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Effectiveness of Combination Antimicrobial Therapy for *Pseudomonas aeruginosa* Bacteremia

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It remains controversial whether combination therapy, given empirically or as definitive treatment, for *Pseudomonas aeruginosa* bacteremia is associated with a better outcome than monotherapy. The aim of the present study was to compare the rates of survival among patients who received either combination therapy or monotherapy for *P. aeruginosa* bacteremia. We assembled a historical cohort of 115 episodes of *P. aeruginosa* bacteremia treated with empirical antipseudomonal therapy between 1988 and 1998. On the basis of susceptibility testing of the bacteremic *P. aeruginosa* isolate, we defined categories of empirical treatment, including adequate combination therapy, adequate monotherapy, and inadequate therapy, as well as corresponding categories of definitive therapy. Neither the adequacy of the empirical treatment nor the use of combination therapy predicted survival until receipt of the antibiogram. However, the risk of death from the date of receipt of the antibiogram to day 30 was higher for both adequate empirical monotherapy (adjusted hazard ratio [aHR], 3.7; 95% confidence interval [CI], 1.0 to 14.1) and inadequate empirical therapy (aHR, 5.0; 95% CI, 1.2 to 20.4) than for adequate empirical combination therapy. Compared to adequate definitive combination therapy, the risk of death at 30 days was also higher with inadequate definitive therapy (aHR, 2.6; 95% CI, 1.1 to 6.7) but not with adequate definitive monotherapy (aHR, 0.70; 95% CI, 0.30 to 1.7). In this retrospective analysis the use of adequate combination antimicrobial therapy as empirical treatment until receipt of the antibiogram was associated with a better rate of survival at 30 days than the use of monotherapy. However, adequate combination antimicrobial therapy given as definitive treatment for *P. aeruginosa* bacteremia did not improve the rate of survival compared to that from the provision of adequate definitive monotherapy.

Pseudomonas aeruginosa bacteremia occurs most frequently in critically ill patients, particularly those who are immunocompromised, have cancer, or are mechanically ventilated (14, 15, 32, 38). In these patients, bacteremia is often accompanied by symptoms of systemic inflammatory response syndrome (SIRS) (40). Despite recent advances in therapy, *P. aeruginosa* bacteremia remains fatal in more than 20% of cases (28). Over 50% of deaths occur within a few days (3, 13, 18). Therefore, prompt administration of adequate antipseudomonal treatment is essential (3, 24). Paradoxically, it has not been clearly established whether the adequacy of empirical antimicrobial therapy initiated for suspected *P. aeruginosa* bacteremia truly improves survival (3, 28, 30, 39). Initial treatment decisions are difficult to make because *P. aeruginosa* bacteremia is a presumptive diagnosis at first and little is known about the susceptibility of the causative agent until receipt of the antibiogram. No single antimicrobial regimen adequately covers all strains of *P. aeruginosa* (4, 7). Moreover, the value of combination therapy (a combination of a beta-lactam plus an aminoglycoside or one of these agents plus ciprofloxacin) compared to that of monotherapy remains controversial (9, 10, 12, 16, 22, 29, 37, 39).

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We report here on analyses of a retrospective cohort of 115 patients who received empirical therapy for *P. aeruginosa* bacteremia. The patients were monitored from day 1 of documented bacteremia through day 30. The study aims were threefold: (i) to determine whether adequate empirical combination therapy was associated with a lower rate of mortality during early follow-up (from the day of documented bacteremia to the day of receipt of the antibiogram), (ii) whether both empirical and definitive treatments independently predicted survival during late follow-up (from the time of receipt of the antibiogram to day 30 postbacteremia) among patients who were still alive at the time of receipt of the antibiogram, and (iii) whether combination antipseudomonal therapy was superior to monotherapy.

MATERIALS AND METHODS

Study population. The study was performed at the Geneva University Hospital, a 1,000-bed urban tertiary-care center in Geneva, Switzerland. The clinical microbiology laboratory database was searched to identify all patients with a positive blood culture for *P. aeruginosa* from 1 November 1988 to 30 November 1998. Hospital charts were reviewed to further identify patients who presented with symptoms of SIRS at the time of their bacteremia and who had received an empirical antimicrobial therapy that included at least one antipseudomonal agent; no hospital chart was missing. Other data were collected from the same sources. Because of the rather small sample size, multiple entries in the study were permitted when two independent episodes of *P. aeruginosa* bacteremia occurred in the same patient. The criteria used to designate an independent episode of *P. aeruginosa* bacteremia included a documented positive culture for the pathogen, no antecedent of inadequately treated *P. aeruginosa* bloodstream infection, and no positive blood culture for at least 30 days after completion of adequate antimicrobial therapy for a previous episode of *P. aeruginosa* bacteremia.

Dependent variables. The time to death from all causes was used as the primary outcome of interest to avoid potentially arbitrary distinctions between deaths related and unrelated to bacteremia episodes.

Categories of antimicrobial treatment. Empirical antipseudomonal therapy was defined as treatment that included at least one antipseudomonal agent and that was started no later than 24 h after the index positive blood sample for culture had been drawn. Definitive antipseudomonal therapy was defined as treatment that included at least one antipseudomonal agent and that was continued or commenced on the day that the antibiogram results were reported to the clinicians. Analyses were based on an intention-to-treat approach; switching or stopping of the antipseudomonal treatment at any other time during the course of follow-up was not taken into account. We limited our analyses to treatments received on the days that the first positive blood sample was drawn and the results of the antibiogram were received because we lacked information on why antimicrobial therapy was instituted, modified, or stopped at any other time during the follow-up. The lack of an ability to appropriately control for factors that motivate treatment change can result in strong residual confounding by indication (21). Monotherapy consisted of treatment with one of the following antipseudomonal antimicrobials: piperacillin, ceftazidime, imipenem, cefepime, or ciprofloxacin. Piperacillin-tazobactam was used infrequently and was grouped with piperacillin. Combination therapy consisted of the administration of piperacillin, ceftazidime, imipenem, or cefepime together with either an aminoglycoside (gentamicin or amikacin) or ciprofloxacin or the administration of an aminoglycoside together with ciprofloxacin. Antimicrobial therapy was considered adequate when the index bacteremic *P. aeruginosa* isolate was susceptible to the antimicrobial prescribed and the dose and pattern of administration were in accordance with current medical standards (piperacillin, 3 to 4 g every 4 h [q4h] to q6 h; ceftazidime, 2 g q8h; imipenem, 0.5 g q6h; cefepime, 2 g q12h; ciprofloxacin, 0.4 g intravenously q12h or 0.75 g orally q12h; gentamicin, a load of 2 mg/kg of body weight and then 1.7 mg/kg q8h or 5.1 mg/kg q24h). Combination therapy was considered adequate if the index bacteremic strain was susceptible to both drugs. The following antipseudomonal therapies were classified as inadequate: monotherapy with an agent to which the bacteremic *P. aeruginosa* strain was resistant, combination therapy with two agents to which the strain was resistant, and combination therapy with an aminoglycoside in association with another antipseudomonal agent to which the strain was resistant. In our institution gentamicin is not prescribed at doses exceeding 5.1 mg/kg per day. At this standard dose, gentamicin monotherapy has been associated with poor outcomes in patients with *P. aeruginosa* bacteremia (3, 9, 28). For this reason, in accordance with the findings of other investigators (37), gentamicin is not accepted as monotherapy for *P. aeruginosa* bacteremia in our institution, and patients receiving empirical aminoglycoside monotherapy were therefore excluded from the analysis. Several studies have suggested that ciprofloxacin monotherapy might be effective for febrile neutropenic patients and empirical treatment of bacteremia; however, higher incidences of superinfections caused by gram-positive pathogens, as well as poor outcomes in the case of infections caused by resistant gram-negative pathogens, have limited its use (1, 25, 31, 33). In contrast, to our knowledge, no negative data concerning ciprofloxacin monotherapy for the treatment of bacteremia caused by susceptible gram-negative isolates are available (20). Other investigators have accepted ciprofloxacin monotherapy as an adequate alternative for the treatment *P. aeruginosa* bacteremia (28, 37). For these reasons we considered ciprofloxacin monotherapy as an adequate treatment option, as long as the *P. aeruginosa* isolate was susceptible.

