Empirical antimicrobial therapy based on active surveillance cultures in ICU patients

Antibioticoterapia empírica baseada em culturas de vigilância ativa nos pacientes de UTI

Alice Ramos Silva¹, Luis Phillipe Nagem Lopes¹, Fernando Fernandez-Llimos³, Elisangela Costa Lima¹,*

¹Faculty of Pharmacy, Federal University of Rio de Janeiro. Rio de Janeiro, Brazil.
³Laboratory of Pharmacology, Faculty of Pharmacy, University of Porto. Porto, Portugal.

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ABSTRACT

Objective: To assess the predictive value of prior carbapenem-resistant Acinetobacter baumannii (CRAB) and Pseudomonas aeruginosa (CRPA) colonization established in surveillance cultures for subsequent infection by these pathogens in ICU patients.

Methods: A cohort study was performed with patients admitted to the intensive care unit for at least 48 h. Negative and positive predictive values, sensitivity, and specificity of surveillance cultures in CRAB and CRPA were measured.

Results: 693 infected patients were included. Patients previously colonized by CRAB and CRPA were more likely to be infected by these pathogens: adjusted OR: 10.34 (6.58 - 16.45; p < 0.001) and 2.30 (3.88 - 10.26; p < 0.001), respectively. We found high negative predictive values of surveillance cultures for CRAB (87.18%) and CRPA (88.30%) and high specificity 91.96% and 90.13%, respectively.

Conclusions: Patients not colonized by CRAB and CRPA were less prone to infection by these pathogens. These findings may contribute to the choice of empirical antimicrobial therapy and discourage the prescription of antibiotics against these pathogens in patients without previous colonization.

KEYWORDS
Evidence-based pharmacy practice
Intensive care units
Mass screening
Pharmaceutical services
INTRODUCTION

Although microbial drug resistance (MDR) occurs naturally due to bacteria evolution and antibacterial overuse exacerbates the problem, the World Health Organization (WHO) encourages multimodal strategies for nosocomial infection control. For example, active surveillance culture in asymptomatic patients and reduction in antibiotic use are proposed to control MDR spread. The discovery and development of innovative antibiotics that meet antimicrobial resistance demands are scarce. Carbapenem-resistant Acinetobacter baumannii (CRAB) and Pseudomonas aeruginosa (CRPA) are critical pathogens with few treatment options available. More than 80% of Acinetobacter baumannii in Brazil are resistant to carbapenems. Despite the global effort to reduce antimicrobial prescribing, antibiotic consumption has increased in recent years, especially in low- and middle-income countries.

Early initiation of effective antibiotic therapy reduces mortality in septic patients. However, recent data suggest that using empiric antibiotics for less than 72 h may contribute to microbial resistance and may be a helpful tool for pharmacists' intervention on empirical antimicrobial therapies. The positive predictive value is the probability of a positive result being attributed to a sick individual. In contrast, the negative predictive value is the probability of a negative test in a genuinely non-ill individual. We aimed to measure the performance of surveillance cultures in predicting CRAB and CRPA infection in Brazilian ICU patients using negative and positive predictive values, sensitivity, and specificity.

METHODS

We conducted a cohort study in a private tertiary hospital in Rio de Janeiro (Brazil) with 52 intensive care beds in five ICUs. Six clinical pharmacists were part of these ICU multidisciplinary teams.

We selected all patients whose ICU admission period occurred during 2019. We included all patients admitted to the ICU for 48 h or more who had a microbial infection between January 1 and December 31, 2019. We followed up with the included patients from admission until hospital discharge. We included all patients who met the inclusion criteria. Patients younger than 18 years were excluded. Therefore, the monitored individuals constitute a population with no sample. We used the CRAB-infected proportions over the study population.

As part of a set of interventions designed to limit the spread of CRAB and CRPA, the hospital team implemented surveillance culture collection for all patients at ICU admission and then weekly. We included all patients younger than 18 years who met the inclusion criteria. Patients who received blood transfusion up to 7 days before the infection, parenteral nutrition, and ICU length of stay. We retrospectively collected data from medical records from March to June 2022, including demographic data, results of the Simplified Acute Physiology Score 3 (SAPS 3) and the Charlson Comorbidity Index (CCI), mechanical ventilation, renal replacement therapy, vasoactive amine use, any previous colonization reported, blood transfusion up to 7 days before the infection, parenteral nutrition, and ICU length of stay. Prior colonization was defined as positive results for subsequent infections once determining the patient's colonization and may be a helpful tool for pharmacists' intervention on empirical antimicrobial therapies.
CRPA and CRAB in surveillance cultures before infection. We considered infection when the diagnosis was recorded in the medical chart and attributed to the pathogen isolated in a culture collected for diagnostic purposes. Physicians used criteria such as fever, leucocytosis, or leukaemia, C-reactive protein levels, and procalcitonin among other infection signals. Physicians considered and ruled out differential diagnoses.

