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Abstract Neutropenic patients continue to be at increased risk for developing serious infections despite substantial advances in supportive care. Epidemiologic shifts occur periodically and need to be detected early because they influence prophylactic, empiric, and specific therapy strategies. Although effective in preventing bacterial and some fungal infections, prophylaxis must be used with caution because it is associated with the emergence of resistance. The choices for empiric therapy include combination regimens and monotherapy. Specific choices depend on local factors (epidemiology, susceptibility/resistance patterns, availability). Various treatment settings (hospital-based, early discharge, outpatient) are also available, and the choice depends on the patient’s risk category. Early diagnosis and treatment of many fungal and viral infections remains suboptimal. Infection control and prevention are important strategies, especially with the emergence of multidrug-resistant organisms.

I N T R O D U C T I O N

It has been four decades since Bodey et al. first described the relationship between neutropenia and infection (1). Although the risk of infection increases when the absolute neutrophil count (ANC) falls below 1000/mm³, the currently accepted definition of neutropenia is an ANC of ≤500/mm³ (2). The severity and duration of neutropenia are both important and influence not only the frequency and severity of infection but also the response to therapy and overall outcome. It has been estimated that all patients who have severe neutropenia (<100/mm³) for 3 weeks or more will develop a serious infection (3).

In addition to quantitative neutropenia, many patients with hematologic disorders (e.g., acute leukemias) have defects in neutrophil function as well, and are at increased risk of infection despite adequate or even increased numbers of neutrophils.
Chemotherapy-induced neutropenia is often superimposed on other immunologic deficits (impaired humoral or cell-mediated immunity) that might be present because of the underlying malignancy. In such patients, infections associated with those immunologic deficits must be considered in addition to infections generally associated with neutropenia.

The spectrum of infection in neutropenic patients undergoes periodic changes, and geographic/institutional differences are also common. Knowledge of local epidemiology and of susceptibility/resistance patterns is vital to the appropriate management of neutropenic patients. Standard management includes the prompt administration of broad-spectrum, empiric antibiotic therapy after hospitalization (2).

Recent understanding of the syndrome of “febrile neutropenia” has made it possible to recognize low-risk subsets among neutropenic patients, and to consider options such as oral, outpatient therapy (4).

SPECIAL CONSIDERATIONS

Patients with neutropenia often fail to develop symptoms and signs of infection because of a blunted inflammatory response. Only 8% of patients with severe neutropenia who develop pneumonia produce purulent sputum compared to 84% who are not neutropenic (5). Chest radiographs show that neutropenic patients with pneumonia often do not develop pulmonary infiltrates; those with urinary tract infections may not have localized symptoms such as dysuria; and some may have meningitis without overt meningeal symptoms or signs.

Fever may be the initial and often the only sign of infection. Occasionally, an infection may develop in the absence of fever, as with organisms such as Clostridium septicum, or if the patient is receiving corticosteroids. Approximately 50%–60% of febrile episodes in neutropenic patients never have clinical or microbiological evidence of infection, hence the designation “unexplained fever.” Most of these patients respond to antibiotic therapy, which suggests that these fevers are probably caused by low-grade, undetected infections.

Patients with neutropenia can develop infections at unusual sites, with uncommon manifestations, and by opportunistic pathogens that seldom cause infection in immunocompetent hosts. Typhilitis, an inflammatory process most commonly involving the caecum, occurs almost exclusively in patients with acute leukemia (6). Perirectal infections with extensive tissue necrosis extending into the rectum also occur predominantly in patients with acute leukemia (7). Endocarditis is a rare infection in neutropenic patients, presumably because most of these patients are also thrombocytopenic and fail to make the fibrin/platelet mesh that is critical for the formation of bacterial vegetations. Infections can disseminate rapidly in many patients with severe neutropenia, underscoring the importance of early, broad-spectrum antibiotic therapy. However, a low-risk subset also exists, particularly among patients with solid tumors and short-lived neutropenia. Clinical and
statistically derived risk-prediction rules have been developed in order to identify such patients (8–10). Finally, it is important to consider noninfectious causes of fever such as transfusion reactions, chemotherapy or other drug-related fever, allergic reactions, and occasionally tumor fever.

**SPECTRUM OF INFECTION**

Infections that occur during the early phases of a neutropenic episode are predominantly bacterial. Fungal infections are generally seen in patients with severe and prolonged neutropenia and in those receiving multiple courses of broad-spectrum antibiotics. Most large cancer treatment centers have reported a predominance of Gram-positive pathogens as a cause of bacteremia in neutropenic patients (11). However, institutional differences do exist; many centers often encounter Gram-negative bacilli instead. Additionally, most tissue-based infections (pneumonia, typhilitis/enterocolitis, perirectal infections) and polymicrobial infections are frequently Gram-negative (12). Yeasts such as *Candida* spp. and *Trichosporon* spp. and molds such as *Aspergillus* spp., the *Zygomycetes*, and *Fusarium* spp. are the usual causes of fungal infections. Viral infections are uncommon, but herpesviruses (HSV, VZV, CMV, HHV6) and community respiratory viruses are the most frequent pathogens. Table 1 lists the common pathogens encountered in neutropenic patients.

