chemotherapy-induced mucositis or graft versus host disease [99, 105]. Currently, catheter removal in addition to appropriate antifungal therapy is recommended, although this strategy is by no means universally accepted [106–108]. Most *C. albicans* isolates maintain susceptibility to fluconazole and itraconazole. The newer triazole agents such as voriconazole also have potent activity against most pathogenic yeasts. The echinocandins appear to be effective for the treatment of candidiasis caused by most *Candida* species [106]. Treatment of candidiasis with polyenes is seldom necessary. Despite appropriate therapy, the overall mortality in cancer patients with candidemia (which is mainly due to the severity of the underlying disease) approaches 40% [98]. Disseminated *T. beigelii* infections respond less frequently than disseminated candidiasis [104].
Invasive mold infections, due primarily to *Aspergillus* species, are the most frequent cause of serious, often life-threatening infections in patients with neutropenia that persists for more than 2 weeks [109]. Other risk factors include impaired cellular immunity, prolonged corticosteroid administration, allogeneic stem cell transplantation, and advanced age [103]. *A. fumigatus* is the predominant species isolated but non-fumigatus species of *Aspergillus* are emerging as significant pathogens [110–113]. The most common site of involvement is the lungs leading to invasive pulmonary aspergillosis (IPA). Other common sites of involvement include the paranasal sinuses, the central nervous system, the heart and pericardium, the liver, the kidneys, and occasionally, bones and joints. Cough, dyspnea, and hemoptysis are the classic manifestations of IPA but may be absent or muted in many patients due to severe immunosuppression leading to a blunted inflammatory response. Persistent fever in patients with prolonged neutropenia, despite appropriate antibiotic therapy, should raise the suspicion of invasive fungal infection including IPA. Most infections are diagnosed by computerized tomography (CT) imaging. Classic findings include nodular or wedge-shaped densities, the halo sign, and cavitary lesions [114, 115]. These findings change and evolve over time, and in response to therapy, consequently the performance of serial CT imaging has been found to be useful in monitoring patients with IPA. *Aspergillus hyphae* are angioinvasive in nature and result in release of fungal antigens into the bloodstream. Serologic testing to detect galactomannan or beta-D-glucan has been evaluated for the early diagnosis of invasive aspergillosis. The former appears to be more useful than the latter and may also be a predictor of outcome [116–120]. The use of these tests in conjunction with CT imaging has been discussed in various guidelines for the diagnosis and management of invasive fungal infections in neutropenic patients and HSCT recipients [121–123].

Several mold-active agents are now available for the prevention and treatment of invasive aspergillosis. These include amphotericin B and its lipid formulations, itraconazole, posaconazole, and the echinocandins. A detailed discussion of antifungal prophylaxis and therapy is beyond the scope of this chapter, but recent guidelines addressing these issues are available [121–125]. Although still uncommon, zygomycosis (mucormycosis) has emerged as an increasingly important infection in the past 15–20 years especially in patients with hematologic malignancies and HSCT recipients [99, 126, 127]. The increasing frequency of zygomycosis has at least in part been attributed to the use of voriconazole for various indications such as antifungal prophylaxis and empiric, pre-emptive or targeted therapy of invasive fungal infection [128–132]. The most common organisms isolated include *Rhizopus* species, *Mucor* species, and *Cunninghamella* species. Common sites of infection include the paranasal sinuses and orbit, the lungs, skin, and the central nervous system, with pulmonary manifestations being predominant in neutropenic cancer patients. Generalized dissemination occurs in up to 5% of patients. Clinical features are often indistinguishable from other common mold infections. Early diagnosis of zygomycosis is important for timely therapeutic intervention, and ultimately, reduced mortality and improved survival. Conventional methods for laboratory assessment for zygomycosis include direct examination, cytopathologic
examination, and histopathologic examination of respiratory and other relevant specimens. The use of immunohistochemical stains, fluorescent and in situ hybridization, or in situ polymerase chain reaction (PCR) may also be useful. Cultures from various specimens are often negative. There is increased reliance on diagnostic imaging such as CT of the paranasal sinuses and chest, which may reveal early findings even before the development of localizing symptoms [133, 134]. Unlike invasive aspergillosis where recent diagnostic and therapeutic advances have improved overall survival, the outcome of patients with hematologic malignancies who develop zygomycosis has not improved significantly [126, 127, 135]. Only two systemic antifungals have reliable activity against these organisms – amphotericin B and its lipid formulations and the new triazole, posaconazole. Recent guidelines advocate the lipid preparations of amphotericin B as first-line therapy, with posaconazole and combinations of caspofungin with lipid preparations of amphotericin B as second-line therapy [136, 137]. Surgery is recommended for rhinocerebral and soft tissue infections. Reversal of underlying risk factors is important. The duration of therapy remains unclear and should be guided by resolution of all associated symptoms and findings. Maintenance therapy and/or secondary prophylaxis should be considered in patients who remain severely immunosuppressed. Other uncommon but important molds that cause invasive infections in patients with hematologic malignancies include *Fusarium* species and *Scedosporium* species [138]. Unlike most other molds, fungemia is common in patients with fusariosis and may occur in ~40% of patients [139]. Involvement of the paranasal sinuses, lungs, skin, and disseminated infection is also relatively common. Optimum therapy remains to be defined, and the overall outcome is poor. The incidence of Scedosporium infection appears to be increasing, with cases of *S. prolificans* generally occurring after 2000 [140]. As with fusariosis, optimum therapy remains to be defined, and the overall prognosis is poor.

