Empiric therapy of bacterial infections in severe neutropenia

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Infection remains the principal cause of morbidity and mortality in febrile neutropenic episodes in cancer patients. During the 1960s and 1970s, infection was responsible for 80% of deaths in patients with hematological malignancy, but observations from clinical trials completed by the International Antimicrobial Therapy Cooperative Group of the European Organisation for Research and Treatment of Cancer (IATCG-EORTC) show that in recent years, mortality rates due to infection have fallen to approximately 3% in patients undergoing active treatment of the malignancy. For patients considered beyond active treatment, figures are much higher. This improvement is undoubtedly due to the introduction of empirical therapy in the early 1970s. The rationale for developing the concept of empirical therapy was based on the fact that blood culture results may not be available for several days, with disastrous consequences for treatment of a rapidly progressing infection. Therefore, antibiotics are given to febrile neutropenic cancer patients without definitive microbiological proof of infection.

Many studies on empirical therapy have investigated combinations of agents, such as a β-lactam plus an aminoglycoside. Such antibiotic combinations offer broad-spectrum antibacterial coverage and have been shown to provide synergistic bactericidal effects against Gram-negative pathogens in vitro. However, in recent trials on the comparison between mono- and combination therapy the time to defervescence did not significantly differ, suggesting that a more synergistic bactericidal effect, as observed in vitro with combinations, did not have a measurable counterpart in vivo on fever duration. Combinations may also reduce the emergence of resistant isolates that are observed when certain β-lactam antibiotics are used alone. Aminoglycoside-containing regimens are, however, associated with ototoxicity and nephrotoxicity. In efforts to circumvent this, some investigators have used double β-lactam combinations but, recently, monotherapy with newer extended-spectrum agents such as the carbapenems, third- and fourth-generation cephalosporins and fluoroquinolones have become increasingly studied and used as standard empirical therapy.

The criteria for evaluating the response to empirical antibiotic treatment in febrile neutropenia have evolved from a number of clinical trials. These studies have indicated that age, the duration of neutropenia, the nature of the underlying disease, the causative pathogen, the availability of new effective drugs, and the chosen end point all have a profound influence on response rates. Moreover, a clear understanding of the objectives and design of trials is of paramount importance in interpretation of the results and comparison of data from different trials. Recently, there has been a move towards more rational use of antibiotics with the identification of patient subgroups at lower risk of unfavourable outcome, who might be treated more appropriately with less aggressive, tailored, empirical therapy. This review examines the effectiveness of empirical therapy in studies from different centers during the last 20 years, and looks towards possibilities for modification of treatment strategies in the future, to combat emergence of new pathogens and the development of resistance in established pathogens.

Key words: Neutropenia, Streptococcus viridans, epidemiology, monotherapy

DEFINITION OF NEUTROPENIA

Neutropenia is defined as the presence of an absolute granulocyte count of < 500 cells/mm³ [1]. The incidence and severity of infection is related to the extent and duration of neutropenia, and is greatest when the granulocyte count falls to below 100 cells/mm³ for
prolonged periods of time [2,3]. This is defined as profound prolonged neutropenia. This is in contrast to patients with chronic severe neutropenia, such as in Kostmann’s syndrome, where the neutropenia is chronic. Patients with granulocyte counts of between 500 and 1,000 cells/mm³, which are expected to decrease within hours, are eligible for inclusion in most trials, since a rapid decline is often associated with infection. Duration of neutropenia, at < 500 cells/mm³ or < 100 cells/mm³ in profoundly neutropenic patients, is a very important parameter in classifying patients into subgroups for evaluation of response to empirical therapy. Short neutropenia, of less than one week’s duration, is mainly associated with the treatment of solid tumors, whereas neutropenia of more than two weeks’ duration is generally associated with the treatment of hematological malignancies.

