39 Respiratory Infection in Immunocompromised Neutropenic Patients

S.W. Crawford

39.1 Scope of Problem

Neutropenia is increasingly common in the hospital. The rise in incidence is due to proliferation of indications for and centers performing hematopoietic stem cell transplantation, hematologic effects of AIDS, and myelosuppressive side-effects of anti-viral and cancer chemotherapies (Table 39.1). As a result, these neutropenic patients are increasingly common in the intensive care units. These patients are often lymphopenic, anemic, and thrombocytopenic. They are at risk for multiple organ failures and various infections. This chapter will focus on respiratory infections in the neutropenic patient.

Table 39.1. Some causes of neutropenia

Drug myelosuppression
Chemotherapy
Ganciclovir
Trimethaprim-sulfamethoxazole
Viral infection
Late stages of AIDS
Herpes viruses
Congenital deficiency
Inherited cyclic neutropenia
Functional defects
Corticosteroids
Chediak-Higashi syndrome
Myeloperoxidase deficiency
Chronic granulomatous diseases

39.2 Neutropenia and the Risk Factors for Infection

The neutrophil plays a key role in the host defense of extracellular bacteria (especially encapsulated organisms affected by opsonizing antibodies) and the molds and yeasts. The incidence of serious infection in neutropenic patients increases with the depth, rapidity of onset, and duration of neutropenia. The risk of infection increases with an absolute neutrophil count (ANC) $<1,000$ cells/mm^3, and is significantly higher with an ANC <500 cells/mm^3. A rapid decline in ANC and duration of neutropenia $>7-10$ days are associated with an increase in serious, life-threatening infection. Likewise, morbidity and mortality are increased in patients with profound neutropenia (ANC <100/mm^3) [1–3].

A study of severe, short-duration neutropenia demonstrates that fungal infections are rare when the ANC is reduced for less than 5 days. Neutropenic fever developed in 94% of patients after peripheral stem cell transplantation [4]. Profound neutropenia was short-lived (average 5 days) and most patients' fever defervesced in a median of 4 days. Although bacteremia developed in 39% (predominately Gram-positive cocci), only 5% had pulmonary infiltrates and there were no fungi identified and no infection-related deaths.

Neutrophil function before chemotherapy to treat leukemia influences infection rates [5]. Patients with a significant decrease in phagocytic activity of neutrophils developed more severe infection or died more often compared to those with no infection. Study of the neutrophil oxidative burst capacity suggested that the neutrophils may have been pre-activated and have reduced function prior to the initiation of chemotherapy.

Neutropenia associated with myelosuppression, as occurs after chemotherapy, rarely occurs in isolation from other defense defects. Lymphopenia, decreased humoral immunity, and mucosal barrier defects invariably contribute to the defense abnormalities that predispose to infection in these settings.

Both tumors and chemotherapy contribute to infection among neutropenic patients. Obstruction of the lymphatic, biliary tract, gastrointestinal or urinary systems by tumors or as a result of surgical procedures is a common cause of infections. Chemotherapy not only decreases the number of neutrophils, but also results in chemotactic and phagocytic defects. Chemotherapy, radiation, peripheral and central intravenous lines, surgery, or tumor invasion can induce breakdown of skin and mucosal barriers and can result in bacteremia. Mucositis may occur throughout the gastrointestinal system. Translocation of endogenous flora in the GI tract may explain a majority of febrile neutropenic episodes.

39.3 Trends in Infection in the Neutropenic Patient

Historically, Gram-negative bacilli, particularly *P. aeruginosa*, were the most commonly identified pathogens. Data from several sources attest to a decrease in the incidence of pseudomonal bacteremia and an increase in Gram-positive infections. The use of long-term indwelling lines accounts for some of the appearance of Gram-positive infections; the empiric antibiotic regimens that were designed to cover *P. aeruginosa* may be an additional factor. For example, the incidence of bacteremia due to Gram-negative bacilli in Japan decreased (40% to 64%) and infections due to Gram-positive bacteria increased (51% to 24%) in 1991 to 1996 compared to the prior 15 years [6]. According to the 2002 nationwide, concurrent surveillance study (Surveillance and Control of Pathogens of Epidemiological Importance [SCOPE]) Gram-positive organisms caused 65% of bloodstream infections, Gram-negative organisms caused 25%, and fungi caused 9.5%. The most-common organisms were coagulase-negative staphylococci (CoNS) (31%), *Staphylococcus aureus* (20%), enterococci (9%), and *Candida* species (9%) [7].

