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Full Length Research paper

Multidrug-resistant pathogens causing ventilator-associated pneumonia: Risk factors, empirical antimicrobial therapy and outcome of patients in an intensive care unit (ICU) of a Brazilian university hospital

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Ventilator-associated pneumonia (VAP), multidrug-resistant (MDR) microorganisms and inappropriate empirical therapy poses a major therapeutic challenge in developing countries. The aim of this study was to investigate the risk factors of VAP due to MDR pathogens, to assess the rate of inappropriateness of empirical antimicrobial therapy and its subsequent impact on the outcome of VAPs. From May 2009 to August 2010, in a clinical-surgical intensive care unit (ICU) of a Brazilian hospital, patients with VAP were empirically treated with antibiotics. A case-control study was carried out using patients with VAP by MDR pathogens (case) and non-MDR pathogens (control). Appropriateness of empirical antimicrobial therapy and 30-day hospital mortality were evaluated. We found that among 320 patients requiring tracheal intubation for more than 48 h, 81(25.3%) developed VAP and 43(47.3%) due to MDR pathogens. The risk factors for this latter group were: Length of hospital stay, use of corticoids and prior use of antibiotics. Empirical antimicrobial therapy was inappropriate in 30.9% of patients, with 84.0 and 70.0% these with VAP by MDR pathogens and mixed etiology, respectively. VAP caused by MDR pathogens and the inappropriate empirical antimicrobial therapy were significantly associated with 30-day ICU mortality.

Key words: Ventilator-associated pneumonia, antimicrobial resistance, intensive care unit, empirical antimicrobial therapy, 30-day hospital mortality.

INTRODUCTION

Ventilator-associated pneumonia (VAP) is the main infectious complication in the intensive care unit (ICU) because of its frequency, high mortality and considerable hospital cost (Depuydt et al., 2008; Garcin et al., 2009; Nicasio et al., 2010).

Brazil and Latin American countries, in general, have higher levels of bacterial resistance among most of its key pathogens, compared with Europe and United States, particularly among non-fermentative Gram-negative bacilli and extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, but also among some Gram-positive organisms (mainly *Staphylococcus aureus*) (Rossi, 2011).

Gram-negative organisms predominate in hospital-acquired pneumonia, particularly *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and the Enterobacteriaceae. Unfortunately, the resistance of these organisms to antibiotics, mainly to carbapenems, challenges the appropriateness of empirical antibiotic prescription (Peleg and Hooper, 2010; Magnotti et al., 2011). To ensure appropriate empirical antimicrobial therapy, current guidelines for the treatment of VAP advocate for empiric combination therapy with broad-spectrum antibiotics in those patients with risk factors for resistant microorganisms (Joffe et al., 2008; Nicasio et

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al., 2010), which are more frequently associated with late-onset VAP, prior hospitalization or previous antibiotic therapy within the past 90 days (Joseph et al., 2010).

Inappropriate empirical antimicrobial therapy is known to adversely affect outcome in pneumonia associated with mechanical ventilator (Waele et al., 2010) and needs to be tailored to the institutions microbial ecology and the length of time the patient was in hospital before pneumonia developed (Peleg and Hooper, 2010). Appropriate antibiotic use in hospitals entails finding a middle road between their potent ability to reduce the mortality and morbidity of patients with infectious diseases and their potentially hazardous effects, that is, serious adverse events, drug interactions, and induction of resistant strains (Hulscher et al., 2010).

The aim of this study was to investigate the risk factors for developing VAP due to multidrug-resistant (MDR) pathogens, to assess the rate of inappropriateness of empirical antimicrobial therapy and its subsequent impact on the evolution of VAPs in patients interned in a clinical-surgical ICU in a Brazilian University Hospital.

MATERIALS AND METHODS

Setting

The Uberlândia Federal University Hospital Clinic (UFU-HC) is a teaching hospital with 500 beds and a clinical-surgical ICU of adults with 15 beds.

Study design

From May 2009 to August 2010, all patients admitted to the ICU requiring tracheal intubation and mechanical ventilation for more than 48 h and developed VAP were eligible for inclusion in the study. A retrospective case-control study was carried out using patients with VAP by MDR pathogens (case) and non-multidrug-resistant (non-MDR) pathogens (control).

