the dosage need not be increased because the enhanced renal function will produce urinary levels of the same magnitude as in nonpregnant patients provided such antibiotics are excreted unmetabolized mainly by the kidneys. In serious infections and in cases where antibiotics such as the aminoglycosides are used, or when high antibiotic levels are crucial, close monitoring of the resulting plasma levels to ensure adequate dosing is mandatory.

AGNETA PHILIPSON
Department of Infectious Diseases,
Danderyd Hospital,
S-182 88
Danderyd, Sweden

References

Management of infection in granulocytopenic patients
Fever occurs in a substantial proportion of the patients receiving cytotoxic chemotherapy: a 40-70% incidence of febrile episodes has been reported. Once fever develops, a specific microbiological diagnosis can usually be made, a posteriori, in 40-50% of the patients (EORTC, 1982; Pizzo et al., 1982) about half of whom will present with bacteraemia.

Since infection in granulocytopenic patients is difficult to diagnose early and may frequently follow a fulminant course, it has been proposed that febrile neutropenic patients should be treated empirically with antimicrobial agents, without waiting for the microbiological proof (Schimpff et al., 1971). Infection caused by Gram-negative bacilli still represents the major risk in febrile granulocytopenic patients; therefore, the regimens to be recommended must be active against these pathogens. Until recently, adequate coverage of most Gram-negative pathogens could be obtained only by combinations of antibiotics. Most studies, so far, have been conducted with combinations of β-lactam antibiotics or combinations of β-lactam drugs with aminoglycosides. Recent investigations (EORTC, 1982; Gurwith et al., 1978) showed an advantage for the β-lactam plus aminoglycoside combinations. Although aminoglycosides are not very effective as single drug therapy in granulocytopenic patients, their use in empirical therapy may 'buy time', allowing the patient to survive until definitive therapy can be devised. Whether the introduction of the new penicillins or cephalosporins will change this approach remains to be seen.

Empirical therapy in granulocytopenic patients should be undertaken with two active drugs according to recently presented evidence (Klastersky & Zinner, 1982).

The clinical significance of therapy with synergistic combinations in granulocytopenic patients has recently been reviewed (Klastersky & Zinner, 1982). There is an obvious advantage for the synergistic combinations as compared with nonsynergistic ones, the respective rates of response in Gram-negative bacillary infections being 79% and 45% respectively. At present, it appears that an adequate serum bactericidal titre is also necessary for a favourable outcome in severe Gram-negative bacillary infections in nongranulocytopenic patients; it has been found that a titre \( \geq 1 : 8 \) is associated with a better outcome (Klastersky et al., 1974; Platt et al., 1981). Granulocytopenics may require higher serum bactericidal titres.

A definite increase in the proportion of Gram-positive pathogens in granulocytopenic patients has recently been reported (Wade et al., 1982). These infections have been less aggressive than Gram-negative bacillary infections in granulocytopenic patients, leading to few cases of endocarditis and to a comparatively lower mortality rate. Earlier studies in which an antistaphylo-
Granulocytopenic patients remain at high risk of infection as long as the granulocytopenia persists; hospitalization and the antimicrobial therapy which is often administered, further predisposes these patients to infection with hospital-acquired pathogens. The logical approach, under these circumstances, would be an effort to prevent colonization of the granulocytopenic patients whose endogenous flora has been modified. In addition, the duration of antimicrobial therapy might be important. Two studies have been conducted, so far, to evaluate the optimal duration of antimicrobial therapy in granulocytopenic patients after a response had occurred. No major difference was found whether the empirical antibiotics were or were not discontinued on days 7–9 despite persistent granulocytopenia. It remains to be seen whether a relatively short duration of empirical therapy would be suitable in patients with very prolonged periods of granulocytopenia.

About 30% of the granulocytopenic patients who receive empirical antibiotic therapy will not respond within 3 or 4 days. Those who do not respond and in whom a likely pathogen is isolated, most frequently from blood cultures or adequately performed respiratory-tract aspirations, should have the pathogen tested for sensitivity to the antibiotics administered. Antibiotics inadequate in vitro should be adjusted to the microbiological data and the patient should be treated with potentially synergistic combinations of drugs, achieving optimal bactericidal activity in the serum. Supportive care for septic shock and other manifestations of severe infection should obviously be provided as well. If the sensitivity to the empirical therapy of the pathogen isolated is adequate, as indicated by in vitro tests, undrained foci of infection or infected foreign bodies should be considered as possible factors for persisting sepsis and be treated accordingly, under heavy platelet transfusion, if indicated.

It is likely that granulocyte transfusions represent a major adjunct to the therapy of microbiologically-demonstrated sepsis in granulocytopenic patients who do not respond to adjusted antimicrobial therapy (Higby et al., 1975; Vogler & Winston, 1977). The granulocytopenic patients in whom no likely pathogens can be isolated and who do not respond to empirical therapy represent a major problem. Obviously, some of these patients do not have infectious diseases; some, however, may have fungal infections, the diagnosis of which is notoriously difficult. There is ample evidence that the frequency of severe fungal infections has considerably increased during the past years (De Gregorio et al., 1982). There is also some evidence suggesting that the control of fungal infections is better, when the antifungal agent is started early (Pizzo et al., 1982).

A study conducted by the EORTC Antimicrobial Therapy Project Group, which is still in progress, included a total of 61 granulocytopenic patients with unexplained fever not responding to broad-spectrum empirical antimicrobial therapy; they have been randomized to receive or not, on day 4, amphotericin B. The mortality rates were respectively 5/30 (17%) and 7/31 (22%). No patient was found, at post-mortem examination, to have fungal infection in the first group, but 3/7 had disseminated candida infections in the group of patients who died without having received amphotericin B. However, no major difference in the overall mortality could be detected.

A rational approach to the management of febrile episodes and infection in granulocytopenic patients is summarized in Table I. These recommendations should be adapted to the continuous evolution of the underlying diseases in these patients, to the constantly changing pattern of their infections, and to the new possibilities of our therapeutic armamentarium.

JEAN KLastersky
Service de Médecine Interne
et Laboratoire d'Investigation
Clinique H. J. Tagnon,
Institut Jules Bordet,
Centre de Tumeurs de
l'Université Libre de Bruxelles.
1. rue Héger Bordet, 1000 Brussels, Belgium
Table I. Rational approach to the management of granulocytopenic febrile patients

<table>
<thead>
<tr>
<th>Empirical antimicrobial therapy (synergistic, bactericidal)</th>
<th>Response</th>
<th>No response</th>
</tr>
</thead>
<tbody>
<tr>
<td>day 4</td>
<td>70%</td>
<td>30%</td>
</tr>
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</table>

- **Granulocytopenia subsides**
  - Treat as non-granulocytopenic patients
  - Continue therapy for a total duration of 9 days (or longer?)

- **Granulocytopenia persists**
  - Treat as non-granulocytopenic patients
  - Continue therapy for a total duration of 9 days (or longer?)

- **Proven infection**
  - Adjust antimicrobial therapy
    - (Serum bactericidal titre \( \geq 1:16 \))
  - Look for and treat localized infections
  - Granulocyte transfusions

- **Fever of unknown origin**
  - (1) Empirical administration of amphotericin B
  - (2) ? granulocyte transfusions

References


