SUPPLEMENT ARTICLE

Management of Fever in Neutropenic Patients with Different Risks of Complications

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Risk stratification of febrile neutropenic patients can have important implications in terms of management. The first prospectively validated risk scoring system was developed in 1992. A subsequent scoring system was developed in 2000, in which a score of ⩽21 predicts a <5% risk for severe complications. Oral combination therapy in an ambulatory or home care setting is acceptable for low-risk patients. Hospital admission is mandatory for high-risk patients. Intravenous monotherapy can be given if neutropenia is anticipated to be of short duration; it is also acceptable if neutropenia is expected to be more prolonged but the patients is stable and do not have an infectious focus. All other patients should receive combination therapy with an aminoglycoside, if infection with a gram-negative pathogen is suspected, or a glycopeptide, if a gram-positive organism is suspected. However, antimicrobial therapy with coverage against gram-negative organisms should always be provided because of the significant mortality associated with these infections.

Fever in neutropenic patients is a frequent complication of chemotherapy for cancer. It occurs in 10%–50% of patients with solid tumors and in >80% of those with blood malignancies. It usually requires treatment for 7–12 days, at an approximate daily cost of more than US$1500, and is associated with a mortality rate of n almost 10%. Hence, febrile neutropenia affects an increasing number of persons worldwide and poses a significant burden in health care and economic terms.

RISK ASSESSMENT AMONG FEBRILE NEUTROPENIC PATIENTS

Considering the great heterogeneity of patient populations with febrile neutropenia, efforts continue to be made to separate patients at low and at high risk of serious complications and to characterize each subpopulation. These efforts will have important implications in terms of management. Treatment strategies for low-risk patients might be simplified (i.e., made more convenient and less expensive) without compromising efficacy.

Attempts at distinguishing between low- and high-risk patients have been based on various variables, including the response to treatment. For example, the rate of response to therapy with ceftazidime plus amikacin differed markedly among patients with unexplained fever (64% responded), those with clinically documented febrile neutropenia (49% responded), and those with microbiologically documented (usually bacteremic) febrile neutropenia (32% responded) [1]. Also, bacteremia per se appears to act as a trigger of causes of mortality. Several trials by the International Antimicrobial Therapy Cooperative Group have shown higher mortality rates among bacteremic patients, compared with nonbacteremic patients, except for deaths mainly due to hemorrhage or extensive cancer. Mortality has also been shown to be lower, although without a statistically significant difference, among patients with uncomplicated bacteremia, compared with patients with complicated bacteremia (i.e, with organ involvement) [2].

The main question at this point is how to predict safely that individual patients will be at low risk of developing complications during an episode of febrile neutropenia. Several pragmatic approaches based on criteria such as the presence of solid rather than blood

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Clinical Infectious Diseases 2004; 39:S32–7

1058-4838/2004/3901S1-0006$15.00

malignancies, expected short duration of neutropenia, good performance status, and absence of clinical signs of severe illness were not without clinical significance but have never been validated prospectively.

Kern et al. [3] and Freifeld et al. [4] have proposed a series of pragmatic exclusion criteria for the prediction of a low risk of complications during febrile neutropenia. Those postulated by Kern et al. [3] include having undergone allogeneic transplantation; presence of renal failure, shock, or respiratory insufficiency; receipt of intravenous supportive therapy; HIV, catheter-related infection, or central nervous system infections; and risk of death within 48 h. Factors listed by Freifeld et al. [4] include presence of hemodynamic instability, abdominal pain, nausea and/or vomiting, diarrhea, neurological or mental changes, catheter-related infection, new pulmonary infiltrates, renal failure, and liver insufficiency. A potential shortcoming of these criteria may be that they can be difficult to assess in clinical settings.

The first prospectively validated risk assessment tool for febrile neutropenic patients was developed by Talcott et al. [5]. It consisted in a clinical model involving 4 categories of patients at risk whose risk status is clinically assessable within 24 h of admission: preexisting inpatients, outpatients with severe comorbidity, outpatients with progressing neoplasia, and all others. Multiple complications were more frequent among preexisting inpatients; overall mortality was 8%, with a 14% rate for outpatients with progressing neoplasia.

