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Antimicrobial use assessment in the Intensive Care Unit of a public and reference hospital for COVID-19 in the Federal District

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Abstract

Objective: To compare Intensive Care Unit antimicrobial consumption in previous periods and during the COVID-19 pandemic, to determine the prevalence of bacterial and fungal microorganisms, the prevalence of coinfection and secondary infections, and describe the profile of antimicrobial resistance throughout the pandemic. **Method:** retrospective observational study, from March to December 2020 in a public COVID reference hospital in the Federal District, including adult patients admitted to the ICU and using antimicrobials. Antimicrobial consumption, expressed in DDD/1000 patient-days and according to the AwaRe categorization, were compared before and during the COVID-19 pandemic. Secondary data were obtained through microbiology laboratory reports. The profile of the population was also characterized. For statistical analysis, the Mann-Whitney U test was used to compare the variables in the studied periods. **Results:** in the study were included 137 patients. There was a significant reduction in antimicrobial consumption in the access group Ampicillin/Sulbactam (P=0.035) during the pandemic. In the Watch group, consumption was significantly higher during the pandemic period for the antimicrobials Ceftriaxone and Piperacilian/Tazobactan (P<0.001; P= 0.015, respectively). In the Reserve group, there was a reduction in Polymyxin B during the pandemic period (P=0.029). There was also a significant reduction (P=0.009) of Echinocandins (Anidulafungin/Micafungin). Only 5.43% of patients had coinfection. Of the 731 cultures collected, 67.48% were positive for gram-negative bacteria, 19.51% for gram-positive bacteria and 13.01% for fungi. Among the microorganisms at greatest risk of antimicrobial resistance, the carbapenem-resistant *Klebsiella pneumoniae* species was identified in 100% of blood cultures and urine cultures and in 92% of tracheal secretion cultures; *Acinetobacter spp* species resistant to carbapenems occurred in 90% of blood cultures and in 98% of tracheal secretion cultures. **Conclusion:** the results showed a trend towards increased consumption of broad-spectrum antimicrobials in the Watch group, but with a reduction in consumption for the Reserve group. The high use of antimicrobials prior to ICU admission, associated with a reduced rate of co-infection, suggests the wide empirical use of antimicrobials in patients without proven bacterial infection. This is of concern in the context of the treatment of multidrug-resistant infections.

Key words: Anti-Microbial Agent; COVID-19; Intensive Care Units; Bacterial Infections; Drug Resistance, Microbial; Coinfection

Avaliação do uso de antimicrobianos na Unidade de Terapia Intensiva de um hospital público e referência em COVID-19 do Distrito Federal

Resumo

Objetivo: Comparar consumo de antimicrobianos da Unidade de Terapia Intensiva nos períodos antes e durante a pandemia de COVID-19, determinar prevalência de microrganismos bacterianos e fúngicos, prevalência de coinfecção e infecções secundárias e descrever perfil de resistência antimicrobiana durante a pandemia. **Métodos: e**studo observacional retrospectivo realizado no período de março a dezembro de 2020 em um hospital público de referência de COVID do Distrito Federal, incluindo pacientes adultos internados na UTI e em uso de antimicrobianos. Foram comparados os consumos de antimicrobianos, expressos em DDD/1000 pacientes-dia e de acordo com a categorização AwaRe, antes e durante a pandemia de COVID-19. Os dados secundários foram obtidos por meio de relatórios do laboratório de microbiologia. Realizado ainda caracterização do perfil da população. Para análise estatística, foi utilizado teste de U de *Mann-Whitney* para comparação das variáveis nos períodos estudados. **Resultados:** Foram incluídos no estudo 137 pacientes. Observou-se uma redução significativa de consumo do antimicrobiano do grupo de acesso Ampicilina/Sulbactam (P=0,035) na pandemia. No grupo Vigilância, houve aumento significante no período da pandemia dos antimicrobianos Ceftriaxona e Piperacilina/Tazobactam (P<0,001; P= 0,015, respectivamente). E no grupo Reserva observou-se redução de Polimixina B durante período de pandemia (P=0,029). Houve também uma redução de forma significativa (P=0,009) das

