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Full Length Research paper

Ventilator-Associated Pneumonia (VAP) caused by Multidrug-Resistant (MDR) *Pseudomonas aeruginosa* vs. other microorganisms at an adult clinical-surgical intensive care unit

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This study aims at investigating whether the development of Ventilator-Associated Pneumonia (VAP) episodes caused by Multidrug-Resistant (MDR) *Pseudomonas aeruginosa* or other microorganisms (*Staphylococcus aureus* and other bacilli) were related to different risk factors. A 1-year retrospective case-control study was conducted in surgical-clinical Intensive Care Unit (ICU). Inclusion criteria were VAP cases (n = 66) caused by MDR *P. aeruginosa* (Group P, n = 31) compared with those caused by other microorganisms (Group C, n = 35). Altogether, the VAP incidence rate of 21.11 per 1, 000 ventilation days was high and compatible with ICUs in developing countries. Most of VAP cases (92.4%) were identified as late-onset pneumonia with 5 early-onset cases associated with Methicillin-Susceptible *Staphylococcus aureus* (MSSA). In a logistic regression analysis, Group P was independently associated with four variables: presence of three or more invasive devices; use of three or more antibiotics; use of aminoglycosides; and absence of immunocompromise. Empirical antibiotic therapy was inadequate in 48.4% of the VAP cases caused by MDR *P. aeruginosa* with crude mortality rate (46.7%) higher than in those which patients received adequate antibiotics (18.7%). The findings to show that there were no outcome differences between the groups regarding critical care unit survival, but there were significant differences between pathogens groups regarding risk factors.

Key words: Nosocomial infection, risk factors, epidemiologic study.

INTRODUCTION

Infections caused by Multidrug-Resistant (MDR) Gram-negative bacteria and *Staphylococcus aureus*, especially MDR *Pseudomonas aeruginosa* have been associated with increased morbidity, mortality and costs (Safdar et al., 2005; Kollef et al., 2006). *P. aeruginosa* is the most common Gram-negative bacilli pathogen causing Ventilator-Associated Pneumonia (VAP) (McClure et al., 2009; Medeiros, 2008; ATS, 2005). It has been shown that VAP caused by these microorganisms are associated with prolonged length of stay in intensive care unit and increased risk of death for critically ill patients (Heyland et al., 1999, Kwa et al., 2007).

There is no much data on device- associated infections rates using standardized definitions reported from developing countries (Carrilho et al., 2007; Costa et al., 2001; Rosenthal et al., 2006). The incidence rates calculated using 1, 000 ventilator-days as denominator reflect more accurately VAP risks. While VAP rates ranged from 4 to 14 per 1, 000 ventilator-days in the United States (USA) (NNIS, 2002) and 10.0 to 52.7 per 1, 000 ventilator-days in developing countries (Rosenthal et al., 2006, Rocha et al., 2008).

Previously reported risk factors for colonization and VAP caused by MDR *P. aeruginosa* and other GRAM-Negative Bacilli (GNB) and Methicillin-Resistant *Staphy-lococcus aureus* (MRSA) strains include prior use of antibiotics, prolonged hospitalization (five or more days),

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previous hospitalization in the preceding 90 days and mechanical ventilation lasting more than 7 days (Rello et al., 2006; Zavascki et al., 2006; Nouér et al., 2005; Cipriano-Souza et al., 2008; American Thoracic Society, 2005). Nonetheless, information regarding the influence of different microorganisms on VAP clinical resolution is very scarce (Vidaur et al., 2008).

The objective of the present study was to verify risk factors differences between nosocomial VAP caused by MDR *P. aeruginosa* and that caused by other isolates as well as outcomes associated with VAP caused by these microorganisms.

MATERIALS AND METHODS Hospital

setting and study population

The Uberlândia Federal University Hospital Clinic is a 500-bed, tertiary-care teaching hospital in the city of Uberlândia, Minas Gerais State, Brazil, with a 15-bed, surgical-clinical adult intensive care unit.

Study design

A retrospective case-control study was performed at a adult ICU in a Uberlândia Federal University Hospital Clinic including all consecutive VAP episodes from December, 2005 to December, 2006, in total of sixty-six VAP episodes (31 cases and 35 controls). The study was approved by the Ethical Committee of the University.