In the last decade there has been an increasing incidence of Gram-positive cocci infection in the neutropenic population. In these patients, infections with enterococci, viridans group streptococci and *Candida* species are significantly more common [7]. Notably, reports of *Candida* species isolates are up 20-fold since the 1980s. *Aspergillus* reports have increase 14-fold. In addition, the number of "unusual" fungal species (*Trichosporon, Fusarium, Mucor)* is also increased.

Importantly, there has been an alarming increase in the frequency of antibiotic resistant organism isolation. These pathogens include coagulase negative staphylococci, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and penicillin (ceftriaxone)-resistant *S. pneumonia*.

39.4 Sites and Causes of Infections

Mortality in the febrile, neutropenic population is high, in the range of 30–50%. Early studies of empiric antibiotics in febrile neutropenia suggested that a majority of patients had occult bacterial infections. However, an infectious source is identified in only approximately 30% of febrile neutropenic episodes. Often the only evidence of infection is bacteremia, which occurs in over 20% of patients. Approximately 80% of identified infections are believed to arise from patients' own endogenous flora. The most commonly identified sources of infection in febrile neutropenic patients with leukemia are the perineal and perirectal areas, followed by the urinary tract, skin (including intravenous lines and wounds) and the lungs. However, among non-hematopoietic cancer patients pulmonary infections predominate. Many infections are detected only at autopsy, particularly disseminated fungal or combined fungal and bacterial infections.

There are numerous infections that cause pneumonia in cancer patients [8–10]. Typical bacteria are most common, accounting for over one-third of infections. Fungi, viruses, *Pneumocystis carinii* (PCP), *Nocardia asteroids*, and *Mycobacterium tuberculosis* account for a measurable number of cases each. Compounding the difficulty in establishing an etiologic agent, mixed infections may be present in up to 20% of cases.

Evidence suggests that fungal infection is a common component of neutropenic fever after chemotherapy. Pneumonia tends to develop several days after the onset of fever. Only 27% of febrile neutropenic patients *with pneumonia* respond without addition of anti-fungal agents. Over half of documented lower respiratory infections are due to fungi. Therefore, it is not surprising that the prognosis is worse for febrile neutropenic patients who develop pneumonia.

Noninfectious etiologies are common for immunocompromised patients with pulmonary infiltrates. Causes include pulmonary embolus, tumor, radiation pneumonia, atelectasis, pulmonary hemorrhage, and drug allergy or toxicity. Aspiration remains an important source of pulmonary infection in all compromised patients.

39.5 Bacterial Pathogens

Viridans streptococci (both *mitis* and *sanguis*) have become of major concern in the neutropenic host. These organisms are associated with 39% of neutropenic bacteremia after chemotherapy [11]. The complications associated with these organisms are: ARDS, shock, and endocarditis. An ANC $<100/mm^3$ is among the strongest risk factors.

Institutional infection patterns impact the frequency and type of organisms isolated and a variety of nosocomial outbreaks in cancer patients have been reported. Some centers have reported an increased incidence of resistant pathogens such as *Candida krusei* with the routine use of prophylactic antibiotics and antifungals [12–14]. Antibiotic history, recent culture results, exposure to prophylactic antibiotics, and the susceptibility patterns for organisms in the institution should be used to help guide selection of initial antibiotic therapy.

39.6 Fungal Pathogens

Fungal infections probably represent the greatest infectious risk to neutropenic patients. Fungal infections are common among neutropenic patients, and usually arise after prolonged neutropenia and antibiotic use. Empiric antibiotics promote oral and vaginal colonization with yeast, most commonly *Candida albicans*. Hepato-splenic involvement is common in patients with disseminated candidiasis after chemotherapy. Often, symptoms are absent until the neutropenia resolves. Current diagnostic tests lack sufficient sensitivity to distinguish invasive yeast infection from colonization [15].

The incidence of nosocomial candidal infections continues to rise in the United States, and *C. albicans* is the most commonly identified species. Candidal infections are associated with the highest mortality rates of all hospital-acquired bloodstream infections, with substantial related increases in hospital costs, particularly length of stay.

