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ORIGINAL ARTICLE

Empirical antimicrobial therapy based on active surveillance cultures in ICU patients

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

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KEYWORDS

Evidence-based pharmacy practice
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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.

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PALAVRAS-CHAVE

Assistência farmacêutica
Prática farmacêutica baseada em evidências
Programas de rastreamento
Unidades de terapia intensiva

RESUMO

Objetivo: Avaliar o valor preditivo da colonização prévia por *Acinetobacter baumannii* (CRAB) e *Pseudomonas aeruginosa* (CRPA) resistente a carbapenêmicos estabelecida em culturas de vigilância para infecção subsequente por esses patógenos em pacientes internados em UTI.
Métodos: Foi realizado um estudo de coorte com pacientes internados na unidade de terapia intensiva por pelo menos 48 h. Foram medidos os valores preditivos negativos e positivos, sensibilidade e especificidade das culturas de vigilância em CRAB e CRPA.
Resultados: Foram incluídos 693 pacientes infectados. Pacientes previamente colonizados por CRAB e CRPA tiveram maior probabilidade de serem infectados por esses patógenos: OR ajustado: 10,34 (6,58 - 16,45; p < 0,001) e 2,30 (3,88 - 10,26; p < 0,001), respectivamente. Encontramos altos valores preditivos negativos de culturas de vigilância para CRAB (87,18%) e CRPA (88,30%) e alta especificidade 91,96% e 90,13%, respectivamente.
Conclusões: Pacientes não colonizados por CRAB e CRPA mostraram-se menos propensos à infecção por esses patógenos. Esses achados podem contribuir para a escolha da terapia antimicrobiana empírica e desencorajar a prescrição de antibióticos contra esses patógenos em pacientes sem colonização prévia.

INTRODUCTION

Although microbial drug resistance (MDR) occurs naturally due to bacteria evolution[1] and antibacterial overuse exacerbates the problem[2], the World Health Organization (WHO) encourages multimodal strategies for nosocomial infection control[3]. For example, active surveillance culture in asymptomatic patients and reduction in antibiotic use are proposed to control MDR spread[4].

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[5-8]. More than 80% of *Acinetobacter baumannii* in Brazil are resistant to carbapenems[9]. Despite the global effort to reduce antimicrobial prescribing[7], antibiotic consumption has increased in recent years[10], especially in low- and middle-income countries[11].

Early initiation of effective antibiotic therapy reduces mortality in septic patients[12]. However, recent data suggest that using empiric antibiotics for less than 72 h may contribute to microbial resistance[13,14]. Infections by MDR are more prevalent in hospital settings, especially in the intensive care unit (ICU)[15]. Therefore, a challenge for the multidisciplinary team in intensive care units (ICUs) is balancing broad-spectrum antibiotics with appropriate empirical antibiotic therapy[12]. Furthermore, low- and middle-income countries like Brazil face difficulties in implementing a robust antimicrobial stewardship program[16], with less than half of hospitals having these programs[17].

Studies differ on the usefulness of surveillance culture in empiric antibiotics[18,19]. Spoto et al.[18] postulated that identifying pathogens in surveillance cultures can help to choose empirical antimicrobials. In contrast, Rottier et al.19 noted that using previous colonization to prescribe antibiotics can lead to overprescription. A *quasi-experimental* study published in 2018 showed that pharmacists could use methicillin-resistant *Staphylococcus aureus* surveillance cultures to reduce vancomycin consumption[20].

Colonization is the first infection stage[21]. Surveillance cultures can predict etiologic agents of subsequent infections once determining the patient's colonization18 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[22]. 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[23]. 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[24]. The surveillance cultures used were rectal swabs.

The patients were followed until ICU discharge or death. 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

CRPA and CRAB in surveillance cultures before infection[25].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 leukopenia, C-reactive protein levels, and procalcitonin among other infection signals. Physicians considered and ruled out differential diagnoses[23].

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.[26] as high and very high (≥ 3 points). Regarding the SAPS 3 score, we distinguished the sample as more significant than 57 points or not[27]. 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 logistic regression models, we included variables with a $p < 0.2$ value in the univariate analysis. Finally, we measured positive and negative predictive values, sensitivity, specificity, and likelihood ratio using the epiR package.We calculated the test statistical power using the IBM SPSS Statistics 28.0.1.0 program.

Ethical Approval

The IDOR - *Instituto D'OR de Ensino e Pesquisa* Research Ethics Committee approved the study under CAAE 25683019.4.0000.5249 on March 19, 2020. Therefore, this study followed Brazilian legislation, and the institutional requirements did not require written informed consent for participation.

