

UNIVERSIDADE FEDERAL DE MINAS GERAIS  
FACULDADE DE FARMÁCIA  
DEPARTAMENTO DE PRODUTOS FARMACÊUTICOS

AMANDA FONSECA MEDEIROS

**AVALIAÇÃO DO USO DE ANTIMICROBIANOS E RESISTÊNCIA MICROBIANA:  
ANÁLISE DE SÉRIES TEMPORAIS DOS RESULTADOS DE UM PROGRAMA DE  
GERENCIAMENTO DE ANTIMICROBIANOS EM UM HOSPITAL PÚBLICO DE  
ENSINO**

Belo Horizonte

2022

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ENSINO**

Dissertação apresentada ao Programa de Pós-Graduação em Medicamentos e Assistência Farmacêutica da Faculdade de Farmácia da Universidade Federal de Minas Gerais, como requisito parcial à obtenção do grau de Mestra em Medicamentos e Assistência Farmacêutica.

Orientadora: Profa. Dra. Maria Auxiliadora Parreiras Martins

Coorientadores: Profa. Dra. Caryne Margotto Bertollo e Dr. Renan Pedra de Souza

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**AValiação DO USO DE ANTIMICROBIANOS E RESISTÊNCIA MICROBIANA: ANÁLISE DE SÉRIES TEMPORAIS DOS RESULTADOS DE UM PROGRAMA DE GERENCIAMENTO DE ANTIMICROBIANOS EM UM HOSPITAL PÚBLICO DE ENSINO**

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que já afeta a minha geração, e poderá afetar a dele e de seus filhos.

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*“-Mari, vamos comer brigadeiro!*

*-Eu não gosto de brigadeiro.*

*-Mas você já comeu?*

*-Você já comeu blusa?”*

*Mariana Fonseca, minha prima aos ~4anos, respondendo genialmente sobre a forma como lidamos (**ou não**) com o desconhecido.*

## RESUMO

A resistência microbiana a medicamentos (RMM) é considerada um dos principais desafios globais em saúde pública atualmente devido a seu potencial impacto na saúde humana e animal, assim como o aumento significativo nos custos de saúde. Os *Antimicrobial Stewardship Programs* (ASP) ou Programas de Gerenciamento de Antimicrobianos representam uma estratégia útil que consiste em um conjunto de ações para promover o uso responsável de antimicrobianos (ATM), e que pode ter sido impactada pela pandemia da COVID-19. Este estudo teve como objetivo analisar o ASP com base no modelo de avaliação de qualidade envolvendo as dimensões de "estrutura", "processo" e "resultado" proposto por Donabedian e avaliou a evolução temporal do consumo de ATM e a distribuição epidemiológica de microrganismos resistentes a múltiplas drogas (MDRO), entre 2015 e 2021. O local da pesquisa foi um hospital de ensino, público, geral, que pertence ao Sistema Único de Saúde. As atividades do ASP eram capitaneadas nesta instituição pela comissão de controle de infecções hospitalares (CCIH), pela farmácia hospitalar (FH) e pelo laboratório de apoio diagnóstico (LAD), tendo sido estes atores caracterizados sob a perspectiva Donabediana. A distribuição entre as dimensões foi orientada pela lista de verificação dos elementos essenciais do ASP que compõem os requisitos regulatórios nacionais. A lista de verificação foi aplicada em julho de 2022. O consumo de ATM foi medido em doses diárias definidas (DDD), e calculado por 1000 pacientes-dia. A coleta de dados foi realizada por extração de relatórios de consumo de ATM. Em seguida, os dados foram tabulados em uma planilha do Microsoft Office Excel (2003), plotados em série ao longo dos anos, mensalmente, de janeiro de 2015 a dezembro de 2021. A incidência do MDRO foi coletada dos relatórios especializados da CCIH. Para explicar as mudanças no consumo de ATM e a incidência de MDRO ao longo do tempo, calculamos a taxa de crescimento anual composta, que apresenta a variação média anual como uma proporção (%) do consumo no ano inicial. Todas as análises estatísticas foram realizadas utilizando o software estatístico R (versão 4.0; *R Foundation for Statistical Computing*, Viena, Áustria). Mapeou-se a estrutura, os principais processos e indicadores relacionados à CCIH, FH e LAD, caracterizando o ASP na instituição. Dos 60 itens que compõem a lista de verificação, o hospital atendeu os requisitos em 73,3% dos itens (n=44). Quanto aos resultados de consumo de ATM, daptomicina e linezolida tiveram as maiores variações de consumo no período (39,4 e 27,7%, respectivamente), seguidos pelos antibacterianos polipetídeos (9,8%). Os MDRO do grupo ESKAPE com maior variação no período foram *Staphylococcus (aureus, sp)* (29,2%), *Enterococcus (faecium, faecalis, sp)* (27,8%) e *Acinetobacter (baumannii, sp)* (18,4%). Outros

MDRO, fora do grupo ESKAPE, com variação significativa foram: *Providencia sp* (51,2%) e *Clostridioides difficile* (37,7%). Conclui-se que embora o hospital ainda não tenha um modelo clássico de ASP, houve investimentos para melhorar a qualidade da utilização de ATM e cumprir as diretrizes internacionais. A pandemia pode ter deteriorado ainda mais o cenário de aceleração do aumento da RMM. Isto justifica investigações adicionais dos dados de vigilância sobre as tendências epidemiológicas da RMM.

Palavras-chave: Gestão de Antimicrobianos; Resistência Microbiana a Medicamentos; Avaliação de Processos e Resultados em Cuidados de Saúde; Farmacoepidemiologia; Revisão de Uso de Medicamentos; COVID-19; Agentes antibacterianos.

## ABSTRACT

Antimicrobial resistance (AMR) is considered one of the major global challenges in public health nowadays due to its potential impact on human and animal health and the significant increase in healthcare costs. Antimicrobial Stewardship Programs (ASP) represent a useful strategy consisting of actions to promote responsible antimicrobial use (ATM), which the COVID-19 pandemic may have impacted. This study analyzed the ASP based on the quality assessment model involving the dimensions of "structure", "process", and "outcome" proposed by Donabedian and evaluated the temporal evolution of ATM consumption and the epidemiological distribution of multidrug-resistant microorganisms (MDRO) between 2015 and 2021. The study site was a general, public teaching hospital that belongs to Brazil's Unified Health System. The activities of the ASP were managed in this institution by the hospital infection control committee (HICC), hospital pharmacy (HP) and the diagnostic support laboratory (DSL), and these actors were characterized from the Donabedian perspective. The distribution among the dimensions was guided by the checklist of the essential elements of ASP that make up the national regulatory requirements. The checklist was applied in July 2022. ATM consumption was measured in defined daily doses (DDD) and calculated per 1000 patient-days. Data collection was performed by extraction of ATM consumption reports. The data were tabulated in a Microsoft Office Excel (2003) spreadsheet, plotted monthly from January 2015 to December 2021. The incidence of MDRO was collected from the HICC's specialized reports. To account for changes in ATM consumption and MDRO incidence over time, we calculated the compound annual growth rate, which presents the average yearly change as a proportion (%) of consumption in the initial year. All statistical analyses were performed using R statistical software (version 4.0; R Foundation for Statistical Computing, Vienna, Austria). The structure, main processes and indicators related to HICC, HP and LDS were mapped, characterizing the ASP in the institution. Of the 60 items that compose the checklist, the hospital met 73.3% of the requirements items (n=44). As for the ATM consumption results, daptomycin and linezolid had the highest variations in consumption in the period (39.4 and 27.7%, respectively), followed by the polymyxins antibacterials (9.8%). The MDROs in the ESKAPE group with the greatest variation in the period were *Staphylococcus (aureus, sp)* (29.2%), *Enterococcus (faecium, faecalis, sp)* (27.8%) and *Acinetobacter (baumannii, sp)* (18.4%). Other MDRO, outside the ESKAPE group, with significant variation were *Providencia sp* (51.2%) and *Clostridioides difficile* (37.7%). In conclusion, although the hospital does not yet have a classical ASP model, there were investments to improve the quality

of ATM use and comply with international guidelines. The pandemic may have further deteriorated the scenario of an accelerating increase in ATM. This warrants further investigation of surveillance data on the epidemiological trends of AMR.

