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Influence of Multidrug Resistance and Appropriate Empirical Therapy on the 30-Day Mortality Rate of *Pseudomonas aeruginosa* Bacteremia

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Infections due to multidrug-resistant (MDR) *Pseudomonas aeruginosa* are increasing. The aim of our study was to evaluate the influences of appropriate empirical antibiotic therapy and multidrug resistance on mortality in patients with bacteremia due to *P. aeruginosa* (PAB). Episodes of PAB were prospectively registered from 2000 to 2008. MDR was considered when the strain was resistant to ≥3 antipseudomonal antibiotics. Univariate and multivariate analyses were performed. A total of 709 episodes of PAB were studied. MDR PAB ($n = 127$ [17.9%]) was more frequently nosocomial and associated with longer hospitalization, bladder catheter use, steroid and antibiotic therapy, receipt of inappropriate empirical antibiotic therapy, and a higher mortality. Factors independently associated with mortality were age (odds ratio [OR], 1.02; 95% confidence interval [CI], 1.002 to 1.033), shock (OR, 6.6; 95% CI, 4 to 10.8), cirrhosis (OR, 3.3; 95% CI, 1.4 to 7.6), intermediate-risk sources (OR, 2.5; 95% CI, 1.4 to 4.3) or high-risk sources (OR, 7.3; 95% CI, 4.1 to 12.9), and inappropriate empirical therapy (OR, 2.1; 95% CI, 1.3 to 3.5). To analyze the interaction between empirical therapy and MDR, a variable combining both was introduced in the multivariate analysis. Inappropriate therapy was significantly associated with higher mortality regardless of the susceptibility pattern, and there was a trend toward higher mortality in patients receiving appropriate therapy for MDR than in those appropriately treated for non-MDR strains (OR, 2.2; 95% CI, 0.9 to 5.4). In 47.9% of MDR PAB episodes, appropriate therapy consisted of monotherapy with amikacin. In conclusion, MDR PAB is associated with a higher mortality than non-MDR PAB. This may be related to a higher rate of inappropriate empirical therapy and probably also to amikacin as frequently the only appropriate empirical therapy given to patients with MDR PAB.

Pseudomonas aeruginosa is one of the leading causes of nosocomial bloodstream infections and the third most frequent cause of Gram-negative infections in the United States (31). This pathogen causes severe infections, especially in immunocompromised hosts, and it is associated with a high mortality rate (29). In recent years, the number of multidrug-resistant (MDR) strains has increased, and this reduces the probability of administering an appropriate empirical treatment (19). In critically ill patients with septic shock, every hour of delay in the administration of appropriate antibiotic therapy has been associated with a cumulative increase in the risk of death (11–15). Other observations have also supported the importance of appropriate empirical therapy in patients with bacteremia in general (26) or due to particular pathogens, such as methicillin-resistant *Staphylococcus aureus* (22) or *Escherichia coli* (21). For *Pseudomonas aeruginosa* bacteremia (PAB), previous studies found that inappropriate empirical therapy was a risk factor for mortality when considering all patients (2, 9) or for a subset of patients with more severe infection (8, 27). However, the influence of multidrug resistance on the probability of receiving appropriate empirical therapy was not evaluated. Some authors have described a higher mortality rate among patients with MDR strains (1, 7, 8, 10, 16, 25, 28), but these patients more frequently received incorrect empirical therapy and had more severe underlying diseases and longer hospital stays than patients infected by susceptible *Pseudomonas aeruginosa* strains (24). Therefore, the individual influence of each one of these variables on the mortality of PAB is still not well defined.

The aim of our study was to determine the influence of appropriate empirical therapy and other important factors, particularly MDR, on the mortality of 709 consecutive patients with *P. aeruginosa* bacteremia.