### 1.7.1 Viral Infections

Viral infections per se are uncommon in patients with hematologic malignancies who do not receive HSCT. Most HSV and VZV infections in this setting result from reactivation of the latent viruses from previous exposure, and primary infections are rare [141, 142]. Most US adults are HSV-1 or HSV-2 seropositive, and reactivation can occur in up to 60% of patients undergoing intensive chemotherapy for hematologic malignancies. Reactivation usually occurs soon after chemotherapy, while patients are still severely neutropenic, and much of the morbidity caused by oral mucositis has been attributed to HSV reactivation in this setting. Consequently, several guidelines recommend HSV prophylaxis in patients undergoing HSCT or remission induction therapy for leukemia [10, 143]. Reactivation of latent VZV also occurs but to a lesser extent, and the risk is considered insufficient to warrant routine prophylaxis.

Over the past two decades, the importance of community respiratory viruses as significant causes of morbidity and mortality in HSCT recipients and patients with hematologic malignancies has been recognized [144–150]. These include human
influenza viruses (A and B), respiratory syncytial virus (RSV), human parainfluenza viruses, human metapneumovirus, human coronaviruses, and human rhinoviruses. Many of these (e.g., the influenza viruses and RSV) have a seasonal preponderance, although some are encountered year round. Upper respiratory tract infections (URTI) predominate, with rhinorrhea being the most common manifestation. Progression to lower respiratory tract infection (LRTI) can lead to respiratory failure and a fatal outcome depending on host factors and the intrinsic virulence of specific viruses. Testing for respiratory viruses is recommended in high-risk patients. Specimens for diagnostic testing include nasopharyngeal swabs, washes, or aspirates, tracheal aspirates, and bronchoalveolar lavage specimens. Laboratory tests include nucleic acid amplification testing, direct antigen detection, and isolation of the virus by cell culture. Optimum therapy for most of these infections remains to be determined (except for human influenza viruses). Pooling of published studies from various centers in the absence of sufficiently powered, randomized, controlled trials, suggests that treatment of LRTI with ribavirin and intravenous immunoglobulin may improve outcome in RSV infections [151]. This approach is also used to prevent the development of LRTI in HSCT recipients with URTI.

1.8 Summary

Infections cause a substantial amount of morbidity and mortality in patients with acute leukemia and other hematologic malignancies. Neutropenia is the predominant predisposing factor, although other factors also contribute to the development of infection. Bacterial infections predominate during the initial phases of severe neutropenia. Invasive fungal infections develop in patients with persistent and profound neutropenia. Viral infections appear to be increasing in frequency and severity. Early diagnosis and the administration of pre-emptive therapy, especially when dealing with invasive fungal infections, are important as infection prevention. The development of resistance and the limited availability of therapeutic agents with activity against resistant pathogens are areas of global concern. As a result, programs for antimicrobial stewardship and infection control need to be strictly adhered to.