Hence, we distinguished the following categories of treatment: adequate empirical combination therapy (AECT), adequate empirical monotherapy (AEMT), inadequate empirical therapy (IET), adequate definitive combination therapy (ADCT), adequate definitive monotherapy (ADMT), and inadequate definitive therapy (IDT).

Covariates. Other potential prognostic factors were assessed, including age, sex, calendar year of the patient episode (treated as a dichotomic variable [1993 to 1998 versus 1988 to 1992]), clinical mode of presentation, type of bacteremia (mono- or polymicrobial), hospital unit, underlying medical condition, initial neutropenia, steroid treatment, and primary site of infection.

Statistical analysis. Patients for whom the date of receipt of the antibiogram was missing were excluded from analysis. Statistical analyses were done with the STATA program (version 6.0). Categorical variables were compared by Fisher's exact tests. The Kruskal-Wallis test was used to compare the time to receipt of the antibiogram across treatment groups. All statistical tests were two tailed.

(i) Survival over entire follow-up. We used the Kaplan-Meier product-limit method to estimate by univariate analysis the risk of death by empirical treatment categories. The reference time for this preliminary analysis was the day of the index positive blood culture. Patients were monitored until day 30 postbacteremia or were censored from analysis (because of either death or transfer to another hospital). The log-rank test was used to compare the cumulative probability of death across treatment groups.

(ii) Early follow-up. Early follow-up started on the date of bacteremia and extended to the end of the last day before receipt of the antibiogram. Contingency tables were used to compare baseline patient characteristics across empirical treatment groups. We calculated Kaplan-Meier estimates of the cumulative risk of death by patient characteristics. The corresponding unadjusted and multivariate-adjusted hazard ratios of death were estimated by Cox proportional hazard regression analysis. Treatment variables were always entered and retained in the multivariate models. Covariates were considered for inclusion if they were associated with survival with a P value of <0.20 by univariate analysis. To limit overfitting (11), only important confounding factors (i.e., variables whose inclusion or exclusion changed regression coefficients of treatments variables by $>10\%$) were retained in the model; no interaction term was examined.

(iii) Late follow-up. Analyses similar to those described above were performed for late follow-up, which started on the day of receipt of the antibiogram and extended to the end of day 30 postbacteremia. Analyses were restricted to patients who were still alive and who were monitored at the time that the antibiogram was received. Contingency tables assessed the patients' characteristics at the time of bacteremia by definitive treatment groups.

Detailed treatment history. To better define relations between survival and specified categories of therapies, we identified modifications of empirical therapies before receipt of the antibiogram, as well as changes in definitive therapies occurring after receipt of the antibiogram. In this analysis, discontinuation following treatment completion was not considered a modification of therapy.

Definitions. Underlying diseases were considered if they were present at the time of bacteremia and were defined clinically, analytically, hematologically, or histologically by use of standard criteria (17). Sepsis, severe sepsis, and shock were defined as described previously (40). Neutropenia was defined as a granulocyte count of less than 0.50×10^9/liter (6). Steroid therapy was considered notable if the patient had been receiving at least 30 mg of prednisone daily for at least 10 days before the bacteremia. Definitions of the source of bacteremia were as described elsewhere (2). The day of antibiogram receipt was defined as the day when the clinical microbiology laboratory notified the clinician that the antibiogram had been completed. In our internal experience, the delay between the sending of the report and its physical receipt by the clinicians did not exceed 6 h. Antimicrobial susceptibility was determined by disk diffusion methods according to the recommendations of the National Committee for Clinical Laboratory Standards (NCCLS) (36). An isolate was considered susceptible, intermediate, or resistant according to the criteria of the NCCLS. The isolates with intermediate susceptibility were classified as resistant for analysis.

RESULTS

Baseline characteristics. We identified 120 culture-proven episodes of *P. aeruginosa* bacteremia treated empirically with at least one antipseudomonal agent during the study period. Five (4.2%) episodes were excluded because of a missing date of receipt of the antibiogram or missing data on empirical treatment. Analyses were restricted to 115 episodes of *P. aeruginosa* bacteremia in 113 patients. Two patients experienced a second episode of bacteremia after completion of an adequate antipseudomonal therapy and intervals of 30 and 54 days, respectively. Exclusion of these episodes had virtually no effects on the overall results. For ease of presentation, we use the terms episode and patient interchangeably.

About half of the 115 patients were aged 65 years or older; most were men (Table 1). Half of the bacteremia episodes occurred between 1993 and 1998. A majority of patients were hospitalized on the medical ward or surgical intensive care unit; 19% presented with shock and 12% presented with severe sepsis. Eighty percent of the episodes were monobacterial. The most commonly identified sources of *P. aeruginosa* infection were the respiratory and urinary tracts. About 90% of patients had an underlying disease; 30% were neutropenic; 10% were receiving a steroid treatment. At one time or another during follow-up, 33 patients (28.7%) received imipenem, 22 (19.1%)

TABLE 1. Baseline characteristics of 115 *P. aeruginosa* bacteremic episodes empirically treated with an antipseudomonal antimicrobial regimen[a]