MATERIALS AND METHODS

Study design. The study was conducted in an 850-bed university center that provides specialized and broad medical, surgical, and intensive care for an urban population of 500,000 people. Since 1991, our unit has been prospectively identifying and monitoring all patients with bacteremia admitted to our hospital. The present report refers to all patients with bacteremia due to *P. aeruginosa* from January 2000 to December 2008. The Ethics Committee board of our institution approved the study.

Data collection and definition. (i) Assessed clinical variables. Factors potentially associated with mortality were prospectively gathered from all patients by clinical investigators and retrospectively analyzed. Clinical and microbiological variables were age, gender, comorbidities, prognosis of the underlying disease (according to a modification of the McCabe and Jackson criteria) (20), treatment with antibiotics or steroids in the previous month, recent hospitalization (within the last month), surgery and other invasive procedures, origin of infection (community, nosocomial, or health care related), source of bacteremia, shock on presentation, antimicrobial susceptibility pattern, empirical antibiotic treatment, appropriateness of empirical therapy, and 30-day mortality.

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(ii) Definitions. MDR was considered when the strain was resistant to ≥3 antipseudomonal antibiotics (ciprofloxacin, ceftazidime, piperacillin-tazobactam, meropenem, and amikacin) (6). Appropriate empirical therapy was considered when the patient received at least one *in vitro* active antimicrobial agent within 24 h after blood cultures were obtained and before susceptibility results were available and if the dosage and route of administration were in accordance with the current medical standards. Specific dosages of antibiotics were not recorded. However, local guidelines during the study period recommended the administration of aminoglycosides in a single daily dose of 5 to 7 mg/kg of body weight for gentamicin and tobramycin and 15 to 20 mg/kg for amikacin in patients with normal renal function. Sources of infection were grouped according to their mortality risk as follows: (i) low risk (<15%), urinary tract, vascular catheter, skin and soft tissue, biliary tract, and bone and joint; (ii) intermediate risk (15 to 30%), unknown, abdominal, and other infections (pacemaker infection, endocarditis, and otolaryngology infections); (iii) high risk (>30%), respiratory.

Microbiological procedures. Antimicrobial susceptibility testing was performed by using a microdilution system (Phoenix system [Becton, Dickinson, Franklin Lakes, NJ] or Etest [AB Biodisk, Solna, Sweden]). Current Clinical and Laboratory Standards Institute (CLSI) breakpoints for each year were used to define susceptibility or resistance to these antimicrobial agents. The antibiotics tested were piperacillin-tazobactam, ceftazidime, cefepime, imipenem, meropenem, ciprofloxacin, gentamicin, tobramycin, amikacin, and colistin. For the purpose of analysis, intermediate susceptibility was considered resistant.

Statistical analysis. Data from different groups of patients were compared using chi-square or Fisher's exact tests for categorical variables and the Student *t* test or Mann-Whitney U test for continuous variables. Patient's characteristics or exposures with a *P* value of ≤0.20 in the univariate analysis were subjected to further selection by using a forward stepwise nonconditional logistic procedure, and the criteria for variables to step in and out were a *P* value of 0.10 and 0.10, respectively. A two-tailed *P* value of <0.05 was regarded as significant. To evaluate model calibration, the Hosmer-Lemeshow (H-L) test for goodness of fit was applied. Due to the fact that inappropriate empirical therapy was more frequent in MDR PAB, a new variable combining empirical antibiotic therapy and MDR was created to better define the effect of the appropriateness of empirical treatment on mortality. This composite variable was included in the multivariate analysis with four categories, as follows: appropriate therapy and non-MDR (reference category), appropriate therapy and MDR, inappropriate therapy and non-MDR, and inappropriate therapy and MDR. The analysis was carried out using SPSS software (version 17.0; SPSS, Inc., Chicago, IL).

