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Prevalence, outcomes, and predictors of multidrug-resistant nosocomial lower respiratory tract infections among patients in an ICU

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ABSTRACT

Objective: To determine the prevalence, outcomes, and predictors of multidrug-resistant nosocomial lower respiratory tract infections (LRTI) in patients in an ICU. **Methods:** This was an observational cohort study involving patients with nosocomial LRTI (health care-associated pneumonia, hospital-acquired pneumonia, or ventilator-associated pneumonia). Data were prospectively collected between 2015 and 2019. The multidrug-resistant pathogens (MDRPs) identified in the isolates studied included resistant to extended-spectrum cephalosporin-resistant and carbapenem-resistant *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, carbapenem-resistant Enterobacteriaceae, and methicillin-resistant *Staphylococcus aureus* at microbiological diagnosis. **Results:** During the study period, 267 patients in the ICU were diagnosed with LRTI, microbiological confirmation of LRTI having been obtained in 237. Of these, 146 (62%) had at least one MDRP isolate. Patients infected with MDRP were found to have poorer outcomes than patients infected with susceptible strains, such as prolonged mechanical ventilation (18.0 days vs. 12.0 days; $p < 0.001$), prolonged ICU length of stay (23.0 days vs.16.0 days; $p < 0.001$), and higher mortality (73% vs. 53%; $p < 0.001$) when compared with patients infected with susceptible strains. Hospital length of stay ≥ 5 days (OR = 3.20; 95% CI: 1.39-7.39; $p = 0.005$) and prolonged use vasoactive drugs (OR = 3.15; 95% CI: 1.42-7.01; $p = 0.004$) were independent predictors of LRTI caused by MDRPs (LRTI-MDRP). The presence of LRTI-MDRP was found to be an independent predictor of death (OR = 2.311; 95% CI: 1.091-4.894; $p = 0.028$). **Conclusions:** Prolonged use of vasoactive drugs and prolonged hospital length of stay were independent predictors of LRTI-MDRP in this population of critically ill patients with very poor outcomes.

Keywords: Drug resistance, multiple; Healthcare-associated pneumonia; Pneumonia, ventilator-associated; Cross infection; Intensive care units.

INTRODUCTION

The increased prevalence of pathogens that express resistance to β-lactams due to the production of extended-spectrum β-lactamases, AmpC β-lactamases, and carbapenemases, in addition to the alteration of the cell wall promoting methicillin resistance, has compromised the therapeutic effectiveness of current treatments. Hospitalized patients with infections caused by multidrug-resistant pathogens (MDRPs) are at a higher risk of receiving inappropriate therapy and, consequently, of treatment failure, increasing the burden of disease in ICUs.[1]

Pneumonia in critically ill patients at a higher risk of MDRP infection may be healthcare-associated pneumonia (HCAP), hospital-acquired pneumonia (HAP), or ventilator-associated pneumonia (VAP), which are usually associated with extrapulmonary complications and high mortality.[2] Patient characteristics, infection with specific pathogens, and severity of illness influence the selection of antibiotics. Antibiotic resistance is a major concern in lower respiratory tract infection (LRTI) globally, especially because of its association with prolonged hospital length of stay and high mortality.[2] Appropriate antibiotic therapies are fundamental to better outcomes in critically ill patients suffering from infections. It is therefore important to identify those patients who are at a higher risk of MDRP infections. Understanding epidemiological features and risk factors for pulmonary infections due to MDRPs is important to inform earlier and more appropriate treatment options.

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There are known risk factors for MDRP such as sociodemographic factors, severity of disease, comorbidities, and previous use of antibiotics, among many others that can vary according to the population and type of health care setting.[2-6] We hypothesized that patients with LRTI caused by MDRPs (LRTI-MDRP) have worse outcomes and possibly different patterns of inflammatory response, as well as different features, in comparison with those with infections secondary to susceptible organisms. We aimed to evaluate the outcomes and to identify early predictors of LRTI-MDRP.

