The changing pattern of infection in neutropenic patients

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Over the past 20 years there has been a dramatic shift in the pattern of infection in neutropenic patients. During the 1970s Gram-negative organisms caused approximately 70% of all bacteraemias, but by the late 1980s the situation had reversed and approximately 70% of bacteraemias were due to Gram-positive organisms. The main contributors to this increase in Gram-positive infections have been the coagulase-negative staphylococci and the viridans streptococci. More recently, enterococci have emerged as significant pathogens in this patient group, and the development of glycopeptide resistance in the enterococci is of particular concern since this class of antibiotics is widely used in neutropenic patients. Among Gram-negative organisms, the emergence of resistance to fluoroquinolones, particularly in *Escherichia coli*, is a worrying feature which may lead to a reassessment of the use of quinolone prophylaxis in this setting.

Introduction

Infection remains an extremely frequent complication of neutropenia caused by cytotoxic chemotherapy or following bone marrow or peripheral blood stem cell transplantation. However, the past two decades have seen major changes in the type and range of pathogens causing infection, and dramatic improvements in the outcome of infected patients. Despite these improvements, there is no room for complacency, as the emergence of new groups of antibiotic-resistant bacteria is once again threatening our ability to manage these infections.

This review will attempt to describe and explain the changing trends in infection in neutropenia over the past 20 years, to look in detail at some of the microorganisms currently causing problems, and to predict the problems likely to emerge in the future.

Changing patterns of infection in the neutropenic host

In the early 1970s, infection was the most important cause of death in patients with acute leukaemia, with about 70% of this group dying of infectious complications. The most common types of fatal infection were pneumonia and septicaemia, and bacteria accounted for about 70% of these. Gram-negative bacilli were responsible for about 80% of all bacterial infections, and most of these were caused by *Escherichia coli*, *Klebsiella* spp. and *Pseudomonas aeruginosa*.1

The next 20 years saw a dramatic shift in the pattern of infection, with Gram-positive bacteria taking over as the leading cause of infection and Gram-negative organisms declining, to cause ≈30% of all bacteraemias.2 The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer (EORTC) has been engaged in research into antibiotic treatment for infections in neutropenic cancer patients since 1974, and data from these studies provide a snapshot of the changing pattern of infection over two decades.3–9 In the earlier studies from the 1970s, Gram-negative bacteria were responsible for about 70% of all cases of single-organism bacteraemia. This situation had completely reversed by the late 1980s, with 70% of single-organism bacteraemias being due to Gram-positive organisms, a proportion that has remained relatively stable since (Table). The major groups of organisms contributing to this shift towards Gram-positive infections have been the coagulase-negative staphylococci (CNS), the viridans streptococci and, more recently, the enterococci, each of which will be discussed in some detail.

Even within the groups of organisms there have been changes. In the 8 year period between EORTC trials IV and XI, the percentage of Gram-negative bacteria identified as *P. aeruginosa* decreased from 26% to 13%. The percentage of all single-organism bacteraemias identified as being caused by *P. aeruginosa* decreased from 15% to

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4% during this period. Although this fall in the incidence of *P. aeruginosa* infections has been noted in many institutions, some centres, particularly those with a predominately elderly population, still report *P. aeruginosa* infections as a frequent problem.

Our own experience (unpublished) at the Christie Hospital in Manchester over the period 1985 to 1992 mirrors the broader picture, with Gram-positive organisms being responsible for about two-thirds of all single-organism bacteraemias throughout this period. Coagulase-negative staphylococci have consistently been the most commonly isolated bacteria, with the viridans streptococci forming the second largest group. Of the Gram-negative organisms, *E. coli* remained the most frequent isolate.

The reasons for this widely encountered reversal in the pattern of infecting organisms in neutropenic bacteraemias remain unclear. The role of antibacterial prophylaxis is important, but centres that have never used prophylaxis have noted similar trends in the pattern of infection and the increase in Gram-positive bacteraemias predated the widespread use of quinolone prophylaxis. The selective pressure exerted by antimicrobial treatment is also likely to play a part, as many patients receive several courses of chemotherapy and have numerous infective episodes. Patients are exposed to multiple doses of antibiotics, many of which will be specifically targeted at Gram-negative bacteria. Some of the detailed predisposing factors for infection with CNS and viridans streptococci will be discussed later, but it is also possible that some of these isolates were initially dismissed as contaminants and were not recorded as true pathogens.