DEFINITION OF RESPONSE RATES

Cancer patients with profound neutropenia (< 100 cells/mm³) present some of the most stringent conditions for testing empirical antibiotic regimens. Optimal management of these patients remains controversial, in particular, with regard to whether they should receive a β-lactam alone or in combination with an aminoglycoside (Table 1). Controversies regarding the definition of response rates and the appropriate management of infection can be highlighted with the example of two studies, from the National Cancer Institute (NCI) and the IATCG-EORTC. In a large study at the National Cancer Institute (NCI) in the USA [4], cefazidime monotherapy was compared with triple therapy (cefalothin, gentamicin, carbenicillin) in the initial management of fever and neutropenia in 550 evaluable patients with cancer. Response rates were similar for both regimens (77% and 78%) in patients with unexplained fever, but the majority of cases of documented infection required additional antimicrobial treatment such as an aminoglycoside or glycopeptide. The investigators concluded, however, that single-agent therapy was as safe and effective as standard combination treatment, provided patients with documented infection or protracted neutropenia were given additional treatment.

Another strategy of combination therapy was tested in an equally large study by the IATCG-EORTC, in which a combination of cefazidime plus a long course (9 days) of amikacin was compared with cefazidime plus a short course (3 days) of amikacin in 872 profoundly neutropenic patients [5]. The results showed that there was no significant difference in response rate to either the short or long course of amikacin in patients presenting with fever of unknown origin (76% and 81%, respectively) and clinically documented infection (68% and 66%, respectively). However, the subgroup of 129 patients with microbiologically documented, single-organism, Gram-negative bacteremia, responded significantly more to long-course amikacin therapy (81% response rate) than to short-course treatment (48%). A more marked difference was evident in bacteremic patients with persistent neutropenia, of whom just 6% responded to cefazidime plus short-course amikacin compared with 50% responding successfully to long-course therapy. These outcomes suggested that every patient should receive combination therapy, and that re-evaluation could be done by the third day. The combination could be stopped if microbiological results were negative, but a full course of combination therapy should be continued in bacteremic patients, particularly in those patients with profound neutropenia. There was no evidence of reduced nephrotoxicity in patients receiving the shorter amikacin regimen.

The apparent difference emerging from these two studies can be partially explained by considering the definitions of success and failure. The IATCG-EORTC defined success as resolution of fever and signs of infection achieved by the empirical regimen tested; any modification to the regimen was classified as a failure. In contrast, the NCI considered that any recovery from infection during febrile neutropenia was successful, irrespective of modification to the regimen. Only death from infection was judged to represent failure. In order to reconcile these
differences in definition, a consensus conference of the Immunocompromised Host Society (IHS) was convened in the early 1990s. It was agreed that in future studies, success should be defined as resolution of fever and signs of infection, with no recurrence, and if modification to the initial antimicrobial regimen (including antifungal, antibacterial, antiviral and antiparasitic agents) was required, this was to be classified as failure (Table 2) [6].

Other factors also contributed to the apparently contradictory outcomes. The IATCG-EORTC study recruited adults only, whereas a large proportion of the patients in the NCI study were children, who are known to be less at risk from severe infection than adults. Importantly, the majority of patients in the IATCG-EORTC study were leukemics with a duration of neutropenia of between 15–20 days, but most of the underlying diseases in the NCI study were solid tumors and the duration of neutropenia was usually < 10 days. This difference alone would influence the success of any empirical therapy strategy.

When considering monotherapy or combination therapy it is important to consider the definition of failure. The choice between monotherapy and combination therapy will also be influenced by the risk of acquiring severe infections. Patients at low risk, such as those with solid tumors and a short duration of neutropenia, may be adequately treated with monotherapy. Combination therapy can be considered for adults with hematological malignancies and with a long duration of neutropenia. An acceptable alternative to combination therapy could be initial monotherapy with a broad-spectrum antibiotic, with treatment modification as dictated by clinical and microbiological documentation at 72–96 hours of therapy.

EPIDEMIOLOGY OF FEBRILE NEUTROPENIA

Gram-positive bacteria are now the predominant cause of infections in granulocytopenic cancer patients [7]. The most frequently isolated pathogens are staphylococci (particularly coagulase-negative strains) and alpha-hemolytic streptococci (Figure 1). Treatment of these infections is further complicated by the increasing incidence of drug-resistant organisms, particularly with respect to Staphylococcus aureus, coagulase-negative staphylococci (CNS) and also streptococci and enterococci. The increase in incidence of Gram-positive bacteria has several possible causes. These include mucosal and skin damage, an increase in the use of indwelling catheters, and an increase in the use of prophylactic agents such as the fluoroquinolones. Perhaps the most important factor is severe mucositis that is observed following the increased use of Ara-C, VP16 and anthracyclines in cancer patients, which allows free access of mouth flora into the blood stream (Table 3).