METHODS

Study design, setting, and participants

This observational cohort study was a retrospective analysis of a prospective collection of data from subjects with LRTI who were admitted to a 40-bed, mixed ICU at the *Hospital de Base*, a tertiary care university hospital, located in the city of São José do Rio Preto, Brazil. Data were collected between August 1, 2015 and August 1, 2019. The sample size was determined by a convenience sample of patients with microbiologically confirmed LRTI who were included in our registry database during the study period. The study was approved by the local institutional review board (Protocol no. 12569319.1.0000.5415) and followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[7]

Inclusion criteria were being ≥ 18 years of age and diagnosed with an LRTI (HCAP, HAP, or VAP). Hospital and ICU lengths of stay prior to the diagnosis of LRTI were recorded for each subject (days from admission to diagnosis). Antibiotic treatment was prescribed in accordance with local guidelines. HCAP was defined in accordance with the 2007 Infectious Diseases Society of America/American Thoracic Society criteria.[8] HAP was defined as the presence of clinical signs and symptoms of pneumonia with a new or progressive infiltrate on chest radiography occurring after hospitalization for > 48 h or within 7 days after hospital discharge or at least 48 h for non-intubated patients. Clinical signs and symptoms were cough, tachypnea (RR > 25 breaths/min), purulent sputum, hypoxemia, need for mechanical ventilation, and acute changes in the ventilator support system to increase oxygenation, as well as at least one of the following signs: fever (body temperature ≥ 38°C) and total number of peripheral leukocytes ≥ 10,000 or ≤ 4,500 cells/mm^3.[9] VAP was defined as the presence of a new or progressive infiltrate and signs of infection in a patient receiving mechanical ventilation via an endotracheal tube for at least 48 h. ARDS was diagnosed on the basis of the 2012 Berlin definitions.[10]

Data collection

Data on clinical characteristics, laboratory tests, and types of organ support needed were collected. The SOFA score, the Simplified Acute Physiology Score III (SAPS III), and the Clinical Pulmonary Infection Score (CPIS) were calculated.[11-13] Qualitative and quantitative cultures from endotracheal aspirates (n = 210) or sputum (n = 27) were performed as per standard methods. Data on C-reactive protein (CRP) levels measured within the first 48 h after admission, corticosteroid use, and duration of mechanical ventilation and of vasopressor use were collected. The lowest serum albumin level obtained within the first 48 h from admission was recorded. Radiological assessment included chest radiography and CT (or chest CT angiography).

Patients were divided into two groups: MDRP− and MDRP+. The MDRP− group included LTRI-related non-multidrug resistant strains in the isolates studied, whereas the MDRP+ group included at least one of the following multidrug-resistant strains: *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* strains with a multidrug resistant phenotype, that is, resistance to more than one antimicrobial agent in three or more different antimicrobial categories, including extended-spectrum cephalosporins (ceftriaxone, ceftazidime, and cefepime) and/or carbapenems (imipenem and meropenem).[14] Carbapenem-resistant Enterobacteriaceae and methicillin-resistant *Staphylococcus aureus* were also included in that group. All isolates were revised and classified by a microbiologist. The outcomes evaluated were death, bacteremia, ARDS, and hospital and ICU lengths of stay.

Statistical analysis

For statistical analysis, we used descriptive statistics and comparison of proportions. In the case of a non-Gaussian distribution, continuous variables were analyzed using the Kruskal-Wallis test. Categorical variables were analyzed using either the Pearson's chi-square test or the Fisher's exact test. Univariate and multivariate (forward stepwise technique) logistic regression analyses were performed to determine the independent predictors of the presence of MDRPs. Median values were used as breakpoints to determine binary categories for continuous variables. Dependent variables were LRTI-MDRP and death. The independent variables with a value < 0.25 in the univariate analysis were selected for the binary logistic regression analysis. The variables tested for LRTI-MDRP in the multivariate analysis were sex, SOFA score, SAPS III, COPD (reference: no COPD), CRP-to-albumin ratio, use of corticosteroids (reference: no use), use of vasoactive drugs, hospital and ICU lengths of stay prior to LRTI diagnosis, and reason for hospital admission (reference: surgery). The variables tested for death in the multivariate analysis were age, SOFA score, SAPS III, COPD (reference: no COPD), CRP-to-albumin ratio, and reason for hospital admission (reference: surgery). Variance inflation factors were calculated to test for multicollinearity; for all of the covariates, a factor < 5 was suggestive of no multicollinearity. Adjusted odds ratios and 95% confidence intervals were calculated

for the predictors. A p value < 0.05 was considered statistically significant.

