Journal of Hospital Infection 103 (2019) 121–127

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevier.com/locate/jhin

Predicting acquisition of carbapenem-resistant Gram-negative pathogens in intensive care units

L.F. Dantas [a], B. Dalmas [b], R.M. Andrade [c,d], S. Hamacher [a], F.A. Bozza [e,f,*]

[a] *Industrial Engineering Department, Pontifical Catholic University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil*
[b] *Mines Saint-Etienne, Université Clermont Auvergne, CNRS, UMR 6158 LIMOS, Centre CIS, Saint-Etienne, France*
[c] *Copa D'Or Hospital, Rio de Janeiro, RJ, Brazil*
[d] *Department of General Medicine, Federal University of the State of Rio de Janeiro, Rio de Janeiro, RJ, Brazil*
[e] *D'Or Institute for Research and Education (IDOR), Rio de Janeiro, RJ, Brazil*
[f] *National Institute of Infectious Disease Evandro Chagas (INI), Oswaldo Cruz Foundation (FIOCRUZ), Rio de Janeiro, RJ, Brazil*

ARTICLE INFO

Article history:
Received 8 February 2019
Accepted 21 April 2019
Available online 27 April 2019

Keywords:
Carbapenem resistance
Multi-drug resistance
Gram-negative
Healthcare-associated infection
Predictive models
Intensive care units

SUMMARY

Background: Infections by multidrug-resistant Gram-negative (MDRGN) bacteria are among the greatest contemporary health concerns, especially in intensive care units (ICUs), and may be associated with increased hospitalization time, morbidity, costs, and mortality.
Aim: The study aimed to predict carbapenem-resistant MDRGN acquisition in ICUs, to determine its risk factors, and to assess the impact of this acquisition on mortality rate.
Methods: A matched case–control study was performed in patients admitted to the ICU at a large Brazilian hospital over a five-year period. Cases were defined as patients who acquired carbapenem-resistant MDRGN bacteria during hospitalization. Controls were defined as patients who had no detection of carbapenem-resistant MDRGN bacteria. Cases were matched to controls according to the admission period. Risk factors were identified by multiple logistic regression using a stepwise selection method.
Findings: In total, 343 cases and 1029 controls were analysed. The 30-day mortality rate for subjects with ICU-associated carbapenem-resistant MDRGN was 37.6%. Five variables were identified as statistically significant and more relevant for the acquisition of multidrug-resistant strains: increased Simplified Acute Physiology Score 3, patients with severe chronic obstructive pulmonary disease and exposure to haemodialysis catheter, central venous catheter, or mechanical ventilation. Models developed displayed good results with an accuracy of ~90%. Patients who acquired MDRGN were 2.72 times more likely to die than non-MDRGN acquisition patients.
Conclusion: Finding risk factors and developing predictive models may benefit patients through early detection and by controlling the spread of MDR. The presence of mechanical ventilation and central venous catheter were the main risk factors demonstrated, and their use requires special attention.

* Corresponding author. Address: Instituto Nacional de Infectologia Evandro Chagas (INI), FIOCRUZ, Av Brasil 4365, Manguinhos, Rio de Janeiro, RJ 21045-900, Brazil. Tel.: +55 21993031551.
E-mail address: fernando.bozza@ini.fiocruz.br (F.A. Bozza).

https://doi.org/10.1016/j.jhin.2019.04.013
0195-6701/

Introduction

Infections by antibiotic-resistant bacteria are among the most significant current threats to global health. Although these bacteria have become a cause of community-acquired infections, in general, they are associated with hospital-acquired infections (HAIs) [1,2]. These infections are frequently related to increased mortality, hospitalization time, and economic costs, mainly in the context of intensive care units (ICUs) where severely ill patients have a higher risk of developing a hospital infection and frequently require antibiotics and invasive procedures [3–6].

Although both Gram-positive and Gram-negative bacteria have demonstrated increasingly resistant patterns, the recent appearance of Gram-negative strains resistant to almost all antibiotics is an additional concern [7,8]. According to the global priority list of antibiotic-resistant bacteria developed by the World Health Organization (WHO), the Gram-negative pathogens resistant to carbapenems (*Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and Enterobacteriaceae) are a critical priority (number 1) for research and development [9]. In Brazilian hospitals, a significant proportion of infections are caused by these three Gram-negative bacteria and they are a major concern on infection control initiatives in ICUs [10].

Studies evaluating populations with multidrug-resistant Gram-negative (MDRGN) bacteria have shown high mortality rates ranging from 26% to 80% [5]. A recent meta-analysis reported 1.78 times higher mortality in patients with MDRGN infections than patients with non-MDRGN infections, but the precise rate of death attributable to resistant infections is not known [6,8].

