ORIGINAL RESEARCH

Multidrug-Resistant Bacteria on Critically Ill Patients with Sepsis at Hospital Admission: Risk Factors and Effects on Hospital Mortality

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Purpose: To evaluate the effect of MDRO infection on hospital mortality and the risk factors among critically ill patients with sepsis at hospital admission.

Patients and Methods: A cross-sectional study was performed between April 2019 and May 2020, followed by a cohort to evaluate hospital mortality that prospectively included all consecutive patients 18 years or older with sepsis admitted within 48 hours of hospital admission to an adult ICU in Brazil. Patients' characteristics, blood samples within one hour of ICU admission, and microbiological results within 48h of hospital admission were collected. In addition, descriptive statistics, binary logistic regression, and propensity score matching were performed.

Results: At least one MDRO was isolated in 85 patients (9.8%). The extended-spectrum beta-lactamase-producing Enterobacterales are the most frequent organism (56.1%). Hypoxemic acute respiratory failure (OR 1.87, 95% CI 1.02–3.40, p = 0.04), Glasgow Coma Score below 15 (OR 2.57, 95% CI 1.38–4.80, p < 0.01), neoplasm (OR 2.66, 95% CI 1.04–6.82, p = 0.04) and hemoglobin below 10.0 g/dL (OR 1.82, 95% CI 1.05–3.16, p = 0.03) were associated with increased MDRO. Admission from the Emergency Department (OR 0.25, 95% CI 0.14–0.43, p < 0.01) was associated with decreased MDRO. In the multivariate analysis, MDRO at hospital admission increased hospital mortality (OR 2.80, 95% CI 1.05–7.42, p = 0.04). After propensity score-matching adjusted to age, APACHE II, SOFA, and dementia, MDRO at hospital admission was associated with significantly high hospital mortality (OR 2.80, 95% CI 1.05–7.42, p = 0.04). The E-value of adjusted OR for the effect of MDRO infection on hospital mortality was 3.41, with a 95% CI of 1.31, suggesting that unmeasured confounders were unlikely to explain the entirety of the effect.

Conclusion: MDRO infection increased hospital mortality, and MDRO risk factors should be accessed even in patients admitted to ICU within 48 hours of hospital admission.

Keywords: drug resistance, multiple, bacterial, community-acquired infections, sepsis, risk factors, mortality

Introduction

Sepsis remains a significant cause of death in critically ill patients, with more than a third of septic patients dying during the hospital stay. Furthermore, it accounts for a considerable amount of the intensive care unit (ICU) costs.[1–3] In an attempt to reduce mortality and morbidity from sepsis and septic shock, initiatives, such as the Surviving Sepsis Campaign, were established to support the choice of therapies, improving the care of sepsis.[4–7]

Despite the advances in its knowledge and management, sepsis treatment remains a challenge. Nowadays, antibiotics are still the only effective drugs against sepsis, mainly when used early. Indeed, the outcomes of patients with sepsis, regardless of the resistance condition of the agent causing the infection, improve significantly if timely and appropriate therapy. On the other hand, inappropriate antibiotic therapy is undoubtedly associated with several serious consequences, including increased mortality.[7–12] However, the treatment with broad-spectrum antibiotics in patients with a low risk of multidrug-resistant organisms (MDRO) infection may expose patients to the risk of the emergence of drug-resistant pathogens.[13–17]

In recent decades, a surge of MDRO in community-acquired infections has been identified, such as extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-*Enterobacteriaceae*) and methicillin-resistant *Staphylococcus aureus* (MRSA).[18–21] Furthermore, MDRO infections are traditionally associated with nosocomial infections, and there is a rising risk of this condition not being suspected or even identified late in community-acquired infections. These aspects may increase the chance of instituting inadequate initial empirical antibiotic therapy and mortality in these infections.[21–23]

Regarding the increased prevalence of MDRO, the primary purpose of the study was to evaluate the effect of MDRO infection at hospital admission on hospital mortality among critically ill adult patients with sepsis at hospital admission. The secondary purposes were to identify the prevalence of MDRO infection, and factors associated with MDRO infection at hospital admission and hospital mortality.

Materials and Methods

Study Design and Participants

This was a cross-sectional study performed between April 2019 and May 2020, followed by a cohort to evaluate hospital mortality that prospectively included all consecutive patients 18 years or older with sepsis admitted within 48 hours of hospital admission to the Hospital Santa Luzia Rede D'Or São Luis adult ICU. The Hospital Santa Luzia Rede D'Or São Luis adult ICU is a 60-bed mixed medical/surgical adult ICU at a private tertiary hospital in Federal District, Brazil.

