Pseudomonas aeruginosa Infections: Factors Relating to Mortality with Emphasis on Resistance Pattern and Antimicrobial Treatment

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A retrospective case-control study was conducted to investigate the risk factors for death among intensive care unit patients with *Pseudomonas aeruginosa* infection. Out of 131 patients investigated, 67 (51.1%) died within 30 days of being diagnosed with this infection. The mean duration of hospital stay before this diagnosis was 28.5 ± 26.5 days. No association was found between bacterial resistance and death in this study (multiresistant p= 0.26; panresistant p= 0.42), but the adequacy of the initial treatment was inversely proportional to the degree of resistance. There was a tendency towards greater mortality among patients who received combination therapy (empirical p= 0.09; definitive p= 0.08), despite the greater frequency of appropriate treatment in these patients and the similar degree of severity in the two groups. This finding may be explained by pharmacodynamic parameters that were not studied or by the extensive use of aminoglycosides in the combination therapy, which play a controversial role in combination therapy due to their potential for renal toxicity. The multivariate analysis in our study demonstrated that age [odds ratio (OR) 1.04], septic shock (OR 15.4) and hypoalbuminemia (OR 0.32) were independent risk factors for death.

Key-Words: Risk factors, case-control study, *Pseudomonas aeruginosa*, death.

Pseudomonas aeruginosa has evolving virulence characteristics and antimicrobial resistance patterns which make it a difficult target for antibiotic therapy [1-3]. It was the most frequently found bacterium in lower airway infections in Brazilian hospitals of the SENTRY study [4], displaying a resistance of 49% to imipenem and of 49.8% to ceftazidime. The MYSTIC program carried out in 20 Brazilian hospitals also found that *P. aeruginosa* was the most frequent Gram-negative isolated from nosocomial infections, with resistance rates of 64% to meropenem, 63.8% to piperacillin/tazobactam, 63.4% to amikacin and 55.8% to ceftazidime [5]. The USA's national nosocomial infections surveillance system (NNIS) showed that in 2003 *P. aeruginosa* accounted for 18.1% of the cases of pneumonia, 9.5% of surgical wound infections and 16.3% of urinary infections among ICU patients and increases of 17.7%, 27.3% and 26.4% in resistance to imipenem, quinolone and third-generation cephalosporin, respectively, in that country [6].

The factors that predict a fatal outcome vary among studies and include septic shock, pneumonia, advanced age, severity of the underlying disease, use of inappropriate antimicrobials and emergence of antimicrobial resistance during treatment [7-11]. Rello et al. [12] estimated a mortality rate of 13.5% attributable to pneumonia associated with mechanical ventilation caused by *P. aeruginosa*. A systematic review of the literature emphasized that the previous use of antibiotics is the principal risk factor for acquiring multiresistant *P. aeruginosa* [13].

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Timely recognition of variables presenting a risk of death among patients infected with *P. aeruginosa* may lead to changes in patient management by the medical team, with earlier and better-targeted interventions. The aim of this study was to define risk factors associated with unfavorable clinical outcomes in *P. aeruginosa* infections among critically ill patients, with special emphasis on bacterial resistance and antimicrobial treatment.

Material and Methods

This retrospective case-control study comprised 131 patients admitted to an ICU from four tertiary-level hospitals in Recife, Brazil, between January 2006 and August 2007. Cases presented positive cultures for *P. aeruginosa* and criteria of infection based on NNIS criteria of the Centers for Disease Control [14] and progressed to death within 30 days. Controls presented positive cultures for *P. aeruginosa* and the same NNIS criteria for infection and were discharged within 30 days of the diagnosis. Only the first episode of infection per site and per patient was considered. Patients under 16 years and those with cystic fibrosis were excluded. This study was approved by the Ethics Committee of the Oswaldo Cruz University Hospital.