Equinocandinas (Anidulafungina/Micafungina). Apenas 5,43 % dos pacientes apresentavam coinfecção. Das 731 culturas coletadas, 67.48% foram positivas para bactérias gram-negativas, 19,51% para bactérias gram-positivas e 13,01% para fungos. Entre os microrganismos de maior risco de resistência a antimicrobianos, a espécie *Klebsiella pneumoniae* resistente à carbapenêmicos foi identificada em 100% das hemoculturas e culturas de urina e em 92% das culturas de secreção traqueal; a espécie *Acinetobacter spp* resistentes à carbapenêmicos ocorreu em 90% das hemoculturas e em 98% das culturas de secreção traqueal. **Conclusão:** os resultados apontaram um aumento de consumo de antimicrobianos de amplo espectro do grupo de Vigilância, porém com redução de consumo para grupo Reserva. O elevado uso de antimicrobiano prévio a internação em UTI, associado a reduzida taxa de coinfecção sugere ampla utilização empírica de antimicrobianos em pacientes sem infecção bacteriana comprovada. Isto é preocupante no contexto do tratamento de infecções multirresistentes.

Palavras-chave: Agente Antimicrobiano, COVID-19; Unidades de Terapia Intensiva; Infecções Bacterianas; Resistência Microbiana a Medicamentos, Coinfecção

Introduction

At the end of 2019, the World Health Organization (WHO) began to be notified of cases of pneumonia of unknown etiology detected in China. A new coronavirus was soon identified as the cause of the pneumonia cases: the Severe Acute Respiratory Syndrome virus, SARS-CoV-2. Thus, the disease that started in China was designated as Coronavirus 2019 (COVID-19). At the end of January 2020, the WHO declared a public health emergency and in March 2020 defined it as a pandemic[1].

Although many people infected with the coronavirus are asymptomatic or present the disease in its mild form, 20% develop the disease in its severe or critical form, which requires hospitalization and between 3% and 20% of hospitalized people die depending on the severity of the disease[2-4]. Age is the strongest risk factor for severe COVID-19 outcomes, and patients with one or multiple associated comorbidities (especially lung diseases, heart conditions, diabetes, and obesity) are also at greater risk of developing the severe form of the disease[5-7].

Clinical experience with previous viral epidemics suggests risks of bacterial co-infection[8], but since the beginning of the COVID-19 pandemic, experts have been warning about the antibiotic overuse risks[9-10]. Studies of patients hospitalized with coronavirus disease 2019 reveal that some countries have widespread use of antimicrobial therapies as part of a care package[11]. In COVID-19 patients with co-infections, treatment with antimicrobials or antivirals is appropriate, but these patients may be in the minority[12]. The incidence of bacterial co-infection in COVID-19 ranges from 3% to 30%[13-14].

The problem of Antimicrobial Resistance (AMR) is a major global emergency that requires urgent action. With the emergence of the pandemic, concerns about AMR have been reignited, especially by the increased use of antibiotics to treat COVID-19 patients. The main reasons for the antibiotics use in virus-positive patients include the possibility of bacterial co-infections, the difficulty of differentiating COVID-19 from bacterial infections in the early stages of the pandemic, and changes in infection prevention and control practices in overburdened health systems[15]. AMR is expected to cause 10 million deaths a year by 2050[16]. Furthermore, it is likely that AMR has caused more COVID-19 deaths, since studies indicate that bacterial co-infection and secondary infection complicate COVID-19, although data is scarce[17].

In hospital intensive care units (ICUs), a high antimicrobials use is expected due to the severity of the diseases treated and the multiple interventions with patients[18]. Studies carried out in several countries have found an increase in antimicrobial consumption in ICUs during the pandemic[19-21]. Antimicrobials are used empirically, which can lead to long-term resistance. Therefore, monitoring antimicrobial use in the pandemic scenario is crucial to identify evidence of misuse or overuse and reduce indiscriminate use.