Keywords: Antimicrobial Stewardship; Drug Resistance, Microbial; Outcome Assessment, Health Care; Pharmacoepidemiology; Drug Utilization Review; COVID-19; Antibacterials agents.

## LISTA DE ABREVIATURAS E SIGLAS

Anvisa - Agência Nacional de Vigilância Sanitária

ASP - *Antimicrobial Stewardship Programs*

ATB - Antibacteriano

ATM - Antimicrobiano

CCIH - Comissão de Controle de Infecção Hospitalar

CDC - *Centers for Disease Control*

CLSI - *Clinical and Laboratory Standards Institute*

COVID-19 - *Coronavirus disease*

CVC - Cateter Venoso Central

DDD - Dose Diária Definida

ESBL - *Enterobacteriaceae* produtora de beta-lactamase de espectro estendido

FH - Farmácia Hospitalar

FAO - Organização das Nações Unidas para a Alimentação e Agricultura

IRAS - Infecções Relacionadas à Assistência à Saúde

LAD - Laboratório de apoio diagnóstico

MDRO - Microrganismo resistente a múltiplas drogas

MRSA - *Staphylococcus aureus* resistente à meticilina

OIE - Organização Mundial de Saúde Animal

OMS - Organização Mundial da Saúde

OPAS - Organização Pan-Americana da Saúde  
PGUAH - Programas de Gerenciamento do  
Uso de Antimicrobianos hospitalares

RMM - Resistência microbiana a medicamentos

SUS - Sistema Único de Saúde

UTI - Unidade de Terapia Intensiva

VRE - *Enterococco* resistente à vancomicina

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## 1 CONSIDERAÇÕES INICIAIS

O aforismo “Primum Non Nocere”, é a premissa básica norteadora das condutas dos profissionais da saúde, que significa “primeiro não causar dano”. Essa frase célebre, atribuída ao pai da medicina – Hipócrates – traduz com exatidão o que ainda hoje é um grande desafio nesta área. Os eventos adversos compreendem as ocorrências clínicas desfavoráveis, que podem atingir o paciente durante o cuidado assistencial e que não estavam relacionados à evolução natural da doença de base (SILVA; RODRIGUES; RODRIGUES, 2021). Uma revisão sistemática avaliando mais de 74.000 prontuários demonstrou a incidência de eventos adversos em 9,2% dos pacientes internados e mais de 43% desses eventos foram considerados evitáveis (DE VRIES et al., 2008).

Um dos eventos adversos mais prevalentes em hospitais são as infecções, também chamadas de Infecções Relacionadas à Assistência à Saúde (IRAS) (BRASIL, 2021a; OPAS, 2020; WHO, 2014, 2021a). Há alta prevalência de IRAS nas unidades de terapia intensiva (UTI) voltada para assistência ao adulto no Brasil, sendo grande parte delas diagnosticadas com critérios clínicos e não microbiológicos (MACHADO et al., 2022). Um estudo multicêntrico realizado no sudeste brasileiro mostrou uma prevalência pontual de IRAS em um dia de 51,2% dos pacientes internados em uma UTI (BRAGA et al., 2018) delimitando a urgência em pautar essa temática na agenda de saúde pública nacionalmente.

Para tratamento dos pacientes que adquiriram IRAS são empregados antimicrobianos (ATM) – fármacos com capacidade de inibir o crescimento de microrganismos ou levá-los a morte. Entre os ATM encontram-se agentes que atuam contra bactérias, fungos, vírus e parasitas, e por isso, têm sido extensamente utilizados para profilaxia ou tratamento de infecções. Esse uso nem sempre é criterioso, como mostra um estudo realizado nos Estados Unidos da América com enfoque no uso de antibacterianos, em que se estimou que 30% desses medicamentos eram desnecessários ou inadequados (FLEMING-DUTRA et al., 2016).

A utilização excessiva desse arsenal terapêutico, seja na saúde humana, animal, ou na indústria agrícola é considerada uma das principais razões para a aceleração da resistência microbiana a medicamentos (RMM), imputando custos cada vez maiores e reforçando não só sua relevância terapêutica, mas também a sustentabilidade financeira dos sistemas de saúde (HOFER, 2019; SILVA; RODRIGUES; RODRIGUES, 2021; WHO, 2021b). A RMM é um dos principais desafios mundiais em saúde pública e tem aumentado gradualmente em todos os

continentes (CDC, 2019; CULTRERA et al., 2021; LLOR; BJERRUM, 2014; WHO, 2014, 2016). Responsável por cerca de 700.000 mortes a cada ano, estima-se que a RMM possa levar a 10 milhões de mortes por ano até 2050 (O'NEILL, 2016).

Sendo multifatorial, a resistência microbiana é influenciada para além da má utilização desses medicamentos, mas também pelos padrões de fabricação de antimicrobianos com qualidade fora das especificações dos códigos sanitários, perpassando ainda pela atuação insuficiente ou descoordenada de programas de prevenção e controle de infecções, e até mesmo pelas díspares realidades no monitoramento laboratorial (ARAÚJO; PEREIRA, 2018; BRASIL. MINISTÉRIO DA SAÚDE., 2019; BRASIL, 2017a).

Nesse contexto da RMM, alguns patógenos tem se destacado negativamente como ameaça global à saúde humana devido a seu potencial de multirresistência e virulência, conhecidos pelo acrônimo – ESKAPE, que elenca: *Enterobacter spp.*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* e *Enterococcus faecium*. Esses patógenos tem grande relevância clínica e compõe a lista de agentes prioritários para a pesquisa e desenvolvimento de novos agentes antibacterianos da Organização Mundial de Saúde (OMS) (MANCUSO et al., 2021).

Tamanha magnitude levou este tema a Assembleia Mundial de Saúde - órgão decisório na Organização Mundial de Saúde (OMS), composto por todas as delegações de países membros da OMS, responsáveis por discutir as prioridades na agenda de saúde. Em maio de 2015, na 68ª Assembleia Mundial da Saúde foi firmado o plano de ação global de prevenção e controle da resistência aos antimicrobianos (WHO, 2015a, 2015b).

Vislumbrando articulação no combate à resistência, uniram esforços a Organização das Nações Unidas para a Alimentação e Agricultura (FAO), a Organização Mundial de Saúde Animal (OIE) e a Organização Pan-Americana da Saúde (OPAS), compondo a chamada Aliança Tripartite (OPAS-FAO-OIE). Desde 2010, esta Aliança coordena ações no âmbito do projeto intitulado Trabalhando juntos para combater a resistência aos antimicrobianos (OPAS, 2020).

