Empirical Treatment of Febrile Neutropenia: Evolution of Current Therapeutic Approaches

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Administration of empirical antibiotic therapy is now standard practice in the management of febrile neutropenia, but there has been considerable debate about the selection of an efficacious empirical antimicrobial regimen over the past 2 decades. A variety of approaches, including both monotherapeutic and multidrug regimens, have been demonstrated to be effective, although no one regimen has been proven to be superior to another. Changes in the epidemiology of infectious organisms and the growing emergence of highly drug-resistant strains make it necessary to continually reevaluate the therapeutic options. Fortunately, the number of therapeutic options has also been broadening as new antimicrobial agents, including third-generation cephalosporins and carbapenem antibiotics such as imipenem and meropenem, become available. Optimal management is directed by the findings of a clinical evaluation of the patient as well as an awareness of institutional patterns of infection and susceptibility of likely infecting organisms.

With the advent of complicated multidrug immunosuppressive and cytotoxic chemotherapeutic regimens, infectious complications in the neutropenic host have become a major medical issue. Infectious complications are the leading cause of morbidity and mortality in patients with cancer. According to the Infectious Diseases Society of America (IDSA) guidelines, a neutropenic patient with leukocyte levels of <500/mm³ who becomes febrile has a >60% chance of being infected, although recent trends indicate slightly fewer microbiologically documented infections (between 30% and 50%) [1–5]. The number of patients at risk of infection continues to grow as the intensity and duration of chemotherapeutic regimens are extended [6]. Fortunately, many febrile episodes in the neutropenic patient can be treated successfully with early initiation of empirical antimicrobial therapy.

Although the administration of empirical antibiotic therapy is now standard practice in the management of febrile neutropenia, there is still considerable controversy about the selection of an efficacious empirical antimicrobial regimen. A variety of approaches, including both monotherapeutic and multidrug regimens, have been discussed in the literature over the past 2 decades. However, it is necessary to reevaluate continually the therapeutic options as changes in the epidemiology of infectious organisms occur, especially with the growing emergence of highly drug-resistant strains.

The number of therapeutic options in the management of febrile neutropenia has also been expanding, with the addition of third-generation cephalosporins and then of carbapenem antibiotics such as imipenem and meropenem, and, most recently, with the prospect of fourth-generation cephalosporins to enrich the armamentarium. The purpose of this article is to review the evolution of current approaches to the empirical management of febrile neutropenia and to consider how new antimicrobial and immunomodulating therapies may affect management of infectious disease in the immunosuppressed cancer patient in the future.

Historical Perspective

The value of initiating empirical antimicrobial therapy with the onset of fever in a neutropenic patient was not recognized until relatively recently. Before 1960, it was common to wait until a bacterial pathogen was isolated before administering antibiotics to a neutropenic patient who was febrile. Later in that decade, however, came recognition of the fact that the immune response is commonly muted in the neutropenic patient, resulting in diminished signs of infection such as inflammation (including erythema and edema) and purulent discharge. Thus, fever is often the only sign of infection in the neutropenic patient [7].

During the 1960s, the recognition of the impairment of the inflammatory response in neutropenia was accompanied by the knowledge that the degree and duration of granulocytopenia were potent factors in the overall risk of infection [8]. It also became apparent that without antibiotic therapy, the virulent gram-negative infections that then predominated could cause rapid and fatal sepsis [9]. Unfortunately, there were only a limited number of antimicrobial agents that could be used for empirical therapy at that time. Most provided coverage against Escherichia coli and Klebsiella pneumoniae but had limited activity against Pseudomonas aeruginosa [10].

Extended-spectrum carboxypenicillins (i.e., carbenicillin and ticarcillin) as well as aminoglycosides (i.e., gentamicin, tobramycin, amikacin, and netilmicin) became available in the mid-1970s. Third-generation cephalosporins were introduced in the
early 1980s, followed by the carbapenems, monobactams, and quinolones. The availability of these agents, typically used in combination regimens, has had a profound impact on survival rates for febrile neutropenic patients. In the 1950s, gram-negative bacteraemias were associated with mortality rates of up to 90% among patients with neutropenia. By the 1980s, following the widespread use of empirical antimicrobial therapy, the mortality rate had fallen to 10% to 30%, depending on the causative organism [7, 11].

Despite these advances, the clinical management of neutropenia in febrile patients continues to be complicated by the changing spectrum of bacterial pathogens. In addition, many of the commonly used regimens have one or more liabilities, including complicated dosing schedules, high costs for acquisition and/or administration, and the potential for significant toxicity, which is noted especially in regimens containing an aminoglycoside.

