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Empirical and subsequent use of antibacterial agents in the febrile neutropenic patient

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Abstract. The objectives of this analysis were an assessment of the feasibility of a more individually tailored approach of empirical antibiotic therapy in febrile neutropenia and an exploration of the reasons to modify the initial regimen.

Design, setting and subjects. The main source was a database on febrile neutropenic cancer patients from an unblinded large trial conducted in 35 centres world-wide. This was supplemented by data from patients enrolled in a consecutive series of randomized trials at the Department of Haematology, University Hospital Nijmegen.

Interventions. Diagnostic procedures were standardized, types of possible infections defined and the reasons for modifying an empirical regimen were recorded.

Main outcome measures. Survival of the febrile neutropenic episode, development of microbiologically and clinically defined infection in relation to

causative organisms, and results of modification.

Results. Monotherapy was as effective as combination therapy with an overall mortality of $\leq 7\%$, with 21% of neutropenic episodes accompanied by a clinically defined infection proving fatal compared with only 4% of episodes without a focus. At the end of treatment the empirical regimen had been added to in 60% of cases in the multicentre trial, in contrast to 39% in our own institution, in many cases simply because of continuing fever.

Conclusion. The development of local guidelines for individually tailoring antibiotic therapy by complementing the empirical regimen is a feasible option for achieving an optimal anti-infective strategy for febrile neutropenic cancer patients.

Keywords: bone-marrow transplantation, empirical antibiotics, fever, infection, leukaemia, neutropenia.

Introduction

Aggressive bone-marrow ablative chemotherapy and bone-marrow transplantation have become acceptable treatment options for patients with an otherwise incurable malignant disease. However, profound and prolonged neutropenia occurs which carries with it an inherent risk of life-threatening infection necessitating the implementation of appropriate anti-infective strategies in institutes which care for such patients. As neutropenic patients are unable to produce an adequate inflammatory response, any fever that develops should be considered to be due to infection until proven otherwise. Early mortality due to infection has been reduced by the universal adoption of the so-called empirical approach whereby broad spectrum antibiotics are given in order to provide protection against the fulminant infection due to Gram-negative bacilli [1].

Traditionally, empirical regimens have consisted of a combination β -lactam and an aminoglycoside and discussions about the number and kinds of antibiotics still lingers on [2]. The results of many of the older studies are now outdated due to changes in the spectrum of micro-organisms causing infection in neutropenic patients as well as in the management of malignant diseases. Besides the obvious variation between hospitals in the most prevalent pathogens, there has been a major shift from Gram-negative to Gram-positive bacterial pathogens as well as a shift in the relative frequency of individual Gram-negative bacillary species particularly *Pseudomonas aeruginosa*. This phenomenon is thought to be the combined result of the selective pressure of prophylactic antimicrobial regimens of the commensal flora, the disruption of physical barriers by indwelling intravascular catheters, such as the Hickman tunnelled

catheter, and the mucosal damage induced by more aggressive cytotoxic therapy. The constitution of the optimal empirical regimen remains an issue because of the change in the spectrum of pathogens, the availability of novel antibiotics and flaws in the clinical trials published hitherto. The major randomized trials of the last decade failed to show any substantial difference between the efficacy of the antibacterial agents compared. There are no reasons for thinking that this will change in the future due to the fact that fever was unexplained in the majority of episodes treated and actually represented a low enough risk that using any of the modern potent antibacterial agents would virtually guarantee success. Analysing the various risk groups separately is usually frustrated by a lack of sufficient numbers to allow reliable conclusions. Nevertheless, common sense dictates that it must be possible to achieve an approach more tailored to the empirical treatment of the individual febrile neutropenic patients. This is borne out by circumstantial evidence as patients with a clinically manifest focus of infection clearly represent a different population than do those in whom a site is not detected. Local circumstances are already accepted as a basis for individualizing treatment but the sites of infection that are present at the onset of fever have been largely ignored even though they can provide an important clue as to the causative agent.