Only the first episode of VAP was considered for each patient. Endotracheal aspirate was collected by probe no. 12 early in the morning by health professionals (physiotherapists or nurses) in charge of the procedure, and transported in a sterile tube to the Microbiology Laboratory. Isolates were identified by conventional biochemical tests as previously described (Koneman, 2008).

The following patient data were retrieved: age, gender, invasive procedures, admission diagnosis, previous use of antibiotics and corticoids, length of hospital stay and duration of mechanical ventilation. Empirical antimicrobial therapy was evaluated according to American Thoracic Society guidelines (ATS, 2005) and microbiological findings were used to determine whether the empirical treatment targeted the identified bacteria. The hospital mortality was assessed within 30 days after VAP onset. The Ethics Committee for Human Research of the Uberlândia Federal University (UFU) approved the project.

Definitions

1. Ventilator-associated pneumonia: The patients were under mechanical ventilator for a period ≥ 48 h after being admitted to the ICU, with new and/or progressive radiological infiltrate and at least under two of the following criteria: purulent sputum, temperature higher than 38.5°C or lower than 35°C, and leukocyte count higher than 10000/µl with deviation to the left or lower than 3000/µL; and positive quantitative culture of the endotracheal aspirate (count ≥ 10^6 CFU/ml). Early-onset VAP was defined as VAP that occurred during the first four days of mechanical ventilation, and late-onset VAP after four or more days (Trouillet et al., 1998; Leroy et al., 2003; Alp and Voss, 2006, Joseph et al., 2010).

2. Multidrug-resistance: MDR pathogens were defined as those resistant to three or more antimicrobial classes. *A. baumannii* was classified as multidrug-resistant if resistant to four or more antimicrobial classes. Data on the disk diffusion susceptibilities of these organisms were interpreted according to Clinical and Laboratory Standards Institute (CLSI, 2009) criteria, by the diameter of inhibition halo formed, using the following antimicrobial discs (Oxoid LTD., England): oxacillin (1 ug), penicillin (10 mg), erythromycin (15 mg), cefoxitin (30 mg), clindamycin (2 mg), rifampicin (5 mg), chloramphenicol (30 mg), vancomycin (30 mg), ciprofloxacin (5 mg), gentamicin (10 mg), cefepime (30 mg), tetracycline (30 mg) and sulphazotrim (25 mg) for Gram-positive; imipenem (10 mg), ciprofloxacin (5 mg), ceftriaxone (30 mg), gentamicin (10 mg), piperacillin-tazobactam (100/10 mg) , polymyxin B (300 u), cefepime (30 mg), aztreonan (30 mg), sulphazotrim (25 mg) and tetracycline (30 mg) for Gram-negative.

3. Inappropriate empirical antimicrobial therapy: This was defined when at least one isolated bacteria were not covered by any antibiotic administered, or when the microorganism was resistant to all antibiotics included in the empiric regimen (Kollef, 2000; Magnotti et al., 2011).

Statistical analysis

Univariate comparisons were carried out by the Qui-Square (x^2) and Fisher's exact tests. Multivariate analysis was carried out by simple or multiple logistic regression when appropriate. The survive curve was drawn using Kaplan-Meier method. The results were considered statistically significant at level of 5%. The epidemiological data were analyzed through the programs Epi-Info version 5.0 (Stone Montain, GA, USA), and BioEstat 5.0 (Belém, PA, Brazil).

RESULTS

A total of 617 adult patients were admitted to adult ICU of the UFU-HC from May 2009 to August 2010. Among the 320 (51.9%) patients who were submitted to mechanical ventilation for longer than 48 h, VAP was diagnosed in 81(25.3%) patients, comprising 71(87.7%) with monomicrobial and 10(12.3%) polymicrobial etiology. The pathogens responsible for VAP are listed in Table 1. MDR pathogens were isolated in 43 of 81(47.3%) episodes. Twenty (24.7%) patients developed early-onset VAP including six (30.0%) patients with VAP due to MDR organisms. Sixty-one (75.3%) patients developed late-onset VAP, and 34 (55.7%) among them caused by MDR pathogens.