Evaluation of the Febrile Neutropenic Patient

The selection of an optimal regimen for a given patient should take into account likely pathogens, individual patient-related factors that may contribute to the risk of toxicities (e.g., administration of an antineoplastic agent with overlapping toxicity), and cost issues. A prompt but thorough physical examination, recording of the medical history, and consideration of unusual exposures or risk factors should guide initial decisions in therapeutic management. Specimens for culture should be obtained from all appropriate sites: the IDSA Working Committee has recommended that at least two sets of blood cultures should be performed for all patients, for examination for bacteria and fungi [1].

Criteria for Fever and Neutropenia

Certain criteria for fever and neutropenia must be met before the process of selecting an empirical antimicrobial regimen begins. A febrile state is commonly defined as (1) a single oral temperature reading of >38.3°C, without obvious mitigating environmental causes (such as blood transfusion), or (2) a persistent fever (temperature of >38.0°C) on at least two consecutive evaluations (at ≥4-hour intervals) within a 24-hour period [1].

Criteria for defining neutropenia generally rely on an absolute neutrophil count of <500/mm^3 or >500/mm^3 but <1,000/mm^3 in patients whose neutrophil counts are expected to fall below 500/mm^3 within a 24- to 48-hour period [1]. Both the degree and duration of neutropenia are independent risk factors for infection [1, 9, 12, 13]. Reduced fatality rates and better outcomes have been noted among patients whose granulocytopenic episodes were <7 days in duration in comparison with those among patients whose granulocytopenic episodes were longer [8].

Common pathogens. Empirical antibiotic therapy is built around the provision of broad-spectrum coverage against the predominant organisms likely to infect the neutropenic host. Gram-negative bacilli, arising primarily from the alimentary tract, have been the most frequent pathogens in the neutropenic patient. These commonly include *E. coli*, *Klebsiella* species, and *P. aeruginosa* [7, 12, 14]. Other gram-negative organisms seen in this setting are *Serratia marcescens*, *Enterobacter* species, and *Acinetobacter* species—all associated with high resistance rates that often mandate double gram-negative antibiotic coverage [15].

Within the past decade, gram-positive organisms have emerged as increasingly important pathogens in febrile neutropenic patients [7, 16–18]. Commonly encountered organisms include *Staphylococcus epidermidis*, methicillin-resistant *Staphylococcus aureus* (MRSA), β-hemolytic *Streptococcus*, and, increasingly, diphtheroid and clostridial species [7]. In a study of 550 episodes of fever in neutropenic patients in the medical and pediatric oncology branches of the National Cancer Institute, 63% of isolated bacterial pathogens were gram-positive organisms [19]. Similar trends have been noted at other cancer centers [1]. One explanation for this changing pattern of pathogenicity may lie in the increasing utilization of indwelling central venous catheters [16].

It is not known if the use of third-generation cephalosporins, which are highly effective against gram-negative organisms, has also encouraged the proportion of gram-positive infections to rise. The risk of secondary bacterial, mycotic, or viral infections is also increased in neutropenic patients. Nosocomially acquired aspergillosis, Legionnaires’ disease, and other diseases caused by drug-resistant microorganisms mandate frequent reevaluation of the patient throughout the course of treatment. Legionnaires’ bacillus has been the culprit in a number of outbreaks of nosocomially acquired infection associated with high mortality among neutropenic patients [20–22].

Invasive fungemia in particular is a growing cause of morbidity and mortality in this population. Increasing numbers of *Candida* species other than *albicans* have been isolated from febrile neutropenic patients; one study suggested an isolation rate of >50% [23]. Species such as *Candida tropicalis*, *Candida krusei*, and *Torulopsis glabrata* are being seen with increased frequency.

Strategies for Antimicrobial Therapy

It is impossible to provide precise recommendations for initial empirical antibiotic therapy for febrile neutropenia, as the selection of a specific regimen is dictated by institutional variations in the spectrum of infections, susceptibility patterns of the infecting microorganisms, and individual clinical situations. Certain guidelines for initial therapy, however, are well-accepted. For one, initial empirical treatment must rapidly produce bactericidal serum levels. It must also provide broad-spectrum coverage for bowel-, skin-, and intravenous catheter-
associated flora, including both gram-negative and gram-positive organisms—predominantly *E. coli*, *P. aeruginosa*, and *Klebsiella* species, as well as *Staphylococcus* and *Streptococcus* species.

