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# REVIEW
# Infections in neutropenic patients I: Aetiology

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Improvement in supportive care including the introduction of new antibiotics, antiviral and antifungal agents and haematopoietic growth factors have all contributed to a decreased chemotherapy-related mortality and morbidity in cancer patients. However, infections/septic shock during neutropenia still constitutes a major threat to these patients. Most patients develop fever during neutropenia and in 20–40% a manifest bacteremia is documented. In patients with prolonged neutropenia, the risk for fungal infections is increased. The spectrum of bacterial, fungal and viral infections in the neutropenic patient is reviewed.

**Keywords:** neutropenia; septicemia; fungal infections.

## INTRODUCTION

With the introduction of modern chemo- and radio-therapy, an increasing fraction of patients with previously lethal malignant diseases can be cured. Myelosuppression is often the dose limiting toxicity and the resulting neutropenia constitutes a major threat to the patient. The risk for serious infections increases with the depth and duration of the neutropenia [1]. During profound neutropenia most patients develop fever and in 20–40% a manifest bacteremia is documented [2]. Although broad-spectrum antibiotics are promptly instituted, some patients with potentially curable diseases will die from septic shock. The early mortality rate (within 72 hours) due to bacteremia in patients with neutropenia ranges from 0 to 12% in different studies [3–6]. The spectrum of infections seen in immunocompromised patients varies depending on the underlying disease and its treatment.

In general, infections caused by bacteria and fungi are predominant in neutropenic patients while intracellular organisms (e.g. mycobacteria, viruses and parasites) are more frequent in patients with impaired cell-mediated immunity.

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## BACTERIAL INFECTIONS

The spectrum of causative agents in bacteremia in neutropenic patients has fluctuated: during the 1950s and 1960s Gram-positive bacteria were most commonly encountered [7], during the 1970s Gram-negative isolates dominated [8] and since the 1980s Gram-positive bacteria have reemerged as prevailing pathogens [2,5,9,10]. These changes are illustrated by the changing proportion between Gram-positive and Gram-negative single-organism bacteremias documented in EORTC trials from 1973 to 1991 (Table 1).

### Gram-negative bacteremia

The most common Gram-negative isolates are *Escherichia coli, Klebsiella pneumoniae* and *Pseudomonas aeruginosa* which together account for more than 90% of the Gram-negative bacteremias in most series (Table 1) [11,12]. There is clear evidence that these bacteria mainly arise from the gastrointestinal tract and translocation of bacteria from the gut to blood by the dominant fecal strains of *Enterobacteriaceae* or *P. aeruginosa* was observed in 45 of 55 neutropenic patients with Gram-negative bacteremia [13]. In patients with concomitant gut colonization of *Enterobacteriaceae* and *P. aeruginosa*, the latter organism was most likely to be isolated from blood whether or not the *Pseudomonas* had the highest bacterial counts [13]. The invasive properties of *Pseudomonas* were also documented in a study by Schimpff *et al.* [14]. Thus,

**Table 1.** Distribution of isolates in single-organism bacteremia in EORTC trials [65]

| EORTC trial | I | | III | | V | | VIII | |
|---|---|---|---|---|---|---|---|---|
| Time period | 1973-78 | | 1980-83 | | 1986-88 | | 1989-91 | |
| | no. | (%) | no. | (%) | no. | (%) | no. | (%) |
| Gram-positive bacteria | | | | | | | | |
| *S. aureus* | 28 | (20) | 14 | (10) | 20 | (9) | 13 | (8) |
| Coagulase negative staphylococci | 5 | (3) | 24 | (17) | 49 | (23) | 39 | (26) |
| *Streptococcus* spp. | 5 | (3) | 18 | (13) | 50 | (23) | 48 | (32) |
| Other | 4 | (3) | 2 | (1) | 16 | (8) | 4 | (3) |
| Total | 42 | (29) | 58 | (41) | 135 | (63) | 104 | (69) |
| Gram-negative bacteria | | | | | | | | |
| *E. coli* | 46 | (32) | 38 | (27) | 45 | (21) | 20 | (13) |
| *P. aeruginosa* | 18 | (12) | 18 | (13) | 14 | (7) | 10 | (7) |
| Other | 39 | (27) | 27 | (19) | 19 | (9) | 17 | (11) |
| Total | 103 | (71) | 83 | (59) | 78 | (37) | 47 | (31) |
| Total | 145 | | 141 | | 213 | | 151 | |

patients with leukemia who were colonized with Pseudomonas in the gut subsequently became bacteremic with the same strain. This was not true for *E. coli* and *K. pneumoniae* colonization which only occasionally led to bacteremia. More than 50% of bacteremias in that study were acquired during hospitalization [14]. There is a substantial mortality among neutropenic patients with Gram-negative bacteremia and the prognosis of both *E. coli* and *P. aeruginosa* bacteremia is worsened by a decreasing neutrophil count, delay in appropriate antibiotic therapy and concomitant pneumonia [15,16].