This study was conducted with the primary objective of comparing antimicrobial consumption in the ICU of a public hospital in the periods before and during the COVID-19 pandemic. The secondary objectives were to determine the prevalence of bacterial and fungal microorganisms in samples from different cultures, the prevalence of co-infections and secondary infections and to describe the antimicrobial resistance profile.

Methods

Study design, population, and data collection

The retrospective observational study was conducted at a public tertiary care hospital belonging to the Federal District Health Department, which is considered a referral center for the treatment of COVID-19 positive patients.

The population included in the study consisted of adult patients (aged ≥18 years) admitted to the ICU during the period in which care was primarily dedicated to patients with a diagnosis of presumed or confirmed COVID-19 infection (March to December 2020) and who used antimicrobials. Exclusion criteria included patients under the age of 18; with a negative diagnosis for COVID-19 according to laboratory criteria (RT-PCR or TR-Ag Antigen Test with reactive results) or by clinical-imaging criteria defined by the Ministry of Health[22]; and who did not have a clinical indication for the use of antimicrobials.

Data on age, gender, previous comorbidities, length of ICU stay, clinical outcome and presence of infection were collected and used to build a profile of the population.The research was approved by the Ethics Committee of the Foundation for Teaching and Research in Health Sciences/FEPECS/SES/DF, under protocol number CAAE nº 38737420.9.0000.5553, and the Free and Informed Consent Form (FICF) was authorized.

Terminologies and outcomes

All adult patients included in the study were assessed for the presence of bacterial/fungal co-infection on admission, as well as assessed for secondary infection during their hospitalization. The term “co-infection” was used to refer to individuals who were admitted to hospital (1) confirmed to be infected with the

pandemic virus and (2) infected with a community-acquired bacterium or fungus (identified by cultures requested on hospital admission). "Healthcare-associated infection" or "secondary infection" refers to bacterial/fungal infection that occurred in patients at least 48 hours after hospital admission for infection linked to the pandemic virus[23]. For the purposes of this study, Multiple Antimicrobial Resistant Microorganisms (MDROs) were defined as microorganisms resistant to three or more classes of antimicrobials regardless of the mechanism of resistance in a bacterial strain intrinsically susceptible to these classes[24].

The study's primary outcome of interest was to compare antimicrobial consumption. For the calculation, the Defined Daily Dose (DDD) consumption measurement tool was used, expressed in DDD/1000 patient-days, considering the WHO standardization. Antimicrobials were listed according to the Anatomical Therapeutic Chemical (ATC) methodology and the World Health Organization's AWaRe (Access, Watch and Reserve) classification. As established by the WHO[25], the aim of the ATC/DDD system is to serve as a tool for monitoring and investigating medication use, with the aim of improving the quality of consumption. The AWaRe classification describes antimicrobials in three main categories - Access, Surveillance and Reserve - considering the impact of different antimicrobials and different classes on antimicrobial resistance, to emphasize the importance of their rational use[26]. The reference data needed for the evaluation was obtained from the electronic address (https://www.whocc.no/atc_ddd_index/), as well as from the documentary collection of the institution's Hospital Pharmacy and the patient-day figures reported monthly by the Hospital Infection Control Center.

For the secondary outcome, microbiological data from the institution's microbiology laboratory were considered in order to describe the prevalence of microorganisms, as well as to outline the antimicrobial resistance profile and determine the prevalence of co-infection and secondary infections during the period analyzed.

Microbiology

For patients admitted to the ICU, cultures with microbiological growth were considered for diagnostic purposes (urine, blood, and tracheal secretions), thus discarding cultures for surveillance purposes (rectal and nasal swabs). The cultures were sown appropriately on specific media and incubated in a MicroScan Walk-Away automated microbiology system. Positive results were analyzed according to BRCast criteria and subjected to Antibiotic Sensitivity Testing (AST).

Data analysis

The main outcome was to assess whether there was a change in the antimicrobial consumption profile during the pandemic. Data was collected from May 2019 to December 2020, with the period from May 2019 to February 2020 (10 months) being defined as pre-pandemic and the period from March 2020 to December 2020 (10 months) as the pandemic period.