RESULTS

From January 2000 to December 2008, a total of 709 consecutive episodes of *Pseudomonas aeruginosa* bacteremia were identified. The mean age (± standard deviation [SD]) of the entire cohort was 61.84 ± 16 years (median, 64.68; range, 17 to 102; interquartile range [IQR], 51.99 to 73.60), 66.7% were males, for 71% the infection source was nosocomial, and the 30-day mortality was 19.9% (141 of 709). The resistance rates to ceftazidime, piperacillin-tazobactam, meropenem, ciprofloxacin, and amikacin were 15.6% (111/709), 15.2% (108/709), 14% (99/709), 23.5% (167/709), and 0.4% (3/709), respectively. All isolates were susceptible to colistin, and the multidrug resistance rate, according to the definition stated in Materials and Methods, was 17.9% (127/709).

Clinical characteristic of patients with MDR and non-MDR PAB are shown in Table 1. In comparison with non-MDR PAB, MDR PAB episodes were more frequently hospital acquired (85% versus 68%; $P < 0.0001$) and were positively associated with a longer hospital stay (31.83 ± 30 days versus 16.38 ± 18 days; $P < 0.0001$), bladder catheterization (53.5% versus 37.5%; $P < 0.0001$), prior corticosteroid therapy (41.7% versus 33.8%; $P = 0.03$), prior antibiotic treatment (85.8% versus 53.4%; $P < 0.0001$), receipt of inappropriate empirical antibiotic therapy (62.2% versus 27%; $P < 0.0001$), and a higher 30-day mortality rate (32.3% versus 17.2%; $P < 0.0001$). The specific sources of PAB, the prevalence of MDR for each source, and the 30-day mortality are summarized in Table 2.

A total of 141 (19.9%) patients with PAB died. Factors associated with 30-day mortality in the univariate analysis included an ultimately or rapidly fatal underlying disease ($P < 0.0001$), liver cirrhosis ($P = 0.02$), MDR PAB ($P < 0.0001$), mechanical ventilation ($P < 0.0001$), septic shock ($P < 0.0001$), a high-risk source ($P < 0.0001$), and receiving inappropriate empirical antibiotic therapy ($P = 0.001$) (Table 3). In comparison with patients with non-MDR PAB who received appropriate empirical therapy,

TABLE 1 Clinical characteristics of patients with MDR or non-MDR *P. aeruginosa* bacteremia

Characteristic	No. (%)[a] of patients with characteristic and: Non-MDR PAB ($n = 582$)	MDR PAB ($n = 127$)	*P* value
Mean (SD) age (yrs)	62.17 (16)	60.30 (17)	0.24
Male gender	379 (65.1)	94 (74)	0.06
Acquisition			
Community	118 (20.3)	1 (0.8)	
Nosocomial	396 (68)	108 (85)	<0.0001
Health care related	66 (11.3)	18 (14.2)	
An ultimate/final fatal underlying disease	305 (52.4)	73 (57.5)	0.58
Mean (SD) days to death after admission	16.38 (18)	31.83 (30)	<0.0001
Hematological cancer	79 (13.6)	16 (12.6)	0.89
Solid organ cancer	103 (17.7)	18 (14.2)	0.36
Solid organ transplant	60 (10.3)	20 (15.7)	0.09
Neutropenia (<500 cells)	71 (12.2)	17 (13.4)	0.44
COPD[b]	70 (12)	16 (12.6)	0.88
Chronic renal failure	56 (9.6)	17 (13.4)	0.2
Hemodialysis	28 (4.8)	6 (4.7)	1
Diabetes mellitus	104 (17.9)	21 (16.5)	0.8
Liver cirrhosis	30 (5.2)	10 (7.9)	0.29
HIV infection	19 (3.3)	8 (6.3)	0.12
Prior antibiotic therapy	311 (53.4)	109 (85.8)	<0.0001
Prior steroid therapy	197 (33.8)	53 (41.7)	0.03
Bladder catheter	218 (37.5)	68 (53.5)	<0.0001
Mechanical ventilation	81 (13.9)	21 (16.5)	0.49
Septic shock	109 (18.7)	31 (24.4)	0.25
Mortality risk group[c]			
Low risk	291 (50)	74 (58.3)	
Intermediate risk	183 (31.4)	28 (22)	0.09
High risk	108 (18.6)	25 (19.7)	
Inappropriate empirical antibiotic	157 (27)	79 (62.2)	<0.0001
30-day mortality	100 (17.2)	41 (32.3)	<0.0001