Age was categorized into two groups according to the median (≤ 75 or > 75 years). The Charlson Comorbidity Index was classified according to Charlson et al. as high and very high (≥ 3 points). Regarding the SAPS 3 score, we distinguished the sample as more significant than 57 points or not. Categorical variables were expressed as absolute and relative frequencies, and we performed Pearson’s chi-squared to compare groups. Then, we performed simple regression to measure the crude odds ratio of infection in patients previously colonized by CRAB and CRPA. After that, we obtained the adjusted odd ratios using two multivariate logistic regression models using CRAB and CRPA infections as outcomes. In the multiple regression model, previous colonization by CRAB and CRPA was a factor associated with these pathogen infections. CRAB and CRPA infection prevalences were 16.74% and 16.59%, respectively. CRAB surveillance cultures presented a specificity of 91.93% and a sensitivity of 49.32%. In CRPA surveillance cultures, specificity was 90.13% and sensitivity was 40.0% (Table 3).

DISCUSSION

Clinical pharmacists may be crucial in antimicrobial stewardship programs (ASP). Literature has demonstrated that pharmacists have contributed to vancomycin deprescription in patients with negative surveillance cultures for MRSA and the reduction of empirical consumption of broad-spectrum antimicrobials. Unfortunately, these studies did not include CRAB and CRPA. Our results showed that surveillance cultures were effective predictors of subsequent CRAB and CRPA infection in the studied population. Noncolonized patients were less prone to...
OR (95%CI)
study conducted in an ICU found a low positive
study with septic patients. The delay in administering
other hand, recent data suggested that empiric broad-
bacteria. Indeed, balancing adequate empiric
spectrum antibiotic therapy for less than 72 h was a risk
factor for the emergence of multidrug-resistant
antibiotics. The choice of empirical antibiotics should be based on previous colonization, local epidemiology, and
other risk factors for infection by MDR pathogens. In
addition, CRAB and CRPA are major public health
Table 2 — Logistic regression for outcome infection with carbapenem-resistant Pseudomonas aeruginosa and
Acinetobacter baumannii in previously colonized patients (Rio de Janeiro, Brazil).

<table>
<thead>
<tr>
<th>Previous colonization</th>
<th>Crude OR (95%CI)</th>
<th>P-value</th>
<th>Adjusted¹ OR (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbapenem-resistant</td>
<td>11.12 (7.15 - 17.52)</td>
<td>&lt; 0.0001</td>
<td>10.34 (6.58 - 16.45)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbapenem-resistant</td>
<td>6.09 (3.83 - 9.69)</td>
<td>&lt; 0.0001</td>
<td>2.30 (3.88 - 10.26)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td></td>
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<td></td>
<td></td>
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</tbody>
</table>

OR = Odd ratio; CI = confidence interval; ¹Independent variables were considered: Age (>75 years old), Charlson Comorbidity
Index > 3, mechanical ventilation, central catheter, renal replacement therapy, Simplified Acute Physiology Score III > 57 points,
amine use and parenteral nutrition use.

Table 3 — Performance of surveillance cultures predicting the etiologic agent in infected patients (Rio de Janeiro, Brazil).

<table>
<thead>
<tr>
<th></th>
<th>CRAB</th>
<th>CRPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy</td>
<td>82.97%</td>
<td>81.82%</td>
</tr>
<tr>
<td>Kappa test</td>
<td>0.45</td>
<td>0.31</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>49.32%</td>
<td>40.00%</td>
</tr>
<tr>
<td>Specificity</td>
<td>91.96%</td>
<td>90.14%</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>62.07%</td>
<td>44.60%</td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>87.18%</td>
<td>88.30%</td>
</tr>
<tr>
<td>Prevalence</td>
<td>16.74%</td>
<td>14.86%</td>
</tr>
</tbody>
</table>

CRAB: Carbapenem-resistant Acinetobacter baumannii. CRPA: Carbapenem-resistant Pseudomonas aeruginosa.