The fourth most common pathogens causing nosocomial bloodstream infections in US hospitals are fungi, predominantly *Candida* species, representing 9.5% of all isolates [7, 16]. Clearly, *Candida* species are increasing in importance in the ICU as well. *Candida albicans* accounts for just over half of candidal species isolated. *C. tropicalis*, *C. glabrata*, and *C. parapsilosis* contribute 44% of isolates [17]. Speciation is importance since *C. tropicalis* and *C. krusei* are resistant to fluconazole, the agent more commonly used to treat yeast infection in the ICU. The crude mortality associated with these pathogens increases with decreasing prevalence. Mortality with the most common, coagulase-negative staphylococci is 21% and rises to 40% with the *Candida* species infections. The mortality attributable to *Candida* has been estimated at 70–88% [18, 19]. Diagnosis of candidiasis in the neutropenic host should be considered an indication for urgent therapy. The death rates among neutropenic patients with candidiasis are as high as 24% within a week of diagnosis and 63% within 3 months [20]. Although lower among patients without neutropenia, the rates are still high.

Candida is a common infection among neutropenic patients but a *rare* cause of pneumonia. Haron reported that there were only 31 cases documented at autopsy over 20 years at the MD Anderson Cancer Center [21]. The clinical and radiographic presentation of these cases was that of bronchopneumonia. There were no distinguishing features of the infection to identify the organism. Of note, most of the patients were *not* neutropenic at time of onset of pneumonia.

Candidiasis is rare in the absence of colonization of the skin, rectum or throat. Gut translocation may account for a substantial proportion of cases. The major threat to life is associated with disseminated, invasive candidiasis. Candidal invasion is associated with identified risk, and thus there are also risks for mortality. The reported risks include:

- Use of three of more antibiotics
- Neutropenia
- Immunosuppression (due to cancer/chemotherapy, steroids, other therapies)
- Concomitant infection
- Spending more than 4 days in the ICU
- Mechanical ventilation >48 h
- An elevated APACHE II score
- Abdominal surgery
- Central venous catheterization
- Total parenteral nutrition (TPN)
- Diabetes mellitus
- *Candida* colonization of more than sites
- Candiduria (>100,000 colonies/ml)
- Thrush

The therapeutic choices for treatment of systemic candida infections include fluconazole, conventional amphotericin B, liposomal amphotericin B, and lipid-complex amphotericin B. All of these are available intravenously. Only fluconazole is available orally; however, this is rarely an issue in the ICU population. There are conflicting data regarding the equivalence of fluconazole with amphotericin B in the neutropenic patient [22–24]. However, fluconazole is associated with less renal dysfunction, hypokalemia, and lower liver enzymes than amphotericin B.

Infections with molds, such as *Aspergillus* sp., vary from localized skin ulcers and invasive pneumonia, to fulminant disseminated disease. *Fusarium* sp. infections have been increasingly reported in the immunocompromised host [23–27]. Reactivation of endemic fungi (histoplasmosis, blastomycosis, and coccidioidomycosis) or tuberculosis mimics the radiographic presentation of invasive fungal pneumonia and should be considered in appropriate patients with prolonged steroids or immune suppression.

A review of the clinical presentations of invasive pulmonary aspergillosis (IPA) in a study of 35 confirmed cases demonstrated that the diagnosis of IPA was not suspected in 40% of the cases [28]. The lungs were involved in 94% and the infection was limited to lungs in 74%. Other sites of infection were the heart, CNS, liver, spleen, and skin. Only 40% were neutropenic at the time of diagnosis but 91% had used steroids in the recent past. Of importance to the management of IPA, concurrent infections were found in 83% of cases. The mortality rate was 94%.

39.7
Viral Pathogens

Viral infections, especially human herpes viruses, are common in the neutropenic population. However, neutropenia per se is not the primary risk factor for viral infection. Cell-mediated immunity (CMI) is the most important host defense against most respiratory viral pathogens. Since many patients with neutropenia also have concomitant defects in CMI, they are at risk. Herpes simplex viruses, HSV-1 and HSV-2, while common causes of skin eruptions, can also cause a wide variety of clinical syndromes, including: encephalitis, meningitis, myelitis, esophagitis, pneumonia, hepatitis, erythema multiforme, and ocular syndromes. Immunocompromised patients with disseminated varicella zoster virus (VZV) infection can have pulmonary involvement and should be placed on respiratory precautions to prevent aerosolized transmission to susceptible individuals. Cytomegalovirus remains a significant cause of diffuse pneumonia and respiratory failure among transplant recipients.