The inclusion criteria were patients 18 or older, sepsis as the primary reason for ICU admission, and ICU admission within 48 hours of hospital admission. The exclusion criteria were patients transferred to an ICU of another hospital, incomplete medical records that would hamper the analysis, and absence of culture collected within 48 hours of hospital admission. Eight hundred and seventy-seven adult patients with sepsis were admitted to the ICU within 48 hours of hospital admission. Thirteen patients were excluded due to transfer to an ICU of another hospital (1.48%), and no patient was excluded due to the other exclusion criteria. Thus, 864 patients were included in the study.

Data Collection

Patients' general characteristics and blood samples within the first hour of ICU admission were collected from the hospital medical records and electronic systems. The variables collected were age, gender, the primary reason for hospital admission, referred unit (Emergency Department (ED), surgery room, ward and nursing home or long-term care facility), site of primary infection, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, functional independence, comorbidities, vasopressor use on the first hour of ICU admission, axillary temperature, Glasgow Coma Score, the fraction of inspired oxygen (FiO_2), and laboratory and microbiological data. Laboratory samples (blood count, serum creatinine, arterial oxygen partial pressure - PaO_2, and arterial lactate) were collected within the first hour of ICU admission. Hypoxemic acute respiratory failure was defined as a PaO_2/FiO_2 ratio below 300. Sepsis was defined according to the Third International Consensus Definitions for Sepsis and Septic Shock.[24] Immunosuppression was defined by at least one of the following medical conditions: active hematologic malignancy, transplantation, immunosuppressive therapy, chemotherapy, and radiotherapy within the 30 days before ED admission, chronic systemic steroid therapy, splenectomy, and autoimmune disease.

Microbiological results performed within 48 hours of hospital admission were recorded, including blood, sputum, tracheobronchial aspirate, urine, wound, and mucosal swab cultures. Per routine clinical practice, mucosal swabs were obtained from all patients at ICU admission as a screening for MDRO. However, MDRO detected on ICU admission only by the mucosal swab was treated as colonization and was not considered sepsis causative microbiological.

Species identification and antimicrobial susceptibility testing were performed using an automated system; susceptibility breakpoints were based on the Brazilian version of the European Committee on Antimicrobial Susceptibility Testing (EUCAST/ BrCAST version) guideline.[25] *Pseudomonas* spp and *Acinetobacter* spp resistant to three classes of antibiotics among anti-pseudomonal penicillins, antipseudomonal cephalosporins, carbapenems, quinolones, and aminoglycosides, ESBL-*Enterobacteriaceae*, carbapenemase-producing *Pseudomonas* spp, *Acinetobacter* spp or Enterobacterales (KPC), vancomycin-resistant *Enterococcus* spp (VRE), staphylococci resistant to oxacillin, and other pathogens with acquired non-susceptibility to at least one agent in three or more antimicrobials categories were considered as an MDRO.[1,26] For ESBL and Carbapenemases producing organisms, phenotypic tests have been performed to define the resistance. ESBL enzyme research was tested through the technique of the E-test, and Carbapenemase (KPC, New Delhi metallo-β -lactamase – NDM, VIMP, and OXA-48) was evaluated using the Blue-Carba test and enzymatic inhibition by phenylburonic acid to inhibit KPC, EDTA to inhibit metallo-β-lactamase, and cloxacillin to inhibit Oxa 48. The predominant Carbapenemases are KPC and NDM. Phenotypic tests for metallo-β-lactamase production in those positive for an enzymatic test by EDTA were taken by genetic method to search for the dominant gene. All were positive for BLANDM, the gene that proves the presence of NDM enzyme production.

The main outcomes evaluated were MDRO infection at hospital admission and hospital mortality. Other outcomes evaluated were ICU length of stay (ICU-LOS), and hospital length of stay (hospital-LOS).

Statistical Analysis

According to their distribution evaluated by the Kolmogorov–Smirnov test with Liliefors correction, quantitative data with normal distribution are expressed as mean ± standard deviation (SD) and quantitative data with non-parametric distribution as median and interquartile range 25–75% (IQR 25–75%). The variables with normal distribution were age and APACHE II. Categorical variables are expressed as numbers and percentages (%).

Patients were grouped according to the independent variable studied, considering the outcome to be analyzed (MDRO infection at hospital admission, ICU-LOS, hospital-LOS, ICU mortality, and hospital mortality). Contingency tables were used for categorical variables, and Pearson's Chi-square test ($\chi2$) or Fisher's exact test was used as appropriate. Regarding the hospital mortality, Student's *t*-test was used to compare age and APACHE II and Mann–Whitney test to compare SOFA between survivors and non-survivors.

