Silva LK, Medeiros AF, Figueiró-Souza AF *et al*. Potential impact of COVID-19 on the consumption profile of reserve antibacterials - AWaRe in an intensive care unit of a public hospital. Rev Bras Farm Hosp Serv Saude. 2023;14(2):0896. DOI: 10.30968/rbfhss.2023.142.0896.

RBFHSS
Revista Brasileira de Farmácia Hospitalar e Serviços de Saúde

Original Paper

Open Access

Potential impact of COVID-19 on the consumption profile of reserve antibacterials - AWaRe in an intensive care unit of a public hospital

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Submitted: 28-12-2022 Resubmitted: 25-05-2023 Accepted: 25-05-2023

Double blind peer review

Abstract

Objective: To evaluate the variation in consumption of antibacterials (ATB), listed by the National Health Surveillance Agency, components of the reserve group according to the Access, Watch, Reserve (AWaRe) classification of the World Health Organization (WHO), in an Intensive Care Unit (ICU) of a public hospital. **Method:** This is a quantitative drug utilization study, with retrospective data collection from November/2018 to October/2022. As recommended by the WHO Study Group on Drug Utilization, the Daily Defined Dose (DDD) per 1000 patient-days was used to evaluate the consumption of daptomycin, parenteral linezolid, polymyxin B and E, tigecycline and ceftazidime-avibactam. The DDD were calculated using the WHO standard DDD formula. The analysis period was divided into three phases: pre-pandemic of the COVID-19, acute phase and post-acute phase of the COVID-19 pandemic. The sum of monthly DDD was compared between the three phases. **Results:** In the ICU of the study hospital, there was an increased consumption of daptomycin and tigecycline during the acute phase, and of all the six ATB during the post-acute phase in comparison to the pre-pandemic period. During the post-acute phase, the consumption of daptomycin, linezolid and polymyxin B was higher than the acute phase. The consumption of polymyxin B, polymyxin E and tigecycline was influenced by market instability. The institutional formulary was changed from the acute phase of the pandemic with incorporation of polymyxin E and ceftazidime-avibactam. **Conclusion:** This study identified variations in the consumption of ATB in the reserve group, which may have been influenced by the COVID-19 pandemic. These data can promote the basis for improvements in local ASP to preserve the effectiveness of these drugs, which should be used as the last therapeutic alternative.

Key words: drug utilization; COVID-19; pharmacoepidemiology; antimicrobial stewardship; prescription drug overuse.

Impacto potencial da COVID-19 no perfil de consumo de antibacterianos de reserva – AWaRe em unidade de terapia intensiva de um hospital público

Resumo

Objetivo: Avaliar a variação de consumo de antibacterianos (ATB), monitorados pela Agência Nacional de Vigilância Sanitária (Anvisa), componentes do grupo reserva de acordo com a classificação *Acess, Watch, Reserve* (AWaRe) da Organização Mundial da Saúde (OMS), em Unidade de Terapia Intensiva (UTI) de hospital público. **Método:** Estudo de utilização de medicamentos, do tipo quantitativo, com coleta retrospectiva dos dados, de novembro/2018 a outubro/2022. A Dose Diária Definida (DDD) por 1000 pacientes-dia foi utilizada na avaliação do consumo de daptomicina, linezolida parenteral, polimixinas B e E, tigeciclina e ceftazidima-avibactam. As DDDs foram calculadas utilizando-se a fórmula de DDD padrão da OMS. O período de análise foi dividido em três fases: pré-pandemia da COVID-19, fase aguda e pós-fase aguda da pandemia da COVID-19. Calculou-se a razão entre a soma das DDD mensais nos períodos avaliados. **Resultados:** Na UTI do hospital de estudo houve aumento de consumo de daptomicina e tigeciclina na fase aguda, e de todos os ATB no pós-fase-aguda em relação à fase pré-pandemia. No pós-fase aguda, o consumo de daptomicina, linezolida e polimixina B aumentou em relação à fase aguda. O consumo de polimixina B, polimixina E e tigeciclina nas fases pós-aguda e aguda foi influenciado, também, por instabilidade no mercado farmacêutico. A partir da fase aguda da pandemia, a lista institucional de ATB padronizados passou a incluir polimixina E e ceftazidima-avibactam. **Conclusão:** Identificou-se por meio desse estudo, variações no consumo de ATB do grupo reserva as quais podem ter sido influenciadas pela pandemia da COVID-19. Esses dados podem fundamentar aprimoramentos do PGA local, a fim de preservar a efetividade desses medicamentos, que devem ser utilizados como última alternativa terapêutica.