The consumption of each antimicrobial is expressed as DDD/1000 patient-days. The data was compiled in a Microsoft Excel (2016) spreadsheet and analyzed using SPSS (Statistical Package for the Social Sciences), version 23 (IBM Corp., 2015), with two-sided tests and a 5% significance level. Descriptive statistics were used to describe the following variables: categorical variables were presented as frequency distribution and percentages, while numerical variables were presented as mean ± standard deviation (SD).

The quantitative variables were assessed in relation to data distribution using the Shapiro-Wilk test. The null hypothesis of normality of data distribution was rejected for most of them and considering the small sample size, the Mann-Whitney non-parametric U test was used to compare these variables in the periods studied.

Results

Population profile

During the period in which the ICU cared for patients positive for the new coronavirus (March to December 2020), 165 patients were admitted, but 137 were included in the study according to the established criteria. Thus, 28 patients were not considered in the study because they met exclusion criteria: 1 patient under the age of 18, 12 patients with symptoms similar to COVID, but with subsequent laboratory and clinical exclusion of COVID and 15 patients admitted to the ICU without a diagnosis of COVID-19 in a period of transition from ICU care to patients not infected with the new coronavirus.

The mean age of the patients included in the study was 61.49 ± 14 years, of whom 62.04% were male and 37.98% female. Among the most frequent comorbidities, overweight/obesity and heart disease were the most prevalent, with 63.50% and 62.04% respectively, followed by diabetes mellitus (34.31%) and respiratory diseases (16.16%). The mean length of stay was 20.56 ± 17.23 days. After clinical improvement, 29.20% of patients were discharged from the ICU, but 70.80% of hospitalized patients died (Table 1).

Among the patients with COVID-19 and a positive culture for microorganisms, the majority (94.57%) developed a secondary infection and 5.43% already had a community-acquired infection.

Antimicrobial consumption

There was a variation in antimicrobial consumption between the AWaRe classification groups. In the Access group, represented by Ampicillin/Sulbactam, there was a significant reduction in consumption (P=0.035) when comparing the pre-pandemic and pandemic periods (Table 2).

Overall, the Surveillance group showed a trend towards increased use, with significantly higher consumption in the pandemic period for the antimicrobials Ceftriaxone and Piperacillin/Tazobactam (P<0.001; P= 0.015, respectively). On the other hand, the antimicrobials Cefepime, Ertapenem and Levofloxacin, despite showing an increased mean consumption, showed no significant difference between the periods compared (Table 2). In contrast, the anti-infectives Ciprofloxacin, Meropenem and Vancomycin showed a decrease, but only significantly for Meropenem and Vancomycin (P=0.063; P= 0.004, respectively).

The Reserve group showed a reduction in consumption of the antimicrobials Tigecycline and Linezolid compared to the period before the pandemic, and a notable reduction for Polymyxin B

Table 1. Patients admitted to the ICU from March to December 2020 characterization.

Variables	Statistics	Frequency / Mean		
Age	(M | Md | DP)	61,49	61	± 14
Gender				
Male	(freq. | % | IC 95%)	85	62.04%	(53.36% – 70.19%)
Female		52	37.98%	(29.81% – 46.64%)
Previous Comorbidities				
Cardiac Diseases		85	62.04%	(53.36% – 70.19%)
Diabetes Mellitus	(freq. | % | IC 95%)	47	34.31%	(26.41% – 42.90%)
Respiratory Diseases		22	16.16%	(10.35% – 23.30%)
Overweight/Obesity		87	63.50%	(54.85% – 71.56%)
ICU length of stay (days)	(M | Md | DP)	20.56	17	± 17.23
Outcome				
Unit discharge	(freq. | % | IC 95%)	40	29.20%	(21.75% – 37.57%)
Death		97	70.80%	(62.43% – 78.25%)
Infection				
Co-infection	(freq. | % | IC 95%)	5	5.43%	(1.79% – 12.23%)
Secondary infection		87	94.57%	(87.77% – 98.21%)

Source: Prepared by the authors based on electronic medical record data, 2020

Table 2. Association analysis of the consumption of each antimicrobial (DDD-patient/day) in ICU patients comparing the pre-pandemic and pandemic periods.