Risk factors for VAPs due to MDR pathogens

The characteristics identified by univariate analysis of patients with VAP caused by MDR versus non-MDR

Table 1. Multidrug-resistant (MDR) and non-multidrug-resistant (non-MDR) pathogens associated with ventilator-associated pneumonia (VAP).

Microorganism	Total N=91 (%)	MDR pathogens N=43 (47.3%)	Non-MDR pathogens N=48 (52.7%)	*P*
Gram-positive	13 (14.3)	4 (9.3)	9 (18.7)	0.97
S. aureus	11 (12.1)	4 (9.3)	7 (14.6)	0.65
coagulase negative	1 (1.1)	-	1 (2.1)	1.00
S. pneumonia	1 (1.1)	-	1 (2.1)	1.00
Gram-negative	78 (85.7)	39 (90.7)	39 (81.3)	0.32
NF-GNB[a]	59 (72.8)	33 (76.7)	26 (54.2)	0.04
P. aeruginosa	32 (39.5)	18 (41.9)	14 (29.2)	0.29
A. baumannii	24 (29.2)	13 (30.2)	11 (22.9)	0.58
Other NF-GNB[b]	3 (3.3)	2 (4.6)	1 (2.1)	0.60
Enterobacteriaceae	19 (23.5)	6 (13.9)	13 (27.1)	0.20
K. pneumonia	9 (11.1)	6 (13.9)	3 (6.3)	0.30
Enterobacter sp.	4 (4.9)	-	4 (8.3)	0.12
M. morgannii	2 (2.5)	-	2 (4.2)	0.50
S. marcescens	2 (2.5)	-	2 (4.2)	0.50
E. coli	2 (2.5)	-	2 (4.2)	0.50

[a]Non-fermentative-Gram-negative bacilli, [b]*Stenotrophomonas maltophilia*, *Burkholderia cepacia*.

pathogens are provided in Table 2. Multiple logistic regression revealed that the risk of VAP by MDR pathogens was more than twice as large among patients with length of hospital stay greater than seven days before VAP onset and those who used corticoids, and more than three times as large among patients who had prior use of antibiotics (Table 3).

Empirical antimicrobial therapy

Twenty-five (30.9%) of the 81 patients with a clinical diagnosis of VAP received inappropriate antimicrobial treatment, with 56(69.1%) patients receiving appropriate antimicrobial agents. The risk of inappropriate antimicrobial therapy was significant, with more than 10 times as large among patients with VAP by MDR pathogens (21 of the 25 patients who were inappropriately treated), by both univariate (OR, 10.22; 95% CI, 2.75 to 41.43; $P < 0.0001$) and multivariate analysis (OR, 10.22; 95% CI, 3.07 to 34.08; $P = 0.0002$). Six (30.0%) of the 20 patients with early-onset VAP received inappropriate treatment due to MDR pathogens. Moreover, inappropriate antimicrobial treatment among patients with polymicrobial VAP was significantly higher than among patients with VAP caused by a single pathogen (70.0 versus 25.3%) by univariate (OR, 6.87; 95% CI, 1.38 to 38.19; $P = 0.008$) and multivariate analysis (OR, 6.87; 95% CI, 1.60 to 29.42; $P = 0.009$).

Outcome

The overall 30-day mortality rate was significantly higher in patients with VAP caused by MDR than in patients with non-MDR VAP [21 (52.5%) vs. 8 (19.5%), $P = 0.01$] (Figure 1), and in the inappropriate antimicrobial treatment group than in the appropriately treated group [13 (23.2%) vs. 16 (64.0%), $P = 0.0004$] (Figure 2).

DISCUSSION

In the present study, the independent risk factors of VAP due to MDR pathogens were previous antibiotic exposure (less than 2 weeks), length of hospital stay greater than seven days before VAP onset and use of corticoids. These factors correspond to those reported in the literature besides the following ones: prolonged time of mechanical ventilation and prior hospitalization in the ICU (Trouillet et al., 1998; Zavascki et al., 2006; Depuydt et al., 2008; Sheng et al., 2010; Park et al., 2011; Ulldemolins et al., 2011).