[a] Values in parentheses are the percentage of patients with the indicated characteristic, with the exception of mean age and mean time to death after hospital admission (for which the SD are reported).
[b] COPD, chronic obstructive pulmonary disease.
[c] See the text for descriptions of risk groups and infection types.

TABLE 2 Distribution of *P. aeruginosa* bacteremia sources, 30-day mortality rates, and prevalence of multidrug resistance

Bacteremia source or original site of infection	*n*[a] (%)	No. (%) of patients with MDR PAB (*n* = 127)	No. (%) of patients who died within 30 days of admission		
			Overall (*n* = 141)	Non-MDR PAB (*n* = 582)	MDR PAB (*n* = 127)
Vascular catheter	200 (28.2)	44 (34.6)	19 (13.5)	8 (1.4)	11 (8.7)
Unknown	164 (23.1)	18 (14.2)	32 (22.7)	25 (4.3)	7 (5.5)
Respiratory	133 (18.8)	25 (19.7)	64 (45.4)	48 (8.2)	16 (12.6)
Urinary tract	93 (13.1)	20 (15.7)	7 (5)	6 (1)	1 (0.8)
Biliary tract	47 (6.6)	6 (4.7)	6 (4.3)	3 (0.5)	3 (2.4)
Abdominal	22 (3.1)	5 (3.9)	6 (4.3)	4 (0.7)	2 (1.6)
Skin and soft tissue	22 (3.1)	4 (3.1)	2 (1.4)	2 (0.3)	0 (0)
Other[b]	25 (3.5)	5 (3.9)	5 (3.5)	4 (0.7)	1 (0.8)
Bone and joint	3 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)

[a] The total number of study subjects was 709.
[b] Other sources included pacemaker infection, endocarditis, and otolaryngology infection.

TABLE 3 Univariate analysis results for the association of clinical, microbiological, and therapeutic characteristics with 30-day mortality

Characteristic	No. (%)[a] of patients with characteristic who:		*P* value
	Died (*n* = 141)	Survived (*n* = 568)	
Mean (SD) age (yrs)	63.98 (14)	61.28 (16)	0.08
Male gender	94 (66.7)	376 (66.2)	0.92
Acquisition			
Community	21 (14.9)	98 (17.2)	
Nosocomial	108 (76.6)	392 (69)	0.17
Health care related	11 (7.8)	73 (12.8)	
An ultimate/final fatal underlying disease	97 (68.8)	277 (48.8)	<0.0001
Mean (SD) days after admission	21.88 (23)	18.59 (21)	0.14
Hematological cancer	17 (12.1)	76 (13.4)	0.78
Solid organ cancer	31 (22)	89 (15.7)	0.1
Solid organ transplant	17 (12.1)	63 (11.1)	0.77
Neutropenia (<500 cells)	23 (16.3)	64 (11.3)	0.15
COPD[b]	20 (14.2)	66 (11.6)	0.47
Chronic renal failure	12 (8.5)	61 (10.7)	0.54
Hemodialysis	4 (2.8)	30 (5.3)	0.27
Diabetes mellitus	24 (17)	100 (17.6)	0.9
Liver cirrhosis	14 (9.9)	26 (4.6)	0.02
HIV infection	5 (3.5)	22 (3.9)	1
Prior steroid therapy	60 (42.6)	188 (33.1)	0.07
Bladder catheter	62 (44)	220 (38.7)	0.35
MDR-PAB	41 (29.1)	86 (15.1)	<0.0001
Mechanical ventilation	35 (24.8)	66 (11.6)	<0.0001
Septic shock	72 (51.1)	68 (12)	<0.0001
Mortality risk group[c]			
Low risk	34 (24.1)	331 (58.3)	
Intermediate risk	43 (30.5)	168 (29.6)	<0.0001
High risk	64 (45.4)	69 (12.1)	
Persistent bacteremia	16 (11.3)	79 (13.9)	0.6
Inappropriate empirical antibiotic	65 (46.1)	176 (31)	0.001

