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Article

Factors Associated with Improved Outcome of *Pseudomonas aeruginosa* Bacteremia in a Finnish University Hospital

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Abstract All 134 episodes of bacteremia caused solely by *Pseudomonas aeruginosa* in a university hospital in the periods 1976–1982 and 1992–1996 were reviewed retrospectively to determine the clinical manifestations, outcome and prognostic factors. The mortality for the 30-day interval after drawing the first positive blood culture was 41%, but dropped from 53% in the first period to 29% in the second period ($P=0.006$). Mortality was highest in patients treated with an aminoglycoside only, as against those treated with other appropriate antibiotics (55% versus 25%, $P=0.001$). Over the two decades studied, use of an aminoglycoside only decreased, use of paracetamol (=acetaminophen) increased, and removal of both urinary and blood vessel catheters became more common. The mortality was 18% in patients with catheter removal (46% in the other patients, $P=0.017$) and 27% in patients who received paracetamol around the time of drawing the first positive blood culture (50% for the other patients, $P=0.010$). Logistic regression analysis showed that shock, central nervous system involvement, preceding thromboembolism and rapidly fatal underlying disease were associated with a fatal outcome, whereas catheter removal, appropriate antibiotic therapy and paracetamol therapy were associated with survival. The improved prognosis of *Pseudomonas aeruginosa* bacteremia over the two decades is thus due mainly to three changes in management of the infection: the more frequent use of new anti-pseudomonal β-lactams and ciprofloxacin instead of aminoglycosides as monotherapy; the more frequent practice of removing catheters; and the increased use of paracetamol around the time of drawing the first positive blood sample.

Introduction

The absolute number of cases of *Pseudomonas aeruginosa* bacteremia has not decreased over the last few decades, despite the increased proportion of gram-positive organisms isolated from blood cultures [1–5]. *Pseudomonas aeruginosa* is still primarily a nosocomial pathogen, although the number of cases of community-acquired bacteremia caused by the organism has increased [6]. The predisposing conditions include compromised immunity, intensive care, respirator therapy, surgical procedures, catheters of various kinds and previous antibiotic therapy [7–12]. The three main portals of entry are the urinary tract, the respiratory tract and in situ intravenous catheters [6–12]. Mortality resulting from *Pseudomonas aeruginosa* bacteremia has declined from 64% in the early 1970s to 18% in the early 1990s [7, 12, 13], but the reasons for this have not yet been determined. The factors predictive of a fatal outcome vary from study to study, and include shock, neutropenia, severe underlying disease, inappropriate antibiotic therapy and antibiotic therapy with a single drug, especially an aminoglycoside [7–10, 12–16].

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The aim of this study was to assess the clinical manifestations, outcome and prognostic factors associated with *Pseudomonas aeruginosa* bacteremia, and to evaluate any changes in these factors over the last 21 years in a university hospital.

Patients and Methods

Patients. All 134 cases of *Pseudomonas aeruginosa* bacteremia evaluated in this study were diagnosed at Meilahti Hospital, which is part of the Helsinki University Central Hospital. Meilahti Hospital has about 700 medical and surgical beds for adult patients (>15-years-old). The record of every case with one or more blood cultures positive for *Pseudomonas aeruginosa* in the periods 1976–1982 and 1992–1996 was reviewed retrospectively. Cases were included in the analysis if at least one blood culture was positive (growth of *Pseudomonas aeruginosa* in either an aerobic or anaerobic culture bottle) and the clinical features were compatible with sepsis. Cases of polymicrobial bacteremia or bacteremia caused by another agent within the preceding or following month were excluded from the analysis (a total of 63 cases with no difference between the two periods), as were a few cases in which blood samples for culture were obtained only through access devices and not by peripheral venipuncture. All patient records were available.

Laboratory Methods. Blood samples were cultured in aerobic and anaerobic blood culture bottles throughout the whole study period (Hemobact A and B, Orion Diagnostica, Finland 1977–1993; BacTAlert, Organon Teknika, USA). Sensitivity was tested by the disk diffusion method (AB Biodisk, Sweden, 1977–1978; Rosco, Denmark, 1979–1994; Oxoid, UK, 1995–1996) applying breakpoints corresponding to MIC values; if necessary, the results were confirmed by MIC determination (Sensititre; Sensititre Product, UK). The MIC breakpoints for susceptibility and resistance conformed with the NCCLS standards [17].