RESULTS

Overall, 267 patients with LRTI were screened. Of these, 237 patients were included after microbiological confirmation, and 146 (62%) of whom were infected with at least one MDRP (Table 1). The mean age was 57.2 ± 17.1 years, and the mean SAPS III, SOFA score, and CPIS were 64.7 ± 16.6; 8.7 ± 3.9; and 6.1 ± 1.9, respectively. The incidence and mortality rates according to the type of LRTI are shown in Figure 1.

The clinical characteristics and outcomes in the MDRP+ and MDRP− groups are shown in Table 1. COPD was significantly more common in the MDRP+ group than in the MDRP− group (10.2% vs. 5.5%; p = 0.029; Table 1). Hospital and ICU lengths of stay prior to the diagnosis of LRTI were significantly longer in the MDRP+ group than in the MDRP− group. The patients in the MDRP+ group, when compared with those in the MDRP− group, used vasopressors (median: 11 [6-18] days vs. 6 [4-12] days; p < 0.001) and were on mechanical ventilation (median: 18.0 [11.5-26.0] days vs. 12.0 [6.0-22.0] days; p < 0.001) for a longer time. In addition, those in the MDRP+ group had longer ICU length of stay (median: 23 [15-33] days vs. 16 [10-24] days; p < 0.001), longer hospital length of stay (median: 31.0 [21.0-50.5] days vs. 26.0 [15.0-41.0] days; p = 0.004), and higher mortality (73% vs. 53%; p = 0.001; Table 1).

In the binary logistic regression analysis, a hospital length of stay ≥ 5 days (OR = 3.20; 95% CI: 1.39-7.39; p = 0.005) and prolonged duration of treatment (≥ 9 days) with vasoactive drugs (OR = 3.15, 95% CI: 1.42-7.01; p = 0.004) were independent predictors of LRTI-MDRP in this population of critically ill patients (Table 2). The presence of LRTI-MDRP was found to be the only independent predictor of death (OR = 2.31; 95% CI: 1.091-4.894; p = 0.028).

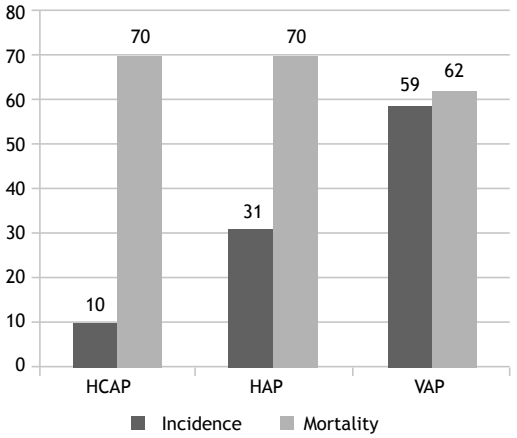

Figure 1. Incidence of lower respiratory tract infections according to diagnosis and respective mortality rates (in %). Observation: rounded numbers. HCAP: health care-associated pneumonia; HAP: hospital-acquired pneumonia; and VAP: ventilator-associated pneumonia.

The main demographic and clinical characteristics of the patients infected with either multidrug-resistant gram-negative or gram-positive strains are shown in Table 3. Figure 2 shows the distribution of MDRPs in number of patients and of isolates.

DISCUSSION

The main findings in our study are as follows: MDRPs were the cause of LRTI in almost two-thirds of the ICU patients; the mortality rate was remarkably high in this heterogeneous population of critically ill patients; prolonged ICU length of stay (≥ 5 days) and prolonged treatment with vasopressors (≥ 9 days) were found to be predictors of LRTI-MDRP; and the presence of LRTI-MDRP was identified as the only independent risk factor for death.