The administration of previous antibiotic therapy has an important effect on the ecology of patient's microflora, which can ultimately lead to infection with resistant strains of high-risk pathogens, and extended length of stay in the hospital also increase the likelihood of being colonized by resistant bacteria which are likely to lead to subsequent severe infections (Rello et al., 1993; Trouillet et al., 1998; Tacconelli et al., 2008; Ulldemolins et al., 2011).

The emergence of ESBLs has necessitated the increased use of carbapenems, but this increased use of "drugs of last resort" may be contributing to the emergence of MDR non-fermenters (Isturiz, 2008). In health-

Table 2. Characteristics of patients with ventilator-associated pneumonia (VAP) by multidrug-resistant (MDR) and non-multidrug-resistant (non-MDR) pathogens.

Variable	MDR pathogens N=40 (49.4%)	non-MDR pathogens N=41 (50.6%)	*P*
Gender			
Male	30 (75.0)	28 (68.3)	0.67
Female	10 (25.0)	13 (31.7)	0.67
Age > 60	13 (32.5)	10 (24.4)	0.57
Length of hospital stay before VAP > 7 days	29 (72.5)	19 (46.3)	0.03
Duration of MV[a] before VAP > 7 days	26 (65.0)	18 (43.9)	0.09
Invasive procedure			
Tracheostomy	9 (22.5)	4 (9.8)	0.06
CVC[b]	36 (90.0)	38 (92.7)	0.71
VP[c]	38 (95.0)	40 (97.6)	0.62
NP[d]	35 (87.5)	37 (90.2)	0.74
Drain	4 (10.0)	6 (14.6)	0.75
Early-onset VAP	6 (15.0)	14 (34.1)	0.08
Late-onset VAP	34 (85.0)	27 (65.8)	0.08
Use o corticoids	23 (57.5)	13 (31.7)	0.03
Previous antibiotic therapy	29 (72.5)	20 (48.8)	0.05
Use of three or more antibiotics	14 (35.0)	12 (29.3)	0.75
Admission diagnosis			
Clinical	13 (32.5)	12 (29.3)	0.94
Surgical	11 (27.5)	7 (17.1)	0.39
Trauma	16 (40.0)	22 (53.7)	0.31
Inappropriate antimicrobial therapy	21 (52.5)	4 (9.8)	<0.0001
Mortality	21 (52.5)	8 (19.5)	0.004

[a]Mecanical ventilation, [b]central vascular catheter, [c]vesical probe, [d]nasogatric probe.

Table 3. Independent risk factors for ventilator-associated pneumonia (VAP) caused by multidrug-resistant pathogens.

Variable	*P*	OR[a]	CI[b]
Length of hospital stay before VAP > 7 days	0.03	2.95	1.09-8.00
Use o corticoids	0.04	2.73	1.03-7.25
Previous antibiotic therapy	0.02	3.22	1.17-8.84

[a]Odds ratio; [b]Confidence Interval.

care setting, multi-drug resistance in Gram-negative bacillary infections has severely restricted therapeutic options, and sometimes no effective drugs are available to treat life-threatening infections (Carlet et al., 2011).

In our study, the empirical antimicrobial therapy was inappropriate in 25 (30.9%) of 81 patients with clinical diagnosis of VAP. In a study of Willemsen et at. (2007), antimicrobial therapy was deemed inappropriate in 351 (37.4%) of the total of 938 patients who were on antimicrobial therapy, and in a study of Teixeira et al. (2007), 69(45.7%) of 151 patients with a clinical diagnosis of VAP received inappropriate antimicrobial treatment.