O arcabouço estruturante desta empreitada se sustenta pelo fomento europeu na implementação dos planos de ação nacional de sete países: Argentina, Brasil, Chile, Colômbia, Paraguai, Peru e Uruguai. Assim, a resposta do setor saúde aos compromissos assumidos pelos Estados Membros da OPAS na Agenda 2030 foram pactuados por meio de metas sendo o

décimo objetivo o enfrentamento das doenças infecciosas (WHO, 2021c), especificamente “Tratar e prevenir doenças infecciosas, incluindo o uso responsável e racional de medicamentos seguros, eficazes, acessíveis, e de qualidade” (CD59/INF/10 19 de julho de 2021). Esta proposta está em consonância com o Plano de Ação Global para a Segurança do Paciente 2021-2030, que visa eliminar danos evitáveis nos cuidados de saúde, como definido no objetivo estratégico 3 - Garantir a segurança de todos os processos clínicos (WHO, 2021d):

“Implementar medidas rigorosas e baseadas em evidências para prevenção e controle de infecções visando minimizar a ocorrência de infecções associadas aos cuidados de saúde e à resistência antimicrobiana.”

Uma estratégia que vem ganhando notoriedade para otimizar o uso de antimicrobianos, são os Programas de Gerenciamento de Uso de Antimicrobianos, internacionalmente conhecidos como “Antimicrobial Stewardship Programs” (ASP). Estes programas usam estratégias para a correta seleção, dosagem, via e duração apropriadas da terapia antimicrobiana (DELLIT et al., 2007). Os ASP vêm melhorando desfechos clínicos, reduzindo a RMM e as infecções associadas aos cuidados de saúde e por isso poupam custos adicionais com cuidados de saúde (WHO, 2019a). A implantação de ASPs foi recomendada como estratégia-chave pela agência norte americana Centers for Disease Control (CDC) nos Estados Unidos, e também pela OMS, endossando a necessidade de multiplicar tais ações em todo o mundo (CDC, 2021; WHO, 2014, 2019a).

Preocupada com esse cenário no Brasil, a Agência Nacional de Vigilância Sanitária (Anvisa) acompanha indicadores de infecção nacionais desde 2010, e vem melhorando a qualidade de seus instrumentos de coleta, trazendo dados que reforçam a necessidade de ações multimodais para o combate a resistência (BRASIL, 2010). Neste percurso, em 2017 foi publicada a política nacional para melhora no uso de antimicrobianos, denominada “Diretriz Nacional para Elaboração de Programa de Gerenciamento do Uso de Antimicrobianos em Serviços de Saúde” (BRASIL, 2017a). Na sequência, o Brasil realizou o primeiro levantamento nacional com o objetivo de estimar os hospitais que dispunham de ASP, além de estimar o nível de aprimoramento desses programas, mapeando as disparidades existentes entre as regiões (BRASIL, 2019).

Segundo inquérito de 2019, apenas 52,5% dos hospitais brasileiros investigados indicaram histórico de implantação de ASP (BRASIL, 2019; MENEZES et al., 2022). Nova avaliação está ocorrendo a nível nacional em 2022 e vislumbra atualizar o diagnóstico desses Programas,

direcionando ações nacionais, estaduais e municipais para a promoção da implementação e aprimoramento do ASP nos serviços de saúde de todo país.

A pandemia de COVID-19, causada pelo vírus SARS-CoV-2, foi um agravante da RMM (CARS et al., 2021; GODMAN et al., 2021; RAWSON et al., 2020; RUSSELL et al., 2021). Uma revisão explorou as coinfeções bacterianas em pacientes com COVID-19 e demonstrou que elas estavam presentes em menos de 4% dos pacientes na admissão (WESTBLADE; SIMON; SATLIN, 2021). O uso de antibióticos em pacientes com SARS-CoV-2 foi maior que a incidência de infecções secundárias e coinfeções notificadas, sugerindo prescrição inadequada e excessiva de antibacterianos (LANSBURY et al., 2020; OPAS, 2021).

A OPAS defende que o aumento do uso de antimicrobianos e das coinfeções - tanto bacterianas quanto fúngicas - associadas à COVID-19 são somente uma pequena parte de uma situação muito maior e complexa, escondendo raízes mais profundas para a aceleração da RMM (OPAS, 2021). Houve um aumento considerável no isolamento, identificação e notificação de patógenos multirresistentes, notadamente patógenos Gram-negativos comuns e resistentes aos carbapenêmicos – como as Enterobacteriaceae produtoras de carbapenemase (OPAS, 2021; PEREZ et al., 2020).

Sob essa perspectiva, para compreender a questão dos desfechos de utilização de antimicrobianos é preciso adotar modelos multidimensionais de avaliação da qualidade em saúde. Dentre as abordagens e metodologias utilizadas nessa área, um racional notório foi concebido por Donabedian (1980), e traz uma ótica sistêmica pautada na tríade “estrutura–processo–resultado” (DONABEDIAN, 1990; MAURER; HOGAN; WALKER, 2021). Uma revisão sistemática da literatura realizada no período de 2008 a 2019, identificou 96 estudos com 214 resultados que examinaram a relação entre intervenções hospitalares e IRAS, mostrando que a avaliação da qualidade é complexa, com potenciais vieses e precisa de maior investigação científica (MAURER; HOGAN; WALKER, 2021).

Nesta conjuntura, considera-se relevante o desenvolvimento de trabalhos científicos que permitam melhor compreensão da dinâmica de enfrentamento das IRAS e da RMM, em todo o mundo, com ênfase em países de baixa e média renda, inclusive compreendendo melhor o cenário brasileiro. Bizerra (2020), em sua dissertação, discutiu a necessidade de outras pesquisas que otimizassem as métricas relacionadas aos ASPs, além da necessidade de desvendar e demonstrar as associações entre as intervenções do Programa e os desfechos mensurados (BIZERRA, 2020).

Assim, o objetivo do presente trabalho foi caracterizar o ASP, conforme o modelo de avaliação da qualidade proposto por Donabedian, além de avaliar o uso de antimicrobianos, por meio de métricas de consumo, e do aparecimento de resistência microbiana na instituição em estudo. Considerou-se essa proposta relevante e atual, podendo vir a preencher uma lacuna científica, frente à escassez de produções brasileiras nesta temática.

## 2 OBJETIVO

### 2.1 Objetivo geral

Caracterizar o ASP de um hospital público de ensino e avaliar o uso de antimicrobianos, por meio de métricas de consumo e deaparecimento de resistência microbiana na instituição.

### 2.2 Objetivos específicos

- Caracterizar o ASP categorizando a estrutura, os principais processos de trabalho para o gerenciamento de antimicrobianos e levantar os indicadores monitorados na instituição;
- Calcular o consumo de antimicrobianos - estratificados por cada grupo/classe e para cada um destes, individualmente, mensalmente, no período de primeiro de janeiro de 2015 a dezembro de 2021;
- Avaliar a tendência de evolução temporal do uso de antimicrobianos por meio de gráficos de tendência que mostram as taxas mensais ao longo do tempo de monitoramento;
- Avaliar a tendência de evolução temporal de isolados de culturas resistentes a antimicrobianos por meio de gráficos de tendência que mostram as taxas mensais ao longo do tempo de monitoramento;
- Analisar as séries temporais de uso de antimicrobianos e isolados resistentes no período em estudo;
- Avaliar o impacto da COVID-19 no comportamento da série temporal de consumo de antimicrobianos e de aparecimento de RMM.