Antimicrobial (ATC and AWaRe classification)	Pre-pandemic period Median (minimum – maximum)	Pandemic period Median (minimum – maximum)	P*
ACCESS			
J01CR01 - Ampicillin/Sulbactam	192.91 (0.00 – 317.46)	21.72 (0.00 – 930.23)	0.035
WATCH			
J01DE - Cefepime	0.00 (0.00 – 10.00)	0.00 (0.00 – 65.36)	1.000
J01DD - Ceftriaxone	0.00 (0.00 – 8.00)	127.14 (3.88 – 328.80)	<0.001
J01MA02 - Ciprofloxacin	22.76 (0.00 – 74.67)	0.00 (0.00 – 146.34)	0.143
J01DH03 - Ertapenem	0.00 (0.00 – 43.33)	0.00 (0.00 – 73.17)	1.000
J01MA12 - Levofloxacin	14.20 (0.00 – 137.46)	14.91 (0.00 – 436.78)	0.912
J01DH02 - Meropenem	1,033.97 (531.37 – 1,378. 15)	748.64 (305.51 – 1,810.34)	0.063
J01CR05 - Piperacillin/Tazobactam	141.21 (12.00 – 318.13)	304.98 (117.02 – 600.82)	0.015
J01XA01 - Vancomycin_IV	219.06 (74.20 – 464.29)	47.08 (0.00 – 551.72)	0.004
RESERVE			
J01XX09 - Daptomycin	50.22 (0.00 – 303.57)	53.55 (0.00 – 185.10)	1.000
J01XX08 -Linezolid	121.35 (42.40 – 247.90)	106.62 (0.00 – 320.00)	0.579
J01XB02 - Polymyxin-B	385.35 (10.00 – 624.28)	209.77 (65.18 – 505.75)	0.029
J01AA - Tigecycline	106.71 (0.00 – 254.61)	31.62 (0.00 – 579.27)	0.280
Not classifield –ANTIFUNGALS			
J02AA01 - Anphotericin B	0.00 (0.00 – 161.18)	0.00 (0.00 – 0.00)	0.280
J02AC01 - Fluconazole	61.79 (0.00 – 415.22)	13.68 (0.00 – 99.77)	0.190
J02AX- Echinocandins (Anidulafungin/Micafungin)	254.50 (69.00 – 390.00)	62.50 (0.00 – 506.00)	0.009
J02AC03 - Voriconazole	0.00 (0.00 – 53.33)	0.00 (0.00 – 11.43)	0,684

Source: Prepared by the authors based on electronic medical record data, 2020.* Mann-Whitney U test

during the pandemic (P=0.029). There was also a reduction in antifungal consumption during the pandemic, but only significantly (P=0.009) for Echinocandins (Anidulafungin/Micafungin).

Microbiology and resistance profile

In total, excluding surveillance cultures, 731 cultures of interest were requested, of which 67.48% were positive for gram-negative bacteria, 19.51% for gram-positive bacteria and 13.01% positive for fungi (table 3). Gram-negative species were the most identified in the cultures requested, with the *Klebsiella pneumoniae* species present in 24% of blood cultures, 24% of tracheal secretions and 31% of urocultures; the *Acinetobacter spp* species identified in 13% of blood cultures, 26% of tracheal secretions and 8% of urocultures; the Enterobacter spp species identified in 4% of blood cultures, 11% of tracheal secretions and 4% of urocultures; and the *Pseudomonas spp* species present in 4% of blood cultures and 7% of tracheal secretions.

Table 3. Distribution of microorganisms identified in cultures from patients admitted to the ICU from March to December 2020.