To evaluate independent factors associated with MDRO infection at hospital admission and hospital mortality, an enter method binary logistic regression analysis was performed, including non-collinear variables associated with the outcome with a *p*-value <0.05 in the univariate analysis and the confounding factors according to previous knowledge with *p*-value <0.20 in the univariate analysis.[27] Non-collinearity was accepted when the tolerance was higher than 0.10 and the variance inflation factor (VIF) was lower than 10.0. The odds ratio (OR) expressed the results with their respective 95% confidence interval (95% CI).

To assess the effect of MDRO infection at hospital admission on hospital mortality, propensity score-matching for MDRO infection at hospital admission applying a logit regression model adjusted to factors independently associated with hospital mortality (age, APACHE II, SOFA, and dementia) and MDRO infection at hospital admission (hypoxemic acute respiratory failure, Glasgow Coma Score below 15, neoplasm, anemia with hemoglobin below 10.0 g/dL, and admission from ED) was performed using the EZR software version 1.54 (Saitama Medical Center, Jichi Medical University, Japan) with a 1:1 pair-matching ratio without replacement on the logit of the propensity score applying a caliper of width equal to 0.2. The OR and 95% CI of the MDRO infection at hospital admission effect on hospital mortality were calculated in the sample after matching and is shown as a forest plot.

For sensitivity analysis, we used the E-value to measure the robustness of the association between MDRO infection at hospital admission and hospital mortality for unmeasured or unadjusted confounding.[28] E-values were computed with an online E-value calculator (https://www.evalue-calculator.com/).[29]

Statistical analyses were performed using IBM Statistical Package for Social Sciences 20.0 for Mac (SPSS 20.0 Mac, SPSS Inc., Chicago, USA), statistical software R version 4.0.5 (R Foundation for Statistical Computing), and EZR software version 1.54 (Saitama Medical Center, Jichi Medical University, Japan). The level of statistical significance was defined as a two-sided *p*-value ≤0.05.

Ethical Approval and Consent Form

The Institutional Review Board of the Education and Research Foundation of Health Sciences (FEPECS), Brasília, Federal District, Brazil, approved the study under opinion number 3,246,136 with a waiver of informed consent. The study was conducted following the Declaration of Helsinki. Since this study had no specific intervention and only used anonymized medical record data that generated results in an aggregate manner that did not allow participants' identification, the written consent form was unnecessary.

Results

Among the 864 patients included in the study, the mean age was 62.5 ± 21.3 years, and APACHE II was 15.1 ± 7.3. Median SOFA was 2.0 (IQR 25–75%: 2.0–4.0), 56.1% were female (485/864), and 9.8% had at least one MDRO isolated at the time of ICU admission (85/864). ICU mortality and hospital mortality were 9.8% (85/864) and 11.6% (100/864), respectively (Supplementary Table S1)

The main sites of primary infection were the lung (50/85, 58.8%), urinary tract (16/85, 18.8%), and digestive/abdominal cavity (9/85, 10.6%). The main MDROs were ESBL-Enterobacterales (64/114, 56.1%), oxacillin-resistant coagulase-negative *Staphylococcus* spp (17/114, 14.9%), methicillin-resistant *Staphylococcus aureus* (10/114, 8.8%), and carbapenemase-producing *Pseudomonas* spp, *Acinetobacter* spp, or Enterobacterales *e* (7/114, 6.1%). (Supplementary Table S2)

Table 1 shows the univariate analysis of variables associated with MDRO infection at hospital admission. Age above 60 years (75.3% versus 56.9%, $p < 0.01$), APACHE II above 16 (71.8% versus 42.6%, $p < 0.01$), two or more system failure on SOFA score (75.3% versus 57.6%, $p < 0.01$), hypoxemic acute respiratory failure (31.8% versus 16.8%, $p < 0.01$), Glasgow Coma Score below 15 (60.0% versus 22.5%, $p < 0.01$), anemia with hemoglobin below 10.0 g/dL (43.5% versus 21.2%, $p < 0.01$), leukocytosis with more than 11,000 leukocytes/mm^3 (44.7% versus 34.0%, $p = 0.05$) were higher in patients with MDRO infection at hospital admission than in patients without MDRO infection. Among the comorbidities, MDRO infection at hospital admission was increased in oncologic patients (29.4% versus 17.7%, $p = 0.01$), immunosuppression (32.9% versus 23.1%, $p = 0.04$), thrombocytopenia with lower than 200,000 platelets/mm3 (41.2% versus 34.0%, $p = 0.05$), and patients with previous stroke with permanent sequels (11.8% versus 4.9%, $p = 0.01$). Patients admitted referred from ED (44.7% versus 77.9%, $p < 0.01$) and functional independence (17.6% versus 40.0%, $p < 0.001$) were associated with decreased MDRO infection at hospital admission.

