Pergamon

European Journal of Cancer Vol. 32A, No. 8, pp. 1332–1339, 1996

Printed in Great Britain
0959–8049/96 $15.00+0.00

PII: S0959-8049(96)00050-0

Original Paper

Early Identification of Neutropenic Patients at Risk of Gram-positive Bacteraemia and the Impact of Empirical Administration of Vancomycin

E.C. Dompeling,[1] J.P. Donnelly,[1] S.C. Deresinski,[2] R. Feld,[3] E.F. Lane-Allman[4] and B.E. De Pauw[1] for The Intercontinental Antimicrobial Study Group*

[1]Division of Hematology, University Hospital St. Radboud, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands; [2]Stanford University School of Medicine, Palo Alto, California 94062, U.S.A; [3]Princess Margaret Hospital, 500 Sherbourne Street, Toronto, Ontario, Canada M4X 1K9; [4]Glaxo Group Research Ltd, Greenford Road, Greenford, Middlesex UB6 0HE, U.K.

The aim of this multicentre randomised trial was to determine whether it was possible to predict gram-positive bacteraemia, and whether the empirical use of vancomycin would lead to reduced morbidity and mortality. 35 of 113 patients (31%; confidence interval, CI 8.5), who presented with a skin or soft tissue infection and had received empirical vancomycin in addition to either ceftazidime or piperacillin–tobramycin, had initial bacteraemia with a single gram-positive bacterium compared with 135 of the 784 (17%; CI 2.6), who presented with another infection and who had been given ceftazidime or piperacillin–tobramycin without vancomycin ($P<0.001$). Empirical vancomycin resulted in a higher rate of eradication ($P = 0.033$, relative risk 1.2), but not a better clinical outcome and was associated with more toxicity ($P=0.042$, relative risk 1.6). Irrespective of the initial treatment regimen, fever lasted an average of 8 days, the empirical regimen was modified in more than 50% of cases and mortality attributed to gram-positive infection was less than 2%. Incorporating vancomycin in the initial empirical antibiotic regimen for febrile neutropenic patients does not appear necessary, even for skin and soft tissue infections associated with gram-positive bacteraemia.

Key words: neutropenic patients, fever, gram-positive bacteraemia, skin and soft tissue infection, early identification, empirical treatment, vancomycin, ceftazidime, piperacillin–tobramycin
Eur J Cancer, Vol. 32A, No. 8, pp. 1332–1339, 1996

INTRODUCTION

DURING THE 1980s, gram-positive bacteria became increasingly more conspicuous in causing infection in neutropenic patients with cancer [1, 2]. Their increasing prominence is due to the greater use of indwelling intravenous catheters [3], the severe mucositis that results from more intensive chemotherapy and radiotherapy [4], and the widespread use of oral antibacterial prophylaxis which has reduced the incidence of gram-negative infections [5]. Since there are no reliable clinical means of distinguishing between patients with fever due to a potentially life-threatening infection from those at lesser risk, empirical antimicrobial regimens must provide adequate cover against gram-negative infections as these can prove rapidly fatal. Standard regimens consist of a β-lactam either alone or in combination with an aminoglycoside, but these are deficient in their activity against many of the common gram-positive bacteria. The glycopeptides, vancomycin and teicoplanin, are the drugs of choice for resistant gram-positive bacteria, particularly the coagulase-negative staphylococci, most of which are resistant to methicillin. While there is a general consensus that these drugs constitute an essential

Correspondence to E.C. Dompeling.
*For participating investigators and institutions we refer to: De Pauw BE, Deresinski SC, Feld R, Lane-Allmann EF, Donnelly JP. Ceftazidime compared with piperacillin and tobramycin for the empirical treatment of fever in neutropenic patients with cancer. *Ann Intern Med* 1994, 120, 834–844.
Received 14 Aug. 1995; revised 8 Jan. 1996; accepted 3 Feb. 1996.
Preliminary data were presented at the 17th International Congress of Chemotherapy, Berlin, June 1991, Abstract no. 1403.

part of the empirical regimen in centres where methicillin resistant *Staphylococcus aureus* are endemic, it is unclear whether specific anti-gram-positive therapy should always be included initially to complement the empirical regimen, given the less aggressive nature of most gram-positive infections.