With the growing number of potent, broad-spectrum parenteral agents and oral antibiotics appropriate for patients without hypotension who are able to receive oral medications, it is now increasingly feasible to tailor therapy to an individual patient’s needs. Still, there is considerable debate about optimal empirical treatment approaches, with much of the controversy focusing on the respective merits and drawbacks of combination antibiotic regimens versus single-agent strategies. Although there are considerable clinical data supporting the efficacy of combination regimens, the newer antibiotics, particularly the third-generation cephalosporins and the carbapenems, show promise when given as monotherapy.

Combination Therapy

The use of combination regimens has been widely adopted as standard clinical practice in the management of fever in neutropenic patients with possible sepsis [1, 2, 4, 5]. The argument in favor of combination therapy includes broad-spectrum coverage, which includes the potential for secondary superinfection and protection against nosocomial pathogens that are resistant to multiple antibiotics. The coadministration of various antibiotics may have a synergistic antimicrobial effect that is greater than that of either antimicrobial agent used alone [6].

It has been argued that the development of drug-resistant strains of bacteria may be avoided by administration of combination drug therapy, although this theory has not always been supported by clinical evidence [27]. A drawback of combination regimens is the increased likelihood of toxicity when the drugs are given at adequate dosages to achieve therapeutic concentrations. Another limitation is cost, which is a growing concern in most institutions. A combination regimen may not prove to be cost-effective once the expense of the multiple drugs and of preparing and administering the regimen is considered, as well as costs associated with monitoring for toxicity.

Combination empirical antibiotic regimens may utilize a variety of antibiotics, but generally combination therapy can be broken down into three categories: (1) an antipseudomonal β-lactam drug plus an aminoglycoside; (2) an antipseudomonal β-lactam drug plus a second β-lactam drug; and (3) an antipseudomonal β-lactam drug, an aminoglycoside, and a glycopeptide. A brief review of each regimen follows.

**Antipseudomonal β-lactam drug plus an aminoglycoside.** The combination of an antipseudomonal penicillin (e.g., ticarcillin-clavulanate, carbencillin, or piperacillin) or a cephalosporin with antipseudomonal activity (e.g., ceftazidime or cefepirone) and an aminoglycoside (e.g., gentamicin, tobramycin, or amikacin) is one of the best-established empirical treatment regimens for the management of febrile neutropenia [1]. Studies conducted by the European Organisation for Research on Treatment of Cancer (EORTC) trials have provided particularly convincing evidence of the benefits of a long course of such therapy.

The fourth EORTC trial compared short (3 days) vs. long (9 days) courses of therapy with an aminoglycoside plus the third-generation cephalosporin ceftazidime in 872 patients with granulocytopenia [2]. Among the 129 evaluable patients with gram-negative bacteremia associated with a single organism, the response rate was 81% in the long-course treatment group, compared with only 48% in the short-course group.

Further modifications of the antipseudomonal β-lactam drug and aminoglycoside regimen were studied in a recent EORTC trial, which suggested that single daily doses of ceftriaxone and amikacin were as effective as multiple daily doses of ceftazidime and amikacin in patients with granulocytopenia [3]. Drawbacks of this particular regimen included toxicities associated with aminoglycoside administration, including nephrotoxicity, ototoxicity, and hypokalemia. Recent trends in the reduction of the frequency of *P. aeruginosa* infections in febrile neutropenic patients may have contributed to the effectiveness of this single-daily-dosing regimen, but the antipseudomonal coverage of ceftriaxone and amikacin remains to be adequately tested. This regimen also failed to provide coverage for coagulase-negative staphylococci and MRSA.

**Combination of two β-lactam agents.** Some centers employ the combination of an antipseudomonal β-lactam drug plus a second β-lactam drug. Such regimens have the advantage of low toxicity profiles, but early studies suggested that double β-lactam coverage was less effective than the β-lactam drug/aminoglycoside combination [2]. More recent studies with newer β-lactam agents with broader activity have shown better results, but these regimens remain costly, and they may select for resistant organisms [1].

**Antipseudomonal β-lactam, aminoglycoside, and a glycopeptide.** The glycopeptide vancomycin can be added to a regimen that includes an antipseudomonal β-lactam agent and an aminoglycoside. The arguments in favor of this strategy include the rising incidence of gram-positive infections such as those due to methicillin-resistant staphylococci, as well as the possible selection for gram-positive infections by certain empirical antimicrobial agents such as ceftazidime. The addition of vancomycin may be of particular value in neutropenic patients at especially high risk for these infections: for example, those with indwelling central venous catheters or with life-threatening sepsis.

