Empiric Therapy of Bacterial Infections in Patients with Severe Neutropenia

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The urgent need to treat presumptive infections in neutropenic patients has meant that initial therapy is empiric based on the pathogens most likely to be responsible for the patient’s rise in temperature or other symptoms of infection. The spectrum of causative pathogens has changed over time and reflects the availability and use of antimicrobial agents. Gram-positive organisms predominated in the 1940s and onward until the widespread use of early penicillins and cephalosporins effectively addressed this problem. The upsurge in infections in the 1970s and 1980s caused by Gram-negative organisms, particularly Pseudomonas aeruginosa, Escherichia coli and Klebsiella spp., has been supplanted by a new wave of infections caused by Gram-positive organisms, this time predominantly Staphylococcus aureus, Staphylococcus epidermidis, and the viridans streptococci. The fourth-generation cephalosporins (cepirome) among other broad-spectrum β-lactams, by virtue of their enhanced antimicrobial activity against Gram-positive pathogens and greater β-lactamase stability, are promising candidates for use in the empiric management of febrile episodes in neutropenic patients. Early clinical trial results are promising and should lead the way for further use of these compounds in this indication. © 1998 Elsevier Science Inc.

INTRODUCTION

Neutrophils make up over 90% of the circulating granulocytes in a normal individual. Their role is to ingest and kill bacteria and, in the presence of a bacterial infection, their numbers will increase from 3.5 to 7.5 × 10⁶ cells/mm³ to >10 × 10⁶ cells/mm³. Neutropenia, defined as a granulocyte count <500 cells/mm³, removes one of the body’s prime defense mechanisms against infection and the degree of neutropenia influences both the incidence and severity of infections in affected individuals. Profound neutropenia, where the circulating granulocyte count falls to below 100 cells/mm³, is associated with the most serious infections and those which are the most refractory to treatment.

Neutropenia is a dose-limiting side effect of many cytotoxic drugs in addition to the primary immune defect of diseases such as acute leukemia and hairy cell leukemia. Infection remains the principal cause of mortality in neutropenic cancer patients. Although the percentage of deaths attributable to infection has fallen considerably from the 70 to 80% recorded in the 1960s and 1970s, a study of the trials published by the International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer (IATCG-EORTC) reveals that approximately 3% of patients receiving active treatment for their malignancies die from a primary bacteremia. This value is considerably higher in those patients for whom active treatment is no longer considered appropriate.

Evaluation of Infections in Neutropenic Patients

The assessment of the response to antimicrobial treatment is complicated by several factors. The very fact that patients are neutropenic means that treatment must be initiated before the presence of an infection has been confirmed microbiologically. The neutropenia induced by the treatment of solid tumors is usually less than 10 days in duration, whereas the neutropenia associated with the treatment of hematologic malignancies often lasts be-
between 15 and 20 days. The degree and severity of the granulocytopenia have a marked effect on the incidence of serious infections (Bodey et al. 1966). This can be seen in Figure 1 where the slope of the two lines is steeper in the group of patients with the more profound granulocytopenia.

Any definition of febrile neutropenia is, by its very nature, arbitrary and many alternatives have been proposed over the past 20 or 30 years, although a body temperature in excess of 102°F is commonly accepted. The consequences of failing to identify a raised temperature in such patients are serious, as a delay in initiating treatment can be fatal. In most circumstances, febrile neutropenia should be regarded as a medical emergency.

The interpretation of results from trials in neutropenic patients can be fraught with difficulty, since different definitions of success and failure have been used. Until recently, the National Cancer Institute (NCI) and IATCG-EORTC used different criteria and comparison of their results was further complicated by the entry criteria for the studies. An analysis of a large study published by each group in the mid 1980s (EORTC, 1987; Pizzo et al. 1986;) also reveals that the IATCG-EORTC study was conducted in adults only, whereas the NCI study contained large numbers of children. Another difference was that the NCI study recruited patients who, mostly, had solid tumors with a shorter duration of neutropenia than the patients in the IATCG-EORTC study, the majority of whom had leukemia.

At a consensus conference hosted by the Immunocompromised Host Society in 1990, it was agreed that success be defined as resolution of fever and signs of infection with no recurrence for more than 1 week after discontinuation of treatment. Failure was defined as death or no response to the antimicrobial treatment. Modification of the initial antimicrobial regimen was also classified as failure.