Later, Klastersky et al. [6] postulated a scoring system based on the logistic equation of the Multinational Association for Supportive Care in Cancer (MASCC) predictive model (table 1). The maximum value in this system is 26, and a score of ≤ 21 predicts a <5% risk for severe complications in febrile neutropenic patients. A comparison of the 2 previously described risk assessment tools showed that, if the model of Talcott et al. [5] is used, many low-risk patients are missed and continue to be categorized as high-risk patients (table 2).

EMPIRICAL ANTIMICROBIAL THERAPY: WHEN IS THE ORAL ROUTE ACCEPTABLE?

In all likelihood, the need for of hospital-based, intravenous empirical therapy with broad-spectrum agents for febrile neutropenic patients can be reasonably challenged when patients have been categorized as belonging to the low-risk group on the basis on a validated scoring system for risk assessment, such as the MASCC score. If oral therapy is used, the demands for cost-effectiveness will be met, and the patients' quality of life will probably improve.

Once patients with good prognosis have been selected, 2 issues need to be considered: use of oral antibiotic therapy and outpatient management. Two studies, by Kern et al. [3] and Freifeld et al. [4], used randomized, double-blind protocols to compare empirical oral therapy with ciprofloxacin plus amoxicillin-clavulanic acid and intravenous therapy with ceftriaxone plus amikacin in low-risk febrile neutropenic patients. Success rates were 86% for the oral therapy and 84% for the intravenous therapy. Only 2 deaths or serious complications occurred among the 161 evaluable patients in the oral therapy arm. Further oral therapy was impossible for 6 patients. These results confirm that oral antibiotic treatment can be given to appropriate patients, that is, those with solid tumors who have a low-risk status safely documented by a validated score, who are nonallergic and able to swallow.

The issue of outpatient management is more controversial and perhaps needs to be contemplated on an individual basis. A study currently in progress, designed to validate the MASCC score for the identification of high- and low-risk febrile neutropenic patients, is evaluating outpatient management of these patients. Patients consecutively presenting with febrile neutropenia are assessed with the MASCC score. If this score is <21, patients are hospitalized and given intravenous broad-spectrum antibiotics. Patients with a score of ≥ 21 receive oral combination therapy with amoxicillin/clavulanic acid plus ciprofloxacin and stay in the hospital for observation for 24 h. The next day, if the score is still ≥ 21, they are discharged to receive the same regimen at home, provided that appropriate surveillance at home is available. Of the 433 patients with episodes of febrile neutropenia admitted thus far, 330 had a MASCC score of ≥ 21; of these, 127 were enrolled in the validation study. Fifty-three were discharged, and 73 remained hospitalized. Of note, the most frequent reason for remaining hospitalized was the patient's or the physician's reluctance to accept discharge. The success rate in the outpatient management arm is 96%. Two patients had to be readmitted because of unstable clinical status or relapse of fever and chills. Eight of the 73 patients on the inpatient management arm had complications, and 1 died of

Table 1. Scoring system for risk of complications among febrile neutropenic patients, based on the Multinational Association for Supportive Care in Cancer predictive model [6].

Characteristic	Point score
Burden of illness	
No or mild symptoms	5
Moderate symptoms	3
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumor or no previous fungal infection in hematologic tumor	4
Outpatient status	3
No dehydration	3
Aged <60 years	2

Table 2. Comparison of predictive models of Talcott et al. [5] and the Multinational Association for Supportive Care in Cancer (MASCC) [6] for febrile neutropenic patients.

Characteristic	Talcott et al.	MASCC
Patients at low risk	26	63
Positive predictive value	93	91
Negative predictive value	23	36
Specificity	90	68
Sensitivity	30	71
Global miscalculation	59	30
Deaths among low-risk patients	3 (3)	4 (1.6)[a]

NOTE. Data are %, except for deaths, which are no. (%) of patients.
[a] The mortality rate in the high-risk group was 11% (16 of 140 patients).

disseminated fungal infection. Treatment costs fell dramatically with outpatient management.

