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**REVIEW ARTICLE**

# Bacterial infection in neutropenic cancer patients: an overview

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## INTRODUCTION

Infection remains the most common complication of myelosuppressive antineoplastic therapy, and is associated with substantial morbidity and mortality despite major advances in supportive care (1).

Bacterial infections are predominant during the early stages of neutropenia, whereas fungal infections are more common in patients with prolonged and severe neutropenia (2). The spectrum of bacterial and fungal infection undergoes periodic change and is impacted upon by several factors including the use of antibacterial/antifungal prophylaxis, the use of foreign medical devices (e.g. various catheters), the nature and intensity of the antineoplastic regimen, surgical procedures, and local epidemiological factors.

The standard of care for the treatment of febrile neutropenic patients is the administration of broad-spectrum antibiotic therapy with the intention to "cover" the majority of bacterial pathogens encountered in this setting. In order to achieve the best possible coverage with the initial empiric regimen, it is essential to monitor changes in the epidemiology of infections in this setting, and take into consideration local susceptibility/ resistance patterns (3).

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### Etiology of fever

Fever is the most common, and sometimes the only manifestation of infection in neutropenic patients, as the usual signs/symptoms of inflammation may be blunted in this setting. Approximately 20-25% of such episodes will be due to a microbiologically documented infection (i.e. positive cultures from a normally sterile site). A similar proportion (20-25%) will be due to clinically documented infections (i.e. a clinical site of infection such as cellulitis or pneumonia but with no microbiologic documentation). The majority of episodes (45-50%) have neither a microbiologically nor a clinically documented infection. Such episodes are termed "unexplained fever" and are presumed to be caused by infection, since the majority respond to anti-infective therapy. A small proportion of febrile episodes (approximately 5%) are due to non-infectious causes (e.g. tumor fever, drug fever).

### Sites of infection

The most common sites of infection and the frequency of infection at these sites are listed in table 1. These include bloodstream infections, respiratory tract infections (both upper and lower respiratory tract), urinary tract infections, and sites

along the gastro-intestinal tract. Most bacteremias, urinary tract infections, and some skin and skin structure infections are microbiologically documented, whereas most infections at other sites are clinically documented. The majority of these are diagnosed using a combination of clinical features and information from radiographic imaging, ultrasonography, serologic testing, or other laboratory diagnostic techniques.

**Table 1**. Common sites of infection in neutropenic patients

| Site of infection | Frequency (%) |
|---|---|
| Bloodstream* | 20-25 |
| Respiratory tract | 25-30 |
| Urinary tract | 10-15 |
| Skin/Skin structure | 10-15 |
| Gastrointestinal tract† | 5-10 |
| Other sites# | 1-5 |

* Including catheter-related infections
† Esophagitis, neutropenic enterocolitis, peri-rectal sites, bilary tract infections
# Meningitis, septic arthritis and other uncommon infections

Despite the fact that bloodstream infections account for only 20-25% of microbiologically documented infections in patients with neutropenia, most surveys describing the etiology of bacterial infections in such patients provide detailed information only on bloodstream infections caused by single organisms (monomicrobial infections), and exclude or provide very little information about infections at other site, and about polymicrobial infections (4,5). This paints an incomplete and inaccurate picture since blood stream infections are caused predominantly by gram-positive pathogens whereas infections at many other sites are predominantly gram-negative or polymicrobial (6). For example, the EORTC and SCOPE data indicate that 75-70% of bacterial infections are caused by gram-positive pathogens although information about monomicrobial bacteremias only, was provided. This type of information led to the widespread use (misuse?) of agents such as vancomycin and teicoplanin as part of the initial empiric regimen in neutropenic patients. Increased glycopeptide usage has been associated with increased costs, increased toxicity, and reduced susceptibility (MIC creep) or overt resistance (VISA, VRSA, VRE) among gram-positive pathogens, without significant improvement in overall outcome (mortality) of gram-positive infections (7-10).

When data from non-bacteremic sites of infection and polymicrobial infection are presented, a substantially different picture emerges (2,6). Gram-positive organisms account for <50% of documented infections, gram-negative pathogens for 20-25%, and polymicrobial infections for 25-30%. Several studies have documented that approximately 80% of polymicrobial infections have a gram-negative component, and approximately 35% are caused by multiple species of gram-negative pathogens (11,12). This changes the approach that needs to be taken when selecting agents/regimens for initial empiric therapy in febrile neutropenic patients.