A large proportion of our ICU population with LRTI was infected with MDRPs (62%). At ICU admission, SAPS III and the SOFA score were not significantly different when we compared the LRTI patients with susceptible and resistant strains; nevertheless, those in the MDRP+ group had higher mortality rates and higher resource utilization as shown by the longer use of mechanical ventilation and vasopressors, as well as longer ICU and hospital lengths of stay in comparison with those in the MDRP− group. The mortality rate was 73% in the MDRP+ group.

Other authors have reported similar results (higher mortality rates) when they compared hospitalized adults infected with carbapenem-resistant *K. pneumoniae* with matching controls infected with susceptible *K. pneumoniae* strains.[15,16] The mortality of patients infected with multidrug-resistant bacteria was significantly higher than that of those infected with non-multidrug-resistant bacteria [51.85% vs. 30.56%] in patients with VAP in a county hospital in China.[17] In a study conducted in Brazil, the mortality rate for VAP caused by MDRPs was 61.3%, whereas that for VAP not caused by MDRPs was 25.0%.[18] Differences in the severity of disease, as shown by high SOFA scores and SAPS III, can explain the even higher mortality observed in our study. Our data suggest that multidrug resistance is the cause of high mortality since isolation of an MDRP was found to be the only independent predictor of death, even when variables such as age, SAPS III, and SOFA score entered the logistic regression model. One fundamental reason for higher mortality might be a delay in providing appropriate antibiotic therapy.[19] In addition, *A. baumannii* and *K. pneumoniae* had the highest prevalence in our patients with LRTI, both of which are related to worse prognosis.

We found that a hospital length of stay ≥ 5 days and being on vasopressors for ≥ 9 days more than tripled the likelihood of having LRTI-MDRP. Other studies have reported many other risk factors associated with MDRPs in hospitalized patients such as mechanical ventilation, previous use of antibiotics, and indwelling catheters.[4] In a review including a total of 92 studies, the risk factors most frequently reported as significantly associated

Table 1. Demographic and clinical characteristics of the sample as a whole and of the two study groups.[a]

Characteristic	Total	Group		p
		MDRP−	MDRP+	
	(N = 237)	(n = 91)	(n = 146)	
Age, years	57.2 ± 17.1	57.3 ± 16.6	57.2 ± 17.5	0.800
Male sex	160 (67.5)	66 (72.5)	94 (64.4)	0.193
Severity scores				
SAPS III	64.7 ± 16.6	62.5 ± 17.7	66.0 ±15.7	0.193
SOFA at admission	8.7 ± 3.9	9.3 ± 4.0	8. 3 ± 3.8	0.098
CPIS	6.1 ± 1.9	6.0 ± 1.8	6.1 ± 1.9	0.680
CRP (day 1)	19.3 ± 14.1	19.4 ±16.0	19.1 ± 12.8	0.647
CRP-to-albumin ratio	7.6 ± 6.9	5.9 ± 5.0	8.4 ± 7.6	0.083
Type of admission				
Medical	135 (57.0)	52 (57.2)	83 (56.8)	0.965
Surgical	102 (43.0)	39 (42.9)	63 (43.2)	0.965
Trauma	52 (21.9)	23 (25.27)	29 (19.86)	0.330
Comorbidities				
COPD	20 (8.4)	5 (5.5)	15 (10.23)	0.029
Diabetes mellitus	23 (9.7)	10 (11.1)	13 (8.9)	0.689
Smoking	21 (8.9)	9 (9.8)	12 (8.21)	0.554
Cardiovascular disease	52 (21.9)	21 (23.1)	31 (21.2)	0.739
Respiratory disease	51 (21.5)	16 (17.6)	35 (23.9)	0.240
Corticosteroid use	31 (13.1)	8 (8.8)	23 (15.8)	0.109
LRTI				
HCAP	23 (9.7)	12 (13.2)	11 (7.5)	0.150
HAP	73 (30.8)	29 (31.9)	44 (30.1)	0.779
VAP	139 (58.6)	51 (56.0)	88 (60.3)	0.585
ICU LOS prior to LRTI diagnosis	3 [0-6]	2 [0-4]	4 [1-9]	< 0.001
Hospital LOS prior to LRTI diagnosis	5.5 [2-13]	4 [1-7]	7 [4-15]	< 0.001
Supportive therapies				
Vasoactive drugs	224 (94.9)	84 (92.3)	140 (95.9)	0.155
Vasoactive drugs, days	9 [5-16]	6 [4-12]	11 [6-18]	< 0.001
Mechanical ventilation	210 (88.6)	85 (93.40)	125 (86.20)	0.076
Mechanical ventilation, days	16 [9-24]	12 [6-22]	18 [12-26]	< 0.001
Outcomes				
ARDS	36 (15.2)	13 (13.9)	23 (22.1)	0.742
Bacteremia	70 (32.6)	23 (25.1)	47 (44.9)	0.528
ICU LOS, days	20 [13-30]	16 [10-24]	23 [15-33]	< 0.001
Hospital LOS, days	30 [18-45]	26 [15-41]	31 [21-51]	0.004
In-hospital mortality	154 (65.2)	48 (53.0)	106 (73.0)	< 0.001