Variable	No. (%) of episodes
Sex (men)	85 (73.9)
Calendar time (1993 to 1998)	56 (48.7)
Hospital unit	
Medical	55 (47.8)
Surgical	20 (17.4)
Medical intensive care	16 (13.9)
Surgical intensive care	24 (20.9)
Clinical presentation	
Simple sepsis	79 (68.7)
Severe sepsis	14 (12.2)
Septic shock	22 (19.1)
Monobacterial bacteremia	92 (80.0)
Primary site(s) of *P. aeruginosa* infection	
Respiratory tract	24 (20.9)
Urinary tract	22 (19.1)
Vascular system	5 (4.3)
Other	21 (18.3)
Unknown	57 (49.6)
Underlying medical condition	
Cancer	52 (15.2)
AIDS	6 (5.2)
Diabetes	9 (7.8)
Respiratory dysfunction	23 (20.0)
Renal failure	19 (16.5)
Other[b]	50 (43.5)
None of the above	15 (13.0)
Neutropenia	34 (29.6)
Steroid treatment	11 (9.6)
Bacteremic strain resistant to the following no. of antipseudomonal agents:	
0	75 (65.2)
1	19 (16.5)
≥2	21 (18.3)

[a] The median age was 65 years (age range, 6 to 91 years).
[b] Heart failure, pancreatitis, and severe nonpseudomonal infection.

received piperacillin, 22 (19.1%) received ceftazidime, 12 (10.4%) received cefepime, 56 (48.7%) received gentamicin, 16 (13.9%) received amikacin, and 27 (23.5%) received ciprofloxacin. Resistance to at least one antipseudomonal agent was documented for 35% of the *P. aeruginosa* blood isolates.

Entire follow-up. Complete follow-up was achieved for 114 participants (99%). One patient was transferred to another hospital on the third day of follow-up. Forty-three patients (37.4%) had received AECT, 55 (47.8%) had received AEMT, and 17 (14.8%) had received IET. Forty-five patients died within 30 days of bacteremia (cumulative risk, 39.4%; 95% confidence interval [CI], 31.1 to 49.0); 33 deaths (73.3%) were directly attributed to bacteremia. The unadjusted probabilities of surviving until day 30 were 72.1% (95% CI, 56.1 to 83.1) for the AECT group, 61.2% (95% CI, 47.0 to 72.7) for the AEMT group, and 29.4% (95% CI, 10.7 to 51.2) for the IET group (Fig. 1) (global test, $P = 0.01$).

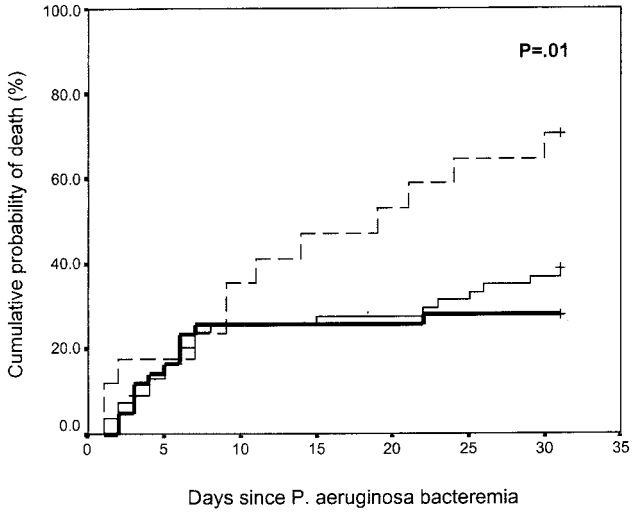

FIG. 1. Cumulative risk of death for patients who received adequate empirical combination therapy (bold solid line), adequate empirical monotherapy (narrow solid line), and inadequate empirical therapy (broken line).

Early follow-up. The median time from bacteremia to receipt of the antibiogram was 5 days (90th percentile, 7 days). The mean times until receipt of the antibiogram were 5.5 days for the IET group, 5.2 days for the AEMT group, and 5.1 days for the AECT group ($P = 0.60$). Most patients' baseline characteristics were similar across empirical treatment groups (Table 2). However, patients who had received AECT were significantly more likely to have had their bloodstream infection between 1988 and 1992 ($P = 0.001$). Sixteen patients died before the antibiogram was received (cumulative risk, 18.5%; 95% CI, 11.5 to 21.1). By univariate analysis there was no relation between empirical therapies and risk of death before receipt of the antibiogram (Table 2). By univariate analysis, the risk of death was significantly lower among patients over 64 years of age and among those whose bacteremia episode occurred after 1992. Higher risks were observed among patients who were hospitalized in the surgical intensive care unit, who presented with severe sepsis or shock, and who had bacteremia of respiratory origin.

By multivariate analysis, the risk of death before receipt of the antibiogram was also similar for the AEMT group (adjusted hazard ratio [aHR], 0.81; 95% CI, 0.31 to 2.1; $P = 0.66$) and the IET group (aHR, 1.2; 95% CI, 0.29 to 5.2; $P = 0.79$) compared to that for the AECT group (Table 3). Being older was independently associated with a lower risk of death (aHR, 0.22, 95% CI, 0.06 to 0.81; $P = 0.02$); having presented with severe sepsis (aHR, 31.5; 95% CI, 3.5 to 286; $P = 0.002$) and shock (aHR, 38.0; 95% CI, 5.4 to 268; $P < 0.001$) was associated with a higher risk.

Late follow-up. Of the 99 patients still alive and under follow-up at the time that the antibiogram was received, 1 was excluded from further analysis because of missing information on the definitive therapy. Of the 98 remaining patients, 46 (46.9%) had received ADCT, 33 (33.7%) had received ADMT, and 19 (19.4%) had received IDT (Table 4). Definitive treatment groups were similar with regard to most characteristics

TABLE 2. Baseline characteristics of study subjects in relation to categories of empirical antimicrobial therapy and summary of univariate survival analysis until receipt of the antibiogram[a]