### 3 MÉTODOS

#### 3.1 Desenho do estudo

Trata-se de um estudo farmacoepidemiológico, com enfoque na utilização de medicamentos, coleta de dados secundários de forma retrospectiva, compreendendo análise documental relativa ao ASP e aos indicadores de resultados das ações de controle de infecção de um hospital público de ensino

#### 3.2 Local e amostra

O local de estudo foi um hospital geral, público, de ensino, integrado ao Sistema Único de Saúde (SUS), referência para média e alta complexidade, na região sudeste do Brasil. A unidade possui 392 leitos e é um centro de referência para mais de 1,2 milhões de pessoas que vivem na região metropolitana de Belo Horizonte, Minas Gerais. A população assistida é principalmente adulta e com perfil heterogêneo. O hospital atende cerca de 50 mil pacientes por ano, variando entre média e alta complexidade para assistência clínica, cirúrgica e emergências traumatológicas e não traumatológicas, assim como o cuidado materno-infantil.

O formulário padronizado para monitoramento do uso de antimicrobianos, incluindo os medicamentos padronizados, está disponível na prescrição eletrônica. O sistema computadorizado requer o registro do motivo da indicação de todos os antimicrobianos prescritos. Os antimicrobianos de reserva, de amplo espectro e/ou de alto custo são dispensados somente após revisão por um farmacêutico clínico e pelo comitê de controle de infecções hospitalares (CCIH). As principais estratégias de controle de infecção focalizadas na RMM no hospital de estudo envolvem a pesquisa ativa, avaliação antimicrobiana, análise e disseminação de resultados epidemiológicos e visitas técnicas.

#### 3.3 Avaliação do Programa de Gerenciamento do Uso de Antimicrobianos

O ASP implantado no hospital investigado foi avaliado empregando a lista de verificação dos elementos essenciais dos Programas de Gerenciamento do Uso de Antimicrobianos Hospitalares (PGUAH), adaptada do CDC - *Core Elements of Hospital Antibiotic Stewardship Programs*. A adaptação foi realizada pela Anvisa, responsável no Brasil pelas ações de controle

de infecções e monitoramento do uso de medicamentos em hospitais e na comunidade (BRASIL, 2017a). O PGUAH compreende três seções com sete tópicos específicos para responder “sim” ou “não”. As seções para avaliação são: Apoio da alta direção do hospital; Definição de responsabilidades de todos os profissionais envolvidos; Educação; Desenvolvimento de ações para melhorar a prescrição de antimicrobianos; Monitoramento do programa; e Divulgação de resultados.

### 3.4 Avaliação do consumo de antimicrobianos

Foram incluídos todos os antimicrobianos utilizados no período de estudo, monitorados nos hospitais com leitos de UTI conforme definição da Gerência de Vigilância e Monitoramento em Serviços de Saúde da Anvisa, padronizados na instituição em estudo. São eles: amicacina, ampicilina-sulbactam, cefepime, ceftazidima, ceftriaxona, ciprofloxacino oral, ciprofloxacino parenteral, levofloxacino parenteral, linezolida parenteral, meropenem, piperacilina-tazobactam, polimixina B, polimixina E, teicoplanina, vancomicina, daptomicina, tigeciclina, anfotericina B, anidulafungina, fluconazol e micafungina.

A nota técnica 01/2020, recomenda que a unidade de medida para monitorar o consumo de antimicrobianos seja a dose diária definida (DDD):

DOSE DIÁRIA DEFINIDA (DDD): é a dose de manutenção média presumida por dia para um medicamento usado para sua principal indicação terapêutica em adultos de 70Kg. Esta é a unidade utilizada pelo Conselho Nórdico sobre Medicamentos, pioneiro nos estudos de utilização de medicamentos e é a unidade recomendada pelo Grupo de Estudos de Utilização de Medicamentos da Organização Mundial de Saúde (OMS). (WHO, 2022)

As DDD estabelecidas pela OMS para os antimicrobianos são revisadas regularmente e podem ser obtidas no site da Organização (WHO, 2022). A DDD foi calculada por meio de planilha do Microsoft Excel<sup>®</sup> (2003), utilizando a seguinte fórmula:

**Fórmula de cálculo:**

$$\text{DDD}/1000 \text{ pacientes-dia} = (A \div B) \div P$$

A=Total do antimicrobiano consumido em gramas (g), no mês de vigilância\*

B=Dose diária padrão do antimicrobiano calculado em gramas para adulto de 70kg, sem Insuficiência Renal (OMS)\*

P=Pacientes-dia (soma do número total de pacientes internados, a cada dia) no mês de vigilância

Os dados de consumo foram calculados com base nos registros de dispensação e devolução de antimicrobianos pelo serviço de farmácia hospitalar, extraídos do software de gestão hospitalar MV 2000i<sup>®</sup> e MV Soul<sup>®</sup>. A unidade de cálculo foi realizada em gramas da substância dispensada, como os dados primários foram obtidos em quantidade de apresentações do medicamento dispensadas, por via de administração, estas foram transformadas em gramas.

### 3.5 Monitoramento do aparecimento de resistência microbiana

Foi extraído o número total de culturas microbiológicas – clínicas e de vigilância, por mês, e incluídos os isolados microbiológicos classificados como resistentes conforme critérios do *Clinical and Laboratory Standards Institute* (CLSI). Com estes dados foi calculada a proporção de isolados multirresistentes, via Microsoft Excel<sup>®</sup> (2003). Estes dados foram extraídos do software de gestão laboratorial Matrix<sup>®</sup>. Também foram incluídos os dados de microrganismos resistentes a múltiplas drogas (MDRO), depreendidos dos relatórios do serviço de controle de infecção hospitalar, compilados via software Sistema Automatizado de Controle de Infecções Hospitalares (Sacih), MV 2000i<sup>®</sup> e MV Soul<sup>®</sup>. Não houve mudança nos critérios e estratégias de vigilância microbiológica no período de estudo.

Além disso, os MDRO isolados e identificados foram categorizados, mês a mês, por tipo. Os dados sobre MDRO foram classificados de acordo com a lista proposta pela OMS que menciona os patógenos prioritários, a nível global, para pesquisa e desenvolvimento. O grupo designado pela sigla ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* e *Enterobacter species*) representa o mais alto "status de prioridade" devido á sua significativa ameaça aos humanos. Resultados inconclusivos foram excluídos da amostra, abrangendo microorganismos categorizados pelo laboratório de análises clínicas, no banco de dados, como "outros Gram-positivos", "outros Gram-negativos", "outros" ou "em identificação".

### 3.6 Análise de séries temporais

A taxa de crescimento anual composta (CAGR) foi utilizada para calcular as mudanças anuais no consumo de antimicrobianos e a incidência de patógenos MDRO. O primeiro cálculo da CAGR foi obtido por meio da função TAXAJURO do Microsoft Excel<sup>®</sup> (2003) subtraindo-se o último ano do estudo (2021) até o primeiro ano (2015), correspondendo à notação CAGR<sub>t</sub>. O segundo cálculo da CAGR foi obtido pela mesma função (TAXAJURO) subtraindo-se o último ano (2021) até o primeiro ano antes da pandemia (2019), correspondendo à notação CAGR<sub>p</sub>. Foi calculado um coeficiente delta ( $\Delta$ ) por meio da subtração do CAGR<sub>p</sub> pelo CAGR<sub>t</sub>. Todas as análises estatísticas foram realizadas utilizando o software estatístico R (versão 4.0; R *Foundation for Statistical Computing*, Viena, Áustria). O estudo foi conduzido e relatado de acordo com as diretrizes do Reforço do Relatório de Estudos Observacionais em Epidemiologia (STROBE-AMS) que relata estudos epidemiológicos focados na relação entre MDRO e uso de antimicrobianos.