Categories and Definitions. Underlying diseases were grouped into four classes according to the principle of differential prognoses introduced by McCabe and Jackson [20], and as applied in a previous study of ours [21].

Nosocomial infection was defined as infection in which signs and symptoms appeared more than 48 h after admission to hospital or there was a confirmed hospital-acquired portal of entry (e.g. an infected operation wound).

The following were considered to be complications: shock (systolic blood pressure <90 mmHg or intravenous vasopressor treatment required); respiratory insufficiency (respirator therapy required); acidosis (pH <7.3 more than once); disseminated intravascular coagulation (DIC), (thrombocytopenia, i.e. blood platelet count $<100\times10^9$/l, accompanied by fibrin degradation products and/or a positive ethanol gelation test and/or elevated D-dimer concentration); central nervous system (CNS) involvement (lowered level of consciousness, confusion or focal neurological signs).

Antimicrobial therapy was defined as appropriate if the strain isolated was susceptible to the antibiotic given and the doses were adequate, as shown by the dosage and the serum concentrations measured, assuming this information was available. Antimicrobial therapy was regarded as combination therapy if two antibiotics were given and the strain isolated was susceptible to both. The first appropriate antibiotic given was listed as the definitive therapy if continued for at least 7 days or until death of the patient within that time. If a second appropriate antibiotic was given within 7 days of the start of the first, the second antibiotic was listed as the definitive therapy. Combination therapy was listed as the definitive therapy if started within 7 days of the start of the first appropriate antibiotic. Thus, if the first antibiotic was replaced by a second antibiotic for a few days and then by an antibiotic combination within 7 days of the start of the first appropriate antibiotic, the combination was listed as the definitive therapy.

Administration of nonsteroidal anti-inflammatory drugs (NSAIDs) or antipyretic agents was recorded for the period up to 24 h before and 48 h after drawing the first positive blood sample.

The severity of illness at the time of drawing the first positive blood culture (±18 h) was scored applying clinical criteria modified from those described elsewhere [22, 23]. Points were allotted as follows: *mental status*: disorientation = 1; lowered level of consciousness with reaction to speech = 2; lowered level of consciousness with reaction only to physical stimulus = 3; unconsciousness = 4; *blood pressure*: systolic blood pressure <90 mmHg = 1; requirement for intravenous vasopressor agents = 2; *respiratory status*: continuous positive airway pressure ventilation = 1; respirator therapy = 2; *cardiac rhythm*: sinus tachycardia of ≥120 beats/min = 1; atrial fibrillation, ventricular extrasystole or other less severe arrhythmias = 1; ventricular tachycardia = 2; cardiac arrest = 4; *temperature*: 36–37.5 °C = 0; 37.6–39.9 °C = 1; ≥40 °C or <36 °C = 2.

Statistical Methods. For statistical analysis patients were divided into subgroups in two ways: (i) cases occurring in the period 1976–1982 and cases occurring in the period 1992–1996; (ii) patients who died within a month of documentation of a positive blood culture and patients who survived. The statistical methods used for categorized variables were Pearson's chi-square test, with Yates' correction if needed, and Fisher's two-tailed exact test; for continuous variables, the Mann-Whitney U test and the Kruskal-Wallis test; and for life tables, the Mantel-Cox test. Logistic regression analysis was used to determine independent risk factors for death. Selection of variables for the final analysis was done in two steps. In the first step, the significant variables from the univariate analyses were analysed as subgroups in separate models. In the second step, the significant factors obtained from these models were combined in the semifinal model. The significant factors obtained from this model were then combined with the classical prognostic factors old age and rapidly fatal underlying disease for the final analysis. A P value of 0.05 or less was considered significant. Computations were done with BMDP programmes [18, 19].

Results

Comparison of the Study Periods. Overall, 134 episodes of *Pseudomonas aeruginosa* bacteremia in 132 patients were analysed, 66 in the first period (1976–1982), and 68 in the second period (1992–1996). None of the patients had been completely healthy previously: 56% had rapidly fatal diseases, 34% ultimately fatal diseases and 10% non-fatal diseases. While these proportions persisted over the 21 years, the frequency of some underlying factors differed between the two study periods (Table 1).

