Infections in Patients With Hematologic Neoplasms and Hematopoietic Stem Cell Transplantation: Neutropenia, Humoral, and Splenic Defects

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Infections are common in patients with hematologic neoplasms and following allogeneic hematopoietic transplantation. Neutropenia and defects in adaptive B-cell–mediated immunity and/or lack of splenic function predispose patients to a host of diverse and often serious infections. It is important to recognize that patients who undergo treatment for hematologic neoplasms may have mixed immune defects, and their vulnerability to infection may continue to change, in part as a reflection of the dynamic developments in the practice of oncology. The main obstacle in providing targeted, evidence-based antimicrobial treatment is the unpredictable results of even the new generation of diagnostic assays. A definite diagnosis for most end-organ opportunistic diseases requires tissue samples that are seldom available. Because immune defects may coexist, empirical therapy is directed toward a wide spectrum of pathogens. Real-time information about innate and adaptive immune functions and the role of acute and chronic phase molecules may improve target-specific therapy.

Patients who undergo treatment for hematologic neoplasms may develop defects involving innate and adaptive immune responses [1]. It is common for patients with cancer to have multiple immune defects. For example, patients with chronic lymphocytic leukemia (CLL) or other B cell neoplasms may have underlying leukemia-induced or treatment-induced (anti-CD20) hypogammaglobulinemia. Similarly, patients with CLL after treatment with fludarabine and/or anti-CD52 (alemtuzumab) therapy develop profound, often sustained defects in helper and cytotoxic T-cell functions [2, 3]. Moreover, in patients who undergo radiation therapy, tissue damage and inflammation have been accompanied by dysfunction among various facets of the innate and adaptive immune system.

The other important challenge in administering care for these patients is the limitations of conventional diagnostic assays in severely immunocompromised patients with cancer. Definite diagnosis of most opportunistic infections, including invasive fungal diseases, brain abscesses, paranasal sinus infections, opportunistic lung infections, and viral end-organ disease, still remains difficult to diagnose with tests performed on body fluid specimens [4–6].

This 2-part review will address a systematic evaluation of infections associated with specific immune defects.

NEUTROPENIA

Severe and persistent neutropenia is a well-recognized risk factor for infection in patients undergoing anti-neoplastic therapy [7]. In patients with severe neutropenia (absolute peripheral neutrophil counts [ANC] <500 cells/mL), especially an ANC <100 cells/mL, the risk of systemic bacterial and fungal infections increases at a near-exponential rate [7]. Patients with myeloid cell line
cancer often have functionally impaired immature or neoplastic dysfunctional granulocytes; these patients, despite having a normal peripheral granulocyte count, are susceptible to infections, as outlined in Table 1. Antineoplastic agents may disrupt chemotaxis and phagocytosis and may compromise the neutrophils' ability to eliminate intracellular microorganisms. Profound and often prolonged periods of drug-induced myelosuppression that last beyond 4 weeks are not uncommon in patients receiving high-dose salvage chemotherapy. This functional impairment of neutrophils may also result from radiation therapy and adrenal glucocorticosteroid; these interventions may also contribute to delay in recovery of neutrophil counts. Other factors that may lead to neutrophil dysfunction include prolonged hypoxemia, severe acidosis, and hypovolemic states. A prolonged hyperglycemic state predisposes to recurrent infections by disrupting antioxidant-dependent intercellular microbial elimination [8]. In individuals with chemotherapy-induced agranulocytosis, early recovery of functional granulocyte levels remains imperative for resolution of infection and survival [6]. Myeloid growth factors, such as recombinant granulocyte colony stimulating factor (G-CSF) and granulocyte macrophage colony stimulating factor (GM-CSF), have significantly reduced the duration of chemotherapy-induced neutropenia and, in some cases, have been shown to favorably impact survival and infection-related deaths [9–13]. Furthermore, it is important to recognize that patients with hematologic malignancy are susceptible to a variety of infections that may present either sequentially or concurrently. A high level of suspicion must be maintained for polymicrobial infections, which may account for nearly 15% to 20% of all microbiologically documented infections in high-risk patients with cancer [14]. The following infections are regularly seen in neutropenic patients with cancer.