It is remarkable that studies published on the management of infectious complications in neutropenic patients focus almost entirely on the empirical phase of treatment, i.e. the first 3–4 days after the onset of fever. Few details are provided on the complications that occur afterwards even though a considerable number of patients do not respond completely to the empirical treatment. This makes modification of treatment the rule rather than the exception in prolonged neutropenia [3,4]. As mentioned earlier, the origin of fever remains obscure in a substantial number of cases making rational decisions on subsequent antimicrobial treatment difficult, which is precisely why the large multicentre randomized studies can send the practising physician along the wrong track. For instance, when confronted with persisting fever in a stable neutropenic patient one doctor may perceive the need to adjust the empirical regimen, while his colleague is more confident and is prepared to wait for the results of diagnostic tests. In terms of trial outcome, the first case would be deemed a failure and the second a success. Thus, not only are the antibiotics on

trial but so too are the doctors which means that the final results of the study depend heavily on the behaviour of the physicians involved [5]. This need not be a problem provided that the reasons for modification are reported in detail. Unfortunately, this is rarely the case so the reader must read the report thoroughly if he is to put the seemingly objective results into perspective and avoid drawing the wrong conclusions. Indeed, if no guidelines for adjusting empirical regimen are available, it will be almost inevitable that antibiotics will be overused and chosen in a haphazard fashion particularly if there are no local guidelines or policies for prescribing antibiotics.

The aim of the present paper is to provide arguments for an individual approach to the treatment of infection in the neutropenic patient and a strategy for both the empirical and subsequent antimicrobial treatment using the results of a series of prospective trials on the efficacy and safety of broad-spectrum antibiotic empirical regimens.

Patients and methods

Patients

The database on patients recruited to a large multicentre trial [4,6,7] of the empirical management of febrile neutropenic patients was the main source of data for analysing factors that might predict the outcome of empirical antibiotic therapy. This was supplemented by the data from a consecutive series of randomized trials conducted at our own institution [8–18].

Diagnostic procedures

Fever was defined as a single axillary temperature of 38.5°C or at least two readings of >38°C taken 2 h apart. Patients aged >14 years suffering from a haematological malignancy were included provided that intensive chemotherapy had induced neutropenia with granulocyte counts of $<0.5 \times 10^9/L$. Therapy was started once a comprehensive clinical examination of the skin, oral cavity and perianal region had been completed, a chest radiograph had been made and tests for laboratory investigations had been taken. Ten millilitres of blood were obtained for culture from each of two separate veins and another 10 mL were taken via a central venous catheter when present. A specimen of urine was obtained for culture as were other appropriate specimens from any local site of infection when present. Isolates were identified

and their antimicrobial susceptibility was determined using standard techniques. Patients were examined daily with special attention being paid to detecting possible sites of infections of the lungs, perianal area, central venous catheter exit site and tract, skin, and oral cavity. In most cases, further specimens of blood and urine were obtained for culture and a chest radiograph was taken 72 h after start of treatment and when a change in antimicrobial therapy was considered necessary by the physician in charge. Invasive diagnostic techniques such as bronchoalveolar lavage were performed on a case-by-case basis. Biochemical profiles were determined once weekly and haematological profiles at least three times weekly.

Definitions

Clinical sepsis was characterized by a sudden rise in temperature to at least 39°C, accompanied by rigors and/or chills, tachycardia, tachypnoea, or malaise with or without hypotension. The detection of a pulmonary infiltrate on the chest radiograph or physical abnormalities consistent with a pulmonary infiltrate was considered to represent a lower respiratory tract infection unless a non-infectious origin had been established. Ulceration of the skin, pyodermatitis, or cellulitis constituted a skin and soft-tissue infection and was deemed to be related to the intravascular catheter when inflammation or tenderness was present around its exit site or along its track or when a seropurulent exudate was produced. As it is all but impossible to distinguish between mucositis and infection, any complaints of local pain accompanying ulceration, erythema, tenderness, swelling or pseudomembranes in the throat, nose or oral cavity were deemed an upper respiratory tract infection. Similarly, abdominal pain and tenderness, diarrhoea or abnormalities found on an abdominal ultrasound or CT-scan that suggested a lesion, represented gastrointestinal infection unless they could be clearly attributed to cytotoxic chemotherapy. Urinary tract infection was defined by painful micturition and bacteriuria of $>10^5$ cfu/mL urine. Death was attributed to infection when it occurred as a direct consequence of either the presenting or subsequent infection.