Data collection

In order to analyze predisposing factors for developing VAP, the following variables were evaluated: age, sex, underlying disease, late-onset VAP (4 or more days), immunocompromise, trauma, surgery and parenteral antibiotic exposure over the last week before pneumonia onset. Only one episode per patient was considered for this analysis.

Definitions

Pneumonia was considered ventilator associated when its onset occurred after 48 h of mechanical ventilation and it was diagnosed when new, persistent pulmonary infiltrates appeared on chest radiographs plus two of the following three clinical criteria: temperature more than 38ºC or less than 36ºC, leukocytosis more than 12, 000 cells/mm^3 or leucopenia less than 4, 000 cells/mm^3 and purulent secretion (Parker et al., 2008; Rello et al., 2006; Zhuo et al., 2008) . The threshold for quantitative endotracheal aspirate culture used for diagnosing pneumonia was $l0^6$ or more colony-forming units/ml (cfu/ml) (Nseir et al., 2008; Zhuo et al., 2008; Rello et al., 2006).

MDR microorganisms were defined as those resistant to three or more classes of antibiotics except MDR *P. aeruginosa* when it was included carbapenems (imipenem, meropenem) resistance.

Two groups were defined: (1) Group P, in which we recorded all VAP cases which yield of *P. aeruginosa*, (2) Group C (control), in which we recorded all cases caused by microorganisms other than *P. aeruginosa.*

Empirical antibiotic coverage was deemed adequate if the isolate was sensitive to at least one of the medications received (Parker et al., 2008).

Table 1. Isolates in 66 episodes of VAP and resistance patterns in the control and case group.

Microorganisms	N (%)	* MDR - N (%)
P. aeruginosa	31(46.9)	19(61.3)
Acinetobacter spp.	02(3.03)	01(50.0)
Enterobacteriaceae	06(9.09)	04 (66.7)
S. aureus	27(40.9)	11(40.7)
Total	66(100.0)	35(53.03)

*Multidrug resistance: Imipenem resistance, cephalosporins 3ª/4ª generation resistance, methicillin resistance.

Microbiological procedures

Quantitative analysis from morning endotracheal aspirate was performed after tube vortexing, two 100-fold serial dilutions were made and 0.1 ml aliquots of the original suspension and each dilution were inoculated on *Pseudomonas* agar, MacConkey agar and Manitol salt agar. Microorganisms identification to the genera/ species level was performed by classic techniques standards (Koneman et al., 2001). The positive control strains were the *P. aeruginosa* ATCC 27853, *S. aureus* ATCC 25923, *Escherichia coli* ATCC 25922.

Antimicrobial susceptibility testing

Antibiotic susceptibility was determined on Mueller Hinton agar using the disk diffusion method according to CLSI (Clinical Laboratory Standards Infections, 2008) guidelines.

Statistical analysis

Univariate analysis was performed in order to compare variables for groups of interest's outcome. The X^2 statistic or Fisher's exact test was performed to compare categorical variables. The logistic regression model was used for multivariate analysis. P-values lower than 0.05 were considered significant (Ayres et al., 2000).

RESULTS

In total, 209 patients were admitted in the ICU with mechanical ventilation for more than 48 h. Amongst them, 66 episodes of VAP were identified (31 cases and 35 controls). The device-related incidence rate for VAP in our unit was of 22.1/1.000 ventilation days.

Etiologies distribution according to resistance patterns among the microorganisms is shown in Table 1. *P. aeruginosa* was isolated in 31(46.9%) episodes of VAP with positive quantitative cultures, about two third this strains comported as Multidrug-Resistant. These 31 episodes (Group P) were compared with 35 remaining VAP episodes by other microorganisms (Group C). In this group, the most common pathogen was *S. aureus* (40.9%), which 40.7% were MRSA and 16 were MSSA.