## Common bacterial pathogens

*Gram-positive organisms:* The most commonly isolated gram-positive pathogens from neutropenic patients are Coagulase-negative staphylococci (CoNS) followed by Staphylococcus aureus, Enterococcus species, and viridans group streptococci (VGE) (4,13). Organisms colonizing the skin also cause infections frequently including catheter-related bacteremias. These include Bacillus species and Corynebacterium species. Some recent reports have focused on the increasing frequency of infections caused by Stomatococcus mucilaginosus, particularly in patients who develop severe oral mucositis (14,15). Although Listeria monocytogenes and Rhodococcus equi are encountered more frequently in patients with impaired cellular immunity, they need to be considered when such patients are rendered neutropenic (16,17). Streptococcus species including Streptococcus pneumoniae and beta-

haemolytic streptococci (Lance- field group A, B, C, G and F) are also important pathogens in neutropenic patients (2,18,19). (Table 2)

**Table 2**. Common causes of infection in neutropenic patients

| |
|---|
| **Gram-positive bacteria** |
| Coagulase-negative staphylococci |
| Staphylococcus aureus |
| Enterococcus species |
| Viridans group streptococci |
| Bacillus species |
| Corynebacterium species |
| Streptococcus pneumoniae |
| Beta-hemolytic streptococci (Groups A, B, C, G, F) |
| Stomatococcus mucilaginosus |
| **Gram-negative bacteria** |
| Escherichia coli |
| Klebsiella species |
| Other Enterobacteriaceae |
| Pseudomonas aeruginosa |
| Pseudomonas (non-aeruginosa) species |
| Acinetobacter species |
| Stenotrophomonas maltophilia |
| **Anaerobes** |
| Bacteroids species |
| Clostridium species |

Many gram-positive pathogens have developed resistance to agents commonly used for prophylaxis (the fluoroquinolones) and/or empiric therapy (beta-lactams) of febrile episodes in neutropenic patients. At most cancer treatment centers more than 90% of CoNS and >50% of S. aureus isolates are methicillin-resistant. Approximately 17-20% of Enterococcus species are glycopeptide resistant (20). Non-susceptibility to penicillin among VGS approaches 60% and 20% of these isolates have high level penicillin resistance (MIC ≥2.0 µg/ml) (18). Similar non-susceptibility and resistance rates have been documented for S. pneumoniae isolates (21). Even among susceptible gram-positive organisms, increased MIC's (MIC creep) and widespread tolerance (MCB ≥from 32 times the MIC) have been documented. Increasing levels of resistance are of great concern since the pipeline for new drugs is relatively empty (22). This also highlights the critical role of antimicrobial stewardship and infection control in the overall management of febrile episodes in neutropenic patients (23).

*Gram-negative organisms:* Escherichia coli, Klebsiella species, and Pseudomonas aeruginosa are the most common gram-negative pathogens isolated from neutropenic patients and collectively account for 60-65% of documented bacterial infections (1,24). Other Enterobacteriaceae, Acinetobacter species, Stenotrophomonas maltophilia and non-aeruginosa Pseudomonas species are also encountered frequently (25,26). As with gram-positive pathogens, resistance levels among gram-negative pathogens have risen to alarming levels, and some organisms have developed unique and/or multiple mechanisms of resistance, rendering them multi-drug-resistant defined as resistance to at least 3 classes of antibiotics (27,28). Organisms of particular concern include ESBL producers, Acinetobacter species, Stenotrophomonas maltophilia, Pseudomonas aeruginosa, and Klebsiella spp. producing carbapenemases (KPC).

Gram-negative infections have traditionally been associated with greater morbidity and mortality than gram-positive infections with a few notable exceptions (MRSA, VRE). Consequently, antimicrobial prophylaxis in neutropenic patients has been targeted primarily against these organisms. The agents used most often for this indication are the fluoroquinolones (ciprofloxacin, levofloxacin). The use of prophylactic agents has reduced the frequency of febrile episodes in neutropenic patients, and the frequency of documented gram-negative infections as well (29,30). However, most studies have not shown a decrease in mortality as a result of this strategy, and many have documented either no impact on, or an increase in the frequency of gram-positive infections. However, one recent meta-analysis has pooled data from several studies indicating a reduction in overall mortality (31). This strategy has resulted in a substantial increase in the level of

fluoroquiolone resistance in common gram-negative pathogens (e.g. E. coli and P. aeruginosa) and most societies/guidelines caution against the routine use of prophylaxis in neutropenic patient (1,32).

