Surveillance cultures as a tool for choosing empirical antibiotic therapy

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Research Article

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Abstract

Background

A daily challenge for the multidisciplinary team in intensive care units (ICUs) is balancing broad-spectrum antibiotics with the appropriate empirical antibiotic therapy.

Aim

To establish the carbapenem-resistant Gram-negative bacilli screening cultures predictives values.

Methods

We conducted a retrospective study. We included patients admitted to the intensive care unit for at least 48 hours. We measured carbapenem-resistant negative and positive predictive values, sensitivity, and specificity in Gram-negative bacilli screening cultures.

Results

We included 331 infected patients. We found high negative predictive values in Gram-negative carbapenem-resistant bacilli screening cultures: *A. baumannii*: 95% (91- 97); *P. aeruginosa*: 86% (82 - 92); *Enterobacteriaceae* spp.: 93% (89 - 95). On the other hand, low positive predictive values were found: *A. baumannii* 27% (15 – 43); *P. aeruginosa* 35% (15 – 43) and *Enterobacteriaceae* spp.: 22% (9 – 42). In the same way, screening culture's sensibility was 41% (24 – 61) for *A. baumannii*, 27% (16 – 41) for *P. aeruginosa*, and 21% (8 – 41) for *Enterobacteriaceae* spp. The specificity for *A. baumannii* was 89% (85 – 93).

Conclusions

If uncolonized patients, screening cultures effectively predict that patients will rarely be infected with carbapenem-resistant Gram-negative bacilli. Despite previous colonization being an infection factor risk by these pathogens, most colonized patients, when they developed an infection, were not caused by carbapenem-resistant Gram-negative bacilli. So, screening cultures can be an important tool for pharmacist intervention. Thus, we suggest starting empirical antibiotics aimed at carbapenems-resistant Gram-negative bacilli only in cases where infected patients previously colonized by these pathogens with signs of organ dysfunction.

Introduction

Antibiotic therapy evaluation is essential for critical patient pharmaceutical care [1]. A daily challenge for the multidisciplinary team in intensive care units (ICUs) is balancing broad-spectrum antibiotics with the appropriate empirical antibiotic therapy[2]. In addition, expert consensus recommends early appropriate antibiotics administration in septic patients [3, 4]. However, the consumption of high-spectrum antimicrobials is a major global concern [5–7].

The patient's previous colonization and clinical factors guide the choice of empirical treatment [8]. Although screening cultures are not diagnostic tests, they are often used as guides in choosing antibiotic therapy until knowledge of the etiological agent [9]. However, there is disagreement regarding the predictive values of cultures from screenings of extended beta-lactamase-producing Gram-negative bacilli (*K. pneumoniae* and *Enterobacter* spp.). Positive predictive value (PPV) is the probability of a specific diagnostic test finding positive values for really ill individuals. On the other hand, the negative predictive value (NPV) is the test's ability to present a negative result for individuals who do not have the disease [10].

Two robust studies with more than three thousand patients each conducted in the ICU differed in their respective findings [11, 12]. The study conducted in the French ICUs demonstrated that previous colonization by third-generation cephalosporin-resistant *Enterobacteriaceae* was the leading risk factor for subsequent infection[12]. Previously, Rottier et al. (2015) stated that preceding colonization with *Enterobacteriaceae* resistant to third-generation cephalosporins has low positive predictive value for infections caused by these pathogens, and strict adherence to guidelines would unnecessarily encourage the use of broad-spectrum antibiotics [11]. In addition, we have no data about the carbapenem-resistant Gram-negative bacilli as *A. baumannii* and *P. aeruginosa*.

Therefore, the multidisciplinary intensive team must understand the real role of screening cultures in predicting the etiologic agent responsible for subsequent infections. Thus, this study aimed to establish the predictive value of screening carbapenem-resistant Gram-negative bacilli cultures and producing extended-spectrum β-lactamase *Enterobacteriaceae* spp.