**EMPIRIC THERAPY**

The administration of empiric, broad-spectrum antibiotic therapy is considered the standard of care for febrile episodes in neutropenic patients (2). Several therapeutic choices are available (Table 2). Individual institutions must tailor the use of specific agents based on local epidemiology and local susceptibility/resistance patterns. Some experts favor combination regimens that are potentially bactericidal over single-agent regimens (monotherapy), especially in high-risk patients with documented Gram-negative infections. However, most head-to-head clinical trials have not demonstrated the superiority of combination therapy over monotherapy (2). Combination regimens may reduce the overall emergence of resistance, but may be associated with increased toxicity and cost.

Combinations that do not include a glycopeptide (e.g., vancomycin) consist of an aminoglycoside (e.g., amikacin, tobramycin, gentamicin) along with a cephalosporin (e.g., cefepime, ceftazidime), carbapenem (e.g., imipenem, meropenem), quinolone (e.g., ciprofloxacin), or an antipseudomonal penicillin/beta-lactamase inhibitor (e.g., piperacillin/tazobactam). When more potent Gram-positive coverage is indicated, combining vancomycin with ceftazidime, imipenem, meropenem, or a quinolone might be indicated. Other specific Gram-positive agents (e.g., linezolid, quinupristin/dalfopristin) are not yet indicated for use in empiric regimens.
TABLE 1  Common causes of documented infections in neutropenic patients

<table>
<thead>
<tr>
<th>Bacteria</th>
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<tbody>
<tr>
<td>Gram-positive</td>
</tr>
<tr>
<td>Staphylococcus spp.</td>
</tr>
<tr>
<td>Viridans streptococci</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
</tr>
<tr>
<td>Corynebacterium spp.</td>
</tr>
<tr>
<td>Bacillus spp.</td>
</tr>
<tr>
<td>Gram-negative</td>
</tr>
<tr>
<td>Escherichia coli</td>
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<tr>
<td>Pseudomonas aeruginosa</td>
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<tr>
<td>Klebsiella spp.</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
</tr>
<tr>
<td>Proteus spp.</td>
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<tr>
<td>Stenotrophomonas maltophilia</td>
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<table>
<thead>
<tr>
<th>Fungi</th>
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<tbody>
<tr>
<td>Candida albicans and other Candida spp.</td>
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<tr>
<td>Trichosporon beigelli</td>
</tr>
<tr>
<td>Aspergillus fumigatus and other Aspergillus spp.</td>
</tr>
<tr>
<td>Zygomycetes</td>
</tr>
<tr>
<td>Fusarium spp.</td>
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<table>
<thead>
<tr>
<th>Viruses</th>
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<tr>
<td>Herpesviruses</td>
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<tr>
<td>Respiratory syncytial virus</td>
</tr>
<tr>
<td>Influenza virus</td>
</tr>
<tr>
<td>Parainfluenza virus</td>
</tr>
<tr>
<td>Adenovirus</td>
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</table>

Based on current susceptibility patterns, cefepime, meropenem, and imipenem are the most appropriate agents for monotherapy (13, 14).

The response rates of most empiric regimens range from 55% to 85% (2). It is customary to treat for 72–96 h before making alterations, in order to allow the initial regimen to produce a response. These alterations depend on the clinical setting (e.g., suspected catheter-related infection, abdominal or pelvic focus, central nervous system infection) and microbiologic data. The most common modifications are the addition of a glycopeptide, if not used initially, or the addition of an antifungal agent. Strengthening Gram-negative or anaerobic coverage when indicated is also commonplace. The choice of antifungal agents depends on the use of antifungal prophylaxis and the nature of the fungal infections (yeast versus mold). In general, amphotericin B or one of its lipid preparations is used in this setting. Newer agents such as voriconazole and caspofungin are also being evaluated for empiric antifungal therapy in persistently febrile neutropenic patients (15).
INFECTIONS IN NEUTROPENIC PATIENTS

TABLE 2  Traditional choices for empiric therapy in febrile neutropenic patients

| Combination Regimens (without glycopeptide) | +antipseudomonal penicillin |
| Aminoglycoside | ± beta/lactamase inhibitor |
| | +extended spectrum cephalosporin |
| | +carbapenem or quinolone |

| Combination Regimens (with a glycopeptide)* | +antipseudomonal penicillin |
| Vancomycin | ± beta/lactamase inhibitor |
| | +extended spectrum cephalosporin |
| | +carbapenem |
| | +quinolone or monobactam |

| Single-Agent Regimens (monotherapy) | +antipseudomonal penicillin + beta/lactamase inhibitorc |
| Carbapenemb | |
| Extended spectrum cephalosporin | |
| Antipseudomonal penicillin | |

*a Linezolid and quinopristin/dalfopristin not recommended for empiric therapy.
b Imipenem and meropenem (but not ertapenem).
c May need additional clinical data.