Microorganism	Frequency	Percentage	Confidence interval
Gram-negative bacteria	166	67.48%	(62.24% –73.28%)
Gram-positive bacteria	48	19.51%	(14.75% – 25.02%)
Fungi	32	13.01%	(9.07% – 17.86%)

Source: Prepared by the authors based on MicroScan microbiological reports, 2020

Table 4. Microbiological profile per ICU culture sample from March to December 2020.

Isolated microorganisms	Number of microorganisms isolated per type of sample						
	Blood		Tracheal Secretion		Urine		Total
	Nº	%	Nº	%	Nº	%	
Gram-positive bacteria							
Enterococcus spp.	3	4%	1	1%	0	0%	4
Staphylococcus aureus	5	7%	6	4%	0	0%	11
Staphylococcus coagulase-negativa	26	37%	6	4%	0	0%	32
Streptococcus spp.	0	0%	1	1%	0	0%	1
Gram-negative bacteria							
Acinetobacter spp	9	13%	39	26%	2	8%	50
Burkholderia cepacia cplx	0	0%	4	3%	1	4%	5
Citrobacter freundii	0	0%	1	1%	1	4%	1
Enterobacter spp.	3	4%	16	11%	1	4%	20
Klebsiella pneumoniae	17	24%	36	24%	8	31%	61
Proteus mirabilis	0	0%	3	2%	0	0%	3
Pseudomonas spp.	3	4%	10	7%	0	0%	13
Stenotrophomonas maltophilia	0	0%	5	3%	0	0%	5
Serratia marcescens	2	3%	4	3%	0	0%	6
Fungi							
Candida albicans	0	0%	11	7%	9	35%	20
Candida glabrata	1	1%	0	0%	0	0%	1
Candida guilliermond	0	0%	1	1%	0	0%	1
Candida parapsilosis	1	1%	1	1%	0	0%	2
Candida tropicalis	0	0%	4	3%	4	15%	8

Source: Prepared by the authors based on MicroScan microbiological reports, 2020

As for gram-positive bacteria, the most prevalent species was coagulase-negative *Staphylococcus*, present in 37% of positive blood cultures and 4% of tracheal secretion cultures. The next most prevalent species was *Staphylococcus aureus*, which was present in 7% of positive blood cultures and 4% of positive tracheal secretion cultures (Table 4).

The most prevalent fungi were *Candidas Albicans*, identified in 7% of tracheal secretions and 35% of urine cultures, and *Candidas tropicalis*, present in 3% of tracheal secretions and 15% of urine cultures.

Among the microorganisms defined by the World Health Organization as those to be intensively monitored due to alarming resistance to antimicrobials and high treatment costs[27], this study identified the presence of the main batteries: the *Klebsiella pneumoniae* species resistant to carbapenems was identified in 100% of blood cultures and urine cultures and in 92% of tracheal secretion cultures. The carbapenem-resistant *Acinetobacter spp* species was found in 90% of blood cultures and in a higher percentage (98%) of tracheal secretion cultures. The *Pseudomonas spp* species with a multidrug resistance profile was identified in 33% of blood cultures and 41% of tracheal secretion cultures. To a lesser extent, the gram-positive species *Staphylococcus aureus* resistant to methicillin (oxacillin) was identified in 12% of blood cultures and 33% of tracheal secretion cultures (Table 5).

Table 5. Bacterial resistance profile by ICU culture sample from March to December 2020.

Insulated batteries and resistance profile	Resistance rate by cultures		
	Blood	Tracheal Secretion	Urine
Vancomycin-resistant *Enterococcus spp.*	0%	0%	-
Methicillin (oxacillin)-resistant *Staphylococcus aureus*	12%	33%	-
Carbapenem-resistant *Acinetobacter spp.*	90%	98%	100%
Carbapenem-resistant *Klebsiella pneumoniae*	100%	92%	100%
Carbapenem-resistant *Pseudomonas spp.*	33%	41%	0%

Source: Prepared by the authors based on MicroScan microbiological reports, 2020

Discussion

The first case of COVID-19 in Brazil was reported in February 2020 and in the study hospital in March 2020. From February 2020 to the current year, Brazil has confirmed 36,989,373 COVID-19 cases with 698,056 deaths[28]. There was a high proportion of males (62.04%) compared to females (37.98%) and several studies have reported a higher risk of severe illness with COVID-19 in males.[29-30]. Among the main comorbidities identified in the study and reported in the literature, the most prevalent was the presence of overweight/obesity identified in 63.50% of patients, followed by heart disease (62.04%) and Diabetes Mellitus (34.31%). These comorbidities are considered risk factors for developing serious infections[22].