Classification of infection

Fever was attributed to a microbiologically defined infection (MDI) when bacteraemia was detected in at least one blood culture yielding any bacterium except

coagulase-negative staphylococci and skin coryneforms for which two identical cultures of blood obtained within 2 h of each other were necessary. The cause of fever accompanied by a focus of infection was deemed a clinically defined infection (CDI) unless a micro-organism other than commensal flora had been isolated in which case it was considered an MDI. All other fevers were considered unexplained if neither a CDI nor MDI had been determined within the first 72 h after starting empirical treatment. Any new infective event that occurred during or after stopping treatment was classified as a subsequent infection.

Modifications to therapy

Data from the patients who were enrolled in randomized trials at our own institute were used to assess the adherence of clinicians to a set of rules that provided guidance for modifying initial therapy by addition or substitution. Briefly, these were deterioration of vital signs, progression of an existing CDI during persisting neutropenia, persistence of a presumed pathogen, isolation of pathogen resistant *in vitro* to the empirical regimen in the absence of clinical improvement, occurrence of a new MDI, CDI or episode of unexplained fever, unexplained fever persisting for more than 5 days, and adverse drug reactions attributable to an empirical antibiotic [19]. The reasons for altering therapy were recorded in the patient's case notes or the case report form. A change in therapy made according to these guidelines was considered to be an objectively verifiable reason for modification. All other changes in antibiotic therapy, including the cases where no clear explanation could be found in the case notes, were categorized as subjective reasons for modification. Dosage adjustments and replacing the empirical regimen with oral prophylaxis were not considered to be modifications. A change in therapy during the first 72 h was defined as an early modification.

Discontinuation of empirical therapy

Broad-spectrum antimicrobial coverage was to be discontinued once the granulocyte count had risen to $>0.5 \times 10^9/L$ and there had been no signs and symptoms of infection for at least 2 days or for at least 5 consecutive days when neutropenia persisted.

Classification of outcome

Clinical outcome was evaluated according to the criteria of Pizzo and co-workers [3]: 'Success without

modification' was applied to any neutropenic episode which the patient survived and became free of all signs and symptoms of infection with a return of the temperature to below 37.5°C for at least 2 days without modifying the initial empirical regimen. 'Success with modification' referred to any patient who survived the neutropenic episode but for whom empirical therapy had been changed in any way other than a dosage adjustment. Patients who died because of infection were regarded as 'failures'. Each episode of empirical treatment was evaluated after 72 h of therapy and at the end of treatment.

Results

Outcome of empiric therapy

The demographic characteristics of the study population are given in Table 1. Monotherapy was shown to be as effective as a traditional combination of a

Table 1 Demography of the study population in the multicentre trial and retrospective survey

	Piperacillin+		Retrospective survey
	Ceftazidime	Tobramycin	
Assessable febrile episodes	389	395	1951
Males/females	224/165	204/191	1112/839
Mean age (years)	44.5	45.4	44
Underlying diseases			
Haematological malignancies	314 (80%)	316 (80%)	1389 (71%)
Solid tumours	14 (4%)	24 (6%)	117 (6%)
Bone marrow transplants	61 (16%)	55 (14%)	445 (23%)
Granulocytopenia			
Days granulocytes $<0.5 \times 10^9/L$	18 ± 1.5	18 ± 1.5	22 ± 2
Days granulocytes $<0.1 \times 10^9/L$	13 ± 1.3	13 ± 1.1	14 ± 1
Empirical regimens			
Monotherapy	389	0	1446 (75%)
Aminoglycoside combinations	0	395	245 (13%)
Double β -lactam combination	—	—	100 (5%)
Glycopeptide combinations	—	—	140 (7%)
Cephalosporin+ lincosamide	—	—	20 (1%)