**Table.** Changing patterns of infecting organisms in EORTC studies (see text)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Dates</th>
<th>Evaluable cases</th>
<th>Type of bacteraemia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>single-organism</td>
</tr>
<tr>
<td>I</td>
<td>1973–6</td>
<td>453</td>
<td>145</td>
</tr>
<tr>
<td>II</td>
<td>1977–80</td>
<td>419</td>
<td>111</td>
</tr>
<tr>
<td>III</td>
<td>1980–3</td>
<td>582</td>
<td>141</td>
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<tr>
<td>IV</td>
<td>1986–7</td>
<td>872</td>
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</tr>
<tr>
<td>V</td>
<td>1988–90</td>
<td>694</td>
<td>151</td>
</tr>
<tr>
<td>IX</td>
<td>1991–2</td>
<td>706</td>
<td>161</td>
</tr>
<tr>
<td>XI</td>
<td>1993–4</td>
<td>958</td>
<td>199</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Gram-positive</th>
<th>Gram-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>42 (29%)</td>
<td>103 (71%)</td>
</tr>
<tr>
<td>II</td>
<td>37 (33%)</td>
<td>74 (67%)</td>
</tr>
<tr>
<td>III</td>
<td>58 (41%)</td>
<td>83 (59%)</td>
</tr>
<tr>
<td>IV</td>
<td>90 (41%)</td>
<td>129 (59%)</td>
</tr>
<tr>
<td>V</td>
<td>104 (69%)</td>
<td>47 (31%)</td>
</tr>
<tr>
<td>IX</td>
<td>108 (67%)</td>
<td>53 (33%)</td>
</tr>
<tr>
<td>XI</td>
<td>138 (69%)</td>
<td>61 (31%)</td>
</tr>
</tbody>
</table>

4% during this period. Although this fall in the incidence of *P. aeruginosa* infections has been noted in many institutions, some centres, particularly those with a predominately elderly population, still report *P. aeruginosa* infections as a frequent problem.

Owing to the ubiquity of CNS as colonizers of the normal host, it has generally been assumed that infecting strains originated from the patient’s own flora. However, there have now been a number of reports of outbreaks of infection due to a single strain of CNS, at least one of these occurring in the setting of granulocytopenic patients being managed in a leukaemia unit. In this particular outbreak the airborne route was postulated to be a major mode of spread and it was shown that the outbreak strain could persist in the environment.

Multiple antibiotic resistance was noted even in the early descriptions of infection due to CNS, and has persisted over the years. The widespread incidence of methicillin-resistant CNS has led to the glycopeptides, vancomycin and teicoplanin, being regarded as the treatment of choice for infections due to CNS, although there is continuing concern about the development of glycopeptide resistance in CNS.
**Viridans streptococci**

The viridans streptococci are normal inhabitants of the mouth, oropharynx and intestinal tract. They were initially considered to be pathogenic only in the setting of infective endocarditis, but have now become prominent as one of the leading organisms causing bacteraemia in neutropenic patients.

Reports of viridans streptococci causing infections in cancer patients first appeared in 197621,22 and numerous subsequent studies have looked at incidence, risk factors and outcome of infection. There are wide variations in the proportion of neutropenic bacteraemias reported as being due to viridans streptococci. In the EORTC study comparing ceftriaxone/amikacin with ceftazidime/amikacin7 viridans streptococci were, for the first time, the most frequently isolated organisms. Interestingly, in the most recently published EORTC trial9 they have once again slipped back to second place behind the CNS, and a falling incidence has also been noted in our own centre.

A variety of possible risk factors for viridans streptococcal bacteraemia has been suggested, although case-control studies have seldom been performed to validate these. The presence of neutropenia and oral mucositis have been frequent and important associations, suggesting that mucositis may provide a portal of entry with neutropenia allowing persistence of infection and septicaemia.23 A recent study has described the isolation of oral streptococci with the same ribotype as the blood isolates in seven patients,24 further strengthening the case for a damaged oral cavity as the portal of entry of viridans streptococci. Other associations have included the administration of high-dose cytosine arabinoside,25 the use of quinolone or co-trimoxazole prophylaxis, and treatment of gastritis with H2-receptor antagonists.26

Although most patients with viridans streptococcal bacteraemia present with a fever that responds to antibiotics, it is now clear that a subgroup of these develop a characteristic clinical picture, with hypotension, a rash and/or adult respiratory distress syndrome, and a high mortality rate.27,28

A number of the reports on viridans streptococci in neutropenia have commented on the fact that, when identified, a small number of streptococcal species have caused the majority of bacteraemias. Unfortunately, the taxonomy and nomenclature of viridans streptococci remain confusing, with different identification schemes yielding differing results. In our own institution, by means of the identification method of Beighton et al.29 the majority of bacteraemic isolates were either Streptococcus oralis or Streptococcus mitis30 and, allowing for the different descriptions of species used in other laboratories, these results are in accord with others. The reasons for the preponderance of particular strains in this setting remain unclear.