Although most studies have addressed the influence of risk factors on infection, the prediction of MDRGN acquisition including colonization and infection is also relevant. Infection usually occurs after colonization, and the timing of colonization is essential to determine the origin of the multidrug-resistant bacteria [1]. Efforts directed at identifying colonization can help to avoid transmission risks and to decrease the rates of future infections [11].

Several predisposing factors have been associated with increased risks of infection or colonization, such as the patient's demographic characteristics, comorbidities, and use of invasive procedures. Several statistical methods have been used to evaluate the relationship between these factors and MDRGN acquisition, such as logistic regression, multi-state Markov models, decision tree analysis, and artificial neural networks [3,6,12]. Statistical models can monitor and predict the possibility of MDRGN bacteria being acquired in the hospital before it occurs, thereby reducing deaths, complications, and hospital costs [13].

Although few studies on the risk factors for MDRGN infections have been developed in low- and middle-income countries' (LMIC) hospitals, there is a shortage of statistical models that can be used to predict acquisition in this setting [10,14]. Moreover, studies available in the literature tend to examine only infected patients, but the colonization timing is also a vital issue to be included in the models. Therefore, this study aims to identify risk factors associated with MDR acquisition and to develop models that can predict the possibility of ICU patients acquiring these pathogens. This study analysed the acquisition of carbapenem-resistant Enterobacteriaceae, *A. baumannii* and *P. aeruginosa*, and the impact of this acquisition on mortality.

Methods

Setting and study population

A matched case–control study was performed between January 1st, 2012 and December 31st, 2016 involving hospitalized patients in eight adult ICUs at a large Brazilian hospital. The hospital has 207 beds (90 adult ICU beds) and is a tertiary care facility with ~9300 annual hospital admissions.

A case–control design was used to compare two groups of patients. Cases were defined as patients colonized or infected by carbapenem-resistant Gram-negative bacteria identified by positive culture after 72 h of hospital admission. Colonization refers to all patients who had any positive cultures for carbapenem-resistant Gram-negatives that did not require antimicrobial treatment, and infection refers to patients with an infection documented by the clinicians with the initiation of treatment [15,16]. Hospital-acquired infections were defined according to the National Healthcare Safety Network criteria [17]. The detailed protocol for surveillance is presented in Supplementary Appendix A.

The controls were defined as patients who had no detection of MDRGN bacteria. The controls were randomly selected from potential controls matched by the admission date in the hospital at a 3:1 proportion (control:case).

Information from the infection control team was used to identify all patients with a positive culture for carbapenem-resistant MDRGN, *A. baumannii*, *P. aeruginosa*, or Enterobacteriaceae, and the Epimed Monitor System® database to identify all admissions and the demographic and clinical variables. Information of clinical isolates with species identification and phenotypic antimicrobial susceptibility testing (AST) was obtained from the microbiology service. Phenotypic AST was performed on the Vitek 2 platform (bioMérieux, Marcy l'Etoile, France) and interpreted according to the Clinical and Laboratory Standards Institute (CLSI) reference tables [18]. Carbapenem resistance was defined phenotypically by CLSI criteria and MDR by a standard definition [18,19].

First introduced during the 1980s, carbapenems still play a critical role as some of the last-line agents for the treatment of antibiotic-resistant Gram-negative pathogens [20]. Due to the global importance and the epidemiological relevance in Brazil and other LMICs, we decided to focus on Gram-negatives with resistance to carbapenem.

The selection included all subjects matching inclusion criteria during the study period: patients aged >18 years, patients with a length of stay ≥72 h in the hospital, patients admitted to the ICU, and patients who did or did not acquire MDRGN bacteria up to 60 days of hospital stay. Only the first episode of carbapenem-resistant MDRGN bacterial isolation was considered for each subject.

Between January 1st, 2012 and December 31st, 2016, there were 512 adult patients with 648 records with a positive culture for carbapenem-resistant MDR in ICU, of which 500 records were deemed to be hospital-acquired infections or colonization by Gram-negative bacteria. In the same time period, there were 12,695 patients admitted to the adult ICU without any identification of MDRGN bacteria.

After applying the inclusion criteria, we included a total of 343 patients (case group), as shown in Supplementary Appendix B, and a matched sample with 1029 non-MDRGN inpatients (control group).