Distribution of etiologies according to previous days of mechanical ventilation is shown in Figures 1 and 2. *P. aeruginosa* developed after about 21 days of mechanical ventilation compared with about 14.7 days for MRSA and

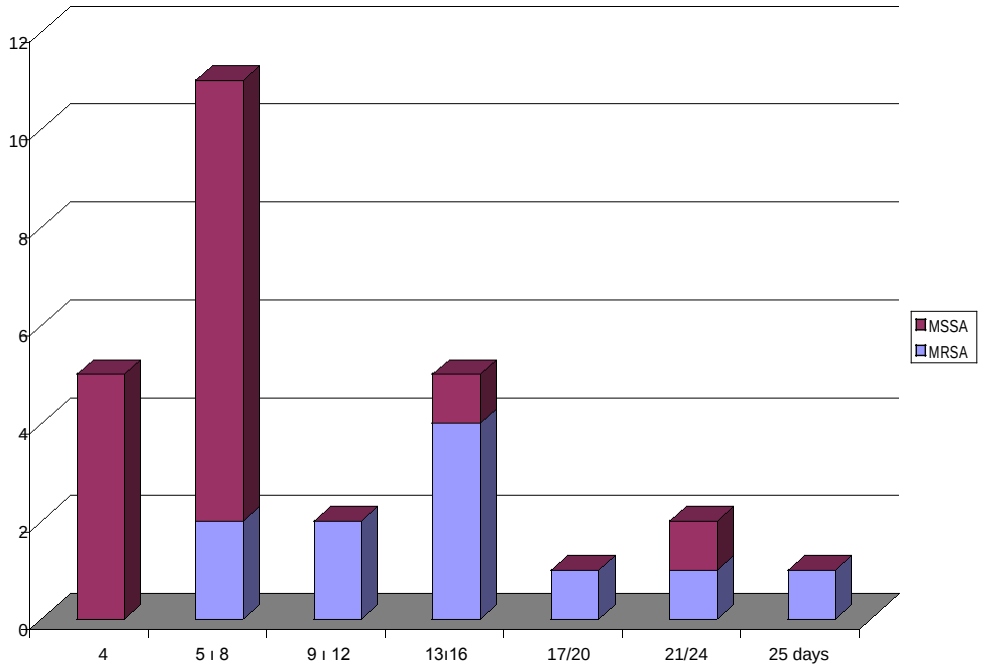

Figure 1. Temporal distribution of Ventilator-associated pneumonia due by *S. aureus*.