### 3.7 Aspectos éticos

O estudo foi aprovado pelo Comitê de Ética em Pesquisa (CEP) da Universidade Federal de Minas Gerais, sob o código CAAE 54060321.8.0000.5149 (Anexo A). O termo de consentimento livre e esclarecido foi dispensado já que os dados foram analisados de modo agregado.

#### **4 RESULTADOS**

Artigo 1 - *Building an Antimicrobial Stewardship Program: a narrative of six years under the Donabedian perspective*, submetido ao periódico: *Frontiers in Pharmacology* (ISSN 1663-9812), fator de impacto 5,988 (JCR 2021)

## **Building an Antimicrobial Stewardship Program: a narrative of six years under the Donabedian perspective**

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## ABSTRACT

**Introduction:** Antimicrobial resistance (AMR) is increasing and represents one of the world's major challenges. AMR increase morbimortality, length of hospital stay and costs. Antimicrobial Stewardship Programs (ASP) is one of the key strategies to promote the rational use of antimicrobials since AMR is mostly driven by antimicrobial consumption. **Objective:** To describe the ASP implementation in a teaching hospital from the perspective of Donabedian quality assessment. **Method:** This was an observational descriptive study with secondary data collection, including document review of the ASP. The study setting was a general public 392-bed hospital. The ASP activities were performed by the hospital infection control committee (HICC), hospital pharmacy (HP) and diagnostic support laboratory (DSL). The description of the three services mainly involved in the ASP was based on a quality assessment model involving the dimensions of “structure”, “process” and “result” proposed by Donabedian. The distribution among dimensions was guided by the checklist of essential elements of the ASP that compose the Brazilian regulatory requirements. The checklist was applied in July, 2022, and the ASP results described from 2016 to 2021. **Results:** ASP actions have been gradually implemented since 2008 with the implementation of HICC and improved over the years. Regarding structure, the investments in technology were mapped, quantifying 26 computers and three software programs employed to computerize the ASP processes performed in specific physical areas by HICC, HP and DSL. Institutional guidelines used by HICC, HP and DSL guided clinical practices to operationalize ASP. The evaluation metrics improved for 10 indicators and worsened for four indicators. From the 60 items composing the checklist, the hospital met the requirements in 73.3% of the items (n=44). **Conclusion:** This study described the implementation of ASP in a teaching hospital, applying the Donabedian perspective. Although the hospital still does not have a classic ASP model, there were investments to improve structure, processes and results, aiming to comply with international guidelines. A high proportion of key elements of ASP in the hospital were followed according to the Brazilian regulatory requirements. Aspects related to antimicrobial consumption and the emergence of microbial resistance deserve further investigations.

**Keywords:** Antimicrobial Stewardship; Drug Resistance, Microbial; Outcome Assessment, Health Care; Outcome and Process Assessment, Health Care; Quality Assurance, Health Care; Pharmacoepidemiology

## INTRODUCTION

Antimicrobial resistance (AMR) is one of the world's major challenges in terms of global health, food safety, environmental well-being and socio-economic development, presenting a gradual increase on all continents (WHO, 2019b). AMR is considered a major public health threat contributing to elevated morbidity, mortality, prolonged hospital stays and significantly increased hospital costs (O'RIORDAN et al., 2021; VICENTINI et al., 2022).

Inappropriate or excessive use of antimicrobials are important determinants of AMR due to the ecological impact of these agents (VICENTINI et al., 2022). Previous estimates reported that 25-50% of hospitalized patients use antibiotics, of which 20-50% are unnecessary or inappropriate (KALLEN et al., 2019; VAN DEN BOSCH et al., 2016). The pace of development of new antimicrobials is slower than the global demand (WHO, 2017, 2021e). Therefore, the development of strategies to promote appropriate use of antimicrobials is essential to reduce the selective pressure for emergence of AMR and to improve patient safety (VICENTINI et al., 2022).

As a result of the growth of AMR, multiple international and national initiatives have been implemented to increase the appropriate use of antimicrobials and reduce AMR (DA SILVA et al., 2021; GODMAN et al., 2021). Antimicrobial Stewardship Program (ASP) has been reported as an effective strategy to optimize the use of antimicrobials in hospitals (VICENTINI et al., 2022). ASP comprises a coherent set of collective actions, developed daily, aiming to: i) promote responsible use of antibiotics; ii) achieve treatment effectiveness; iii) reduce the likelihood of infections and; iv) minimize adverse events, including AMR (DYAR et al., 2017; VICENTINI et al., 2022).

The Brazilian Health Regulatory Agency (Anvisa) published in 2017 the National Plan for Antimicrobial Resistance Prevention and Control in Health Services. This is a reference to guide strategies and actions focus on the detection, prevention and control of the dissemination of resistant microorganisms by employing a systematic and fast approach, based on scientific and laboratory evidence (BRASIL, 2017b). Afterwards, the National Guidelines for the Management Program of Antimicrobial Use in Health Services was published, encouraging the implementation of ASP in Brazilian hospitals (BRASIL, 2017a). The guideline was developed to comprehensively present the key elements of an ASP that should be adapted according to reality, local needs, epidemiological and microbiological profiles, barriers and hospital resources aiming to optimize the use of antimicrobials (BRASIL, 2017a).

Most studies describing the process of ASP implementation in hospitals and the assessment of its performance over time have been developed in high-income countries (COX et al., 2017). There are few studies discussing the experience of ASP implementation in low- and middle-income countries, such as Brazil (BIZERRA, 2020; MENEZES et al., 2022; SATO et al., 2021), as well as the methods for program evaluation and feedback to healthcare teams and hospital leadership. Thus, the aim of this study was to describe the ASP implementation in a teaching hospital from the Donabedian perspective, assessing the structure, work processes and the evaluation metrics monitored over six years.

## **MATERIAL AND METHODS**

This was an observational descriptive study with secondary data collection, including document review of the ASP and evaluation metrics obtained from the actions of infection control. The study setting was a general public teaching hospital which belongs to the Brazilian Unified Health System. This 392-bed hospital is a referral center for more than 1.2 million people living in the metropolitan region of Belo Horizonte, Minas Gerais State, in the Southeast Brazil. The hospital provides care for about 50 thousand patients per year, encompassing medium and high complexity assistance for clinical, surgical and polytrauma emergencies, as well as maternal and child care. The study protocol was approved by the Institutional Ethics Committee of the Universidade Federal de Minas Gerais (CAAE 54060321.8.0000.5149). Informed consent form was waived due to the aggregated analyses of data.

The ASP activities of the study hospital are guided by the hospital infection control committee (HICC), hospital pharmacy (HP) and diagnostic support laboratory (DSL). The description of the three main services involved in the ASP was based on a quality assessment model involving the dimensions of “structure”, “process” and “result”, according to the triad proposed by Donabedian (DONABEDIAN, 1990). The distribution among dimensions in the quality assessment was guided by the checklist of essential elements of the Hospital Antimicrobial Use Management Program, adapted by Anvisa from the Core Elements of Hospital Antibiotic Stewardship Programs proposed by the Center for Disease Control (CDC). Anvisa is responsible for infection control and monitoring drug usage in hospitals and community in Brazil (BRASIL, 2017a). The checklist was applied and comprises six sections with specific items with “yes/no” questions. The sections consist of: i) support from the hospital senior management; ii) definition of responsibilities of professional teams; iii) educational activities; iv) actions to improve antimicrobial prescribing; v) monitoring of the program; vi)

dissemination of results. For the purpose of the present study, the checklist was applied in July, 2022. A flowchart of the process of use of antimicrobials was also provided.