In summary, a subgroup of febrile neutropenic patients is at minimal risk for serious complications or death. These patients can probably be treated with relatively simple and inexpensive antibiotic regimens and might be discharged earlier from the hospital.

FEBRILE NEUTROPENIC PATIENTS AT HIGH RISK FOR COMPLICATIONS

A prospective multicenter survey is in progress to establish the duration of neutropenia in a mixed population of patients with solid tumors or leukemia who have fever and profound neutropenia. In this survey, the MASCC index has had a positive predictive value of 91%. Among the 663 patients enrolled thus far, serious complications have occurred in 40% of the high-risk patients and only 13% of the low-risk patients. Mortality rates have been 15% for high-risk patients and only 1% for low-risk patients.

When clinical presentations are examined, fever of unknown origin, allegedly the most benign presentation, has been more frequent among low-risk than among high-risk patients (49% vs. 35%). In the bacteremic subpopulation, infection with gram-negative organisms, which is associated with a higher mortality, have been more prevalent among high-risk than among low-risk patients (59% vs. 31%), whereas the opposite applies to infection with gram-positive organisms (38% vs. 62%). In the subpopulation with bacteremia, 76% of low-risk patients were free of complications, compared with 32% of high-risk patients. Mortality also was much higher in the high-risk than in the low-risk group: 28% vs. 2%. These data underscore the importance of the high-risk status among bacteremic patients.

The occurrence of medical complications has also been examined in terms of risk status (table 3). In the population with bacteremia due to a single gram-negative pathogen, only 25% of high-risk patients had an uncomplicated outcome, compared with 85% in the low-risk group. Forty-five percent of high-risk patients died, whereas there have been no deaths in the low-risk group. In the subpopulation with bacteremia due to gram-positive organisms, differences have been less impressive. Of note, none of the high-risk patients with bacteremia due to gram-positive organisms have died.

Risk status was stratified into 4 categories according to MASCC score: A (score of 7–14, "worst" bad prognosis), B (15–16), C (17–18), and D (19–20, "best" bad prognosis). Sixty-eight percent of patients in category D have had an uncomplicated outcome, compared with only 35% of those in category A, whereas mortality rates have been 13% in category D and 26% in category A (table 4).

Other characteristics of high-risk febrile neutropenic patients include a significantly longer duration of neutropenia, a lack of differences with respect to the occurrence of complications and mortality rates between patients with hematological malignancies and those with solid tumors, and an increased incidence of complications among patients who do not respond to the initial empirical therapy (58% vs. 23%). A similar trend is observed among low-risk febrile neutropenic patients.

All febrile episodes in neutropenic patients are not identical, even within the high-risk group. Hence, efforts should be made to identify, on clinical and microbiological grounds, those patients at high risk of developing complications and/or dying during an episode of febrile neutropenia, because these patients might benefit from a more aggressive treatment approach, such as combination therapy.

THE MANAGEMENT OF FEBRILE NEUTROPENIC PATIENTS

Infections due to gram-negative organisms. In a pioneering study conducted by McCabe and Jackson in 1962 [7, 8] in

Table 3. Medical complications in 72 febrile neutropenic patients with bacteremia due to a single pathogen, according to pathogen and Multinational Association for Supportive Care in Cancer (MASCC) score.

	No (%) of patients, by class of pathogen and risk group			
	Gram-negative		Gram-positive	
Outcome	Low risk (n = 13)	High risk (n = 20)	Low risk (n = 26)	High risk (n = 13)
Resolution				
Without complications	11 (85)	5 (25)	20 (77)	9 (69)
With complications	2 (15)	6 (30)	5 (19)	4 (31)
Death	0	9 (45)	1 (4)	0

NOTE. Low-risk was defined as an MASCC score of ⩾21; high-risk was defined as a score of <21. $P < .001$ for comparison of the death rates among low-risk versus high-risk patients with bacteremia due to gram-negative pathogen. $P < .001$ for comparison of the death rates among high-risk patients with bacteremia due to gram-negative pathogen versus high-risk patients with bacteremia due to gram-positive pathogen.