[a] Values in parentheses are the percentage of patients with the indicated characteristic, with the exception of mean age and mean time to death after hospital admission (for which the SD are reported).
[b] COPD, chronic obstructive pulmonary disease.
[c] See the text for descriptions of risk groups and infection types.

mortality was higher in those with non-MDR PAB who received inappropriate empirical therapy (33/157 [21%] versus 67/425 [15.8%]; $P = 0.11$), in those with MDR PAB receiving inappropriate therapy (31/79 [39.2%]; $P < 0.0001$), and in those with MDR PAB receiving appropriate therapy (10/48 [20.8%]; $P = 0.36$).

The best multivariate model predicting 30-day mortality is shown in Table 4. Factors independently associated with 30-day mortality were age ($P = 0.022$), septic shock ($P < 0.0001$), liver cirrhosis ($P = 0.005$), an intermediate-risk ($P = 0.002$) or high-risk ($P < 0.0001$) source of infection, and, with use of appropriate empirical therapy in non-MDR PAB as the reference group, receiving inappropriate therapy for non-MDR PAB (OR, 2.18; 95% confidence interval [CI], 1.215 to 3.899; $P = 0.009$) or receiving inappropriate therapy for MDR PAB (OR, 4.09; 95% CI, 2.156 to 7.778; $P < 0.0001$). A nonsignificant trend toward higher mortality in patients with MDR PAB who received appropriate therapy was also observed ($P = 0.072$). In order to evaluate the quality of empirical therapy, the specific antibiotics administered for MDR PAB were reviewed. The most frequent empirical therapy was monotherapy with amikacin (47.9%), followed by amikacin plus colistin (18.8%), monotherapy with a carbapenem (14.6%), a carbapenem plus amikacin (8.3%), and piperacillin-tazobactam plus amikacin (4.2%).

TABLE 4 Multivariate analysis of risk factors associated with 30-day mortality in *P. aeruginosa* bacteremia

Factor	OR (95% CI)	*P* value
Age	1.02 (1.002–1.033)	0.022
Septic shock	6.58 (4.022–10.767)	<0.0001
Liver cirrhosis	3.30 (1.423–7.649)	0.005
Risk level of infection source		
Low (<15%)	(Used as reference)	
Intermediate (15–30%)	2.47 (1.410–4.326)	0.002
High (>30%)	7.27 (4.092–12.928)	<0.0001
Empirical antibiotic therapy		
Non-MDR with appropriate agent	(Used as reference)	
Non-MDR with inappropriate agent	2.18 (1.215–3.899)	0.009
MDR and inappropriate agent	4.09 (2.156–7.778)	<0.0001
MDR and appropriate agent	2.25 (0.930–5.436)	0.072

DISCUSSION

The 30-day mortality rate for PAB was 19.9%, and this was significantly higher when the infecting strain was MDR (17.2% versus 32.3%; $P = 0.0001$). Similar to previous published experiences (2, 8, 9, 13, 26, 27), the analysis of our patients showed an association between mortality and increasing age, patient's comorbidity (liver cirrhosis), shock on presentation, the source of infection (respiratory, unknown, and abdominal sources), and the appropriateness of empirical antibiotic therapy. Among these factors (besides perhaps an earlier and systematic goal-directed approach to maintain tissue perfusion in patients with septic shock), the only factor that could have been improved at the moment of bacteremia clinical presentation was the percentage of patients receiving appropriate empirical therapy. The worldwide increase of MDR in *Pseudomonas* spp. is directly impacting the proportion of patients adequately treated from the first presentation. Indeed, in our series, inappropriate empirical therapy was significantly more frequent in MDR PAB than in non-MDR PAB (62.2% versus 27%; $P = 0.0001$).