The empirical prescription of antibiotics in hospitalized patients with coronavirus disease 2019 (COVID-19) has been a frequent event since the beginning of the pandemic at the end of 2019[31]. This study found that 100% of the patients included had used at least one antimicrobial regimen prior to being admitted to the ICU, although for the same patients, only 20% requested cultures prior to starting treatment with anti-infectives, highlighting one of the factors that can aggravate the serious problem of antibiotic resistance: empirical use of antimicrobials.

Although most COVID-19 patients were treated with antibiotics on admission at the start of the pandemic, studies have found that bacterial co-infections are uncommon. A cohort study of COVID-19 patients in 38 hospitals in Michigan found that only 3.5% had bacterial co-infections, although 59.5% received antibacterial medications[29]. This was also confirmed in a meta-analysis in which the reported prevalence of coinfections was 3.5%[32].

This study found that only 5.43% of infections were confirmed as co-infections, which is similar to the results in the literature. Most of the patients (67.15%) included in our study developed secondary infections and this result is consistent with another reported literature[32-33]. Possibly the initial clinical uncertainty and discomfort in not taking immediate therapeutic action for patients who continued to show signs of worsening despite supportive care, including ongoing fever, signs of inflammation with progressive hypoxemia, laboratory markers, and/or radiological findings of increasing disease severity, contributed to the inappropriate prescription of antibiotics[34].

When analyzing the consumption profile of each antimicrobial in the Surveillance group, we identified that the variety of antibiotics consumed followed the trend of positive cultures, mostly positive for gram-negative bacteria, and thus allowing adequate coverage for secondary infectious treatment caused by gram-negative microorganisms. The reduction in consumption of the main antimicrobials that provide coverage for the treatment of gram-positive bacteria, such as Linezolid and significantly Vancomycin ($P<0.004$), corroborate the hypothesis of adequate coverage for the treatment of infections caused by gram-negative bacteria. However, the exceptional increase in consumption ($P<0.001$) of the antibiotic Ceftriaxone in the Surveillance group should be highlighted, due to the incentive to use the antibiotic on hospital admission, which had an impact on ongoing consumption in the Intensive Care Unit. This fact was observed in several studies which identified that approximately half of hospitalized patients received Ceftriaxone commonly prescribed in association with azithromycin[35]. This probably reflects difficulties in distinguishing COVID-19 from community-acquired pneumonia.

Following the growing trend of use in the Surveillance group, we observed a significant increase in the consumption of Piperacillin+Tazobactan, and this may also be related to the increase in infections already considered secondary caused by microorganisms from the hospital environment. On the positive side, a reduction, albeit without a significant difference, was observed for broad-spectrum antimicrobials that are widely used in the ICU, such as Meropenem and Ciprofloxacin. These are already the most widely used antibiotics in Brazil, according to a study that included data from ICUs, surgical clinics and pediatrics at a teaching hospital in 2018[36].

A Brazilian study conducted in an ICU evaluating antimicrobial consumption during the COVID-19 pandemic used the AWaRE classification and drew attention to an increase in consumption of antimicrobials in the reserve group [37]. In contrast, our study shows a decrease in consumption in the reserve group, with a significant reduction in Polymyxin B and a non-significant reduction in the other antibiotics in the reserve group. This is a positive point, as the high-priority pathogens on the WHO list, such as non-fermenting MDR Gram-negative bacilli, can only be treated with antibiotics from the Reserve group. The increased consumption of these antibiotics unnecessarily raises concerns about the therapeutic options available for treating infections in the ICU[38].