### Table 2 Criteria for evaluation of empirical antibiotic treatment in neutropenia

<table>
<thead>
<tr>
<th>Success</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution of fever and signs of infection</td>
<td>Change in initial antimicrobial regimen (including addition of antifungal, antibacterial, antiviral or antiparasitic agent)</td>
</tr>
<tr>
<td>No recurrence for ≥ 1 week after discontinuation</td>
<td>Non-evaluable (FUO only): no response to initial antimicrobial regimen leading to change in antimicrobial treatment</td>
</tr>
<tr>
<td>Initial response but regimen modified: eradication of initial pathogen, but a second infection/fever develops requiring another antimicrobial agent</td>
<td></td>
</tr>
</tbody>
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IHS consensus conference [6]. With permission of J Infect Dis.
Viridans group streptococci have become a major concern in neutropenic patients undergoing chemotherapeutic treatment, and are responsible for up to 39% of bacteremic cases and 22% of all infections [8]. A survey of data from three IATCG-EORTC trials, together with the results from trials conducted in Nebraska, USA and Lausanne, Switzerland, has established that viridans streptococci are now a major cause of bacteremia during neutropenia, with a mortality rate of 10–15% [8,9]. This heterogeneous group of organisms forms part of the normal oropharyngeal flora. Isolates recovered from bacteremic neutropenic patients have the same ribotype as those found in the oral flora [9], demonstrating that damaged oral mucosa, resulting from mucositis, induced by cytosine arabinoside chemotherapy, for example, may be a portal of entry for streptococci found in blood cultures. Other risks include severe neutropenia, prophylaxis with co-trimoxazole or quinolones and strong colonization of patients [8] (Table 3). The species identified most frequently are S. mitis, S. oralis and S. sanguis. Oral administration of penicillin as prophylaxis can decrease the incidence of viridans streptococcal bacteremia [10]. This is now followed by the fact that isolates are increasingly displaying high-level resistance to penicillin (MIC ≥ 2 mg/L), which complicates subsequent management [10].

While Gram-positive organisms have increased, there has been a corresponding reduction in the number of Gram-negative isolates in febrile neutropenic patients (Figure 1). Gram-negative pathogens are mainly Escherichia coli and Klebsiella spp. with Pseudomonas aeruginosa present in about 5–10%. However, considerable variation may exist between geographically defined areas. Many patients have repeated courses of antibiotic therapy and consequently suffer bacteremia from organisms resistant to multiple, broad-spectrum antibiotics such as Enterobacter spp. [11]. Gram-negative bacteremia was a leading cause of death in febrile neutropenic patients accounting for approximately 30% of deaths by infection in some studies [12]. However, recently, mortality from Gram-negative bacteremia was found to be similar to that from Gram-positive bacteremia at approximately 10% (Table 4) [13-15]. Perhaps the most feared among the cases of bacteremia today are the streptococci, as suggested by a meta-analysis of eight

### Table 3 Risk factors for Gram-positive infections in the neutropenic host

<table>
<thead>
<tr>
<th>Predisposing factors</th>
<th>Infecting pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin damage (punctures)</td>
<td>Staphylococci, Corynebacterium spp.</td>
</tr>
<tr>
<td>Foreign bodies (catheters)</td>
<td>Staphylococci, Corynebacterium JK</td>
</tr>
<tr>
<td>Mucosal damage (chemotherapy, radiation therapy, viral infection)</td>
<td>α-hemolytic viridans streptococci, anaerobes, staphylococci</td>
</tr>
<tr>
<td>Endogenous flora</td>
<td>Coagulase-negative staphylococci, enterococci, Gram-positive anaerobes</td>
</tr>
<tr>
<td>Antimicrobial prophylaxis</td>
<td></td>
</tr>
<tr>
<td>• Non-absorbable antimicrobials</td>
<td>Coagulase-negative staphylococci, anaerobes</td>
</tr>
<tr>
<td>• Fluoroquinolones</td>
<td>α-hemolytic viridans streptococci</td>
</tr>
</tbody>
</table>