Urinary tract infections were more common during the first period: 41% versus 22%, $P=0.019$. Otherwise the frequencies of foci of infection were similar for the two periods: pneumonia in 48% of cases, deep abscesses (other than renal) in 7%, pancreatitis in 6%, peritonitis in 6%, cholangitis or cholecystitis in 5%, renal

Table 1 Main underlying diseases and predisposing factors in patients with *Pseudomonas aeruginosa* bacteremia in the periods 1976–1982 and 1992–1996

Underlying factor	Number (%) of cases			*P* value
	1976–1982	1992–1996	Total	
Age				
<40 years	14 (21)	5 (7)	19 (14)	
40–60 years	25 (38)	28 (41)	53 (40)	
>60 years	27 (41)	35 (52)	62 (46)	
Male gender	46 (70)	39 (57)	85 (63)	
Nosocomial infection	59 (89)	61 (90)	120 (90)	
Antibiotic therapy[a]	56 (85)	61 (90)	117 (87)	
Intravenous or arterial catheter[b]	51 (77)	52 (76)	103 (77)	
Urinary catheter[b,c]	32 (49)	35 (51)	67 (50)	
Cardiovascular disease	31 (47)	32 (47)	63 (47)	
Invasive procedure[a]	25 (38)	31 (46)	56 (42)	
Renal or urological disease	27 (41)	25 (37)	52 (39)	
Systemic corticosteroid therapy[a]	28 (42)	22 (32)	50 (37)	
Cytotoxic therapy[a]	24 (36)	23 (34)	47 (35)	
Hepatobiliary or pancreatic disease	20 (30)	25 (37)	45 (34)	
Hematological malignancy	24 (36)	21 (31)	45 (34)	
Surgery[a]	19 (29)	27 (40)	46 (34)	
Granulocytopenia[b,d]	18 (27)	19 (28)	37 (28)	
Respirator therapy	17 (26)	16 (24)	33 (25)	
Intensive care therapy[b]	15 (23)	17 (25)	32 (24)	
Other infection	18 (27)	14 (21)	32 (24)	
Radiation therapy[e]	6 (9)	19 (28)	25 (19)	0.005
Parenteral nutrition	15 (23)	10 (15)	25 (19)	
Thromboembolic event	15 (23)	8 (12)	23 (17)	
Alcohol abuse	10 (15)	13 (19)	23 (17)	
Nonhematological malignancy	6 (9)	15 (22)	21 (16)	0.039
Chronic obstructive pulmonary disease	2 (3)	10 (15)	12 (9)	0.018

[a] In the month preceding the first positive blood culture
[b] In the two weeks preceding the first positive blood culture
[c] Both indwelling catheters and repeated short term catheters
[d] Granulocyte count $<1.0\times10^9$/l
[e] At any time in the past

abscesses in 2%, endocarditis in 2%, infected intravascular catheters in 7%, other foci in 22%, and no known foci in 16%.

Of the 134 patients, 131 received antibiotics, 111 of these being appropriate. Of the 20 patients given inappropriate antibiotics, 11 received the drugs in the first period and 9 in the second period. Three patients in the first period were not treated. Both the initial and definitive antibiotics used for therapy differed between the two study periods (Table 3). Combination therapy consisted mainly of a β-lactam plus an aminoglycoside, but the combination of a β-lactam plus ciprofloxacin was also used with increasing frequency. The overall duration of antimicrobial treatment in the patients who survived was similar in each period (mean 23 days, SD $\pm$ 17, range 0–81).

NSAIDs or antipyretic agents were given to 66% of the patients. This proportion increased from the first period to the second (55% versus 77%, $P=0.010$). The most frequently used antipyretic drug was paracetamol (38%), the use of which also increased (22% versus 54%, $P=0.001$). Ten percent of patients were treated with granulocyte growth-stimulating agents, all in the 1990s. Intravenous or indwelling urinary catheters were removed in 16% of the patients, less often in the first period (9% versus 24%, $P=0.024$). Nine of the 24 catheters were removed because of a confirmed local infection. In both periods, 30% of the patients were treated in an intensive care unit.