References

1. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management. Cancer. 2004;100:228–37.
2. Bodey GP, Buckley M, Sathe YS, Freireich EJ. Quantitative relationships between circulating leukocytes and infection in patients with acute leukemia. Ann Intern Med. 1966;64:328–40.
3. Edmond MB, Ober JF, Weinbaum DL, Pfaller MA, Hwang T, Sanford MD, et al. Vancomycin-resistant Enterococcus faecium bacteremia: risk factors for infection. Clin Infect Dis. 1995;20:1126–33.
4. Kern WV, Klose K, Jellen-Ritter AS, Oethinger M, Bohnert J, Kern P, et al. Fluoroquinolone resistance of Escherichia coli at a cancer center: epidemiologic evolution and effects of
discontinuing prophylactic fluoroquinolone use in neutropenic patients with leukemia. Eur J Clin Microbiol Infect Dis. 2005;24:111–8.
5. Fihman V, Le Monnier A, Corvec S, Jauregy F, Tankovic J, Jacquier H, et al. Stenotrophomonas maltophilia—the most worrisome threat among unusual non-fermentative gram-negative bacilli from hospitalized patients: a prospective multicenter study. J Infect. 2012;64:391–8.
6. Lai CC, Wang CY, Chu CC, Tan CK, Lu CL, Lee YC, et al. Correlation between antibiotic consumption and resistance of Gram-negative bacteria causing healthcare-associated infections at a university hospital in Taiwan from 2000 to 2009. J Antimicrob Chemother. 2011;66:1374–82.
7. Sanyal SC, Mokaddas EM. The increase in carbapenem use and emergence of Stenotrophomonas maltophilia as an important nosocomial pathogen. J Chemother. 1999;11:28–33. Rolston.
8. Rolston K, RI, LeBlanc BJ, Streeter HL, Ho DH. Susceptibility surveillance among gram-negative bacilli at a comprehensive cancer center. J Infect. 2003;98(244):3–7.
9. Rolston KV. Challenges in the treatment of infections caused by gram-positive and gram-negative bacteria in patients with cancer and neutropenia. Clin Infect Dis. 2005;40 Suppl 4:S246–52.
10. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2011;52:e56–93.
11. Elting LS, Bodey GP, Fainstein V. Polymicrobial septicemia in the cancer patient. Medicine (Baltimore). 1986;65:218–25.
12. Rolston KV, Bodey GP, Safdar A. Polymicrobial infection in patients with cancer: an under-appreciated and underreported entity. Clin Infect Dis. 2007;45:228–33.
13. Klastersky J, Ameye L, Maertens J, Georgala A, Muanza F, Aoun M, et al. Bacteremia in febrile neutropenic cancer patients. Int J Antimicrob Agents. 2007;30 Suppl 1:S51–9.
14. Yadegarynia D, Tarrand J, Raad I, Rolston K. Current spectrum of bacterial infections in patients with cancer. Clin Infect Dis. 2003;37:1144–5.
15. Zinner SH. Changing epidemiology of infections in patients with neutropenia and cancer: emphasis on gram-positive and resistant bacteria. Clin Infect Dis. 1999;29:490–4.
16. Wisplinghoff H, Seifert H, Wenzel RP, Edmond MB. Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematologic malignancies and solid neoplasms in hospitals in the United States. Clin Infect Dis. 2003;36:1103–10.
17. Husni R, Hachem R, Hanna H, Raad I. Risk factors for vancomycin-resistant Enterococcus (VRE) infection in colonized patients with cancer. Infect Control Hosp Epidemiol. 2002;23:102–3.
18. Han XY, Kamana M, Rolston KV. Viridans streptococci isolated by culture from blood of cancer patients: clinical and microbiologic analysis of 50 cases. J Clin Microbiol. 2006;44:160–5.
19. Bucanave G, Micozzi A, Menichetti F, Martino P, Dionisi MS, Martinelli G, et al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. N Engl J Med. 2005;353:977–87.
20. Cullen M, Steven N, Billingham L, Gaunt C, Hastings M, Simmonds P, et al. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. N Engl J Med. 2005;353:988–98.
21. Sipsas NV, Lewis RE, Tarrand J, Hachem R, Rolston KV, Raad II, et al. Candidemia in patients with hematologic malignancies in the era of new antifungal agents (2001–2007): stable incidence but changing epidemiology of a still frequently lethal infection. Cancer. 2009;115:4745–52.
22. Hachem R, Hanna H, Kontoyiannis D, Jiang Y, Raad I. The changing epidemiology of invasive candidiasis: Candida glabrata and Candida krusei as the leading causes of candidemia in hematologic malignancy. Cancer. 2008;112:2493–9.
23. Bodey GP, Mardani M, Hanna HA, Boktour M, Abbas J, Girgawy E, et al. The epidemiology of Candida glabrata and Candida albicans fungemia in immunocompromised patients with cancer. Am J Med. 2002;112:380–5.
24. DiNubile MJ, Hille D, Sable CA, Kartsonis NA. Invasive candidiasis in cancer patients: observations from a randomized clinical trial. J Infect. 2005;50:443–9.
25. Jossi M, Ambrosioni J, Macedo-Vinas M, Garbino J. Invasive fusariosis with prolonged fungemia in a patient with acute lymphoblastic leukemia: case report and review of the literature. Int J Infect Dis. 2010;14:e354–6.
26. Nucci M, Anaissie E. Fusarium infections in immunocompromised patients. Clin Microbiol Rev. 2007;20:695–704.
27. Chen CY, Sheng WH, Lai CC, Liao CH, Huang YT, Tsay W, et al. Mycobacterial infections in adult patients with hematologic malignancy. Eur J Clin Microbiol Infect Dis. 2012;31:1059–66.