Gram-positive bacteraemia accompanies approximately 20% of episodes of first fever [2, 6, 7] but, in their retrospective analysis, Rubin and colleagues observed that treatment with vancomycin was required in only 57% of these [8]. Therefore, at least 80% of febrile neutropenic patients could be overtreated with a glycopeptide antibiotic when such therapy is given routinely initially, leading to unnecessary costs, increased risk of toxicity and the potential for the development of antibiotic resistance [9, 10]. Patients at high risk of gram-positive infection may be those most likely to benefit from the empirical addition of a glycopeptide, but it is questionable whether they can be identified at the onset of fever. Based on our previous experience [11], we hypothesised that these were likely to be patients with skin and soft tissue infection such as cellulitis, catheter-related infections and other skin lesions, and so they were given vancomycin in addition to the core regimen of ceftazidime or piperacillin and tobramycin as part of a large multicentre randomised trial of the empirical treatment of fever in neutropenic patients with cancer [12]. This allowed us to determine whether is was possible to predict gram-positive bacteraemia and see whether or not the inclusion of vancomycin would lead to a decrease in morbidity and mortality.

PATIENTS AND METHODS

Study design, patient inclusion and management

From 1988 to 1989, 35 centres in Europe, Canada, the United States of America, Asia and Australia participated in a non-blinded, randomised study of the management of fever in neutropenic cancer patients. Patients older than 12 years were eligible for inclusion when febrile with a single temperature of 38.5°C or had at least two readings of >38°C taken 2 h apart, and neutropenic with a granulocyte count <500 cells/mm^3 or one that was expected to fall to this level during the next 3 days following intensive chemotherapy for leukaemia, lymphoma or other malignancies or after bone marrow transplantation. Patients who had received previous parenteral antibiotic therapy during the same neutropenic episode were excluded, as were those who were allergic to any of the trial antibiotics, whose creatinine exceeded 265 μmol/l or who only received palliative treatment for their underlying disease. All prophylactic antibacterial agents were stopped at the onset of fever, except for tuberculostatics and prophylaxis against *Pneumocystis carinii* infection with sulphamethoxazole–trimethoprim administered twice weekly. Patients were evaluated clinically before randomisation and during follow-up as previously described [12], and at least 10 ml of blood drawn from two separate venepunctures were also obtained for culture, with another 10 ml being drawn from a central venous catheter when present.

Informed consent was obtained from patients or their parents or guardians. The protocol was approved by the ethics committees of the participating institutions.

Study population

879 neutropenic patients were enrolled, with 1086 episodes of fever. Patients had been stratified into those presenting with suspected abdominal anaerobic infections or skin or soft tissue infections likely to be due to gram-positive bacteria, and those who presented with other infections who comprised the main group. One hundred and eighteen episodes had to be excluded because of protocol violations. In addition, the 71 episodes of presumed anaerobic infection were excluded from the present analysis leaving 897 assessable episodes.

Skin or soft tissue infections were apparent at the onset of 113 episodes of fever (12.6%), and, therefore, vancomycin was administered together with ceftazidime as empirical therapy in 61 cases and with the combination of piperacillin and tobramycin in the remainder. Of the 784 remaining episodes, ceftazidime was given alone in 389 episodes and piperacillin plus tobramycin was given to the rest. Treatment was discontinued once all signs and symptoms of infection had resolved for at least 2 consecutive days after the granulocyte count had risen to >500/mm^3 or for at least 5 days when neutropenia persisted.

Vancomycin treatment

One gram of vancomycin was given every 12 h. The protocol allowed for the later addition of vancomycin to ceftazidime or the combination when a clinically significant gram-positive organism was resistant to the initial empirical regimen, or persisted after at least 48 h of therapy, or when clinical deterioration occurred in the setting of presumed or proven gram-positive bacteraemia. The reason for adding vancomycin and for making all other modifications to study therapy was recorded in the case record form.

Microbiology

Bacteraemia was defined by the occurrence of similar strains of coagulase-negative staphylococci or skin coryneforms in two blood cultures or a single positive culture of any other organism. Antimicrobial susceptibility was determined by agar diffusion, and zones of inhibition of less than 18 mm in diameter indicated resistance to ceftazidime and piperacillin, and zones of less than 15 mm to tobramycin. A strain was considered resistant to the combination when resistant to both piperacillin and tobramycin. Methicillin resistance was determined according to local practice.

Assessment of efficacy

Defervescence was considered to have occurred when the temperature had returned to below 37.5°C for at least 2 days.