### Table 4 Comparison of 30-day mortality rates between Gram-positive and Gram-negative infections in neutropenic patients

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Gram-positive bacteremia</th>
<th>Gram-negative bacteremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>2567</td>
<td>362</td>
<td>171</td>
</tr>
<tr>
<td>- survived (%)</td>
<td>91.9</td>
<td>89.2</td>
<td>89.5</td>
</tr>
<tr>
<td>- died (%)</td>
<td>8.1</td>
<td>10.8</td>
<td>10.5</td>
</tr>
<tr>
<td>- died of primary infection (%)</td>
<td>1.4</td>
<td>3.0</td>
<td>3.5</td>
</tr>
<tr>
<td>- died of further infection (%)</td>
<td>1.3</td>
<td>1.1</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Data from EORTC trials VIII, IX and XI [13-15].
different studies, in which an average mortality rate of 17% was observed in cases of streptococcal bacteremia (Table 5) [8,16-22].

**MANAGEMENT OF FEBRILE NEUTROPENIA**

As infection is a major cause of death in the immunocompromised host [12,23-26] antimicrobial therapy must be initiated as soon as infection is suspected in neutropenic patients [27,28]. Patients with neutropenia of < 10 days duration and no clinical site of infection may be treated satisfactorily with single-agent antibiotic therapy. This, together with the possibility of managing these individuals as outpatients, is one of several options now being explored for simplification of empirical therapy in low-risk cancer patients (Table 6).

Problems remain with the treatment of patients with longer lasting neutropenia, of more than two weeks’ duration. Response rates to standard ceftazidime/amikacin combination in the most recent IATCG-EORTC studies have declined in patients with documented bacteremia (Table 7) [13,14]. Indeed, the shifting spectrum of causative pathogens in bacteremia has had profound consequences for the effectiveness of empirical treatment in neutropenic patients. The response rates, as measured by the success of empirical therapy, to a variety of aminoglycoside/β-lactam combination therapies have

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Streptococcal bacteremia</th>
<th>Deaths</th>
<th>%</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen</td>
<td>1983</td>
<td>10</td>
<td>1</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Brown</td>
<td>1984</td>
<td>26</td>
<td>2</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Menichetti</td>
<td>1987</td>
<td>10</td>
<td>3</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Micozzi</td>
<td>1990</td>
<td>21</td>
<td>1</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>GIMEMA</td>
<td>1990</td>
<td>25</td>
<td>3</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Elting</td>
<td>1991</td>
<td>46</td>
<td>11</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Awada</td>
<td>1992</td>
<td>78</td>
<td>20</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Bochud</td>
<td>1994</td>
<td>26</td>
<td>1</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>242</td>
<td>42</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>

Table 6 Options for simplified empirical treatment for low-risk febrile neutropenic cancer patients

- Single daily dose iv combination therapy
- Single-agent iv therapy
- Outpatient iv therapy
- Sequential iv — oral therapy
- Initial oral therapy

Table 7 Response rates for ceftazidime-amikacin empirical therapy in neutropenic patients with microbiologically documented infection

<table>
<thead>
<tr>
<th></th>
<th>EORTC</th>
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<tbody>
<tr>
<td></td>
<td>Trial VIII</td>
</tr>
<tr>
<td>Microbiologically documented infection</td>
<td></td>
</tr>
<tr>
<td>with bacteremia:</td>
<td></td>
</tr>
<tr>
<td>Gram-positive</td>
<td>59/104 (57%)</td>
</tr>
<tr>
<td>Gram-negative</td>
<td>46/90 (51%)</td>
</tr>
<tr>
<td>Polymicrobial</td>
<td>22/50 (44%)</td>
</tr>
<tr>
<td></td>
<td>19/27 (70%)</td>
</tr>
<tr>
<td></td>
<td>5/13 (39%)</td>
</tr>
</tbody>
</table>