Data preparation

We obtained all patients' data from the Epimed Monitor System® (http://www.epimedsolutions.com). All data were anonymized and aggregated before being provided to us for analysis. The medical records were reviewed and variables were extracted as follows: gender, age, Simplified Acute Physiology Score 3 (SAPS 3), Charlson Comorbidity Index, admission type, underlying and associated diseases, such as hepatic failure, solid metastatic tumour, immunosuppression, steroid use, acquired immune deficiency syndrome, uncomplicated diabetes, complicated diabetes, dementia, rheumatic disease, stroke sequelae, or severe chronic obstructive pulmonary disease (COPD), previous exposure to invasive procedures, such as central venous catheter (CVC), mechanical ventilation, arterial catheter, bladder/urinary catheter or haemodialysis catheter, length of stay, and outcome (discharge from hospital or death).

For the carbapenem-resistant MDRGN group, previous use of invasive procedures was considered if it occurred between 24 h and 30 days prior to the positive culture date. For non-MDRGN patients, it was considered if used at any time during their stay. The Charlson Comorbidity Index is an aggregate measure for prognosticating comorbidities. SAPS 3 is a patient severity index based on physiological data.

The ICU admission type was considered by elective surgery, emergency surgery, or medical admission (e.g. sepsis/infection, cardiovascular disease, neurological disease, respiratory disease, or gastrointestinal disease).

Statistical analysis

Comparative analyses were performed between the case and control groups. For univariate analysis, continuous variables were matched between patient groups using Student's *t*-test or Wilcoxon signed-rank test, and categorical variables were compared using χ^2-test or Fisher's exact tests, as appropriate. Risk factors with $P < 0.25$ were considered as candidates for inclusion in the multiple logistic regression [21]. A stepwise regression method (described in the next section) was used to select the statistically significant variables. The data set (1372 inpatients) was randomly divided into two groups: 80% to build the model (training set) and 20% to test it (test set).

Variable selection

The task of determining which predictors are associated with the response to find the best model is referred to as variable selection [22]. Thus, we applied a stepwise regression method using the training set to select the best subset of variables and obtain the optimal prediction with the fewest statistically significant factors, the reduced model [3,23,24]. For that process, we used Akaike's Information Criterion (AIC), which deals with the trade-off between goodness-of-fit and complexity of the model to minimize the information loss among the candidate models. The method used was the backward algorithm, starting with all variables in the model and removing the variable with the largest *P*-value until the stop criterion was reached [22].

In addition to the reduced model, other multiple logistic regression models were developed to obtain good predictions using similar information groups that focused on the presence or lack of invasive devices, similar to Chang *et al.* [3]. All analyses were performed by using R software version 3.4.3.

Performance analysis

First, we used a stratified K-fold cross-validation technique to avoid overfitting and to assess how well the models are able to predict different subsets of the data [22]. The test set was then used as a final evaluation of prediction power from the models.

Receiver-operating characteristic (ROC) curves were used and the confusion matrix to evaluate the performance of each group. ROC curves are useful for comparing different classifiers since they take into account all possible thresholds.

From the multiple logistic regression model, we can estimate the carbapenem-resistant MDRGN bacteria acquisition probability for each individual by feeding the model with the values for the predictive variables associated with the particular patient. The likelihood ratio test identifies whether the observed difference in model fit is statistically significant.

Mortality analysis

Comparative analyses were also performed between survivor patients and patients who died after admission to adult ICUs, using the same methodology of the previous analysis. The mortality analysis considered the MDRGN acquisition (or non-acquisition) as one of the independent variables and the outcome (survivors or death) as the dependent variable. We aimed to evaluate the impact of carbapenem-resistant MDRGN acquisition (colonized and infected patients both included) on mortality rate, adjusting for all variables.

The cases were defined as patients who died during the hospital stay and controls were defined as patients who were discharged (survivors), considering all patients who did or did not acquire carbapenem-resistant MDRGN bacteria in the hospital up to 60 days. Between January 1st, 2012 and December 31st, 2016, a total of 13,038 patients admitted to an adult ICU were analysed, of whom 11,834 survived (cases), and 1204 died (controls).

Results

Descriptive analysis and variable selection

The study population included a total of 343 cases and 1029 controls. Considering only the first episode of carbapenem-resistant MDRGN isolation for each subject, *A. baumannii* was the most frequently isolated (164 cases) followed by *P. aeruginosa* (98 cases) and Enterobacteriaceae (81 cases). The highest mortality was associated with *P. aeruginosa* acquisition as 62.2% of the patients colonized or infected by this pathogen died at the hospital. Among the non-MDRGN group, the mortality rate was 10%. See Supplementary Appendix C for the distribution of pathogens for each factor.