Table 1 Univariate Analysis of Variables Associated with Multidrug Resistant Organisms (MDRO) Infection at Hospital Admission Among Adult Critically Ill Patients with Sepsis Admitted to Intensive Care Unit from the Community (n = 864)

Variable	MDRO Bacterial Infection (n = 85)	Without MDRO Bacterial Infection (n = 779)	p- value
Age above 60 years, n (%)	64 (75.3)	443 (56.9)	<0.01
Female gender, n (%)	42 (49.4)	443 (56.9)	0.19
Referrer, n (%)			
Emergency Department	38 (44.7)	607 (77.9)	<0.01
Ward	24 (28.2)	126 (16.2)	<0.01
Nursing home or long-term care facility	23 (27.1)	46 (5.9)	<0.01
Surgery room	6 (7.1)	2 (0.3)	<0.01
Site of primary infection, n (%)			
Lung	51 (60.0)	446 (57.3)	0.63
Urinary tract	16 (18.8)	139 (17.8)	0.82
Digestive/Abdominal Cavity	9 (10.6)	76 (9.8)	0.81
Skin and soft tissue	3 (3.5)	34 (4.4)	0.72
Others[a]	6 (7.0)	97 (12.2)	-
APACHE II above 16, n (%)	61 (71.8)	332 (42.6)	<0.01
Two or more system failures on SOFA score, n (%)	64 (75.3)	449 (57.6)	0.02

(Continued)

Table 1 (Continued).

Variable	MDRO Bacterial Infection (n = 85)	Without MDRO Bacterial Infection (n = 779)	p- value
Comorbidities, n (%)			
Diabetes mellitus	25 (29.4)	213 (27.3)	0.68
Immunosupression	28 (32.9)	180 (23.1)	0.04
Neoplasm	25 (29.4)	138 (17.7)	0.01
Psychiatric Disease	14 (16.5)	102 (13.1)	0.39
Congestive heart failure	11 (13.4)	80 (10.3)	0.45
Chronic kidney disease	11 (13.4)	62 (8.0)	0.12
Chronic kidney disease on RRT	4 (4.7)	20 (2.6)	0.26
COPD	5 (5.9)	62 (8.0)	0.50
Stroke with permanent sequel	10 (11.8)	38 (4.9)	0.01
Dementia	7 (8.2)	30 (3.9)	0.06
Liver cirrhosis	0 (0.0)	4 (0.5)	0.66
Functional independence, n (%)	15 (17.6)	317 (40.0)	<0.01
Hypoxemic acute respiratory failure, n (%)	27 (31.8)	131 (16.8)	<0.01
Vasopressor on the first hour of ICU admission, n (%)	7 (8.2)	35 (4.5)	0.13
Axillary temperature below 35°C, n (%)	3 (3.5)	20 (2.6)	0.60
Axillary temperature above 38°C, n (%)	1 (1.2)	20 (2.6)	0.43
Glasgow Coma Score below 15, n (%)	51 (60.0)	183 (22.5)	<0.01
Anemia with Hb below 10.0 g/dL, n (%)[b]	37 (43.5)	161 (21.2)	<0.01
Leukopenia with less than 4500 leukocytes/mm^3, n (%)	8 (9.4)	119 (15.3)	0.15
Leukocytosis with more than 11,000 leukocytes/mm^3, n (%)	38 (44.7)	265 (34.0)	0.05
Thrombocytopenia with lower than 200,000 platelets/mm3, n (%)	35 (41.2)	420 (53.9)	0.03
Serum creatinine above 1.4 mg/dL, n (%)[c]	21 (24.7)	165 (21.2)	0.46
Arterial lactate above 2.0 mg/dL, n (%)	30 (35.3)	232 (30.0)	0.31

Notes: [a]Gynecologic/obstetric, central nervous system, bone, joints, endocarditis, and unknown origin. [b]Hemoglobin was not reported in 20 patients. [c]Serum creatinine was not reported in one patient.
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; RRT, Renal replacement therapy; COPD, Chronic obstructive pulmonary disease; Hb, Hemoglobin; MDRO, Multidrug-resistant organisms; ICU, Intensive care unit; SD, Standard deviation; IQR 25–75%, Interquartile range 25–75%.

Table 2 shows the multivariate analysis of variables associated with MDRO infection at hospital admission. Hypoxemic acute respiratory failure (OR 1.87, 95% CI 1.02–3.40, $p = 0.04$), Glasgow Coma Score below 15 (OR 2.57, 95% CI 1.38–4.80, $p < 0.01$) neoplasm (OR 2.66, 95% CI 1.04–6.82, $p = 0.04$) and anemia with hemoglobin below 10.0 g/dL (OR 1.82, 95% CI 1.05–3.16, $p = 0.03$) were independently associated with a high rate of MDRO infection at hospital admission, while admission from ED (OR 0.25, 95% CI 0.14–0.43, $p < 0.01$) was independently associated with a low rate of MDRO infection at hospital admission.