Palavras-chaves: uso de medicamentos; COVID-19; farmacoepidemiologia; gestão de antimicrobianos; uso excessivo de medicamentos prescritos.

Introduction

During the 20th century, improvements in hygiene conditions, vaccine immunization and antimicrobial (ATM) use on a global scale contributed to the reduction of mortality due to infectious diseases. However, excessive and inappropriate ATM use promotes selective pressure and the development of antimicrobial resistance (AMR), a growing and urgent global health threat[1].

AMR occurs when a microorganism stops responding to an ATM and should be addressed in terms of human health, animal and agricultural production and the environment[1]. In order to help health services around the world to optimize the use of antibacterials (ATB), the World Health Organization (WHO) published an Action Plan to fight AMR and developed the AWaRe classification (Access, Watch, Reserve), in which ATBs are categorized into three groups – Access, Watch and Reserve. The AWaRe classification mainly takes into account the ATBs' potential to induce AMR[2].

In Brazil, the National Health Surveillance Agency (ANVISA) has been promoting initiatives to reduce AMR and improve patient safety in health services[3]. In intensive care units (ICUs), the complexity of the provided care and the high frequency of invasive procedures increase the risk of healthcare-associated infections (HAIs)[4]. Furthermore, factors that are prevalent in ICUs – prolonged hospitalization times and colonization by multidrug-resistant (MDR) microorganisms – have been identified as predictive causes for the occurrence of HAIs[5]. Since 2016, Brazilian hospitals with ICU beds have to monitor and report to ANVISA the consumption of certain ATMs, expressed as Defined Daily Dose (DDD)[3].

DDD is a unit of measurement based on the mean daily maintenance dose of the drug for an adult patient, expressed in grams, considering the main therapeutic indication for that medication. The WHO recommends using DDD as the unit of measurement in medication use studies in order to enable the presentation and comparison of consumption data at the international, national and regional levels[6]. In addition to that, DDD is an indicator required by ANVISA in the evaluation of the monthly consumption of ATM in hospitals with ICU beds for adults. This data is regularly monitored as a risk management indicator that comprises the National Evaluation of Patient Safety Practices in Services with ICUs[3].

On March 11th, 2020, the WHO declared the COVID-19 disease a pandemic. The initial lack of knowledge, overcrowding of health services, absence of initial therapeutic protocols, prolonged hospitalizations, high rates of ICU admissions and excessive ATM prescription for bacterial co-infection prophylaxis, can be related to an increase in the consumption of ATBs, especially for those of broad spectrum, contributing to escalation of AMR[7-9]. A number of studies indicate a much lower incidence rate of secondary infections than the ATB use rate in hospital care during this pandemic, indicating probable misuse of these medications[7-10].

Based on the importance of slowing down AMR development and on the positive aspects of using the AWaRe classification as a support, the current study aims to evaluate the consumption trend of ATBs monitored by ANVISA in an ICU for adults of a public hospital, in three time periods (before the COVID-19 pandemic, COVID-19 pandemic acute phase, and COVID-19 pandemic post-acute phase) through the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) classification.

Methods

This is a quantitative drug utilization study, with retrospective data collection, encompassing the period from November 2018 to October 2022. This historical series was divided into three phases: before the COVID-19 pandemic (from November 2018 to February 2020), COVID-19 pandemic acute phase (from March 2020 to June 2021) and COVID-19 pandemic post-acute phase (from July 2021 to October 2022).

March 2020, when WHO declared the COVID-19 disease as a pandemic, was defined as the beginning of the acute phase[11]. The definition of the onset of the post-acute phase, was based on a study that characterized five phases of the COVID-19 pandemic in Brazil[12], in which the authors listed four transmission indicators published in MonitoraCOVID-19: number of cases, deaths, positivity in RT-PCR tests and vaccination. July 2021, defined as the beginning of the pandemic Phase Four[12], was considered as the start of the post-acute phase of the pandemic in the current study.