28. Vigil KJ, Johnson JR, Johnston BD, Kontoyiannis DP, Mulanovich VE, Raad II, et al. Escherichia coli Pyomyositis: an emerging infectious disease among patients with hematologic malignancies. Clin Infect Dis. 2010;50:374–80.
29. van Burik JA, Colven R, Spach DH. Cutaneous aspergillosis. J Clin Microbiol. 1998;36:3115–21.
30. Walsh TJ. Primary cutaneous aspergillosis–an emerging infection among immunocompromised patients. Clin Infect Dis. 1998;27:453–7.
31. Ibrahim NK, Sahin AA, Dubrow RA, Lynch PM, Boehnke-Michaud L, Valero V, et al. Colitis associated with docetaxel-based chemotherapy in patients with metastatic breast cancer. Lancet. 2000;355:281–3.
32. Gomez L, Martino R, Rolston KV. Neutropenic enterocolitis: spectrum of the disease and comparison of definite and possible cases. Clin Infect Dis. 1998;27:695–9. Nesher.
33. Nesher L, Rolston KV. Neutropenic enterocolitis, a growing concern in the era of widespread use of aggressive chemotherapy. Clin Infect Dis. 2013;56:711–7.
34. Schimpff SC, Wiernik PH, Block JB. Rectal abscesses in cancer patients. Lancet. 1972;2:844–7.
35. Barnes SG, Sattler FR, Ballard JO. Perirectal infections in acute leukemia. Improved survival after incision and debridement. Ann Intern Med. 1984;100:515–8.
36. Rolston K, Bodey GP. Diagnosis and management of perianal and perirectal infection in the granulocytopenic patient. In: Jack S, Remington M, editors. Current clinical topics in infectious diseases. Cambridge, MA: Blackwell Scientific Publications; 1989. p. 164–71.
37. Gudiol C, Bodro M, Simonetti A, Tubau F, Gonzalez-Barca E, Cisnal M, et al. Changing aetiology, clinical features, antimicrobial resistance, and outcomes of bloodstream infection in neutropenic cancer patients. Clin Microbiol Infect. 2013;19(5):474–9.
38. Rolston KV, Yadeegarynia D, Kontoyiannis DP, Raad II, Ho DH. The spectrum of Gram-positive bloodstream infections in patients with hematologic malignancies, and the in vitro activity of various quinolones against Gram-positive bacteria isolated from cancer patients. Int J Infect Dis. 2006;10:223–30.
39. Raad I, Kassar R, Ghannam D, Chaftari AM, Hachem R, Jiang Y. Management of the catheter in documented catheter-related coagulase-negative staphylococcal bacteremia: remove or retain? Clin Infect Dis. 2009;49:1187–94.
40. Klotchko A, Wallace MR, Licitra C, Sieger B. Staphylococcus lugdunensis: an emerging pathogen. South Med J. 2011;104:509–14.
41. Kleiner E, Monk AB, Archer GL, Forbes BA. Clinical significance of Staphylococcus lugdunensis isolated from routine cultures. Clin Infect Dis. 2010;51:801–3.
42. Fadel HJ, Patel R, Vetter EA, Baddour LM. Clinical significance of a single Staphylococcus lugdunensis-positive blood culture. J Clin Microbiol. 2011;49:1697–9.
43. Banerjee C, Bostamante CI, Wharton R, Talley E, Wade JC. Bacillus infections in patients with cancer. Arch Intern Med. 1988;148:1769–74.
44. Ozkocaman V, Ozcelik T, Ali R, Ozkalemkas F, Ozkan A, Ozakin C, et al. Bacillus spp. among hospitalized patients with haematological malignancies: clinical features, epidemics and outcomes. J Hosp Infect. 2006;64:169–76.
45. Kassar R, Hachem R, Jiang Y, Chaftari AM, Raad I. Management of Bacillus bacteremia: the need for catheter removal. Medicine (Baltimore). 2009;88:279–83.
46. Martins C, Faria L, Souza M, Camello T, Velasco E, Hirata Jr R, et al. Microbiological and host features associated with corynebacteriosis in cancer patients: a five-year study. Mem Inst Oswaldo Cruz. 2009;104:905–13.
47. Adderson EE, Boudreaux JW, Hayden RT. Infections caused by coryneform bacteria in pediatric oncology patients. Pediatr Infect Dis J. 2008;27:136–41.
48. Ghide S, Jiang Y, Hachem R, Chaftari AM, Raad I. Catheter-related Corynebacterium bacteremia: should the catheter be removed and vancomycin administered? Eur J Clin Microbiol Infect Dis. 2010;29:153–6.
49. Ramos ER, Hachem R, Youssef S, Fang X, Jiang Y, Raad I. The crucial role of catheters in micrococcal bloodstream infections in cancer patients. Infect Control Hosp Epidemiol. 2009;30:83–5.
50. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O’Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;49:1–45.
51. Sañdar A, Rolston KV. Vancomycin tolerance, a potential mechanism for refractory gram-positive bacteremia observational study in patients with cancer. Cancer. 2006;106:1815–20.
52. Sakoulas G, Moise-Broder PA, Schentag J, Forrest A, Moelling Jr RC, Eliopoulos GM. Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant Staphylococcus aureus bacteremia. J Clin Microbiol. 2004;42:2398–402.
53. van Hal SJ, Lodise TP, Paterson DL. The clinical significance of vancomycin minimum inhibitory concentration in Staphylococcus aureus infections: a systematic review and meta-analysis. Clin Infect Dis. 2012;54:755–71.
54. Sakoulas G. Daptomycin for soft tissue infection and neutropenia in a myelogenous leukemia patient who failed prior vancomycin therapy. Clin Adv Hematol Oncol. 2008;6:813–5.