The severity of illness at the time of drawing the first positive blood sample did not differ between the two periods, 66% of the patients scoring ≤ 2 points, 15% 3 or 4 points, and 19% >4 points. Fifty-six percent of the patients had at least one of the following complications: CNS involvement (49%), shock (39%), respiratory insufficiency (35%), acidosis (22%) or DIC (4%). These figures were similar for the two periods. Arrhythmia was found in 13% of the patients. Thromboembolic complications were more frequent during the first period (21% versus 7%, $P=0.022$). Of the 79 patients who survived, six later experienced a relapse of the sepsis.

Overall mortality within 1 month of drawing the first positive blood culture was 41%, decreasing from 53% in the first period to 29% in the second period ($P=0.006$). Of the 55 deaths, 18 occurred on the day of drawing the first positive blood culture, 10 during the next 2 days, 9 during the next 4 days, and 18 from 1

Table 2 Prognostic factors for mortality in patients with *Pseudomonas aeruginosa* bacteremia in the periods 1976–1982 and 1992–1996

Factor(s)	No. of deaths/ no. of patients	Mortality (%)	Odds ratio	*P* value[a]
Seriousness of underlying disease				<0.0001
Non-fatal	1/13	8		
Ultimately fatal	8/46	17		
Rapidly fatal	46/75	61		
Underlying conditions				
Recent thromboembolism	18/23	78	7.2	0.0001
Hepatic cirrhosis	4/4	100		0.0266
Obstructive urinary disease	3/22	14	0.2	0.0043
Focal infection				
Cholecystitis or peritonitis	10/14	71	4.2	0.0146
Urinary tract infection	11/42	26	0.4	0.0182
Preceding treatment				
Parental nutrition	17/25	68	4.0	0.0024
Non-urological surgery	17/27	63	3.1	0.0096
Intensive care[c]	19/32	59	2.7	0.0157
Intubation[c]	16/27	59	2.5	0.0313
Systemic corticosteroids[d]	28/51	55	2.5	0.0106
Current treatment				
NSAID[e,f]	27/88	31	0.3	0.0005
Paracetamol	14/51	27	0.4	0.0102
Growth factor	2/14	14	0.2	0.0315
Catheter removal	4/22	18	0.3	0.0171

[a] All *P* values were determined by Pearson's chi-square test with Yates' correction if needed, and Fisher's two-tailed exact test
[b] Classification of McCabe and Jackson [20]
[c] In the 2 weeks preceding the first positive blood culture
[d] In the 3 months preceding the first positive blood culture
[e] Including paracetamol
[f] Within 24 h before and 48 h after the first positive blood culture

week to 1 month later. The two periods were similar in this respect. Of the 18 patients who died 1 week to 1 month later, nine died of the *Pseudomonas aeruginosa* bacteremia, and this infection was a factor contributing to the death of most of the other nine patients.

Prognostic Factors. The outcome was not age or sex related, and mortality in the nosocomial cases did not differ from that in the community-acquired cases. The underlying conditions and current treatments (except antibiotic therapy) associated with differences in the mortality are shown in Table 2.

Only four patients were afebrile during the whole bacteremic episode (maximum temperature $<37.5\,^{\circ}C$). Three of these patients died, as did 11 of the 16 patients who were afebrile at the time of drawing the first positive blood culture (± 18 h; $P=0.016$).

Of the three patients who received no antibiotic treatment, only one died, while 15 of the 20 patients receiving inappropriate antibiotics died. Thus, altogether 16 of the 23 patients not receiving appropriate antimicrobial therapy died (70% versus 35% of the patients receiving appropriate antibiotic, $P=0.002$). Twenty-four (41%) of the 58 patients who first received an inappropriate antibiotic later replaced by an appropriate antibiotic died, the mortality rate being the same as in those treated with an appropriate antibiotic from the outset. Moreover, the interval between drawing the first positive blood culture and the start of appropriate antibiotic treatment did not differ between survivors and non-survivors (0.21 ± 4.0 days versus -0.08 ± 3.7 days). The different antibiotics used for initial treatment were not associated with differences in mortality. However, comparison of antibiotics used for definitive treatment showed that aminoglycoside monotherapy was associated with a significantly higher mortality (Table 3, Figure 1).