The clinical outcome was evaluated at the end of treatment according to the criteria previously reported [12]. If treatment had to be discontinued for reasons unrelated to infection, e.g. a non-infectious death, a case was considered 'not assessable'. Treatment leading to complete resolution of signs and symptoms of infection was considered a 'success without modification', unless other agents were given together with the empirical regimen, when empirical therapy was deemed a 'success with modification'. Only death attributable to any infection, whether primary or subsequent, was regarded as 'treatment failure'.

Eradication was defined as the absence of the original pathogen(s) from blood cultures taken during treatment. Recovery of the original pathogen after treatment was regarded as relapse. Isolation of a new pathogen from any clinical site of infection during treatment was considered a superinfection and a new infection when it was isolated after treatment.

Assessment of toxicity

All patients were assessed for toxicity and all adverse events were assessed for their relation to the study treatment by the investigator. A skin rash was considered evidence of an allergic reaction when it was temporally related to antimicrobial therapy. Nephrotoxicity was defined as an increase of at least 50% in the baseline concentrations of serum creatinine, and hepatotoxicity as a 2-fold or greater increase in baseline concentrations of bilirubin, serum transaminases or alkaline phosphatase.

Statistics

All means are presented with their 95% confidence intervals (CI). Comparison of means was made using analysis of variance and categorical data were analysed by means of the χ^2-test.

The effect of adding vancomycin to the empirical regimen on clinical outcome, eradication, toxicity and the emergence of subsequent infections was evaluated using the Mantel–Haenszel test after taking the confounding factor of each empirical regimen into account and the data were expressed as a relative risk.

RESULTS

Patient demography

The four treatment groups were similar in terms of age, sex, underlying disease, the proportion of patients given a bone marrow transplant and the degree and duration of neutropenia (Table 1). The majority of patients in all the treatment groups were managed with a central venous access device.

Gram-positive infections

Bacteraemia due to a single gram-positive organism occurred in 170 of the 897 (19%) of the first febrile episodes during neutropenia (Table 2). A higher proportion of patients allocated to receive vancomycin from the beginning had monomicrobial gram-positive bacteraemia (35 of 113, 31%; CI 8.5) than did those given the other regimen alone (135 of 784, 17%; CI 2.6, $P<0.001$). Polymicrobial bacteraemia involving gram-positive bacteria occurred twice as often amongst patients given vancomycin from the start. Coagulase-negative staphylococci, both alone and together with other bacteria, were isolated from the blood more frequently in patients that received the vancomycin-containing empirical regimens (28 of 113, 25%) than in the remainder (79 of 784, 10%; $P<0.001$).

Unfortunately, data on susceptibility testing in primary monomicrobial gram-positive bacteraemia were incomplete. Forty-one of 79 isolates of coagulase-negative staphylococci were tested for the susceptibility to the empirical regimens of which 20 (49%) were susceptible. Of the 63 isolates of coagulase-negative staphylococci tested for susceptibility to methicillin, 38 (60%) were resistant. Details are provided in Table 3. Of 12 of the 17 isolates of *Staphylococcus aureus* tested, all were susceptible to the initial regimen and resistance to methicillin was found once in 10 strains tested. Susceptibility to the empirical regimen was demonstrated in 97% of the viridans streptococci and 73% of other gram-positive organisms that were tested.

Overall clinical outcome

Infectious mortality in all treatment groups was similar (Table 4).

3 patients treated initially with ceftazidime alone (0.8%) and 6 given piperacillin and tobramycin alone (1.7%) died due to gram-positive infection, both primary and subsequent. One patient initially treated with piperacillin and tobramycin in combination with vancomycin for gram-positive infection died. Details of the fatal gram-positive infections are summarised in Table 5. Only 2 patients died of gram-positive infection within the first 72 h of empirical treatment.

Six of the deaths occurring in the ceftazidime group were caused by other bacterial infections, six by fungal infections, and one each by a viral and a *Pneumocystis carinii* infection. The deaths of patients treated with piperacillin and tobramycin as the empirical regimen were attributed to other bacteria in 6 cases, fungi in 7, virus in 1, both a fungus and a virus in 1 and to *Pneumocystis carinii* in 2 cases. The cause of death was thought to have been infectious although the cause was not determined in 4 patients treated with ceftazidime and in 6 patients treated with piperacillin and tobramycin. One of the patients treated with ceftazidime in combination with vancomycin died due to a fungal infection and 2 of presumed infection. 2 patients treated with piperacillin–tobramycin in combination with vancomycin also died, presumably due to infection.

