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Factors associated with epidemic multiresistant *Pseudomonas aeruginosa* infections in a hospital with AIDS-predominant admissions

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ABSTRACT

Introduction: Infections caused by multiresistant *Pseudomonas aeruginosa* (MR-PA) have been associated with persistent infections and high mortality in acquired immunodeficiency syndrome (AIDS) patients. Therefore, understanding the predisposing factors for infection/colonization by this agent is critical for controlling outbreaks caused by MR-PA in settings with AIDS patients.

Objective and methods: To analyze the presence of factors associated with the acquisition of an epidemic MR-PA strain in a hospital with AIDS-predominant admission. A case-control study was carried out in which cases and controls were gathered from a prospective cohort of all hospitalized patients in an infectious disease hospital during a five-year study period.

Results: Multivariate logistic regression analysis demonstrated that enteral nutrition (OR = 14.9), parenteral nutrition (OR = 10.7), and use of ciprofloxacin (OR = 8.9) were associated with a significant and independent risk for MR-PA acquisition.

Conclusions: Although cross-colonization was likely responsible for the outbreaks, the use of ciprofloxacin was also an important factor associated with the acquisition of an epidemic MR-PA strain. More studies are necessary to determine whether different types of nutrition could lead to modification of gastrointestinal flora, thereby increasing the risk for infection/colonization by MR-PA in this population.

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Introduction

Infections caused by multiresistant *Pseudomonas aeruginosa* (MR-PA) are usually associated with high mortality rates,[1] especially in patients with acquired immunodeficiency syndrome (AIDS).[2] In addition, persistent MR-PA infections have been observed in these patients.[2] Therefore, understanding the predisposing factors for infection/colonization by MR-PA is critical to decrease the incidence and mortality rates of MR-PA infections in this special population.

Several previous studies have assessed the risk factors for the acquisition or emergence of MR-PA, including antimicrobial use, previous hospitalization, severity of illness, surgery, and immunosuppression.[1,3-20] Among immunocompromised patients with human immunodeficiency virus (HIV) infection or AIDS, few studies have shown prior hospitalization, antimicrobial use, and CD4 cell count below 50/mm^3 as risk factors for *P. aeruginosa* infection.[21-23] None of these HIV/AIDS studies assessed the risk factors for acquisition of MR-PA strains.

During an outbreak of nosocomial infections, an unique genotype is expected to be present, and a common source or horizontal transmission is likely to occur. Although antimicrobial pressure may play a lesser role, it is still present and is a contributing factor to epidemics.[24] Case-control studies performed solely in patients colonized with a single clone could potentially measure the contribution of antibiotics to the outbreak of infections caused by the resistant organism.

Understanding the risk factors for acquisition of MR-PA infection/colonization could help to control and prevent its occurrence. It could also contribute to early diagnosis and treatment of MR-PA infection, thereby reducing MR-PA mortality rates. This knowledge would be especially important in settings in which most admitted patients are immunocompromised and the pathogen causes outbreaks, persistence, and high mortality rates due to infections.[2]

Material and methods

Study design, institution and population

This case-control study was designed from a prospective surveillance program utilized for controlling nosocomial infection in an infectious disease hospital with 26 beds, including two to four intensive care beds, located in Rio de Janeiro, Brazil. The surveillance, description of MR-PA outbreaks, intervention control program, antibiotic susceptibility profile, and molecular characteristics of MR-PA isolates, as well as the clinical characteristics of patients with MR-PA infection/colonization were described in detail elsewhere.[2] During the five-year study period (April 2002 to February 2007), two outbreaks caused by MR-PA were detected.[2] Pulsed field gel electrophoresis (PFGE) typing performed on all randomly preserved MR-PA strains isolated during the study period, including strains from the outbreaks, the inter-epidemic period, and environmental samples collected close to MR-PA–positive patients, showed that all strains had the same genetic profile.[2]

Both cases and controls selected for this risk factor study were included only once. The study was approved by the institutional ethics committee.

