2005

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***Antimicrob. Agents Chemother.* 2005, 49(4):1306. DOI: 10.1128/AAC.49.4.1306-1311.2005.**

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2005, p. 1306–1311 Vol. 49, No. 4
0066-4804/05/$08.00+0 doi:10.1128/AAC.49.4.1306–1311.2005

Pseudomonas aeruginosa Bloodstream Infection: Importance of Appropriate Initial Antimicrobial Treatment

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Received 9 August 2004/Returned for modification 23 October 2004/Accepted 6 December 2004

***Pseudomonas aeruginosa* bloodstream infection is a serious infection with significant patient mortality and health-care costs. Nevertheless, the relationship between initial appropriate antimicrobial treatment and clinical outcomes is not well established. This study was a retrospective cohort analysis employing automated patient medical records and the pharmacy database at Barnes-Jewish Hospital. Three hundred five patients with *P. aeruginosa* bloodstream infection were identified over a 6-year period (January 1997 through December 2002). Sixty-four (21.0%) patients died during hospitalization. Hospital mortality was statistically greater for patients receiving inappropriate initial antimicrobial treatment ($n = 75$) compared to appropriate initial treatment ($n = 230$) (30.7% versus 17.8%; $P = 0.018$). Multiple logistic regression analysis identified inappropriate initial antimicrobial treatment (adjusted odds ratio [AOR], 2.04; 95% confidence interval [CI], 1.42 to 2.92; $P = 0.048$), respiratory failure (AOR, 5.18; 95% CI, 3.30 to 8.13; $P < 0.001$), and circulatory shock (AOR, 4.00; 95% CI, 2.71 to 5.91; $P < 0.001$) as independent determinants of hospital mortality. Appropriate initial antimicrobial treatment was administered statistically more often among patients receiving empirical combination antimicrobial treatment for gram-negative bacteria compared to empirical monotherapy (79.4% versus 65.5%; $P = 0.011$). Inappropriate initial empirical antimicrobial treatment is associated with greater hospital mortality among patients with *P. aeruginosa* bloodstream infection. Inappropriate antimicrobial treatment of *P. aeruginosa* bloodstream infections may be minimized by increased use of combination antimicrobial treatment until susceptibility results become known.**

Bacterial bloodstream infections are serious infections associated with significant mortality and health-care costs (36). In many hospitals, *Pseudomonas aeruginosa* has become the most common gram-negative bacterial species associated with serious hospital-acquired infections, particularly within intensive care units (24, 29, 33). The hospital mortality associated with *P. aeruginosa* bloodstream infections is reported to be greater than 20% in most series and is highest among patients receiving inappropriate initial antimicrobial treatment (4, 6, 25, 32, 37). Unfortunately, prior studies of *P. aeruginosa* bloodstream infection varied in how they defined appropriate antimicrobial therapy and did not specifically examine the influence of administering combination antimicrobial agents as a determinant of appropriate treatment. Additionally, two recent meta-analyses recommend the use of monotherapy with a beta-lactam antibiotic for the empirical treatment of neutropenic fever and severe sepsis, infections where *P. aeruginosa* is often an important pathogen (26, 27).

Due to the clinical importance of bloodstream infections due to *P. aeruginosa*, we performed a retrospective cohort analysis with two main goals. First, we wanted to determine whether the administration of appropriate initial antimicrobial treatment was associated with better clinical outcomes for *P. aeruginosa* bloodstream infections. Our second goal was to examine the relationship between the empirical administration of combination gram-negative antimicrobial therapy and appropriate treatment for *P. aeruginosa* bloodstream infections.

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MATERIALS AND METHODS

Study location and patients. This study was conducted at a university-affiliated, urban teaching hospital, Barnes-Jewish Hospital (1,200 beds). During a 6-year period (January 1997 to December 2002), all hospitalized patients with a positive blood culture for *P. aeruginosa* were eligible for this investigation. This study was approved by the Washington University School of Medicine Human Studies Committee.

Study design and data collection. A retrospective cohort study design was employed with the main outcome measure being hospital mortality. We also assessed secondary outcomes, including the administration of appropriate initial antimicrobial treatment, length of hospitalization, and the occurrence of persistent bacteremia due to *P. aeruginosa*.