The demographic and clinical characteristics of both groups are summarized in Table I. The patients with carbapenem-resistant MDRGN acquisition were older, had greater severity indices, had a higher probability of being admitted for emergency surgery, sepsis/infection or respiratory disease, and received more invasive devices compared to patients without MDRGN pathogens.

We first selected the variables to identify the risk of carbapenem-resistant MDRGN acquisition through univariate analysis (Table I). The variables with $P < 0.25$ were fed into a multiple logistic regression for selection of a reduced model. There were significant differences in age, gender, SAPS 3, admission type, Charlson Comorbidity Index, invasive devices, and the presence of hepatic failure, dementia, stroke sequelae, and severe COPD.

Applying the stepwise logistic regression using the training set (1098 inpatients), we analysed the best subsets of variables. The lower the AIC value, the lower the loss of information among the candidate models and, consequently, the better the model. All multiple logistic regression models and their respective AIC values can be seen in Supplementary Appendix D. The best subset selected by the stepwise method was considered the reduced model.

Table II presents the results of the reduced/final model, including coefficients, odds ratio (OR) with 95% confidence interval (CI), and *P*-values for each independent variable. The reference level for each category is indicated in parenthesis for each variable. In this case, OR >1 predicts a higher likelihood of acquiring MDRGN bacteria compared to the reference level.

Risk factors identified as the most relevant for acquisition of multidrug-resistant species were SAPS 3 (OR: 1.03; 95% CI: 1.01–1.04), severe COPD (1.90; 1.10–3.27), and exposure to medical devices, especially mechanical ventilation (14.46; 8.45–24.70), central venous catheter (3.97; 2.04–7.70), or haemodialysis catheter (2.20; 1.31–3.69). The presence of mechanical ventilation prior to index culture was the most relevant risk factor.

Other models were then developed, aiming to compare different variable groups. The definition and variables in each group are shown in Table III.

Table I
Descriptive statistics of potential predictors of carbapenem-resistant MDRGN acquisition ($N = 1372$)

Variables	MDRGN ($N = 343$)	Non-MDRGN ($N = 1029$)	*P*-value
Outcome, no. (%)			<0.001
Survivor	156 (45)	927 (90)	–
Death	187 (55)	102 (10)	–
Age (years), median (IQR)[b]	77 (64–86)	74 (59–85)	0.008
SAPS, median (IQR)[a]	61 (52–62)	47 (37–54)	<0.001
Charlson Comorbidity Index, median (IQR)[b]	2 (0–3)	1 (0–2)	<0.001
Female, no. (%)[c]	166 (48)	558 (54)	0.070
Admission type, no. (%)[c]			<0.001
Elective surgery	23 (7)	196 (19)	–
Emergency surgery	41 (12)	48 (5)	–
Clinical type, no. (%)			
Sepsis/infection	133 (39)	301 (29)	–
Cardiovascular	21 (6)	187 (18)	–
Neurological	22 (6)	82 (8)	–
Respiratory	47 (14)	49 (5)	–
Gastrointestinal	15 (4)	70 (7)	–
Others	41 (12)	96 (9)	–
Comorbidities, no. (%)			–
Hepatic failure[d]	3 (1)	2 (0.2)	0.103
Solid metastatic[c] tumour	20 (6)	48 (5)	0.472
Immunosuppression[c]	15 (4)	54 (5)	0.617
Steroid use[c]	12 (3)	31 (3)	0.788
AIDS[d]	2 (1)	8 (1)	0.748
Uncomplicated[c] diabetes	66 (19)	191 (19)	0.841
Complicated[c] diabetes	24 (7)	63 (6)	0.654
Dementia[c]	61 (18)	88 (9)	<0.001
Rheumatic disease[d]	1 (0.3)	6 (1)	0.687
Stroke sequelae[c]	18 (5)	32 (3)	0.096
Severe COPD[c]	80 (23)	103 (10)	<0.001
Transplantation[c]	39 (11)	117 (11)	1
Invasive procedures use, no. (%)[c]			–
Haemodialysis catheter	123 (36)	50 (5)	<0.001
Arterial catheter	280 (82)	205 (20)	<0.001
Bladder catheter	310 (90)	497 (48)	<0.001
Central venous catheter	322 (94)	324 (31)	<0.001
Mechanical ventilation	302 (88)	119 (12)	<0.001

MDRGN, multidrug-resistant Gram-negative; IQR, interquartile range; AIDS, acquired immune deficiency syndrome; COPD, chronic obstructive pulmonary disease; SAPS 3, Simplified Acute Physiology Score 3.
[a] Student's *t*-test.
[b] Wilcoxon test.
[c] χ^2-Test.
[d] Fisher's exact test.