CRAB and CRPA infection. Negative surveillance culture for CRAB and CRPA may be helpful for antibiotic therapy
desescalation in Brazil.

However, studies investigating SC predictive value are divergent. For example, an Australian study conducted in an ICU found a low positive predictive value (only 29.8%) and a high negative predictive value (greater than 90%). According to these authors, SC is essential information about the probability of infection by multidrug-resistant pathogens. They promoted SC as a tool for choosing empirical antibiotic therapy for ICU patients who subsequently develop an infection. Conversely, Rottier et al. measured positive predictive values of previous colonization of cephalosporin-resistant Gram-negative bacilli. The authors found a positive predictive value of 6.1%, lower than the Australian study and discouraged SC use for empirical antibiotic guidance.

Notwithstanding, Rottier et al. conducted the study with septic patients. The delay in administering adequate antibiotics is a mortality-inducing factor in the septic population. Studies showed that administering appropriate antibiotics within one hour of sepsis recognition protects against ICU mortality. On the other hand, recent data suggested that empiric broad-spectrum antibiotic therapy for less than 72 h was a risk factor for the emergence of multidrug-resistant bacteria. Indeed, balancing adequate empiric antibiotic treatment and excessive broad-spectrum antibiotic use is a challenge in ICUs.

Massart et al. also evaluated predictive values of cephalosporin-resistant Gram-negative bacilli previous colonization. The authors found that the positive and negative predictive values of colonization for infection etiology were 31.6% and 95.2%, respectively, while the sensitivity and specificity were 40.0% and 93.2%. Despite the different previous colonizations investigated, they reported negative predictive value, specificity, and sensitivity similar to our study. However, the positive predictive value differed probably due to the low prevalence. The prevalence of cephalosporin-resistant Gram-negative bacillus infections was 6.1% in the Massart study, lower than the CRAB and CRPA infection prevalence observed in our center.

A multicenter study conducted in Canada and the United States investigated SC utility in guiding empirical treatment in Gram-negative bloodstream infections. The study found that the positive predictive value of previous colonizations for subsequent infection was 66%. Unlike Rottier et al., the authors suggested that prior colonization should be considered when choosing empirical antibiotic therapy. Low- and middle-income countries such as Brazil have a high prevalence of CRAB and CRPA, but we found a positive predictive value similar to the North American study. We did not find published SC accuracy data.

Our study has some limitations. We included only single-center ICU patients using a retrospective data collection, which may limit the generalizability of the results. However, our study is the first clinical pharmacy research that proposes CRAB and CRPA surveillance cultures as a tool in pharmaceutical care. Clinical pharmacy research generates knowledge for patient-centered medication decision making. Moreover, our results corroborate previously published data.

We found high negative predictive values, specificity, and accuracy, and observed that patients not colonized by CRAB and CRPA were less likely to be infected by these microorganisms. Consequently, we suggest that the multidisciplinary team could use surveillance cultures to reduce broad-spectrum antimicrobial use. Nonetheless, the prescription of empirical broad-spectrum antimicrobials based on previous colonization is contradictory. Indeed, prior MDR colonization is a risk factor for subsequent infection. The choice of empirical antibiotics should be based on previous colonization, local epidemiology, and other risk factors for infection by MDR pathogens. In addition, CRAB and CRPA are major public health...
problems’, especially in LMICs40.

CONCLUSION

The high negative predictive values combined with the high specificity observed for CRAB and CRPA suggest that noncolonized patients are less prone to infection by pathogens. Thus, our findings contribute to understanding the role of SC in deprescribing broad-spectrum antimicrobials in noncolonized patients. However, quasi-experimental studies that tested antibiotic therapy deprescription protocols in surveillance cultures are necessary to better understand the topic.

REFERENCES


13. da Fonseca Pestana Ribeiro JM, Park M. Less empiric broad-spectrum antimicrobials for infection by pathogens. Thus, our findings contribute to understanding the role of SC in deprescribing broad-spectrum antimicrobials in noncolonized patients. However, quasi-experimental studies that tested antibiotic therapy deprescription protocols in surveillance cultures are necessary to better understand the topic.


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Conception and design of the study: ARS, ECL
Data analysis and interpretation: ARS, LPNL, ECL, FFL
Data collection: ARS, LPNL
Writing of the manuscript: ARS, LPNL, ECL, FFL
Critical revision of the text: ECL, FFL
Final approval of the manuscript: ARS, LPNL, FFL, ECL
Statistical analysis: ARS
Overall responsibility for the study: ARS, ECL

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