JHPHS
Journal of Hospital Pharmacy and Health Services

Original Paper

Open Access

Availability of antimicrobials in a university hospital complex in southeastern Brazil

Giuliana Amanda DE OLIVEIRA[1], Adriano Max REIS[2*]

[1]Hospital das Clínicas da Universidade Federal de Minas Gerais/Empresa Brasileira de Serviços Hospitalares , Belo Horizonte, Brazil;
[2]Department of Pharmaceutical Products, Faculty of Pharmacy, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil.

Corresponding author: Adriano Max Reis, amreis@outlook.com

Submitted: 05-02-2025 Resubmitted: 26-04-2025 Accepted: 29-04-2025

Double blind peer review

Abstract

Objective: This study aimed to determine the profile of antimicrobials available in a university hospital complex in southeastern Brazil . **Methods:** Drug utilization study. Antimicrobials available in clinical practice were identified by researching the Anatomical Therapeutic Chemical (ATC) classification system, The new antimicrobials were identified through research Food and Drug Administration, the European Medicines Agency and the Brazilian National Health Surveillance Agency (ANVISA). The antimicrobials available at the university hospital complex were identified by consulting the hospital drug formulary. Antibacterials were classified according to the WHO AWaRE system. Forgotten antibiotics, defined as old antibiotics, often without patent, used in specific indications that provide treatment for infections of multi-resistant bacteria were identified. **Results:** A total of 301 antimicrobials for systemic use were identified, 20 antifungals, 43 antivirals and 238 antibacterials, 46.2% registered in Brazil and 19.6% available at the university hospital complex. Among antibacterials, 37 were classified as forgotten antibiotics and 21 as new antibacterials. Regarding the ATC classification the available medications were from the following groups: Antibacterials for systemic use (76.3%), followed by antifungals for systemic use (18.6%) and Antivirals for systemic use (5.1%). According to the WHO AWaRE, 21 of the 45 antibacterials available were in the Access group (46.7%), 17 (37.8%) in the Watch group, and 7 (15.5%) in the Reserve group. Concerning the 21 new antimicrobials agents, seven are registered in Brazil and belongs to the Reserve group of AWaRE classification. **Conclusion:** The antimicrobials available at the university hospital complex are predominantly antibacterials belonging to the Access group of the AWaRE classification, as well as several forgotten antibiotics. Antibacterials needed to treat infections caused by multidrug-resistant bacteria are also available. antifungals from different therapeutic classes are also available, but the number of antivirals is low. The incorporation of new antimicrobials into the drug formulary of the university hospital complex was reduced.

Keywords: antimicrobial agents; hospitals; drug resistance

Disponibilidade de antimicrobianos em um complexo hospitalar universitário no sudeste do Brasil

Resumo

Objetivo: Este estudo teve como objetivo determinar o perfil dos antimicrobianos disponíveis em um complexo hospitalar universitário do sudeste brasileiro. **Métodos:** Estudo de utilização de medicamentos. Os antimicrobianos disponíveis na prática clínica foram identificados por meio de pesquisa na classificação Anatômica Terapêutica Química (ATC). Os novos antimicrobianos foram identificados na *Food and Drug Administration*, na *European Medicines Agency* e na Agência Nacional de Vigilância Sanitária (ANVISA). Os antimicrobianos disponíveis no complexo hospitalar foram identificados por meio de consulta ao formulário de medicamentos do hospital. Os antibacterianos foram classificados de acordo com o sistema WHO AWaRE. Os antibióticos esquecidos, definidos como antibióticos antigos, muitas vezes sem patente, usados em indicações específicas que fornecem tratamento para infecções de bactérias multirresistentes, foram identificados. **Resultados:** Foram identificados 301 antimicrobianos de uso sistêmico, sendo 20 antifúngicos, 43 antivirais e 238 antibacterianos, 46,2% registrados no Brasil e 19,6% disponíveis no complexo hospitalar. Dentre os antibacterianos, 37 foram classificados como antibióticos esquecidos e 21 como novos antibacterianos. Em relação à classificação Anatomical Therapeutic Chemical, os medicamentos disponíveis eram dos seguintes grupos: antibacterianos de uso sistêmico (76,3%), seguidos por antifúngicos de uso sistêmico (18,6%) e antivirais de uso sistêmico (5,1%). Segundo a classificação WHO AWaRE, 21 dos 45 antibacterianos disponíveis estavam no grupo acesso (46,7%), 17 (37,8%) no grupo alerta e 7 (15,5%) no grupo reservado . Considerando 21 novos antimicrobianos, sete estão registrados no Brasil e pertencem ao grupo reservado da classificação AWaRE. **Conclusão:** Os antimicrobianos disponíveis no complexo hospitalar universitário são predominantemente antibacterianos pertencentes ao grupo acesso da classificação AWaRE, além de vários antibióticos esquecidos. Antibacterianos necessários para tratar infecções causadas por bactérias multirresistentes também estão disponíveis. Antimicóticos de diferentes classes terapêuticas também estão disponíveis, mas o número de antivirais é baixo. A incorporação de novos antimicrobianos ao formulário de medicamentos do complexo hospitalar universitário foi reduzida.