**Enterococci**

Enterococci are becoming an increasingly common cause of hospital-acquired bacteraemia, being cited as the third commonest pathogen in some series.31 This finding has been paralleled in the setting of neutropenic cancer patients. Another interesting change has been in the distribution of species causing infection, with *Enterococcus faecalis* taking over from *Enterococcus faecalis* as the predominant cause of serious infections.

Unfortunately, at the same time as enterococci have been increasing in frequency, they have been developing antibiotic resistance; this has become a serious problem, with vancomycin (or glycopeptide) resistance being cause for considerable concern. When this occurs against a background of resistance to other antimicrobials, e.g. β-lactam resistance and high-level gentamicin resistance in *E. faecium*, it can lead to cases where enterococci are resistant to all currently available agents.32

The glycopeptides (vancomycin or teicoplanin) inhibit cell wall synthesis by binding to cell wall precursors on the surface of the cell. Resistance occurs when strains of enterococci produce structurally related ligases (VanA and VanB) which synthesize altered precursors that bind the glycopeptides with a reduced affinity, allowing cell wall production in the presence of antibiotic.33

Outbreaks of infections due to these vancomycin-resistant enterococci (VRE) have been described in a number of settings, including that of the neutropenic cancer patient.34,35 Faecal colonization almost always precedes bacteraemia, which tends to occur in only a small number of colonized patients. Bacteraemia is often associated with a fatal outcome, although this may reflect the relationship between bacteraemia and severe underlying disease, rather than any particular virulence of the organism.

In the outbreak setting, VRE are usually readily recovered from a number of environmental sources; electronic rectal thermometers,36 air-fluidized microsphere beds37 and malfunctioning bedpan washer–disinfectors38 have all been implicated in transmission. However, it is likely that in most circumstances the organism is transferred from patient to patient, or from environment to patient, on the hands of staff members. The emergence of VRE as significant nosocomial pathogens is perceived worldwide as a major threat, both because of the problems associated with treating infections due to this organism and because of the possibility that vancomycin-resistant genes present in VRE may be transferred to other Gram-positive microorganisms such as *Staphylococcus aureus* or CNS. Transfer of vancomycin resistance from enterococci to *S. aureus* has been achieved in vitro,39 but not yet in vivo. Recommendations for the prevention and control of the spread of vancomycin resistance in the USA have recently been published.40
Quinolone-resistant E. coli

As has already been noted, the incidence of Gram-negative bacteraemia in neutropenic patients was declining before the widespread use of quinolones for antibacterial prophylaxis, but there is little doubt that quinolones were responsible for the extremely low rates of Gram-negative bacteraemia in centres where their use became routine.

Although quinolone resistance in a variety of species, such as staphylococci, enterococci and Pseudomonas spp., has been recognized for some time, levels of resistance in E. coli were extremely low. Over the past few years, however, reports have been emerging from Europe concerning fluoroquinolone-resistant E. coli strains causing bacteraemias in neutropenic cancer patients.

In centres participating in trials organized by the International Antimicrobial Therapy Cooperative Group of the EORTC, bacteraemic isolates are usually sent to a central laboratory for verification. A II 92 strains of E. coli isolated during the period 1983–90 were susceptible to quinolones. However, 11 of 40 strains isolated between 1991 and 1993 were highly resistant (MICs ≥ 16 mg/L) and these strains had all been recovered from patients who had received fluoroquinolones as prophylaxis. In contrast, only one of 29 patients infected with fluoroquinolone-sensitive strains had been given quinolone prophylaxis.

One centre that had noted an increasing rate of isolation of resistant strains investigated whether this was due to cross-infection with a single resistant strain, by subjecting resistant isolates to pulsed-field gel electrophoresis. This showed a number of distinct types, indicating that spread of a single clone could not explain the observed epidemiological picture.

The development of quinolone resistance in E. coli gives cause for considerable concern, particularly as there is now evidence that it is emerging in the non-neutropenic patient, with some strains arising from the community. Against this background, it is likely that the risks and benefits of prophylaxis in neutropenia will need critical reassessment.

Conclusions

The neutropenic host is extremely vulnerable to a range of bacterial infections. Indeed, for some of the rarer opportunistic organisms, this is sometimes the only setting in which infection occurs. However, in most patients, a small number of organisms, predominantly Gram-positive, cause most infections.

Improvements in infection-control practices, new developments in antimicrobials, and carefully performed large, randomized, controlled trials, have all contributed to a dramatic improvement in the outcome of infection in neutropenia. However, the emergence of resistance to antimicrobials widely used in this setting, particularly the glycopeptides and the quinolones, is of great concern, and we need to continue carefully to monitor trends in infection in the future and modify our guidelines for treatment accordingly.

References