For all study patients the following characteristics were recorded by one of the investigators (S. T. Micek, A. E. Lloyd, or R. M. Reichley): age, gender, race, severity of illness based on the simplified acute physiology (SAP) score (21) and the all patient refined diagnosis related group (APR-DRG) score (30), the presence of underlying malignancy, neutropenia, infection source, and patient location at the time of infection. Specific processes of medical care examined during patients' hospital stays included mechanical ventilation for respiratory failure and the administration of vasopressors for circulatory shock. Variables describing the bloodstream infections and their treatment were also recorded, including administration of combination antimicrobials for gram-negative bacteria versus monotherapy and the appropriateness of initial antibiotic treatment. All patient-level data were recorded from automated patient medical records (EMTEK Health Care Systems Inc., Tempe, Ariz., and Clinical Desktop, BJC Healthcare, St. Louis, Mo.) and the Barnes-Jewish Hospital Pharmacy automated database, all of which contain prospectively entered information.

A computerized list of patients with a positive blood culture was generated daily by the Microbiology Laboratory at Barnes-Jewish Hospital, which allowed identification of potential study patients. Patients could be entered into the study more than once only if the subsequent episode of *P. aeruginosa* bacteremia occurred during a new hospital admission and at least 30 days had elapsed between positive blood cultures for *P. aeruginosa* (5).

Definitions. All definitions were selected prospectively as part of the original study design. We calculated SAP scores on the basis of clinical data available from the first 24-h period following identification of a positive blood culture (21). The APR-DRG was also employed to measure severity of illness, using a proprietary method (1, 30). APR-DRGs include four severity-of-illness classes (minor, moderate, major, and extreme) within each DRG, assigned according to a clinical algorithm evaluating multiple comorbidities, age, procedures, and principal diagnoses (1).

The antimicrobial guidelines for Barnes-Jewish Hospital during the study period recommended empirical treatment of suspected hospital-acquired bloodstream infections with a combination of an antistaphylococcal drug (vancomycin for methicillin-resistant staphylococci) and at least one antibiotic, usually a beta-lactam, with gram-negative activity. For patients at increased risk for infection with antibiotic-resistant gram-negative bacteria (e.g., *P. aeruginosa* and *Acinetobacter* species), two antibiotics directed against gram-negative bacteria were initially recommended (an antipseudomonal beta-lactam or a carbapenem in combination with an aminoglycoside or a fluoroquinolone). The Barnes-Jewish Hospital formulary promoted the use of ceftazidime up to 1997 and thereafter cefepime as the primary antipseudomonal beta-lactam antibiotic. Imipenem and ciprofloxacin were the formulary carbapenem and fluoroquinolone antibiotics, respectively, available for clinical use during the entire study period. The antibiotic guidelines recommended modifying the initially prescribed empirical antimicrobial regimens based on the results of clinical cultures and the antimicrobial susceptibility of the identified pathogens. De-escalation or narrowing of the initial empirically prescribed antimicrobial regimens was monitored by hospital pharmacists and had to be approved by the patient's primary physician team (2, 16).

For purposes of this investigation, inappropriate antimicrobial treatment of a bloodstream infection was defined as the microbiological documentation of infection (i.e., a positive blood culture result) that was not effectively treated at the time the causative microorganism and its antibiotic susceptibility were known (15, 17, 19). The microbiology laboratory performed antimicrobial susceptibility testing of clinical isolates by the Kirby-Bauer disk diffusion method according to guidelines and breakpoints established by the National Committee for Clinical Laboratory Standards (23), using 150-mm round plates of Mueller-Hinton agar (BBL, Becton-Dickinson, Cockeysville, Md.). A technologist experienced in reading zones of inhibition with a ruler against a black background measured the zone diameters manually. Inappropriate antimicrobial treatment included the absence of gram-negative antimicrobial agents with in vitro activity against *P. aeruginosa* and the administration of gram-negative antimicrobial agents to which the *P. aeruginosa* isolates were resistant based on susceptibility testing.

Circulatory shock was defined as systolic arterial pressure lower than 90 mm Hg for at least 1 h despite adequate fluid replacement and more than 5 μg of dopamine/kg of body weight or current treatment with epinephrine or norepinephrine (25). Additionally, urinary output of less than 0.5 ml/kg of body weight for at least 1 h was required for circulatory shock. Respiratory failure was defined as the need for mechanical ventilation applied by either an endotracheal tube or by mask.