Characteristic	% of episodes with:			No. who died/total no. (Kaplan-Meier %)[b]	Univariate HR (95% CI)	*P* value
	Adequate combination therapy (n = 43)	Adequate monotherapy (n = 55)	Inadequate therapy (n = 17)			
All patients	100.0	100.0	100.0	16/115 (18.5)		
Empirical antimicrobial therapy						
Adequate combination therapy	100.0	0.0	0.0	7/43 (29.7)	1.0 (referent)	
Adequate monotherapy	0.0	100.0	0.0	6/55 (11.1)	0.67 (0.23–1.9)	0.46
Inadequate therapy	0.0	0.0	100.0	3/17 (17.7)	1.1 (0.29–4.5)	0.86
Age (yr)						
<65	41.2	49.1	51.2	13/56 (34.7)	1.0 (referent)	
≥65	58.8	50.9	48.8	3/59 (5.1)	0.20 (0.06–0.69)	0.01
Calendar time						
1988 to 1992	69.8	47.3	17.6	9/39 (36.4)	1.0 (referent)	
1993 to 1998	30.2	52.7	82.4	7/76 (9.5)	0.38 (0.14–1.0)	0.05
Hospitalized on surgical intensive care unit						
No	83.7	80.0	64.7	9/91 (13.2)	1.0 (referent)	
Yes	16.3	20.0	35.3	7/24 (35.7)	3.2 (1.2–8.5)	0.02
Clinical presentation						
Simple sepsis	67.4	69.1	70.6	1/79 (1.3)	1.0 (referent)	
Severe sepsis	18.6	10.9	0.0	7/14 (42.9)	28.1 (3.4–229.9)	0.002
Shock	14.0	20.0	29.4	10/22 (56.3)	45.5 (5.9–348.3)	<0.001
Type of bacteremia						
Pseudomonas alone	74.4	85.5	76.5	12/92 (20.9)	1.0 (referent)	
Poymicrobial	25.6	14.5	23.5	4/23 (17.4)	0.88 (0.27–2.8)	0.83
Underlying medical condition(s)[c]						
No	14.0	14.5	5.9	2/15 (13.3)	1.0 (referent)	
Yes	86.0	85.5	94.1	14/100 (19.6)	1.8 (0.22–14.6)	0.58
Immunological risk factor(s)						
None of the following	55.8	67.3	70.6	7/73 (12.2)	1.0 (referent)	
Neutropenia	39.5	25.5	17.6	6/34 (18.3)	2.0 (0.68–5.8)	0.21
Steroid treatment	7.0	10.9	11.8	3/11 (59.1)	3.4 (0.95–12.0)	0.06
Neutropenia and/or steroid treatment	44.2	32.7	29.4	9/42 (33.4)	2.6 (0.96–7.0)	0.06
Primary site(s) of infection						
Unknown	51.2	52.7	35.3	7/57 (13.0)	1.0 (referent)	
Respiratory tract	20.9	16.4	35.3	8/24 (55.0)	2.9 (1.1–7.5)	0.03
Urinary tract	20.9	20.0	11.8	0/22 (0.0)	0.0 (ND[d])	ND
Vascular system	4.7	5.5	0.0	0/5 (0.0)	0.0 (ND)	ND
Other	20.9	14.5	23.5	3/21 (14.3)	1.2 (0.30–4.4)	0.83

[a] Seven episodes of bacteremia were excluded from this analysis either because of missing empirical treatment (n = 2) or missing dates of receipt of the antibiogram (n = 5).
[b] Kaplan-Meier product limit estimate of cumulative risk of death from all causes.
[c] Cancer, AIDS, diabetes, respiratory dysfunction, renal failure, heart failure, pancreatitis, and/or severe nonpseudomonal infection.
[d] ND, not defined.

recorded at the time of bacteremia. However, definitive antimicrobial therapy of a particular type (i.e., adequate combination therapy, adequate monotherapy, or inadequate therapy) was significantly more likely to have followed an empirical treatment of the same type ($P < 0.001$). Twenty-nine patients died before the end of follow-up (cumulative risk, 32.4%; 95% CI, 23.3 to 43.9).

In contrast to the risk of death during early follow-up, the risk of death after receipt of the antibiogram varied according to empirical therapy. By univariate analysis, the risk of death was significantly higher for the IET group (crude hazard ratio [cHR], 6.8; 95% CI, 2.3 to 20.3) and marginally higher for the AEMT group (cHR, 2.5, 95% CI, 0.88 to 6.9) than for the AECT group (Table 4). The multivariate Cox proportional hazard model was stratified on severe sepsis and shock to limit violation of the proportional hazard assumption. After further controlling for independent prognostic factors and definitive treatment, patients in the AEMT group were 3.7 times more

TABLE 3. Results of a Cox proportional hazard model describing independent relations between empirical antimicrobial therapy and risk of death during early follow-up[a]

Characteristic	Hazard ratio	95% CI	*P* value
Empirical antimicrobial therapy			
Adequate combination therapy	1.0		
Adequate monotherapy	0.81	0.31–2.1	0.66
Inadequate therapy	1.2	0.29–5.2	0.79
Age (yr)			
<65	1.0		
≥65	0.22	0.06–0.81	0.02
Clinical presentation			
Simple sepsis	1.0		
Severe sepsis	31.5	3.5–286.4	0.002
Shock	38.0	5.4–267.8	<0.001

[a] Early follow-up started on the date of bacteremia and extended to the end of the last day before receipt of the antibiogram. Similar results were obtained after exclusion of the 26 patients who had a known urinary or vascular source of *P. aeruginosa* infection.

likely (95% CI, 1.0 to 14.1; $P = 0.05$) and patients in the IET group were 5.0 times more likely (95% CI, 1.2 to 20.4; $P = 0.02$) to have died during late follow-up than patients in the AECT group (Table 5). There was no independent difference in the risk of death between patients in the IET and AEMT groups (aHR, 1.3; 95% CI, 0.54 to 3.3; $P = 0.52$).

Adequate definitive therapies were associated with better outcomes, but there was no evidence for the superiority of combination therapy over monotherapy. By univariate analysis, the risk of death for the ADMT group (cHR, 1.2; 95% CI, 0.50 to 2.9) was similar to that for the ADCT group, but the risk of death was significantly higher for the IDT group (cHR, 3.6, 95% CI, 1.4 to 8.9) than for the ADCT group (Table 4). Hospitalization on the surgical intensive care unit and severe sepsis or shock at the time of bacteremia were significant predictors of poor survival. There was a trend for bacteremia of urinary and vascular origin to be associated with a better prognosis. By multivariate analysis, the risk of death was significantly higher for the IDT group (aHR, 2.6; 95% CI, 1.1 to 6.7; $P = 0.04$) but not for the ADMT group (aHR, 0.70; 95% CI, 0.30 to 1.7; $P = 0.42$) compared to that for the ADCT group (Table 5). Hospitalization on the surgical intensive care unit was independently associated with poor survival (aHR, 3.2; 95% CI, 1.2 to 8.9; $P = 0.02$), and bacteremia of urinary or vascular origin was associated with better survival (aHR, 0.21; 95 CI, 0.05 to 0.94; $P = 0.04$).

Details on treatment changes during follow-up. Empirical treatment was unmodified until receipt of the antibiogram (or death for those who died during early follow-up) in 80 of 115 patients (Table 6). A switch of therapy during early follow-up was recorded for 18.6% of patients in the AECT group, 38.2% of those in the AEMT group (relative risk [RR], 2.1; 95% CI, 1.0 to 4.2; $P = 0.05$), and 35.3% of those in the IET group (RR, 1.9; 95% CI, 0.77 to 4.7; $P = 0.19$) (Table 6). No adequate empirical combination therapy was modified on the day of receipt of the antibiogram, while three AEMTs (8.8%) were replaced by an ADCT and one IET (4.8%) was replaced by an ADMT. Finally, 13 definitive treatments were modified before the end of follow-up or death: 5 of these changes (38.5%) consisted of downgrading of an ADCT to an ADMT, while 3 (23.0%) consisted of upgrading of an ADMT to an ADCT, and 5 (38.5%) consisted of upgrading of an IDT to either an ADMT or an ADCT.