55. Rolston KV. Review: daptomycin for the treatment of gram-positive infections in neutropenic cancer patients. Clin Adv Hematol Oncol. 2008;6:815–7.
56. Sakoulas G, Moelling Jr RC. Increasing antibiotic resistance among methicillin-resistant Staphylococcus aureus strains. Clin Infect Dis. 2008;46 Suppl 5:S360–7.
57. Mahajan SN, Shah JN, Hachem R, Tverdek F, Adachi JA, Mulanovich V, et al. Characteristics and outcomes of methicillin-resistant staphylococcus aureus bloodstream infections in patients with cancer treated with vancomycin: 9-year experience at a comprehensive cancer center. Oncologist. 2012;17:1329–36.
58. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children: executive summary. Clin Infect Dis. 2011;52:285–92.
59. Chaftari AM, Hachem R, Mulanovich V, Chemaly RF, Adachi J, Jacobson K, et al. Efficacy and safety of daptomycin in the treatment of Gram-positive catheter-related bloodstream infections in cancer patients. Int J Antimicrob Agents. 2010;36:182–6.
60. Rolston KV, McConnell SA, Brown J, Lamp KC. Daptomycin use in patients with cancer and neutropenia: data from a retrospective registry. Clin Adv Hematol Oncol. 2010;8:249–56, 90.
61. Bochud PY, Eggiman P, Calandra T, Van Melle G, Saghafi L, Francioli P. Bacteremia due to viridans streptococci in neutropenic patients with cancer: clinical spectrum and risk factors. Clin Infect Dis. 1994;18:25–31.
62. Tunkel AR, Sepkowitz KA. Infections caused by viridans streptococci in patients with neutropenia. Clin Infect Dis. 2002;34:1524–9.
63. Paganini H, Staffolani V, Zubizarreta P, Casimir L, Lopardo H, Luppino V. Viridans streptococci bacteraemia in children with fever and neutropenia: a case-control study of predisposing factors. Eur J Cancer. 2003;39:1284–9.
64. Elting LS, Bodey GP, Keefe BH. Septicemia and shock syndrome due to viridans streptococci: a case-control study of predisposing factors. Clin Infect Dis. 1992;14:1201–7.
65. Razonable RR, Litzow MR, Khaliq Y, Piper KE, Rouse MS, Patel R. Bacteremia due to viridans group Streptococci with diminished susceptibility to Levofoxacin among neutropenic patients receiving levofoxacin prophylaxis. Clin Infect Dis. 2002;34:1469–74.
66. Prabhu RM, Piper KE, Litzow MR, Steckelberg JM, Patel R. Emergence of quinolone resistance among viridans group streptococci isolated from the oropharynx of neutropenic peripheral blood stem cell transplant patients receiving quinolone antimicrobial prophylaxis. Eur J Clin Microbiol Infect Dis. 2005;24:832–8.
67. Gaudreau C, Delage G, Rousseau D, Cantor ED. Bacteremia caused by viridans streptococci in 71 children. Can Med Assoc J. 1981;125:1246–9.
68. Gassas A, Grant R, Richardson S, Dupuis LL, Doyle J, Allen U, et al. Predictors of viridans streptococcal shock syndrome in bacteremic children with cancer and stem-cell transplant recipients. J Clin Oncol. 2004;22:1222–7.
69. Westling K, Julander I, Ljungman P, Thalme A, Nord CE. Reduced susceptibility to penicillin of viridans group streptococci in the oral cavity of patients with haematological disease. Clin Microbiol Infect. 2004;10:899–903.
70. Lyytikainen O, Rautio M, Carlson P, Anttila VJ, Vuonto R, Sarkkinen H, et al. Nosocomial bloodstream infections due to viridans streptococci in haematological and non-haematological patients: species distribution and antimicrobial resistance. J Antimicrob Chemother. 2004;53:631–4.
71. Diekema DJ, Coffman SL, Marshall SA, Beach ML, Rolston KV, Jones RN. Comparison of activities of broad-spectrum beta-lactam compounds against 1,128 gram-positive cocci recently isolated in cancer treatment centers. Antimicrob Agents Chemother. 1999;43:940–3.
72. Wisplinghoff H, Reinert RR, Cornely O, Seifert H. Molecular relationships and antimicrobial susceptibilities of viridans group streptococci isolated from blood of neutropenic cancer patients. J Clin Microbiol. 1999;37:1876–80.
73. Matar MJ, Tarrand J, Raad I, Rolston KV. Colonization and infection with vancomycin-resistant Enterococcus among patients with cancer. Am J Infect Control. 2006;34:534–6.
74. Liss BJ, Vehreschild JJ, Cornely OA, et al. Intestinal colonisation and blood stream infections due to vancomycin-resistant enterococci (VRE) and extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBLE) in patients with haematological and oncological malignancies. Infection. 2012;40(6):613–9.
75. Rolston KV. Letter to the Editor: Regarding: Kraft S, Mackler E, Schlickman P, Welch K, DePestel DD (2011) Outcomes of therapy: vancomycin-resistant entercoccal bacteremia in hematology and bone marrow transplant patients. Supp Care Cancer 19;1969–1974. Support Care Cancer. 2012;20:1117–8.
76. Bodey GP, Ho DH, Elting L. Survey of antibiotic susceptibility among gram-negative bacilli at a cancer hospital. Am J Med. 1988;85:49–51.
77. Rolston KV, Elting L, Waguespack S, Ho DH, LeBlanc B, Bodey GP. Survey of antibiotic susceptibility among gram-negative bacilli at a cancer center. Chemotherapy. 1996;42(5):348–53.
78. Jacobson K, Rolston K, Elting L, et al. Susceptibility surveillance among gram-negative bacilli at a cancer center. Chemotherapy. 1999;45(5):325–34.