There is evidence that the inclusion of vancomycin at the initiation of empirical therapy provides earlier, more effective treatment than conventional combination regimens [28, 29]. Other investigators argue that the addition of vancomycin to the empirical regimen can be delayed until there is clinical or microbiological evidence that it is needed, an approach that is more cost-effective and does not impose significant risk on the patient [19]. Complicating this issue is the alarming rise in glycopeptide resistance among gram-positive organisms.
The emergence of bacterial resistance to vancomycin and teicoplanin presents a serious threat to the successful treatment of these infections [30]. The presence of plastic indwelling catheters, such as those used to administer chemotherapy, has been associated with the emergence of resistant strains of coagulase-negative staphylococci [31]. One might argue that a more judicious use of current antibiotics is warranted by this event [32, 33].

Monotherapy

Although the concept of empirical monotherapy is not new, it is only recently that potent broad-spectrum antibiotics with the capability of achieving bactericidal levels for a variety of organisms have become available. These agents, which include selected third-generation cephalosporins and the carbapenems, offer good coverage against certain gram-positive organisms and gram-negative organisms, including Pseudomonas species. The carbapenems have the additional advantage of providing coverage against anaerobes as well. Quinolones have also been proposed as monotherapeutic agents, but their limited activity against many streptococci and lack of coverage against most anaerobes may make their use problematic.

The potential benefits of monotherapy include reduced antibiotic administration costs, reduced equipment needs for intravenous administration, and less frequent monitoring of drug levels. Because the nephrotoxicity and ototoxicity associated with aminoglycosides are avoided, these newer agents also allow the concomitant administration of other nephrotoxic pharmacologic agents, such as chemotherapy, immunosuppressives, and amphotericin B.

Third-generation cephalosporins. Third-generation cephalosporins have been extensively studied as monotherapeutic antibiotic agents for febrile neutropenic patients with cancer. Of the many third-generation agents available, ceftazidime has emerged as a logical choice for monotherapy because of its significant activity against P. aeruginosa and its low toxicity. Several studies have indicated that ceftazidime can be used effectively in the initial empirical treatment of febrile neutropenia [14, 34–37].

An early trial at the National Cancer Institute showed that ceftazidime was as effective as a combination regimen of cephalothin, gentamicin, and carbencillin for initial empirical therapy in 550 evaluable episodes of fever and neutropenia [34]. Successful outcomes were achieved for 186 (98%) of the patients randomized to ceftazidime monotherapy, vs. 199 (98%) of those randomized to the combination regimen. Another study demonstrated that empirical monotherapy with ceftazidime alone was as effective as ceftazidime plus cephalexin in 90 patients with febrile neutropenia [35]. Clinical and bacteriologic response rates were 77% and 70%, respectively, for ceftazi-dime monotherapy and 88% and 79% for the combination.

There were also no differences in efficacy among initial empirical regimens employing ceftazidime alone, ceftazidime plus vancomycin, or the combination of cephalothin, carbenicillin, and gentamicin in a randomized trial of pediatric cancer patients who had 206 episodes of fever and neutropenia [36]. The rates of complete response to initial therapy among patients with documented infection were 61% for the combination of cephalothin, carbenicillin, and gentamicin; 56% for ceftazidime alone; and 50% for ceftazidime plus vancomycin.

An evaluation of 50 febrile episodes in 40 neutropenic patients that was conducted in Germany confirmed the efficacy of ceftazidime as initial empirical monotherapy [14]. Ceftazidime monotherapy resulted in clinical response in 29 episodes (58%) within 48 hours; 7 (14%) responded to the addition of vancomycin within the next 72 hours; and 5 (10%) required the addition of amphotericin B to the ceftazidime/vancomycin combination regimen before the patient became afebrile.

Recently, an international trial led by De Pauw demonstrated that ceftazidime alone was as effective as but safer than the combination of piperacillin and tobramycin for empirical initial monotherapy in a multicenter randomized trial of 876 episodes of febrile neutropenia in 696 patients, most of whom had acute leukemia or bone marrow transplantation. The rates of satisfactory response were 62.7% and 61.1%, respectively, for ceftazidime monotherapy and the piperacillin and tobramycin combination [37]. Adverse events were reported in 8% of the episodes treated with ceftazidime vs. 20% of episodes treated with the combination regimen (P < .001).

The major concern with cephalosporin monotherapy is its limited activity against gram-positive bacteria, especially Enterococcus species, MRSA, coagulase-negative Staphylococcus species, and anaerobes. Another concern is the growing resistance of gram-negative organisms, specifically Pseudomonas species, to these drugs. It is often necessary to modify the initial ceftazidime monotherapy regimen by the addition of another antibacterial agent and/or antifungal (or antiviral and antifungal) therapy [14, 34, 35].