Palavras-chave: agentes antimicrobianos; hospitais; resistência a medicamentos

CC BY

JHPHS
Journal of Hospital Pharmacy and Health Services

Introduction

Antimicrobial resistance is a significant public health concern, considered by the World Health Organization (WHO) as one of the biggest threats to global health and one of the most daunting challenges of our time[1]. One of the main determinants of antimicrobial resistance is the inappropriate use of antimicrobials agents in healthcare settings[2,3]. The lack of availability and access are equally problematic as they can increase inadequate treatments[4].

Access to antimicrobials is crucial for health systems to respond effectively to emerging threats and achieve universal healthcare. However, ensuring access to antimicrobials is a complex issue and involves scientific, economic, and structural determinants such as research and development, registration, distribution, and proper use, and actions to promote it must be global and integrated[5].

To ensure broad and timely availability of effective antibiotics is one strategy to curbing the development and spread of antimicrobial resistance; this captures both investing in research and development for new antimicrobial and safeguarding continued access to new and existing antimicrobial[6].

Although the research and development of new antimicrobials are decisive actions to combat resistant microorganisms, a significant reduction in the development of new antimicrobials is evident[7]. As a result, the number of new substances in this therapeutic class is still declining. Large pharmaceutical industries have reduced the interest in developing new antibiotics and left the market for medium and small companies. Therefore, public policies are essential to foster the research of new antimicrobials and curb barriers to registering and marketing these drugs[2].

In the global fight against antimicrobial resistance was published the 2024 WHO Bacterial Priority Pathogens List (WHO BPPL). The Who BPPL acts as a guide for prioritizing research and development and investments in antimicrobial resistance, emphasizing the need for regionally tailored strategies to effectively combat resistance.[8] In 2022 was published the WHO fungal priority pathogen list aiming to focus attention and resources priority fungal pathogens to create new treatments, diagnostic tools and infection prevention measures[9].

Besides the increasingly low incidence of new antimicrobials, the non-supported production and supply of old antimicrobials has become a severe issue that limits treatment options for common infections around the globe. Many infections caused by pathogens susceptible to older antimicrobials on the market, with a narrower spectrum and lower toxicity risk, are often treated with more recent medications, thus increasing the possibility of resistant strains. Commercial factors also cooperate for the unavailability of antimicrobials[10].

Investigating the use of antimicrobials in hospitals allows identifying the antimicrobial agents available for prescription, identifying inappropriate use, and providing indicators to evaluate the management programs of these drugs [3]. Infection control actions, rational and antimicrobial use, and incentives for hand hygiene to minimize multi-resistance are also examples of the strategies adopted in health institutions to combat the global health problem of antimicrobial resistance[2] .

Given the above, this study aimed to determine the profile of antimicrobials available in a university hospital complex in a Brazilian southeastern capital.

Methods

This cross-sectional drug utilization study analyzed antimicrobial registration data from 2013 to 2023 available in sites of *U.S. Food and Drug Administration* (FDA), *European Medicines Agency* (EMA), and National Health Surveillance Agency (ANVISA), alongside consumption reports from a university hospital complex in southeastern Brazil. The data collection was conducted from 1st June 2023 to 30 July 2023. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were adopted for this study.

In Brazil, medicines are registered in ANVISA. The Ministry of Health publishes the National List of Essential Medicines (BLEM) through the National Commission for the Incorporation of Technologies in the Unified Health System. BLEM guides drug selection at different care levels. Antibacterials agents were classified in the BLEM 2022 edition per the WHO AWaRE Classification.

The investigated hospital complex is part of a national network of university hospitals. The university hospital complex encompasses two hospitals and five outpatients services . It is situated in southeastern Brazilian capital, has an approximately 500-bed capacity and is a state reference in medium- and high-complexity care in transplants, oncology, hematology, and ophthalmology, among other medical and surgical specialties. The complex hospital is part of the public emergency and urgency network and has an emergency service for treating non-traumatic clinical and surgical cases, in addition to the maternity service being a reference for high-risk births and an emergency ophthalmology service. The Pharmacy and Therapeutic Committee is responsible for update the Drug Formulary of hospital investigated. The selection of antimicrobials to be included in the drug formulary is carried out by The Pharmacy and Therapeutic Committee and The Infection Control Committee. The criteria used for including antimicrobials in formulary encompasses effectiveness, safety, profile of resistence and cost. Regarding antibacterials preferentially is selected from access or watch group of WHO AWaRE system.

Antimicrobials available in clinical practice were identified by researching the Group J Antiinfectives for Systemic Use in the ATC classification on the "WHO Collaborating Centre for Drug Statistics Methodology" website (https://www.whocc.no/atc_ddd_index/).

In the present study were included systemic antimicrobials (J01–antibacterials, J02– antifungals, J05–antivirals) considering Anatomical Therapeutic Chemical -ATC classification on the "WHO Collaborating Centre for Drug Statistics Methodology. Exclusions included antimycobacterials (J04) and specific antiviral subgroups (J05): J05AE–Protease Inhibitors, J05AF–Nucleosides and Nucleotides Reverse Transcriptase Inhibitors, J05AG–Non-nucleosides Reverse Transcriptase Inhibitors, J05AJ–Integrase Inhibitors, and J05AX–Other antivirals.