Mortality was associated with the severity of illness, 25% of the patients with a score of ≤ 2 points, 55% of those with a score of 3 to 4 points, and 85% of those with a score of >4 points dying ($P<0.0001$).

Patients receiving paracetamol had a better prognosis than those who did not (Table 2, Figure 2). This difference was also observed in the 68 patients in the second study period, 6 (16%) of the 37 paracetamol-treated patients dying versus 26 (84%) of the others ($P=0.009$). Moreover, the scores for severity of illness in the paracetamol-treated and untreated groups did not differ.

Mortality in patients with complications was 71% versus 3% in patients without ($P<0.0001$). In patients

Table 3 Appropriate definitive antimicrobial therapy[a] in patients with *Pseudomonas aeruginosa* bacteremia in the periods 1976–1982 and 1992–1996

Definitive therapy	Number (%) of cases			
	1976–1982	1992–1996	Total*	Deaths (%)**
Aminoglycosides	34 (65)	4 (7)	38 (34)	21 (55)
Antipseudomonal β-lactams	2 (4)	19 (32)	21 (19)	6 (29)
Carbenicillin, piperacillin (+tazo)	2 (4)	2 (3)	4 (4)	2 (50)
Ceftazidime	0 (0)	9 (15)	9 (8)	2 (22)
Imipenem, meropenem	0 (0)	8 (14)	8 (7)	2 (25)
Combination therapy	16 (31)	25 (42)	41 (37)	11 (27)
Ciprofloxacin	0 (0)	11 (19)	11 (10)	1 (9)

[a] See definition in methods section
* $P<0.0001$ for the differences between the two periods
** $P=0.009$ for the differences in mortality between the four main antibiotic groups mentioned

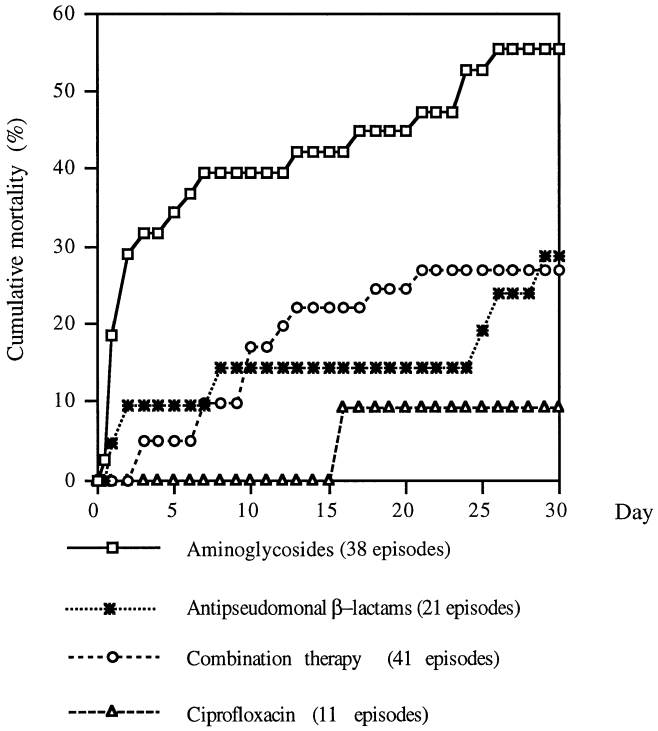

Figure 1 Cumulative mortality for 111 episodes of *Pseudomonas aeruginosa* bacteremia treated with appropriate antibiotics ($P=0.003$ in the Mantel-Cox test for life tables)