MDRP: multidrug-resistant pathogens; SAPS III: Simplified Acute Physiology Score III; CPIS: Clinical Pulmonary Infection Score; CRP: C-reactive protein; LRTI: lower respiratory tract infection; HCAP: healthcare-associated pneumonia; HAP: hospital-acquired pneumonia; VAP: ventilator-associated pneumonia; and LOS, length of stay. [a]Values expressed as n (%), mean ± SD, or median [IQR].

with gram-negative carbapenem-resistant infections were previous antibiotic use, previous colonization, mechanical ventilation, dialysis, hospital length of stay, comorbidities, APACHE II score, and intubation.[3] The population included in our study was homogeneous in terms of severity of the disease; almost all of the patients were intubated or in septic shock, which poses difficulties for comparing our population with those from other studies, because these variables could not be tested in the regression analysis.

In our study only COPD was associated with MDRPs. Prolonged use of vasoactive drugs and prolonged hospital length of stay were associated with LRTI-MDRP. Increased mortality has been reported in patients infected with carbapenem-resistant *K. pneumoniae* who had other comorbidities.[20] In a prospective parallel matched cohort study in Europe, an excess hospital length of stay of 5 days could be attributed to resistance to third-generation cephalosporins in *Escherichia coli* bloodstream infections.[21] The reason for the association of duration of treatment with vasoactive drugs with MDRP infections is yet to be known. We can speculate that it may be a surrogate marker for difficult-to-treat infections, inappropriate initial antibiotic therapies, or

Table 2. Multivariate logistic regression with independent predictors of multidrug-resistant pathogen infection and death in patients with lower tract respiratory infection.[a]

	OR	95% CI	p
MDRP			
Vasoactive drugs, days	3.159	1.423-7.013	0.004
Hospital LOS prior to LRTI diagnosis	3.205	1.390-7.390	0.005
COPD	9.770	1.062-89.870	0.014
Death			
MDRP	2,311	1.091-4.894	0.028

MDRP: multidrug-resistant pathogens; LOS, length of stay; LRTI: lower respiratory tract infection; ref: reference; and CRP: C-reactive protein. [a]Variables entering logistic regression: sex; SOFA; SAPS III; COPD (ref: no COPD); CRP-to-albumin ratio; corticosteroids (ref: no use); vasoactive drugs, days; hospital LOS prior to LRTI diagnosis; and type of admission (ref. surgical). Cutoff points: SOFA (≤ 9), SAPS III (≤ 65.5), CRP-albumin rate (≤ 6), vasoactive drugs; days (≤ 9), and hospital LOS prior to LRTI diagnosis (≤ 5).