Inclusion and exclusion criteria

Patients were eligible for inclusion as cases upon their first detection of MR-PA from clinical or surveillance cultures. Patients were included as cases only if their first positive MR-PA sample was collected after 48 hours of admission to the study hospital. Potential case patients were excluded if they had MR-PA isolated prior to the study period, before or during the first 48 hours of hospital admission. Control patients, three to each case, were randomly selected from the group of concurrently hospitalized patients who remained hospitalized through the date that MR-PA was isolated from the original case patient. Potential control patients were excluded if they had MR-PA isolation in any biological material prior to or during the study hospitalization. Control patients were also excluded if they were treated empirically with polymyxin B, which could prevent the detection of MR-PA strains in clinical and surveillance cultures. All case and control patients were adults. There was no matching between cases and controls with the purpose of examining all potential variables as factors associated with MR-PA acquisition in the study hospital.

Collection of variables

For each selected patient complete medical record, laboratory results, and infection control database were reviewed to confirm the prospectively collected data. Factors associated with infection/colonization with MR-PA included gender, age, referred from another hospital, underlying disease, time at risk (which was defined either as the length of stay prior to the date that MR-PA was first detected in case patients, or as the entire length of stay for the control patients), and the following variables during time at risk: intensive care unit (ICU) hospitalization, presence of central vascular catheter, mechanical ventilation, use of bladder catheter, thoracic drain, any kind of drainage, hemodialysis, bronchoscopy, total parenteral nutrition, enteral nutrition, and antibiotic therapy utilized for more than two days.

Statistical analysis

For data processing, Epi Info 6.0 (CDC, Atlanta – USA), Statistical Package for Social Sciences 15.0 (SPSS Inc., Chicago, Illinois – USA), and R 2.4.1. (package logistf) softwares were used. Exploratory analysis was performed for all variables to describe the distribution, central tendency, and variability. Univariate analysis was used to compare case and control groups through the chi-square (χ^2) or Fisher's exact test when required for dichotomous variables. The difference between means for continuous independent variables was tested using the paired Student's t-test. A p-value of < 0.05 was considered significant in all statistical tests.

Multiple logistic regression analysis was used to determine statistically significant factors independently associated with MR-PA acquisition. Those variables with p-values < 0.20 in univariate analyses were included in the multivariate analysis. Firth's correction was used for correcting the estimates and confidence intervals (CIs) by penalized likelihood in univariate and multivariate analyses.[25] Variables were checked for confounding, collinearity, and interaction. The goal was to derive a model with the smallest set of independent variables to predict acquisition of MR-PA. A significance level (p-value) of 0.05 was required for maintaining the variables in the model.

Results

Study population

Among 44 patients who were identified as having *P. aeruginosa* isolates in clinical or surveillance samples during the study period, 29 were excluded from the case-control study for the following reasons: 26 patients had isolates with a non-MR-PA susceptibility pattern, two patients had isolates with these resistant patterns prior to or during the first 48 hours of admission, and one patient had no records available for review. Except for this last patient, all the patients from MR-PA outbreaks (n = 11) were selected as case patients. Among the 15 case patients 13 had MR-PA infection, and two had colonization with MR-PA strains.

A total of 45 control patients were selected according to the inclusion and exclusion criteria.

Patient characteristics and risk factors

Case patients were similar to control patients with respect to gender, age, and referral from other hospitals (Table 1). Most of the cases and controls were immunocompromised (14/15 cases [93%]; 31/45 controls [69%]) due to AIDS (nine cases and 28 controls) or human T-lymphotropic virus (HTLV-1) infection (four cases and two controls); one control was co-infected with HIV and HTLV-1. All cases and controls with HTLV-1 had urinary tract infections (UTIs) caused by other bacterial species identified previous to the acquisition of MR-PA for the cases, and upon admission (two patients) or during hospitalization (one patient) for controls. Time at risk was not different (p = 0.38) between the cases (mean 33.5 days; SD 43.3; median 24 days) and controls (mean 24.3 days; SD 18.6; median 19 days).

Case patients were more likely to have experienced the following, prior to being infected or colonized by the MR-PA strain, than control patients, during their entire hospitalization period (Table 1): bladder (OR = 29.0) or central vascular (OR = 16.20) catheter insertion; admission into ICU (OR = 12.07); hemodialysis (OR = 11.86); enteral (OR = 10.61) or parenteral (OR = 8.11) nutrition; mechanical ventilation (OR = 9.82); or use of amikacin (OR = 35.61), vancomycin (OR = 10.45), cefepime (OR = 6.85), or ciprofloxacin (OR = 4.83).