The dimension of “results” was extracted from the HICC reports that follow the standard of the National Healthcare Safety Network (NHSN) (DUDECK et al., 2013) protocols. Data collection corresponded to the timeframe of 2016-2021. HICC reports are computerized employing the software SACIH<sup>®</sup> which is an automated system for hospital infection control, covering the following metrics: risk of health care-associated infection, risk of surgical site infection, risk of post-surgical infection and risk of infection in the intensive care unit (ICU). The incidence densities were described for: catheter-associated urinary tract infection in the ICU; pneumonia associated with mechanical ventilation in the ICU; primary sepsis associated with central venous catheter in the ICU; vascular access infection associated with central venous catheter in the ICU; infection caused by species of *Acinetobacter baumannii*; infection caused by species of *Pseudomonas aeruginosa*; infection caused by methicillin-resistant *Staphylococcus aureus* (MRSA); infection in the general internal medicine; infection caused by bacteria of the group CESP that includes *Citrobacter*, *Enterobacter*, *Serratia*, *Providencia* and *Proteus*; and infection caused by carbapenem-resistant *Klebsiella pneumoniae* (KPC). Data are compiled from HICC, HP and DSL under the supervision of the former and used for metrics’ calculation, employing the SACIH<sup>®</sup> software. The results were presented by year of extraction and the variation encountered for the period of study was estimated from the time series, subtracting the value obtained in 2021 by that of 2016.

## RESULTS

The three hospital services directly involved with ASP (HICC, HP and DSL) are hierarchically linked to the senior leadership. There is no precise date that marks the beginning of ASP in the institution. The policies and actions have been gradually implemented since 2008 with the implementation of the HICC and improved over the years. All procedures followed the Brazilian regulatory requirements and ASP results were evaluated every six months by a multi-professional committee. The team members directly responsible for ASP have their responsibilities pre-defined in the description of their institutional positions. The hiring process is performed by public selection resulting in reduced turnover and, consequently, minimized impact on the communication among professionals and information management.

Considering the Donabedian triad, the quality assessment of the domains “structure”, “process” and “results” will be presented for each service involved in ASP (Supplementary

material I). Starting with HICC, the department counted on 13 professionals during all the study period (2016-2021). The HICC performed epidemiological surveillance applying the NHSN/CDC methodology in a systematic, active and continuous form. Inpatients were monitored for health care-associated infections in all topographies and notifications were performed following the diagnostic criteria established by Anvisa (BRASIL, 2017c). All recommendations for precaution and/or treatment of infections were recorded by HICC in the computerized system to be checked and followed-up by the healthcare team. These data could also be compiled as indicators for assessing the performance of the service on a monthly basis. The results were presented every six months to other healthcare professionals involved in the process.

The HP received investments in human resources increasing the number of pharmacists from nine in 2016 to 15 in 2021, and the total of other professionals in the HP from 82 in 2016 to 110 in 2021. Besides, HP activities were expanded in 2016 with the restructuring of clinical pharmacy. The service operated 24 hours a day in a physical area distributed into a central pharmacy and six satellite units. Medication prescription was developed by using a Computerized Physician Order Entry (CPOE). Antimicrobials were dispensed according to medical prescription and the analysis of drug indication. The first dose of restricted use antimicrobials was released immediately after the prescription. Then, the pharmacist performed a detailed evaluation of the indication, safety, effectiveness and convenience to substantiate the decision for completing drug therapy. There was no referral pharmacist specifically assigned to the management of antimicrobials and the release of restricted use antimicrobials could be discussed with HICC by any professional on duty. Figure 1 shows the flowchart of antimicrobial use starting from the assessment of clinical condition and the decision for prescription of antimicrobials, or not, until the completing of antimicrobial therapy.



The LDS had 47 professionals in 2016 and 48 in 2021, with an additional microbiology analyst. The laboratory belongs to the hospital structure and could perform tests in the fields of microbiology, biochemistry, haematology and others required for special conditions. The processes were developed in a modern technological platform, with traceable information throughout the entire diagnostic chain, from the pre-analysis to final results. The data could be integrated through an interface between the laboratory computer system and the hospital management software, ensuring bidirectional connection of information and greater efficiency in decision making. The collection of biological material for microbiological tests was guided by the infection suspected and developed according to the institutional protocols to ensure quality of tests. Upon receiving the material, the process chain was started including: microscopy, culture, isolation and identification of pathogens, as well as determination of their sensitivity profile.

From the 60 items composing the Anvisa checklist, the hospital met the requirements in 73.3% of the items (n=44). The highest proportion of compliance referred to the development of actions to improve antimicrobial prescribing (89.3%; n=25/28) and to the support from senior management (77.8%; n=7/9). According to the definitions of responsibilities, six out of seven items were not met. The main reasons for non-compliance were related to the lack of formalization and definition of responsibilities for ASP team members.

The subsections of Anvisa checklist presenting some level of inadequacy were: i) support from the hospital senior management in regard to the availability of departments to contribute to the management of antimicrobial use, as well as the staffing to operate ASP; ii) definition of responsibilities of professional teams; iii) educational activities since the hospital did not offer educational programs for patients, companions/caregivers on the correct use of antimicrobials; iv) actions to improve antimicrobial prescribing in regard to the use pharmacokinetics/pharmacodynamics knowledge to optimize antimicrobial dosing regimens to treat infection caused by microorganisms with reduced sensitivity, absence of automatic stop orders time-sensitive for specific prescriptions of antimicrobials, especially those administered for surgical prophylaxis, and use of biomarkers for the management of antimicrobial use; v) monitoring of the program with the incorporation of indicators of antimicrobial consumption, such as measures of length of therapy (LOT) and days of therapy (DOT).

The results for indicators measured in the study period (2016-2021) are depicted in Table 1. There were a positive variation for 10 indicators and a negative variation for four indicators. The indicators with worse results were risk of post cesarean section infection, risk

of infection in the intensive care unit, density of incidence of infection in the general internal medicine and density of incidence of infection caused by KPC.

**Table 1 - Main results for metrics regarding actions of hospital infection control**

Indicador	2016	2017	2018	2019	2020	2021	$\Delta^{**}$
Risk of health care-associated infection	3,2	2,1	1,9	1,6	1,6	1,8	-1,4
Risk of surgical site infection	5,6	2,8	4,1	4,8	3,3	3,3	-2,3
Risk of post-cesarean section infection	2,3	1,1	1,1	2,6	1,2	3,5	1,2
Risk of infection in the ICU	18	12	26	18	12	22	4
Density of incidence of infection catheter-associated urinary tract infection in the ICU	4,3	4,3	3,3	3,5	1,6	2,5	-1,8
Density of incidence of pneumonia associated with mechanical ventilation in the ICU	23,7	10,9	13,1	6	15,1	15,7	-8
Density of incidence of primary sepsis associated with central venous catheter in the ICU	11,8	7,3	4,2	2,9	3,2	5	-6,8
Density of incidence of vascular access infection associated with central venous catheter in the ICU	1,7	1,1	1,1	1,3	1,4	0,8	-0,9
Density of incidence of infection caused by <i>Acinetobacter baumannii</i>	1,4	0,7	0,6	0,7	0,8	1,3	-0,1
Density of incidence of infection caused by <i>Pseudomonas aeruginosa</i>	1,1	0,8	0,6	0,7	0,9	0,6	-0,5
Density of incidence of infection caused by methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	0,6	0,3	0,2	0,2	0,3	0,5	-0,1
Density of incidence of infection in the general internal medicine	7,9	6,6	6,9	7,2	4,9	8,6	0,7
Density of incidence of infection caused by bacterias of the do group CESP*	1,2	1,3	1,5	1,1	1,3	0,8	-0,4
Density of incidence of causada por <i>Klebsiela pneumoniae</i> resistente a carbapenêmicos (KPC)	0,3	0,5	0,8	0,6	0,7	0,8	0,5

\*CESP – *Citrobacter, Enterobacter, Serratia, Providencia, Proteus*

\*\*Note: Delta coefficient ( $\Delta$ ) was calculated by the difference of the value obtained in 2021 minus the value in 2016. This table displays the annual estimates and does not constitute a statistical trend analysis.