Methods

The retrospective observational study was carried out in a tertiary hospital in Rio de Janeiro with 52 intensive care beds. The six clinical pharmacists are part of the ICUs multidisciplinary team. It included patients admitted in ICUs who presented infection in 2019. We excluded patients with an ICU stay of fewer than 48 hours, aged less than 18 years old, and who did not use antimicrobials. Microbial samples were collected weekly for screening for clinically relevant bacterial cultures.

We characterized the study population based on data from medical records. We collected age, gender, Simplified Acute Physiology Score 3 (SAPS 3), Charlson Comorbidity Index (CCI), mechanical ventilation, renal replacement therapy [13], vasoactive amine, previous colonization, blood transfusion up to seven days before the infection [14, 15], parenteral nutrition[16], and previous exposure to systemic antimicrobials up to 90 days before the infection [17]. We adopt the infection definition as the case that a

pathogen isolated in culture for diagnosis with clinical interpretation of the infectious process [18]. The outcome was infection by carbapenem-resistant Gram-negative bacilli (GNB) or extended-spectrum beta-lactamase-producing GNB in patients previously colonized by these.

We defined prior colonization positive results for extended-spectrum beta-lactamase-producing *Enterobacteriaceae*, carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Enterobacteriaceae* spp. in surveillance cultures before infection[12].

We used the Rstudio® program for statistical analysis. A 95% confidence interval was adopted with a p-value <0.05 to be considered statistically significant. First, we performed a descriptive analysis. The quantitative variables were expressed as median or mean, and data dispersion was estimated using the interquartile range (25%-75%) or standard deviation. The categorical variables were expressed as absolute and relative frequencies.

We assessed the data using the non-parametric MannWhitney test for continuous variables. The chi-square tests or Fisher's exact test compared categorical variables. We submitted the variables with p-values less than 0.2 to the logistic regression model

We calculated the relative infection risk in patients previously colonized with extended-spectrum beta-lactamase-producing *Enterobacteriaceae* spp., carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant *Acinetobacter baumannii*, isolated carbapenem-resistant *Enterobacteriaceae* spp. Finally, we measured the positive and negative predictive values, sensitivity, specificity, and likelihood ratio by epiR package. The local research ethics committee approved the study under CAAE: 25683019.4.0000.5249.

Results

Six hundred and fifty-one patients had at least one microorganism isolated during the study period of 4,250 admissions in 2019. Of these, 282 were excluded from admission to the ICU for less than 48 hours (Figure 1). The characterization of the study population is presented in Table 1.

Table 1
– Clinical and demographic characterization, N = 331, Rio de Janeiro, 2021.

Variable	Absolute frequency or median[#]
Demographic	
Female	158 (47.7)
Age (years old)	79 (69 – 88)
Charlson Comorbidity Index	2 (1 – 3)
SAPS 3	52 (47 – 60)
Mortality	
Mortality within thirty days	92 (27.8)
Mortality within twelve months	144 (43.5)
Previous colonization	
Carbapenem-resistant *Acinetobacter baumannii*	44 (13.3)
Carbapenem-resistant *Pseudomonas aeruginosa*	43 (13.0)
Carbapenem-resistant *Enterobacteriaceae* spp.	28 (8.7)
Vancomycin-resistant *Enterococcus* spp.	9 (2.7)
ESBL	44 (13.3)
Mechanical ventilation	133 (40.2)
ICU length stay until the infection*	10 (4 – 24)
Hospital length stay until the infection*	17 (7 – 70)
Hospital length stay	43 (20 – 93)
Amine use	136 (41.1)
Parenteral nutrition	40 (12.1)
Use of the previous antibiotic	204 (61.4)
Number of infections per patient	2 (1 – 3)
Transfusion	51 (15.4)

*;,ICU = Intensive Care Unit; ESBL = Extended-spectrum beta-lactamase-producing *Enterobacteriaceae*;. [#]The categorical variables were expressed in absolute frequencies and, in between parenthesis, the relative frequencies. The continuous variables were expressed in median and, in between parenthesis, the 25%-75% interquartile range. SAPS 3 = Simplified Acute Physiology Score 3.