However, on multivariate analysis (Table 2), after adjusting for all significant variables, only the following variables remained significantly and independently associated with MR-PA acquisition: enteral nutrition (OR = 14.93; 95% CI 3.29-94.13), parenteral nutrition (OR = 10.74; 95% CI 1.51-91.88), and the use of ciprofloxacin (OR = 8.87; 95% CI 1.56-66.38).

Outcomes

Death during hospitalization occurred in 11 of 15 case patients (73%), compared with four control patients (9%) (p < 0.001). Except for one case patient who was lost during follow up, the only two case patients who outlived hospitalization died roughly four months thereafter with recurrent MR-PA infections. Thus, the mortality rate was 92% (11/12) among case patients during the five years of study. The median length of hospital stay was significantly greater for case patients (33 days) than for control patients (18 days) (p = 0.007).

Discussion

The present analysis stemmed from a case-control study from a prospective cohort gave a stronger epidemiological point of view. Strain typing methods were used in all randomly preserved epidemic and inter-epidemic strains, confirming the clonality of MR-PA strains.[2] Thus, the effect of the clonal dissemination on the acquisition of MR-PA isolates could be assessed. Therefore, in this discussion section, other factors related to the epidemiology of the outbreaks that were also identified in univariate analysis but not maintained in the final model will be considered.

Several studies published to date that have used molecular analysis to assess risk factors have shown similarities between MR-PA strains, and have linked some of the identified risk factors with cross-transmission.[1,3,6,13,14,17,19,20] Hemodialysis was one of the factors that was associated with the outcome in univariate analysis in the present study but was not kept in the final model. Temporal, spatial and clinical associations between this variable and the dependent variable (infection or colonization by MR-PA strain during hospitalization) were observed during the study.[2] From an observational standpoint, it is possible that undergoing hemodialysis was related to MR-PA cross-infection among the studied population.[2] Four sequential patients from the first outbreak acquired MR-PA infection after undergoing hemodialysis performed by the same technician. After assigning a different technician to each patient, control of the first outbreak was obtained.[2] From this point on, hemodialysis was no longer related to MR-PA acquisition in any other patient.[2] Some authors have implicated hemodialysis[4,6,11,26] or renal failure[8,9,12] as factors associated with MR-PA acquisition[4,6,8,11,12] or infection[9,26] in multivariate[4,8,9,11,12,26] or univariate analysis.[6] Although unpredictable drug metabolism associated with altered creatinine clearance in patients with renal insufficiency may explain the association between hemodialysis and MR-PA acquisition,[8,12] the molecular analyses of the tested strains corroborate the observation that it was probably related to the horizontal transmission of MR-PA during the first outbreak.[2] When resistance results from a cloning mechanism, the potential risk factors should be evaluated considering failure of measures to prevent cross-transmission of the microorganism.

Table 1 – Association of studied variables with multiresistant *Pseudomonas aeruginosa* infection/colonization