## DISCUSSION

ASP is a complex intervention that relies on the interaction between multiple actors (HUGHES et al., 2022). Incorporating the Donabedian perspective and its dimensions to the ASP evaluation allowed integrating aspects of impact on quality and patient safety. The dimension of "structure" evaluated the existing conditions for managing the use of antimicrobials in terms of human resources, device and facilities. The dimension of "process" encompassed technical-assistance procedures that allow the operationalization of patient care. Finally, the dimension of "result" included the performance evaluation of the management of the use of antimicrobials. The evaluation of these dimensions allowed obtaining a comprehensive overview of the use of antimicrobials, incorporating a multifactorial view. Thus, it was possible to identify opportunities for interventions and improvement in the process of antimicrobial use. Failures could also be discussed, including human and organizational factors, as well as the performance results (SOARES, 2018).

The “structure” involves the organization, requirements and needs of the multidisciplinary team providing means to implement and support the multifaceted activities of an ASP (O’RIORDAN et al., 2021). The study hospital was assessed as having an adequate physical structure. There were hardware and software available for the activities performed by each of the three departments with active participation in the management of antimicrobial use. This structure enabled the integration of actions, better traceability of processes and optimization of working hours. Besides, there was greater environmental sustainability due to the electronic filing of documents and reduced use of paper sheets and prints. The use of antimicrobials in a system with adequate informational support was also a positive factor, showing greater traceability and control along the chain.

The assessment of the dimension of “structure” using the ASP checklist revealed that the study hospital lacked a specific operational team responsible for ASP implementation and development. This situation has been reported as the main barrier for ASP implementation in adult ICUs in Brazil, according to a survey developed by Anvisa in 2019 (BRASIL, 2019). To obtain better results, international and national guidelines recommend that ASP should be developed by a specialized team (BARLAM et al., 2016; BRASIL, 2017a; DOERNBERG et al., 2018). In general, HICC and HP develop accumulate activities involving ASP and other different tasks in their daily routine. The

ideal team would be multi-professional, including an infectious disease specialist, a clinical pharmacist trained in infectious diseases, and a clinical microbiologist (DELLIT et al., 2007). It is also important to add a data specialist and a hospital epidemiologist to work integrated with the HICC, HP, Pharmacy and Therapeutics Committee, Quality Management Center and Patient Safety (BARLAM et al., 2016; BLEASDALE; BARNDEN; BARNES, 2019; DELLIT et al., 2007; DOERNBERG et al., 2018; LUTHER et al., 2018).

The support of the hospital leadership is a structuring element to enhance local results (BRASIL, 2017a, 2021b; DELLIT et al., 2007) by formally assuming a commitment with ASP through a policy that provides funding, clear definition of responsibilities and sufficient human resources, that are in line with the international recommendations (DELLIT et al., 2007) Despite the importance of this element, in regulatory terms, the hospital complies with the current requirements of Anvisa which are designed in a basic level (BRASIL, 2017a, 2021b, [s.d.]). Brazil still has a long way to implement broader and more efficient ASP actions in hospitals.

The dimension “process” involving healthcare teams was mostly characterized by the fragmentation of the activities performed and by the way of communication with prescribers on actions to improve the prescription of antimicrobials that occurred via instant messaging applicative and/or records in medical charts. The audit of the use of antimicrobials should be prospective, but this recommendation may not have been followed due to the lack of exclusive professionals and a specific operational team assigned for this function. Thus, the detection of a necessary intervention and the feedback to the attending physician may be delayed.

Education is an essential element of ASP, but passive educational strategies (lectures, events, booklets) without active interventions have shown to be little effective for changing the practices of antimicrobial prescribing and their impact is not sustained over time (BARLAM et al., 2016; DELLIT et al., 2007). The study hospital offered continuing education using active methodologies focused on raising awareness of professionals on the need to promote appropriate use of antimicrobials and to prevent multidrug resistance. This education program included physician training on good practices of antimicrobial prescribing. The teaching role was extended to undergraduate and graduate students by integrating hospital practices with the curricula covering topics on the rational use of antimicrobials (BRASIL, 2017a; DONABEDIAN, 1990; O’RIORDAN et al., 2021). Future perspectives comprise the need to expand education

programs to empower patients and companions/caregivers and to improve patients self-care.

The adoption of guidelines contributes to the quality of patient care, adequate decision-making and reduction of heterogeneity in clinical practice (GYSENS, 2018). Protocols were widely disseminated in the hospital and kept available for clinical staff, covering the main infectious diseases requiring antimicrobial use. The implementation of guidelines can be facilitated by educational interventions with feedback on the use of antimicrobials and patient outcomes (GYSENS, 2018). The elaboration and review of protocols, as well as training in practice, should be systematic and adherence to clinical protocols should be monitored. The effect of training should be measured and assessed according to the quality of antimicrobial prescribing, the expansion of microbial resistance and other indicators recommended by Anvisa (BARLAM et al., 2016; BRASIL, 2017a). Pharmacoepidemiological studies should be conducted to improve knowledge on the use of antimicrobials providing consistent data for the revision of institutional guidelines and internal policies.

The Infection Disease Society of America (IDSA) suggested that computerized clinical decision support can facilitate the procedures of ASP (BARLAM et al., 2016). The computer system integrates CPOE and clinical data in the study hospital. However, the functions of the computer system and the lack of data input on medication administration do not allow issuing automatic orders to stop specific antimicrobial prescriptions, especially those involving surgical prophylaxis, representing a process to be improved.

Interventions in the dimension of “process” are considered as part of the most effective ASP strategies to improve antimicrobial prescribing in hospitals (DAVEY et al., 2017; O’RIORDAN et al., 2021). Economic assessment should be performed before the implementation or adaptation of ASP interventions (NATHWANI et al., 2019). For instance, procalcitonin-guided antibiotic therapy has been reported to be effective and safe in reducing the length of antibiotic treatment of sepsis and respiratory tract infection (ELNAJDY; EL-DAHIYAT, 2022). However, there is no evidence of cost-effectiveness for incorporation of this biomarker in different healthcare systems (WESTWOOD et al., 2015). Therefore, the IDSA warning prevails regarding that the evidence to support the use of procaciltonin biomarker remains under construction (BARLAM et al., 2016). Pharmacokinetic and pharmacodynamic modeling has been reported as a useful strategy to provide a more rational individualization of antimicrobial dosing regimens, increasing

the effectiveness of infection treatment. However, modeling strategies are not widely available in hospitals due to the lack of specialized resources, such as specific software and qualified staff (OWENS; BULIK; ANDES, 2018).