The time to defervescence was similar for all four treatment groups and the initial antibiotic regimen was modified in the majority of cases (Table 4). However, the first modification was made significantly later in the treatment groups in which vancomycin was incorporated in the empirical regimen. Vancomycin was added to the empirical regimen of ceftazidime as first modification in 28% and as a later modification in 15% of cases and to the combination of piperacillin and tobramycin in 33% and 13%, respectively. The average number of antimicrobial agents eventually added to each of the four regimens was not different. Treatment was stopped in approximately 25% of patients while they were still neutropenic and, in the remainder, when neutropenia had resolved.

Clinical outcome of primary gram-positive bacteraemia

In the subgroup of patients who had a monomicrobial gram-positive bacteraemia at the time of randomisation, the proportion of episodes responding to the initial regimen without modification was similar in the four treatment groups, whether or not vancomycin was given empirically. Modification was deemed necessary in 33 of 56 (59%) assessable episodes treated with ceftazidime alone, 50 of 73 (68%) of episodes treated with piperacillin and tobramycin alone, and in 11 of 18 (61%) and 8 of 14 (57%) episodes treated empirically with ceftazidime and vancomycin, or piperacillin–tobramycin and vancomycin, respectively. Treatment failure, not only due to the primary gram-positive infection but also attributable to other micro-organisms causing subsequent infections, occurred in 3 of 56 (5%) and 8 of 73 (11%) of patients not treated empirically with vancomycin and, due to presumed infection, in 1 of 18 (6%) and in 1 of 14 (7%) when the glycopeptide had been incorporated in the initial regimen, together with ceftazidime or piperacillin and tobramycin, respectively.

Microbiological outcome

Overall, eradication of bacteraemia was achieved in 72 of 91 (79%) assessable cases treated with ceftazidime alone and in 73 of 107 (68%) cases treated with piperacillin and tobramycin alone. The incorporation of vancomycin in the initial empirical regimens resulted in significantly higher eradi-

Table 1. Demographic and clinical characteristics

	No empirical vancomycin (n = 784)		Empirical vancomycin (n = 113)	
	Ceftazidime (n = 389)	Piperacillin–tobramycin (n = 395)	Ceftazidime (n = 61)	Piperacillin–tobramycin (n = 52)
Age, years, mean (CI)	44.5 (1.7)	45.4 (1.8)	43.9 (4.5)	42.0 (4.7)
Sex, % males	58	52	57	46
Underlying disease				
Acute leukaemia, %	70	66	70	77
Bone marrow transplant, %	16	14	11	13
Central venous line, %	69	71	87	87
Granulocyte count at entry, %	(n = 284)	(n = 282)	(n = 42)	(n = 38)
<100/mm^3	68	67	67	66
100–500/mm^3	21	18	24	8
>500/mm^3	11	15	10	26
Duration of neutropenia, days,				
mean (CI) <500/mm^3	17.9 (1.5)	18.0 (1.4)	20.0 (4.4)	19.1 (4.1)
<100/mm^3	13.4 (1.3)	12.7 (1.1)	14.9 (2.8)	15.7 (3.8)
Granulocyte count at study end, %	(n = 323)	(n = 321)	(n = 54)	(n = 42)
<500/mm^3	24	21	24	29
Oral antibacterial prophylaxis, n (%)				
Fluoroquinolone	41 (11)	29 (7)	4 (7)	2 (4)
Co-trimoxazole	45 (12)	85 (22)	3 (5)	9 (17)
Other regimens	68 (17)	48 (12)	14 (23)	14 (27)
None	235 (60)	233 (59)	40 (66)	27 (52)
Bacteraemias, n (%)	124 (32)	138 (35)	30 (49)	25 (48)
Gram-positive	58 (15)	77 (19)	19 (31)	16 (31)
Gram-negative	45 (12)	32 (8)	3 (5)	7 (13)
Miscellaneous	3 (1)	5 (1)	0 (0)	0 (0)
Polymicrobial	18 (5)	24 (6)	8 (13)	2 (4)
Other microbiologically documented infections, n (%)	28 (7)	32 (8)	6 (10)	9 (17)
Clinically documented infections, n (%)	41 (11)	41 (10)	25 (41)	18 (35)
Unexplained fever, n (%)	196 (50)	184 (47)	—	—

Table 2. Episodes of initial gram-positive bacteraemia in relation to initial infection