Variable	Absolute frequency or median[#]
Renal Replacement Therapy	87 (26.3)

*;,ICU = Intensive Care Unit; ESBL = Extended-spectrum beta-lactamase-producing *Enterobacteriaceae*;,. [#]The categorical variables were expressed in absolute frequencies and, in between parenthesis, the relative frequencies. The continuous variables were expressed in median and, in between parenthesis, the 25%-75% interquartile range. SAPS 3 = Simplified Acute Physiology Score 3.

There was no methicillin-resistant *Staphylococcus aureus* isolated in the screening culture. Nine vancomycin-resistant *Enterococcus* spp were isolated in screening cultures and none in the diagnosis culture. The previous colonization by carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant *Acinetobacter baumannii*, and carbapenem-resistant *Enterobacteriaceae* showed to be associated with risk factors for subsequent infection for these pathogens. However, previous colonization by extended-spectrum beta-lactamase-producing *Enterobacteriaceae* was not found as a risk factor for subsequent infection by ESBL pathogens in this study (Figure 2).

Table 2 presents each previous colonization's positive and negative predictive values, sensitivity, specificity, likelihood ratio, and accuracy. Screening cultures showed high negative predictive values and specificity and low positive predictive values and sensitivity. Finally, we present the odds ratio adjusted for the covariates in Table 3. All carbapenem-resistant Gram-negative bacilli displayed values with statistical significance.

Table 2
Previous colonization predictive values. N=331.

	Carbapenem-resistant *Acinetobacter baumannii*	**Carbapenem-resistant *Pseudomonas aeruginosa***	**Carbapenem resistant *Enterobacteriaceae***	**Beta-lactamase-producing *Enterobacteriaceae***
Sensitivity (CI)	41.0 (24.0– 61.0)	27.0 (16.0 – 41.0)	21.0 (8.0 – 41.0)	11.0 (4.0 – 24.0)
Specificity (CI)	89.0 (85.0 – 93.0)	90.0 (86.0 – 93.0)	93.0 (90.0 – 96.0)	92.0 (88.0 – 95.0)
Positive predictive value (CI)	27.0 (15.0 – 43.0)	35.0 (15.0 – 43.0)	22.0 (9.0 – 42.0)	18.0 (6.0 – 37.0)
Negative predictive value (CI)	95.0 (91.0 – 97.0)	86.0 (82.0– 90.0)	93.0 (89.0 – 95.0)	86.0 (82.0 – 90.0)
Positive likelihood ratio	3. 91 (2.27- 6.72)	2.69 (1.54 – 4.69)	3.09 (1.36 –7.02)	1.35 (0.54 – 3.36)
Negative likelihood ratio	0.66 (0.48- 0.89)	0.81 (0.69 – 0.96)	0.84 (0.69 –1.03)	0.97 (0.87 – 1.08)
Accuracy	12.82	15.75	6.85	5.79

Legend. CI = Confidence Interval. Values in %.

Table 3
Odds ratio subsequent infections analysis in previously colonized patients using multiple regression

Colonizations	**OR (CI)**	**P-value**
Carbapenem- resistant *Acinetobacter bauamannii*	3.25 (1.18 – 8.91)	0.021
Carbapenem- resistant *Pseudomonas aeruginosa*	3.10 (1.34 – 7.08)	0.007
Carbapenem- resistant *Enterobacteriaceae* spp.	10. 20 (2.64 – 38.74)	<.001

OR = Odd ratio; CI = Confindece interval

Discussion

The PPVs found were low and the NPVs high, suggesting that screening cultures were efficient in establishing that carbapenem-resistant Gram-negative bacilli and extended-spectrum beta-lactamase-producing GNB rarely infect patients not colonized by these pathogens. On the other hand, previously colonized patients will not necessarily be infected by the pathogens. The sensitivity and specificity values reinforced this finding. In addition, the observed accuracy of predicting etiologic agents by screening cultures was low.