The presence of MDR or unexpected pathogen may reduce the appropriateness of antimicrobial treatment (Teixeira et al., 2007, Welte and Pletz, 2010; Ulldemolins et al., 2011). We identified multidrug-resistant bacteria and polymicrobial VAP as independent risk factor for inappropriate empirical treatment, which itself was signifi-cantly related to increased in-hospital mortality. Empirical

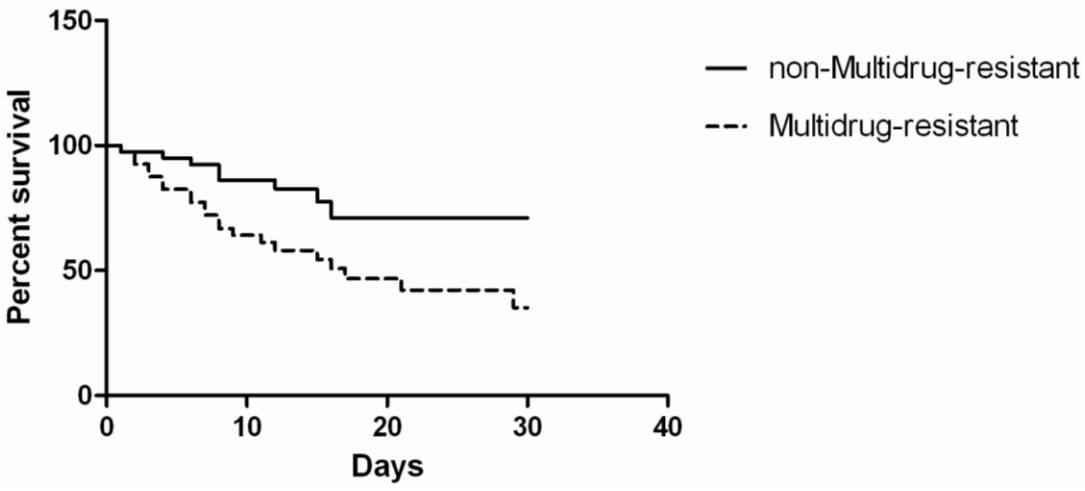

Figure 1. Kaplan-Meier analysis of multidrug-resistant (MDR) or non-multidrug-resistant (Non-MDR) pathogens causing ventilator-associated pneumonia (VAP) episodes according to 30-day mortality (P = 0.01) log rank test.

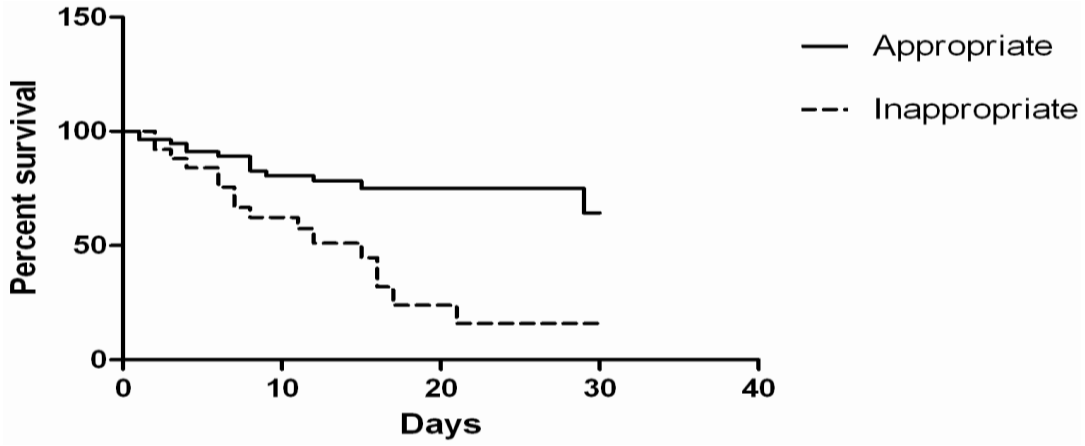

Figure 2. Kaplan-Meier analysis of empirical antimicrobial treatment of all ventilator-associated pneumonia (VAP) episodes according to 30-day mortality (P = 0.0004) log rank test.

antimicrobial therapy was inappropriate; it was higher (52.5%) in patients with VAP due to MDR pathogens versus 9.8% in that cause by non-MDR pathogens and in 70.0% of the patients with polymicrobial VAP versus 25.3% in case of patients with monomicrobial VAP. Most cases of MDR, VAP are expected to occur later, but 30.0% of our patients with early-onset VAP received inappropriate antimicrobial therapy due to MDR pathogens. These findings may be explained by the fact that many patients previously exposed to antibiotics, were previously admitted in other hospital wards, or with history of recent hospitalization or transferred from other healthcare facility (Friedman et al., 2002; Teixeira et al., 2007; Ulldemolins et al., 2011).

