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Prevalence and temporal trends of critical infections due to multidrug-resistant bacteria (ESKAPE) in nine tertiary hospitals of Rio de Janeiro in the COVID-19 era

Abstract

Introduction: Antimicrobial resistance is a serious threat to public health worldwide. This fact becomes more relevant in the COVID-19 era considering the inappropriate use of antimicrobials. An important representative of multidrug-resistant (MDR) bacteria is the ESKAPE group. The prevalence of these pathogens in Rio de Janeiro in COVID-19 patients is still unknown. The aim of the current study was to determine the prevalence and temporal trends of critical infections due to ESKAPE microorganisms in nine tertiary hospitals of Rio de Janeiro in the COVID-19 pandemic.

Methods: Prospective study performed in nine tertiary private hospitals of Rio de Janeiro between March 2020 and October 2021. Electronic medical records were retrieved from the computerized database of the hospitals clinical microbiology laboratories. Bacterial identification/antibiotic susceptibility testing were performed by automated methodologies and statistical analyses were performed for comparative purposes.

Results: In total, 1812 cultures from 1653 patients were evaluated. The data revealed that among the ESKAPE microorganisms, the highest prevalence was for *Klebsiella pneumoniae* and *Acinetobacter baumannii*. In the analysis of the temporal trends of the distribution of the MDR bacteria, we observed that the COVID-19 patients had a stable distribution during the study period, while the prevalence for these pathogens increased in the non-COVID-19 patients

Conclusion: We confirmed an increase in the prevalence of MDR bacteria (including ESKAPE group) in COVID-19 patients, specifically of non-fermenting Gram-negative bacteria. We also observed that the indiscriminate use of antibiotics in COVID-19 patients had a cumulative impact on infections of non-COVID-19 patients.

Keywords: multidrug-resistant bacteria, ESKAPE, COVID-19, critical infection, Rio de Janeiro, epidemiology

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Abbreviations: COVID-19, coronavirus disease 2019; MDR, multidrug-resistant; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; ESKAPE, *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* spp; WHO, World Health Organization; ICU, intensive care unit ; RT- PCR, real-time polymerase chain reaction; VRE, Vancomycin-resistant *Enterococcus*; MRSA, methicillin-resistant *Staphylococcus aureus*; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; CRE, carbapenem-resistant *Enterobacteriaceae*

Introduction

Bacterial and fungal co-infections in patients with severe acute respiratory syndrome related to coronavirus-2 infection (SARS-CoV-2) are factors that increase the Coronavirus Disease 2019 (COVID-19) patient mortality rates and healthcare-associated costs of care worldwide.[1,2] The increased incidence of infections caused by multidrug-resistant bacteria (MDR) in critically ill COVID-19 patients is multifactorial, but is strongly associated with increased use of invasive devices and the broad-spectrum antimicrobials misuse.[3-5]

Currently, there is an important group within the MDR bacteria, those with the acronym ESKAPE (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* spp.), which represent a recognized risk in critical infections for their ability to develop mechanisms of resistance that allow them to escape the effects of many antimicrobial drugs.[6] The scarcity of available effective therapies for these MDR pathogens puts this group on the list of bacteria in need of urgent investigation according to The World Health Organization (WHO), aiming for the development of new antimicrobial agents.[7]

Despite the adoption of measures to control the spread of MDR bacteria in hospital environments, especially in intensive care units (ICUs), the impact of the COVID-19 pandemic also poses a risk for the control of the spread of MDR bacteria in non-COVID-19 critical care sectors.[8]

In Brazil, there are few studies that show the epidemiology of infections by MDR bacteria (including those from the ESKAPE group) in patients treated in ICUs during the COVID-19 pandemic.[9] The aim of this study was to identify the prevalence and temporal trends of these infections in critically ill patients from nine urban hospitals in the city of Rio de Janeiro, in the two sectors: units with care for COVID-19 patients and units with care for non-COVID-19 patients.

Material and methods

A prospective cohort study was conducted between March 2020 and October 2021 from nine tertiary hospitals in Rio de Janeiro to identify the prevalence of infections due to MDR bacteria, including ESKAPE pathogens. Patients over 18 years of age with a confirmed SARS-CoV-2 infection (ie, a positive real-time polymerase chain reaction [RT-PCR] assay for COVID–19) and non-COVID-19 adult patients were eligible for the study. Total rates were analysed, as well as rates per clinical specimen, hospital and MDR pathogens.

Electronic medical records were retrieved from the computerized database of the hospitals` clinical microbiology laboratories. Bacterial species identification and antibiotic susceptibility testing were performed using the automated methodologies (BD Phoenix® M50 system, Sparks, MD, USA). The rates of MDR bacterial infections prevalence were compared using the Chi-square test p-values <0.05 were considered statistically significant. A comparative analysis of the prevalence and trends of MDR bacteria (including ESKAPE group pathogens) was performed in both sectors: COVID-19 and non-COVID-19 patient ICUs, comparing the correlation coefficient of Pearson during the study period of the two cohorts. All statistical analysis was done using the STATA® software (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP. USA).