The positive predictive values and sensitivity for subsequent infections by extended beta-lactamase-producing *Enterobacteriaceae* found by Massart et al. (2020)[12] were twice as high compared to the study by Rottier et al. (2015)[11]. Both studies were carried out in ICU. Our findings are consistent with those stipulated by Rottier and colleagues [11]. However, these authors did not determine the negative predictive values. Therefore, we compared our NPV and specificity with those pointed out by Massart and collaborators, and the results are similar [12] (NPV >85% and specificity greater than 90% in both studies).

We did not previously find the predictive carbapenem-resistant Gram-negative screening cultures values in the literature. However, prior colonization by carbapenem-resistant GNB is a significant risk factor for subsequent infection by these pathogens[19], and our data showed this relationship. Although, we observed that patients previously colonized with carbapenem-resistant GNB did not present infection by these pathogens most of the time.

The pharmacist is an essential member of the antimicrobial stewardship program within hospitals[20]. The clinical pharmacist participation in the antibiotic choice contributes to more appropriate use, especially in developing countries[21]. We suggest that the screening cultures analysis can be an important tool for pharmaceutical intervention regarding empirical antimicrobials. Our results indicate that previously colonized septic patients should receive antibiotic therapy considering the previous colonization (e.g., carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant *Acinetobacter baumannii*, and carbapenem-resistant *Enterobacteriaceae*). A delay in administering adequate antibiotic treatment is a factor for mortality in this population [3, 9]. However, as most of the patients are not infected by the pathogens by which they are previously colonized, it would be reasonable to reserve broad-spectrum antibiotics for unstable patients with organ dysfunction. Antibiotics used to treat carbapenem-resistant non-fermenting Gram-negative bacilli are considered a last therapeutic resort[22] and should only be reserved if these pathogens have a strong suspicion of infection.

Although low and middle-income countries (LMIC) publish fewer studies and are less robust than high-income countries[23], LMIC has the highest carbapenem-resistant GNB infection prevalence. This study involved only one center and retrospective data collection. Despite these limitations, we measured for the first time the predictive values of non-fermenter carbapenem-resistant Gram-negative bacilli. These pathogens are a major public health problem [6], especially in LMIC [24]. The results obtained provide evidence on the role of culture screening in predicting etiological agents responsible for infections in critically ill patients. In addition, they may contribute to choosing appropriate empirical antibiotic therapy for patients in the ICU, promoting more rational antimicrobials use.

Conclusion

Previous colonization by carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant *Acinetobacter baumannii*, and carbapenem-resistant *Enterobacteriaceae* showed risk factors for subsequent infection. However, the screening cultures' negative predictive values and observed specificity were high, indicating that uncolonized patients will rarely become infected by these pathogens. This result may contribute to the choice of empirical antibiotic therapy, discouraging the prescription of antibiotics against carbapenem-resistant *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Enterobacteriaceae* spp.

Declarations

DECLARATIONS OF COMPETING INTEREST

None.

AUTHOR'S CONTRIBUTIONS

Conception and design of the study: ECL, AROS, and DRS. Contribution of materials/analysis tools: LPNG and CO. Analyses of the data: ECL, AROS, CO, LPNF, and DRS. Writing the manuscript: ECL, AROS, DRS. All authors read and approved the final version of the manuscript.

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Figures

Figure 1

Flowchart of patient selection in the study, Rio de Janeiro, 2020.