Broad-spectrum antibiotics used empirically to assure appropriate initial therapy paradoxically increase the selection pressure for antibiotic resistant microorganisms and are associated with development of resistant microbial flora (Joffe et al., 2008). To limit selection pressure, de-escalation of initial broad-spectrum antibiotics has been suggested: narrowing the spectrum of antibiotics, shortening the duration of the antibiotics, or both (Höffken and Niederman, 2002; ATS, 2005; Joffe et al., 2008).

In our investigation, 32.1% patients were given three or more antibiotic empirically, any without adopting the de-escalating antibiotic strategy after microbiological results. These conditions contribute to the emergence of antibiotics-resistant and multidrug-resistant microorganisms reported by many authors (Trouillet et al., 1998; Kollef, 2005; Waele et al., 2010).

The initial choice of the empirical antimicrobial scheme for the treatment of VAPs is of critical importance in

determining the patient's clinical evolution, particularly against hospital mortality, especially for those with antibiotic-resistant pathogens (Kollef et al., 2006; Chang et al., 2011). Early aggressive and appropriate therapeutics directed against more probable microorganisms, based on local vigilance data, is associated to reduced mortality rates and is important to optimize the management of VAP (Rello et al., 1997; Luna et al., 1997; Hoffkën and Niederman, 2002; Masterton, 2007; Chang et al., 2011).

In our study, the overall 30-day mortality rate was significantly higher in patients with VAP caused by MDR than in patients with non-MDR VAP and in the inappropriate antimicrobial treatment group than in the appropriately treated group. Depuydt et al. (2008) showed similar results with 30-day ICU- and in-hospital mortality rate significantly higher in patients with VAP caused by MDR pathogens than in patients with non-MDR VAP (37.0 vs. 20.0%; $P = 0.02$). Use of appropriate empirical antimicrobials greatly affects morbidity and mortality in hospitalized patients (Ulldemolins et al., 2011).

A large multicenter international study evaluated the effect of appropriateness on mortality and hospital length of stay in a large cohort of hospitalized patients with severe infections. All-cause 30-day mortalities were significantly higher in patients with inappropriate initial antibiotic treatment (20.1 vs 11.8%; $P = 0.001$), and hospital length of stay was increased by more than 2 days in the inappropriate treatment group ($P = 0.02$) (Fraser et al., 2006).

In Brazil, Teixeira et al. (2007) showed that inappropriate antimicrobial therapy was significantly associated with 28-days mortality and MDR bacteria was the main cause of inappropriate empirical antimicrobial therapy. Other studies showed that the inappropriateness of empirical antimicrobial therapy for VAP is associated with a poor prognosis (Kuti et al., 2008; Garcin et al., 2009; Uldemolins et al., 2011).

Our study has limitations. First, this was a single-center study and our findings may be attributed to institution-specific variables. Thereby, it raises the possibility of institutional bias either in patient selection or in other institutional practices. Second, determinants of MDR were identified using a case-control design, with patients with VAP caused by non-MDR pathogens as controls rather than patients at risk of developing VAP (source patients). As antibiotic exposure is likely to suppress the growth of susceptible bacteria, these control patients may have received fewer antibiotics than the overall source patients, leading to overestimation of the association between antibiotic exposure and MDR (Depuydt et al., 2008). Third, information about patient's condition and severity of underlying illness (for example, the APACHE II score) was unavailable and the analysis of co-morbidity conditions was compromised by the lack of data on the patient's underlying disease status. Another limitation was the small sample size.

In conclusion, length of hospital stay greater than seven days before VAP onset, use of corticoids and previous use of antibiotics were independent risk factors for VAP by MDR microorganisms. The empirical antibiotic treatment was inappropriate in 30.9% of the patients with VAP and 84.0 and 70.0% due to MDR bacterial and mixed etiology, respectively. Moreover, VAP caused by MDR pathogens and the inappropriate empirical antimicrobial therapy were significantly associated with 30-day ICU mortality.

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