Prediction analysis

We used the five-fold cross-validation technique to avoid overfitting and to evaluate whether the models were good predictors for different subsets of this database. The means and standard deviation (SD) results for each group are shown in

Table II
Multiple logistic regression (carbapenem-resistant MDRGN vs non-MDRGN) using a training set ($N = 1098$): reduced model

Variables (reference)	β	OR	95% CI	*P*-value
Intercept	−4.959			
SAPS 3	0.025	1.03	(1.01–1.04)	<0.001
Severe COPD				
No		1		0.021
Yes	0.642	1.90	(1.10–3.27)	
Haemodialysis catheter				
No		1		0.003
Yes	0.788	2.20	(1.31–3.69)	
Central venous catheter				
No		1		<0.001
Yes	1.380	3.97	(2.04–7.70)	
Mechanical ventilation				
No		1		<0.001
Yes	2.671	14.46	(8.45–24.70)	

MDRGN, multidrug-resistant Gram-negative; β, regression coefficient; OR, odd ratio; CI, confidence interval; SAPS, Simplified Acute Physiology Score; COPD, chronic obstructive pulmonary disease.

Table III
Definition of variable groups for analysis and evaluation of models using the test set ($N = 274$)

Group	Model	Variables	Accuracy	Sensitivity	Specificity	PPV	NPV	AUC	Likelihood ratio test (*P*-value)		
1	Full model	Age + gender + CVC + mechanical ventilation + hepatic failure + dementia + haemodialysis catheter + arterial catheter + bladder catheter + stroke sequelae + severe COPD + admission type + SAPS 3 + Charlson	0.883	0.875	0.886	0.700	0.959	0.902	Ref.	–	–
2	Reduced model	CVC + mechanical ventilation + haemodialysis catheter + severe COPD + SAPS 3	0.891	0.875	0.895	0.718	0.959	0.914	0.473	Ref.	–
3	Information on admission	Hepatic failure + dementia + stroke sequelae + severe COPD + admission type + Charlson comorbidity index + age + gender + SAPS 3	0.759	0.578	0.814	0.486	0.863	0.797	<0.001	<0.001	Ref.
4	Invasive procedures use	CVC + mechanical ventilation + haemodialysis catheter + bladder catheter + arterial catheter	0.891	0.875	0.895	0.718	0.959	0.896	0.004	<0.001	<0.001

PPV, positive predictive value; NPV, negative predictive value; AUC, area under the receiver operating characteristic curve; CVC, central venous catheter; COPD, chronic obstructive pulmonary disease; SAPS 3, Simplified Acute Physiology Score 3.

Supplementary Appendix D. The low SDs of the models (from 0.018 to 0.099) for all performance measurements confirmed that there was no overfitting.

The performance of each multiple logistic regression model using the test dataset (274 inpatients) along with the likelihood ratio test can be seen in Table III. The cut-off point for predicted values was 0.30 to improve accuracy and sensitivity and to reduce false negatives.

The performance of the reduced model may be considered good (accuracy: 0.891; sensitivity: 0.875; specificity: 0.895) and is the best compared to the other groups. The likelihood ratio tests did not identify differences between groups 1 and 2. Therefore, we can use the model with fewer variables (group 2) without loss of performance.

Using only medical devices as variables (group 4), we also found a good performance that was similar to that of the reduced model. However, the model with only variables already present at admission (group 3) produced worse prediction rates (accuracy: 0.759; sensitivity: 0.578; specificity: 0.814). Evaluating the PPV values confirms that models 1, 2, and 4 provide the ability to predict who will acquire carbapenem-resistant MDRGN bacteria, and model 3 is insufficient for this prediction.

The ROC curves for the test set are shown in Figure 1, which compares the true-positive rate (sensitivity) and false-positive rate (1 − specificity), considering all possible cut-offs. The values for the area under the ROC curve are shown in Table III. Therefore, we can confirm that group 3 is the only weak model for predicting MDR bacteria acquisition. Models 1, 2, and 4 had high and similar AUC values, indicating good prediction.

Mortality

The hospital mortality rate for subjects who acquired carbapenem-resistant MDRGN bacteria during the hospital stay was 54.5%, and the 30-day mortality rate after positive culture was 37.6%. The comparative analyses were performed between death (1204 cases) and survivor (11,834 controls) groups using stepwise logistic regression. Supplementary Appendix E presents the result of the final model selected. Even adjusting for other variables, the presence of carbapenem-resistant MDRGN bacteria proved to be a relevant risk factor in death. The results suggest that patients who acquired carbapenem-resistant MDRGN bacteria are 2.72 times more likely to die than non-MDRGN patients.