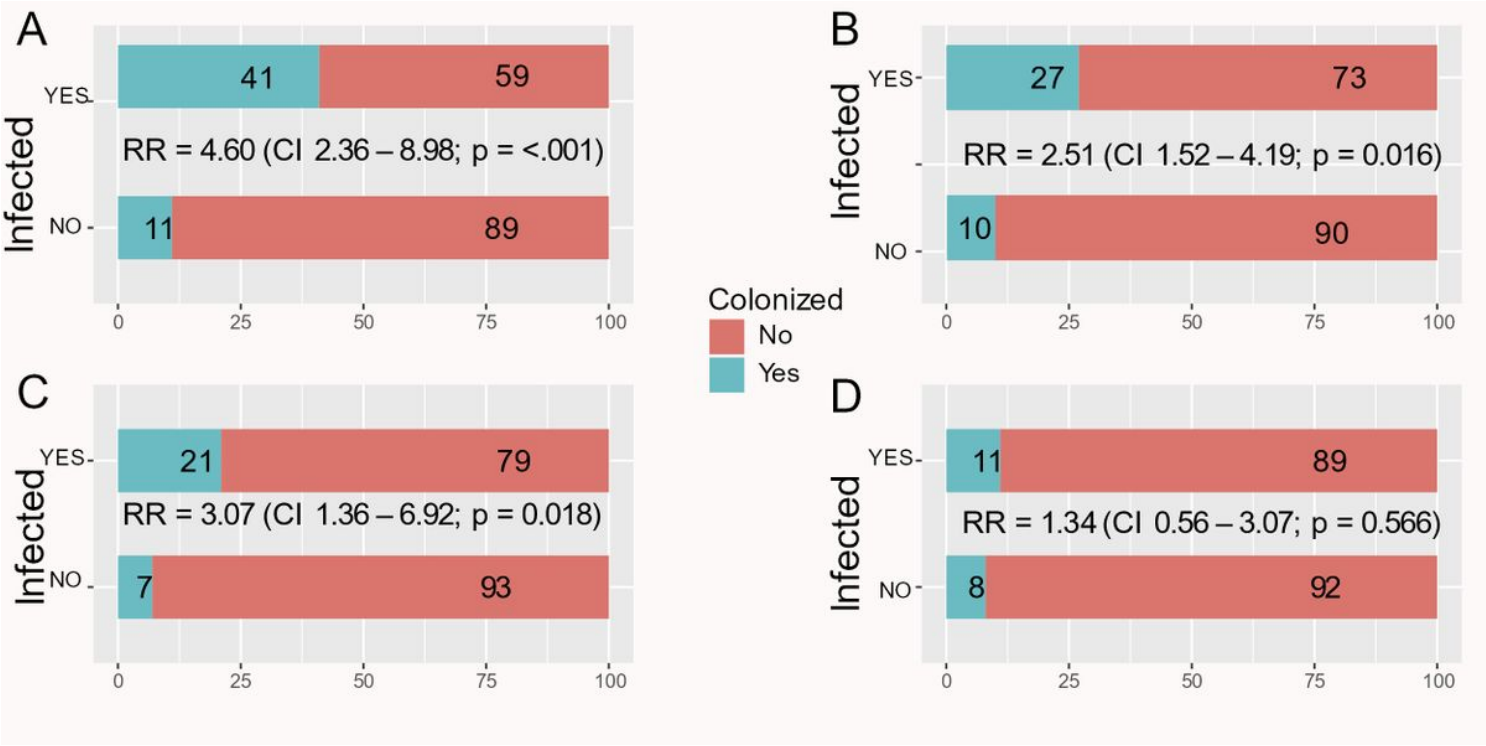

Figure 2

Relative risks of previous colonization to subsequent infection of patients included in the study. N = 331.

Legend: A = Carbapenem-resistant *Acinetobacter baumannii*; B = Carbapenem-resistant *Pseudomonas aeruginosa*; C = Carbapenem-resistant *Enterobacteriareaceae*; D = Extended-spectrum beta-lactamase-producing *Enterobacteriareaceae.* CI = Confidence Interval; RR = relative risk. The x-axis is expressed as relative frequencies (0% - 100%).