Pizzo and co-workers noted that in a total of 550 evaluable episodes of fever and neutropenia, ~66% of patients who were randomized either to ceftazidime monotherapy or to the combination of cephalexin, gentamicin, and carbencillin were treated throughout their neutropenic episode without a change in the antibiotic regimen; 33% required the addition of another antibacterial agent or the addition of an antifungal (or antiviral and antifungal) drug to the original empirical regimen [34].

Carbapenems. The carbapenem antibiotics offer a broader spectrum of activity than the third-generation cephalosporins. In addition to providing excellent gram-negative coverage, which includes activity against P. aeruginosa, the carbapenems offer good activity against gram-positive organisms and anaerobes [38]. This spectrum of activity has spurred a great deal of interest in the potential of carbapenems as monotherapeutic agents for febrile neutropenia.

Imipenem, which is the first of the carbapenems to be made commercially available, is given in fixed combination with the dehydropeptidase inhibitor cilastatin, as it is susceptible to
degradation by this renal enzyme. A summary of the results of five noncomparative and seven comparative trials of imipenem/cilastatin in patients with febrile neutropenia found a range of clinical cure rates from 70% to 100%; bacteriological cure rates ranged from 68% to 84% [39].

Recent randomized trials have demonstrated that empirical monotherapy with imipenem/cilastatin is as effective as ceftazidime alone [4, 37, 40] or various combination regimens, including double β-lactam-drug therapy [5, 41–43], in the management of febrile neutropenia. Like those of other β-lactam drugs, the side effects most commonly reported in imipenem/cilastatin clinical trials are rash, diarrhea, and nausea. However, imipenem/cilastatin may be associated with a higher incidence of nausea than ceftazidime or cefoperazone plus piperacillin [42] or amikacin plus piperacillin [44] when given at therapeutic dosages.

One concern with imipenem/cilastatin therapy is that it has been associated with an increased incidence of seizures in patients with CNS dysfunction and/or renal failure. The resistance to imipenem that is appearing among P. aeruginosa, Serratia species, and Enterobacter species is another concern with imipenem/cilastatin therapy. Susceptibility studies suggest a mechanism for imipenem resistance other than β-lactamase production. Quinn et al. have hypothesized that the presence of a unique porin on the bacterial surface regulates susceptibility to imipenem, but this theory has yet to be substantiated [45].

Carbapenem Clinical Trials

**Imipenem vs. ceftazidime monotherapy.** In a recent study conducted at the National Cancer Institute, 204 patients with febrile neutropenia were randomized to initial empirical monotherapy with ceftazidime (90 mg/[kg • d] at a maximum daily dose of 6 g) and 195 patients were randomized to imipenem/cilastatin (23% and 22%, respectively) [40]. However, imipenem/cilastatin therapy was complicated by significantly more gastrointestinal toxicity. Toxin assay–documented Clostridium difficile superinfections occurred in 11% (21 of 195) of the episodes treated with imipenem/cilastatin, compared with 4% (9 of 204) of those treated with ceftazidime (P = .02). Only 3% of the ceftazidime-treated patients experienced nausea and vomiting, compared with 21% of the imipenem/cilastatin patients; therapy was discontinued for 10% of the imipenem/cilastatin group because of these side effects. The investigators noted that the emetic effect of imipenem/cilastatin may have been related to the relatively high doses used in this trial.

In another study, 89 neutropenic patients who had 100 febrile episodes received initial empirical monotherapy with either ceftazidime (2 g q8h) or imipenem/cilastatin (500 mg q6h) [4]. Patients randomized to imipenem/cilastatin had a significantly better clinical response than did those randomized to ceftazidime (77% vs. 56%; P = .04). Fevers responded even better to imipenem/cilastatin in a comparison with ceftazidime among patients with microbiologically documented infection (81% vs. 33%; P = .02). There were no significant differences in the incidence of relapse or superinfection between the two groups. The investigators reported that both regimens were well tolerated, although after antibiotic administration three patients in the imipenem/cilastatin group and none in the ceftazidime group had nausea and vomiting that required antiemetic therapy.

**Imipenem vs. combination regimens.** Empirical monotherapy with imipenem/cilastatin (12.5 mg/kg q6h) was compared prospectively with monotherapy with ceftazidime (1 g q4h) and with combination regimens of either imipenem or ceftazidime plus amikacin (200 mg/m² q6h) in 750 assessable episodes of febrile neutropenia in 567 patients [5]. The most effective regimen was the imipenem/cilastatin plus amikacin combination regimen (76% response), but it was not statistically significantly superior to imipenem/cilastatin monotherapy (72%) or ceftazidime plus amikacin combination therapy (71%). Ceftazidime monotherapy was significantly less effective (59% response rate; P = .009) than imipenem monotherapy or either of the combination regimens.