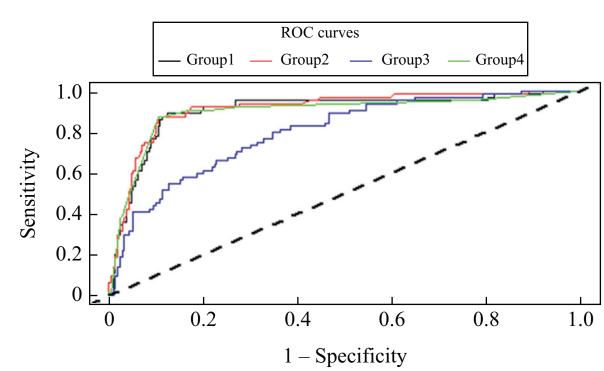

Figure 1. Comparison of the area under the receiver-operating characteristic curves (AUC) among all groups using the test set ($N = 274$).

Discussion

This study aimed to predict carbapenem-resistant MDRGN acquisition during ICU stays, to identify the risk factors associated with this acquisition, and to assess its impact on mortality. Carbapenem-resistant MDRGN is a global threat and a major concern for infection control specialists around the world. Recently, there has been a myriad of information about the mechanism of resistance to carbapenems and review articles on specific agents; however, very few original studies have asked questions about risk factors, predictors of acquisition, or mortality rates, especially in hospital from LMIC.

The predictors observed as significant for carbapenem-resistant MDRGN acquisition were SAPS 3, severe COPD, exposure to a central venous line, mechanical ventilation, and haemodialysis catheter. The use of mechanical ventilation (OR: 14.46) was the most important factor in carbapenem-resistant MDRGN acquisition. Our study resulted in good predictive models with accuracies of ~90% using logistic regression. In addition, we concluded that patients who acquired carbapenem-resistant MDRGN were 2.72 times more likely to die than non-MDRGN patients.

Carbapenem-resistant MDRGN (500 cases) were more commonly isolated than Gram-positive species (89 cases). According to previous studies of Gram-negative infections in Brazil, *A. baumannii* is the most prevalent carbapenem-resistant MDRGN bacterium, which supports the findings of this study ($N = 164$, 47.8%), followed by *P. aeruginosa* ($N = 98$, 28.6%) and then Enterobacteriaceae ($N = 81$, 23.6%) [25,26]. The distribution of the isolates of carbapenem-resistant Enterobacteriaceae was as follows: *Klebsiella pneumonia* (65.6%), *Escherichia coli* (13.3%), *Enterobacter cloacae* (12.5%), *Klebsiella oxytoca* (3.1%), *Citrobacter freundii* (2.3%), *Proteus vulgaris* (1.6%), and *Serratia marcescens* (1.6%).

The results for risk factors are consistent with previous studies in which the severity of illness, chronic respiratory disease, and the use of invasive devices, such as central venous or arterial catheters, mechanical ventilation and urinary catheters, were most likely to result in isolation of multidrug-resistant organisms [27–32].

Besides identifying risk factors associated with carbapenem-resistant MDRGN acquisition, our study developed predictive models of high performance. We conclude that a reduced model including only the factors SAPS 3, severe COPD, central venous line, mechanical ventilation, and haemodialysis catheter can be used to obtain good prediction results.

Using only invasive procedures as variables for predicting carbapenem-resistant MDRGN is also a significant finding since efforts can be made to mitigate acquisition by implementing care bundles, removing devices earlier, using alternative procedures or reducing their utilization. In some developing countries, the frequency of infections associated with the use of CVC, ventilators, and other invasive devices can be up to 19 times higher than those reported from Germany and the USA [33]. By contrast, the model considering only information acquired at the time of admission does not give a good prediction.

The predictive models found in the literature are restricted to a specific type of infection, as in Chang *et al.*, or aim only at the analysis of significance [3]. Therefore, it was not possible to compare the performance analysis of our predictive model with previous studies.

In the carbapenem-resistant MDRGN group, 37.6% of patients died within 30 days of a positive culture, and 54.5% of patients died during the hospital stay. The reported mortality rates for patients with MDRGN infections in the literature ranged between 14% and 92%, and the attributable mortality varied between 7% and 44% [8]. The reasons for this variation could be from the MDR definition to the rate of treatment compliance, use of medical devices, age, or severity index, among other factors. In our study, the presence of carbapenem-resistant MDRGN bacteria impacted mortality and was demonstrated to be a relevant risk factor in hospitals, justifying efforts directed at control of colonization and infection.