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<th>Immune defect, bacteria</th>
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Patients with mixed immune defects included recipients of allogeneic hematopoietic stem cell transplant; those with acute or chronic graft-versus-host disease; myelodysplastic syndrome; adult T-cell leukemia/lymphoma; those who received antineoplastic agents such as cyclophosphamide or fludarabine and anti-CD20 agents; human herpesvirus 6. Varicella zoster virus is rarely associated with systemic dissemination in patients with humoral immune defects or even those with mixed immune dysfunctions. *S. stercoralis* may lead to serious, life-threatening hyperinfection syndrome in patients with mixed cellular immune defects.
**Bacterial Infections**

In the first week of neutropenia, hematogenous bacterial infections due to *Staphylococcus aureus* and Gram-negative bacteria, such as *Escherichia coli* and *Pseudomonas aeruginosa*, are important [15, 16]. In neutropenic patients with chemotherapy-induced mucositis, alpha hemolytic streptococci may lead to rapidly progressive shock, and despite appropriate therapy, infection-related mortality remains high [17]. Indwelling intravascular devices, mucosal damage of the orointestinal and genitourinary tract, and fluoroquinolone prophylaxis may also increase the risk for hematogenous staphylococcal, alpha hemolytic streptococcal, enterococcal, drug-resistant Enterobacteriaceae, and nonfermentative Gram-negative bacterial infections [1, 6]. Widespread use of indwelling intravascular catheters has significantly impacted the increased frequency of staphylococcal and *Candida* species hematogenous infection [18, 19]. In a series of patients undergoing antineoplastic therapy, placement of intravascular catheters during profound granulocytopenia was associated with a 5-fold increased risk of catheter-related infection [20].

In the past decade, because of common fluoroquinolone prophylaxis given to patients during high-risk periods, the incidence of Gram-negative hematogenous infection has decreased overall, whereas the incidence of breakthrough infections due to multidrug-resistant enterococci, alpha-hemolytic streptococci, and *Clostridium difficile*-associated diarrhea appears to have increased [21, 22]. Enterobacteriaceae such as *E. coli*, *Klebsiella* species, *Enterobacter* species, *Citrobacter* species, and *P. aeruginosa* have replaced susceptible Gram-negative bacteria and are still a significant cause of morbidity in patients with profound neutropenia. The host’s endogenous flora are the likely source for most of these infections. Prophylactic use of antibiotics, such as carbenapens and fluoroquinolones, has been linked to the sporadic emergence of multidrug-resistant bacteria in patients’ microflora, although, upon discontinuation of prophylaxis, most patients are recolonized with the primary susceptible micro-flora [23–25]. Increased frequency of nonfermentative Gram-negative bacteria, such as *Stenotrophomonas maltophilia*, often results in a difficult-to-treat end-organ disease involving lungs and other sites [26–28]. Prior use of carbenapens or quinolones and recent critical care stays were independently associated with life-threatening drug-resistant *S. maltophilia* infection in patients at a comprehensive cancer center [29]. Unlike *E. coli*, bacteremia due to *Enterobacter*, *Acinetobacter*, and *Bacillus* species is frequently associated with infected indwelling intravascular catheters, and unless the infected device is removed, these infections may persist or recur despite appropriate antibiotic therapy.

Anaerobic bloodstream infection due to *Clostridium* species, including *Clostridium septicum*, *Clostridium perfringens*, and *Bacteroides* species may present as acute febrile illness with rapid onset of cardiovascular collapse and multisystem failure [17, 30, 31]. Patients with severe orointestinal mucosal disruption are at risk of *Stomatococcus mucilaginosus*, *Capnocytophaga gingivalis*, and enterococcal (vancomycin resistance *Enterococcus faecium* [VREF]) bacteremia [32, 33]. Brain abscesses may occasionally complicate the course of hematogenous *S. mucilaginosus* infection. Toxin-producing *Clostridium difficile* is an important cause of disabling diarrhea and severe colitis, which may lead to life-threatening complications. *C. difficile* infection has been shown to increase the risk of bacterial translocation from the intestinal tract and to contribute as an independent risk for bacteremia with VREF [34].