The study setting is a general teaching hospital, operating 24 hours, daily, and patients of all clinical profile are attended without regulation by demand. It is located in Belo Horizonte, Minas Gerais, and is a referral center for more than 1.5 million people living in the metropolitan region. It has 392 beds (31 ICU beds and 12 semi-intensive care beds) with a mean of 240 hospitalizations/month. The Hospital Infection Control Committee (HICC) is responsible for the implementation and maintenance of the Antimicrobial Stewardship Program (ASP). It is a reference institution for clinical, surgical, traumatology and non-traumatology emergencies, in addition to providing care to high-, medium- and usual-risk pregnant women. It also has the mission of allying the care activities to good teaching, research and extension practices[13].

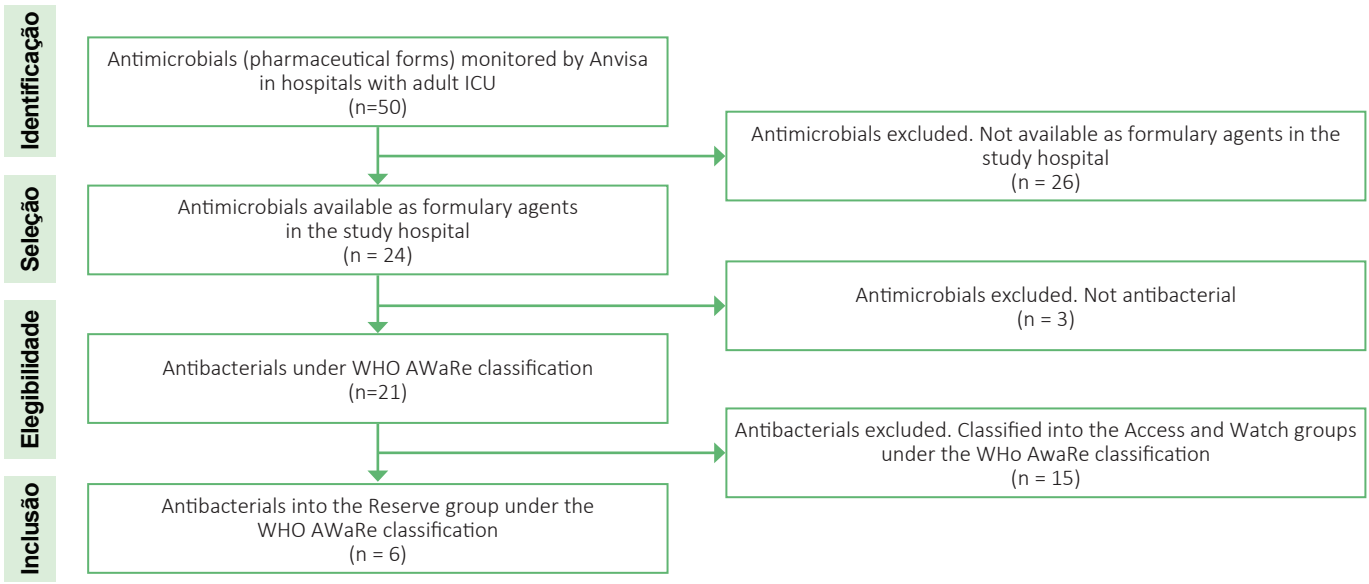
The consumption profile of the ATBs belonging to the List of Priority Medications in Brazilian Adult ICUs monitored by ANVISA[3] and to the Reserve group of the WHO AWaRe classification[2], was evaluated. A total of six drugs were assessed: daptomycin, parenteral linezolid, polymyxin B, tigecycline, ceftazidime-avibactam and colistin, the latter two were incorporated in the drug formulary during the acute phase of the COVID-19 pandemic (Figure 1).

Consumption of these medications was quantified by means of a monthly calculation corresponding to the DDD/1,000 patient-days of each ATB in the adult ICU of this hospital. The WHO standard DDD formula was used (DDD=[(A/B)/P]x1,000); where A: total ATB consumption in the month considered; B: DDD of the ATB (based on ATC code); and P: number of patient-days in the month considered[6].