Blood culture technique. Blood cultures were obtained from two peripheral sites by nurses or hospital-trained phlebotomists. Before collecting the blood cultures, skin was disinfected with 70% isopropyl alcohol followed by 2% iodine tincture. The antecubital fossae were the preferred sampling sites, using sterile needles and syringes. When only one peripheral site was available and the patient had a central vein catheter in place, the second blood culture sample was obtained from the central vein catheter. Injection of 5 ml or less of blood into a blood culture bottle was not permitted, to avoid false-negative results (35). All blood samples were inoculated into aerobic medium and processed using the BACTEC blood culture system (Becton Dickinson, Sparks, Md.).

Statistical analysis. All comparisons were unpaired, and all tests of significance were two-tailed. Continuous variables were compared using the Student *t* test for normally distributed variables and the Mann-Whitney U test for nonnormally distributed variables. The chi-square or Fisher's exact test was used to compare categorical variables. The primary data analysis compared hospital nonsurvivors with survivors. Values are expressed as the mean ± standard deviation (continuous variables) or as a percentage of the group from which they were derived (categorical variables). All *P* values were two-tailed, and *P* values of 0.05 or less were considered to indicate statistical significance.

TABLE 1. Baseline characteristics of patients at admission and infection source[a]

Variable	Survivors (n = 241)	Nonsurvivors (n = 64)	P value
Age (yrs)	58.8 ± 17.9	56.0 ± 17.4	0.256
Male gender, n (%)	134 (55.6)	39 (60.9)	0.444
Race, n (%)			
White	164 (68.0)	52 (81.3)	0.114
African American	68 (28.2)	11 (17.2)	
Other	9 (3.7)	1 (1.6)	
Neutropenia, n (%)	54 (22.4)	12 (18.8)	0.528
Underlying malignancy, n (%)	100 (41.5)	26 (40.6)	0.900
Patient location, n (%)			
Intensive care unit	116 (48.1)	52 (81.3)	<0.001
Hospital ward	116 (48.1)	11 (17.2)	
Other	9 (3.7)	1 (1.6)	
SAP score	10.9 ± 4.6	13.8 ± 5.2	0.007
APR-DRG score	3.3 ± 0.7	3.9 ± 0.4	<0.001
Infection source, n (%)			
Lung	42 (17.4)	24 (37.5)	0.005
Urinary tract	49 (20.3)	7 (10.9)	
Soft tissue or wound	31 (12.9)	8 (12.5)	
Unknown	119 (49.4)	25 (39.1)	

[a] Values presented are means ± standard deviations.

We performed multiple logistic regression analysis using SPSS, version 11.0 for Windows (SPSS, Inc., Chicago, Ill.). Multivariate analysis was performed using models that were judged a priori to be clinically sound (7). This was prospectively determined to be necessary to avoid producing spuriously significant results with multiple comparisons. All potential risk factors significant at the 0.2 level were entered into the model. A stepwise approach was used to enter new terms into the logistic regression model, where hospital mortality was the dependent outcome variable and 0.05 was set as the limit for the acceptance or removal of new terms.

RESULTS

Patients. A total of 596 consecutive patients with bloodstream infection due to *P. aeruginosa* were evaluated. Two hundred twenty-four (37.6%) patients were excluded from analysis due to the presence of polymicrobial bloodstream infection. Sixty-seven (11.2%) patients, with a hospital mortality of 55.2%, were excluded due to incomplete information regarding antimicrobial treatment during the first 24 h following the collection of blood cultures. The remaining 305 patients constituted the study cohort. The mean age of the patients was 58.2 ± 17.8 years (range, 16 to 97 years), and the mean SAP score was 11.5 ± 4.9 (range, 3 to 26). There were 173 (56.7%) men and 132 (43.3%) women; 216 (70.8%) patients were white, 79 (25.9%) were black, and 10 (3.3%) were either Hispanic or Asian American.

Patient characteristics according to hospital mortality. Hospital nonsurvivors were statistically more likely to be in an intensive care unit setting at the time the bloodstream infection was diagnosed, to have the lung identified as the source of *P. aeruginosa* bloodstream infection, and to have greater SAP scores and APR-DRG scores (Table 1). Additionally, hospital nonsurvivors statistically more often required vasopressors for circulatory shock and mechanical ventilation for respiratory failure and developed acute renal failure (Table 2).