Table 3. Demographic and clinical characteristics of the patients infected with multidrug-resistant Gram-negative or multidrug-resistant Gram-positive strains.[a]

Variable	Group		p
	MDR Gram-negative (n = 114)	MDR Gram-positive (n = 32)	
Age, years	57.7 ± 17.4	55.4 ± 18.1	0.714
Male sex	75 (65.8)	19 (59.4)	0.506
CRP-to-albumin ratio	8.7 ± 7.8	6.8 ± 6.6	0.400
Severity scores			
SAPS III	67.1 ± 16.2	62.4 ± 13.4	0.220
SOFA at admission	8.6 ± 3.9	7.3 ± 3.1	0.072
CPIS	6.1 ± 2.0	6.2 ± 1.5	0.264
Type of admission			
Medical	66 (58.0)	17 (53.1)	0.631
Surgical	48 (42.0)	15 (46.9)	0.631
Coexisting diseases			
COPD	11 (9.6)	4 (12.5)	0.639
Corticosteroid use	16 (14.0)	3 (9.4)	0.489
Hospital LOS prior to LRTI diagnosis	5.0 [2.0-11.7]	9.0 [4.0-23.2]	0.013
Vasoactive drugs, days	14.5 ± 13.3	12.5 ± 10.2	0.464
In-hospital mortality rates	81 (71.7)	25 (78.1)	0.468

MDR: multidrug resistant; ; CRP: C-reactive protein; SAPS III: Simplified Acute Physiology Score III; CPIS: Clinical Pulmonary Infection Score; LOS: length of stay; and LRTI: lower respiratory tract infection. [a]Values expressed as n (%), mean ± SD, or median [IQR].

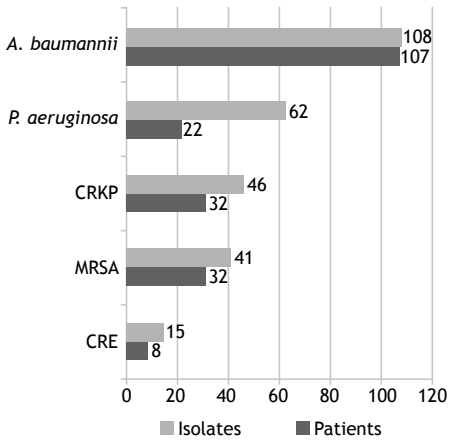

Figure 2. Distribution of multidrug-resistant pathogens and number of isolates in the sample. A.: *Acinetobacter*; P.: *Pseudomonas*; CRKP: carbapenem-resistant *Klebsiella pneumoniae*; MRSA, methicillin-resistant *Staphylococcus aureus*; and CRE: carbapenem-resistant Enterobacteriaceae.

more severe disease; consequently, sepsis reversal would take a longer time.

Infections caused by resistant pathogens are associated with increased costs.[22] Effective antimicrobial stewardship and infection prevention programs are needed to prevent these infections. Difficulties in weaning patients from vasoactive drugs should be a warning signal for MDRP infections, and this hypothesis should be tested in prospective studies. It is therefore of utmost importance to be aware of the risk factors for MDRPs and to develop strategies to identify patients at a higher risk in order to seek appropriate and adequate antibiotic therapies, along with antibiotic stewardship policies.

This study has various weaknesses. First, the single-center and university setting nature of this study might preclude the generalization of the findings to other hospitals or populations of hospitalized patients. Second, this population of critically ill patients is unique;

because almost all patients were admitted to the ICU on antibiotic therapy, used indwelling catheters, were intubated, and developed sepsis, it was impossible to identify any of these variables as predictors of LRTI-MDRP; therefore, attention to other risk factors must be part of our daily patient care. Nonetheless, we hope that our results will increase awareness for clinicians working in ICUs. The main strength of our study was the careful and prospective collection of data that were revised by a microbiologist.

In conclusion, in ICU patients with LRTI infections, prolonged hospital length of stay and prolonged use of vasopressors were predictive of infections caused by MDRPs and were associated with poor outcomes.

AUTHOR CONTRIBUTIONS

SML: study design; study proposal; data analysis; and drafting and revision of the manuscript. ABSO: study design; data acquisition and interpretation; data analysis; drafting of the manuscript; and approval of the final version. GHS, MFBN, TAM, and AHNS: data acquisition; revision of the manuscript; and approval of the final version. JVG and MCLN: data interpretation and analysis; drafting of the manuscript; and approval of the final version.

CONFLICTS OF INTEREST

None declared.

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