Antibacterials included in the study were classified according to the WHO AWaRE system published in 2022 in access, watch, or reserve[11]:

Access – Antibacterials listed as first and second options for the empirical treatment of several common or severe infections, usually low-risk, narrow-spectrum agents. The definition of access to these medicines refers to their availability anywhere with quality, dose, duration, formulation, and price[11];

CC BY

JHPHS Journal of Hospital Pharmacy and Health Services

Watch – Antibacterials with a broader spectrum than the access group are at increased risk of toxicity or resistance selection. Thus, they are often monitored to ensure their rational use, and their use for prophylactic animal purposes in animals for food production or even in agriculture is not recommended[11];

Reserve – Antimicrobials considered as a last resort in the treatment of infections. When necessary, they should be accessible, but in specific environments and situations.

Their choice should be grounded on robust clinical evidence rather than empirical treatments. National and international supervision programs monitor the use of these antibacterials. The reserve group also includes newer antibiotics[11].

The new antimicrobials for systemic use registered from 2013 to 2023 were identified through research at site of FDA (https://www.accessdata.fda.gov/), EMA (https://www.ema.europa.eu/en/medicines/), and the Brazilian National Health Surveillance Agency-ANVISA (https://consultas.anvisa.gov.br). Forgotten antibiotics were classified based on Tebano *et al*.[12] and Puccini *et al*.[13], defined as old antibiotics, often without patent, used in specific indications that provide treatment for infections of multi-resistant bacteria.

The antimicrobials available at the university hospital complex were identified by consulting the university hospital complex drug formulary and researching computerized consumer reports of hospital .

The database was developed in Excel software, and statistical analysis was performed through the SPSS version 25.0 software, determining frequencies and proportions.

Lastly, there was no need to seek approval by the Research Ethics Committee, given that the research was with administrative databases, whose information is aggregated and without individual identification (Resolução 510, Conselho Nacional de Saúde). The research management unit of the investigated institution approved access to the data and authorized the research.

Results

We identified 301 antimicrobials for systemic use, 20 antifungals (J02), 43 antivirals (J05), and 238 antibacterials (J01). Among antibacterials, 37 were classified as forgotten antibiotics and 21 as new antibacterials. Figure 1 shows a flowchart of antimicrobial identification.

Regarding availability in Brazil, 139 (46.2%) of the 301 antimicrobials identified were registered with ANVISA, 46 (15.3%) were found in the BLEM, and 59 (19.6%) were available at the hospital complex. Regarding inclusion in the pharmaceutical formulary, 57 were standardized, and 2 antibacterials (levofloxacin and ceftazidime + avibactam) were not standardized in the hospital complex, although they were available for use at the institution.

Table 1 presents the 59 antimicrobials identified in the hospital complex according to the ATC classification. Group drugs J01 – Antibacterials for systemic use corresponded to 76.3% of antimicrobials, J02 – antifungals for systemic use 18.6%, and J05 – Antivirals for systemic use 5.1%.

The pharmacological subgroups of antibacterials with the highest proportions of medications available in the hospital complex were J01D - Other beta-lactams (26.7%); J01C - beta-lactams (13.3%); J01X - Other antimicrobials (17.8); J01F - Macrolides, lincosamides, and streptogramins (8.9%) and J01M – Quinolones (8.9%) (Table 1).

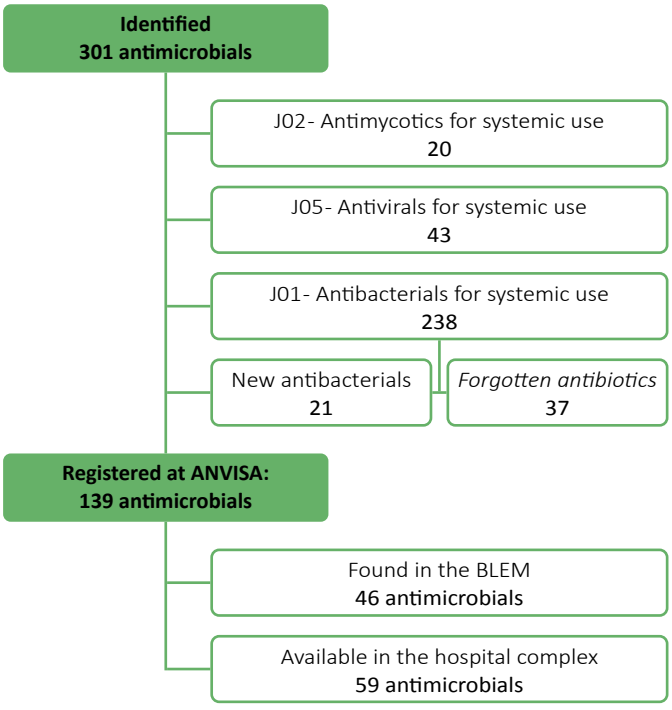
The antifungals for systemic use included medications from all ATC pharmacological groups, with a mean of three drugs per group, except imidazole derivatives, which contained only one. On the other hand, the systemic antivirals available were from only two groups (J05AB – Nucleosides and nucleotides and J05AH – Neuraminidase inhibitors) (Table 1).