Monotherapy subanalysis. The adequacies of both aminoglycoside monotherapy and ciprofloxacin monotherapy for *P. aeruginosa* bacteremia are controversial. Therefore, we conducted complementary univariate analyses to describe the risk of death among patients treated with aminoglycoside or ciprofloxacin monotherapy and examined the impact of alternative definitions of monotherapy adequacy on the results of multivariate analysis. The crude cumulative risk of death during follow-up was 35.0% (95% CI, 18.5 to 59.7%) for 20 patients who received an active aminoglycoside monotherapy empirically. The crude cumulative risks of death were 25% (95% CI, 11.3 to 50.0%) before receipt of the antibiogram and 15.2% (95% CI, 4.0 to 48.8%) after receipt of the antibiogram. Among 12 patients who received active ciprofloxacin monotherapy empirically, the crude cumulative risks of death were 33.3% (95% CI, 14.0 to 66.3%) over the entire follow-up, 0% before receipt of the antibiogram, and 34.4% (95% CI, 14.4 to 68.0%) after receipt of the antibiogram. The crude risk of death before receipt of the antibiogram was marginally higher among patients who received empirical aminoglycoside monotherapy than among patients who received empirical ciprofloxacin monotherapy ($P = 0.07$; HR was undefined). There was a trend in the opposite direction for the risk of death after receipt of the antibiogram (cHR, 0.21; 95% CI, 0.11 to 1.9; $P = 0.16$). In our main analysis sections, to reflect the consensus that has been achieved in our institution, we excluded patients who received empirical combination therapy with an active aminoglycoside associated with a nonantipseudomonal agent and included in the inadequate therapy groups patients who received an active aminoglycoside in combination with an inactive antipseudomonal agent. In contrast, we included in the adequate monotherapy groups patients who received active ciprofloxacin in combination with either a nonantipseudomonal agent or an inactive antipseudomonal agent. As a complement, we conducted two additional multivariate analyses. In the first one, monotherapy with an active aminoglycoside and monotherapy with active ciprofloxacin were both considered adequate; in the second one, neither regimen was considered adequate. Both analyses confirmed that inadequate empirical and definitive therapies were associated with poor outcomes; both analyses also supported the notion that the type of empirical therapy is not an independent predictor of death before receipt of the antibiogram (data not shown). Moreover, the aHRs at 30 days for patients in the AEMT group compared to that for patients in the AECT group were 2.0 in the first analysis (95% CI, 0.67 to 6.2) and 2.3 in the second analysis (95% CI, 0.62 to 8.7). Although neither result was statistically significant, both concur with the findings of the main multivariate analyses in suggesting that adequate empirical combination therapy was associated with better outcomes at day 30 than adequate empirical monotherapy.

TABLE 4. Baseline characteristics of study subjects in relation to categories of definitive antipseudomonal therapy and summary of univariate survival analysis from receipt of the antibiogram to end of follow-up for 98 patients[a]

Characteristic	% of episodes with:			No. who died/total no. (Kaplan-Meier %)[b]	Univariate HR (95% CI)	*P* value
	Adequate combination therapy (n = 46)	Adequate monotherapy (n = 33)	Inadequate therapy (n = 19)			
All patients	100.0	100.0	100.0	29/98 (32.4)		
Empirical antimicrobial therapy						
Adequate combination therapy	58.7	12.1	26.3	5/36 (16.0)	1.0 (referent)	
Adequate monotherapy	30.4	81.8	42.1	15/49 (33.9)	2.5 (0.88–6.9)	0.09
Inadequate therapy	10.9	6.1	31.6	9/13 (71.2)	6.8 (2.3–20.3)	0.001
Adequate monotherapy or inadequate therapy	41.3	87.9	73.7	24/62 (42.1)	3.2 (1.2–8.4)	0.02
Definitive antimicrobial therapy						
Adequate combination therapy	100.0	0.0	0.0	10/46 (21.7)	1.0 (referent)	
Adequate monotherapy	0.0	100.0	0.0	9/33 (32.5)	1.2 (0.50–2.9)	0.68
Inadequate therapy	0.0	0.0	100.0	10/19 (57.9)	3.6 (1.4–8.9)	0.006
Adequate monotherapy or inadequate therapy	0.0	100.0	100.0	19/52 (42.2)	1.8 (0.86–4.0)	0.12
Age (yr)						
<65	47.8	39.4	42.1	11/43 (28.8)	1.0 (referent)	
≥65	52.2	60.6	57.9	18/55 (35.4)	1.3 (0.60–2.7)	0.54
Calendar time						
1988 to 1992	50.0	45.5	36.8	8/30 (31.1)	1.0 (referent)	
1993 to 1998	50.0	54.5	63.2	21/68 (33.1)	1.1 (0.51–2.6)	0.74
Hospitalized on surgical intensive care unit						
No	78.3	84.8	89.5	20/81 (28.0)	1.0 (referent)	
Yes	21.7	15.2	10.5	9/17 (52.9)	2.9 (1.3–6.6)	0.009
Clinical presentation						
Simple sepsis	76.1	78.8	84.2	17/77 (24.1)	1.0 (referent)	
Severe sepsis	8.7	9.1	10.5	4/8 (100.0)	2.6 (1.0–6.7)	0.05
Shock	15.2	12.1	5.3	8/13 (61.5)	4.1 (1.7–9.8)	0.002
Type of bacteremia						
Pseudomonas alone	78.3	87.9	78.9	24/80 (32.3)	1.0 (referent)	
Poymicrobial	21.7	12.1	21.1	5/18 (30.2)	1.0 (0.42–2.6)	0.95
Underlying medical condition(s)[c]						
No	10.9	21.2	5.3	2/13 (16.1)	1.0 (referent)	
Yes	89.1	78.8	94.7	27/85 (34.8)	2.3 (0.56–9.1)	0.25
Immunological risk factor(s)						
None of the following	60.5	81.3	72.2	18/65 (30.4)	1.0 (referent)	
Neutropenia	39.5	18.8	27.8	8/28 (31.8)	1.1 (0.47–2.5)	0.87
Steroid treatment	13.3	7.1	13.3	4/8 (50.0)	2.0 (0.69–5.8)	0.20
Primary site(s) of infection						
Unknown	47.8	45.5	68.4	15/50 (33.4)	1.0 (referent)	
Respiratory tract	17.4	15.2	15.8	7/16 (44.4)	1.5 (0.63–3.6)	0.35
Urinary tract	17.4	33.3	10.5	3.21 (19.6)	0.39 (0.12–1.2)	0.11
Vascular system	8.7	3.0	0.0	0/5 (0.0)	0.0 (ND[d])	ND
Other	26.1	9.1	15.8	6/18 (33.3)	1.1 (0.41–2.8)	0.89
Time between bacteremia and receipt of antibiogram (days)						
<5	52.2	51.5	31.6	16/47 (34.0)	1.0 (referent)	
≥5	47.8	48.5	68.4	13/51 (25.7)	0.89 (0.42–1.9)	0.75

[a] One additional patient was excluded from this analysis because of missing definitive treatment.
[b] Kaplan-Meier product limit estimate of cumulative risk of death from all causes.
[c] Cancer, AIDS, diabetes, respiratory dysfunction, renal failure, heart failure, pancreatitis, and/or severe nonpseudomonal infection.
[d] ND, not defined.