Patients with MDRO infection at hospital admission had increased ICU-LOS (median 13.0 days, IQR 25–75% 6.5–29.5 days versus 4.0 days, IQR 25–75% 3.0–8.0 days, $p < 0.01$), hospital-LOS (median 20.0 days, IQR 25–75% 11.0–42.5 days versus 8.0 days, IQR 25–75% 5.0–7.0 days, $p < 0.01$), ICU mortality (25.0% versus 8.1%, $p < 0.01$), and hospital mortality (29.4% versus 9.5%, $p < 0.01$) (Supplementary Table S3).

Table 3 shows the univariate analysis of variables associated with hospital mortality. MDRO infection at hospital admission (25.0% versus 7.9%, $p < 0.01$), hypoxemic acute respiratory failure (33.0% versus 16.4%, $p < 0.01$), vasopressor use on the first hour of ICU admission (18.0% versus 3.1%, $p < 0.01$), and serum creatinine above

Table 2 Multivariate Analysis of Variables Associated with Multidrug-Resistant Organisms Infection at Hospital Admission

Variable	OR (95% IC)	*p*-value	Tolerance	VIF
Age above 60 years	1.03 (0.41–2.59)	0.94	0.233	4.286
Admission from Emergency Department	0.25 (0.14–0.43)	<0.01	0.836	1.196
APACHE II above 16	1.04 (0.52–2.08)	0.90	0.493	2.030
Functional independence	0.55 (0.20–1.52)	0.25	0.227	4.414
Two or more system failures on SOFA score	1.29 (0.66–2.52)	0.50	0.710	1.407
Immunosuppression	1.88 (0.76–4.68)	0.17	0.814	1.299
Neoplasm	2.66 (1.04–6.82)	0.04	0.397	2.517
Chronic kidney disease	2.28 (0.94–5.30)	0.07	0.814	1.229
Stroke with permanent sequel	1.01 (0.44–2.35)	0.98	0.891	1.122
Dementia	1.05 (0.40–2.75)	0.91	0.929	1.077
Hypoxemic acute respiratory failure	1.87 (1.02–3.40)	0.04	0.864	1.157
Glasgow Coma Score below 15	2.57 (1.38–4.80)	<0.01	0.637	1.570
Anemia with Hb below 10.0 g/dL	1.82 (1.05–3.16)	0.03	0.832	1.201
Leukopenia with less than 4500 leukocytes/mm^3	1.33 (0.54–3.28)	0.53	0.833	1.201
Leukocytosis with more than 11,000 leukocytes/mm^3	0.74 (0.43–1.27)	0.74	0.854	1.171
Thrombocytopenia with lower than 200,000 platelets/mm^3	1.06 (0.62–1.79)	0.83	0.854	1.171

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; Hb, Hemoglobin; ICU, Intensive care unit; MDRO, Multidrug-resistant organisms; OR, Odds ratio; 95% IC, 95% confidence interval; VIF, variance inflation factor.

Table 3 Univariate Analysis of Variables Associated with Hospital Mortality (n = 864)

Variable	Non-Survivors (n = 100)	Survivors (n = 764)	*p*- value
Age, years, mean (SD)	77.6 (15.6)	63.6 (21.4)	<0.01
MDRO infection at ICU admission, n (%)	25 (25.0)	60 (7.9)	<0.01
APACHE II, mean (SD)	22.8 (7.2)	14.1 (6.7)	<0.01
Surgical admission, n (%)	0 (0.0)	8 (1.0)	0.37
Functional independence, n (%)	15 (15.0)	316 (41.4)	<0.01
SOFA, median (IQR 25–75%)	5.0 (3.0–7.0)	2.0 (2.0–3.8)	<0.01
Comorbidities, n (%)			
Diabetes Mellitus	25 (25.0)	213 (27.9)	0.54
Immunosuppression	35 (35.0)	173 (22.6)	0.01
Neoplasm	31 (31.0)	132 (17.3)	<0.01
Psychiatric Disease	14 (14.0)	102 (13.4)	0.86
Congestive heart failure	13 (13.0)	78 (10.2)	0.39
Chronic kidney disease	11 (11.0)	62 (8.1)	0.33
COPD	10 (10.0)	57 (7.5)	0.37
Stroke with permanent sequel	9 (9.0)	39 (5.1)	0.11

(Continued)

Table 3 (Continued).