According to the WHO AWaRE classification, 21 of the 45 antibacterials available were in the Access group (46.7%), 17 (37.8%) in the Watch group, and 7 (15.5%) in the Reserve group. Table 2 shows the antibacterials available at the hospital complex according to the AWaRE classification.

Twenty three of the 37 Forgotten antibacterials identified in the study are registered with ANVISA, while eight are found in the BLEM, and 14 are available at the hospital complex for consumption. Table 3 presents the list of these antibacterials and where they are registered and inserted in the national context and the institution investigated.

Seven (33.3%) of the 20 new antimicrobials are registered with ANVISA, and only 1 (4.7%) is available for consumption at the hospital investigated and belongs to the Reserve group of the AWaRE classification. Table 4 shows the availability of new antibacterials by medicines agency where are registered.

Figure 1. Antimicrobial identification flowchart



CC BY

JHPHS Journal of Hospital Pharmacy and Health Services

Table 1. ATC Level 4 classification of antimicrobials for systemic use available at the investigated hospital complex

Classification	Drugs	N	%
J01 Antibacterials for systemic use		**45**	**76.3**
J01A Tetracyclines			
J01AA – Tetracyclines	Doxycycline, tigecycline		
J01B Amphenicols			
J01BA – Amphenicols	Chloramphenicol		
J01C Beta-lactam antibacterials, penicillins			
J01CA – Penicillins with extended spectrum	Amoxicillin, ampicillin		
J01CE – Beta-lactamase sensitive penicillins	Potassic benzylpenicillin, benzathine benzylpenicillin, procaine + potassic benzylpenicillin		
J01CF – Beta-lactamase resistant penicillins	Oxacillin		
J01CR – Combinations penicillins + beta-lactamase inhibitors	Ampicillin + sulbactam, piperacillin + tazobactam, amoxicillin + clavulanic acid		
J01D Other beta-lactam antibacterials			
J01DB – First-generation cephalosporins	Cefadroxil, cefalexin, cefalotin, cefazolin		
J01DD – Third-generation cephalosporins	Cefotaxime, ceftazidime, ceftriaxone, ceftazidime + avibactam		
J01DE – Fourth-generation cephalosporins	Cefepime		
J01DF – Monobactams	Aztreonam		
J01DH – Carbapenems	Ertapenem, meropenem		
J01E Sulfonamides and trimethoprim			
J01EC – Intermediate-acting sulfonamides	Sulfadiazine		
J01EE – Combinations of sulfonamides and trimethoprim	Sulfamethoxazole + trimethoprim		
J01F Macrolides, lincosamides, and streptogramins			
J01FA – Macrolides	Azithromycin, erythromycin, clarithromycin		
J01FF- Lincosamides	Clindamycin		
J01G Aminoglycosides			
J01GA – Streptomycins	Streptomycin		
J01GB – Other aminoglycosides	Amikacin, gentamicin		
J01M Quinolones			
J01MA – Fluoroquinolones	Ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin		
J01X Oher antibacterials			
J01XA – Glycopeptides	Teicoplanin, vancomycin		
J01XB – Polymyxins	Colistimethate, Polymyxin B		
J01XD – Imidazole derivatives	Metronidazole		
J01XE – Nitrofuran derivatives	Nitrofurantoin		
J01XX – Other antibacterials	Daptomycin, linezolid		
J02 antifungals for systemic use		**11**	**18.6**
J02AA – Antibiotics	Amphotericin B, liposomal amphotericin B, amphotericin B lipid complex		
J02AB – Imidazole derivatives	Ketoconazole		
J02AC – Triazole and tetrazole derivatives	Fluconazole, itraconazole, voriconazole		
J02AX – Other antifungals for systemic use	Anidulafungin, caspofungin, micafungin		
J05 Antivirals for systemic use		**3**	**5.1**
J05A Direct-acting antivirals			
J05AB – Nucleosides and nucleotides	Aciclovir, ganciclovir		
J05AH – Neuraminidase inhibitors	Oseltamivir		

CC BY

JHPHS
Journal of Hospital Pharmacy and Health Services

Table 2. Table of antibacterials for systemic use according to AWaRE classification available at the investigated university hospital complex

Access	Watch	Reserved
Amikacin	Azithromycin	Aztreonam
Amoxicillin	Cefepime	Colistimethate sodium
Amoxicillin + clavulanic acid	Cefotaxime	Ceftazidime + avibactam
Ampicillin	Ceftazidime	Daptomycin
Ampicillin + sulbactam	Ceftriaxone	Linezolid
Benzathine benzylpenicillin	Ciprofloxacin	Polymyxin B
Potassic benzylpenicillin	Clarithromycin	Tigecycline
Procaine benzylpenicillin + potassic benz.	Erythromycin	
Cefadroxil	Ertapenem	
Cefalexin	Streptomycin	
Cefalotin	Levofloxacin	
Cefazolin	Meropenem	
Clindamycin	Moxifloxacin	
Chloramphenicol	Norfloxacin	
Doxycycline	Piperacillin + tazobactam	
Gentamicin	Teicoplanin	
Metronidazole	Vancomycin	
Nitrofurantoin		
Oxacillin		
Sulfadiazine		
Sulfamethoxazole + trimethoprim		