RESULTS

During the study period, 7,953 patients were admitted to the ICU; 693 patients met the inclusion criteria. CRAB infection affected 146 (21.1%) patients. Previous colonization was present in 72 (62.1%) of those infected with CRAB, as shown in Table 1. These values provided a statistical power greater than 95%. In univariate analysis, patients infected with CRAB were more mechanically ventilated [68 (59.6%) *vs.* 273 (47.5%); p-value = 0.023]. Central venous catheter use was also more prevalent in CRAB-infected patients [80 (69.6%) *vs.* 295 (51.3%); p-value < 0.001]. In CRPA-infected patients, mechanical ventilation use was more frequent [n = 63 (61.2%)].

Table 2 presents the crude and adjusted odds ratios of the CRAB and CRPA surveillance cultures. 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)28. Literature has demonstrated that pharmacists have contributed to vancomycin deprescription in patients with negative surveillance cultures for MRSA[20,29]and the reduction of empirical consumption of broad-spectrum antimicrobials[20,29,30]. 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

Table 1 — Study population characterization. Values as n (%).

Variable	Total	Infection			
		CRAB		CRPA	
	N = 693	n = 116	p-value*	n = 103	p-value*
Age (>75 y)	375 (54.1)	53 (45.7)	0.058	51 (49.5)	0.364
SAPS3 (> 57 pts)	290 (41.8)	53 (45.7)	0.414	50 (48.5)	0.166
Renal replacement therapy	158 (22.8)	26 (22.6)	1.000	30 (29.1)	0.103
Mechanical ventilation	341 (49.5)	68 (59.6)	0.023	63 (61.2)	0.014
Amine use	307 (44.6)	57 (49.6)	0.280	51 (49.5)	0.295
Catheter central venous	375 (54.3)	80 (69.6)	<0.001	54 (52.4)	0.791
Parenteral nutrition	77 (11.2)	18 (15.7)	0.130	7 (6.8)	0.180
Charlson Comorbidity index ≥ 3 points	219 (31.6)	36 (31.0)	0.972	28 (27.2)	0.352
Previous colonization					
CRAB	146 (21.1)	72 (62.1)	< 0.001		
CRPA	115 (16.6)			46 (44.7)	< 0.001

SAPS III = Simplified Acute Physiology Score II. CRAB: Carbapenem-resistant *Acinetobacter baumannii*. *CRPA:* Carbapenem-resistant *Pseudomonas aeruginosa*. *Pearson's chi-square test.

Table 2 — Logistic regression for outcome infection with carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in previously colonized patients (Rio de Janeiro, Brazil).

Previous colonization	Crude		Adjusted[1]	
	OR (95%CI)	P-value	OR (95%CI)	P-value
Carbapenem-resistant *Acinetobacter baumannii*	11.12 (7.15 – 17.52)	< 0.0001	10.34 (6.58 - 16.45)	< 0.0001
Carbapenem-resistant *Pseudomonas aeruginosa*	6.09 (3.83 – 9.69)	< 0.0001	2.30 (3.88 - 10.26)	< 0.0001

OR = Odd ratio; CI = confidence interval; [1]Independent 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).

	CRAB	CRPA
Accuracy	82.97%	81.82%
Kappa test	0.45	0.31
Sensitivity	49.32%	40.00%
Specificity	91.96%	90.14%
Positive Predictive Value	62.07%	44.60%
Negative Predictive Value	87.18%	88.30%
Prevalence	16.74%	14.86%

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 deescalation in Brazil.

However, studies investigating SC predictive value are divergent[18,19,24,31]. 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[31]. 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[19,31].

Notwithstanding, Rottier et al. conducted the study with septic patients[19]. The delay in administering adequate antibiotics is a mortality-inducing factor in the septic population[12]. Studies showed that administering appropriate antibiotics within one hour of sepsis recognition protects against ICU mortality[32-34]. 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[35].Indeed, balancing adequate empiric antibiotic treatment and excessive broad-spectrum antibiotic use is a challenge in ICUs[12].

Massart et al. also evaluated predictive values of cephalosporin-resistant Gram-negative bacilli previous colonization[25].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[36]. 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%[37]. Unlike Rottier et al.[19], the authors suggested that prior colonization should be considered when choosing empirical antibiotic therapy[37]. Low- and middle-income countries such as Brazil have a high prevalence of CRAB and CRPA38, 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[39]. Moreover, our results corroborate previously published data[18,30].

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[20]. Nonetheless, the prescription of empirical broad-spectrum antimicrobials based on previous colonization is contradictory[19,24,37]. 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[7], especially in LMICs[40].

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.

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