The reports of consumption of the selected ATBs in the adult ICU were obtained from the MV2000i® hospital management software (from November 2018 to October 3rd, 2021) and the MVSoul® software (from October 4th, 2021, to October 2022). The monthly values of patient-days were obtained through the database provided by the Information Technology team at the study hospital. The ATB consumption comparison was made between the study periods: pre-pandemic phase; acute phase; post-acute phase. The ratios were calculated between the monthly DDD sums in the acute and pre-pandemic phase, the post- acute pandemic phase and pre-pandemic phase, and the post-acute pandemic phase and acute pandemic phase.

The current study was conducted in accordance with the *Strengthening the Reporting of Observational Studies in Epidemiology for antimicrobial stewardship* (STROBE-AMS)[14] guidelines and approved by the Research Ethics Committee (CAAE 54060321.8.0000.5149), and the Informed Consent Term was waived.

Figure 1. Flowchart corresponding to selection of the antibacterials evaluated in the study.



ICU: Intensive Care Unit; WHO: World Health Organization; AWaRe: Access, Watch and Reserve.

Results

Among the six ATBs selected for evaluation in the present study, daptomycin, parenteral linezolid, tigecycline and polymyxin B were available as formulary agents in the institution in the period before the COVID-19 pandemic. In the post-acute phase of COVID-19 pandemic, the six ATBs assessed in the study were available as formulary agents. For all ATBs, significant variability was observed in the DDD/1,000 patients-day values throughout the months under study. However, in general, higher DDD values were recorded during the acute and post-acute pandemic phases in relation to the pre-pandemic period (Figure 2).

In the hospital's ICU there was an increase in the consumption of daptomycin and tigecycline during the acute phase in relation to the pre-pandemic phase, with ratios of 1.36 and 4.16, respectively. During the post-acute phase, consumption of all the ATBs evaluated was higher than the values recorded in the pre-pandemic phase. When comparing ATB consumption in the post-acute phase with the pandemic acute phase, there was an increase for daptomycin (1.43), linezolid (4.37) and polymyxin B (1.29) (Table 1).

In the acute phase, there was a reduction in the consumption of polymyxin B and parenteral linezolid in relation to the pre-pandemic phase (Table 1), and linezolid was not consumed from April 2020 to November 2020 (Figure 2). The consumption of polymyxin B showed variability during the pandemic acute phase, reaching the lowest DDD values in November 2020 (0.00), February 2021 (5.90) and June 2021 (7.94) (Figure 2). The consumption of colistin and tigecycline in the hospital's ICU was lower in the post-acute phase when compared to the pandemic acute phase (ratios of 0.74 and 0.81, respectively) (Table 1). In addition, there was no tigecycline consumption in the last four months evaluated in the post-acute phase (Figure 2).