Table 3 . *Forgotten antibiotics* available in Brazil and at the investigated university hospital complex

Drug	Registration in Brazil	Included in the BLEM	Available at the Hospital Complex
Fusidic acid	■		
Ampicillin + sulbactam	■		■
Aztreonam	■		■
Benzathine benzylpenicillin	■	■	■
Potassic benzylpenicillin	■	■	■
Procaine benzylpenicillin*	■	■	■
Cefepime	■		■
Cefoperazone + Sulbactam			
Cefoxitin	■		
Cefpodoxime	■		
Ceftibuten			
Chloramphenicol	■	■	■
Cloxacillin oral	■		
Cloxacillin IV	■		
Colistin **	■		■
Dicloxacillin			
Ertapenem	■		■
Spectinomycin	■		
Phenoxymethylpenicillin	■		
Flucloxacillin			
Fosfomycin oral	■		
Fosfomycin parenteral			
Methenamine			
Mecillinam			
Nafcillin			
Nitrofurantoin	■	■	■
Oxacillin	■	■	■
Pivmecillinam			
Polymyxin B	■		■
Pristinamycin			
Quinupristin + Dalfopristin			
Trimethoprim ***	■	■	■
Teicoplanin	■		■
Thiamphenicol			
Temocillin			
Ticarcillin			
Tobramycin	■	■	

* Fixed-dose association combined with benzylpenicillin potassium
** In the form of colistimethate sodium
*** Fixed dose association combined with sulfamethoxazole

■ Yes ☐ No

CC BY

JHPHS Journal of Hospital Pharmacy and Health Services

Table 4. New Antimicrobials Registered from 2013 to 2023 by Medicines Agencies

Drug	ATC Level 4	Registration year			Main activity spectrum
		FDA	EMA	ANVISA	
Brincidofovir	J05AB17	2021	2013	-	Human smallpox virus
Cefiderocol	J01DI04	2019	2020	-	ESBL-E, AmpC, CRE (KPC, OXA, MBL), MDR *Pseudomonas aeruginosa*, MDR *Acinetobacter baumannii*, MDR *Stenotrophomonas maltophilia*
Ceftazidime + avibactam	J01DD52	2015	2016	2018	ESBL-E, AmpC, CRE (KPC, OXA-48), MDR *Pseudomonas aeruginosa*
Ceftobiprole medocaril	J01DI01	-	-	2022	KPN; AmpC
Ceftolozane + tazobactam	J01DI54	2014	2015	2018	ESBL-E, AmpC, MDR *Pseudomonas aeruginosa*
Dalbavancin	J01XA04	2014	2015	-	MRSA, *Streptococcus ssp*
Delafloxacin	J01MA23	2017	2019	2020	MRSA, *Streptococcus pneumoniae*, *Streptococcus ssp*, ESBL-E, *Pseudomonas aeruginosa*
Eravacycline	J01AA13	2018	2018	-	MRSA, *Streptococcus ssp*, VRE, ESBL-E,d AmpC,d CRE (KPC, MBL), MDR *Acinetobacter baumannii*, MDR *Stenotrophomonas maltophilia*, NTM
Ibrexafungerp	J02AX07	2021	-	-	*Candida albicans*
Isavuconazole	J02AC05	2015	2015	2019	*Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger, Rhizopus oryzae, Mucormycetes ssp*
Imipenem + cilastatin + relebactam	J01DH56	2019	2020	-	ESBL-E; AmpC; CRE (KPC); MDR *Pseudomonas aeruginosa*
Lefamulin	J01XX12	2019	2020	-	MRSA, *Streptococcus pneumoniae*, *Streptococcus ssp*, DRNG
Meropenem + vaborbactam	J01DH52	2017	2018	-	ESBL-E; AmpC; CRE (KPC)
Omadacycline	J01AA15	2018	-	-	MRSA, *Streptococcus pneumoniae*, *Streptococcus ssp*, VRE, ESBL-E,d AmpC, CRE (KPC), MDR A baumannii, MDR S maltophilia, NTM
Oritavancin	J01XA05	2014	2015	-	MRSA, *Streptococcus ssp*, VRE
Oteseconazole	J02AC06	2022	-	-	*Candida ssp.*
Peramivir	J05AH03	2014	-	-	Influenza A Virus
Plazomicin	J01GB14	2018	-	-	MRSA; ESBL-E; AmpC; CRE (KPC, OXA)
Remdesivir	J05AB16	2020	2020	2021	SARS-CoV-2
Rezafungin	J02AX08	2023	-	-	*Candida albicans, Candida glabrata, Candida parapsilosis, Candida tropicalis*
Tedizolid	J01XX11	2014	2015	2017	MRSA, *Streptococcus pneumoniae*, *Streptococcus ssp*, VRE, MDR *Mycobacterium tuberculosis*

Abbreviations: AmpC, β-lactamase-producing bacteria; BLI, β-lactamase inhibitor; CRE, carbapenem-resistant Enterobacterales; DRNG, drug-resistant *Neisseria gonorrhoeae*; ESBL-E, extended-spectrum β-lactamase-producing Enterobacterales; KPC, *Klebsiella pneumoniae* carbapenemase; MBL, Metallo-β-lactamase; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; OXA, oxacillinase; VRE, vancomycin-resistant enterococci.