There was a reduction in the use of antifungal drugs, in particular a significant reduction in the use of echinocandins (Anidulafungin and Micafungin), which are the first line of treatment for candidemia. This reduction is of great importance, as the number of positive cultures for fungi was low and would not justify the high use of antifungals.

Gram-negative microorganisms were the most prevalent (67.48%) in patient infections and this is similarly seen in studies reported in other parts of the world that describe superinfections or secondary bacterial infections[33-34,39]. In our study, we found *Klebsiella pneumoniae*, *Acinetobacter* and *Pseudomonas* species to be the predominant pathogens causing hospital-acquired infections. The *Klebsiella pneumoniae*, *Acinetobacter* isolates already had a high carbapenem resistance profile, >92% and >90%. Many carbapenem-resistant *Acinetobacter* infections (pneumonia, bloodstream among others) tend to occur in patients in intensive care units and are of particular concern because they are often difficult to treat with available antibiotics, as well as increasing length of stay, costs and increasing mortality[35]. The three isolates are real threats to public health that require urgent and aggressive action.

Secondary infections are particularly worrying when caused by microorganisms with multiple resistance, as they lead to more frequent use of broader-spectrum antimicrobial agents, which are considered the last line of treatment. The WHO tool makes it possible to assess antimicrobial consumption according to the classifications of Access, Surveillance and Reservation. The general aim of this tool is to reduce the use of antibiotics in the Surveillance and Reserve groups (considered the most crucial antibiotics for human medicine and with the highest resistance risk) and increase the antibiotics use in the Access group. Evaluating the antimicrobials consumption in the ICU in the periods before and during the pandemic, we observed that the antimicrobial representing the Access group, Ampicillin + Sulbactam, had a significant reduction in its consumption comparing the two periods. Increasing the consumption of antimicrobials in this group will be one of the future focuses of action if we are to achieve the objective proposed by the tool.

This study has some inherent design limitations. For the antimicrobial consumption comparison analysis, a single center with 20 beds and for a short period of time was considered, because after December 2020, the ICU care profile was changed to care for patients who were not carriers of the new coronavirus and COVID-positive patients were transferred to other Intensive Care Units, restricting the number of patients included in the study. An initial view of a health problem with some hypotheses has been presented, but it is not the intention of this study to obtain definitive information on associations between risk factors and health outcomes. Another limitation, all cultures collected for diagnostic purposes were considered, although some may be just colonization and the patients did not receive antibiotic therapy for the pathogen isolated especially considering the urine cultures.

Conclusion

The results obtained show a trend towards increased antimicrobials consumption in the Surveillance group, which includes antimicrobials that are more likely to be a warning of resistance and therefore prioritized as targets for management and monitoring programs. These findings are worrying, since the excessive antimicrobials use in the pandemic, especially those related to the Surveillance and Reserve groups, may reduce the therapeutic options available.

Despite the recommendations for empirical antibiotic therapy in the clinical suspicion of infection in critically ill patients affected by COVID-19, this study suggests that bacterial co-infection in this population is rare. The results obtained in this study helped to elucidate the profile of COVID-19 positive patients who required admission to the ICU and to characterize the variation in antimicrobial consumption patterns according to the three groups of the AWaRe tool. Future studies are needed to measure the impact of increased antimicrobial consumption on the sensitivity profile of microorganisms in the Intensive Care Unit. Even more studies on the real risk factors for bacterial infections in COVID-19 patients are also needed to then determine the rational and guided use of antimicrobials.

With the novel coronavirus pandemic, the threat of antimicrobial resistance is not only present, but has become even more prominent. Therefore, new actions such as the implementation of antimicrobial stewardship programs integrated into infection prevention and control programs are necessary to contain the indiscriminate use of antimicrobials and prevent the spread of multiple resistance microorganisms.

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Conflict of interest declaration

The authors declare no conflicts of interest in relation to this article.

Collaborators

AKSS: Main author of the work, responsible for data collection, interpretation and writing the article. ALS and MRCGN: Supervisors of the work, responsible for the methodological design, structuring and critical review of the work and the article. All the authors approved the final version of the article.

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