The Changing Nature of Infections in Neutropenic Patients

Over the past 30 or 40 years there have been several shifts in the types of microorganisms causing infection in neutropenic patients. In the pre-antibiotics era of the 1940s and into the 1950s, *Staphylococcus aureus* was the most frequently isolated pathogen in neutropenic patients. Once the β-lactamase-resistant antistaphylococcal antibiotics were marketed and provided effective therapy for the staphylococci, Gram-negative organisms such as *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella* spp. predominated in the 1960s and 1970s. Infections caused by *P. aeruginosa* have declined dramatically in the past 10 years to be replaced by strains of Gram-negative bacteria resistant to multiple antibiotics and recently Gram-positive cocci such as *S. aureus*, the viridans group streptococci, and *Streptococcus viridans* have been much more frequently isolated. Some of these changes are reflected clearly in the data presented in Figure 2, taken from eight EORTC trials performed over a period of more than 20 years.

The Importance of Viridans Streptococci in Neutropenic Infections

Viridans streptococci used to be considered, with the exception of the ability to cause endocarditis, relatively unimportant pathogens. A report from the
M.D. Anderson Cancer Center in Houston, Texas cites an increase in the incidence of viridans streptococcal bacteremia from 1 case per 10,000 admissions in 1972 to 47 cases per 10,000 admissions in 1989 (Elting et al. 1992). A recent review article confirms that the viridans streptococci are, indeed, important pathogens in neutropenic patients, with one report citing this group of organisms as the cause of up to 39% of bacteremias (Bochud et al. 1994a).

Data from the same set of EORTC trials discussed in the preceding section clearly show the increasing importance of viridans streptococci as pathogens in the infections of hematology and oncology patients. In EORTC trial I, run between 1973 and 1976, there were no recorded instances of viridans group streptococcal infections. This changed radically in subsequent studies with a 10% incidence of infections due to viridans streptococci being recorded in EORTC trial IV (1983 to 1985) and 28% during trial VIII (1988 to 1991).

There are several possible reasons for the increasing number of infections caused by Gram-positive organisms seen in the latest studies of neutropenic patients. An increase in the use of indwelling catheters and in the use of prophylactic agents such as the fluoroquinolones are two such reasons. In a case-control study of predisposing factors Elting et al. (1992) noted that there was a statistically increased incidence ($p < 0.0001$) of a viridans streptococcal bacteremia with prophylactic administration of a fluoroquinolone or trimethoprim-sulfamethoxazole. More recently, Bochud et al. (1994b) reported that viridans streptococcal bacteremia developed in 22 of 259 (8.5%) neutropenic patients who received quinolone prophylaxis compared with 3 episodes (3.7%) in 82 patients who had received a quinolone and penicillin.

The principal cause may, however, be the gastrointestinal tract ulceration, including severe mucositis, induced by antineoplastic agents such as VP-16, ara-C, and the anthracyclines, which allows direct entry of the surface bacterial flora into the bloodstream of the patient. Treatment of chemotherapy-induced gastritis with antacids or H2 antagonists can allow the gastric overgrowth of organisms resistant to oral prophylactic agents and is associated with an increased risk of streptococcal infection (Elting et al. 1992b). Table 1 is a list of the potential causes of Gram-positive infections in neutropenic patients and the likely infecting pathogens.

**Choices for Empiric Therapy of Fever in Neutropenic Patients**

The often fatal consequences of treatment failure in infected neutropenic patients have ensured that for many years combination antimicrobial therapy has been the principal treatment choice. Balanced against this risk in delaying therapy is the desire to use the most appropriate antimicrobial regimen and the belief that the use of antibiotics in the absence of proof of infection will lead to the emergence of resistance to these and other antibiotics.

The choice of antibiotic regimen is also influenced by the predominant pathogens. As was discussed in an earlier section (see “The Changing Nature of Infections in Neutropenic Patients”), the spectrum of pathogens isolated from neutropenic patients with bacteremia has altered radically in the past 20 years or so.

**Combination Therapy**

The combination of an aminoglycoside and a β-lactam antibiotic has been the “gold standard” in the treatment of febrile episodes in neutropenic patients for many years. Early regimens paired cephalothin with gentamicin and the EORTC series of antibiotic studies have moved through many different pairings of antibiotics, sometimes using three antibiotics to try to enhance antibacterial activity. Table 2 provides a summary of the antibiotic
regimens used in some previous EORTC antimicrobial therapy studies.