Discussion

The main antibacterials included in the AWaRE classification and the forgotten antibiotics are available at the university hospital complex investigated. Antibacterials required for treating infections caused by multidrug-resistant pathogens (MDRP) are also available. Furthermore, the incorporation of new antimicrobials into the hospital's drug formulary was small.

Optimizing the use of antimicrobials is one of the WHO's strategic objectives, according to the "WHO Global Action Plan on Antimicrobial Resistance", which addresses several resources to combat antimicrobial resistance[14].In this sense, the WHO published the AWaRE classification in 2017, a tool built with expert consensus based on the antibacterial action spectrum, the anticipated risk of developing resistance, the toxicity risk, and clinical utility. The list has been revised and updated since then. It aims to use antibacterials from the Access group as the first line of treatment when possible and reduce the use of items from the Watch and Reserve groups, which pose a greater risk of selecting resistant strains so that they are only used in situations where they are indicated[15].

A systematic review investigating the relationship between exposure to AWaRE antibacterials, and the isolation of multi-resistant bacteria showed that the use of watch and reserve antibacterials is more likely to contribute to resistance than access antibacterials, corroborating the relevance and applicability of classification as a global strategy to combat bacterial resistance[15].

CC BY

The availability pattern of AWaRE antibacterials in the investigated university hospital complex, with more access antibacterials and fewer Watch and Reserve drugs, aligns with WHO guidelines. This standard facilitates implementing the AWaRE classification as an instrument for improving the quality of antibacterial prescriptions in the hospital complex, which would be a relevant strategy for improving the management of antimicrobials in the institution. Nevertheless, we can infer that selecting antimicrobials for inclusion in the investigated institution's formulary is based on scientific evidence and national and international guidelines[16]. Another point of the present study is that antibiotics are relevant in treating various infections, with a cost often more affordable due to patent loss, which improves access in low- and middle-income countries to treat bacterial infections.

In Brazil, around 50% of these medicines are registered with ANVISA, but availability in the university hospital complex studied and in the National List of Essential Medicines (BLEM) is lower. It is important to highlight the availability of forgotten antibiotics of great relevance in clinical practice at the institution, such as colistin, polymyxin B, ceftriaxone, oxacillin, and benzylpenicillins. A critical gap regarding the availability of forgotten antibiotics is parenteral fosfomycin, which applies to several infections caused by multidrug-resistant bacteria[13,17]. However, it is not found in Brazil because the price is not attractive to pharmaceutical industry. Actions to ensure availability of antimicrobial that meet public health and patient needs should be developed by health authorities[5,6].

The shortage of forgotten antibiotics is an issue in Brazil, Europe, and the USA, threatening effective antimicrobial management program actions. The outpatient and hospital levels were severely affected by the shortage of benzathine benzylpenicillin, for example, compromising the control of neonatal syphilis in Brazil from 2013 to 2017[18].

Clinical studies to expand the evidence on the effectiveness and optimizing the use of forgotten antibiotics have been developed in recent years[13,17]. It is crucial to ensure the availability of these medicines in the countries' pharmaceutical market to incorporate this scientific knowledge into clinical practice, avoiding shortages. Actions that ensure availability and access to these antibacterials avoid changes to drug formularies and treatment guidelines due to prolonged shortages, contributing to keeping them among the drugs prescribed in clinical practice [13,17]. Public-private partnerships may be used to produce forgotten antibiotics contributing to ensure access to these medicines.

The Infectious Diseases Society of America (IDSA) has created a guide that lists the antibacterials necessary to treat resistant gram-negative infections. Most antibacterials recommended in this guide are available at the hospital investigated [19].However, only ceftazidime + avibactam is available at the hospital among the new beta-lactams mentioned in the guide and sold in Brazil. Fosfomycin, eravacycline and plazomicin are unavailable because they are not registered with ANVISA and minocycline are not included in the drug formulary of hospital complex.

Another major issue in the hospital setting is the increase in multidrug-resistant gram-positive pathogens, particularly pathogens on the WHO list of priorities for developing new antibiotics, such as methicillin-resistant Staphylococcus aureus and vancomycin-resistant Enterococcus faecium, resulting in significant morbidity and mortality[8,20]. The current first-choice treatment for these infections is vancomycin or daptomycin, available at the hospital, and no new antibacterial has been explicitly identified to combat multidrug-resistant gram-positive microorganisms[2,] . Based on the spectrum of action of available medications, we can infer that the treatment of several infections is not compromised despite the low incorporation of new antibacterials at the hospital.

There has also been a significant increase in fungal infections, mainly attributed to immunocompromised patients due to neoplasms, organ transplants, autoimmune diseases, and the use of catheters and prostheses[20]. However, there has been minimal progress in developing new antifungals in recent decades [21].