Table 4. Clinical outcome among high-risk febrile neutropenic patients, defined as a Multinational Association for Supportive Care in Cancer (MASCC) score of <20.

Risk group	MASCC score	*n*	Outcome, no (%) of patients		
			Resolution without complications	Resolution with complications	Death
A	7–14	31	11 (35)	12 (39)	8 (26)
B	15–16	34	20 (59)	8 (24)	6 (18)
C	17–18	53	35 (66)	9 (17)	9 (17)
D	19–20	63	43 (68)	12 (19)	8 (13)
Total	…	…	109	41	31

NOTE. $P < .01$ for the overall comparison of rates of resolution without complications (χ^2 test for trend).

which various antibiotics and combinations were given to patients with granulocytopenia who had leukemia and infections due to gram-negative organisms, a 91% mortality rate was reported. Almost 25 years later, in a 1986 European Organization for Research and Treatment of Cancer (EORTC) study [9], the mortality rate in a similar population treated empirically with ceftazidime plus amikacin was 9%. The reasons for this difference are, undoubtedly, multifactorial, but a major factor is probably the early institution of empirical combination therapy. Table 5 provides additional data derived from more recent trials comparing different combination regimens with monotherapy for the treatment of infections in adult and pediatric febrile neutropenic patients [10–14].

Among the newer cephalosporins, cefepime has been used frequently for the empirical treatment of febrile neutropenia, both as monotherapy and in combination with aminoglycosides. It possesses a spectrum of action against gram-negative bacilli comparable to that of ceftazidime but appears to be somewhat more active against gram-positive bacteria [15]. A trial by the French Cefepime Study Group comparing cefepime and ceftazidime, both in combination with amikacin, showed an equivalent response rate for these regimens. A glycopeptide was added to the regimens of 60% of patients in the cefepime plus amikacin group and to those of 51% of patients in the ceftazidime plus amikacin groups [16]. Bohme et al. [17] conducted a trial designed to compare combination therapy with piperacillin and tazobactam versus monotherapy with cefepime for the initial empirical treatment of febrile neutropenic patients (figure 1). Infections due to gram-negative organisms responded to treatment less frequently. Time to persistent defervescence was similar in both study arms, as were the response rates after different types of therapy modification, including addition of gentamicin, vancomycin, or amphotericin B. The response rates, both with and without therapy modifications, was 96% in both study arms. Overall, no significant differences were found between the responses to the 2 therapeutic regimens. Other trials of cefepime monotherapy report similar findings [18–20]. These data suggest that monotherapy with broad-spectrum agents, such as cefepime, piperacillin/tazobactam, and carbapenems, can be an acceptable option for the management of febrile neutropenic patients, depending, of course, on the local ecology. Still, there are subgroups of patients who will benefit from more aggressive treatment approaches.

Infections due to gram-positive organisms. A central issue is whether vancomycin should be part of the initial empirical therapy for these infections or if it can be safely withheld until a gram-positive etiology is confirmed. European Organization

Table 5. Comparison of different combination regimens versus monotherapy in adult and pediatric febrile neutropenic patients.

Study, year	Regimen	Class of patients, risk group(s)	No. of episodes	Response rates, % of patients[a]
Giamarellou et al. [10], 2000	Ceftazidime + amikacin vs. ciprofloxacin	Adult, low- and high-risk	246	51 vs. 50
Agaoglu et al. [11], 2001	Ceftazidime + amikacin vs. cefepime + netilmicin	Pediatric, high-risk	73	79 vs. 78
	Ceftazidime + amikacin vs. meropenem	Pediatric, high-risk	73	79 vs. 73
Duzova et al. [12], 2001	Piperacillin + amikacin vs. meropenem	Pediatric, low-risk	90	64 vs. 76
Cornely et al. [13], 2001	Ceftriaxone + tobramycin[b] vs. cefotaxime	Adult, high-risk	160	47 vs. 45
Ariffin et al. [14], 2000	Ceftriaxone + amikacin[b] vs. ceftazidime + amikacin	Pediatric, low- and high-risk	191	55 vs. 51

[a] Response rate for regimens without modification. Values are outcomes for the 2 regimens listed, respectively.
[b] Once-daily.