## Gram-positive bacteremia

Coagulase negative staphylococci (CNS), *Staphylococcus aureus* and alpha streptococci are the most common Gram-positive bacteria found in blood cultures from neutropenic patients (Table 1) [11,12,17]. Although *S. aureus* tends to be more virulent and capable of inducing septic shock [18], CNS infections may carry both a high morbidity and mortality [19]. Furthermore, the rate of CNS infections increases in neutropenic patients (Table 1) [20]. The frequency of methicillin-resistant CNS isolates has increased, though most strains are still susceptible to vancomycin [21]. There is a fear that vancomycin-resistant strains of enterococci will transfer the responsible gene to CNS and thereby cause a difficult therapeutic dilemma.

The incidence of alpha streptococcal bacteremia has increased (Table 1) which is associated with a substantial mortality (6–30%) and morbidity such as septic shock (7–18%) and adult respiratory distress syndrome (ARDS; 3–33%) [22]. Predisposing factors for severe streptococcal infection were prophylactic antibiotics, profound neutropenia and the use of acid-reducing drugs for treatment of gastritis as reported by Elting *et al.* [23].

## Anaerobic bacterial infections

Anaerobic bacteria account for approximately 5% of bacteremias in the neutropenic patient [24]. *Bacteroides fragilis* and *Clostridium* spp. are the most frequently encountered. It is important to be aware of the possibility of mixed anaerobic and aerobic infections in the oral and perianal regions [25]. Another feared complication of chemotherapy-induced neutropenia is neutropenic enterocolitis. This condition is characterized by fever and abdominal pain often accompanied by vomiting and/or diarrhoea and is mainly caused by anaerobic bacterias [26,27]. A conservative attitude with bowel rest, decompression, nutritional support, and broad spectrum antibiotics is to be preferred before surgery [27]. Granulocyte count restitution is essentially why haematopoetic growth factors should be tried and the use of granulocyte transfusions may be considered.

One specific, although not systemic, nosocomial anaerobic infection is caused by the toxin producing *Clostridium difficile,* inducing a spectrum of gastrointestinal symptoms from diarrhoea to fulminant colitis [28]. Antibiotic treatment predisposes to this infection but patients may be colonized also without prior exposure to antibiotics [29]. Furthermore, it is well known that other more diffuse symptoms besides diarrhoea, such as abdominal pain, distention and even constipation, may be due to *C. difficile* infection in neutropenic patients [30].

## Mycobacterial infections

Mycobacterial infections do not constitute a major problem in patients with neutropenia but both mycobacterium tuberculosis and atypical mycobacteria must be kept in mind when evaluating neutropenic patients with fever not responding to

antibiotics or antifungal drugs [31]. The patient's age, geographical origin and social living conditions are of importance when considering start of empirical anti-tuberculous treatment. Furthermore, a finding of bone marrow granulomas strongly motivates empirical treatment before results of cultures are available [32].

## FUNGAL INFECTIONS

Patients with prolonged neutropenia are predisposed to become infected with candida or aspergillus [33] and fungal infections constitute a majority of fatal infections in patients with acute leukemia [34,35]. Furthermore, the isolation of candida in blood cultures has become more common in neutropenic patients [36]. The dominating candida species is *Candida albicans* although increasing incidences of *Candida (Torulopsis) glabrata*, *Candida tropicalis* and *Candida krusei* have been reported in patients receiving prophylactic ketokonazole or fluconazole treatment [37,38]. Patients receiving intensive chemotherapy often become colonized with candida in urine and feces [39] and they also have a high risk (unless prophylactic fluconazole therapy is given) to develop oropharyngeal candidiasis [40]. The risk of disseminated disease increases with the number of sites colonized and the duration of neutropenia [8,41]. Most candida infections disseminate from the gastrointestinal tract but candida may also be an aetiologic agent in pneumonia, as demonstrated in 103 neutropenic patients with clinically and microbiologically documented lung infiltrates from which candida were isolated in 24% [42]. This issue is, however, controversial since there are no strict criteria to differentiate between colonization of candida in the respiratory tract and a true infection caused by candida. Despite extensive serological studies [43] and occasional reports of a highly predictive test (candida antigen) [44], no established method for early diagnosis of disseminated candidiasis with both a high specificity and sensitivity has emerged [45]. Another important clinical entity in the spectrum of candida related disorders in neutropenic patients is chronic disseminated candidiasis (previously named hepatosplenic candidiasis) which is a disorder characterized by persistence of fever after granulocyte recovery, elevated serum alkaline phosphatase and abdominal pain [46,47].