The combination of ceftazidime and amikacin has been used extensively in recent years but the response rate in microbiologically documented infections with bacteremia has deteriorated from 51% in trial VIII (1988 to 1990) to 35% in trial IX (1991 to 1992). The trend is particularly apparent in Gram-positive infections with a response rate of only 25% in trial IX compared with 44% in trial VIII (Cometta et al. 1996; EORTC, 1993).

Adding in vancomycin or teicoplanin to a β-lactam/aminoglycoside combination is probably still only justified if a methicillin-resistant *S. aureus* or coagulase-negative staphylococcus infection is anticipated. In centers where most bloodstream infections are caused by β-lactam-resistant Gram-positive pathogens, it would be appropriate to consider using a glycopeptide in the initial antimicrobial regimen (EORTC, 1991). The well-known toxicities of vancomycin and its potential for engendering microbial resistance should encourage physicians to continue restricting the use of these valuable agents.

The combination of the β-lactamase inhibitor tazobactam and piperacillin has been used as first-line empiric therapy in patients with hematologic malignancy in combination with amikacin (Cometta et al. 1995; Micozzi et al. 1993) or gentamicin (Kelsey et al. 1992). All authors concluded that the combination was effective but Micozzi et al. (1993) suggested the modification of the regimen by the addition of a glycopeptide in unresponsive cases. Cometta et al. (1995) demonstrated that the combination of piperacillin-tazobactam-amikacin was significantly more effective than ceftazidime-amikacin (50% versus 35% response rate).

### TABLE 1 Risk Factors for Gram-Positive Infections in the Neutropenic Patient

<table>
<thead>
<tr>
<th>Predisposing Factors</th>
<th>Infecting Pathogens</th>
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<tbody>
<tr>
<td>Skin damage (punctures)</td>
<td>Staphylococci, <em>Corynebacterium</em> spp.</td>
</tr>
<tr>
<td>Foreign bodies (catheters)</td>
<td>Staphylococci, <em>Corynebacterium</em> JK.</td>
</tr>
<tr>
<td>Mucosal damage (chemotherapy, radiation therapy, viral infection)</td>
<td>Viridans streptococci</td>
</tr>
<tr>
<td>Endogenous flora</td>
<td>Anaerobes, staphylococci</td>
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<tr>
<td>Antimicrobial prophylaxis</td>
<td>Coagulase-negative staphylococci</td>
</tr>
<tr>
<td>Nonabsorbable antimicrobials</td>
<td>Enterococci, Gram-positive anaerobes</td>
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<tr>
<td>Fluoroquinolones</td>
<td>Viridans streptococci</td>
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</tbody>
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### TABLE 2 Summary of Antibiotic Regimens Used in Some Previous EORTC Antimicrobial Therapy Studies

<table>
<thead>
<tr>
<th>EORTC Trial</th>
<th>Antimicrobial Regimens</th>
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<tbody>
<tr>
<td>I</td>
<td>CBC + CTN versus CBC + GTN versus CTN + GTN</td>
</tr>
<tr>
<td>II</td>
<td>CBC + AMK versus CBC + AMK + CZN</td>
</tr>
<tr>
<td>III</td>
<td>TCN + AMK versus AZN + AMK versus CTX + AMK</td>
</tr>
<tr>
<td>IV</td>
<td>CTZ versus CTZ + AMK</td>
</tr>
<tr>
<td>V</td>
<td>CTZ + AMK versus CTZ + AMK + VCM</td>
</tr>
<tr>
<td>VIII</td>
<td>CTZ + AMK</td>
</tr>
<tr>
<td>IX</td>
<td>CTZ + AMK</td>
</tr>
</tbody>
</table>

AMK, amikacin; AZN, azlocillin; CBC, carbenicillin; CTN, cefalothin; CTX, cefotaxime; CTZ, ceftazidime; CN, Cefazolin; GTN, gentamicin; TCN, ticarcillin; VCM, vancomycin.

### Monotherapy

Until recently, few studies had been carried out on the efficacy of antimicrobial monotherapy in bacterial infections in neutropenic patients. The inherent danger in using a single antibiotic which might not provide cover against the pathogen, once isolated and identified, was sufficient to ensure that most clinicians would initiate empiric therapy with two or more antibiotics. It was only with the introduction of the third-generation cephalosporins, the carbapenems, and, more recently, the fourth-generation cephalosporins and newer quinolones that monotherapy became a viable proposition.