Similar to Patel *et al.*, the ICU patients infected by carbapenem-resistant MDRGN have an increased risk of mortality and the effect is greatest up to seven days after positive culture (16.3% died), compared to 15 days (9.0% died) or 30 days (12.2% died) after positive culture [30]. The impact of MDR bacteria on mortality cannot easily be assessed, as it is difficult to compare the effects of inappropriate and appropriate treatment [7]. Our study therefore did not consider the attributable mortality.

This study has some limitations. The main limitation is that these results cannot be directly extrapolated to other healthcare institutions, given the specificity of the case mix at the study hospital, but the methods described and the analytical process can be adapted or extended. Heterogeneous Gram-negative bacteria were included and analysed collectively, but patients colonized by these bacteria may have different risk factors and prognosis. Moreover, clinical data may be conflicting, since patients who have the same conditions may have different types and timing of observations, such as the use of invasive support. There is no information regarding prior antibiotic use, thereby limiting the number of independent variables that could be included. Finally, the relevance of colonization and infection in attributable mortality is not clear, since it could not be easily assessed.

In conclusion, we believe that identifying risk factors and developing predictive models may benefit patients at risk of acquiring multidrug-resistant bacteria. Infection control policies can be established for early detection and to control the spread of these bacteria, such as identifying subject groups for which culture test is needed. The high mortality and risk factors presented in our study highlight the need to develop effective strategies. The presence of mechanical ventilation and CVC are the main risk factors found; therefore, their use warrants further research.

Acknowledgements

The authors would like to thank all staff from the hospital for their help with data collection.

Conflict of interest statement
None declared.

Funding sources
This work was supported by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) (grant numbers 169049/2017-5 to L.F.D., 306802/2015-5 and 403863/2016-3 to S.H., 310523/2016-8 to F.A.B.); the

Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) - PDSE 88881.190042/2018-01 and Finance Code 001; the Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ); and the Pontifícia Universidade Católica do Rio de Janeiro.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2019.04.013.