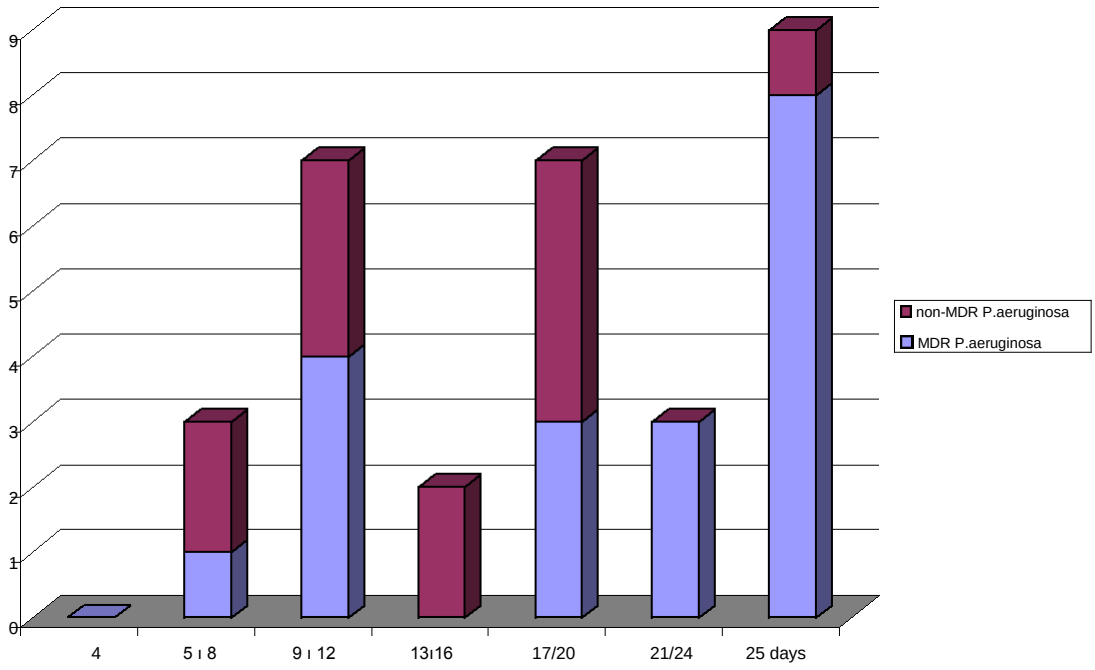

Figure 2. Temporal distribution of MDR and non-MDR *P. aeruginosa* (group P).

7.25 days for MSSA (in Group C). *P. aeruginosa* was identified only in late-onset pneumonia and MSSA identified in all early-onset VAP.

The characteristics of the patients with VAP caused by *P. aeruginosa* and other microorganisms are detailed in Table 2. Five variables including ASIS Score, malnutrition, previous hospitalization, late onset VAP and use of aminoglycosides were significantly associated with VAP caused by *P. aeruginosa* in the univariate analysis. In contrast, remaining variables were not significant. After adjustment for confounding factors, in the final of multi-variable logistic regression models (Table 3), only use of

Table 2. Risk factors and outcome for VAP caused by *P. aeruginosa* vs. other pathogens: Univariate analysis.

Variable		Group * P(n = 31) N (%)	Group **C (n = 35) N (%)	OR (95% CI)	p- value
Age (years)	≥ 60	08 (25.8)	11(31.4)	0.7 (0.2 - 2.5)	0.6
ASIS score	4	25 (80.6)	16(45.7)	4.9 (1.4 - 17.6)	* 0.007
	Clinical	15(48.4)	16(45.7)	0.7(0.2- 2.2)	0.6
Admission category	Surgical	07(22.6)	07(20.0)	1.1(0.2- 5.3)	0.8
	Trauma	09(29.0)	12(34.3)	0.7(0.2- 2.2)	0.6
Immunocompromise		17(54.8)	22(62.8)	0.7 (0.2 - 2.1)	0.5
Previous surgery		22(70.9)	18(51.4)	2.3(0.7- 7.3)	0.1
Malnutrition		16(51.6)	09(25.7)	3.0 (0.9 - 9.9)	* 0.03
Hospitalization within the preceding year		28(90.3)	22(62.8)	5.5 (1.2 - 28.0)	* 0.02
ICU stay (days)7		31(100.0)	33(94.3)	ND	0.5
Duration of ventilation (days)	4 - 5	31(100.0)	35(100.0)	-	-
Late-onset VAP (days)	4 - 5	31(100.0)	30(85.7)	ND	* 0.03
Presence of ≥ 3 invasive device		30(96.8)	30(85.7)	5 (0.5 - 120.1)	0.2
Antibiotic exposure	-lactams	30(96.8)	34(97.1)	0.9 (0.07-34.0)	0.5
	Cephalosporins 3[a]/4[a] generation	25(80.6)	27(77.1)	1.2 (0.7 - 4.7)	0.9
	Carbapenemas	16(51.6)	18(51.4)	1.0 (0.3 - 2.9)	0.8
	Fluoroquinolones	09(29.0)	06(17.1)	2.9 (0.5 - 7.5)	0.3
	Vancomycin	25(80.6)	24(68.6)	1.9 (0.5 - 6.9)	0.2
	Aminoglycosídes	12(38.7)	03(8.6)	6.7 (1.5 - 34.8)	* 0.008
	Anaerobicidal	07(22.6)	09(25.7)	0.8 (0.2 - 3.0)	0.7
	≥ 3 antibiotics	20(64.5)	17(48.6)	1.9 (0.6-5.8)	0.1
Mortality		10(32.2)	13(37.1)	0.8 (0.3-2.5)	0.6

*P = VAP caused by *P. aeruginosa*; **C = Control (VAP caused by other than *P. aeruginosa),* ND, non-defined, * p 0.05

Table 3. Risk factors for VAP *P. aeruginosa* vs. other pathogens: Multivariate Analysis.