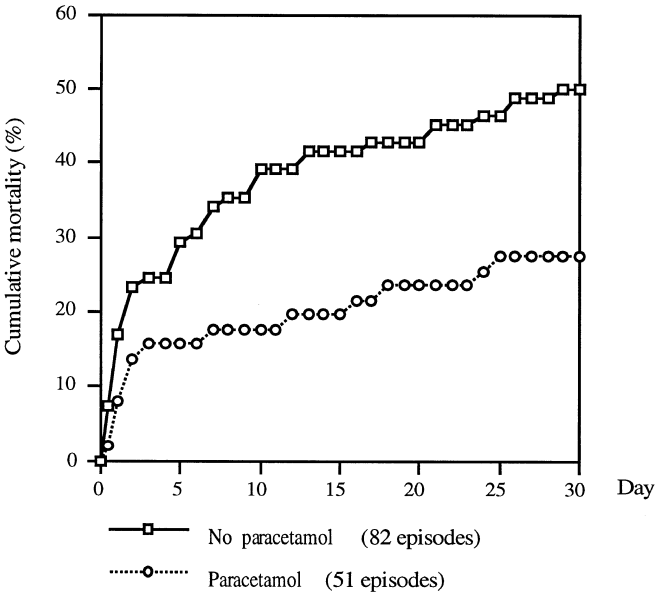

Figure 2 Cumulative mortality for 133 episodes of *Pseudomonas aeruginosa* bacteremia either not treated or treated with paracetamol in the 24 h before or 48 h after the first positive blood culture ($P=0.011$ in the Mantel-Cox test for life tables)

with respiratory insufficiency or acidosis, the mortality was 83% ($P<0.0001$ for each), and in patients with shock or CNS involvement the mortality was 77% ($P<0.0001$ for each). All six patients with DIC died. Acute thromboembolic complications and arrhythmias were also associated with increased mortality, the rates being 63% and 67%, respectively ($P=0.034$ and $P=0.018$).

Logistic Regression Analysis of Prognostic Factors. In the final analysis, four significant factors from the semifinal analysis were combined with the classical prognostic factors of old age and rapidly fatal underlying disease (Model 1 in Table 4). The only protective factor in this model was catheter removal. If we remove this from the model and replace it with the use of paracetamol up to 24 h before and 48 h after drawing the first positive blood culture, this drug was significantly associated with survival (Model 2 in Table 4). Likewise, replacing catheter removal with use of appropriate antibiotic therapy, appropriate antibiotic therapy is associated with survival (OR = 0.126, 95% CI = 0.018–0.885, $P<0.05$).

Discussion

In this retrospective study of 134 episodes of *Pseudomonas aeruginosa* bacteremia documented in the periods 1976–1982 and 1992–1996, the overall mortality for the 30-day interval after drawing the first positive blood culture was 41%. Over these 21 years, the mortality rate decreased from 53% in the first period to 29% in the second period. This finding is in agreement

Table 4 Final logistic regression analysis of factors influencing the outcome of *Pseudomonas aeruginosa* bacteremia

	Odds ratio	95% confidence interval	*P* value[a]
Model 1			
Catheter removal[b]	0.12	0.016–0.916	<0.05
Age >60 years	0.85	0.26–2.83	NS
Rapidly fatal underlying disease[c]	4.25	1.09–16.5	<0.05
Shock	7.34	2.09–25.8	<0.01
Preceding thromboembolic complication	10.4	1.57–68.8	<0.02
CNS involvement	25.2	6.79–93.4	<0.001
Model 2			
Paracetamol treatment[d]	0.26	0.068–0.981	<0.05
Age >60 years	0.70	0.21–2.40	NS
Preceding thromboembolic complication	4.19	0.76–23.2	NS
Rapidly fatal underlying disease[c]	7.12	1.81–28.0	<0.01
Shock	9.27	2.60–33.1	<0.001
CNS involvement	20.3	5.36–77.1	<0.001

[a] *P* values were determined by the final model of logistic regression analysis for prognostic factors
[b] Blood vessel catheters or urinary catheters
[c] According to the classification of McCabe and Jackson [20]
[d] Within 24 hours before and 48 hours after the first positive blood culture

with the results of repeated studies of bacteremia in the same institutions [6, 10, 12, 24, 25], but the reasons for the drop in mortality have not previously been analysed. Since there have been no changes during the 21-year period in the severity of the underlying diseases, the severity of illness at the time of drawing the first positive blood culture or the frequency of underlying conditions predictive of a fatal outcome, the improved prognosis cannot be due to changes in factors inherent in the patients.