Data adapted from the EORTC trials VIII, IX [13,14].
Clinical Microbiology and Infection, Volume 3 Supplement 1, April 1997

deleed over the last 20 years, from 71% for cephapothin or carbenicillin combined with various aminoglycosides in the first IATGC-EORTC trial (1973–1976) to 25% for ceftazidime combined with amikacin in the ninth trial (1991–1992) (Table 8) [13,14,29–31]. In these studies, failure was defined as a change to empirical therapy, therefore the decline probably reflects the inadequate cover against Gram-positive pathogens.

To address this problem, a trial was designed by IATGC-EORTC in which vancomycin was added to the standard combination of ceftazidime plus amikacin as initial empirical treatment of febrile neutropenic patients [32]. Gram-positive bacteremia was present in 63% of 213 single-organism bacteremias. In these cases, there was a significantly lower incidence of treatment failures in the group receiving triple therapy (28%) than in the group receiving standard treatment. Failure was mainly attributed to the necessary addition of vancomycin to the ceftazidime/amikacin arm, when patients had not defervesced by 48 hours. Interestingly, the time to defervescence in these patients was identical, irrespective of whether vancomycin was instituted, thus questioning the need for triple therapy. The fact that the median time to defervescence is about 5 days [33], even when patients receive entirely adequate antibiotic treatment with full microbiological coverage, must be taken into consideration. To determine the need for including vancomycin in the treatment of patients who have not defervesced by 48–72h, a double-blind, placebo-controlled trial is currently underway, in which patients with persistent fever will be randomized to receive either vancomycin or placebo.

The use of a glycopeptide (vancomycin or teicoplanin) combined with an aminoglycoside/β-lactam regimen as empirical therapy for fever is warranted only in patients with suspected methicillin-resistant S. aureus (MRSA) or CNS infections, as well as susceptible Gram-positive infections not responding to initial therapy [32,34]. These infections tend to occur more often in patients with indwelling central venous catheters, although these devices do not constitute the only causative factor. In centers where most bloodstream infections are caused by β-lactam-resistant Gram-positive bacteria, the glycopeptides could be considered in the initial empirical regimen [32]. However, because of their potential toxicity (especially when combined with an aminoglycoside) and their unknown cost efficiency, including glycopeptides in the first line empirical treatment of all febrile neutropenic patients is controversial. Moreover, the potential for the widespread use of glycopeptides in engendering resistance, especially in enterococci, should encourage any clinical trials aiming to find strategies to reduce the use of glycopeptides to strict indications.

The addition of the β-lactamase inhibitor tazobactam extends the spectrum of the ureidopenicillin piperacillin to include β-lactamase-producing organisms. In vitro studies showed that piperacillin-tazobactam had activity comparable with that of ceftazidime against Gram-negative bacteria isolated from bacteremic granulocytopenic cancer patients and was superior to ceftazidime against S. aureus and viridans streptococci [35], suggesting that piperacillin-tazobactam may have a role in the empirical treatment of febrile neutropenic infection.

**COMBINATION THERAPY VERSUS MONOTHERAPY**

Epidemiological changes have prompted the need for empirical combinations that include drugs to cover Gram-positive pathogens. However, efforts are being made to replace empirical combination therapy with monotherapy for various reasons, including toxicity.
and economy. Potential candidates for monotherapy are outlined in Table 1. There is potentially a higher risk of selection of resistant mutants with certain β-lactams being used as monotherapy than with combination therapy [5,36], although this is controversial in non-neutropenic patients, and has not been observed in the most recent well designed trials [14].