Variable	No. (%) of patients		Unadjusted OR	p-value
	Case group (n = 15)	Control group (n = 45)	(95% CI)	
Characteristic				
Male gender	11 (73)	29 (64)	1.4 (0.4-5.4)	0.568
Median age, years	50	40	1.0 (1.0-1.1)	0.121
Referred from another hospital	2 (13)	2 (4)	3.2 (0.5-22.9)	0.225
Median hospital stay, days	33	18	1.0 (1.0-1.1)	0.007
Underlying disease (AIDS and HTLV)	14 (93)	31 (69)	4.5 (0.9-43.3)	0.060
ICU stay	12 (80)	10 (22)	12.1 (3.3-54.9)	< 0.001
Procedure				
Central vascular catheter	13 (87)	11 (24)	16.2 (4.1-92.5)	< 0.001
Mechanical ventilation	11 (73)	9 (20)	9.8 (2.8-39.8)	< 0.001
Bladder catheter	14 (93)	11 (24)	29.0 (6.1-285.9)	< 0.001
Thoracic drain	2 (13)	1 (2)	5.5 (0.7-64.0)	0.108
Any kind of drainage	3 (20)	3 (7)	3.4 (0.7-18.1)	0.141
Hemodialysis	4 (27)	2 (4)	11.9 (1.9-128.1)	0.021
Bronchoscopy	0	4 (9)	3.4 (0.3-455.3)	0.357
Type of nutrition	-	-	-	0.001
Total parenteral nutrition	3 (20)	3 (7)	8.1(1.4-52.0)	-
Enteral nutrition	8 (53)	6 (13)	10.6 (2.7-47.9)	-
Antibiotic therapy				
Ceftazidime	0	3 (7)	2.6 (0.2-350.8)	0.499
Cefepime	11 (73)	12 (27)	6.9 (2.0-26.8)	0.001
Ceftriaxone	2 (13)	4 (9)	1.7 (0.3-8.7)	0.537
Ciprofloxacin	5 (33)	4 (9)	4.8 (1.2-21.2)	0.029
Levofloxacin	1 (7)	1 (2)	3.1 (0.2-40.1)	0.357
Imipenem	4 (27)	5 (11)	2.9 (0.7-12.0)	0.147
Meropenem	1 (7)	3 (7)	1.3 (0.1-8.4)	0.825
Piperacillin-tazobactam	2 (13)	5 (11)	0.7 (0.2-4.5)	0.711
Polymyxin B	0	0	-	-
Ofloxacin	1 (7)	4 (9)	1.1 (0.2-11.1)	0.962
Amikacin	4 (27)	0	35.6 (3.4-4849.2)	0.001
Ticarcillin-clavulanic acid	0	2 (4)	1.8 (0.1-251.1)	0.698
Vancomycin	8 (53)	4 (9)	10.5 (2.8-45.5)	< 0.001
Sulfamethoxazole-trimethoprim	7 (47)	20 (44)	1.1 (0.3-3.5)	0.873

OR, odds ratio; CI, confidence interval; AIDS, acquired immunodeficiency syndrome; HTLV, human T-lymphotropic virus; ICU, intensive care unit.

Table 2 – Factors significantly associated with multiresistant *Pseudomonas aeruginosa* infection/colonization on multivariate logistic regression analysis

Factor	Crude OR	Adjusted OR	95% CI	p-value
Ciprofloxacin				
Yes	4.8	8.9	1.6-66.4	0.013
No	1.0	1.0	-	-
Type of nutrition				
Parenteral feeding	8.1	10.7	1.5-91.9	0.018
Enteral feeding	10.6	14.9	3.3-94.1	0.003
Without nutrition	1.0	1.0	-	-

OR, odds ratio; CI, confidence interval.

Case patients were admitted to the ICU and underwent several invasive procedures more frequently than control patients. None of these variables were remained significant in the multivariate analysis. However, all these factors were previously described as risks for MR-PA acquisition in multivariate analysis, and all could be related to MR-PA cross-transmission. It should not be surprising that urinary catheterization was among these factors in the univariate analysis of the present study. A number of studies have shown urinary catheterization as an independent risk factor for MR-PA infection/colonization.[5,7,10,16,18] However, none of these studies used genotypic methods to show similarity between strains, but Eagye et al. considered cross-infection related to this association.[18] Studies have suggested that HTLV-1-infected patients are at increased risk for UTI.[27] Patients with HTLV-1 infection and myelopathy/tropical spastic paraparesis were well represented among cases (five of 15 cases). All had prolonged urinary catheterization due to neurogenic bladder, and had non-MR-PA UTIs before MR-PA acquisition. In all these patients, the urinary catheter was the likely source for their MR-PA acquisition (four UTIs, one urinary sepsis, and one urinary-tract colonization by MR-PA).[2] All of them had previously used antibiotics to treat their non-MR-PA UTIs or for other reasons. Those antibiotics could be responsible for MR-PA selection, though cross infection might be another explanation for their MR-PA acquisition. Although molecular typing was not performed on all isolates, it was performed for those isolates that were randomly preserved. Two of the PFGE tested strains were isolated from the two HTLV-1 patients, one during the inter-epidemic period, and the other in the second outbreak. In addition, most of the positive cases using bladder catheters were temporally and spatially related with another positive case in the ICU or wards.[2] All of these elements indicate the need to focus on the prevention of catheter-associated UTIs, especially in HTLV-1 patients.