Variable	Non-Survivors (n = 100)	Survivors (n = 764)	p- value
Dementia	12 (12.0)	25 (3.3)	<0.01
Liver cirrhosis	1 (1.1)	3 (0.3)	0.40
Hypoxemic acute respiratory failure, n (%)	33 (33.0)	125 (16.4)	<0.01
Vasopressor on the first hour of ICU admission, n (%)	18 (18.0)	24 (3.1)	<0.01
Serum creatinine above 1.4 mg/dL, n (%)[a]	40 (40.4)	146 (19.1)	<0.01
Arterial lactate above 2.0 mg/dL, n (%)	41 (41.0)	242 (31.7)	0.06

Note: [a]Serum creatinine was not reported in one patient.
Abbreviations: MDRO, Multidrug-resistant organisms; ICU, intensive care unit; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; COPD, Chronic obstructive pulmonary disease; SD, Standard deviation; IQ 25–75%, Interquartile range 25–75%.

1.4 mg/dL (40.4% versus 19.1%, $p < 0.01$) were increased in non-survivors (25.0% versus 7.9%, $p < 0.01$). Non-survivors were older (77.6 ± 15.6 years versus 63.6 ± 21.4 years, $p < 0.01$), and had higher APACHE II (22.8 ± 7.2 years versus 14.1 ± 6.7 years, $p < 0.01$), and SOFA (median 5.0, IQR 25–75% 3.0–7.0 versus 2.0 days, IQR 25–75% 2.0–3.8, $p < 0.01$) than survivors. Among the comorbidities, immunossupression (35.0% versus 22.6%, $p = 0.01$), neoplasm (31.0% versus 17.3%, $p = 0.001$), and dementia (12.0% versus 3.3%, $p < 0.01$) were increased in non-survivors. Non-survivors had a decreased functional independence (15.0% versus 41.4%, $p < 0.01$) than survivors.

Table 4 shows the multivariate analysis of variables associated with hospital mortality. Age (OR 1.04, 95% CI 1.02–1.07, $p < 0.01$), APACHE II (OR 1.07, 95% CI 1.01–1.13, $p = 0.02$), SOFA (OR 1.23, 95% CI 1.09–1.50, $p < 0.01$), MDRO bacterial infection at hospital admission (OR 2.00, 95% CI 1.06–3.77, $p = 0.03$) and dementia (OR 2.57, 95% CI 1.10–5.98, $p = 0.03$) were independently associated with an increased hospital mortality.

Figure 1 shows the effect of MDRO infection at hospital admission on hospital mortality after propensity score-matching adjusted to age, APACHE II, SOFA, and dementia. MDRO infection at hospital admission was associated with

Table 4 Multivariate Analysis of Variables Associated with Hospital Mortality

Variable	OR (95% IC)	p-value	Tolerance	VIF
MDRO infection at hospital admission	2.00 (1.06–3.77)	0.03	0.922	1.085
Age	1.04 (1.02–1.07)	<0.01	0.342	2.922
APACHE II	1.07 (1.01–1.13)	0.02	0.268	3.725
SOFA	1.28 (1.09–1.50)	<0.01	0.362	2.766
Functional independence	1.80 (0.68–4.78)	0.24	0.342	2.923
Immunosuppression	0.89 (0.40–1.99)	0.64	0.389	2.568
Neoplasm	1.89 (0.88–4.36)	0.10	0.417	2.396
Dementia	2.57 (1.10–5.98)	0.03	0.956	1.046
Hypoxemic acute respiratory failure	0.97 (0.51–1.84)	0.92	0.738	1.355
Vasopressor on the first hour of ICU admission	2.14 (0.89–5.14)	0.12	0.814	1.228
Arterial lactate above 2.0 mg/dL	1.18 (0.71–1.96)	0.54	0.980	1.020
Serum creatinine above 1.4 mg/dL	1.00 (0.56–1.81)	1.00	0.723	1.384

Abbreviations: MDRO, Multidrug-resistant organisms; ICU, intensive care unit; APACHE II, Acute. Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; OR, Odds ratio; 95% IC, 95% confidence interval; VIF, variance inflation factor.
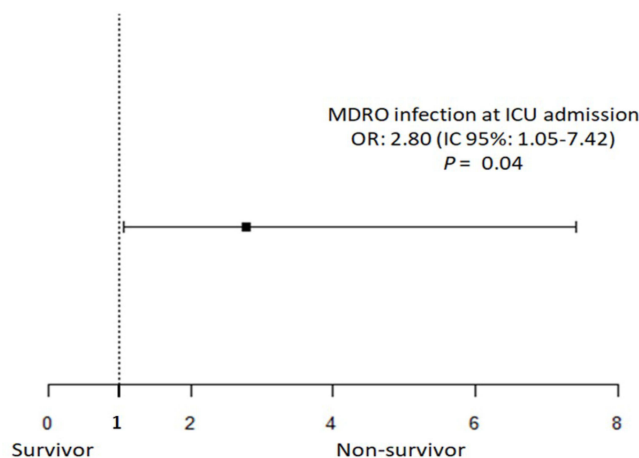
MDRO infection at ICU admission
OR: 2.80 (IC 95%: 1.05-7.42)
P = 0.04