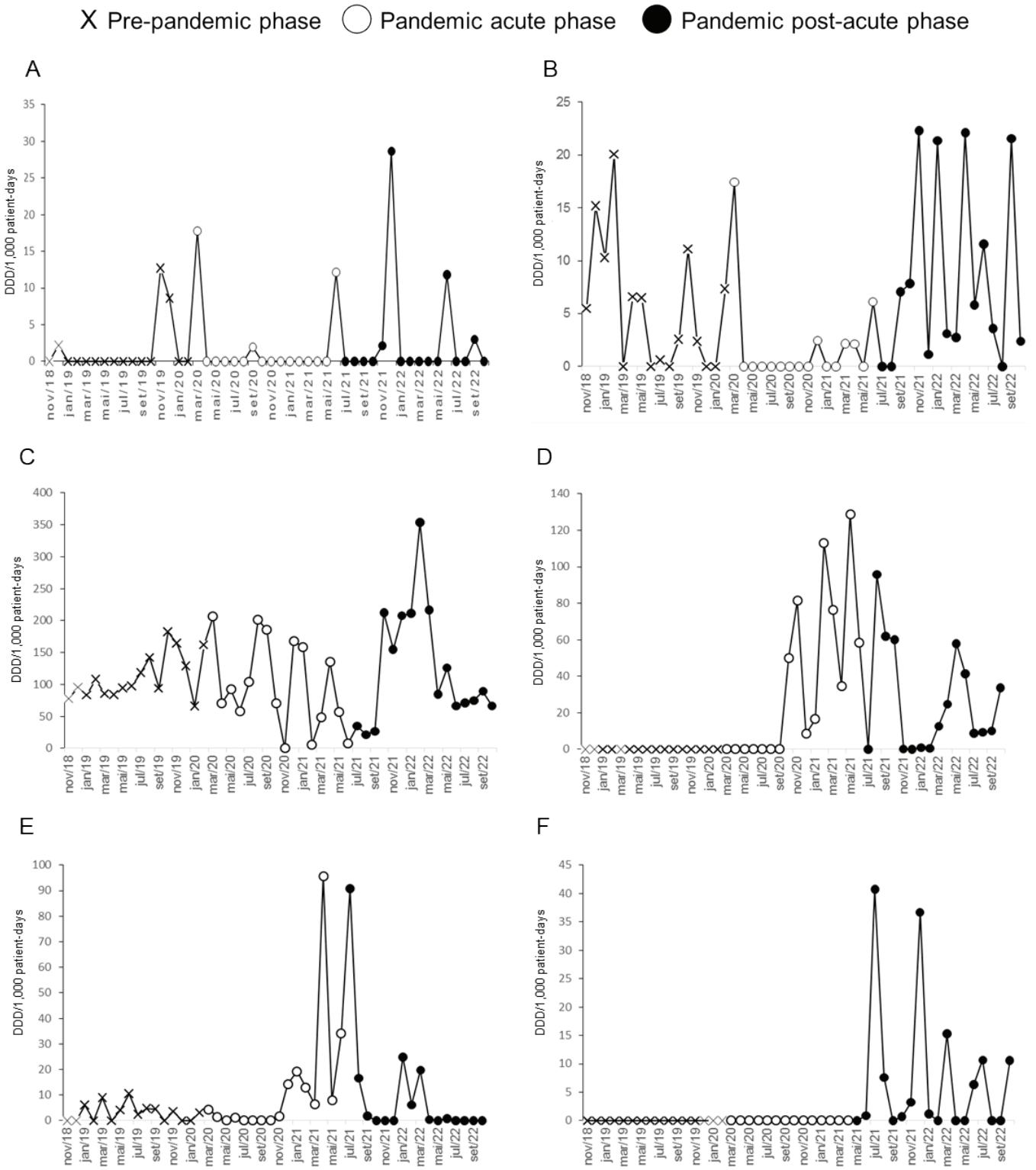
Colistin was listed in the formulary in October 2020, during the pandemic acute phase. Therefore, no comparison with the pre-pandemic phase was made. The ceftazidime-avibactam ATB was listed in the formulary in June 2021 (Figure 2), the last month of the period defined as the pandemic acute phase, making it impossible to compare consumption of this drug between the phases (Table 1).

Table 1. Evolution in the consumption of the antibacterials belonging to the List of Priority Medications in Brazilian adult intensive care units monitored by ANVISA, components of the reserve group according to the WHO AWaRe classification. Belo Horizonte, 2022.

	DDD/1000 patients-day in the period			Consumption ratio between phases		
ATB	**Pre-pandemic phase**	**Acute phase**	**Post-acute phase**	**Acute / Pre-pandemic**	**Post-acute / Pre-pandemic**	**Post-acute / Acute**
Daptomycin	24	32	46	1,36	1,94	1,43
Linezolid	88	30	133	0,34	1,50	4,37
Polymyxin B	1787	1572	2020	0,88	1,13	1,29
Colistin	0[a]	568	418	-[c]	-[c]	0,74
Tigecycline	48	200	161	4,16	3,36	0,81
Ceftazidime/avibactam	0[a]	1[b]	133	-[c]	-[c]	-[c]

ATB: Antibacterial; DDD: Defined Daily Dose. [a]Medication not standardized during the period; [b]Medication standardized in the last month of the period; [c]Comparison not made due to non-consumption during one of the periods.