Variable	OR (95% CI)	p value
Immunocompromise	0.082(0.007 - 0.98)	0.048
Presence of ≥ 3 invasive devices	38.47(1.20 - 1230.62)	0.039
Use of aminoglycosides	30.57(1.51 - 618.74)	0.026
Use of ≥ 3 antibiotics	0.065(0.004 - 1.066)	0.055

OR- odds ratio; considering p 0.05.

three or more antibiotics, use of aminoglycosides and pre- and presence of three or more invasive devices remained significant for VAP caused by *P. aeruginosa*. Additionally, the use of fluorquinolone (OR: 8.35, 95%CI: 0.51 - 137.23) and vancomycin (OR: 3.2, 95%CI: 0.24 - 42.79) were risk factors associated with Group P (high odds ratio). On the other hand, presence of immunocompromise was independently associated with VAP by other pathogens (Group C) (Table 3).

The inadequate antibiotic therapy in the Group P was significantly higher (48.4%) by statistical analysis than that observed (22.8%) in the Group C. Moreover, the mortality rate was similar among the two groups either when the ICU mortality (32% vs. 37%) or in patients within adequate therapy (46.7% vs. 50.0%) (Tables 2 and 4).

DISCUSSION

There are scarce studies assessing rates of device-associated infections using standardized definitions from developing countries (Carrilho et al., 2007; Costa et al., 2001; Rosenthal et al., 2006). The VAP incidence rate in this study was high (21.11 per 1, 000 ventilation days) considering that rates more commonly range from 4 to 14 per 1, 000 ventilator-days in the USA, but compatible with ICUs in developing countries. The overall rate of VAP was 24.1 per 1, 000 ventilator days in International Nosocomial Control Consortium (INICC) among 85 developing countries around the world (Rosenthal et al., 2006). Recently, Rocha et al. (2008), in the case-control study evaluated VAPs at the same unit observed in this study,

Table 4. Treatment and outcome of patients with Ventilator-Associated Pneumonia (VAP) caused by *P. aeruginosa* and other microorganisms.

Microorganism	N (%)	Adequate treatment N (%)	Mortality N (%)	Inadequate treatment N (%)	Mortality N (%)
Group * P	31(100.0)	16 (51.6)*	03 (18.7)	15 (48.4)*	07(46.7)
Group **C	35 (100.0)	27(77.1)*	09 (33.3)	08 (22.8)*	04 (50.0)
Total	66 (100.0)	43 (65.1)	12 (27.9)	23 (34.8)	11(47.8)

*P = VAP caused by *P. aeruginosa*; **C = Control (VAP caused by other than *P. aeruginosa), *p 0.05*

similarly found a high frequency (24.7 per 1, 000 ventilator-days).

Previously published studies related to pseudomonal VAP have included comparisons with infections due to microorganisms usually associated with early-VAP such as *Streptococcus pneumoniae*, MSSA and *Haemophilus influenzae* (Valles et al., 2003, Kollef et al., 1995, Rello et al., 2006). This study is the first in Brazil to compare MDR *P. aeruginosa* VAP with those caused by other microorganisms usually associated with late- onset VAP, such as MRSA, MDR *Enterobacteriaceae* and *Acinetobacter spp*. In the study, it was found a high rate (53.03%) of MDR microorganisms such as imipenem-resistant *P. aeruginosa* (61.3%), MRSA (40.7%) and third/fourth generation cephalosporin-resistant *Enterobacteriaceae* (66.7%). The results were similar to those previously reported by Rocha et al. (2008) in the same unit. Infections caused by this microorganisms have become a growing problem, are associated with increased hospital LOSs and costs as well as with increased rates of mortality (Giske et al., 2008).

Previously reported risk factors for VAP caused by MDR *P. aeruginosa* and other GNB and MRSA strains include prior use of antibiotics, prolonged hospitalization, previous hospitalization and mechanical ventilation lasting more than 7 days (Rello et al., 2006; Zavascki et al., 2006; Nouér et al., 2005; Cipriano Souza et al., 2008; American Thoracic Society, 2005; Parker et al., 2008). In this study, ASIS score, hypoalbuminemia, previous hospitalization, late-onset pneumonia and use of aminoglycosides were risk factors significantly associated, in the univariate analysis, with VAP caused by *P. aeruginosa*.