There was a total of 41 superinfections, which were distributed evenly among the four treatment groups [5]. The most common side effects were diarrhea and rash. Seizures occurred in nine patients receiving the imipenem-containing regimens but in none of those randomized to the ceftazidime-containing regimen (P = .002).

Another trial in a total of 131 febrile episodes in 106 neutropenic patients demonstrated that the efficacy and tolerability of monotherapy with imipenem/cilastatin (500 mg q6h) are comparable to those of combination therapy with ceftazidime (2 g q8h) plus tobramycin (3–5 mg/[kg • d]) [43]. Out of a total of 86 patients who had evaluable episodes of febrile neutropenia, 35 of 45 in the imipenem/cilastatin monotherapy group (78%) and 29 of 41 (71%; P = .45) in the ceftazidime plus tobramycin combination therapy group had successful outcomes without a change in the initial study drug regimen.

There was no statistically significant differences between treatment regimens in terms of response rates to microbiologically documented infections or in terms of the number of superinfections (eight in the imipenem/cilastatin group and three in the ceftazidime plus tobramycin group). Of the 131 patients included in the safety evaluation, 25 (38%) in the imipenem/cilastatin monotherapy group and 11 (17%) in the ceftazidime plus tobramycin combination therapy group had one or more
of drug-related adverse events \( (P = .001) \) [43]. The most frequently reported adverse effects in this study was nausea or emesis (in 16 imipenem/cilastatin recipients and five ceftazidime plus tobramycin recipients; \( P = .008 \)).

Imipenem monotherapy was also shown to be as effective as the two combination regimens, with a response rate of 82% (111 of 136 patients); the 2-g daily dose of imipenem was as effective as the 4-g daily dose.

The investigators noted that seizures occurred in 3 of 29 patients (10.3%) receiving the higher dosage of imipenem (4 g/d), 3 of 136 (2.2%) receiving cefoperazone plus piperacillin, none of 132 patients receiving ceftazidime plus piperacillin, and 1 of 106 patients (0.9%) receiving the lower dosage of imipenem (2 g/d) \( (P < .005 \) vs. ceftazidime plus piperacillin) [42]. Gastrointestinal symptoms were the most common adverse effects in this trial; diarrhea occurred most frequently in patients receiving cefoperazone, and nausea occurred significantly more frequently with use of imipenem (10%) than with either cefoperazone plus piperacillin (2%; \( P = .005 \)) or ceftazidime plus piperacillin (1%; \( P < .001 \)). Although superinfections with \( \beta \)-lactam-resistant, gram-negative organisms were rare, they occurred more frequently \( (P = .06 \) with double \( \beta \)-lactam therapy (11 of 268 patients; 4.1%) than with imipenem monotherapy (1 of 135; 0.7%); *Stenotrophomonas maltophilia* superinfections occurred only in the imipenem group (3 of 135; \( P = .06 \)).

*Meropenem.* Both imipenem/cilastatin and meropenem are highly active against gram-negative and gram-positive organisms, although meropenem is slightly more active against gram-negative organisms and imipenem/cilastatin is slightly more active against gram-positive organisms [46, 47]. Meropenem is more stable to renal dehydropeptidase [48] and can therefore be given without cilastatin [49].

One of the limitations of imipenem/cilastatin is the occurrence of drug-related nausea and/or vomiting, which appears to be related to both the dose and the speed of administration [44, 50, 51]. The overall toxicity profile of meropenem, including gastrointestinal tolerability, compares favorably to that of imipenem/cilastatin as well as other \( \beta \)-lactam agents [41, 51]. In a recent comparative trial of meropenem and ceftazidime monotherapy in febrile neutropenia, no instances of nausea were reported in either treatment group [52]. Kelly et al. have reported that meropenem can be given without associated nausea and vomiting, even when administered by rapid (5-minute) bolus injection [53].

Another important aspect of meropenem’s safety profile is that it appears to have a lower potential to induce seizures than do other \( \beta \)-lactam drugs [41]. Early studies in an animal model suggested that meropenem was less seizurogenic than imipenem/cilastatin [54]. Imipenem (both alone and in combination with cilastatin) produced a significant increase in the incidence of metrazole-induced convulsions at a minimum dose of 200 mg/kg, while meropenem did not cause significant potentiation of metrazole-induced seizures at any dose tested (50–400 mg/kg). Other investigators have confirmed that meropenem has weak convulsant activity in an animal model, probably related to its relatively weak inhibition of receptor binding of \( \gamma \)-amino butyric acid in comparison with that of imipenem as well as other \( \beta \)-lactam drugs [55].