Table 2 Survival of bacteraemia in the multicentre trial

	Ceftazidime	Piperacillin-tobramycin
Assessable febrile episodes	389	395
Bacteraemias	163	173
Gram-negative	62	61
• Survived primary infection	92%	93%
• Ultimate survivors	87%	79%
Gram-positive	101	112
• Survived primary infection	98%	95%
• Ultimate survivors	91%	87%
Clinically defined infections	41	41

broad spectrum penicillin and an aminoglycoside. At the end of treatment with ceftazidime, 35% of episodes were registered as successes, 60% of cases survived the neutropenic episode after the addition of other antibiotics, while 6% of patients died of infection. Success was achieved in 33% of episodes treated with piperacillin plus tobramycin, additional antimicrobials were given in 59% and 8% died of infection. Even within the various subgroups, including Gram-negative bacteraemias, no differences were found (Table 2, Fig. 1). In a retrospective analysis the success of monotherapy in treating infection due to Gram-negative bacilli was confirmed with eradication being achieved in 179 out of 201 (89%) cases, including 50 out of 57 (88%) due to *Pseudomonas aeruginosa*.

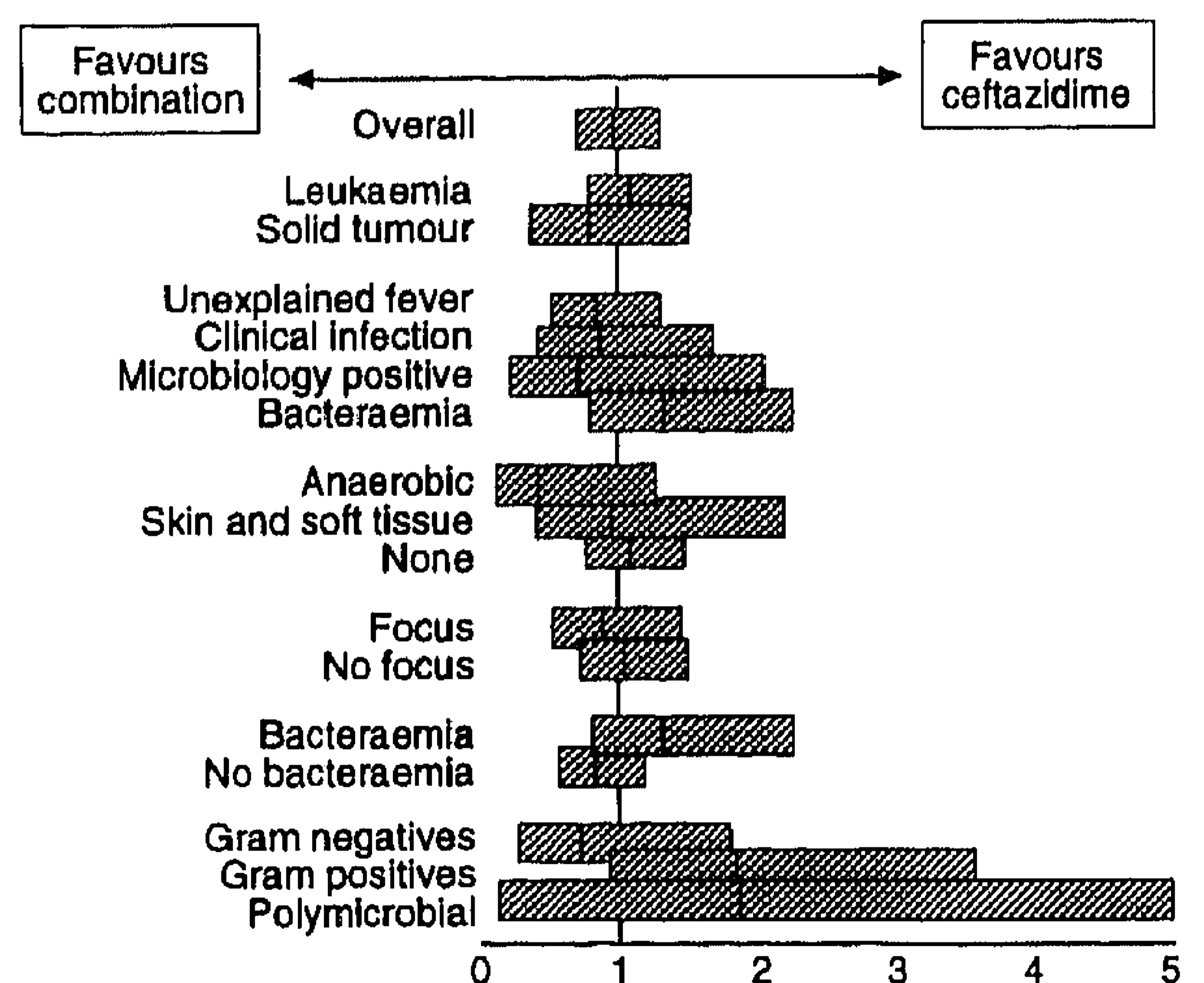


Fig. 1 Odds ratios of efficacy of two regimens in various subgroups of infection.

Relation symptoms of infection and causative micro-organisms

In the multicentre randomized trial, 113 additional patients at high risk of Gram-positive infection, namely those with skin and soft tissue infection such as cellulitis and catheter-related infections, were given vancomycin from the start to supplement the core regimens. A higher proportion of patients, allocated to receive vancomycin from the beginning, had Gram-positive bacteraemia (31%) than did those given the core regimens alone (19%), indicating that, to a certain extent, it is possible to predict the occurrence of a Gram-positive organism as cause of the infection. This prospective finding corroborates the observation from the retrospective survey where sites of infection provided a clue to the infecting organism. Many skin and soft-tissue infections were associated with prosthetic devices involving mainly slime-producing strains of