79. Rolston KV, Tarrand JJ. Pseudomonas aeruginosa—a frequent pathogen in patients with cancer: 11-year experience at a comprehensive cancer center. Clin Infect Dis. 1999;29:463–4.
80. Rolston KV, Kontoyiannis DP, Yadegarynia D, Raad II. Nonfermentative gram-negative bacilli in cancer patients: increasing frequency of infection and antimicrobial susceptibility of clinical isolates to fluoroquinolones. Diagn Microbiol Infect Dis. 2005;51:215–8.
81. Aboutayfacl H, Sader HS, Rolston K, Dshpande LM, Toleman M, Bodey G, et al. blaVIM-2 and blaVIM-7 carbapenemase-producing Pseudomonas aeruginosa isolates detected in a tertiary care medical center in the United States: report from the MYSTIC program. J Clin Microbiol. 2007;45:614–5.
82. Toleman MA, Rolston K, Jones RN, Walsh TR. blaVIM-7, an evolutionarily distinct metallo-beta-lactamase gene in a Pseudomonas aeruginosa isolate from the United States. Antimicrob Agents Chemother. 2004;48:329–32.
83. Chatzinikolaou I, Abi-Said D, Bodey GP, Rolston KV, Tarrand JJ, Samonis G. Recent experience with Pseudomonas aeruginosa bacteremia in patients with cancer: Retrospective analysis of 245 episodes. Arch Intern Med. 2000;160:501–9.
84. Tverdek FP, Wu C, Mihu C, et al. Antimicrobial stewardship initiative in cancer patients: The MD Anderson Cancer Center Experience. Infectious diseases society of America (IDSA) annual meeting, San Diego. 17–21 Oct Abstract# 37545.
85. Safdar A, Rolston KV. Stenotrophomonas maltophilia: changing spectrum of a serious bacterial pathogen in patients with cancer. Clin Infect Dis. 2007;45:1602–9.
86. Aisenberg G, Rolston KV, Dickey BF, Kontoyiannis DP, Raad II, Safdar A. Stenotrophomonas maltophilia pneumonia in cancer patients without traditional risk factors for infection, 1997–2004. Eur J Clin Microbiol Infect Dis. 2007;26:13–20.
87. Vartivarian S, Anaissie E, Bodey G, Sprigg H, Rolston K. A changing pattern of susceptibility of Xanthomonas maltophilia to antimicrobial agents: implications for therapy. Antimicrob Agents Chemother. 1994;38:624–7.
88. Noskin GA. Tigecycline: a new glycylcycline for treatment of serious infections. Clin Infect Dis. 2005;41 Suppl 5:S303–14.
89. Krueger TS, Clark EA, Nix DE. In vitro susceptibility of Stenotrophomonas maltophilia to various antimicrobial combinations. Diagn Microbiol Infect Dis. 2001;41:71–8.
90. Cayo R, Yanez San Segundo L, Perez del Molino Bernal IC, Garcia de la Fuente C, Bermudez Rodriguez MA, Calvo J, et al. bloodstream infection caused by Acinetobacter junii in a patient with acute lymphoblastic leukaemia after allogenic haematopoietic cell transplantation. J Med Microbiol. 2011;60:375–7.
91. Turkoglu M, Mirza E, Tunccan OG, Erdem GU, Dizbay M, Yagci M, et al. Acinetobacter baumannii infection in patients with hematologic malignancies in intensive care unit: risk factors and impact on mortality. J Crit Care. 2011;26:460–7.
92. Aisenberg G, Rolston KV, Safdar A. Bacteremia caused by Achromobacter and Alcaligenes species in 46 patients with cancer (1989–2003). Cancer. 2004;101:2134–40.
93. Mann T, Ben-David D, Zlotkin A, Shachar D, Keller N, Toren A, et al. An outbreak of Burkholderia cenocepacia bacteremia in immunocompromised oncology patients. Infection. 2010;38:187–94.
94. Bloch KC, Nadarajah R, Jacobs R. Chryseobacterium meningosepticum: an emerging pathogen among immunocompromised adults. Report of 6 cases and literature review. Medicine (Baltimore). 1997;76:30–41.
95. Simor AE, Ricci J, Lau A, Bannatyne RM, Ford-Jones L. Pseudobacteremia due to Pseudomonas fluorescens. Pediatr Infect Dis. 1985;4:508–12.
96. Anaissie E, Fainstein V, Miller P, et al. Pseudomonas putida. Newly recognized pathogen in patients with cancer. Am J Med. 1987;82:1191–4.
97. Bow EJ, Laverdiere M, Lussier N, Rotstein C, Cheang MS, Ioannou S. Antifungal prophylaxis for severely neutropenic chemotherapy recipients: a meta analysis of randomized-controlled clinical trials. Cancer. 2002;94:3230–46.
98. Pappas PG, Rex JH, Lee J, Hamill RJ, Larsen RA, Powderly W, et al. A prospective observational study of candidemia: epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients. Clin Infect Dis. 2003;37:634–43.
99. Maschmeyer G. The changing epidemiology of invasive fungal infections: new threats. Int J Antimicrob Agents. 2006;27 Suppl 1:3–6.
100. Beck-Sague C, Jarvis WR. Secular trends in the epidemiology of nosocomial fungal infections in the United States, 1980-1990. National Nosocomial Infections Surveillance System. J Infect Dis. 1993;167:1247–51.
101. Girmenia C, Martino P, De Bernardis F, Gentile G, Boccanera M, Monaco M, et al. Rising incidence of Candida parapsilosis fungemia in patients with hematologic malignancies: clinical aspects, predisposing factors, and differential pathogenicity of the causative strains. Clin Infect Dis. 1996;23:506–14.
102. Safdar A, Perlin DS, Armstrong D. Hematogenous infections due to Candida parapsilosis: changing trends in fungemic patients at a comprehensive cancer center during the last four decades. Diagn Microbiol Infect Dis. 2002;44:11–6.