Severe leukopenia (leukocyte count $<1.0\times10^9$), implying neutropenia, was not a predictive factor per se in our analysis, as Vidal et al. [12] also recently reported, although in the same institution neutropenia had previously been found to be a predictive factor in a study of *Pseudomonas aeruginosa* bacteremia [10]. The authors attributed this discrepancy to the earlier implementation of appropriate antibiotic treatment and to the use of more effective antibiotics. In our study, an appropriate antibiotic was administered promptly in both periods (within 2 days of drawing the first positive blood culture in 97% of cases with appropriate antibiotic therapy). The better outcome in neutropenic patients in the later study period (mortality 25% versus 67% in the first period, $P=0.001$) seems to be due partly to the more frequent use of combination therapy in these patients (70% in the later period versus 41% in the earlier period, $P=0.08$) and may also be due to single-drug therapy with antibiotics other than aminoglycosides.

The choice of antibiotic for initial treatment was not associated with outcome, but the choice of antibiotic for definitive treatment was, findings which concur with those of Bryant et al. [26] in a study of gram-negative bacteremia, as well as those of Gallagher et al. [14] in a study of *Pseudomonas aeruginosa* bacteremia. In our study patients treated with an aminoglycoside only had the highest mortality (55% versus 25% in other patients, $P=0.0014$). Similar findings concerning initial antibiotic treatment have been reported previously in *Pseudomonas aeruginosa* bacteremia in general and in immunocompromised children, and in gram-negative bacteremia in neutropenic patients [8, 15, 16, 27]. In our study, combination therapy with two or more antibiotics active in vitro against *Pseudomonas aeruginosa* and monotherapy with an antibiotic other than an aminoglycoside (an anti-pseudomonal β-lactam or ciprofloxacin), were equally effective, as also ascertained by Bodey et al. [8] and Vidal et al. [12]. In contrast, Hilf et al. [9] found combination therapy better than monotherapy, but did not report the type of monotherapy used. Chen et al. [15] reported a better outcome using combination therapy, but in their study monotherapy meant treatment with an aminoglycoside only, none of their patients being treated with an antipseudomonal β-lactam or ciprofloxacin alone. Because of the poor prognosis associated with aminoglycoside monotherapy and the questionable effectiveness of combination therapy with an aminoglycoside and an antipseudomonal β-lactam, it would be worthwhile testing the effectiveness of combination of an anti-pseudomonal β-lactam and ciprofloxacin, as suggested by Rolston and Bodey [28].

In 16% of our patients a catheter was removed shortly after drawing the first positive blood culture, the proportion of such patients increasing during the study period from 9% to 24%. Catheter removal (urinary and blood vessel catheters) was associated with confirmed infection at the same site in only 32% of cases. Catheter removal was an independent factor predictive of survival in logistic regression analysis, although

removal because of infection at the catheter site was only necessary in one-third of cases. This contrasts with the findings of Mosca et al. [29] in a study of catheter-related sepsis, which indicated that removal of a non-infected catheter is unnecessary. However, the pathogens found in their study did not include *Pseudomonas aeruginosa*. In the study by Benezra et al. [30], removal of a blood vessel catheter was beneficial in cases of *Pseudomonas aeruginosa* tunnel infection. The good outcome of catheter-associated *Pseudomonas aeruginosa* bacteremia reported by Vidal et al. [12], which they attribute to prompt removal of the catheters, agrees with our results. Catheter removal in all cases of *Pseudomonas aeruginosa* bacteremia is thus recommended, as is already practiced in septicemia caused by *Bacillus* species and fungi in neutropenic cancer patients [31].

Thirty-eight percent of our patients received paracetamol around the time of drawing the first positive blood culture. The proportion of these patients increased from 22% in the first period to 54% in the second period. Twenty-seven percent of paracetamol-treated patients died as against 50% of those not treated, although the underlying conditions and the severity of illness were similar in the two groups. If we replaced catheter removal as the only factor predictive of survival in logistic regression analysis with paracetamol therapy, then this therapy was revealed to be an independent protective factor, analogous to our finding in *Escherichia coli* bacteremia [21].

The improvement in the prognosis of *Pseudomonas aeruginosa* bacteremia over the last two decades would thus seem to be due to three changes in management of the infection: decreased use of aminoglycosides monotherapy combined with increased use of new antipseudomonal β-lactams and ciprofloxacin as monotherapy; more frequent removal of catheters; and increased administration of paracetamol at the time of drawing the first positive blood culture.

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