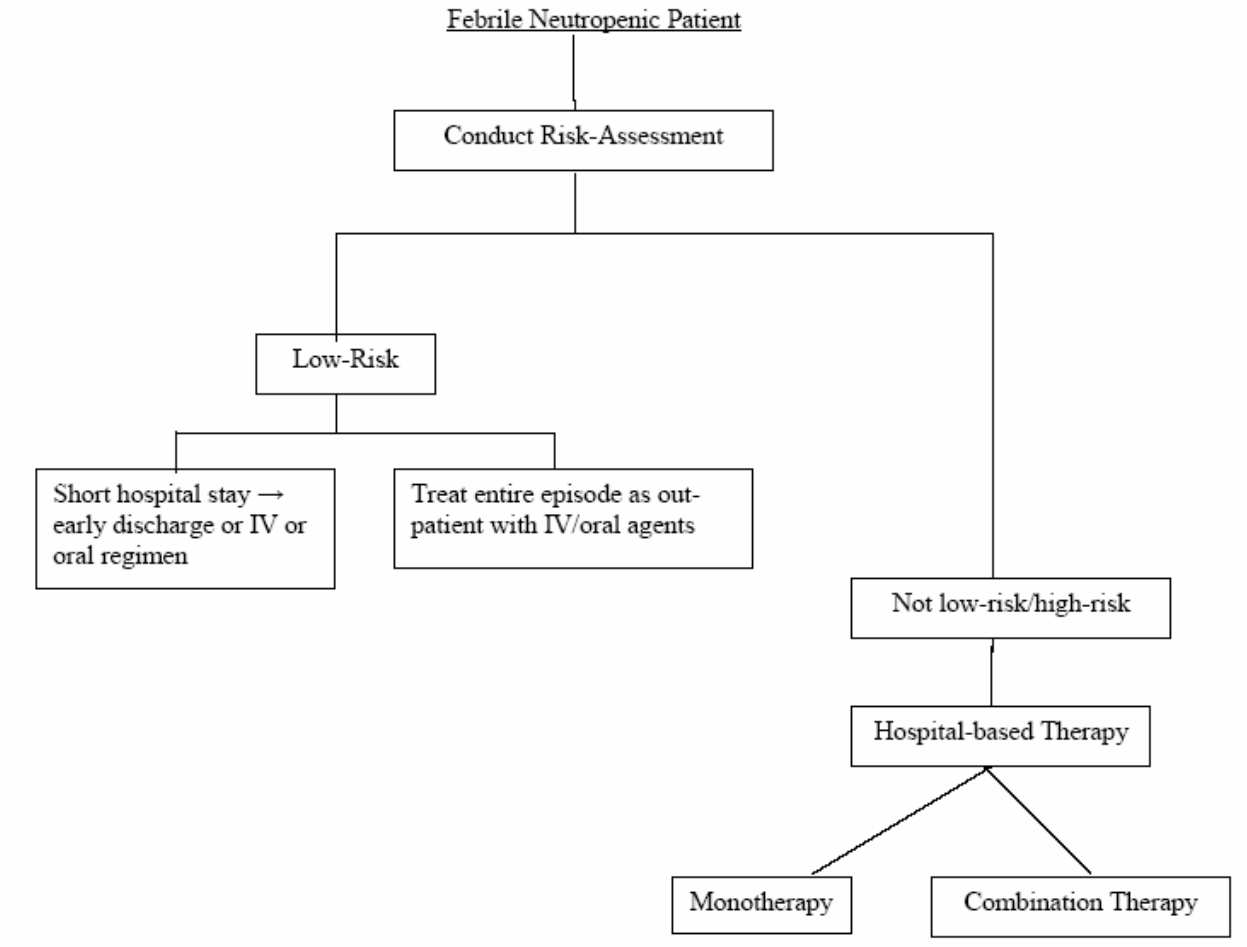
## Polymicrobial Infection

As already indicated, polymicrobial infections are at least as frequent, if not more so, than single organism gram-negative infections (11,12). The majority of these infections are deep tissue infections such ass pneumonia, neutropenic enterocolitis, perirectal infection, biliary-tract infections. Approximately 10-15% of bacteremias and urinary tract infections are polymicrobial as well (33).