Nasogastric feeding and enteral nutrition were previously observed as factors associated with MR-PA infection or acquisition after adjusting for the severity index,[5,15] although these studies did not include patients with HIV or AIDS. Artificial feeding appears to be responsible for a weakening of the mucous membranes in the digestive system, relative immunodeficiency, modification of the commensal gut flora, and an increased risk of bacterial translocation from the gastrointestinal tract into the general circulation.[5,28] Both total enteral nutrition (TEN) and total parenteral nutrition (TPN) induce modifications in the intestinal microflora.[28] During TPN, a homogeneous decrease occurs in both aerobic and anaerobic bacteria, whereas during TEN anaerobic bacteria are decreased, and aerobic bacteria are increased. This imbalance may play a role in the pathophysiology of TEN-induced diarrhea.[28] Additionally, enteral glutamine supplementation prevents bacteraemia by *P. aeruginosa* in adult burn patients.[29] A significant link between enteral and parenteral nutrition and MR-PA infection/colonization was found. However, since only MR-PA-negative patients in close contact with an MR-PA-positive case had rectal swabs performed in the present study, MR-PA colonization in the gastrointestinal tract was not investigated. Because case patients in this study were mostly immunocompromised and had AIDS, the alterations caused by enteral feeding could be compounded by gastrointestinal problems usually experienced by these patients. Therefore, the finding that the type of nutrition is a factor associated with MR-PA acquisition deserves further investigation. The role of enteral nutrition in AIDS patients and its relation with MR-PA acquisition should be further evaluated in order to prevent infection with MR-PA strains. Nevertheless, the possibility of cross-transmission interfering with these findings cannot be ruled out.

As reported by several authors, prior exposure to ciprofloxacin is an important risk for MR-PA infection/acquisition.[4-7,9,12,16] To our best knowledge, this is the first study that describes this factor during MR-PA clonal dissemination over a long period of time, confirming the role of this antibiotic in contributing to MR-PA epidemic. The risk of acquiring MR-PA during MR-PA epidemics in this study hospital was almost nine times greater in patients who had received ciprofloxacin than in those who had not received this antibiotic. In addition, some differences were observed in the antibiotic susceptibility pattern of the MR-PA isolate strains during the two outbreaks. However, all preserved isolates had an identical genetic pattern by PFGE.[2] These differences suggest that MR-PA probably acquired a new resistance mechanism or derepressed one during the study.[2] Sequential emergence of resistance is likely because different antibiotics were administered at different times following the development of resistance in our patients.[2] Therefore, cross-transmission was an important feature of the outbreaks, whereas prior use of ciprofloxacin was also an important factor that may have contributed to the differences in antibiotic susceptibilities.

The present study has several limitations. First, while surveillance cultures by rectal swabs were performed systematically during outbreaks, they were performed non-systematically during inter-epidemic periods.[2] Also, selective media for rectal swabs to detect target antibiotic-resistant Gram-negative bacteria, including MR-PA, was not used.[2] Therefore, some bias could have occurred in the selection of the control group, leading to an underestimation of the effect of factors associated with MR-PA acquisition. To what extent cross-transmission of MR-PA among patients influenced the results, and whether this may have weakened the association between MR-PA acquisition and antibiotic use, is not possible to ascertain. Additionally, the present study was conducted in an infectious disease hospital, with AIDS as the predominant admission diagnosis. Therefore, these findings might not be applicable to other settings. Finally, given the fairly small number of patients, the present study may have lacked statistical power for detecting the effects of some other studied variables. The number of case patients was probably restricted by improved infection control.[2] In addition to host or environmental factors, intrinsic virulence factors might contribute to the ability of strains to infect or colonize.

Conclusion

The findings from this study are important to guide prevention measures, early diagnosis, and treatment of MR-PA infection in the study population. Infection

control measures are extremely important in limiting the dissemination of MR-PA and in preventing infections, while an antimicrobial stewardship program is required to prevent resistance development in the hospital setting. These measures would increase the chances of effectively treating infected patients and decrease the probability of cross-transmission events of MR-PA strains. Other factors associated with MR-PA acquisition, such as nutrition type, deserve further study in order to continue to improve prevention and treatment.

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Conflict of interest

All authors declare to have no conflict of interest.

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