Results

In total, 1812 cultures from 1653 patients (28.9% with confirmed diagnosis of COVID-19) were evaluated from nine tertiary urban hospitals (H1 to H9), of which four had ICUs exclusive for attendance of COVID-19 patients, one cardiology hospital, one obstetrics hospital and one cancer hospital (Table 1).

Table 1 Distribution of MDR bacteria (including ESKAPE group) in Nine Tertiary Hospitals of Rio de Janeiro in the COVID-19 era

Variables	Non-COVID-19 (N = 1812)	COVID-19 (N = 524)	p-Value
Clinical specimen			
Blood	317 (24.6)	111 (21.1)	0.1
Urine	495 (38.4)	156 (29.7)	< 0.05
Tracheal aspirate	463 (35.9)	250 (47.7)	< 0.05
Bronchoalveolar lavage	7 (0.5)	5 (0.9)	0.3
Others	5 (0.3)	2 (0.3)	0.8
Units			
H 1 *	317 (24.6)	154 (29.3)	< 0.05
H 2 *	213 (16.5)	98 (18.7)	0.2
H 3 *	211 (16.3)	130 (24.8)	< 0.05
H 4 *	81 (6.2)	46 (8.7)	< 0.05
H 5 ǂ	104 (8)	23 (4.3)	0.1
H 6 Ɣ	60 (4.6)	33 (6.3)	0.1
H 7	78 (6)	7 (1.3)	< 0.05
H 8 Ω	108 (8.3)	16 (3)	< 0.05
H 9	116 (9)	17 (3.2)	< 0.05
Microrganisms			
Acinetobacter baumannii	364 (28.2)	183 (34.9)	< 0.05
Enterobacter aerogenes	3 (0.2)	1 (0.1)	0.4
Enterobacter cloacae	16 (1.2)	2 (0.3)	0.1
Enterococcus faecalis	29 (2.2)	11 (2)	0.7
Enterococcus faecium	27 (2)	3 (0.5)	0.2
Escherichia coli	9 (0.7)	(-)	0.4
Klebsiella oxytoca	15 (1.1)	5 (0.9)	0.6
Klebsiella ozaenae	10 (0.7)	8 (1.5)	0.1
Klebsiella pneumoniae	575 (44.6)	243 (46.3)	0.3
Pseudomonas aeruginosa	182 (14.1)	49 (9.3)	< 0.05
Staphylococcus aureus	58 (4.5)	19 (3.6)	0.5
ESKAPE Microrganisms			
Enterobacter spp	19 (1.4)	3 (0.4)	0.09
MRSA	58 (4.5)	19 (3.6)	0.4
CRKP	575 (44.6)	244 (46.5)	0.4
CRAB	364 (28.2)	183 (34.9)	< 0.05
CRPA	182 (14.1)	49 (9.3)	< 0.05

* Hospitals with intensive care units for the care of patients with COVID-19; ǂ Cardiology hospital; Ɣ Obstetrics hospital; Ω Cancer Hospital

VRE, vancomycin-resistant *Enterococcus;* MRSA, methicillin-resistant *Staphylococcus aureus*; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; CRE, carbapenem-resistant *Enterobacteriaceae*

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Types of infections

The samples analysed were obtained mainly from tracheal aspirate (39,3%), urine (35,9%), blood (23,6%) and bronchoalveolar lavage (0,6%), excluding samples with a high possibility of contamination or colonization (nasal or rectal swabs).

Microorganisms observed

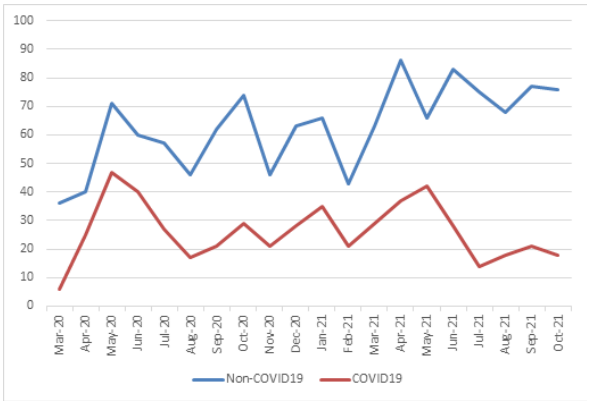
Among the ESKAPE microorganisms, the highest prevalence was for Carbapenem-resistant *Klebsiella pneumoniae* (45.1%) and Carbapenem-resistant *Acinetobacter baumannii* (30.1%) followed by Carbapenem-resistant *Pseudomonas aeruginosa* (12,5%), and Methicillin-resistant *Staphylococcus aureus* (4,2%). Other MDR bacteria observed less frequently were vancomycin-resistant *Enterococcus* spp (3,8%) and other species of Carbapenem-resistant *Enterobacteriaceae* (3,7%).

ESKAPE pathogens in the COVID-19 and Non-COVID-19 ICUs

When comparing the prevalence of ESKAPE bacteria in the two groups, we observed that there were more cases of CRAB in COVID-19 patients (34.9%) than in the ICUs of non-COVID-19 patients (28.2%). On the other hand, the prevalence of CRPA was higher in the ICUs of non-COVID-19 patients (14.1%) than in the ICUs of patients with COVID-19 (9.3%) ($p < 0.05$).