TABLE 5. Results of a stratified Cox proportional hazard model describing independent relations between both empirical and definitive antimicrobial therapy and risk of death during late follow-up[a]

Characteristic	Hazard ratio	95% CI	*P* value
Empirical antimicrobial therapy			
Adequate combination therapy	1.0		
Adequate monotherapy	3.7	1.0–14.1	0.05
Inadequate therapy	5.0	1.2–20.4	0.02
Definitive antimicrobial therapy			
Adequate combination therapy	1.0		
Adequate monotherapy	0.70	0.30–1.7	0.42
Inadequate therapy	2.6	1.1–6.7	0.04
Hospitalization on the surgical intensive care unit			
No	1.0		
Yes	3.2	1.2–8.9	0.02
Bacteremia of urinary or vascular origin			
No	1.0		
Yes	0.21	0.05–0.94	0.04

[a] The model was stratified on dummy variables coding for severe sepsis and shock to account for violations of the proportional hazard assumption. Late follow-up started on the day of receipt of the antibiogram and extended to the end of day 30 post bacteremia.

DISCUSSION

In our cohort of patients with *P. aeruginosa* bacteremia and SIRS, adequate empirical combination therapy was independently associated with better survival at 1 month compared to that achieved with adequate empirical monotherapy. In contrast, the rates of mortality prior to receipt of the antibiogram were similar among those who had received no, one, or two adequate antipseudomonal agents. Adequate definitive monotherapy and adequate definitive combination therapy were both independently associated with better survival outcome compared to survival achieved with inadequate definitive therapy.

Both the importance of an appropriate empirical therapy and the role of combination therapies for *P. aeruginosa* bacteremia are controversial. Unfortunately, cases of *P. aeruginosa* bacteremia have only rarely been included in randomized treatment trials. Indeed, in a review of 10 randomized trials of antimicrobial therapy in patients with cancer and neutropenia, only 90 of a total of 909 episodes of bacteremia were caused by *Pseudomonas* species, and there was no subgroup analysis of treatment efficacy by organism (16). Therefore, present guidelines rely mostly on observational studies. Inappropriate definitive therapy for *P. aeruginosa* bacteremia was a predictor of poor clinical outcome in most recently published observational studies (3, 9, 24, 28, 39), and the importance of the appropriateness of definitive treatment for *P. aeruginosa* bacteremia is therefore generally accepted. A delay in the administration of appropriate antimicrobial therapy has been associated with lower cure rates in some studies (3, 30); however, this was not confirmed by others (28, 39). Similarly, combination therapy was superior to monotherapy in one study (22), but not in others (3, 9, 28, 37, 39). A major shortcoming of previous observational studies is the possible bias due to the death of some patients before they matched the definition for a particular treatment category (e.g., therapy was received for at least 2 days) (22). Comparison between the available studies is also made difficult by different study designs. Some were prospective (22, 39), some excluded polymicrobial bacteremia (9, 28), some did not use overall survival as the main outcome (3, 9), and, most importantly, some did not account for the results of in vitro susceptibility testing in the definition of adequate therapy (3, 9). Moreover, monotherapy with an aminoglycoside, which nowadays is not accepted as an appropriate therapy for *P. aeruginosa* bacteremia unless high doses (7 mg/kg/day) are used, was considered appropriate in previous studies (3, 9, 28). In other studies, this issue was not addressed (22, 39), and it is therefore possible that the superiority of combination therapy over monotherapy resulted from the inclusion in the monotherapy group of patients who had been treated with standard doses of an aminoglycoside alone (22). Present guidelines for the treatment of suspected *P. aeruginosa* bacteremia recommend the rapid introduction of empirical antimicrobial therapy that includes at least one antipseudomonal agent. Some investigators, because of worry regarding initial resistance to the empirically chosen antipseudomonal agent, suggest the addition of an aminoglycoside for 3 to 5 days (10, 12). This is indeed a serious concern, as the prevalence of resistance of the invasive strain to antipseudomonal agents was higher in our cohort than in older series (3, 22, 28). Empirical combination therapy could also reduce the risk of selection of resistant clones during initial therapy (5, 7, 26, 34, 35). This is supported by our recent findings suggesting differences in the susceptibility patterns of bacteremia-causing *P. aeruginosa* isolates previously exposed to monotherapies and combination therapies (4). The emergence of antimicrobial resistance during therapy for *P. aeruginosa* bacteremia is difficult to detect and may lead to inappropriate definitive therapy, with increased rates of mortality and prolonged hospital stays (8, 24, 27). Moreover, greater killing might be achieved by combination therapies acting synergistically; this might be of particular importance early during the infectious process, when a rapid reduction of the pathogen burden might prevent the evolution toward sepsis. One concern with combination therapies is the risk of nephrotoxicity or ototoxicity when aminoglycosides are used (12). It is therefore recommended that aminoglycosides be given only for a short time (3 to 5 days) (10, 12). This approach is supported by the present study, which suggests that empirical combination therapy increases survival at 30 days, even if it is given for only 3 to 5 days and is followed by monotherapy.

Why does empirical therapy not influence mortality until receipt of the antibiogram? One reasonable hypothesis is that some patients are so sick that they will die within the first days following *P. aeruginosa* bacteremia, independently of any antimicrobial therapy. In contrast, patients in better clinical condition at the time of *P. aeruginosa* bacteremia might survive a few days independently of the appropriateness of antimicrobial treatment. Evidence supporting this hypothesis comes from the observation that clinical presentation at the onset of bacteremia is the strongest independent indicator of survival.