	Other infections* No empirical vancomycin (n = 784)	Skin or soft tissue infection Empirical vancomycin (n = 113)	P-value
Monomicrobial gram-positive bacteraemia			
Number of episodes, (%)†	135 (17)	35 (31)	<0.001
Number of strains, (%)†			
Coagulase-negative staphylococci	57 (7)	22 (19)	
Staphylococcus aureus	13 (2)	4 (4)	
Viridans streptococci	48 (6)	8 (7)	
Other gram-positive bacteria	17 (2)	1 (1)	
Polymicrobial bacteraemia involving at least one gram-positive bacterium			
Number of episodes, (%)†	36 (5)	10 (9)	=0.09
Total no. of gram-positive strains‡	55	15	
Coagulase-negative staphylococci	22	6	
Staphylococcus aureus	2	0	
Viridans steptococci	16	5	
Other gram-positive bacteria	15	4	

*All episodes except skin or soft tissue infection. †Percentages of all episodes in the treatment group. ‡Note the number of strains exceeds the number of episodes.

Table 3. Susceptibility to the empirical regimen and to methicillin of 79 isolates of coagulase-negative staphylococci from monomicrobial bacteraemia

Methicillin	Empirical regimen: Susceptible (n = 20)	Resistant (n = 21)	Not tested (n = 38)
Susceptible (n = 25)	12	3	10
Resistant (n = 38)	2	16	20
Not tested (n = 16)	6	2	8

cation rates: 21 of 23 (91%) cases treated with vancomycin and ceftazidime and 17 of 18 (94%) cases with vancomycin in combination with piperacillin and tobramycin (P=0.033, relative risk 1.2).

Bacteriological clearance was not achieved by ceftazidime alone in 13 of 44 (30%) episodes involving a single gram-positive bacterium nor by piperacillin and tobramycin alone in 23 of 63 (37%) episodes. Bacterial persistence was encountered in 1 of 16 (6%) episodes of bacteraemia with a single gram-positive bacterium treated with vancomycin and ceftazidime empirically, and in 1 of 10 (10%) episodes treated with vancomycin, piperacillin and tobramycin empirically (P=0.013, relative risk 1.4). Coagulase-negative staphylococci persisted in 9 of 20 (45%) episodes treated with ceftazidime alone, and in 14 of 27 (52%) episodes treated with piperacillin and tobramycin. None of the coagulase-negative staphylococci persisted in patients receiving vancomycin-containing regimens.

New bacteraemia caused by *Enterococcus faecalis* occurred once after discontinuing ceftazidime alone and by coagulase negative staphylococci twice after stopping piperacillin and tobramycin.

Table 4. Overall clinical outcome

	Ceftazidime alone (n = 367)*	Piperacillin–tobramycin alone (n = 355)*	Ceftazidime and vancomycin (n = 53)*	Piperacillin–tobramycin and vancomycin (n = 45)*
Success, n (%)	127 (35)	117 (33)	22 (42)	19 (42)
Success with modification	219 (60)	209 (59)	28 (53)	23 (51)
Failure (infectious mortality)	21 (6)	29 (8)	3 (6)	3 (7)
Attributable to gram-positive infection	3 (0.8)	6 (1.7)	0 (0)	1 (2)
Days to no fever, mean (CI)	7.6 (0.8)	7.5 (0.7)	7.7 (2.2)	8.0 (2.2)
Days on study	17.0 (1.1)	16.6 (1.1)	18.3 (3.1)	18.3 (3.4)
Days to first modification†	6.5 (0.6)	5.9 (0.5)	8.8 (1.5)	9.3 (2.3)
Number of modifications	2.5 (0.2)	2.6 (0.2)	2.5 (0.8)	1.8 (0.4)

*Number of assessable episodes. †P<0.001 (analysis of variance).