Figure 2. Evolution in the consumption of antibacterials (A) daptomycin, (B) parenteral linezolid, (C) polymyxin B, (D) colistin, (E) tigecycline and (F) ceftazidime-avibactam, in the ICU of the study hospital in the following COVID-19 pandemic phases: (x) pre-pandemic, (o) acute and (•) post-acute, expressed in DDD/1,000 patient-days/month. ICU: Intensive Care Unit; DDD: Defined Daily Dose. Belo Horizonte, 2022.



Discussion

The present study described the changes in consumption of ATBs of the Reserve group of the WHO AWaRe classification, monitored by ANVISA in the adult ICU of a public teaching hospital between the pre-COVID-19 pandemic period, COVID-19 pandemic acute phase and COVID-19 pandemic post-acute phase. Changes were also observed in the ATBs listed in the drug formulary of the institution. They were necessary to adapt the treatment demands to the availability of medications in the pharmaceutical market throughout the period studied and the occurrence of infections by microorganisms resistant to the options available in the hospital.

The consumption evaluations of certain ATMs, which must be monitored in hospitals with adult ICUs as determined by ANVISA, are part of the national strategy to promote patient safety and reduce AMR spread. Monitoring is based in the DDD method, aiming to correlate ATM consumption with the microorganisms that are isolated in Brazilian ICUs. In this way, it is possible to define targets adapted to the national reality to curb AMR[3]. This strategy is added to the adoption of the AWaRe classification in the Brazilian National List of Essential Medications (RENAME) in 2022[15]. This classification can help ASPs to promote a reduction in ATB consumption in the Reserve and Watch groups and increase the consumption and availability of ATBs from the Access group[2].

Among the ATBs in the Reserve group whose consumption is monitored by ANVISA, polymyxins B and E are frequently indicated in the treatment of severe infections caused by Gram-negative resistant bacteria. These drugs have similar chemical structures, mechanisms of action, resistance patterns and antimicrobial spectrum, but there are pharmacokinetic and pharmacodynamic differences. As clinical implications of these differences, there is inferiority of colistin in reaching, relatively quickly and predictably, the desired plasma concentration, the need for dose adjustment according to renal function, greater interindividual variability in pharmacokinetics and greater nephrotoxicity. These factors corroborate the preferential use of polymyxin B in invasive infections by Gram-negative microorganisms, with the exception of lower urinary tract infections, given renal clearance of the colistimethate prodrug, which is then converted into its active form, colistin, in the urinary tract[16].

In the pre-pandemic period, only polymyxin B was available in the institutional formulary, with increasing consumption of this medication being observed in the institution's ICU. This trend was noticed in adult ICUs from the state of Minas Gerais and in Brazil as a whole, during the 2019-2020 period[17], which may suggest an increase in AMR in national health services, resulting in the need to expand the antibacterial therapy spectrum. During the acute phase of the pandemic, there was certain difficulty to acquire polymyxin B in the Brazilian market[18-19]. This can justify the reduction in consumption of this medication noticed in the ICU of this hospital in relation to the pre-pandemic phase. Faced with therapeutic demand and a very unstable pharmaceutical market, colistin was established as a therapeutic alternative to polymyxin B in October 2020, becoming part of the institutional therapeutic arsenal.

In the post-acute phase of the COVID-19 pandemic, normalization of the polymyxin B stock may have contributed to the increase in its consumption in the hospital ICU and to the reduction in colistin consumption. However, as of April 2022, the institution's HICC, together with the Pharmacy service, restricted the consumption of polymyxin B, which was only dispensed for patients with renal dysfunctions upon prior pharmaceutical evaluation, aiming to prioritize the consumption of colistin. This action plan aimed at avoiding waste, as colistin had stock in the institution and expiration date closer than polymyxin B[20].

The variation in the availability of polymyxins may also have influenced the consumption of tigecycline, a broad-spectrum ATB, with coverage of Gram-positive and negative microorganisms[21]. In the pre-pandemic period, in the ICU of that institution, tigecycline consumption was irregular, with no consumption in several months during the period researched, and lower than the value observed in the acute phase. Similarly, throughout Brazilian adult ICUs, consumption of tigecycline was low in the 2018-2020 period[17], probably due to its restricted indication, given the increased risk of mortality associated with its use and its strategic role in the treatment of infections caused by MDR[21], categorizing it as reserve ATB[2]. In this hospital setting, the low consumption can also be explained by restricted dispensing of this medication, only as culture-guided pharmacotherapy.