After the approval of isavuconazole in 2015 by the FDA, new antifungals (ibrexafungerp, oteseconazole, and rezafungin) were authorized for sale from 2021, but at moment only isavuconazole has been registrated in Brazil. The therapeutic arsenal of antifungals of the hospital complex investigated includes echinocandins for the treatment of invasive candidiasis, voriconazole for invasive aspergillosis, besides other triazoles and polyenes, providing an appropriate approach to the most prevalent systemic mycoses.

In this sense, we should underscore the unavailability of flucytosine. WHO considers it an essential medicine, without patent and with high clinical value for treating cryptococcal meningitis, evidenced in a high-quality clinical trial published in 2018 [21]. Furthermore, it is also indicated in combination with other drugs to treat infections caused by pathogens such as resistant Candida spp and other rare fungi[20] . However, sales in Brazil were interrupted in the 1990s by decision of the exclusive manufacturer. Shortages of flucytosine oral and parenteral pharmaceutical forms are also frequently reported in Europe, South America, Asia, and Africa[22,23].

As with forgotten antibiotics, effective public policies are essential to ensure the availability of flucytosine in different regions of the world. However, the actions developed by non-governmental organizations such as Médecins Sans Frontières (MSF) and Global Action for Fungal Infections (GAFFI) have been insufficient to promote its replenishment in the pharmaceutical market[22] .

Antivirals and searching for new substances to treat infections have gained significant visibility, especially since the COVID-19 pandemic. There was significant control of the epidemic by introducing vaccines and other new therapies. However, the emergence of variants and increased virus transmission rates resume concern about these microorganisms[24].

Besides developing tools for classifying and better using existing antimicrobials, encouraging research on new substances, and other strategies, knowing the profile of antimicrobials available at different health institutions can also guide decisions about antimicrobial therapy guidelines.

The investigated university hospital complex is a reference unit for oncology, hematology, and transplants, which determines the profile of antifungals and antivirals available for prescription. The incorporation of new antivirals in Brazil only covered medicines for treating influenza and COVID in recent years.

The hospital's antibacterial profile aligns with the findings of a systematic review of studies on antimicrobial use in Brazil[25]. The available antimicrobials allow the prescriber to treat the most prevalent infections at the institution, considering the infection's clinical aspects and the patient's clinical specificities in the decision-making process for prescribing antibacterials.

CC BY

JHPHS
Journal of Hospital Pharmacy and Health Services

The appropriate use of antimicrobials is an essential indicator of the quality of healthcare and patient safety, and efficient management of these medications can optimize clinical outcomes and reduce adverse events, besides preventing and controlling the increase in antimicrobial resistance. In this sense, the present antimicrobial availability study provided essential elements to promote the updating of antimicrobial selection, infection treatment guidelines, and other antimicrobial management program actions. It highlighted the relevance of government actions to ensure access to antimicrobials in the countries, aiming to avoid inappropriate use that can contribute to the emergence of antimicrobial resistance[4-6] .

Potential solutions to issue of access of antimicrobials encompassing but not limited to increased awareness, improvement in healthcare infrastructure, models for sustained manufacturing and supply chains. Besides, improving antimicrobial stewardship at hospital, empowering healthcare professionals, and emphasizing infection prevention are crucial [4-6,26]. The AWaRe (Access, Watch, Reserve) classification of antibacterial is also one strategy to improve access to appropriate treatment and reduce inappropriate use of antibiotics[11,15].

The countries should incentivize research and development of newer antimicrobials working closely with World Health Organization to ultimately ensure access to treatment. Greater innovation and investment are also required in epidemiological and operational research to mitigate antimicrobial resistance[4-6,26] .

The applications in care practice highlight the crucial points of the study conducted. However, it has some limitations, such as being performed in a single highly complex hospital in the Brazilian southeast, which prevents generalizations to institutions in other regions and different complexity levels. Another limitation is the identification of new antimicrobials researched only at ANVISA, EMA, and FDA. However, the possibility of under-identification is reduced, as most new medicines are initially registered with the FDA.

Conclusion

The antimicrobials available at the university hospital complex are predominantly antibacterials belonging to the Access group of the AWaRE classification, besides several forgotten antibiotics. Antibacterials needed to treat infections caused by multidrug-resistant bacteria are also available. antifungals from different therapeutic classes are also available, but the number of antivirals is low. The incorporation of new antimicrobials into the drug formulary of the hospital complex was reduced.

The timely availability of antimicrobials in hospital contribute to mitigate antimicrobial resistance and achieve better health and economic outcomes. Supporting innovation and ensuring sustained access to effective antimicrobail are uppermost for addressing amtimicrobial resistence .