Table 5. Mortality attributable to gram-positive infections

Empirical regimen	Organism	Susceptibility to empirical regimen	Susceptibility to methicillin	Attributable cause of death	Day died*
Ceftazidime alone	*E. faecalis, C. freundii*	Resistant	n.t.	Primary bacteraemia	2
	Coagulase-negative straphylococci	Resistant	Resistant	Primary bacteraemia	8
	Enterococcus spp	n.t.†	n.t.	Superinfection	7
Piperacillin–tobramycin alone	*S. aureus*	n.t.	Resistant	Primary bacteraemia	2
	Coagulase-negative staphylococci	n.t.	Susceptible	Primary bacteraemia	4
	viridans streptococcus	Susceptible	n.t.	ARDS following primary bacteraemia	7
	viridans streptococcus	Susceptible	n.t.	ARDS following primary bacteraemia	8
	S. pneumoniae, Acinetobacter spp	Susceptible	n.t.	Primary bacteraemia	4
	Lactobacillus spp	n.t.	n.t.	Superinfection with bacteraemia and pneumonia	41
Piperacillin–tobramycin and vancomycin	*S. aureus*	n.t.	Resistant	Superinfection with pneumonia	14

*Day after empirical therapy was begun. †Not tested. ARDS, acute respiratory distress syndrome.

Adverse experiences

Superinfection rates were similar whether they initially received vancomycin as part of the empirical regimen (ceftazidime and vancomycin: 15%, piperacillin and tobramycin and vancomycin: 8%) or not (ceftazidime alone: 10%, piperacillin and tobramycin alone: 10%). The number of gram-positive organisms cultured from the blood or lung during antimicrobial therapy was similar in all treatment groups; 19 isolates (ceftazidime alone), 10 (piperacillin and tobramycin alone), 3 (ceftazidime and vancomycin) and one (piperacillin, tobramycin and vancomycin).

4 patients treated with ceftazidime alone died of fungal superinfection as did 8 who had received piperacillin and tobramycin alone, and one who had been given ceftazidime and vancomycin empirically.

The empirical use of vancomycin was associated with added toxicity (Table 6) (P=0.042, relative risk 1.6), but there were no statistically significant differences in the types of adverse events.

DISCUSSION

Within the context of a large multicentre trial of the management of febrile, neutropenic patients with particularly haematological malignancies, we were able to identify a group of patients with a skin or soft tissue infection who were twice as likely to have bacteraemia due to gram-positive bacteria, particularly the coagulase-negative staphylococci, solely on the basis of their presenting clinical symptoms. This illustrates the fact that, even at the onset of fever, febrile neutropenic patients do not comprise a homogenous population. Microbiologically defined infection, including those accompanied by bacteraemia, clinically defined infection and unexplained fever each account for approximately a third of febrile neutropenic episodes [2, 11]. The lower respiratory tract accounts for almost 60% of the cases presenting with clinically manifest infection at the onset of fever or later, skin and soft tissue lesions contribute almost 20% and the remainder are equally divided between the upper respiratory tract and other sites [13]. Approximately 4% of episodes without a focus of infection culminate in death in comparison with 21% of episodes in which a focus is identified. This difference can be explained by the high mortality rates associated with pulmonary infiltrates and the subsequent development of evident foci of infection [13]. Also, after excluding urinary tract infection, the presence of an infectious focus is associated with a significantly longer duration of fever in response to which treatment is prolonged, resulting in more frequent modification of the empirical regimen [11]. Thus, patients with a clinically defined infection clearly represent a different population from those without any clinically identifiable infection focus. Moreover, certain sites of infection, such as those involving the skin or soft tissue may provide a clue to the causative organism, as was demonstrated in this study. Therefore, given the variety of factors including local circumstances, cultures results and clinical condition that are cited as a basis for individualising treatment, it seems surprising that the presenting signs and symptoms of infection have been largely ignored especially as this might lead to a needless delay in selecting appropriate antimicrobial therapy.

In the present study, patients presenting initially with a skin or soft tissue infection were assigned non-randomly to an empirical antibiotic regimen which included vancomycin. Those without a skin or soft tissue infection served as a control group for assessing the impact of adding the glycopeptide since they too developed gram-positive bacteraemia. Apart from the presenting focus of infection, the treatment groups were well balanced for demographic and clinical characteristics. Gram-positive bacteria persisted in the bloodstream of patients treated empirically without vancomycin more often than in those given the drug from the start, yet the inclusion of the glycopeptide had little impact on the clinical outcome.

No patient given vancomycin empirically died as a result of primary bacteraemia with gram-positive bacteria but 7 of the patients treated with the empirical regimens that did not include the glycopeptide proved fatal due to primary bacteraemia and another 2 due to superinfections with gram-positive bacteria. Despite the fact that vancomycin was included in the initial regimen, 1 patient died from a gram-positive superinfection.