Wong and colleagues at Children’s Hospital of Los Angeles undertook an evaluation of the safety and efficacy of imipenem/cilastatin in 21 children with bacterial meningitis (ages 3 to 48 months) [56]. The study was terminated when seizure activity developed in seven (33%) of the patients following antibiotic administration, leading the investigators to question the advisability of giving imipenem/cilastatin to children with bacterial meningitis.

In contrast to the previous clinical trial, Klugman and colleagues reported a lower incidence of seizures when meropenem was used for the empirical treatment of bacterial meningitis in children [57]. To date, the overall incidence of seizures in meropenem clinical trials is 0.38% (<0.05% drug-related), compared with the incidence of up to 3% (0.9% drug-related) reported with use of imipenem/cilastatin in phase 3 trials and postmarketing surveillance [41, 47, 58, 59].

Early clinical trials support the potential value of meropenem as empirical monotherapy for patients with febrile neutropenia [52, 60]. In an ongoing, double-blind trial of 123 febrile neutropenic patients who were randomized to empirical therapy with either meropenem or ceftazidime, resistant enterobacter bacteremia developed in one unblinded patient who received ceftazidime; pseudomonas bacteremia developed in another and progressed to meningitis [52]. In a recently completed trial, the efficacy of meropenem monotherapy was compared with that of a combination of ceftazidime plus amikacin in granulocytopenic patients with cancer. Efficacy was similar in both treatment groups (56% vs. 52%, respectively), and tolerability and safety were also similar [60].

**Modification of Antimicrobial Management**

After the initiation of empirical antibiotic therapy, several outcomes can be predicted. In the best case, cultures will identify a microorganism and these findings can guide future therapy. If no organism is identified within 72 hours of treatment and the patient defervesces, therapy should continue for 7–10 days or until the granulocytopenia resolves (resulting in a count of >1,000 cells/mm³) without further febrile episodes [61].
Return of a febrile state or additional clues, such as hemodynamic compromise, should prompt reinitiation of therapy.

If the fever persists longer than 72 hours and no organism is identified, the patient should be reevaluated for a possible nonbacterial cause, a bacterial infection that is resistant to the agent(s) in the initial empirical regimen, emergence of a second bacterial infection, nontherapeutic serum and tissue levels of the antibiotic, drug-related fever, or infection at avascular sites. Guidelines for antimicrobial therapy published by the IDSA in 1990 suggest that even if fever persists for up to 5 days, the initial empirical regimen can be continued as long as the patient’s clinical condition does not deteriorate, especially if the neutropenia is expected to resolve shortly [1].

An adjustment of the initial regimen should be considered when fever persists for >3 days and there is evidence of disease progression [1]. If it is not already being administered, vancomycin should be considered to provide additional gram-positive coverage. This is particularly desirable if infection due to MRSA, Enterococcus species, S. epidermidis, or hemolytic Streptococcus is suspected, especially in patients with mucosal lesions or catheter-access sites, which are common portals of infection by these organisms [1].

If the initial regimen was polytherapy with an antipseudomonal β-lactam drug, aminoglycoside, and vancomycin, a switch to monotherapy may be considered. Monotherapy with a third-generation cephalosporin such as cefazidime or with a carbanem agent such as meropenem is particularly appropriate if amphotericin B might be added to the regimen, in order to avoid the additional nephrotoxicity associated with concomitant administration of amphotericin B with an aminoglycoside.

Continuation of febrile episodes to day 7 warrants the addition of antifungal therapy, such as with fluconazole or amphotericin B [8, 12, 62, 63]. Systemic fungal infections, usually due to Candida or Aspergillus species, have been found in up to 33% of febrile neutropenic patients who remain unresponsive after 1 week of antibiotic therapy [8]. Nevertheless, empirical use of antiviral or antiparasitic agents is indicated only if clinical data suggest the presence of viral or parasitic infections. Use of antivirals is not recommended when no mucosal or dermal lesions are present [1].

**Prophylaxis and Adjunctive Therapy**

Antimicrobial prophylaxis may be considered as a way of averting the potentially catastrophic effects of septicemia in an immunocompromised host. As with any antibiotic therapy, the risk of selection of resistant pathogens vs. the risk of development of gram-negative or gram-positive sepsis must be carefully weighed prior to initiation of antimicrobial prophylaxis.