Antimicrobial treatment characteristics. The antimicrobial susceptibilities of the *P. aeruginosa* bloodstream isolates obtained during the study period are presented in Table 3. Sev-

TABLE 2. Specific organ dysfunction and secondary outcomes

Variable	Survivors (n = 241)	Nonsurvivors (n = 64)	P value
Circulatory shock requiring vasopressors, n (%)	63 (26.1)	45 (70.3)	<0.001
Respiratory failure, n (%)	62 (25.7)	45 (70.3)	<0.001
Acute renal failure, n (%)	24 (10.0)	18 (28.1)	<0.001
Subsequent bacteremia, n (%)	16 (6.6)	7 (10.9)	0.247
Hospital length of stay, days[a]	23.9 ± 29.1 (14.0, 4.25–23.75)	44.5 ± 40.8 (27.5, 11.375–43.625)	<0.001

[a] Values are presented as mean ± SD (median, interquartile range).

enty-five (24.6%) patients were treated with inappropriate initial antimicrobial regimens for *P. aeruginosa* bloodstream infections. Nine (12.0%) patients treated with inappropriate initial antimicrobial regimens received no initial gram-negative antibiotics directed against *P. aeruginosa*. Sixty-six (88.0%) patients receiving inappropriate therapy were treated with antibiotics having recognized activity against *P. aeruginosa* but for which the isolated bacteria were actually resistant by in vitro susceptibility testing. Patients receiving inappropriate initial antimicrobial treatment had statistically greater APR-DRG scores (3.6 ± 0.6 versus 3.3 ± 0.7; $P = 0.014$) and statistically lower rates of neutropenia (5.3% versus 27.0%; $P < 0.001$) and underlying malignancy (30.7% versus 44.8%; $P = 0.031$) compared to patients receiving appropriate initial antimicrobial treatment.

Hospital mortality was statistically greater for patients receiving inappropriate initial antimicrobial treatment ($n = 75$) compared to appropriate initial treatment ($n = 230$) (30.7% versus 17.8%; $P = 0.018$). Twenty-nine patients (9.5%) had inappropriate treatment administered beyond 24 h from initial antimicrobial treatment but for less than 48 h before changing to appropriate antimicrobials. These patients had similar hospital mortality to patients receiving appropriate treatment between 24 and 48 h after the start of antibiotics ($n = 276$) (20.7% versus 19.2%; P was not significant). Three patients received inappropriate antimicrobial treatment beyond 48 h (100% hospital survival). Inappropriate initial antimicrobial administration was statistically more likely to occur among patients receiving monotherapy directed against gram-negative bacteria compared to those receiving combination therapy (34.5% versus 20.6%; $P = 0.011$). Treatment with ceftazidime or cefepime was statistically greater among patients receiving appropriate initial antimicrobial treatment, while the initial empirical administration of ciprofloxacin was statistically greater among patients receiving inappropriate treatment (Table 4).

Among patients receiving appropriate initial empirical antimicrobial treatment with a single beta-lactam ($n = 95$; mortality = 12.6%), a single aminoglycoside ($n = 29$; mortality = 10.3%), the combination of a beta-lactam and an aminoglycoside ($n = 59$; mortality = 22.0%), or ciprofloxacin alone ($n = 15$; mortality = 6.7%), there was no statistical difference in hospital mortality ($P = 0.214$). Similarly, for appropriate definitive antimicrobial treatment there was no statistical difference in hospital mortality among patients receiving a single beta-lactam ($n = 92$; mortality = 15.2%), the combination of a beta-lactam and an aminoglycoside ($n = 59$; mortality = 22.0%), or ciprofloxacin alone ($n = 14$; mortality = 14.3%) ($P = 0.312$). APR-DRG scores (12.1 ± 4.8 versus 10.4 ± 5.0: $P = 0.091$) and SAP scores (3.4 ± 0.7 versus 3.2 ± 0.8; $P = 0.175$) were not statistically different among patients receiving combination antimicrobial therapy directed against *P. aeruginosa* compared to monotherapy.