The carbapenems are good candidates for monotherapy because of their broad-spectrum of activity. Potential candidates include imipenem-cilastatin and meropenem. Monotherapy with imipenem was compared with ceftazidime in the management of fever and neutropenia in 399 patients with solid tumors, leukemias or lymphomas [37]. Both agents were effective according to the NCI criteria for response, with an overall success rate of 98%, although addition of other antibiotics was necessary in half of all episodes. Imipenem therapy, at the daily dose of 4 x 1 g was, however, associated with significantly greater gastrointestinal toxicity and sometimes seizures, and did not decrease the overall need for antibiotic modifications, despite its broad spectrum of activity. The newer carbapenem, meropenem seems to be a safer and less toxic alternative. In a recent study, meropenem was recently evaluated as monotherapy in comparison with ceftazidime/amikacin, as empirical treatment in severely-ill, high-risk cancer patients with long duration of neutropenia (18–20 days) [14]. Meropenem was as effective as the combination with 56% and 52% of patients responding successfully to treatment, respectively. However, there was a non-significant trend towards time to defervescence being shorter in patients receiving meropenem than ceftazidime plus amikacin (p = 0.07), while in the combination arm more renal toxicity was encountered. In another randomized multicenter trial, meropenem monotherapy was compared to ceftazidime monotherapy in patients with profound and prolonged neutropenia [38]. By the end of the treatment courses, 44% of febrile episodes had responded to meropenem, compared with 41% to ceftazidime. Failure as defined by the addition of other antibacterial agents occurred in 53% of ceftazidime treated episodes versus 41% with meropenem. All patients survived the first 3 days of treatment. Thus, monotherapy prevented early death due to infection, while at the same time avoiding initial combinations with, for example, aminoglycosides or glycopeptides in over 40% of patients.

An alternative agent to be considered for monotherapy is piperacillin-tazobactam. An initial study has demonstrated similar efficacy for piperacillin-tazobactam in combination with amikacin compared to a combination of ceftazidime plus amikacin [15].

The third-generation cephalosporins have demonstrated significant clinical efficacy over the years, but the effectiveness of newer agents such as ceftazidime against Gram-positive organisms is suboptimal, compared with older agents, which include cefotaxime or ceftriaxone. Moreover, their activity against Gram-negative species has been compromised by the enzyme of derepressed, chromosomally-mediated β-lactamases in some bacterial species and by mutation in plasmid-encoded β-lactamases in others. Development of resistance may be particularly devastating in neutropenic patients. Several cases have been reported of breakthrough bacteremia with multiple-resistant Enterobacter spp. in febrile, neutropenic, cancer patients receiving broad-spectrum cephalosporins as monotherapy. Indeed, Enterobacter bacteremia resistant to ceftazidime has emerged during therapy with this agent [11].

The fourth-generation cephalosporins have good activity against streptococci, including viridans group streptococci, and methicillin-susceptible staphylococci, all of which are pathogens most commonly isolated in bacteremic febrile neutropenic patients [38,39]. Moreover, they provide increased coverage against mutant strains of Enterobacteriaceae and P. aeruginosa producing derepressed AmpC β-lactamase. The C-3' quaternary ammonium cepheins, cefpirome and cefepime, possess enhanced activity compared with other cephalosporins and offer advantages against resistant mutants of certain Gram-negative species, by virtue of having a low affinity for chromosomal β-lactamases [39]. Moreover, they are among the most effective β-lactams against strains of Streptococcus pneumoniae displaying intermediate- and high-level resistance to penicillin [40–42].

The antibacterial activity of cefepime has recently been reviewed [43]. In a pilot, open, non-comparative study, empirical cefepime monotherapy was judged to be safe and effective in the treatment of febrile episodes in neutropenic patients [44]. In a randomized study, the combination of cefepime plus amikacin showed equivalent efficacy to ceftazidime plus amikacin in febrile neutropenic patients [45].

In an initial trial, cefpirome was as effective as ceftazidime in the empirical treatment of febrile episodes in patients with neutropenia [46]. A total of 32% of patients in the cefpirome and 35% in the ceftazidime treatment groups remained on monotherapy, whilst 32% and 33% respectively, required the addition of concomitant antibiotics or the initiation of new antibacterial treatments.