103. Safdar A, Armstrong D. Infections in patients with hematologic neoplasms and hematopoietic stem cell transplantation: neutropenia, humoral, and splenic defects. Clin Infect Dis. 2011;53:798–806.

104. Girmenia C, Pagano L, Martino B, D’Antonio D, Fanci R, Specchia G, et al. Invasive infections caused by Trichosporon species and Geotrichum capitatum in patients with hematologic malignancies: a retrospective multicenter study from Italy and review of the literature. J Clin Microbiol. 2005;43:1818–28.

105. Koh AY, Kohler JR, Coggshall KT, Van Rooijen N, Pier GB. Mucosal damage and neutropenia are required for Candida albicans dissemination. Plos Pathog. 2008;4:e35.

106. Pappas PG, Kauffman CA, Andes D, Benjamin DK, Calandra TF, Edwards JE, et al. Clinical practice guidelines for the management of Candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;48:503–35.

107. Nucci M, Anaissie E, Betts RF, Dupont BF, Wu CZ, Buell DN, et al. Early removal of central venous catheter in patients with candidemia does not improve outcome: analysis of 842 patients from 2 randomized clinical trials. Clin Infect Dis. 2010;51:295–303.

108. Brass EP, Edwards JE. Should the guidelines for management of central venous catheters in patients with candidemia be changed Now? Clin Infect Dis. 2010;51:304–6.

109. Steinbach WJ, Marr KA, Anaissie EJ, Azie N, Quan SP, Meier-Kriesche HU, et al. Clinical epidemiology of 960 patients with invasive aspergillosis from the PATH Alliance registry. J Infection. 2012;65:453–64.

110. Denning DW. Invasive aspergillosis. Clin Infect Dis. 1998;26:781–803.

111. Walsh TJ, Groll AH. Overview: non-fumigatus species of Aspergillus: perspectives on emerging pathogens in immunocompromised hosts. Curr Opin Investig Drugs. 2001;2:1366–7.

112. Lass-Florl C, Rath P, Niederwieser D, Kofer G, Wurzner R, Krezy A, et al. Aspergillus terreus infections in haematological malignancies: molecular epidemiology suggests association with in-hospital plants. J Hosp Infect. 2000;46:31–5.

113. Steinbach WJ, Benjamin DK, Kontoyiannis DP, Perfect JR, Lutsar I, Marr KA, et al. Infections due to Aspergillus terreus: a multicenter retrospective analysis of 83 cases. Clin Infect Dis. 2004;39:192–8.

114. Caillot D, Couaillier JF, Bernard A, Casasnovas O, Denning DW, Mannone L, et al. Increasing volume and changing characteristics of invasive pulmonary aspergillosis on sequential thoracic computed tomography scans in patients with neutropenia. J Clin Oncol. 2001;19:253–9.

115. Caillot D, Latrabe V, Thiebaut A, Herbrecht R, De Botton S, Pigneux A, et al. Computer tomography in pulmonary invasive Aspergillosis in hematological patients with neutropenia: an useful tool for diagnosis and assessment of outcome in clinical trials. Eur J Radiol. 2010;74:E173–6.

116. Ostrosky-Zeichner L, Alexander BD, Kett DH, Vazquez J, Pappas PG, Saeki F, et al. Multicenter clinical evaluation of the (1 -> 3) beta-D-glucan assay as an aid to diagnosis of fungal infections in humans. Clin Infect Dis. 2005;41:654–9.

117. Lamoth F, Cruciani M, Mengoli C, Castagnola E, Lortholary O, Richardson M, et al. Beta-glucan antigenemia assay for the diagnosis of invasive fungal infections in patients with hematological malignancies: a systematic review and meta-analysis of cohort studies from the third European conference on infections in leukemia (ECIL-3). Clin Infect Dis. 2012;54:633–43.

118. Wheat LJ, Walsh TJ. Diagnosis of invasive aspergillosis by galactomannan antigenemia detection using an enzyme immunoassay. Eur J Clin Microbiol. 2008;27:245–51.