Like others (39), we observed that inadequate empirical antimicrobial therapies had sometimes not been modified according to the antibiogram results. It is likely that favorable

TABLE 6. Modifications of antimicrobial therapy within 30 days postbacteremia

Treatment type, time of modification	Modification	No. (%) of episodes
Empirical antimicrobial therapy, during early follow-up		
Adequate combination therapy (n = 43)	No modification	35 (81.4)
	Switch to adequate monotherapy	6 (14.0)
	Switch to inadequate therapy	2 (4.6)
Adequate monotherapy (n = 55)	No modification	34 (61.8)
	Switch to adequate combination therapy	12 (21.8)
	Switch to inadequate therapy	9 (16.4)
Inadequate therapy (n = 17)	No modification	11 (64.7)
	Switch to adequate combination therapy	5 (29.4)
	Switch to adequate monotherapy	1 (5.9)
Empirical antimicrobial therapy, at receipt of antibiogram[a]		
Adequate combination therapy (n = 43)	No modification	43 (100.0)
	Switch to adequate monotherapy	0 (0.0)
	Switch to inadequate therapy	0 (0.0)
Adequate monotherapy (n = 34)	No modification	31 (91.2)
	Switch to adequate combination therapy	3 (8.8)
	Switch to inadequate therapy	0 (0.0)
Inadequate therapy (n = 21)	No modification	20 (95.2)
	Switch to adequate combination therapy	0 (0.0)
	Switch to adequate monotherapy	1 (4.8)
Definitive antimicrobial therapy, during late follow-up[b]		
Adequate combination therapy (n = 46)	No modification	39 (92.0)
	Switch to adequate monotherapy	5 (8.0)
	Switch to inadequate therapy	0 (0.0)
Adequate monotherapy (n = 33)	No modification	30 (83.6)
	Switch to adequate combination therapy	3 (16.4)
	Switch to inadequate therapy	0 (0.0)
Inadequate therapy (n = 19)	No modification	11 (70.1)
	Switch to adequate combination therapy	1 (9.0)
	Switch to adequate monotherapy	4 (20.9)

[a] Sixteen patients died before receipt of the antibiogram; data on treatment modification between day 2 and the last day before receipt of the antibiogram were missing for one patient.

[b] Four patients died on the day of receipt of the antibiogram; data on treatment modifications after receipt of the antibiogram were missing for one patient.

evolution, despite treatment inadequacy, influenced the clinician's decisions in this sense. Older age was unexpectedly associated with better survival. However, our restrictive inclusion criteria (positive blood culture for *P. aeruginosa* in association with SIRS and administration of an empirical antimicrobial therapy that included at least one agent with antipseudomonal activity) probably selectively excluded from analysis elderly patients with poor prognoses. Indeed, blood samples for culture were probably less frequently obtained from elderly patients who had underlying conditions associated with a very poor prognosis. The elderly patients included in the analysis were also significantly more likely than younger patients to have characteristics associated with a better outcome (bacteremia of urinary origin, no neutropenia, and no steroid treatment).

Our study design was based on recommendations for high-quality observational studies for the evaluation of therapeutic effectiveness (19, 23). Nevertheless, we cannot exclude the possibility that estimates of treatment effects were biased by an imbalance associated with the therapeutic choices not accounted for in the multivariate analyses. This seems unlikely, because clinicians were uncertain about the diagnosis of *P. aeruginosa* bacteremia and unaware of the susceptibility to antimicrobials of the infecting strain at the time that they initiated empirical antimicrobial therapy. Because our sample size was small from a statistical viewpoint, multivariate analyses assessed only a limited number of therapy categories and controlled for only a few covariates simultaneously. Finally, analysis could not account for intercurrent treatment modifications which should have led to an attenuation of the observed differences in mortality across treatment groups.

We suggest that clinicians who suspect *P. aeruginosa* bacteremia initiate empirical therapy with two antipseudomonal agents. In the case of proven *P. aeruginosa* bacteremia, this combination therapy could be changed to monotherapy on the basis of the specific susceptibility pattern of the initial isolate. It is hoped that such an approach may reduce the risk of

selection of antimicrobial agent-resistant strains and avoid inadequate empirical therapies without increasing the risk of drug toxicity.