**Necrotizing Enterocolitis**

Antineoplastic therapy with agents such as VP16, cytosine arabinoside, and others that are associated with severe gastrointestinal mucosal disruption increases the risk for necrotizing enterocolitis. Clinically, this is a heterogeneous disease and may range from mild to severe [35]. A high index of suspicion is needed for all neutropenic patients who present with fever and abdominal pain with or without diarrhea. The disease is often a polymicrobial process [12] caused by microorganisms belonging to the intestinal microflora, such as Enterobacteriaceae (particularly *E. coli* and *Enterobacter cloacae*), *Pseudomonas* species, and *Bacteroides* species. However, the roles of *Clostridium* species, *Enterococcus* species, including vancomycin-resistant enterococci, and *Candida* species remain uncertain [37]. Radiographic evidence of thickened bowel wall, dilated bowel loops, pneumatosis intestinalis, and signs of hollow viscus perforation are often nonspecific but highly suggestive in susceptible patients. Prompt institution of supportive therapy is crucial, including strict bowel rest, bowel decompression, and early nutritional support (hyperalimentation). Prompt institution of broad-spectrum antimicrobials is critical. Anti-*Candida* therapy with an echinocandin is also sometimes employed. Recovery of agranulocytosis has a favorable impact on outcome, and recombinant myeloid growth factors may also be useful in this setting to hasten recovery from severe neutropenia. Further studies, however, are needed before routine use of G-CSF or GM-CSF is recommended. Surgical intervention may be considered in patients with complications such as bowel necrosis, gastrointestinal hemorrhage, toxic megacolon, bowel perforation, and complicated peritonitis [38]. When possible, surgery may be delayed until the recovery of granulocyte counts [39].

**Fungal Infections**

Invasive candidiasis becomes a concern in patients with severe neutropenia lasting for more than a week [1]. Systemic dissemination mostly arises from the host’s endogenous flora [1, 6]. During this period, other less common and often difficult-to-treat non-*Candida* yeasts may also be encountered, such as
Trichosporon beigelii, Rhodotorula species, and rarely Hansenula anomala, Malassezia furfur, Saccharomyces cerevisiae, or Clavispora species. The risk of hematogenous dissemination of yeasts is further increased in neutropenic patients with an indwelling intravascular catheter and chemotherapy-induced mucosal damage [40]. Disseminated T. beigelii infections, including hepatosplenic abscesses, are associated with a higher mortality, compared with candidemia, and the response to even higher amphotericin B doses (1.0–1.5 mg/kg daily) is less than satisfactory [41].

Some studies have suggested that nosocomial bloodstream candidiasis has increased over the past 4 decades; Candida albicans continues to be the most common yeast associated with invasive disease [42]. At certain cancer centers, an increase in the frequency of Candida parapsilosis infection, in particular, was noted during the mid and late 1990s [42–44]. However, recent data provide a conflicting rate of invasive Candidiasis, showing Candida glabrata and Candida krusei as the leading causes of fungemia in patients with hematologic neoplasms at a large cancer center in the South Central United States [45], an observation also seen in allogeneic stem cell transplant recipients [46]. Other studies have underscored regional differences, because an increase in C. parapsilosis and Candida tropicalis infections during 2001–2007 may reflect divergent use in antifungal drugs for prophylaxis and treatment for the severely immunosuppressed oncology population [47]. The non-albicans Candida species, including C. glabrata and C. krusei, show low susceptibility for fluconazole and itraconazole [47]. In addition, the new-generation triazole drugs, such as voriconazole, that show promising efficacy against most disease-associated species of yeasts, may not be effective against some strains of C. glabrata [48]. Short-term mortality in fungemic patients with cancer is significantly higher (~40%) than mortality in those with systemic infections due to S. aureus or P. aeruginosa [46, 49, 50]. Treatment with echinocandins appears to be effective for patients with disseminated or locally invasive candidiasis due to C. albicans, C. glabrata, and other non-albicans species [51, 52].

In patients in whom neutropenia persists beyond 2 weeks, environmental ubiquitous molds may cause life-threatening infections [1, 6]. Among these, Aspergillus species, especially A. fumigatus, are prominent. Lungs are often involved (invasive pulmonary aspergillosis [IPA]; Figure 1); paranasal sinuses, brain, heart, liver, gastrointestinal tract, and kidneys may also be involved [1, 6, 53]. Additional risk factors for IPA include (1) advanced age, (2) refractory leukemia, (3) salvage chemotherapy, and (4) prolonged high-dose systemic corticosteroids [1, 6, 50, 54]. Cough, dyspnea, and hemoptysis are often missing, and fever may be the only clinical feature seen in nearly one-third of patients with IPA. Most infections are diagnosed on CT scans Figure 2A and 2B): pleural-based lesions often have

Figure 1. The CT scan of the chest is an example of multiple cavitary lung disease due to concurrent necrotizing aspergillosis and zygomycosis in a patient with prolonged neutropenia and relapsed leukemia. This has important implications in choosing appropriate antifungal therapy.