SPECIFIC THERAPY

When a specific pathogen is isolated, therapy can be adjusted to the organism isolated, based on local susceptibility patterns. Table 3 lists the agents used most often, including some newer options. The isolation of a specific pathogen, especially if it is a Gram-positive organism, does not necessarily permit the use of narrow-spectrum agents in patients with severe neutropenia (particularly those with significant mucositis), since these patients may have occult Gram-negative or polymicrobial infections. Our antifungal armamentarium is expanding; several newer triazoles (voriconazole, posaconazole, ravuconazole) and echinocandins (caspofungin, anidulafungin, micafungin) have either recently become available or are nearing approval by the US Food and Drug Administration. Our ability to treat most viral infections is still quite limited; new antiviral agents are needed.

LENGTH OF THERAPY

The length of therapy depends on the type of infection (bacteremia, urinary tract infection, pneumonia, etc.), the organism isolated (S. aureus, coagulase-negative staphylococci, P. aeruginosa, Candida spp., etc.), and the persistence of or recovery from neutropenia. Most experts continue therapy until (a) all signs and symptoms of infection have resolved, (b) the patient has been afebrile for 3–4 days, (c) cultures, if initially positive, have been rendered negative, and (d) radiographic evidence of infection, if initially present, shows signs of resolution. Some experts...
TABLE 3  Therapeutic agents for the treatment of documented infections in febrile neutropenic patients

Antibacterial Agents
Narrow-spectrum (Gram-positive)
  Nafcillin, oxacillin
  Vancomycin (teicoplanin, where available)
  Linezolid
  Quinupristin/dalfopristin
Narrow-spectrum (Gram-negative)
  Aminoglycosides
  Monobactams (aztreonam)
  Quinolones (ciprofloxacin)
  Narrow-spectrum (anaerobic)
  Metronidazole
  Clindamycin
Broad-spectrum
  Meropenem, imipenem
  Cefepime, ceftazidime
  Piperacillin/tazobactam
  Moxifloxacin, gatifloxacin (additional clinical data needed)
  Trimethoprim/sulfamethoxazole

Antifungal Agents
  Amphotericin B (including lipid preparations)
  Fluconazole, itraconazole, voriconazole
  Caspofungin

Antiviral Agents
  Acyclovir
  Valacyclovir
cGanciclovir
  Foscarnet
  Cidofovir
  Ribavirin

recommend continuing therapy until resolution of neutropenia (ANC ≥ 500/mm³ for 2 consecutive days) (2).

RISK ASSESSMENT AND RISK-BASED THERAPY

It has long been recognized that not all febrile neutropenic patients have the same risk of developing serious infection-related or other complications. However, it has only recently become possible to identify low-risk patients accurately and in a timely manner, using clinical criteria and/or statistically derived prediction rules (8–10, 16, 17). Low-risk patients can be discharged early after initial stabilization in the hospital or can be treated for the febrile episode without any hospitalization (8, 18, 19). Most outpatient regimens are quinolone-based (e.g., ciprofloxacin +
amoxicillin/clavulanate or clindamycin) and can be administered orally, although parenteral outpatient therapy is also feasible in low-risk patients who are unable to tolerate oral therapy. An experienced team and the appropriate infrastructure are essential for a risk-based program to be successful.

INFECTION PREVENTION

Antibacterial prophylaxis (generally with a quinolone such as ciprofloxacin) has been found to reduce the frequency of documented Gram-negative infections, but it may have no impact, or occasionally may lead to an increase in Gram-positive infections (20). Increased survival as a result of antibacterial prophylaxis has not been demonstrated. The emergence of resistant organisms is a significant drawback of chemoprophylaxis (21). Consequently, it is recommended only for patients anticipated to have severe and prolonged neutropenia (ANC ≤ 100/mm³ for >10–14 days). Antifungal prophylaxis (e.g., fluconazole/itraconazole) has been shown to reduce the frequency of infections caused by Candida spp. (22, 23). Mold infections are much more difficult to prevent, and effective strategies are yet to be developed. Some of the newer antifungal agents with activity against filamentous fungi (e.g., voriconazole, posaconazole) are being evaluated for the prevention of fungal infections.

SUMMARY

The management of febrile neutropenic patients has evolved considerably. Although hospital-based, empiric therapy remains the standard for high-risk patients, newer strategies such as early discharge or oral, out-patient therapy are becoming the norm for low-risk patients. The most important factors for the selection of antimicrobial agents for empiric use are local microbiology and susceptibility/resistance patterns. Better strategies for infection prevention are needed, particularly for fungal and viral infections. These issues will continue to challenge clinicians caring for febrile neutropenic patients for the foreseeable future.

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