coagulase-negative staphylococci. Upper respiratory tract infections featured *Candida albicans*, herpes simplex virus, viridans streptococci, enterococci or anaerobes. Bacterial infections, including those due to Gram-negative bacilli, accounted for most pulmonary infiltrates that appeared as segmental shadows whilst the majority of the focal pulmonary infiltrates were caused by fungi. Diffuse pulmonary infiltrates were related to adult respiratory distress syndrome (ARDS) following bacteraemia with *viridans streptococci*, pulmonary haemorrhage, infection due to *Pneumocystis carinii*, and, in bone-marrow transplant recipients, cytomegalovirus infec-

tion. Urinary tract infections seldom occurred and usually involved Gram-negative bacilli. In the retrospective series, the outcome of 7% of neutropenic episodes overall proved fatal but included 21% of episodes complicated by a CDI compared with 4% for episodes in which no focus of infection was identified. Pulmonary infiltrates accounted for most of the deaths, as 28% died in contrast to 7% of patients with another focus of infection.

At the onset of fever, clinical sepsis was present in 8%, a CDI in 29%, and 63% showed neither local nor systemic signs and symptoms of infection. Early changes in therapy, i.e. within 72 h, were considered necessary in 11% of cases. After this time, the number of patients without either a CDI or MDI had decreased to 41%, primarily because the results of the blood cultures had become available and revealed that bacteraemia had accompanied 19% of episodes at the onset of fever without evidence of clinical sepsis. New foci of infection had emerged in 12% of cases, mainly of the lungs. The increase in the number of lower respiratory tract infections was based on new pulmonary infiltrates on the follow-up chest radiograph.

Modification of the empirical regimen

By the end of the truly empirical phase the clinical condition had deteriorated in 10% of patients, improved in 25%, and was stable in 65% (Fig. 2). Deterioration was most prominent in patients with bacteraemia due to Gram-negative bacilli CDIs, whereas patients with unexplained fever showed improvement or were in a stable