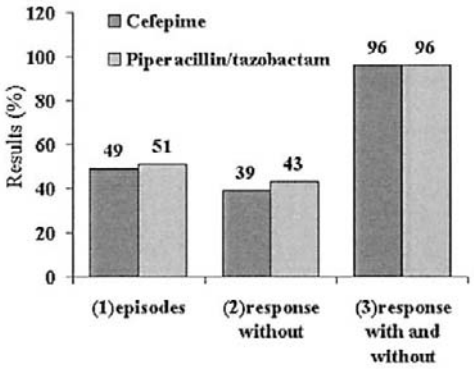

Figure 1. Comparison of cefepime versus piperacillin/tazobactam for the initial empirical treatment of febrile neutropenic patients. Reprinted with permission from [17].

for Research and Treatment of Cancer (EORTC) Trial V showed a better response rate in the vancomycin group, with no differences in mortality, but with a rampant increase in treatment expenses [21]. Therefore, febrile neutropenic patients who have leukemia or lymphoma or have undergone bone marrow transplantation subsequently received piperacillin/tazobactam. Among patients who continued to be febrile after 48–60 h of therapy, those with gram-negative bacterial infections or piperacillin/tazobactam-resistant, or catheter-related infections were excluded from the study, and the remainder were randomized to receive vancomycin or placebo. The results were conclusive: no statistically significant differences were found in time to defervescence or in mortality [21].

These data suggest that initial or delayed administration of vancomycin to febrile neutropenic patients is probably not needed, unless there is an overwhelming suspicion of gram-positive bacterial sepsis. Piperacillin/tazobactam, cefepime, and the carbapenems may be particularly effective in providing coverage against penicillin-susceptible microorganisms, namely streptococci.

CONCLUSION: A PROPOSED RATIONAL APPROACH FOR THE MANAGEMENT OF FEBRILE NEUTROPENIA

1. The first step should be the risk categorization of patients on the basis of a validated risk assessment tool.

2. Low-risk patients might receive oral combination therapy with amoxicillin-clavulanic acid plus ciprofloxacin in an ambulatory or home care setting, provided that appropriate surveillance can be ensured.

3. High-risk patients need to be hospitalized. Those for whom neutropenia is expected to be of brief duration can receive intravenous monotherapy. This also holds true for patients with neutropenia that will probably be more prolonged but who are stable and have no infectious focus.

4. All other patients should receive combination therapy with a glycopeptide if a gram-positive bacterial etiology is suspected or combination therapy with an aminoglycoside if a gram-negative bacterial etiology is suspected. An important caveat is that antimicrobial therapy with coverage against gram-negative microorganisms should be provided anyway because of the high mortality associated with these infections. Whether a granulocyte colony-stimulating factor should be added to the treatment regimen for such patients is an open question.

5. Patients need to be observed on a daily basis and reassessed after 72 h. If signs of clinical response are present, therapy should be continued for ~7 days.

6. If no signs of clinical response are seen, treatment has to be adjusted according to microbial drug-susceptibility, if a pathogen is isolated. In addition, it is appropriate to screen for a localized infection and to consider the use of granulocyte-macrophage colony-stimulating factor.

7. If no pathogen is isolated, additional cultures and serological testing should be performed, and CT of the chest and bronchoalveolar lavage should be performed. Amphotericin B, metronidazole, antiviral agents, and/or granulocyte-macrophage colony-stimulating factor should be added to the regimen as indicated. In addition, noninfectious causes of fever need to be sought [22].

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