Aspergillosis is the second most common fungal infection in neutropenic patients. *Aspergillus fumigatus* and *Aspergillus flavus* are the dominating pathogens and the lung is the primary site of infection. This was illustrated in one study where invasive pulmonary aspergillus infection was the cause of nosocomial pneumonia in 20 of 55 patients undergoing bone marrow transplantation [48]. The mortality rate among these 20 patients was 95% but lower mortality rates have been reported by others [49]. Aspergillus spreads predominately by local invasion/tissue infection and in pulmonary infection subsequent necrosis often extends to the pleura causing a pleuritic chest pain in a majority of patients. In addition, aspergillus infection frequently involves sinuses and in one third of patients with pulmonary involvement a concomitant sinus infection was diagnosed [50]. An early diagnosis and treatment is mandatory and repeated computerized tomography (CT) scans may be of great diagnostic value [51].

*Pneumocystis carinii*, formerly classified as a parasite, is a rather rare fungal pathogen in the neutropenic patient. However, clusters of infections in patients with leukemia and lymphoma have been described [52] and this agent must be kept in mind also in neutropenic patients with bilateral diffuse alveolar pulmonary infiltrates, particularly in patients undergoing bone marrow transplantation [42,53].

## VIRAL INFECTIONS

Mainly viruses from the herpes group (i.e. Herpes simplex virus (HSV), Varicella-zoster virus (VZV) and cytomegalovirus (CMV)) infect patients receiving combination chemotherapy. Recurrent HSV infections may manifest as painful lesions in the oral and perioral areas. HSV oesophagitis is clinically indistinguishable from that of candida origin [54]. Reactivation of HSV is commonly seen in neutropenic patients with haematological malignancies. Twenty-four of 43 patients (72 fever episodes) developed mucocutaneous HSV infection during at least one fever episode [55]. Furthermore, the incidence of fever not responding to antibiotics was higher in patients in whom HSV was isolated. The risk for VZV infection increases with the intensity of treatment and, following bone marrow transplantation, patients have an increased risk for up to 1 year [56]. CMV infections are mainly seen in patients following allogeneic bone marrow transplantation and CMV pneumonitis is a major threat carrying a high mortality rate.

Acyclovir is the key drug in both prophylaxis and treatment of the herpes virus infections and some studies in bone marrow recipients have shown a reduction of herpetic gingivostomatitis and CMV pneumonitis by the use of prophylactic acyclovir [57,58]. Acyclovir has also been shown to reduce the incidence of bacterial infections in acute leukemia patients probably by reducing oral herpetic lesions otherwise used as bacterial entry [59]. Earlier attempts to treat manifest CMV pneumo-

nitis with various antiviral agents, such as acyclovir, ganciclovir and foscarnet, have not significantly reduced mortality [60]. However, the combination of ganciclovir and intravenous immunoglobulin has shown some improvement of survival and is the recommended treatment for CMV pneumonitis in bone marrow transplant recipients [60]. Another category of viral disorders is the nosocomial hepatitis among which hepatitis C appears to have an increased chronicity rate and late seroconversion in patients with haematological disorders [61]. Frequent patient-to-patient transmission of hepatitis C virus in a haematology ward has been described [62].

Influenza A and B are other viral infections that may be severe but in most neutropenic patients are mild and self-limiting [63,64].

## CONCLUSIONS

Gram-positive bacteremias (i.e., CNS and alpha streptococci) dominate in febrile neutropenic patients and some streptococcal species may, as Gram-negative bacteremias, induce septic shock. During prolonged neutropenia fungal infections mainly caused by candida and aspergillus are commonly encountered.

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