Multivariate analysis. Multiple logistic regression analysis identified the administration of inappropriate initial antimicrobial treatment, respiratory failure, and circulatory shock as independent determinants of hospital mortality (Table 5). The APR-DRG scores were not entered into the multivariate analysis because no other variables achieved statistical significance with this variable in the model. All other combinations of variables entered into the logistic regression analysis yielded a final model with inappropriate initial antimicrobial treatment as an independent determinant of hospital mortality. To assess the importance of inappropriate initial antimicrobial treatment in potential intermediate variables and confounding variables, two subgroup analyses were performed. Among the 198 pa-

TABLE 3. Antimicrobial susceptibility of *P. aeruginosa* bloodstream isolates ($n = 305$)[a]

Antimicrobial(s)	% Susceptible in:						
	1997 (n = 52)	1998 (n = 53)	1999 (n = 53)	2000 (n = 50)	2001 (n = 50)	2002 (n = 47)	All years
Cefepime	NF[b]	93.8	90.6	94.0	92.1	91.5	92.3
Ceftazidime	96.1	92.3	NF	NF	NF	NF	94.0
Piperacillin-tazobactam	NF	96.9	92.5	92.0	94.7	91.5	93.7
Imipenem-cilastatin	88.5	89.2	94.3	88.0	84.2	78.7	87.5
Ciprofloxacin	88.5	80.0	83.0	78.0	68.4	78.7	80.0
Gentamicin	92.3	90.8	92.5	92.0	92.1	100.0	93.1
Tobramycin	94.2	96.9	92.5	94.0	97.4	100.0	95.7

[a] Resistance to antimicrobial combinations: cefepime or ceftazidime and aminoglycoside, 2.3%; cefepime or ceftazidime and ciprofloxacin, 4.6%; piperacillin-tazobactam and aminoglycoside, 1.6%; piperacillin-tazobactam and ciprofloxacin, 4%; imipenem-cilastatin and aminoglycoside, 2.3%; imipenem-cilastatin and ciprofloxacin, 5.6%.

[b] NF, nonformulary.

TABLE 4. Appropriateness of initial antimicrobial treatment by antibiotic[a]

Drug class	No. (%) appropriate (n = 230)	No. (%) inappropriate (n = 75)	P value
Cefepime	141 (61.3)	33 (44.0)	0.009
Ceftazidime	36 (15.7)	3 (4.0)	0.009
Piperacillin-tazobactam	5 (2.2)	3 (4.0)	0.686
Imipenem	31 (13.5)	9 (12.0)	0.742
Aminoglycoside[b]	102 (44.3)	30 (40.0)	0.509
Ciprofloxacin	32 (13.9)	19 (25.3)	0.021
Aztreonam	1 (0.4)	0 (0.0)	>0.999
Other	4 (1.7)	2 (2.7)	0.638

[a] Appropriate antimicrobial treatment was defined as in vitro susceptibility testing demonstrating a sensitive isolate of *P. aeruginosa* to the antimicrobial agent prescribed.
[b] Includes gentamicin, tobramycin, and amikacin.

tients without respiratory failure, inappropriate initial antimicrobial treatment (n = 43) was associated with a statistically greater hospital mortality compared to appropriate initial antimicrobial treatment (n = 155) (18.6% versus 7.1%; P = 0.023). Similarly, among the 197 patients without circulatory shock, inappropriate initial antimicrobial treatment (n = 42) was associated with a greater hospital mortality compared with appropriate initial antimicrobial treatment (n = 155) (16.7% versus 7.7%; P = 0.082).

Secondary outcomes. Hospital nonsurvivors had statistically longer hospital lengths of stay than hospital survivors (Table 2). Similarly, patients receiving inappropriate initial antimicrobial treatment had statistically longer hospital lengths of stay than those receiving appropriate treatment (41.4 ± 47.4 days versus 23.9 ± 25.2 days; P = 0.006). Among the hospital survivors, those receiving inappropriate initial antimicrobial treatment (n = 52) had a trend towards longer hospital length of stay compared to patients receiving appropriate treatment (n = 189) (34.0 ± 44.4 days versus 21.1 ± 22.6 days; P = 0.096).

DISCUSSION

Our study demonstrated that inappropriate initial antimicrobial treatment of *P. aeruginosa* bloodstream infection is associated with statistically greater mortality compared to initial treatment with an antimicrobial regimen to which the bacteria were susceptible. Multiple logistic regression analysis identified inappropriate initial antimicrobial treatment as an independent predictor for hospital mortality. Additionally, our data showed that initial treatment with combination antimicrobial agents directed against *P. aeruginosa* was statistically more likely to provide appropriate treatment than was monotherapy. Finally, the use of fluoroquinolone antibiotics was associated with a statistically greater likelihood of inappropriate initial treatment, while cefepime and ceftazidime were statistically more likely to be associated with appropriate therapy.