The prevalence of CRKP was slightly higher in the group of patients admitted to the COVID-19 ICUs, but without reaching statistical significance (44.6% vs 46.5%; $p = 0.04$).

In the analysis of the temporal trends of the frequencies of MDR bacteria (including ESKAPE pathogens) in the two sectors of critical patients, a progressive increase in the number of cases of infections by these bacteria was verified, especially in the sector of care for non-COVID-19 patients ($r^2 = 0.4$) when compared to the COVID-19 patient sector ($r^2 = 0.01$) (Graph 1).



Graph 1 Temporal trends in the prevalence of MDR bacteria (including ESKAPE group) in patients from nine tertiary hospitals in Rio de Janeiro 2020-2021 in the COVID-19 era.

Discussion

In our study, using samples of critically ill patients from nine private hospitals in the city of Rio de Janeiro, Brazil (one of the largest cities in Latin America), we showed some changes in bacterial resistance profiles inside the ICUs that treated critical patients with COVID-19 and non-COVID-19. We found significant increases in infections due to MDR bacteria (including those in the ESKAPE group) in both groups of patients.

During the pandemic, great concern has arisen about the inappropriate use of antibiotics and the proliferation of antimicrobial resistance.[10] Although this disease is caused by a virus, some studies suggest that more than 50% of patients hospitalized for COVID-19 may have secondary bacterial infections or superinfections, mainly bacteraemia and urinary tract infections[11,12] and there are no specific guidelines that indicate which is the appropriate antimicrobial therapy.[13]

We observed that the most commonly identified ESKAPE ICU pathogens in our units were *Klebsiella pneumoniae* and *Acinetobacter baumannii*, which accounted for nearly 70% of all ICU MDR pathogens. This fact is possibly related to the greater impairment of lung function in critically ill patients with COVID-19 and the high prevalence of ventilator-associated pneumonia.[14]

In the study of Polly et al, in Brazil, significant differences were also observed in the incidence density of MDR infections when comparing the pre-pandemic and pandemic period, especially in MRSA and CRAB infections. But the prevalence of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) was not analysed in this study.[15]

It was very interesting that in the ICUs of COVID-19 patients there was a lower prevalence of carbapenem-resistant *Pseudomonas aeruginosa*, MRSA, CREs (other than *Klebsiella pneumoniae*) and VRE. Reports from other cities in Brazil, for example São Paulo, showed an increase in VRE in some units.[15]

Another interesting aspect of the behavior of MDR bacteria during the SARS-Cov-2 pandemic was that, unlike what happened in the influenza A (H1N1) pandemic in 2009, where there was an increase in MRSA co-infections,[16,17] in the COVID-19 pandemic, there was an increase in the number of co-infections due to MDR Gram-negative bacteria and fungi.[18,19] Further studies are needed to understand whether it was the previous microbiological environment of the ICUs that amplified this dissemination of MDR bacteria or whether there are specific characteristics in the viral infections that predispose to colonization and infections by certain MDR bacterial groups.

When comparing the prevalence of MDR pathogens from critically ill patients admitted to ICUs to patients with COVID-19, we observed that there was a temporal trend towards an increase in non-COVID-19 sectors and this fact may be related to the shorter of length of hospital stay of the COVID-19 patients (due to the severity and often fatal outcome), which could interfere with periods of colonization necessary before infections. Another possible cause of the progressive increase in bacterial resistance in non-COVID-19 sectors may be related to cross transfer from health-care professionals or due to difficulties in hospital cleaning processes that we had during the pandemic in almost all units due to lack of human resources and shortages of personal protective equipment.

Our study had some limitations. We did not analyse patterns of fungal resistance, which were of significant importance in COVID-19 patients during the pandemic. Additionally, a comparison of antibiotic use (defined daily dose estimation – DDD) was not performed during the study period in the two settings. Another difficulty that we observed in our study was the lack of information in some units in the pre-pandemic period.

Finally, due to the selection pressure that was exerted on MDR bacteria during the pandemic, new challenges in controlling the spread of MDR bacteria must be faced, especially in hospitals that had ICUs for COVID-19 patients. Gaspari et al, in Italy showed that a robust

adherence to hygiene measures decreases the spread of ESKAPE pathogens in the COVID-19 ICUs.[20]

Conclusion

We confirmed an increase in the prevalence of MDR bacteria (including ESKAPE group) in COVID-19 and non-COVID-19 patients in the pandemic. The most commonly identified ESKAPE ICU pathogens in our units were *Klebsiella pneumoniae* and *Acinetobacter baumannii*, which accounted for nearly 70% of all ICU MDR pathogens. We also observed that the indiscriminate use of antibiotics in COVID-19 patients had a cumulative impact on infections of non-COVID-19 patients. Reinforcing and creating new strategies in infection control are necessary to decrease the prevalence of MDR bacteria in the post pandemic period.

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Conflicts of interest

No conflict of interests is declared.

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