P. aeruginosa is the most common organism isolated from such infections (45-55% of cases), perhaps indicating its ability to invade tissues more so than other organisms. One large study of 507 episodes of polymicrobial infections demonstrated that approximately 80% had a gram-negative component, and approximately 33% had multiple species of gram-negative isolates (11).

Polymicrobial infections are associated with greater morbidity and mortality than single organism infections. One study of the outcomes of bacteremia in neutropenic cancer patients suggested that these infections respond more often to combination antibacterial regimens than to monotherapy (34).

**Figure 1**. Management strategies for febrile episodes in neutropenic patients



Data regarding polymicrobial infections are still quite limited, as many centers fail to report them either in epidemiologic surveys or therapeutic trials. We encourage all investigators taking care of neutropenic patients to include polymicrobial infections in their reports.

## Antimicrobial Therapy

The accepted standard of care is to provide broad-spectrum, empiric coverage to febrile neutropenic patients, based on local epidemiology and susceptibility/resistance patterns (Figure 1) (1,2,32). Until recently, such treatment was always administered in the hospital. It has now become possible to identify a "low-risk" subset among febrile neutropenic patients at the onset of a febrile episode (35,36).

This has made it possible to move the treatment setting from the hospital to the outpatient clinic/home environment (37,38). Consequently, the first step in the management of a febrile neutropenic patient is to conduct a risk assessment using either statistically derived risk assessment tools (e.g. the MASCC risk-index) or simple clinical criteria (35).

If the patient is classified as low-risk, a short period of stabilization in the hospital (4-48 hours) followed by outpatient antibiotic therapy, or treatment of the entire episode in the outpatient setting is appropriate (38). This strategy is associated with a high success rate, a low-rate (<3%) of complications or readmission for any reason, better resource utilization, reduced costs, and an improved quality of life for patients and their caregivers (39). If the patient is not in the low-risk category, standard, hospital–based, parenteral therapy is recommended so that closer monitoring of the patient for response, toxicity, and superinfections or other complications can be achieved (1,2). As previously mentioned, institutional differences in epidemiology, and susceptibility/resistance patterns are not uncommon. Consequently, the specific agent(s) used for therapy will depend on local data.

## Antimicrobial stewardship

The frequency and duration of antibiotic usage in neutropenic patients is probably greater than in any other patient population. Antibiotics are used for a number of indications including prophylaxis, pre-emptive therapy, empiric therapy, specific (targeted) therapy, and maintenance or suppressive therapy. All this creates significant selection pressure for the emergence of organisms that are resistant to the most commonly used antibiotics in this setting. One of the traditional methods for overcoming this problem has been the development of novel agents. However, for the last decade or so, new drug development has almost come to a standstill (22,40). This situation has forced clinicians to take a closer look at their antimicrobial usage habits, and devise methods to improve the appropriate use of these agents. This is now termed "antimicrobial stewardship", and leading societies have published comprehensive guidelines dealing with the establishment and implementation of antimicrobial stewardship programs (23). Various stewardship strategies are outlined in table 3. These strategies, along with strict adherence to infection control policies and practices go a long way in reducing the selection and spread of resistant organisms.

In conclusion, bacterial infections occur frequently in cancer patients especially in the setting of severe neutropenia. The most important aspects of management of these patients are:

- thorough evaluation
- knowledge of local epidemiology and susceptibility/ resistance patterns
- prompt administration of empiric antibiotic therapy based on risk- group
- close monitoring and follow-up
- antimicrobial stewardship and infection control

**Table 3**. Recommendations for antimicrobial stewardship

| |
|---|
| **Baseline data/infrastructure** |
| Determine local epidemiology and resistance patterns |
| Know institutional formulary and prescribing habits |
| Develop multidisciplinary antimicrobial stewardship team (MAST) |
| **Recommendations for antimicrobial usage** |
| Limit antibacterial prophylaxis |
| Encourage targeted/specific therapy |
| Consider formulary restriction and/or pre-authorization |
| Create guidelines and clinical pathways |
| Consider antimicrobial heterogeneity |
| Consider de-escalation (streamlining) of empiric regimen |
| Dose optimization |
| Parenteral to oral conversion |
| Optimization of duration of therapy |
| **Other strategies** |
| Prospective audits of antimicrobial usage with feedback to prescribers |
| Educational activities (Grand Rounds, in-services) |
| Strict adherence to infection control policies |

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