TABLE 5. Multivariate analysis of independent risk factors for hospital mortality[a]

Predictor	Adjusted odds ratio	95% CI	P value
Inappropriate initial antimicrobial treatment	2.04	1.42–2.92	0.048
Respiratory failure	5.18	3.30–8.13	<0.001
Circulatory shock	4.00	2.71–5.91	<0001

[a] CI, confidence interval. Note: other covariates not presented in the table had a P value of >0.05, including race, infection source, acute renal failure, patient location, and SAP score. Hosmer-Lemeshow deciles of risk statistic, P = 0.33.

Previous investigations have shown that antimicrobial regimens lacking activity against identified microorganisms causing serious infections (e.g., hospital-acquired pneumonia, bloodstream infections) are associated with greater hospital mortality (15, 17, 19). More recently, the same finding has been demonstrated for patients with severe sepsis (8, 10, 14). Inappropriate antimicrobial treatment has been shown to be an important independent risk factor for mortality among hospitalized patients with bloodstream infections (15). Unfortunately, changing antimicrobial therapy to an appropriate regimen after susceptibility data become available has not been demonstrated to improve clinical outcome (20, 28). These studies suggest that clinicians should strive to administer appropriate initial antimicrobial treatment for patients with serious infections, including *P. aeruginosa* bloodstream infections. In addition to selecting an appropriate initial antimicrobial regimen, optimal dosing, interval of drug administration, and duration of treatment are required for antimicrobial efficacy, limiting toxicity, and to prevent the emergence of bacterial resistance (18).

This study is unique in having a relatively large population of patients with *P. aeruginosa* bloodstream infection for evaluation. Bryan et al. previously found that appropriate antimicrobial therapy for gram-negative bacteremia, on the calendar day the blood culture was identified to be positive, was not associated with improved survival (4). Appropriate antibiotic treatment subsequent to the first calendar day on which blood cultures were positive did favorably appear to influence outcomes. Vidal et al. were only able to demonstrate an association between inappropriate definitive antimicrobial treatment for *P. aeruginosa* bacteremia and mortality after excluding the subset of patients with catheter-associated bloodstream infection from their analysis (32). Similarly, Chatzinikolaou et al. did not find a relationship between the appropriateness of antibiotic treatment and mortality among cancer patients with *P. aeruginosa* infection (6).

Bodey et al. examined 410 episodes of *Pseudomonas* bacteremia and found that patients receiving appropriate antibiotic therapy had a greater likelihood of achieving a clinical cure of their infection (3). This same group of investigators showed that patients treated with a beta-lactam antibiotic with or without an aminoglycoside had a significantly higher cure rate than patients who received only an aminoglycoside (3). Similarly, Chamot and coworkers demonstrated that patients with *Pseudomonas* bacteremia treated with combination empirical antimicrobial therapy until receipt of the antibiogram had a better 30-day survival compared to monotherapy (5). However, combination antimicrobial therapy given as definitive treatment for *P. aeruginosa* bacteremia did not improve the rate of survival compared to appropriate definitive monotherapy (5). Our study results are consistent with the findings from these two investigations. We showed that initial appropriate antimicrobial treatment for *P. aeruginosa* bacteremia can improve

outcome and that combination antimicrobial therapy may be superior to monotherapy for initial empirical treatment but not for definitive therapy after the antibiogram results are known.

A potential explanation for the discordant findings among the studies of *P. aeruginosa* bloodstream infection is how appropriate antimicrobial treatment was defined. In at least one of the prior studies, appropriate antimicrobial treatment was defined according to the initial drug class selection and not on the basis of in vitro susceptibility testing (6). This definition would classify patients as receiving appropriate initial treatment despite the presence of a *P. aeruginosa* isolate resistant to the prescribed antibiotic(s). In a pediatric study of *Pseudomonas* bacteremia, antimicrobial susceptibility was not identified as a prognostic factor (12). However, the administration of appropriate treatment was not specifically examined. This investigation did find that prior antibiotic administration was associated with greater patient mortality. Interestingly, prior antibiotic treatment has consistently been demonstrated to be a risk factor for subsequent infection with antibiotic-resistant bacteria, including *P. aeruginosa*, and the subsequent administration of inappropriate antimicrobial treatment (9, 15, 19).