Of great concern is the emergence of respiratory viral infections including respiratory syncytial virus (RSV) as significant causes of nosocomial pneumonia. Outbreaks of infection resulting in diffuse pneumonia and respiratory failure have been reported among severely myelosuppressed patients after chemotherapy [29]. These infections should be suspected during winter and spring months, if there is associated airflow obstruction, or if upper respiratory tract symptoms preceded the onset of infiltrates. Many of the outbreaks reported appear to have been nosocomial. Visitors and hospital staff are like responsible for transmission of the virus. Prompt treatment with ribavirin (with or without immunoglobulin) has been reported as beneficial. There are few data from large series to support that these are effective treatments in severely ill neutropenic patients.

39.8
Radiographic Diagnosis

The radiographic appearance of pneumonia in the neutropenic patient carries important diagnostic information as to the possible etiology of infection. A focal or multifocal consolidation of acute onset is most commonly caused by a bacterial infection. However, similar multifocal lesions with a subacute to chronic progression may be due to fungal, tuberculous, or nocardial infections. Large nodules are usually a sign of fungal or nocardial infection in this patient population, particularly if they are subacute to chronic in onset. Viruses (especially CMV) or *P. carinii* usually cause subacute disease with diffuse abnormalities, either peri-bronchovascular or small miliary nodules. The presence of cavitation suggests a necrotizing infection that can be caused by fungi, *Nocardia*, and certain Gram-negative bacilli (most commonly *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*) [9].

Table 39.2. Radiographic mimics of invasive pulmonary aspergillosis

Mucor, *Fusarium*, *Scedosporium*, etc.
Legionella
Nocardia
Rhodococcus
Gram negative enterics
Pulmonary embolism
BOOP

Chest computed tomography of the chest can help to assess the extent of the disease process and more completely define its characteristics. The morphology of the abnormalities found on CT scan can also be very useful in developing a differential diagnosis in the individual patient. Cavitary mass lesions are suggestive of infections with *Nocardia*, *Cryptococcus*, or invasive fungus, such as *Aspergillus*. The invasive fungal pneumonias classically develop cavitation and a surrounding zone of radiographic attenuation. This zone is presumably due to associated edema and hemorrhage. However, this finding is non-specific. Any process or infection resulting in lung infarction can yield similar CT findings (Table 39.2) [30]. In contrast, dense regional or lobar consolidation on CT is suggestive of bacterial pneumonia.

Chest CT scanning may identify the site for optimal sampling and assist in defining the most appropriate invasive procedure. Thus, CT can provide precise guidance for needle biopsy or for thoracoscopic or open lung excision in the case of peripheral lung nodules [31, 32]. CT can also help to predict whether bronchoscopy is likely to be useful. As an example, the demonstration of a feeding bronchus in association with a pulmonary nodule greatly increases the diagnostic yield when bronchoscopy is performed (60 % versus 30 % when the feeding bronchus is not visible). If CT demonstrates centrally located diffuse opacifications, a bronchoscopic approach is the procedure of choice.

39.9
Treatment

39.9.1
Antibacterial Drugs

None of the numerous antibiotic regimens studied as initial empiric therapy in febrile neutropenia has been shown to be clearly superior [33]. The majority of the tested regimens provide coverage targeted at Gram-negative bacilli, especially *P. aeruginosa*. The most common empiric treatment approaches include either "monotherapy" (with agents such as ceftazidime, imipenem, meropenem, or cefepime) or "double coverage" (with a beta-lactam and an aminoglycoside, or double beta-lactams).

Double beta-lactams are generally avoided due to the concern of overlapping toxicities. However, double coverage with the aztreonam and a beta-lactam in patients unable to tolerate an aminoglycoside may be a reasonable alternative. Two drug regimens for empiric therapy of febrile neutropenia are widely used. Clinical trials with monotherapy, either ceftazidime or imipenem cilastatin or meropenem, have demonstrated equal efficacy compared to two drug regimens [34, 35]. In one study treatment with meropenem was compared to ceftazidime in 187 patients; the number of patients on the therapy at 72 h and the completion of treatment was equivalent between the groups (50% versus 56% and 46% versus 49%, respectively) [36]. However, changes in the antibiotic regimen are more common when monotherapy is used [2, 34].