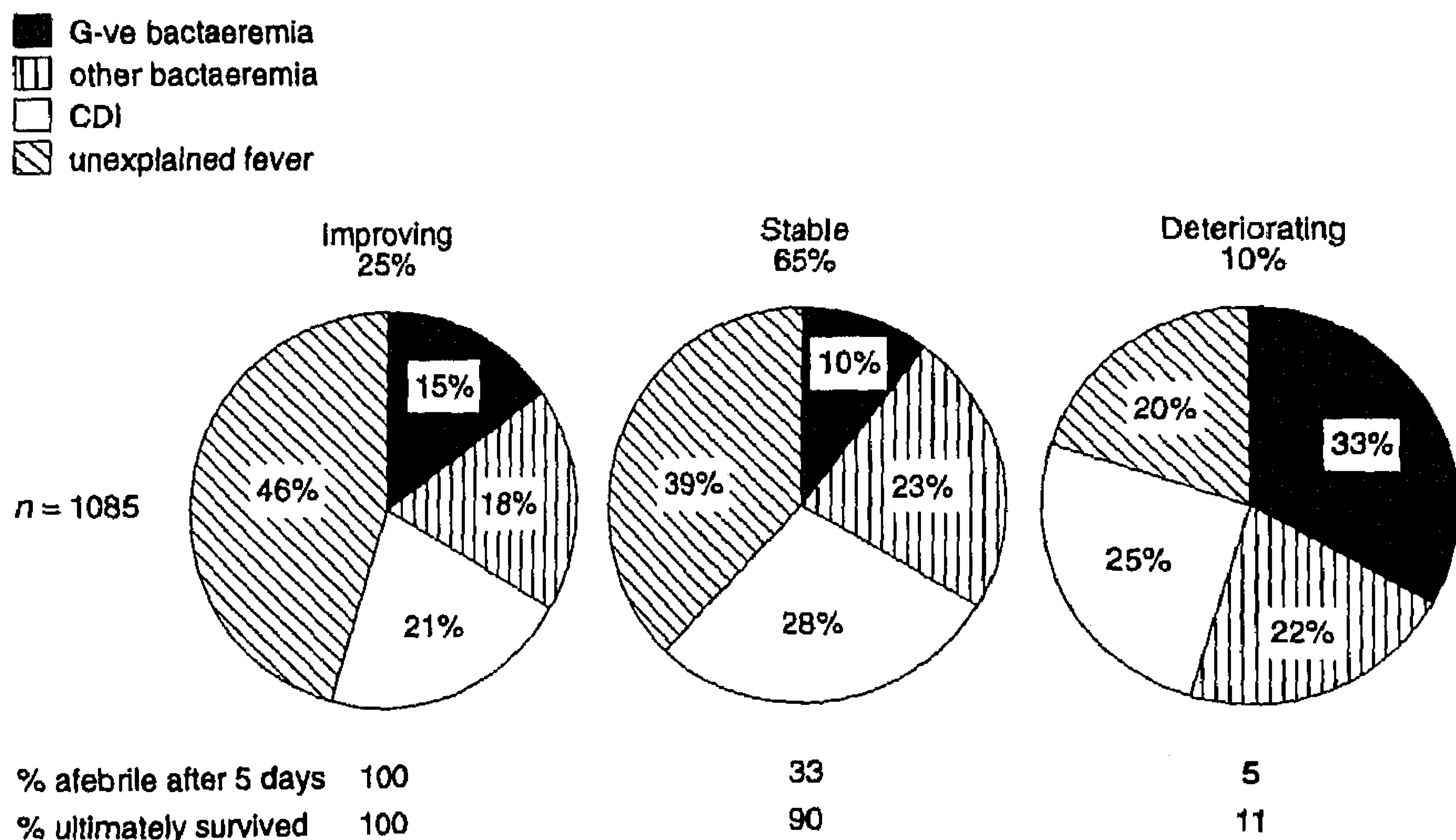


Fig. 2 Change of clinical condition after 3 days in relation to causative organisms and ultimate outcome.

condition. In contrast to the multicentre trial where antibiotics had been added in 60% of cases at the end of treatment, the empirical regimens were modified in 39% of the 1951 cases at our own institution. Seventy-six per cent of the latter modifications were classified as objectively verifiable. In patients with a lower respiratory tract infection the modification rate was to 69%, whilst adjustments were deemed necessary in 51% of cases with a skin and soft tissue infection, in 44% of the febrile episodes accompanied by abdominal complaints, and in 37% of the upper respiratory tract infections. Glycopeptides were used in 22% to complement the empirical regimen. However, empirical administration of teicoplanin for continuing fever alone resulted in a response in 33%, whereas 94% of patients with a persisting Gram-positive responded. The addition of an aminoglycoside to ceftazidime was thought necessary in only 8% of cases and systematically active antifungal agents were administered in 16% of cases.