Harbarth et al. examined 224 episodes of bloodstream infection among patients admitted to a surgical intensive care unit (13). They found that appropriate antimicrobial therapy was an independent determinant of survival and that mortality rates were highest for pathogens most likely to be treated with inappropriate initial antimicrobial regimens (*Candida* species, *Enterobacter* species, and *P. aeruginosa*). Similarly, we previously showed that there is a statistically significant correlation between the rates of inappropriate antimicrobial treatment for individual microorganisms causing bloodstream infection and their associated hospital mortality (15). Three recent studies of patients with severe sepsis, many of whom had bloodstream infections, also demonstrated that inappropriate initial antimicrobial therapy was associated with greater hospital mortality (8, 10, 14). These investigations support the importance of early administration of appropriate antibiotics to patients with serious infections, including bloodstream infection (22).

A potential advantage of combination antimicrobial therapy over monotherapy is the higher probability that the infecting pathogen will be covered by at least one of the components of the regimen. Furthermore, an interaction between two antibiotics may be synergistic, resulting in enhanced bacterial kill activity compared to the additive activities of the antibiotics when assessed separately (11). Finally, use of combination therapy has been claimed to suppress emergence of resistant subpopulations of bacteria (34). On the other hand, benefits of monotherapy may include lower costs, fewer adverse effects, especially when aminoglycosides are avoided, and a narrower spectrum of treatment, possibly reducing the chance of developing a superinfection with resistant bacteria. Two recent meta-analyses have concluded that patients with neutropenic fever and severe sepsis should be treated with empirical monotherapy for presumed infection attributed to gram-negative bacteria, due to fewer adverse effects linked to the antimicrobial treatment (26, 27). Most of the adverse events identified in these analyses were associated with the use of aminoglycosides. Unfortunately, these analyses did not evaluate the importance of appropriate initial antimicrobial treatment and examined small numbers of patients with microbiologically documented infections due to *P. aeruginosa*. The results from our investigation differ, suggesting that patients with *P. aeruginosa* bloodstream infection may benefit from the initial administration of combination antibiotic treatment.

Our study has several important limitations. First, we did not identify risk factors for the presence of *P. aeruginosa* bloodstream infection. Earlier reports have demonstrated that prolonged hospitalization, prior treatment with antibiotics, particularly broad-spectrum antibiotics, and colonization with *P. aeruginosa* increase the likelihood of infection with this pathogen (9, 18, 31). The presence of such risk factors has been advocated as a trigger for the empirical treatment of potentially antibiotic-resistant bacteria (31). Second, our study was performed at a single site and the results may not be applicable to other settings. However, the consistent relationship demonstrated between inappropriate treatment of serious bacterial infections and outcome suggests that this is a more universal finding (17). Third, we did not attempt to directly control the antimicrobial treatment prescribed to patients. It is possible that our results would have varied if more rigid antimicrobial control policies were in place. Nevertheless, only nine (3.0%) patients were treated initially with antimicrobial agents lacking potential activity against *P. aeruginosa*. This was most likely related to the overall prevalence of *P. aeruginosa* as a pathogen in our hospital and the empirical antimicrobial protocols emphasizing the local use of antipseudomonal beta-lactam antibiotics. The greater mortality observed among patients not included in our analysis due to missing data also suggests the potential for a reporting bias in our results. Finally, due to the observational design of this study, a definitive relationship between the use of combination antimicrobial therapy and improved administration of appropriate treatment for *P. aeruginosa* bloodstream infections cannot be inferred.

In summary, we demonstrated that appropriate initial antimicrobial treatment for *P. aeruginosa* bloodstream infection was associated with statistically greater hospital survival. Additionally, the initial empirical use of combination antimicrobial therapy directed against gram-negative bacteria was associated with greater administration of appropriate treatment. The majority of inappropriate initial antimicrobial treatment was the consequence of drug resistance, despite promoting empirical antibiotic regimens with agents having potential activity against *P. aeruginosa*. This underscores the clinical importance of escalating antimicrobial resistance among bacterial pathogens. Future studies are needed to define the optimal strategy for the empirical treatment of patients at risk for *P. aeruginosa* bloodstream infection. Until such data become available, clinicians may consider the use of empirical combination antimicrobial treatment for such patients, balancing this against the potential for greater toxicity and the emergence of antimicrobial resistance.

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