In the multivariate analysis, our findings showed that use of three or more antibiotics, use of aminoglycosides and presence of three or more invasive devices were risk factors independently associated with VAP caused by MDR *P. aeruginosa*, while immunocompromise was associated with VAP caused by other pathogens. Additionally, in the development of VAP the risk factors for *P. aeruginosa* and other microorganisms were not the same, an observation that could have implications for prevention and therapy, as Rello et al. (2006) proposed. This article reports that VAP caused by *P. aeruginosa* was independently associated with just presence of steroid use and acute respiratory distress syndrome.

Nevertheless, we have been unable to demonstrate a survival disadvantage associated with pseudomonal infection when compared with other microorganisms, as previously published (McClure et al., 2009). It could have been because previous published studies reporting excess mortality related to pseudomonal VAP have included comparisons with infections due to microorganisms usually associated with early-VAP (Valles et al., 2003, Kollef et al., 1995), in this study control group involved MDR microorganisms.

VAPs by *Pseudomonas* or MDR microorganisms increased over the course of the ICU stay, highlighting the important role of these pathogens in late-onset VAP occurring after 5 days of mechanical ventilation (American Thoracic Society, 2005). In this study, as previously explained (American Thoracic Society, 2005) VAP caused by *P. aeruginosa* developed after about 21 days of mechanical ventilation, MRSA after 14.7 days, both in late-onset pneumonia. In contrast, MSSA developed after 7.25 days, including the 5 cases of early-onset pneumonia.

Antibiotic exposure remains one of the most important risk factors for the acquisition of antibiotic-resistant Gram-negative bacilli by hospitalized patients (Depuydt et al., 2008; Akinci et al., 2005; Stephan et al., 2001; Trouville et al., 1998). Our findings supported these observations. We have showed previously in the same unit of this study that the high (496.9) definite day dose/1000 patients-day of third/forth generation cephalosporins was associated with high incidence (53.6%) of MDR pathogens as cause of VAP (Moreira 2009-online). In this study, broad- spectrum antibiotic use (97%) as well the use of three or more antibiotic (64.5%) were frequent in the two groups, while the use of aminoglycosides (38.7%), fluorquinolones (29.0%) (OR: 8.3, 95% CI: 0.51 - 137.23) and vancomycin (80.6%) (OR: 3.2, 95%CI: 0.24 - 42.79) were identified as risk factors for MDR *P. aeruginosa.*

In this study, antibiotics as initial VAP treatment were adequate in the most patients (77.1%) in the Group C and in only 51.6% of those with VAP caused by MDR *P. aeruginosa* ($p < 0.05$). Altogether, more than one third (34.8%) of the analyzed patients were received incorrect regimens, linked to increased mortality (47.8%), although not statistically significant, when compared with adequate empiric antibiotic therapy (27.9%). These findings have been observed previously (Kollef et al., 1999; Kollef et al., 2006).

The current study has several limitations that should be borne in mind when interpreting the results. The relatively small sample size may not have sufficient statistical power to identify all potential important risk factors for the

development of VAP due to *P. aeruginosa*; and precluded the demonstration of a significant effect of certain variables in the multivariate analysis (Rello et al., 2006). Additionally, the study was performed in a single center, raising the possibility of institutional bias either in patient selection or in other institutional practices.

In conclusion, the incidence of device- associated infection rate for VAP was high (22.11 /1.000 ventilation days), identified as late-onset VAP (92.4%), caused mainly by MDR *P. aeruginosa*, *S. aureus* and other BGN and inappropriate initial antibiotic therapy was observed in approximately one third of the patients. Risk factors for VAP caused by MDR *P. aeruginosa* and other pathogens were not the same and use of three or more invasive devices, three or more antibiotics and exposure of amino-glycosides were independently associated with MDR *P. aeruginosa.* The findings fail to show in adverse outcome differences between the groups regarding critical care unit survival, but there were significant differences between pathogens groups regarding risk factors.

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