Figure 2. The presence of a “halo sign,” as seen in this leukemic patient with Curvularia species pneumonia (A) often represents early fungal disease (~1 week) [89], whereas the “air crescent” sign (B), when present, indicates inflammatory fungal mass and is an uncommon feature noted during the late phase of invasive fungal infection.
Antifungal therapy for invasive aspergillosis with amphotericin B has been associated with less than satisfactory responses [60]. Voriconazole has been the first new antifungal drug to show promise in the treatment of invasive aspergillosis; however, even with this highly active agent, response rates remain poor for neutropenic patients with cancer [61, 62]. Similarly, posaconazole shows encouraging results for the treatment of invasive fungal disease [63], although variable enteral absorption may result in suboptimal response, especially in patients with intestinal mucositis or graft-versus-host disease [64]. Therefore, combination antifungals have been explored with some success, although mostly in nonneutropenic patients [65]. Immune enhancement strategies, including donor granulocyte transfusions [66] and recombinant Th1 cytokines, such as interferon γ and tissue macrophage active GM-CSF, have been tried [54, 67] but have not conclusively improved outcomes in neutropenic patients with invasive fungal disease. An increase in the cases of invasive zygomycosis was noted in patients with leukemia and stem cell transplantation, which in part reflects limitations in the antifungal spectrum of voriconazole [68, 69]. In patients with invasive zygomycosis, treatment with posaconazole may provide a potential drug with activity against most clinical organisms associated with human zygomycosis [70].

**Hepatosplenic Fungal Abscess**

Multiple micro/macro-abscesses involving the liver and spleen can present as a new febrile episode in leukemic and stem cell transplant recipients recovering from prolonged neutropenia [1, 6, 71]. Candida species are most common, although non-Candida infections in patients receiving antifungal prophylaxis, such as Trichosporon beigeli, Pseudallescheria boydii, and Fusarium, and Alternaria species may also infrequently occur. It is important to obtain a nodule-directed diagnostic biopsy specimen early, because other conditions, such as brucellosis, bartonellosis, tuberculosis, histoplasmosis, Klebsiella pneumoniae, and Burkholderia liver abscess may be difficult to distinguish on the basis of clinical and radiographic features [72]. Intravenous contrast-enhanced computed tomography scan often shows enhanced multiple intrahepatic lesions. Prolonged therapy with high-dose amphotericin B (1–1.5 mg/kg daily), amphotericin B lipid complex (5–7 mg/kg daily), or liposomal amphotericin B (5–10 mg/kg daily) is needed. Recent favorable outcomes with caspofungin for disease that is unresponsive to treatment with amphotericin B have been encouraging [73].

Following recovery from neutropenia, a radiographic worsening has not been unexpected. In our experience, combination antifungal therapy with an echinocandin plus a broad-spectrum triazole along with recombinant myeloid growth factor resulted in favorable outcomes, especially for patients with single antifungal-drug refractory infection. Defervescence may take 2–3 weeks, and prolonged therapy of 12–24 weeks is not uncommon [71, 73]. Prednisone equivalent at a dosage of ≥0.5 mg/kg per day for therapy.
3 weeks or longer has been associated with resolution of symptoms and of inflammatory response in patients with cancer with symptomatic chronic disseminated candidiasis [74]. The role of adjuvant recombinant cytokines, such as GM-CSF, and interferon γ appears encouraging but is not standard practice.

**HUMORAL AND SPLENIC IMMUNE DEFECTS**

Immunoglobulins play a central role in bacterial eradication by either opsonization and enhanced phagocytosis or compliment activation on the bacterial cell surface (*Streptococcus pyogenes, S. aureus*) leading to cell wall lysis. Antibody-dependent cellular cytotoxicity involves activation of lymphocytes by immunoglobulin and leukocyte surface Fc receptor interaction leading to elimination of bacterial and parasitic pathogens by cytolytic perforin released from activated lymphocytes. The antibody-coated organisms also activate monocyte-macrophages (interleukin 12) and promote proinflammatory cytokine release [75].