References

[1] Van Duin D, Paterson DL. Multidrug-resistant bacteria in the community: trends and lessons learned. Infect Dis Clin 2016;30:377–90.
[2] Cardoso T, Almeida M, Carratalà J, Aragão I, Costa-Pereira A, Sarmento AE, et al. Microbiology of healthcare-associated infections and the definition accuracy to predict infection by potentially drug resistant pathogens: a systematic review. BMC Infect Dis 2015;15:565.
[3] Chang YJ, Yeh ML, Li YC, Hsu CY, Lin CC, Hsu MS, et al. Predicting hospital-acquired infections by scoring system with simple parameters. PLoS One 2011;6:e23137.
[4] MacVane SH. Antimicrobial resistance in the intensive care unit: a focus on gram-negative bacterial infections. J Intensive Care Med 2017;32:25–37.
[5] Jarrell AS, Kruer RM, Berescu LD, Pronovost PJ, Trivedi JB. Factors associated with in-hospital mortality among critically ill surgical patients with multidrug-resistant Gram-negative infections. J Crit Care 2018;43:321–6.
[6] Escolano S, Golmard JL, Korinek AM, Mallet A. A multi-state model for evolution of intensive care unit patients: prediction of nosocomial infections and deaths. Stat Med 2000;19:3465–82.
[7] Falagas ME, Rafailidis PI, Matthaiou DK, Virtzili S, Nikita D, Michalopoulos A. Pandrug-resistant *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* infections: characteristics and outcome in a series of 28 patients. Int J Antimicrob Agents 2008;32:450–4.
[8] Vardakas KZ, Rafailidis PI, Konstantelias AA, Falagas ME. Predictors of mortality in patients with infections due to multi-drug resistant Gram negative bacteria: the study, the patient, the bug or the drug? J Infect 2013;66:401–14.
[9] World Health Organization. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics 2017. 2017. Available at: http://apps.who.int/medicinedocs/documents/s23171en/s23171en.pdf [last accessed July 2018].
[10] Braga IA, Campos PA, Gontijo-Filho PP, Ribas RM. Multi-hospital point prevalence study of healthcare-associated infections in 28 adult intensive care units in Brazil. J Hosp Infect 2018;99:318–24.
[11] Kollef MH, Fraser VJ. Antibiotic resistance in the intensive care unit. Ann Intern Med 2001;134:298–314.
[12] Goodman KE, Lessler J, Cosgrove SE, Harris AD, Lautenbach E, Han JH, et al. A clinical decision tree to predict whether a bacteremic patient is infected with an extended-spectrum β-lactamase-producing organism. Clin Infect Dis 2016;63:896–903.
[13] Ferreira E, Pina E, Sousa-Uva M, Sousa-Uva A. Risk factors for health care-associated infections: from better knowledge to better prevention. Am J Infect Control 2017;45:e103–7.
[14] Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009;302:2323–9.
[15] Ehrentraut C, Ekholm M, Tanushi H, Tiedemann J, Dalianis H. Detecting hospital-acquired infections: a document classification approach using support vector machines and gradient tree boosting. Health Informatics J 2018;24:24–42.
[16] Lye DC, Earnest A, Ling ML, Lee TE, Yong HC, Fisher DA, et al. The impact of multidrug resistance in healthcare-associated and nosocomial Gram-negative bacteraemia on mortality and length of stay: cohort study. Clin Microbiol Infect 2012;18:502–8.
[17] Centers for Disease Control and Prevention. National Healthcare Safety Network (NHSN) patient safety component manual. 2019. Available at: https://www.cdc.gov/nhsn/pdfs/pscmanual/pcsmanual_current.pdf [last accessed Apr 2019].
[18] Clinical and Laboratory Standards Institute. M100S 27. 27th ed. Wayne, PA: CLSI; 2017. Available at: https://clsi.org/media/1469/m100s27_sample.pdf [last accessed April 2019].
[19] Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18:268–81.
[20] Papp-Wallace KM, Endimiani A, Taracila MA, Bonomo RA. Carbapenems: past, present, and future. Antimicrob Agents Chemother 2011;55:4943–60.
[21] Hosmer DW, Lemeshow S. Applied logistic regression. New York: Wiley; 2000.
[22] James G, Witten D, Hastie T, Tibshirani R. An introduction to statistical learning with applications in R. New York: Springer; 2013.
[23] Chiang WC, Chen SY, Chien KL, Hui-Min G, Yen AM, Su CP, et al. Predictive model of antimicrobial-resistant gram-negative bacteremia at the ED. Am J Emerg Med 2007;25:597–607.
[24] Vasudevan A, Mukhopadhyay A, Goh EY, Li J, Tambyah PA. Risk factors for infection/colonization caused by resistant Gram negative bacilli in critically ill patients (an observational study of 1633 critically ill patients). Prev Med 2013;57:S70–3.
[25] Góngora Rubio F, Oliveira VD, Rangel RM, Nogueira MC, Almeida MT. Trends in bacterial resistance in a tertiary university hospital over one decade. Braz J Infect Dis 2013;17:480–2.
[26] Luna CM, Rodriguez-Noriega E, Bavestrello L, Guzmán-Blanco M. Gram-negative infections in adult intensive care units of Latin America and the Caribbean. Crit Care Res Pract 2014;2014.
[27] Safdar N, Maki DG. The commonality of risk factors for nosocomial colonization and infection with antimicrobial-resistant *Staphylococcus aureus*, enterococcus, gram-negative bacilli, *Clostridium difficile*, and Candida. Ann Intern Med 2002;136:834–44.
[28] Falagas ME, Kopterides P. Risk factors for the isolation of multi-drug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*: a systematic review of the literature. J Hosp Infect 2006;64:7–15.
[29] Defez C, Fabbro-Peray P, Bouziges N, Gouby A, Mahamat A, Daures JP, et al. Risk factors for multidrug-resistant *Pseudomonas aeruginosa* nosocomial infection. J Hosp Infect 2004;57:209–16.
[30] Patel SJ, Oliveira AP, Zhou JJ, Alba L, Furuya EY, Weisenberg AS, et al. Risk factors and outcomes of infections caused by extremely drug-resistant gram-negative bacilli in patients hospitalized in intensive care units. Am J Infect Control 2014;42:626–31.
[31] Aloush V, Navon-Venezia S, Seigman-Igra Y, Cabili S, Carmeli Y. Multidrug-resistant *Pseudomonas aeruginosa*: risk factors and clinical impact. Antimicrob Agents Chemother 2006;50:43–8.
[32] Willmann M, Klimek AM, Vogel W, Liese J, Marschal M, Autenrieth IB, et al. Clinical and treatment-related risk factors for nosocomial colonisation with extensively drug-resistant *Pseudomonas aeruginosa* in a haematological patient population: a matched case control study. BMC Infect Dis 2014;14:650.
[33] World Health Organization. Health care-associated infections. Fact Sheet 2011. Available at: http://www.who.int/gpsc/country_work/gpsc_ccisc_fact_sheet_en.pdf [last accessed May 2018].