P. aeruginosa was identified using conventional methods. The susceptibility to antibiotics was determined using the Kirby-Bauer disc diffusion method, in accordance with NCCLS, 2004 [15]. Screening for resistance to polymyxin B used the protocol described by Gales [16].

Definition

P. aeruginosa was defined as resistant (resistance *in vitro* to at least one of the anti-*Pseudomonas* antibiotics: piperacillin, ciprofloxacin, ceftazidime or imipenem), multiresistant (resistance to at least three classes of anti-*Pseudomonas* antibiotics) or panresistant (resistance to carbapenems and to all the anti-*Pseudomonas* antibiotics available, with the exception of polymyxin B).

Empirical antibiotic therapy was the therapy given between 8h before the index blood culture was drawn and the time antibiotic susceptibility testing results became available. Empirical antibiotic therapy was considered appropriate if it included antipseudomonal antibiotics to which the isolate displayed *in vitro* susceptibility. Neither aminoglycoside nor aztreonam monotherapy were considered adequate therapy for *P. aeruginosa* bacteremia [17].

Potential risk factors for death among critically ill patients with *P. aeruginosa* infection were identified by means of multivariate analysis. The chi-squared or Fisher test was used for categorical variables. Continuous variables were tested using Student's t or the Mann-Whitney test. Variables for which there was a p value <0.20 in bivariate analysis were included in the logistic regression model for multivariate analysis. Epi Info version 6.04 and SPSS version 8.0 were used for analysis.

Results

A total of 131 episodes of *P. aeruginosa* infection were analyzed. The mortality rate was 51.1% (67 patients). Patient characteristics are shown in Table 1.

Antibiotic susceptibility was generally less than 70% for piperacillin/tazobactam, imipenem, meropenem and amikacin and 31 (23.7%) were resistant to all the agents used in the tests, except polymyxin (Table 2).

The antimicrobial agents most frequently used and their combinations are shown in Table 3. Use of aminoglycosides predominated in both empirical and definitive combination therapy.

Seventy-one patients received monotherapy (56.3%), fifty-five (43.7%) were treated with two anti-*Pseudomonas* drugs and five patients did not receive any antibiotic treatment. The antimicrobial resistance pattern of *P. aeruginosa* was unrelated to mortality, but was inversely related to the adequacy of the initial antimicrobial therapy (Table 4).

There was greater mortality among the patients who received combination antibiotic therapy, although there were no statistical differences between the APACHE II scores for the groups with monotherapy or combination therapy. Empirical treatment presented a greater adequacy when two or more drugs were used (33 out of 54 *versus* 43 out of 71; p = 0.70). The infection site for which combination therapy was most used was the bloodstream.

Forty-seven patients (37.3%) received inappropriate empirical treatment, although this did not result in greater mortality (p = 0.96). Seventy-nine patients (62.7%) received appropriate antibiotics within 24 hours of collection of cultures, while fifteen (11.9%) received appropriate antibiotics only after receiving their results. Thirty-two patients did not receive appropriate definitive treatment (25.4%). The mean duration of the antibiotic treatment was 13.8 ± 7.8 days. Bivariate analysis identified age over 60 years, APACHE II on admission and septic shock as factors associated with death (Table 5). With regard to laboratory parameters, both serum albumin (OR = 0.26; p = 0.001) and blood pH (p = 0.061; R = 0.06) showed associations with mortality, whereas neither the leukocytes (p = 0.724) nor creatinine (p = 0.555) showed any relationship with mortality.

There was a greater frequency of septic shock in the group with inappropriate therapy, both for empirical therapy (29 out of 47 *versus* 36 out of 79; p = 0.11) and for definitive therapy (21 out of 32 *versus* 44 out of 94; p = 0.10).

Multivariate regression analysis identified age (OR 1.04), serum albumin (OR 0.32) and septic shock (OR 15.4) as factors independently associated with death.