**Growth factors**

Only a few randomized studies on the use of colony stimulating factor (CSF) as adjuncts to empiric antibiotic
treatment have been published [47,48]. Both granulocyte (G-) CSF and granulocyte-macrophage CSF, when initiated at the start of febrile neutropenia, can significantly accelerate neutrophil recovery and diminish the duration of fever and febrile neutropenia. In some trials this has led to a diminished hospital stay, fever days on antibiotics, and decreased need for empiric amphotericin B. Adjunctive use of CSFs is considered to be especially useful in those patients at highest risk i.e. with very severe neutropenia (< 0.1 x 10^9/L) or protracted neutropenia (> 10 days), after bone marrow transplantation or with exhausted marrow reserves after multiple chemotherapy cycles. The benefit of G-CSF is more pronounced in microbiologically proven infections than in fever of unknown origin.

CONCLUSION

Combinations of third-generation cephalosporins and aminoglycosides was, until now the standard therapy for empirical treatment of febrile episodes in neutrophenic patients. This approach has provided optimal coverage against Gram-negative bacteria. However, more recently, the prevalence of Gram-positive bacteria has increased, particularly CNS and viridans streptococci.

In response to this, vancomycin has often been used empirically in combination with the broad-spectrum antibiotics. However, this regimen has not improved morbidity or mortality nor reduced time to defervescence. Alternatives to third-generation cephalosporins should be a carbapenem, piperacillin-tazobactam or a fourth-generation cephalosporin. Due to variations in geographically defined areas, the epidemiology of resistance in a given center is an important parameter to consider for choosing the best regimen. Recent clinical trials in febrile neutropenic patients support that fourth-generation cephalosporins have now to be considered as first line armamentarium in this setting and are at least as effective as ceftazidime. Moreover, their specific activity against Gram-positive pathogens fully support their empirical use, especially in patients at high risk for streptococcal bacteraemia whose frequency is increasing in neutropenic patients. These properties are also the rationale to design clinical trials aiming to decrease the empirical use of glycopeptides. Such trials should be encouraged.

DISCUSSION

Prof. W. Wilson: This treatment strategy is similar to the antibiotic prescribing policy in many institutions in the USA. Most hospitals would not recommend vancomycin in the initial treatment regimen. The recommendations of monotherapy are very consistent with many institutions in the USA. A fourth-generation cephalosporin, cefpirome and cefepime would provide good Gram-negative activity and in addition, good Gram-positive activity, an advantage over ceftazidime. Monotherapy with the fourth-generation cephalosporins would be an attractive alternative to ceftazidime as initial therapy of febrile neutropenic patients, even though ceftazidime is still widely used for monotherapy in the USA. An alternative to this regimen would be monotherapy with a carbapenem.

Prof. M. Glauser: Vancomycin is not recommended in the initial treatment regimens for reasons of toxicity, and because of the problems of the emergence of vancomycin-resistant microorganisms.

Prof. P. Martino: Many investigators add vancomycin in the initial regimen because of the risk of staphylococcal infections. There are several studies comparing monotherapy versus combination therapy, but the majority of these have compared monotherapy with a combination of different drugs. A very large study from Bodey et al. compared the activity of ceftazidime alone, ceftazidime/amikacin, imipenem, and imipenem/amikacin. However, no studies have addressed whether combination therapy with amikacin was necessary in this category of patients.

GIMEMA is planning a double-blind study in Italy, comparing piperacillin-tazobactam plus amikacin versus piperacillin-tazobactam plus placebo. This study should address the need of combination therapy with an aminoglycoside. Vancomycin will also be included in the treatment regimen.

Prof. M. Glauser: The next trial of the IATCG of the EORTC will initiate empiric monotherapy with piperacillin-tazobactam. Patients with Gram-positive infections or without documented infections (FUOs who remain febrile after 3 days) will be randomized blindly to receive vancomycin or placebo. Indeed, a significant proportion of patients (about 60%) still remain febrile at 3 days and this study should address the question of whether vancomycin is useful at this stage.

Prof. W. Wilson: Would amphotericin B be administered if the patients were still febrile after this period of time?

Prof. M. Glauser: Amphotericin B would usually be administered if the patients were still febrile after a period of 6 days, but in centers where Aspergillus is endemic, amphotericin B would be administered earlier.

References


42. Klugman KP, Goldstein F, Kolino S, Baquero F. The role of fourth-generation cephalosporins in the treatment of infections caused by penicillin-resistant streptococci. [This supplement].