0 1 2 4 6 8
Survivor   Non-survivor

Figure I Effect of multidrug resistant organism (MDRO) infection at hospital admission on hospital mortality after propensity score-matching adjusted to age, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, and dementia.

significantly high hospital mortality (OR 2.80, 95% CI 1.05–7.42, p = 0.04). The E-value of adjusted OR for the association between MDRO infection at hospital admission and hospital mortality in multivariate analysis was 3.41, with a 95% CI of 1.31, suggesting that unmeasured confounders were unlikely to explain the entirety of the effect.

Discussion

In this study, almost one in every ten patients admitted with sepsis had at least one MDRO infection at hospital admission. This condition was independently associated with increased hospital mortality. Besides, ICU-LOS and hospital-LOS were longer in patients admitted with MDRO infection than those without MDRO infection. Hypoxemic acute respiratory failure, alteration in the level of consciousness (GCS < 15), neoplasm and anemia (Hb <10.0 g/dL) were independently associated with a high rate of MDRO infection. On the contrary, admission referred from ED was independently associated with a decreased MDRO infection at hospital admission. These findings reinforce the importance of being aware of the possibility of MDRO infection even in patients with sepsis at hospital admission to guide an appropriate antibiotic therapy with a broad spectrum, especially in patients with risk factors for MDRO infection.[7–12,30,31]

Previous studies have shown conflicting results regarding MDRO infection and mortality.[1,32–34] Either way, there is an agreement that MDRO is a risk factor for inappropriate antibiotic therapy, which is undoubtedly associated with increased mortality.[7–12,30,31] Similar to our finding, one study that evaluated patients with sepsis from the community, the MDRO was also associated with increased mortality.[1] It might be discussed if other factors that influence the risk for MDRO and mortality might have influenced the high mortality observed among patients with MDRO infections.[1,21] However, in our study, the effect of MDRO infection at hospital admission on hospital mortality remained after adjustment for the propensity score matching with an odds ratio of 2.8.

The incidence of MDRO at hospital admission in our study (9.8%) is slightly lower than observed in a United States study (12.0%)[34] and an Italian study (17.0%)[1] that also included patients with sepsis coming from the community. In a study that evaluated only patients with urinary tract infections presented to an ED, the prevalence of MDRO at hospital admission (6.7%) was lower than observed in our study.[35] It should be noted that the primary site of sepsis in our study was the lung (57.5%), representing more than half of the cases, followed by the urinary tract (17.9%), agreeing with previously published studies.[1,36,37]

As observed in previous studies involving patients with community-acquired infectious and nosocomial infectious[1,21,35,38–42] gram-negative bacteria (GNB) were the most prevalent MDRO in our study, and the ESBL-Enterobacterales was the most isolated agent. However, one finding that should be highlighted is that 6.1% of isolated MDRO were carbapenemase-producing GNB, and 82.9% of patients with MDRO infections at hospital admission were not referred from nursing homes or long-term care facilities. This emergence of carbapenemases-producing GNB is worrisome since the carbapenemases give resistance to a broad range of antibiotics, including the carbapenems, the class

of antibiotics with a broader spectrum for bacterial infectious treatment. Furthermore, carbapenemases-producing GNB commonly has additional resistance mechanisms against beta-lactamase inhibitors and other antimicrobials, including resistance to aminoglycosides and fluoroquinolones.[43] Thus, the presence of a carbapenemase-producing GNB leads to a small range of therapeutic options and greatly increases the risk of inappropriate therapy.[43–45] Indeed, there are reports of community infections by ESBL-producing Enterobacterales that have acquired the ability to produce carbapenemases, especially related to the clone *Escherichia coli* ST131 in India and the United States.[45–48] It is also important to note that, although GNB was the most common MDRO in our study, the patterns of the MDRO infections and the resistance highly depend on the studied region. For example, in the United States, one study observed that the most prevalent MDRO was vancomycin-resistant *Enterococci*, followed by MRSA. At the same time, GNB infections were uncommon, and carbapenemases-producing Enterobacterales was isolated in only one patient.[34] In another study that included only patients with pneumonia presenting to the ED, MRSA was the most prevalent MDRO.[11]