The French Febrile Aplasia Study Group report is one of the few studies to show differences in empiric antibiotic regimen [37]. The empirical use of a piperacillin/tazobactam and amikacin combination had superior response rates compared to ceftazidime and amikacin (48% versus 29%). Notably, the response rates to ceftazidime and amikacin decreased over time as the incidence of Gram-negative infections declined from 22% to 17.5%. The incidence of Gram-positive infections increased from 20% to 28%. This study provides increasing evidence of the fungal infection problem in neutropenic hosts. There was an increase in *Aspergillus*-related deaths (from 1.8% to 5.4%), while the overall infection-related mortality remained unchanged over time. It remains important to continue to monitor microbiology regardless of initial antibiotic choices.

Vancomycin is frequently considered in patients who present with hypotension, mucositis, skin or catheter site infection, a history of MRSA colonization, recent quinolone prophylaxis or persistent fever despite empiric antibiotics. However, addition of vancomycin to the initial empiric antibiotic regimen has not been shown to decrease mortality [2, 38]. The addition of empiric vancomycin did not improve outcome among febrile neutropenic patients with skin and soft tissue infections despite a higher incidence of proven Gram-positive bacteremia compared to patients with other infections (31% versus 17%) [39]. Current recommendations suggest withdrawal of vancomycin after 3 days in culture negative cases [7].

39.9.2
Antifungal Drugs

The incidence of fungal infection (especially *Candida* or *Aspergillus*) rises after patients have experienced more than 7 days of persistent fever and neutropenia [40]. Antifungal therapy is routinely added at 5–7 days of neutropenia in patients with persistent fever. While amphotericin B has been used for empiric therapy the longest, there is growing experience with fluconazole and lipid formulations of amphotericin B.

Fluconazole is well tolerated but is ineffective against *Aspergillus* and some yeast (e.g., *C. krusei* and *C. glabrata*). A retrospective study of hematogenous candidiasis from the M.D. Anderson Cancer Center found that fluconazole prophylaxis appeared to be significant in promoting a shift toward *C. krusei* and *C. glabrata* infection and away from *C. tropicalis* and *C. albicans* [14].

Fluconazole prophylaxis is frequently used in populations at risk for *Candida* infection, such as neutropenic chemotherapy or organ transplant recipients. A review of 355 autopsies after marrow transplantation detected a disturbing trend among those patients who received fluconazole prophylaxis [41]. The treatment was effective in decreasing both *Candida* infections (from 27% to 8%) and fungal liver infection (from 16% to 3%). However, *Aspergillus* infections increased from 18% to 29%. Duration of survival increased but overall mortality was unchanged. The authors surmised that the fluconazole prophylaxis increased duration of survival by decreasing early infection with *Candida* and thus increased the exposure to *Aspergillus* infections. Fluconazole is generally not recommended as empiric therapy because of this study and a meta-analysis demonstrating no benefit on mortality or systemic fungal infections [42].

Recent trials suggest that lipid formulations of amphotericin B are better tolerated and offer similar efficacy. In one large randomized, multicenter trial, 343 neutropenic patients received liposomal amphotericin B (3 mg/kg per day) and 344 amphotericin B (0.6 mg/kg per day) as empiric therapy after at least 5 days of fever and broad-spectrum antibiotics [43]. The outcomes were comparable for the two therapies for overall success (50% versus 49%), resolution of fever during neutropenia (58% versus 58%), absence of documented fungal infection (90% versus 89%), and cure of fungal infection (82% versus 73%). The liposomal preparations were better tolerated than conventional amphotericin with fewer infusion related symptoms including rigors and less nephrotoxicity. However, these new forms of amphotericin are significantly more expensive.

Recent studies suggest that itraconazole in a daily dose of 200–400 mg also may be effective treatment for aspergillosis in patients refractory or intolerant to amphotericin B. Itraconazole is available both in oral and intravenous formulations. Itraconazole was as effective as amphotericin B as empiric therapy for febrile neutropenic patients and was associated with less toxicity [44].

Two newer agents include an azole, voriconazole and an echinocandin, caspofungin. Each have been compared to liposomal amphotericin and show promise in febrile neutropenia [45, 46]. The roles of these agents remain unclear and the potential for combination therapy unexplored.

39.9.3 Colony Stimulating Factors

The role of colony stimulating factors (CSF) continues to expand. In some clinical settings, CSF have been reported to decrease the duration of neutropenia, fever, and hospitalization [47–49]. However, CSF have not been shown to decrease mortality, and are not considered routine at this time [50]. It may be appropriate to consider their use in critically ill patients such as those with pneumonia, hypotension, or organ dysfunction or in patients whose bone marrow recovery is expected to be especially prolonged.

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