However, during the acute phase of the pandemic and with the polymyxin shortage, this restriction was partially suspended. Therefore, an increase in tigecycline consumption was observed in the ICU of the hospital. This change in the institutional protocol was due to the need to use tigecycline as an empirical therapy to treat *Acinetobacter baumannii* infections, whose frequency increased in the institution during 2021 when compared to the values recorded in 2019 and 2020[22]. The strategy of using tigecycline as an alternative to polymyxins was also implemented in an university hospital from South Korea[23]. Another factor that may have contributed to the increase in consumption is the recommendation to use high tigecycline doses as monotherapy for the treatment of *A. baumannii* infections[24]. In addition, an important increase in the incidence of *A. baumannii* infections was observed during the COVID-19 pandemic, both polymyxin- and non-polymyxin resistant[25].

As a result of the reestablishment of polymyxin stocks, in the post-acute phase of the pandemic, in the ICU of the hospital of the study institution there was a reduction in the consumption of tigecycline in relation to the value observed in the acute phase. This is because polymyxins are preferred in the management of *A. baumannii* infections, when compared to tigecycline[24]. During the post-acute phase, tigecycline consumption remained above the values observed in the pre-pandemic phase. The increase in ATB consumption in general has been observed worldwide and different institutions have reiterated the importance of knowing the impact of the pandemic on the use of these medications[7-10]. Tigecycline was not consumed in the institution's ICU during the final months of the period evaluated in this study, which can also reflect the impact of institutional activities for managing ATB use.

In general, the increase in the HAI occurrence risk in the ICU of the hospital[22] exerted an important impact on ATB consumption during the period evaluated. In June 2021, ceftazidime-avibactam was listed in the institutional formulary in the face of an outbreak of a *Serratia marcescens* strain that was extensively resistant to the therapeutic arsenal previously available at that institution. This outbreak can be associated to the high ICU bed occupancy rates and to the use of mechanical ventilators, as a result of the COVID-19 pandemic. During 2020 and 2021, an increase was observed in the incidence density of ventilator-associated pneumonia at the hospital under study[22]. In addition, severely immunocompromised or ill patients are more susceptible to infections by *S. marcescens*[26]. Ceftazidime-avibactam is indicated for the treatment of complicated urinary tract infections, intra-abdominal infections and hospital-acquired pneumonias associated or not with mechanical ventilation, caused by MDR or extensively drug-resistant (XDR) Gram-negative bacteria[27].

As ceftazidime-avibactam became available in the last month of the acute phase of the pandemic, it was not possible to compare consumption of this medication between the periods. During the post-acute phase of the pandemic, there was a trend towards a reduction in the consumption of ceftazidime-avibactam in the ICU of this hospital, which can be related to the reduction in the occupancy rates of ICU beds for COVID-19 patients, thus verifying the effectiveness of vaccination in reducing severe cases[19] and controlling the *S. marcescens* outbreak. Although hospital infection control measures are important for controlling outbreaks, the profile of the institution, the microorganism involved and possible transmission routes should guide the development of specific control measures[28].

With regard to the treatment of infections by MDR Gram-positive bacteria, the available reserve ATBs at the study institution are daptomycin and parenteral linezolid. Linezolid is a bacteriostatic drug with coverage of Gram-positive microorganisms, indicated and approved by the Food and Drug Administration (FDA) for the treatment of skin infections and pneumonia, including cases with bacteremia due to *Enterococcus faecium* and *Vancomycin-resistant E. faecalis* (VRE) and resistant to beta-lactams[29]. In turn, daptomycin is bactericidal, also with coverage for Gram-positive microorganisms and indicated for the treatment of complicated skin and soft-tissue infections, bacteremia and right-sided endocarditis caused by *Methicillin-sensitive Staphylococcus aureus* (MSSA) and *Methicillin-resistant Staphylococcus aureus* (MRSA)[30]. In addition, at the study institution, linezolid and daptomycin are indicated for the treatment of VRE and MRSA infections in patients allergic to glycopeptides such as vancomycin and teicoplanin, as well as in those with renal dysfunction or leukopenic patients.