Discussion

Numerous antibiotics, given alone or in combination have been tested in many trials on empirical antibiotic therapy but no superior regimen has been established. Three different basic strategies are presently recommended [2]: 1) a combination of a β -lactam with an aminoglycoside; 2) two β -lactam antibiotics; or 3) monotherapy with an extended spectrum β -lactam. Monotherapy is readily acknowledged to constitute adequate empirical treatment for unexplained fevers without prolonged neutropenia, but concern has been expressed about relying solely on a single agent for empirical antibiotic treatment. Indeed, most of the randomized controlled trials of empirical monotherapy, employing ceftazidime or imipenem-cilastatin, enrolled too few patients to allow a definite conclusion, although monotherapy did not lead to excess mortality, either overall or in infections caused by Gram-negative bacilli. In the meantime, larger studies, comprising a sufficient number of serious infections in high-risk patients, such as those who were treated for haematological malignancies, have shown equivalent efficacy in comparison with more traditional combinations [4,20,21]. Monotherapy was associated with fewer adverse events and appeared more cost-effective. The main objection to this approach is based on the conclusions of the Antimicrobial Study Group of the European Organisation for Research and Treatment of Cancer

(EORTC) in whose trial ceftazidime in combination with 3 days of amikacin was significantly less effective than ceftazidime in combination with a full course of amikacin, particularly in the treatment of Gram-negative infections [5]. However, the alleged superiority of the full course amikacin arm only became apparent after 3 days, a remarkable observation since, until that moment, both groups had been treated with an identical regimen and only afterwards did one of the groups receive monotherapy. This finding can be explained by the need for an additional antibiotic for fever persisting for more than 3 days was considered a failure in this trial, whereas the median duration of fever in serious infections, even with adequate antibiotic therapy is 4–5 days [4,22]. The fact that the putative difference occurred at the third and crucial day of this unblinded trial suggests that the views of the doctors towards treating serious infections with a single agent may well have exerted considerable influence. Moreover, the striking rate of defervescence in the full combination arm was never seen by other investigators, nor could it be reproduced by the EORTC itself [21,23] in later studies (Table 3).

With the variation in prevalent organisms and the availability of very broad-spectrum antibiotics it may be time to abandon the standard approach and institute a more individually tailored one (Table 4). Patients with a catheter-associated infection or other infections of the skin and soft tissues might benefit from complementing empirical therapy with a glycopeptide. If there is reason to suspect the presence of a

Table 3 Persistence of fever in relation to ultimate outcome of Gram-negative bacteraemias

Study	Percentage of patients with fever at day 3	Successful outcome at the end of treatment
EORTC 1987 [5]		
Ceftazidime + short course amikacin	36%	48%
Ceftazidime + full course amikacin	11%	81%
EORTC 1995 [21]		
Ceftazidime + full course amikacin	60%	62%
Piperacillin-tazobactam + amikacin	55%	75%
EORTC 1996 [23]		
Ceftazidime + full course amikacin	65%	54%
Meropenem alone	60%	70%
Intercontinental Study Group 1994 [4]		
Ceftazidime alone	55%	95%

Table 4 Individually tailored empirical antibiotic therapy, University Hospital Nijmegen