Discussion

In the light of uncertainties about treatment of Pseudomonas infections within the present-day scenario of multiresistance, the authors of the study set out to determine what factors relating to antimicrobial therapy might have an impact on mortality among patients with *P. aeruginosa* infection. For this purpose, they conducted a case-control study in which all possible factors relating to death among patients infected with this pathogen were analyzed. The characteristics of the antimicrobial therapy were included as risk factors. The factors clearly related to death were the more classical ones, such as age, septic shock and serum albumin [2,17,18,19,20]. However, several therapy-related findings were curious, producing some surprising revelations. The first was the high frequency of inappropriate initial treatment, which totaled 47 cases (37.3%). The second was that the adequacy of the treatment did not make any difference to eventual mortality. The third was that combination therapy (regardless of whether it was empirical or definitive) may have been associated with greater mortality (OR 1.97, p = 0.09; OR 2.0, p = 0.08), despite not attaining statistical significance.

The high frequency of inappropriate initial treatment was directly related to bacterial resistance. In other words, within the scenario of multiresistance, it is more difficult to institute the appropriate treatment. This may be explained by a lack of knowledge among the medical team regarding bacterial resistance patterns within the institution, or it may be due to fear of the indiscriminate empirical use of broad-spectrum antibiotics or even of those with a more specific spectrum (such as polymyxin). However, as with the results presented by Osih [17], inadequacy did not produce any difference in mortality. This may be due to the difference between the *in vitro* and *in vivo* effects of the antimicrobial agents in relation to *P. aeruginosa*, such that the treatment may be successful even in the presence of infections caused by multiresistant or panresistant strains. Another argument would be that patients with *P. aeruginosa* infections that appear at an advanced stage of hospitalization have underlying diseases that would lead to death irrespective of the infection, and thus *P. aeruginosa* would not be the cause of death. Lastly, there could be other infectious agents present (the observed frequency of polymicrobial infection is 28.2%) which may have been treated through the therapy used.

Table 1. Characteristics of the 131 patients with *Pseudomonas aeruginosa* infection.

	N	%
Age (mean, yr)	64.2 +18.4	
APACHE II (on admission)	18.0 + 7.6	
SOFA (on admission)	6.5 + 3.3	
Duration of hospitalization before infection (days)	-	-
Sex (male)	66	50.4
Origin		
Community	58	44.3
Nosocomial	70	53.4
Home care	3	2.3
Comorbidities		
Systemic arterial hypertension	73	56.6
Heart disease/ coronary disease	40	31.0
Diabetes mellitus	38	29.5
Cerebrovascular disease	37	28.7
Surgery	25	19.4
Chronic kidney failure	23	18.0
Neoplasia	16	12.4
Immunodepression	15	11.6
COPD	12	9.3
Infection site		
Lung	86	65.6
Bloodstream	24	18.3
Urinary tract	15	11.5
Surgical site	5	3.8
Skin/ soft tissue	1	0.8
Central nervous system involvement	96	73.3
Use of mechanical ventilation	121	92.4
Use of central catheter	130	99.2
Use of bladder catheter	122	93.1
Use of parenteral nutrition	12	9.2
Polymicrobial infection	37	28.2
Hemodialysis	38	29.0
Septic shock	66	50.4
Activated drotrecogin-alpha	1	0.9

Table 2. Pattern of susceptibility to antimicrobial agents among *Pseudomonas aeruginosa* strains.

Sensitivity pattern	Strains tested (N)	Sensitive (%)
Polymyxin B	24	100
Piperacillin-tazobactam	101	64.3
Imipenem	126	62.6
Amikacin	124	61.2
Meropenem	116	60.3
Ciprofloxacin	127	48.0
Aztreonam	128	46.8
Gentamicin	128	44.5
Ceftazidime	76	43.4
Cefepime	116	39.6

Table 3. Antimicrobial agents and combinations most used for empirical and definitive therapy.