CC BY

References

1. World Health Organization. Antimicrobial resistance. Available from: https://www.who.int/health-topics/antimicrobial-resistance. Accessed Apr 26, 2025.
2. Kinch MS, Kraft Z, Schwartz T. Antibiotic Development: Lessons from the Past and Future Opportunities. Pharm Res. 2024;41(5):839-848. doi:10.1007/s11095-024-03694-2
3. Anhøj J, Boel J, Olesen BR, et al. Analysis of antibiotic use patterns in Danish hospitals 2015-2021 using an adapted version of the who aware classification. BMJ Open Qual. 2022;11(4):e002098. doi:10.1136/bmjoq-2022-002098
4. Kållberg C, Årdal C, Salvesen Blix H, et al. Introduction and geographic availability of new antibiotics approved between 1999 and 2014. PLoS One. 2018;13(10):e0205166. doi:10.1371/journal.pone.02051665.
5. Ren M, So AD, Chandy SJ, et al. Equitable Access to Antibiotics: A Core Element and Shared Global Responsibility for Pandemic Preparedness and Response. J Law Med Ethics. 2022;50(S2):34-39. doi:10.1017/jme.2022.776.
6. Organised by: European Observatory on Health Systems and Policies; Chair persons: Dimitra Panteli (Belgium), Elias Mossialos (UK). 10.B. Workshop: Combatting AMR: European collaboration to ensure sustained access to effective antibiotics. Eur J Public Health. 2023;33(Suppl 2):ckad160.639. doi:10.1093/eurpub/ckad160.639
7. Schulz LT, Kim SY, Hartsell A, Rose WE. Antimicrobial stewardship during a time of rapid antimicrobial development: Potential impact on industry for future investment. Diagn Microbiol Infect Dis. 2019;95(3):114857. doi:10.1016/j.diagmicrobio.2019.06.009.
8 Sati H, Carrara E, Savoldi A, et al. The WHO Bacterial Priority Pathogens List 2024: a prioritisation study to guide research, development, and public health strategies against antimicrobial resistance. Lancet Infect Dis. doi:10.1016/S1473-3099(25)00118-5
9 World Health Organization. WHO fungal priority pathogens list to guide research, development and public health action. World Health Organization; 2022 . Available from: https://www.who.int/publications/i/item/9789240060241 Accessed Apr 26, 2025.
10 Tängdén T, Pulcini C, Aagaard H, et al. Unavailability of old antibiotics threatens effective treatment for common bacterial infections. Lancet Infect Dis. 2018;18(3):242-244. doi:10.1016/S1473-3099(18)30075-6
11. WHO. The WHO AWaRE (Access, Watch, Reserve) antibiotic book. Geneva: World Health Organization; 2022.
12. Tebano G, Li G, Beovic B, et al. Essential and forgotten antibiotics: An inventory in low- and middle-income countries. Int J Antimicrob Agents. 2019;54(3):273-282. doi:10.1016/j.ijantimicag.2019.06.017
13. Pulcini C, Mohrs S, Beovic B, et al. Forgotten antibiotics: a follow-up inventory study in Europe, the USA, Canada and Australia. Int J Antimicrob Agents. 2017;49(1):98-101. doi:10.1016/j.ijantimicag.2016.09.029
14. World Health Organization. Global action plan on antimicrobial resistance. Geneva: WHO;2015.
15. Sulis G, Sayood S, Katukoori S, et al. Exposure to World Health Organization's AWaRe antibiotics and isolation of multidrug resistant bacteria: a systematic review and meta-analysis. Clin Microbiol Infect. 2022;28(9):1193-1202. doi:10.1016/j.cmi.2022.03.014
16. CDC. Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta: GA US Department of Health and Human Services;2019.
17. Pulcini C, Beovic B, Béraud G, et al. Ensuring universal access to old antibiotics: a critical but neglected priority. Clin Microbiol Infect. 2017;23(9):590-592. doi:10.1016/j.cmi.2017.04.026
18. Ueleres Braga J, Araujo RS, de Souza ASS. The Shortage of Benzathine Penicillin and Its Impact on Congenital Syphilis Incidence: An Ecologic Study in the City of Rio de Janeiro. Clin Infect Dis. 2021;72(5):e79-e87. doi:10.1093/cid/ciaa1716
19. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections. Clin Infect Dis. doi:10.1093/cid/ciad428.
20. Carmo A, Rocha M, Pereirinha P, Tomé R, Costa E. Antifungals: From Pharmacokinetics to Clinical Practice. Antibiotics (Basel). 2023;12(5):884. doi:10.3390/antibiotics12050884.
21. Molloy SF, Kanyama C, Heyderman RS, et al. Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa. N Engl J Med. 2018;378(11):1004-1017. doi:10.1056/NEJMoa1710922.
22. Molloy SF, Kanyama C, Heyderman RS, et al. Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa. N Engl J Med. 2018;378(11):1004-1017. doi:10.1056/NEJMoa1710922
23. Sprute R, Duda S, Liekweg A, Simon M, Cornely OA. The silent flucytosine shortage in Europe- not a distant problem. Lancet Reg Health Eur. 2023;30:100658. doi:10.1016/j.lanepe.2023.100658
24. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020;323(18):1824-1836. doi:10.1001/jama.2020.6019
25. Pereira LB, Zanetti MOB, Sponchiado LP, et al. Antibiotic use in Brazilian hospitals in the 21st century: a systematic review. Rev Soc Bras Med Trop. 2021;54:e08612020. doi:10.1590/0037-8682-0861-2020
26. Bhandari RK, Pandey AK, Malhotra S, et al. Addressing Challenges in Antibiotic Access: Barriers, Implications and Strategies for Solution. Pharmaceut Med. 2024;38(6):387-397. doi:10.1007/s40290-024-00538-7.

CC BY