Hypoxemic acute respiratory failure, alteration in consciousness level (GCS < 15), neoplasm and anemia (Hb <10.0 g/dL) were independently associated with MDRO-related sepsis among the MDRO risk factors evaluated in our study. Besides, referred ICU admissions from hospital units other than ED were associated with MDRO infection. Classically, the two risk factors mainly reported for MDRO in patients from the community are prior hospitalization in the past 90 days and nursing home or long-term care facility.[21,38,49–51] In this respect, in our study, only 8.0% of patients were referred from nursing homes or long-term care facilities. Besides, the patients referred from ED also had fewer MDRO infections at hospital admission than those from the surgery room and wards. This finding highlights that a patient who passed through another hospital unit from the ED before ICU admission is more prone to have an MDRO infection than an ICU-admitted patient directly from the ED, even if that admission occurred within the first 48 hours of hospitalization. However, it is unclear why our analysis identified patients referred from ED had a reduced risk for MDRO infection. We suspect it may be a surrogate marker for other factors associated with MDRO infection risks, such as recent hospitalization and previous antibiotic use. Besides, even though they were admitted before 48 hours of hospitalization, these patients tend to stay longer in the hospital until the ICU admission than patients admitted directly from the ED, which may have exposed them to contact with MDRO even for a short period. It is essential to note that previous studies that evaluated factors associated with MDRO in patients with community-acquired infections did not assess the hospital unit that referred to the ICU admission or included only patients admitted from the ED.[1,21,34,38,41,49–51]

Our study has some limitations. First, the study included patients from only one center, which has intrinsic limitations for generalizing the results, primarily because different causative pathogens of sepsis, different rates of antibiotic resistance, and risk factors related to different health-care organizations have been recognized worldwide. Second, the study was performed in a private tertiary hospital, limiting the generalization to other Brazilian health-care services, especially public ones, since there is a well-documented difference in access to technologies between Brazilian public and private health-care services.[52] Third, we cannot rule out that the difference in outcomes among the groups may have been affected by factors not evaluated in our study. In an Italian study that assessed a wide range of risk factors for MDRO in a large sample of patients with sepsis from the community, the independent risk factors for MDRO were septic shock and hospitalization in the past 90 days.[1] Regarding septic shock, our study did not show an association between vasopressor use and arterial lactate above 2.0 mg/dL during the first hour of ICU admission and sepsis by MDRO infection at hospital admission. Regarding the previous hospitalization, we did not assess this variable, and also the antimicrobial use in the past 90 days that is another classical risk factor for MDRO infection, especially considering that there were 24.1% immunosuppressed patients (32.9% of patients with MDRO) that is a condition associated with therapeutic or prophylactic antimicrobial use. Although the lack of information on these variables may be one of the study limitations, it depends mainly on the patients' or family members' retrospection, and it is not always informed accurately during the initial management of a patient with sepsis when the initial antibiotic therapy needs to be chosen quickly. Despite these limitations, the sensitivity analysis using the E-value suggests that unmeasured confounders were unlikely to explain the entirety of the effect observed in our study to the point of modifying the observed results. Finally, we did not evaluate the appropriateness of the initial antibiotic therapy. According to our institutional protocol, adult patients with sepsis or septic shock without known traditional risk factors for MDRO infection use Piperacillin and Tazobactam as an empiric treatment for GNB based on Brazilian local

epidemiology. In contrast, patients with a known risk for MDRO infection use carbapenem. It is interesting to note that the hospital mortality in our study (11.6%) was below that observed in previous studies that evaluated patients with sepsis coming from the community, such as an Italian study (25.7%)[1] and a United States study (20.2%).[34] The factors associated with this finding may be associated with the sepsis protocol of our institution that aims to promote rapid recognition and implement early management for this condition, including the appropriate initial antibiotic therapy, considering that only 58.7% of the patients had appropriate empiric antibiotic therapy according to local guidelines and 66.8% according to antibiotic susceptibility of the isolated pathogen in the Italian study.[1] Nevertheless, notwithstanding if the MDRO infection is an independent risk factor for mortality or a risk factor for inappropriate antibiotic therapy,[7–12,28,29] our study shows that identifying septic patients with a high risk for MDRO is crucial for appropriate antibiotic therapy and reduces sepsis mortality. Regardless of the limitations, our findings reinforce the importance of being aware of the possibility of MDRO infection, even in patients with sepsis at hospital admission, since it was associated with a high hospital mortality rate.

Conclusion

In our study, almost ten percent of critically ill patients admitted with sepsis at hospital admission had at least one MDRO infection. This condition was independently associated with increased hospital mortality. Due to the increased risk of MDRO infection, treatment with broader antibiotic choices should be considered in patients with sepsis from the community associated with hypoxemic acute respiratory failure, impaired consciousness, neoplasm, and anemia. Besides, patients referred to ICU from the Emergency Department were at lower risk for MDRO infection than patients from nursing homes, long-term care facilities, or wards, even if the ICU admission occurred within 48 hours of hospital admission.

Disclosure

The authors report no conflicts of interest in this work.

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