Antibiotic treatment	No. of treatments
Empirical therapy	
Monotherapy	
Meropenem/ Imipenem	32 (33.3%)
Piperacillin/tazobactam	18 (18.7%)
Cefepime	4 (4.2%)
Polymyxin B	3 (3.1%)
Combination therapy	
Piperacillin/tazobactam + aztreonam	9 (9.4%)
Piperacillin/tazobactam + amikacin	5 (5.2%)
Meropenem/Imipenem + amikacin	8 (8.4%)
Cefepime + amikacin	4 (4.2%)
Cefepime + ciprofloxacin	4 (4.2%)
Polymyxin B + carbapenem	3 (3.1%)
Imipenem + ciprofloxacin	3 (3.1%)
Piperacillin/tazobactam + ciprofloxacin	3 (3.1%)
Definitive therapy	
Monotherapy	
Meropenem/Imipenem	35 (39.2%)
Piperacillin/tazobactam	16 (18.0%)
Polymyxin B	7 (7.8%)
Cefepime	6 (6.8%)
Combination therapy	
Piperacillin/tazobactam + amikacin	6 (6.8%)
Piperacillin/tazobactam + aztreonam	6 (6.8%)
Imipenem + amikacin	5 (5.6%)
Polymyxin B + carbapenem	4 (4.5%)
Imipenem + ciprofloxacin	4 (4.5%)

Table 4. Association between antimicrobial resistance pattern and adequacy of initial empirical therapy.

Resistance pattern	Initial empirical therapy			
	Adequate		Inadequate	
	N	%	N	%
Resistant (61 strains)	51	87.9	7	12.1
Multiresistant (39 strains)	24	64.9	13	35.1
Panresistant (31 strains)	4	12.9	27	87.1

The possible role of the combination therapy as a risk factor for death was the most surprising finding from the present study. This is at odds with the findings of several authors who have evaluated treatments for *P. aeruginosa* infection [19,21,22].

One might ask whether the combination therapy had been indicated for the more severe cases or those with a greater chance of immunosuppression, who would therefore be at greater risk of death. However, on comparing the APACHE II scores for the two groups, we did not find any differences. Nor did we find any differences in outcome from infections in the presence of immunosuppression. On the other hand, combination therapy was used more often in cases of infection of the bloodstream, generally relating to bacteremia, and thus with a greater risk of death [1,8,23,24]. Moreover, since aminoglycosides were the antimicrobial agents most used in associations and, over the period of this study there was no consensus regarding their use for limited periods, the cause of death could be attributable to their adverse effects. Most of our patients were elderly and kidney failure may have worsened the prognosis for the individuals treated with this medication [9,25]. Obritsch et al. studied the emergence of

Table 5. Prognostic factors for hospital mortality: bivariate analysis.