An NCI study comparing the use of ceftazidime monotherapy with a combination of cefalothin, carbenicillin, and gentamicin as initial empiric therapy of 550 episodes of fever and neutropenia showed no significant differences between regimens in terms of success (Pizzo et al., 1986). This hides the significantly greater number of treatment modifications that were required to the monotherapy regimen, to reflect the need for coverage of anaerobes or for the addition of vancomycin in those patients with documented Gram-positive infections.

Carbapenem antibiotics are attractive candidates for the empiric therapy of infections in neutropenic patients because of their broad spectrum of antimicrobial activity. Imipenem has been compared with ceftazidime in 399 patients with leukemias, lymphomas, or solid tumors (Freifeld et al. 1995). In a study
comparing management of fever, imipenem/cilastatin showed comparable efficacy to ceftazidime, although additional antibiotics were required in half of the episodes. A higher incidence of gastrointestinal toxicity, manifested as nausea and vomiting and *Clostridium difficile* colitis, was seen in patients in the imipenem group, requiring discontinuation of the antibiotic in 10% of patients.

Imipenem alone has been compared with treatments utilizing several different combinations of antimicrobials, with the monotherapy showing similar overall efficacy to these combination regimens. Failures were most often associated with Gram-positive infections and the selecting out in hematology units of *Stenotrophomonas maltophilia*, an organism inherently resistant to imipenem (Elting et al. 1990; Kerr et al. 1990).

The combination of the β-lactamase inhibitor tazobactam and piperacillin has been used successfully as first-line empiric mono-therapy in patients with hematologic malignancy (Hazel et al. 1997), although it has more usually been combined with an aminoglycoside (see previous section). As with other β-lactam antibiotics, there have been individual case reports of neutropenia secondary to piperacillin-tazobactam therapy (Gerber and Wing 1995; Ruiz-Irastorza et al. 1996).

The fourth-generation cephalosporins have potential for the empiric therapy of infections in neutropenic patients because of their potency against the Enterobacteriaceae and the Gram-positive pathogens which predominate in this type of patient. A comparison of cefpirome and ceftazidime as monotherapy in the empiric management of febrile episodes in such patients has been completed recently and is currently being prepared for publication. In both groups additional antibiotics were required during the study in roughly one-third of the patients in each group and a switch in therapy was made in another third of the patients in each group. The clinical response was the same in both treatment groups (72%) but with a higher bacteriologic response in the cefpirome group (89% versus 74%; *p* = 0.06) (Reiffers et al. 1992).

A comparison of cefpirome (2 g twice daily) plus gentamicin versus piperacillin (4 g five times daily) plus gentamicin as empiric therapy for neutropenic fever demonstrated that the cefpirome combination was superior to the piperacillin combination (Browett et al. 1997).

Cefepime, another fourth-generation cephalosporin, has been compared with a combination of piperacillin and gentamicin in the empiric treatment of febrile episodes in neutropenic cancer patients (Yamamura et al. 1997) and with ceftazidime (Cordonnier et al. 1997). Cefepime was equivalent to the comparator regimens in each study with a trend in favor of cefepime in the Cordonnier et al. (1997) study.

**CONCLUSIONS**

Combinations of anti-pseudomonal third-generation cephalosporins and aminoglycosides have been standard empiric therapy for neutropenic patients with febrile episodes. Despite the use of different combinations of these agents, the overall efficacy remains in the region of 60 to 80%. Recently, the prevalence of Gram-positive pathogens has increased, a consequence of the increased use of indwelling central venous catheters, increased doses of cytotoxic agents causing severe mucositis, and the improved prevention of Gram-negative infections. The tendency to add a glycopeptide to these regimens to minimize this problem has the potential to select for the development of resistance (vancomycin), an issue already existing in the United States and some other areas of the world.

Suitable alternatives to the third-generation cephalosporin-aminoglycoside combinations are limited to the carbapenems, piperacillin-tazobactam, and the fourth-generation cephalosporins (cevfpirome and cefepime). The fourth-generation cephalosporins, with their broad spectrum of antibacterial activity, better activity against Gram-positive organisms, and greater stability to β-lactamases than the third-generation cephalosporins, look promising as alternatives for inclusion in treatment regimens for infections in neutropenic patients. Early trial results with cefpirome suggests that it is at least as active as ceftazidime and its use could allow the empiric use of the glycopeptides (vancomycin or teicoplanin for Gram-positive coverage) to be reduced.
REFERENCES