119. Mennink-Kersten MASH, Donnelly JP, Verweij PE. Detection of circulating galactomannan for the diagnosis and management of invasive aspergillosis. Lancet Infect Dis. 2004;4:349–57.
120. Chai LY A, Kullberg BJ, Johnson EM, Teerenstra S, Khin LW, Vonk AG, et al. Early serum galactomannan trend as a predictor of outcome of invasive Aspergillosis. J Clin Microbiol. 2012;50:2330–6.
121. Maschmeyer G, Beinert T, Buchheidt D, Cornely OA, Einsele H, Heinz W, et al. Diagnosis and antimicrobial therapy of lung infiltrates in febrile neutropenic patients: Guidelines of the infectious diseases working party of the German Society of Haematology and Oncology. Eur J Cancer. 2009;45:2462–72.
122. Maertens J, Marchetti O, Herbrecht R, Cornely OA, Fluckiger U, Frere P, et al. European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3-2009 Update. Bone Marrow Transpl. 2011;46:709–18.
123. Walsh TJ, Anaissie EJ, Denning DW, Herbrecht R, Kontoyiannis DP, Marr KA, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis. 2008;46:327–60.
124. Maschmeyer G. The changing face of febrile neutropaenia-from monotherapy to moulds to mucositis. Prevention of mould infections. J Antimicrob Chemother. 2009;63 Suppl 1:i27–30.
125. Cornely OA, Bohme A, Buchheidt D, Einsele H, Heinz WJ, Karthaus M, et al. Primary prophylaxis of invasive fungal infections in patients with hematologic malignancies. Recommendations of the Infectious Diseases Working Party of the German Society for Haematology and Oncology. Haematologica. 2009;94:113–22.
126. Kontoyiannis DP, Wessel VC, Bodey GP, Rolston KVI. Zygomycosis in the 1990s in a tertiary-care cancer center. Clin Infect Dis. 2000;30:851–6.
127. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis. 2005;41:634–53.
128. Marty FM, Cosimi LA, Baden LR. Breakthrough zygomycosis after voriconazole treatment in recipients of hematopoietic stem-cell transplants. N Engl J Med. 2004;350:950–2.
129. Siwek GT, Dodgson KJ, de Magalhaes-Silverman M, Bartelt LA, Kilborn SB, Hoth PL, et al. Invasive zygomycosis in hematopoietic stem cell transplant recipients receiving voriconazole prophylaxis. Clin Infect Dis. 2004;39:584–7.
130. Kontoyiannis DP, Lionakis MS, Lewis RE, Chamilos G, Healy M, Perego C, et al. Zygomycosis in a Tertiary-Care Cancer Center in the era of Aspergillus-active antifungal therapy: a case-control observational study of 27 recent cases. J Infect Dis. 2005;191:1350–60.
131. Pongas GN, Lewis RE, Samonis G, Kontoyiannis DP. Voriconazole-associated zygomycosis: a significant consequence of evolving antifungal prophylaxis and immunosuppression practices? Clin Microbiol Infec. 2009;15:93–7.
132. Trifilio SM, Bennett CL, Yamold PR, McKoy JM, Parada J, Mehta J, et al. Breakthrough zygomycosis after voriconazole administration among patients with hematologic malignancies who receive hematopoietic stem-cell transplants or intensive chemotherapy. Bone Marrow Transpl. 2007;39:425–9.
133. Georgiadou SP, Sipsas NV, Marom EM, Kontoyiannis DP. The diagnostic value of halo and reversed halo signs for invasive mold infections in compromised hosts. Clin Infect Dis. 2011;52:1144–55.
134. Walsh TJ, Gamaletou MN, McGinnis MR, Hayden RT, Kontoyiannis DP. Early clinical and laboratory diagnosis of invasive pulmonary, extrapulmonary, and disseminated mucormycosis (zygomycosis). Clin Infect Dis. 2012;54:S55–60.
135. Kontoyiannis DP, Lewis RE. How I treat mucormycosis. Blood. 2011;118:1216–24.
136. Ruping MJ GT, Heinz WJ, Kindo AJ, Rickerts V, Lass-Florl C, Beisel C, et al. Forty-one recent cases of invasive zygomycosis from a global clinical registry. J Antimicrob Chemother. 2010;65:296–302.
137. Skiada A, Lanternier F, Groll AH, Pagano L, Zimmerli S, Herbrecht R, et al. Diagnosis and treatment of mucormycosis in patients with haematological malignancies: guidelines from the 3rd European Conference on Infections in Leukemia (ECIL 3). Haematologica. 2013;94(4):492–504.
138. Park BJ, Pappas PG, Wannemuehler KA, Alexander BD, Anaissie EJ, Andes DR, et al. Invasive non-Aspergillus mold infections in transplant recipients, United States, 2001–2006. Emerg Infect Dis. 2011;17:1855–64.

139. Campo M, Lewis RE, Kontoyiannis DP. Invasive fusariosis in patients with hematologic malignancies at a cancer center: 1998–2009. J Infect. 2010;60:331–7.

140. Lamaris GA, Chamilos G, Lewis RE, Saad A, Raad II, Kontoyiannis DP. Scedosporium infection in a tertiary care cancer center: a review of 25 cases from 1989–2006. Clin Infect Dis. 2006;43:1580–4.

141. Wade JC. Viral infections in patients with hematological malignancies. Hematology Am Soc Hematol Educ Program. 2006;1:368–74.

142. Redding SW. Role of herpes simplex virus reactivation in chemotherapy-induced oral mucositis. NCI Monogr. 1990;9:103–5.

143. Flowers CR, Seidenfeld J, Bow EJ, Karten C, Gleason C, Hawley DK, et al. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2013;31(6):794–810.

144. Ohrmalm L, Wong M, Aust C, Ljungman P, Norbeck O, Broliden K, et al. Viral findings in adult hematological patients with neutropenia. PLoS ONE. 2012;7:e36543.

145. Karapinar DY, Ay Y, Karzaoglu Z, Balkan C, Ergin F, Vardar F, et al. Experience of pandemic influenza with H1N1 in children with leukemia. Pediatr Hemat Oncol. 2011;28:31–6.

146. Tavil B, Azik F, Culha V, Kara A, Yarali N, Tezer H, et al. Pandemic H1N1 influenza infection in children with acute leukemia: a single-center experience. J Pediatr Hematol Oncol. 2012;34:48–50.

147. Marcolini JA, Malik S, Suki D, Whimbey E, Bodey GP. Respiratory disease due to parainfluenza virus in adult leukemia patients. Eur J Clin Microbiol. 2003;22:79–84.

148. Chemaly RF, Hanmod SS, Rathod DB, Ghantoji SS, Jiang Y, Doshi A, et al. The characteristics and outcomes of parainfluenza virus infections in 200 patients with leukemia or recipients of hematopoietic stem cell transplantation. Blood. 2012;119:2738–45.

149. Srinivasan A, Wang C, Yang J, Inaba H, Shenep JL, Leung WH, et al. Parainfluenza virus infections in children with hematologic malignancies. Pediatr Infect Dis J. 2011;30:855–9.

150. Torres HA, Aguilera EA, Mattiuzzi GN, Cabanillas ME, Rohatgi N, Sepulveda CA, et al. Characteristics and outcome of respiratory syncytial virus infection in patients with leukemia. Haematologica. 2007;92:1216–23.

151. Hirsch HH, Martino R, Ward KN, Boeckh M, Einsele H, Ljungman P. Fourth european conference on infections in leukaemia (ECIL-4): guidelines for diagnosis and treatment of human respiratory syncytial virus, parainfluenza virus, metapneumovirus, rhinovirus, and coronavirus. Clin Infect Dis. 2013;53:258–66.