One patient given piperacillin and tobramycin without vancomycin died of a primary infection with a methicillin-resistant *Staphylococcus aureus*. It is unlikely that this death could have been prevented, given the fact that it occurred within 48 h of starting therapy. The virulence of methicillin-resistant *Staphylococcus aureus* was further demonstrated by the death of a patient who developed a superinfection due to this organism

Table 6. Toxicity

	Ceftazidime alone (n = 389)	Piperacillin–tobramycin alone (n = 395)	Ceftazidime and vancomycin (n = 61)	Piperacillin–tobramycin and vancomycin (n = 52)
All patients with adverse events, n (%)*	30 (8)	78 (20)	11 (18)	12 (23)
Adverse events				
Allergy†	18 (5)	37 (9)	8 (13)	4 (8)
Gastro-intestinal	1 (<1)	5 (1)	1 (2)	0 (0)
Hepatotoxicity	5 (1)	3 (1)	2 (3)	0 (0)
Nephrotoxicity‡	3 (1)	34 (9)	1 (2)	7 (13)
Ototoxicity	0 (0)	4 (1)	0 (0)	1 (2)

*P=0.042. †P=0.143. ‡P=0.195 (Mantel–Haenszel test).

despite having received empirical therapy with vancomycin. 2 patients died after developing acute respiratory distress syndrome following primary bacteraemia due to viridans streptococci despite being treated with piperacillin, a ureidopenicillin that is active *in vitro* against streptococci, although no follow-up cultures were taken to show the organism was eradicated. However, it is doubtful whether antibiotic therapy alone, even if it includes vancomycin, would have prevented this manifestation of sepsis syndrome since patients who develop acute respiratory distress syndrome following bacteraemia with viridans streptococci require adjunctive therapy with corticosteroids [14]. Moreover, giving high-dose corticosteriods to complement the antimicrobial treatment of bacteraemia due to *Streptococcus mitis* may prove more effective in pre-empting the development of acute respiratory distress syndrome by suppressing the mechanisms that induce the syndrome [15]. The death of 1 of the 2 patients treated without vancomycin who died as a result of superinfection with gram-positive bacteria may have been inevitable since lactobacilli were involved in this fatal case and the addition of vancomycin would have had little impact, since these bacteria are only marginally susceptible to the glycopeptides [16]. Therefore, even if vancomycin had been included in the empirical regimen, some of these deaths would still have been unavoidable. In addition, randomised studies of ceftazidime monotherapy [6, 7] and combination antibiotic therapy [2] have failed to demonstrate any survival advantage for patients treated with a glycopeptide antibiotic at the onset of fever.

The empirical use of vancomycin did not result in lower morbidity nor accelerate resolution of infection since the duration of fever was also comparable, whether or not patients were initially treated with the glycopeptide as has been reported in other studies [2, 6, 7]. Furthermore, the use of vancomycin is not without additional renal toxicity [2, 6].

Therapy was modified significantly later for those patients already treated empirically with vancomycin, as would be expected since vancomycin is the drug most commonly added to the initial regimen, but there was no difference in the average number of antimicrobials eventually employed. Also, once treatment with vancomycin has been started, instituting empirical antifungal therapy for persistent fever becomes more likely, reflecting the dwindling possibilities for further treatment modifications rather than any increase in incidence of proven or suspected fungal infections [2].

It was also customary in the present study to add vancomycin once a gram-positive organism was isolated, and, even more frequently, because of persistent fever. It might be argued that this was justified for infection involving coagulase-negative staphylococci since only half of the isolates proved to be susceptible to ceftazidime or the combination of piperacillin and tobramycin. However, half of these bacteria had already been eradicated by these regimens before vancomycin was added, indicating that the results of follow-up cultures were either not known at the time or ignored. Moreover, it has been demonstrated previously that adding a glycopeptide empirically is not only futile because it can be shown to be effective only for patients with microbiologically or clinically defined gram-positive infection [17], but it can also contribute to the emergence of vancomycin-resistant enterococci, particularly after prolonged treatment with the glycopeptide [10].

In conclusion, incorporating vancomycin in the initial empirical antibiotic regimen for febrile neutropenic patients does not appear necessary, even for skin and soft tissue infections associated with gram-positive bacteraemia. Rather, all the data suggest that empirical treatment with a glycopeptide is only essential in centres where methicillin-resistant *Staphylococcus aureus* are a significant endemic problem and that vancomycin should only be added when there are clear, objective grounds for doing so. This necessitates daily clinical examination, relevant microbiological investigations and regular and timely review of the information gathered in order to a make a definitive diagnosis and employ the most suitable treatment. However, this demands no more than is considered good clinical practice and should help save unnecessary costs and keep adverse experiences to a minimum.