Factors	Outcome				OR (CI)	p value
	Death		Discharge/cure			
	N	%	N	%		
Age (years)						
Less than 60 years	19	39.6	29	60.4	1.0 -	
More than 60 years	48	57.8	35	42.2	2.09 (0.95-4.65)	0.06
Gender						
Female	34	52.3	31	47.7	1.0 -	
Male	33	50.0	33	50.0	0.91 (0.43-1.93)	0.928
Fever present at time of diagnosis						
No	29	51.8	27	48.2	1.0 -	
Yes	38	50.7	37	49.3	0.96 (0.45-2.04)	0.96
Central nervous system involvement						
No	13	37.1	22	62.9	1.0 -	
Yes	54	56.3	42	43.7	2.18 (0.91-5.25)	0.082
Immunosuppression						
No	49	50.5	48	49.5	1.0 -	
Yes	18	52.9	16	47.1	1.10 (0.47-2.61)	0.964
Association with pneumonia						
No	19	47.5	21	52.5	1.0 -	
Yes	47	58.0	34	42.0	1.53 (0.66-3.54)	0.368
Association with septic shock						
No	16	24.6	49	75.4	1.0 -	
Yes	51	77.3	15	22.7	10.4 (4.3-25.7)	0.000
Resistance pattern						
Resistant	32	52.5	29	47.5	1.0 -	
Multiresistant	16	41.0	23	59.0	0.63 (0.27-1.42)	0.266
Panresistant	19	61.3	12	38.7	1.43 (0.59-3.46)	0.421
Previous use of antibiotic						
No	08	42.1	11	57.9	1.0 -	
Yes	59	52.7	53	47.3	1.53 (0.52-4.60)	0.545
Delayed empirical therapy						
No	55	56.7	42	43.3	1.0 -	
Yes	11	37.9	18	62.1	0.47 (0.18-1.19)	0.117
Combination empirical therapy						
No	32	45.1	39	54.9	1.0 -	
Yes	34	61.8	21	38.1	1.97 (0.90-4.35)	0.091
Adequate empirical therapy						
No	24	51.1	23	48.9	1.0 -	
Yes	42	53.2	37	46.1	1.09 (0.49-2.41)	0.964
Combination definitive therapy						
No	33	45.2	40	54.8	1.0 -	
Yes	33	62.3	20	37.7	2.00 (0.91-4.43)	0.086
Adequate definitive therapy						
No	17	53.1	15	46.9	1.0 -	
Yes	49	52.1	45	47.9	0.96 (0.40-2.33)	0.914
Catheter removal						
No	14	38.9	22	61.1	1.0 -	
Yes	12	60.0	08	40.0	2.35 (0.77-7.20)	0.133

resistance to *Pseudomonas* during a ten year-period and observed greater rates of resistance in the combination therapy containing ciprofloxacin, especially when associated with cefepime or imipenem. The best combination was aminoglycoside or fluorquinolone in association with piperacillin/tazobactam [26]. A survey conducted in two local hospitals by Figueiredo et al. [27] found that the rate of resistance to ciprofloxacin was high, such that it presented activity against only 49.7% of all of the strains of *P. aeruginosa* and the susceptibility to aminoglycosides was 59.4% for amikacin and 48.6% for gentamicin. Magalhães et al. carried out a molecular analysis on 48 strains of *P. aeruginosa* from Recife/Brazil. They demonstrated that 62.5% of the strains produced metallo-β-lactamase (SPM-1) with a broad resistance profile, such that they were only susceptible to polymyxin and aztreonam [28]. The best association of antimicrobial agents for treating infections due to *P. aeruginosa* is still a matter of controversy.

The indication that delayed therapy could protect against death, albeit without clinical significance (OR 0.47; p = 0.112), was surprising. This may have resulted from delayed therapy for infections of lesser severity. Identifying the time at which the appropriate therapy becomes critical to the outcome for the patient is particularly important because of the delicate balance that exists between the beneficial effect of the appropriate therapy on the patient's survival and development of antimicrobial resistance through excessive use of broad-spectrum antibiotics [17].

The present study is subject to various criticisms, such as the small number of cases and the use of retrospective data from medical records. Nevertheless, methodological precautions were taken to ensure the quality of the study. These included the use of very clear definitions for the therapy (empirical, definitive, inappropriate, delayed and combination), definitions for infections according to the NNIS criteria and use of logistic regression [22,29]. Several findings suggest that its results are coherent, such as the inversely proportional relationship between therapeutic adequacy and the likely degree of resistance; the sensitivity pattern for *P. aeruginosa*, which was very similar to that reported in the MYSTIC study [5] and another study conducted recently in the state of Pernambuco [27]; and, finally, the finding of greater mortality among shock patients and elderly individuals, which is compatible with the literature on severe infections.

In conclusion, the risk factors for death in *P. aeruginosa* infections are similar to those of other severe infections, i.e. age, presence of septic shock and low serum albumin levels [2,3,18]. There was a high frequency of inappropriate treatment, but this does not seem to have influenced the outcome. Thus, treatment should always be attempted. There were indications that combination therapy may be associated with greater mortality.

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