In general, resistant pathogens are more frequently isolated in patients with poor medical conditions (comorbidity, nosocomial acquisition, previous antimicrobial therapy, prolonged hospitalization), making it difficult to analyze the influence of empirical therapy on the outcome of resistant pathogens. Some authors have identified resistance to ceftazidime, carbapenems, or MDR as risk factors for mortality (1, 7, 16, 24, 25, 28). In contrast, Combes et al. (3) evaluated the impact of piperacillin resistance on the outcomes of *P. aeruginosa* ventilator-associated pneumonia in patients who received appropriate empirical antibiotics, and they found that piperacillin resistance was not associated with higher mortality. These results suggest the importance of adjusting for appropriate empirical antibiotic to clarify the influence of resistance on mortality. The present large series of PAB with an MDR prevalence of 17.9% allowed us to perform the analysis of the influence of both MDR and appropriateness of empirical therapy on the mortality of PAB. Since there was an interaction between MDR and receiving inappropriate empirical therapy, a variable combining both was included in the logistic regression analysis. Compared with appropriate therapy in non-MDR episodes, inappropriate therapy in non-MDR PAB (OR, 2.18; 95% CI, 1.215 to 3.899; $P = 0.009$) and inappropriate therapy in MDR PAB (OR, 4.09; 95% CI, 2.156 to 7.778; $P < 0.0001$) were associated with higher mortality. However, the observed nonsignificant trend toward higher mortality in patients with MD PAB who received appropriate therapy suggests an intrinsic influence of MDR on prognosis. This cannot be entirely discarded, since some virulence traits, such as the secretion of type III exotoxins by *P. aeruginosa*, have been independently associated with poor prognosis in patients with bacteremia, and this trait is, in turn, more prevalent in strains resistant to ciprofloxacin, cefepime, and gentamicin (5). An alternative explanation for that trend may lie in the fact that, in our center, MDR *P. aeruginosa* is in general only susceptible to amikacin and colistin. Therefore, in the present study appropriate empirical therapy for many cases of MDR PAB (47.9%) consisted of monotherapy with amikacin. According to previous clinical experiences, single-aminoglycoside therapy may be a suboptimal treatment (18, 23, 30), except for urinary tract infections. Although every effort should be made to administer aminoglycosides in a manner directed to achieve an optimal ratio of the maximal drug concentration in the serum versus the MIC (as a rule, in a high single daily dose) (4, 17), it is not clear whether this approach can overcome the apparent suboptimal efficacy of aminoglycosides as single agents and, certainly, the risk of nephrotoxicity is still of concern.

The present study has some limitations. First, the potential influences of different antibiotics or of combination therapies were not evaluated. Second, MIC values and specific dosages of antibiotics were not recorded; hence, we cannot evaluate the influence of pharmacokinetics-pharmacodynamics parameters. Lastly, despite use of multivariate analysis, inadequate control for confounding by comorbid illness cannot be completely discarded. However, this is the largest series of PAB with a high prevalence of MDR that has demonstrated the importance of appropriate empirical therapy.

In conclusion, the mortality for *P. aeruginosa* infection and the prevalence of MDR strains were high. MDR PAB had a higher 30-day mortality than non-MDR PAB, and according to our analysis this was due to a higher rate of inappropriate empirical antibiotic therapy and because in almost 50% of MDR PAB episodes appropriate empirical therapy consisted of monotherapy with amikacin. These findings strengthen the needs for revision of the empirical regimens for patients at risk of MDR PAB and of developing new antipseudomonal antibiotics.

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