1. EORTC International Antimicrobial Therapy Cooperative Group. Gram-positive bacteraemia in granulocytopenic cancer patients. *Eur J Cancer* 1990, **26**, 569–574.
2. EORTC International Antimicrobial Therapy Cooperative Group and the National Cancer Institute of Canada-Clinical Trials Group. Vancomycin added to empirical combination antibiotic therapy for fever in granulocytopenic cancer patients. *J Infect Dis* 1991, **163**, 951–958.
3. Press OW, Ramsey PG, Larson EB, Fefer A, Hickman RO. Hickman catheter infections in patients with malignancies. *Medicine* 1984, **63**, 189–200.
4. Cohen J, Donnelly JP, Worsley AM, Catovsky D, Goldman JM, Galton DAG. Septicaemia caused by viridans streptococci in neutropenic patients with leukaemia. *Lancet* 1983, **2**, 1452–1454.
5. Karp JE, Merz WG, Hendricksen C, *et al.* Oral norfloxacin for prevention of gram-negative bacterial infections in patients with acute leukemia and granulocytopenia. *Ann Intern Med* 1987, **106**, 1–7.
6. Ramphal R, Bolger M, Oblon DJ, *et al.* Vancomycin is not an essential component of the initial empiric treatment regimen for febrile neutropenic patients receiving ceftazidime: a randomized prospective study. *Antimicrob Agents Chemother* 1992, **36**, 1062–1067.
7. Nováková IRO, Donnelly JP, De Pauw BE. Ceftazidime as monotherapy or combined with teicoplanin for initial empiric treatment for presumed bacteremia in febrile granulocytopenic patients. *Antimicrob Agents Chemother* 1991, **35**, 672–678.
8. Rubin M, Hathorn JW, Marshall D, Gress J, Streinberg SM, Pizzo PA. Gram-positive infections and the use of vancomycin in 550 episodes of fever and neutropenia. *Ann Intern Med* 1988, **108**, 30–35.
9. Schwalbe RS, Stapleton JT, Gilligan PH. Emergence of vancomycin resistance in coagulase-negative staphylococci. *N Engl J Med* 1987, **316**, 927–931.
10. Frieden TR, Munsiff SS, Low DE, *et al.* Emergence of vancomycin-resistant enterococci in New York City. *Lancet* 1993, **342**, 76–79.
11. De Pauw BE, Donnelly JP, Elves A, Verhagen C, Nováková IRO, Van der Meer JWM. Towards individually tailored empiric antibiotic therapy in febrile granulocytopenic patients. *Neth J Med* 1990, **37**, 111–119.
12. De Pauw BE, Deresinski SC, Feld R, Lane-Allman EF, Donnelly JP. Ceftazidime compared with piperacillin and tobramycin for the empiric treatment of fever in neutropenic patients with cancer. A multicenter randomized trial. *Ann Intern Med* 1994, **120**, 834–844.
13. Nováková IRO, Donnelly JP, De Pauw BE. Potential sites of infection that develop in febrile neutropenic patients. *Leukemia Lymphoma* 1993, **10**, 461–467.
14. Arning M, Gehrt A, Aul C, Runde V, Hadding U, Schneider W. Septicemia due to *Streptococcus mitis* in neutropenic patients with acute leukemia. *Blut* 1990, **61**, 364–368.
15. Dompeling EC, Donnelly JP, Raemaekers JMM, De Pauw BE. Pre-emptive administration of corticosteroids prevents the development of ARDS associated with *Streptococcus mitis* bacteremia following chemotherapy with high-dose cytarabine. *Ann Hematol* 1994, **69**, 69–71.

16. Patel R, Cockerill FR, Porayko MK, Osmon DR, Ilstrup DM, Keating MR. Lactobacillemia in liver transplant patients. *Clin Infect Dis* 1993, **18**, 207–212.
17. Nováková IRO, Donnelly JP, Verhagen CS, De Pauw BE. Teicoplanin as modification of initial empirical therapy in febrile granulocytopenic patients. *J Antimicrob Chemother* 1990, **25**, 985–993.

Acknowledgements—This work was funded by Glaxo Group Research Ltd, Greenford, Middlesex, U.K. and its local subsidiaries.