Consumption of daptomycin and linezolid was increased in the ICUs for adults from the Federal District in the 2019-2020 period[17], as well as in a multicenter retrospective observational study carried out in Swiss hospitals from 2009 to 2019[31], which can be related to an increase in the MRSA infection rates[32]. The COVID-19 pandemic exerted diverse impacts on the incidence of MRSA and VRE infections[33-35]. Although some studies indicated an increase in the incidence of MRSA[34] or VRE[35], others reported a reduction in VRE infections[33-34]. During the pandemic acute phase, in the ICU of the hospital under study there was a reduction in the consumption of parenteral linezolid and an increase in the consumption of daptmoycin. In turn, in the post-acute phase of the pandemic, there was an increase in the consumption of parenteral linezolid and daptomycin in relation to the values recorded in the pre-pandemic and acute pandemic phases. The data suggest that the COVID-19 pandemic influenced consumption of these ATBs, categorized as reserve; however, it is not possible to establish a clear relationship with changes in the AMR profile among the etiological agents that circulate in the adult ICU of the institution. Since reserve group ATBs are used as a last resort in the treatment of MDR infections, they should always be used with caution in order to preserve these important therapeutic alternatives.

In the present study, DDD was used as the ATB consumption measure. This unit is recommended by the WHO Medication Use Study Group. This measure allows obtaining an approximate estimation, adjusted by the bed occupancy rate, in addition to assessing the trends in medication consumption. However, DDD does not necessarily reflect the actual consumption of medications, having as intrinsic limitations the definition of mean daily maintenance doses for the main indication of each medication in adults, considering courses of treatment of more than seven days. ATBs that have their individual therapeutic doses based on type and severity of the infection, weight, age, adjustment by renal function and initial dose higher than the maintenance one may differ from the WHO standard DDD[6].

One of the study limitations is its single-center observational nature, precluding data generalization. As a strength, the current study presents strategies adopted in the face of the weaknesses in the local pharmaceutical assistance imposed by the COVID-19 pandemic. Another relevant aspect was that it evaluated consumption of a reserve ATB (polymyxin B) that is part of the institution's empirical antibacterial pharmacotherapy protocol. As a future perspective, there is a need to correlate the consumption trends with the microorganisms that cause the infections, in order to confirm some hypotheses presented, such as an increase in AMR and local variation of MRSA and VRE infections. The patients' clinical characterization, such as renal function and history of adverse reactions, is also important to confirm some hypotheses.

Conclusion

Consumption of the ATBs evaluated in the study varied across the periods analyzed. This variation did not follow any pattern, precluding generalizing the COVID-19 pandemic as a determinant for the increased consumption of these ATBs. Factors such as the profile of the most frequent microorganisms in the health service, infections outbreaks and drugs availability also influenced the consumption of some of these ATBs. The evaluation of how ATB consumption evolved, considering the AWaRe classification, in addition to assisting in the ASP activities developed at the institution under study, presents relevant data that can contribute to strengthening national strategies to reduce AMR spread and to promote patient safety in health services.

Funding sources

The research did not receive funding for its conduction.

Collaborators

LKOS, AFM, CMB and MAPM participated in project design and in data analysis and interpretation, in addition to writing and critical review of the article. AFFS took part in the critical review of the content. All the people involved approved the final version submitted for publication.

Acknowledgments

To the Risoleta Tolentino Neves Hospital (*Hospital Risoleta Tolentino Neves*, HRTN) for consenting to conducting study in the premises of the aforementioned health unit; to the Federal University of Minas Gerais; to the Minas Gerais Research Support Foundation (*Fundação de Amparo à Pesquisa de Minas Gerais*, FAPEMIG); to the National Council for Scientific and Technological Development (CNPq); and to the Coordination for the Improvement of Higher Education Personnel (*Coordenação de Aperfeiçoamento de Pessoal de Nível Superior*, CAPES)– Brazil.

Conflict of interests

The authors declare that there are no conflicts of interests in relation to this article.

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