The emphasis to date has been placed on control of gram-negative sepsis, thus protecting neutropenic patients from bowel-derived organisms. Early studies on the prevention of infection in neutropenic patients concentrated on the use of nonabsorbable antibiotics, such as oral gentamicin, vancomycin, neomycin, and colistin, that would eradicate selected bowel flora. Side effects and poor tolerance, as well as questionable efficacy, encouraged the development of alternative drug therapies.

**Antibacterial Prophylaxis**

In 1984 the EORTC investigated the role of trimethoprim-sulfamethoxazole (TMP-SMZ) in prophylaxis for infection in neutropenic patients [64]. In a study group of 342 patients, 165 received placebo and 177 received single-strength TMP-SMZ twice daily at the onset of neutropenia (defined as <1,000 neutrophils/mm³) or if neutropenia was impending. Infection developed in 64 (39%) of 165 patients receiving placebo, while only 46 of 177 (26%) of patients treated with TMP-SMZ had infection (P = .016). However, the emerging resistance to TMP-SMZ and selection for resistant pathogens have motivated studies searching for a more effective means of prophylaxis.

The broad antimicrobial spectrum and tolerability of oral fluoroquinolones have sparked interest in their potential role in prophylaxis. Ciprofloxacin and norfloxacin have been evaluated as prophylactic treatment in patients with severe granulocytopenia [65, 66]. The effects of these agents on anaerobic flora have been questioned [65].

Data from the autologous bone marrow transplant program at Duke University (Durham, NC) showed that prophylactic ciprofloxacin in conjunction with rifampin reduced the incidence of fever in 99 evaluable transplantation patients with neutropenia from 98% to 57%, decreased the incidence of documented infections from 42% to 13%, and eliminated bacteremia from an incidence of 18% to zero. These patients underwent transplantation after receiving high-dose chemotherapy for primary breast cancer. They also received peripheral blood progenitor cells and hematopoietic growth factor [67].

Interpretation of these results must be tempered, however, by the recognition that prophylactic antimicrobial therapy is not practiced universally and selection for resistant pathogens may occur as a result. The risks of prophylactic therapy for individual patients also must be taken into account.

**Adjunctive Therapies**

There is considerable interest in adjunctive therapies that could actually enhance the immune response in the neutropenic host. One of the earliest approaches was the transfusion of WBCs. This approach, however, has proved to be of limited value because of difficulties in obtaining adequate cells for transfusion, as well as problems including alloimmunization, infection transmission, and adverse reactions to amphotericin B [15].

Use of recombinant products, including biological response modifiers and hematopoietic colony stimulating factor, is an intriguing new approach. These agents may make it possible...
to effectively modulate granulocytopenia and impaired cellular and humoral immune responses in cancer patients. Colony stimulating factor has so far been shown to reduce infectious morbidity, but not mortality, in this population [68, 69].

Conclusions

The past 20 years have yielded many exciting new options for treatment of febrile episodes in the neutropenic cancer patient. Empirical therapy that provides coverage of both gram-negative and gram-positive pathogens is mandatory in light of epidemiologic data suggesting a gradual shift in prevalence from gram-negative to gram-positive organisms in this population. The debate over the utility of combination therapy vs. monotherapy continues, especially with the growing emergence of multidrug-resistant pathogens.

With the advent of third-generation cephalosporins, it became possible to obtain broad-spectrum coverage with a single therapeutic agent. Now carbapenems, with extended coverage against gram-positive organisms, may also be used in monotherapeutic approaches. In a large, recently published EORTC trial, meropenem showed promise for empirical management of fever in the neutropenic patient [60]. Preliminary data suggest that initial monotherapy utilizing these new agents compares favorably with that of conventional combination therapy regimens. Additional clinical experience will reveal the extent to which pathogen resistance is likely to become a significant clinical problem with the newer agents.

A number of clinical studies suggest that monotherapy can be as effective as combination therapy and may offer some advantages in terms of safety and tolerability [2, 34–37, 70, 71]. However, differences in the design and analytical methods of antimicrobial trials make it difficult to draw firm conclusions about their comparative benefits and risks [72]. In its Guidelines for the Use of Antimicrobial Agents in Neutropenic Patients with Unexplained Fever, the IDSA Working Committee reported that there were no striking differences between empirical monotherapy and multiple-drug treatment or among the various combination treatment regimens [1]. The selection of one approach over another must therefore be guided by the circumstances of individual patients and by institutional variations in the spectrum of infections.

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