Many malignancies, particularly hematologic neoplasms, are associated with immunoglobulin dyscrasias. The dysfunctional nonneoplastic B lymphocytes lead to functional hypogammaglobulinemia, and during the advanced stages of malignancy, increased antibody catabolism exacerbates the low circulating immunoglobulin levels. *Streptococcus pneumoniae* and other encapsulated organisms (Table 1) that require C3, C5 opsonization for eradication may cause fulminant septicemia in this setting [76]. Nearly one-third of patients with chronic lymphocytic leukemia have low immunoglobulin G levels [77]. Similarly, those with protein losing–enteropathy caused by intestinal tract chronic graft-versus-host disease may also have low circulating immunoglobulin levels [78]. A high frequency of Gram-negative urinary tract infection and septicemia caused by nonencapsulated microorganisms, such as *Enterobacteriaceae* and *S. aureus*, has been recently reported in patients with multiple myeloma and probably reflects increased urinary tract instrumentation and penicillin prophylaxis [79].

Disseminated *Salmonella* species and *Campylobacter* infections may be encountered in patients with hypogammaglobulinemia. Most data arise from studies of patients with primary immune deficiency syndromes. This may in part represent a concomitant occult defect in cellular immune function [80]. The spectrum of infections in patients with suboptimal splenic function is similar to those in patients with hypogammaglobulinemia and/or hypocomplementemia (Table 1).

**Bacterial Infections**

**Pneumococcal Disease**

*S. pneumoniae* infection in the immunocompromised cancer patient may not follow the classic triad of pneumonia, meningitis, and endocarditis as described by Austrian [81]. Most patients have both underlying B cell defects caused by their basic disease, chemotherapy, anti-CD20, radiation and agents used in preparatory conditioning for allogeneic hematopoietic transplantation, and graft-versus-host disease [82, 83]. Most pneumococcal infections are acquired in the community, but patients who develop pneumococcal bacteremia during a hospitalization generally do so during periods of chemotherapy-induced neutropenia [82]. However, only 18% of patients with cancer and pneumococcal bacteremia were neutropenic in one study [82]. Pneumonia is the most common presenting feature (found in 67% of subjects). In patients with hematologic neoplasms and those who have undergone stem cell transplant, systemic corticosteroid use significantly increases probability of bacteremic pneumonia [82, 83]. As observed in immunocompetent patients with *S. pneumoniae* bacteremia or pneumonia or both, despite high-level resistance to penicillin [84], interestingly, most patients with cancer with multidrug-resistant pneumococcal disease who received discordant β-lactam antimicrobial therapy had favorable outcomes in one study [83].

Intra-abdominal (liver and pancreatic) and deep pelvic (testicular and tubo-ovarian) abscesses, pneumococcal aortitis, inguinal adenitis, phlegmonous gastritis, and necrotizing fasciitis have been described in patients with cancer with pneumococcal disease [1].

The widespread use of conjugate pneumococcal vaccine has resulted in a significant reduction in the burden of pneumococcal disease. However, this has not been the case in adult patients with hematologic neoplasms, because these patients remained highly susceptible to serious invasive disease despite receiving conventional polysaccharide vaccine [85].

**Parasitic Infections**

**Babesiosis**

*Babesia microti* and other less common species are the agents of a tick-borne regional zoonosis [86] that is predominantly present in the northeastern United States. Babesiosis may lead to severe hemolytic anemia, disseminated intravascular coagulation, and renal and respiratory failure in hypoplastic individuals. Patients with cancer who have functional hypoplasmenism, including those with hematologic neoplasms and chronic graft-versus-host disease following allogeneic hematopoietic stem cell transplantation, may be at increased risk of life-threatening Babesiosis. Treatment with atovaquone or with azithromycin or clindamycin plus quinine may not be sufficient. Whole-blood exchange transfusions are occasionally necessary for immunosuppressed patients with high parasitemia [87, 88]. Prevention by avoiding tick-infested areas is also important.

**CONCLUSIONS**

In patients with cancer, immune defects may coexist. Improving the diagnostic reliability of the next generation of laboratory
assays may provide the much-needed tools for antimicrobial stewardship to ensure target- and goal-directed therapy for infections in severely immunosuppressed patients.

Notes

Potential conflicts of interest. All authors: No reported conflicts.
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