Clinical situation	Empirical regimen
Concurrent diseases <ul style="list-style-type: none"> ● Impaired kidney function ● Allergy for a given antibiotic ● Heart dysfunction Concomitant potentially nephro- and ototoxic drugs <ul style="list-style-type: none"> ● Colonization by resistant organism 	Ceftazidime Avoid this class of drugs Avoid drugs with high sodium contents Ceftazidime Specifically targeted prophylaxis Selection on the basis of susceptibility
No focus of infection present <ul style="list-style-type: none"> ● Slow onset of fever ● Sudden onset of fever 	Wait for culture results Ceftazidime
Focus of infection present <ul style="list-style-type: none"> ● Upper respiratory tract ● Lower respiratory tract ● Skin and soft tissue (including central venous line) ● Urinary tract ● Abdominal symptoms 	Meropenem/piperacillin-tazobactam Ceftazidime Early addition of an antifungal agent Meropenem/ceftazidime but consider adding a glycopeptide Ceftazidime Meropenem

methicillin-resistant *Staphylococcus aureus* on the basis of local patterns of resistance, a glycopeptide should be included in the initial regimen. Supplementing empirical therapy with early antifungal therapy seems warranted in patients with focal pulmonary infiltrates. However, in very severe cases of oropharyngeal infection, early use of specific agents such as clindamycin or fluconazole if there is any extension to the oesophagus manifest by retrosternal pain, may result in lower morbidity. Patients who receive other potentially nephrotoxic drugs simultaneously are primary candidates for empirical therapy with ceftazidime or meropenem as a single agent. Considering the probable involvement of anaerobes, a carbapenem or the addition of metronidazole to a standard anti-Gram-negative regimen are logical choices when fever is accompanied by abdominal symptoms. Patients who are known to be colonized by resistant Gram-negative bacilli require coverage with two appropriate antibacterial agents that do not exhibit cross-resistance. Occurrence of sepsis syndrome often reflects the presence of bacteraemia due to Gram-negative bacilli and including an aminoglycoside in the regimen should be considered in spite of the increased risk of nephrotoxicity.

Adapting the initial regimen will be the rule rather than exception in patients with prolonged neutropenia and a clinically defined infection, which is not surprising as it is virtually impossible to cover empiri-

cally every conceivable pathogen during the entire neutropenic episodes. Patients with an obvious focus of infection clearly represent a population that is more difficult to treat than do those without any focus at all [24,25]. It is generally acknowledged that patients with a lower respiratory tract infection respond poorly to standard empirical regimens, not at least because as many as 50% of infiltrates may be due to causes other than bacterial infection. Treatment failures are also commonly encountered in patients with skin and soft-tissue infections that are increasingly seen in relation to Hickman's right atrial tunnelled catheter. However, considering these infections are rarely fatal, the addition of a glycopeptide is only reasonable when there is a poor response to empirical therapy [26]. Viridans streptococci originating from the oral cavity have emerged as the leading cause of bacteraemia in patients with chemotherapy-induced mucositis. Adult respiratory distress syndrome will occur in approximately 10% of patients with bacteraemia due to *Streptococcus mitis* but not *Streptococcus oralis* particularly after high-dose cytarabine and proves fatal in approximately 60% of cases. These so-called 'alpha-strep syndromes' are almost certainly multifactorial in origin and the streptococcal infection probably triggers off sepsis syndrome when there is pre-existing tissue damage and alteration in the systemic or local immunity. Therefore, corticosteroids rather than supplementary

antibiotics should be considered to manage patients affected by this complication [27]. In many cases premature modifications are made because of continuing fever without there being any evidence of clinical deterioration or development of a defined site of infection. This probably reflects either a lack of confidence on the part of the attending physician or an attitude that is driven by the belief that 'it is better to be safe now than sorry later'. Either reason gives cause for concern because, rather than improving outcome, the liberal use of antibiotics actually increases the risk of organ toxicity, the development of resistance and superinfection, and excessive costs [28]. Consequently, a planned-progressive approach to antibiotic therapy involving adjusting the regimen every 2–3 days according to a predetermined schedule until the patient becomes afebrile seems ill advised. It ignores the individual differences between different febrile neutropenic patients and the fact that further infections can and do occur. Instead, an individually tailored approach to therapy of the febrile neutropenic patients such as we propose, seems more rational and might prove more cost-effective if this were confirmed in a formal clinical trial.

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