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REFERENCES

1. **Bayston, K. F., S. Want, and J. Cohen.** 1989. A prospective, randomized comparison of ceftazidime and ciprofloxacin as initial empiric therapy in neutropenic patients with fever. Am. J. Med. **87:**269S–273S.
2. **Bisbe, J., J. M. Gatell, J. Puig, J. Mallolas, J. A. Martinez, M. T. Jimenez de Anta, and E. Soriano.** 1988. *Pseudomonas aeruginosa* bacteremia: univariate and multivariate analyses of factors influencing the prognosis in 133 episodes. Rev. Infect. Dis. **10:**629–635.
3. **Bodey, G. P., L. Jadeja, and L. Elting.** 1985. *Pseudomonas* bacteremia. Retrospective analysis of 410 episodes. Arch. Intern. Med. **145:**1621–1629.
4. **Boffi El Amary, E., E. Chamot, R. Auckenthaler, J. C. Pechère, and C. Van Delden.** 2001. Influence of previous exposure to antibiotic therapy on the susceptibility pattern of *Pseudomonas aeruginosa* bacteremic isolates. Clin. Infect. Dis. **33:**1859–1864.
5. **Bonhoeffer, S., M. Lipsitch, and B. R. Levin.** 1997. Evaluating treatment protocols to prevent antibiotic resistance. Proc. Natl. Acad. Sci. USA **94:** 12106–12111.
6. **Buchanan, G. R.** 1993. Approach to treatment of the febrile cancer patient with low-risk neutropenia. Hematol. Oncol. Clin. N. Am. **7:**919–935.
7. **Carmeli, Y., N. Troillet, G. M. Eliopoulos, and M. H. Samore.** 1999. Emergence of antibiotic-resistant *Pseudomonas aeruginosa*: comparison of risks associated with different antipseudomonal agents. Antimicrob. Agents Chemother. **43:**1379–1382.
8. **Carmeli, Y., N. Troillet, A. W. Karchmer, and M. H. Samore.** 1999. Health and economic outcomes of antibiotic resistance in *Pseudomonas aeruginosa.* Arch. Intern. Med. **159:**1127–1132.
9. **Chatzinikolaou, I., D. Abi-Said, G. P. Bodey, K. V. Rolston, J. J. Tarrand, and G. Samonis.** 2000. Recent experience with *Pseudomonas aeruginosa* bacteremia in patients with cancer: retrospective analysis of 245 episodes. Arch. Intern. Med. **160:**501–509.
10. **Chow, J. W., and V. L. Yu.** 1999. Combination antibiotic therapy versus monotherapy for gram-negative bacteraemia: a commentary. Int. J. Antimicrob. Agents **11:**7–12.
11. **Concato, J., A. R. Feinstein, and T. R. Holford.** 1993. The risk of determining risk in multivariate models. Ann. Intern. Med. **118:**201–210.
12. **Craig, W. A., and D. Andes.** 1997. Aminoglycosides are useful for severe respiratory tract infections. Semin. Respir. Infect. **12:**271–277.
13. **Curtin, J. A., R. G. Petersdorf, and I. L. Bennett.** 1961. *Pseudomonas* bacteremia: review of ninety-one cases. Ann. Intern. Med. **54:**1077–1106.
14. **Diekema, D. J., M. A. Pfaller, R. N. Jones, G. V. Doern, P. L. Winokur, A. C. Gales, H. S. Sader, K. Kugler, and M. Beach.** 1999. Survey of bloodstream infections due to gram-negative bacilli: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, and Latin America for the SENTRY Antimicrobial Surveillance Program, 1997. Clin. Infect. Dis. **29:**595–607.
15. **Edgeworth, J. D., D. F. Treacher, and S. J. Eykyn.** 1999. A 25-year study of nosocomial bacteremia in an adult intensive care unit. Crit. Care Med. **27:**1421–1428.
16. **Elting, L. S., E. B. Rubenstein, K. V. Rolston, and G. P. Bodey.** 1997. Outcomes of bacteremia in patients with cancer and neutropenia: observations from two decades of epidemiological and clinical trials. Clin. Infect. Dis. **25:**247–259.
17. **Fauci, A. S., E. Braunwald, K. J. Isselbacher, J. D. Wilson, J. B. Martin, D. L. Kasper, S. L. Hauser, and D. L. Longo.** 2002. Harrison's principles of internal medicine. McGraw-Hill Book Co., New York, N. Y.
18. **Forkner, C. E., E. Frei, J. H. Edgcomb, and J. P. Utz.** 1958. *Pseudomonas* septicemia. Am. J. Med. **25:**877–888.
19. **Gail, M. H.** 1996. Use of observational data, including surveillance studies, for evaluating AIDS therapies. Stat. Med. **15:**2273–2288.
20. **Gangji, D., F. Jacobs, J. de Jonckheer, L. Coppens, E. Serruys, F. Hanotte, S. Motte, and J. P. Thys.** 1989. Randomized study of intravenous versus sequential intravenous/oral regimen of ciprofloxacin in the treatment of gram-negative septicemia. Am. J. Med. **87:**206S–208S.
21. **Grobbee, D. E., and A. W. Hoes.** 1997. Confounding and indication for treatment in evaluation of drug treatment for hypertension. BMJ **315:**1151–1154.
22. **Hilf, M., V. L. Yu, J. Sharp, J. J. Zuravleff, J. A. Korvick, and R. R. Muder.** 1989. Antibiotic therapy for *Pseudomonas aeruginosa* bacteremia: outcome correlations in a prospective study of 200 patients. Am. J. Med. **87:**542–546.
23. **Horwitz, R. I., C. M. Viscoli, J. D. Clemens, and R. T. Sadock.** 1990. Developing improved observational methods for evaluating therapeutics effects. Am. J. Med. **89:**630–638.
24. **Ibrahim, E. H., G. Sherman, S. Ward, V. J. Fraser, and M. H. Kollef.** 2000. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest **118:**146–155.
25. **Johnson, P. R., J. A. Liu Yin, and J. A. Tooth.** 1992. A randomized trial of high-dose ciprofloxacin versus azlocillin and netilmicin in the empirical therapy of febrile neutropenic patients. J. Antimicrob. Chemother. **30:**203–214.
26. **Kollef, M. H., and V. J. Fraser.** 2001. Antibiotic resistance in the intensive care unit. Ann. Intern. Med. **134:**298–314.
27. **Kollef, M. H., G. Sherman, S. Ward, and V. J. Fraser.** 1999. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest **115:**462–474.
28. **Kuikka, A., and V. V. Valtonen.** 1998. Factors associated with improved outcome of *Pseudomonas aeruginosa* bacteremia in a Finnish university hospital. Eur. J. Clin. Microbiol. Infect. Dis. **17:**701–708.
29. **Leibovici, L., M. Paul, O. Poznanski, M. Drucker, Z. Samra, H. Konigsberger, and S. D. Pitlik.** 1997. Monotherapy versus beta-lactam–minoglycoside combination treatment for gram-negative bacteremia: a prospective, observational study. Antimicrob. Agents Chemother. **41:**1127–1133.
30. **Leibovici, L., I. Shraga, M. Drucker, H. Konigsberger, Z. Samra, and S. D. Pitlik.** 1998. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. J. Intern. Med. **244:**379–386.
31. **Lim, S. H., M. P. Smith, A. H. Goldstone, and S. J. Machin.** 1990. A randomized prospective study of ceftazidime and ciprofloxacin with or without teicoplanin as an empiric antibiotic regimen for febrile neutropenic patients. Br. J. Haematol. **76**(Suppl. 2)**:**41–44.
32. **Martino, R., A. Santamaria, L. Munoz, R. Pericas, A. Altes, G. Prats, and J. Sierra.** 1999. Bacteremia by gram-negative bacilli in patients with hematologic malignancies. Comparison of the clinical presentation and outcome of infections by enterobacteria and non-glucose-fermenting gram-negative bacilli. Acta Haematol. **102:**7–11.
33. **Meunier, F., S. H. Zinner, H. Gaya, T. Calandra, C. Viscoli, J. Klastersky, M. Glauser, and the European Organization for Research on Treatment of Cancer International Antimicrobial Therapy Cooperative Group.** 1991. Prospective randomized evaluation of ciprofloxacin versus piperacillin plus amikacin for empiric antibiotic therapy of febrile granulocytopenic cancer patients with lymphomas and solid tumors. Antimicrob. Agents Chemother. **35:**873–878.
34. **Milatovic, D., and I. Braveny.** 1987. Development of resistance during antibiotic therapy. Eur. J. Clin. Microbiol. **6:**234–244.
35. **Mouton, J. W.** 1999. Combination therapy as a tool to prevent emergence of bacterial resistance. Infection **27**(Suppl. 2)**:**S24–S28.
36. **National Committee for Clinical Laboratory Standards.** 1998. Performance standards for antimicrobial susceptibility testing; eighth informational supplement. M100-S8. National Committee for Clinical Laboratory Standards, Wayne Pa.
37. **Siegman-Igra, Y., R. Ravona, H. Primerman, and M. Giladi.** 1998. *Pseudomonas aeruginosa* bacteremia: an analysis of 123 episodes, with particular emphasis on the effect of antibiotic therapy. Int. J. Infect. Dis. **2:**211–215.
38. **Spanik, S., J. Trupl, A. Kunova, L. Drgona, T. Salek, J. Mardiak, E. Kukuckova, M. Studena, P. Pichna, E. Oravcova, E. Grey, P. Koren, J. Svec, J. Lacka, J. Sufliarsky, and V. Krcmery.** 1997. Risk factors, aetiology, therapy and outcome in 123 episodes of breakthrough bacteraemia and fungaemia during antimicrobial prophylaxis and therapy in cancer patients. J. Med. Microbiol. **46:**517–523.
39. **Vidal, F., J. Mensa, M. Almela, J. A. Martinez, F. Marco, C. Casals, J. M. Gatell, E. Soriano, and D. A. M. Jimenez.** 1996. Epidemiology and outcome of *Pseudomonas aeruginosa* bacteremia, with special emphasis on the influence of antibiotic treatment. Analysis of 189 episodes. Arch. Intern. Med. **156:**2121–2126.
40. **Young, L. S.** 2000. Sepsis syndrome, p. 806–820. *In* G. L. Mandell, J. E. Bennett, and R. Dolin (ed.), Mandell, Douglas, and Bennett's principles and practice of infectious diseases. Churchill Livingstone, New York, N.Y.