Regarding the dimension of “results”, the hospital monitored the consumption of antimicrobials through the defined daily dose (DDD) recommended by WHO. DDD consists of an assumed average maintenance dose per day for a drug used for its main indication in adults (BRASIL, 2017a; WHO, 2022). This measure has been mostly used due to the simplicity of data collection in the computer systems. Although the measure of days of therapy (DOT) is considered more accurate, DDD remains as a feasible alternative for institutions with limitations in collecting data per patient (BARLAM et al., 2016). The assessment of these metrics (DDD or DOT) is highly dependent on the availability of CPOE and electronic records of medication administration to allow data collection at the patient level (KALLEN et al., 2019).

Among the metrics with worsening results, there was an increase in the risk of post-cesarean section infection, risk of infection in the ICU, density of incidence of infection in the general internal medicine and density of incidence of infection caused by KPC. These metrics may have been influenced by the Covid-19 pandemic that caused a substantial overload to healthcare systems with hospital overcrowding, overload of teams, continuous and rapid changes in hospital practices, increased length of hospital stay, greater exposure to invasive devices, and shortage of drugs, materials and medical equipment (LASTINGER et al., 2022). In the study hospital, KPC was a microorganism recognized as one of the main institutional problems. This pathogen was identified by the World Health Organization (WHO) as of global priority due to the high risk of associated mortality, high rate of transmissibility, presenting reduced treatment arsenal and great repercussions for health services and the community (WHO, 2017, 2021e).

Prescribers receive direct and personalized feedback on ASP results with suggestions on procedures to enhance the quality of their prescriptions of antimicrobials. Even so, the study hospital recognizes this communication can be improved. The dissemination of ASP results was done twice a year in meetings involving HICC members and hospital leaderships, but the information was not systematically disseminated to all hospital workers. Future perspectives include the need to expand the process of continuous communication with healthcare professionals aiming to promote their engagement and the development of ASP actions in clinical practice (BARLAM et al.,

2016; BLEASDALE; BARNDEN; BARNES, 2019; BRASIL, 2017a, 2021b; DELLIT et al., 2007; DOERNBERG et al., 2018; DYAR et al., 2017; LUTHER et al., 2018).

The applicability of this study occurs through the possibility of mapping the reality of structure, working processes and results of ASP in Brazil and bringing potentially useful information for planning ASP implementation in other middle-income countries. Multiple influencing factors of ASP were discussed, highlighting not only the complexity of its implementation, but also data to be compared to other hospitals and countries. The employment of quality assessment in the healthcare environment for ASP was a potential strength of this research, along with the discussion of the complexity of this practice adapted to a real micropolitical context. Moreover, in the scope of pharmacoepidemiology, drug utilization studies are important to deepen the assessment of the performance of ASP on the effectiveness and safety of the use of antimicrobials.

The priorities for ASP improvement involve the dimensions of “structure” and “process”, but they are dependent on evidence of cost-effectiveness assessed in the context of middle-income countries. There is a need to broaden the discussion about the heterogeneity of ASPs in Brazil and around the world to refine the improvement of all dimension of quality in health. It is relevant to evaluate the feasibility and measurability of the Core Elements of Hospital Antibiotic Stewardship Programs proposed from CDC and checklist for global ASP, taking into account the specificities of healthcare systems in low- and middle-income countries (PULCINI et al., 2019).

There are some limitations to be addressed. Potential information bias may involve subjectivities related to the hospital self-assessment on the compliance with the essential elements listed for ASPs. Further studies should be developed to investigate the relationship between antimicrobial consumption and the emergence of resistance employing time series, bringing contributions to the decision-making process by the hospital leaderships on ASP actions.

## **CONCLUSION**

This study described the implementation of ASP in a teaching hospital, applying the Donabedian perspective. Although the hospital still does not have a classic ASP model, there were investments to improve structure, processes and results, aiming to comply with the international ASP guidelines. There was a high proportion of key elements of ASP in the hospital, following the national regulatory requirements and showing efforts to strengthen ASP implementation in the hospital. Further studies should

be developed to investigate aspects related to antimicrobial consumption and the emergence of microbial resistance.

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**Conflicts of Interest**

The authors declare no conflict of interest.

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**Author's contributions**

AFM, MAPM and CMB designed the study. EML, SSG and MAC participated in the design and data analysis and interpretation. CMB, AMMR, RPS, MK and MHNGA participated in the review and final approval of the version to be published. All author's interpreted the results and reviewed the text. All authors approved the final version of the manuscript.

## SUPPLEMENTARY MATERIAL

### I - Donabedian Triad of structure x processes x results in the last year of the study

#### Hospital Infection Control Committee (HICC)

STRUCTURE	PROCESS	RESULT
<p><b>Area (square meter)</b></p> <p>82m<sup>2</sup></p>	<p><b>Active search:</b> analysis of all medical records taking into consideration the following epidemiological clues: culture results, antibiotic therapy, radiological exams and signs and symptoms described by the physician. After discharge, surveillance of egresses: carried out by phone call, message via WhatsApp and return to the outpatient clinic, when over 90% of patients were reassessed by the physician.</p>	<p>Overall infection rate;</p> <p>Lethality rate of hospital infections;</p>
<p><b>Computers</b></p> <p>15 units</p> <p><b>Software</b></p> <p>Automated System for Hospital Infection Control (Sacih®), MV 2000i, MV SOUL</p>		
<p><b>Human Resources *</b></p> <p>3 physicians</p> <p>1 statistician</p> <p>5 nurses</p> <p>1 nursing technician</p> <p>3 nursing students</p>	<p><b>Antimicrobial evaluation:</b> performed by the HICC physician, daily, in all patients taking therapeutic or prophylactic antibiotics.</p> <p><b>Analysis and dissemination of epidemiological results:</b> reports are carried out with analysis by the HICC and discussion with clinical staff and management every six months.</p>	<p>Incidence densities of different types of infection.</p>

**Technical visits:** carried out in all hospital departments aiming to verifying if patient care processes are in accordance with the HICC protocols. The solution of non-conformities was discussed with the Quality Management Centre and the sectors involved.

### Hospital Pharmacy (HP)

<p><b>Area (square meter)</b></p> <p>403m<sup>2</sup></p>	<p><b>Selection:</b> the pharmacist participates in the process of drug selection, including antimicrobials, assessing cost-effectiveness and safety. The Pharmacy and Therapeutics Committee is coordinated by a pharmacist who conducts the process together with a multi-professional team.</p>	<p>Antimicrobial cost indicators;</p> <p>Indicators of antimicrobial consumption;</p>
<p><b>Computers</b></p> <p>8 units</p>		
<p><i>Software</i></p> <p>MV 2000, MV SOUL</p>		
<p><b>Human Resources*</b></p> <p>15 pharmacists</p> <p>78 pharmacy assistants</p> <p>12 Assistants of pharmaceutical supply center</p> <p>5 administrative assistants</p>	<p><b>Acquisition planning:</b> carried out annually by a pharmacist, based on consumption and seasonality reports.</p> <p><b>Medication acquisition:</b> carried out by a purchasing department. Technical analyses of documents and drug reports are carried out by a pharmacist.</p>	
	<p><b>Storage:</b> performed by a pharmaceutical supply center, following good medication storage practices. The process is</p>	

coordinated by a pharmacist who gives guidelines to the middle-level team. There are no pharmacy technicians in this unit. All product fractioning and unitization processes are performed at this step.

**Distribution:** this step is done by the middle level team, under the supervision of a pharmacist, based on the average consumption in the department. Satellite pharmacies are resupplied on a daily basis.

**Prescription, dispensing and use:** medication is dispensed in a mixed manner - oral liquid medications not subject to special control are dispensed to departments, and the other medications are dispensed individually to the patient, upon presentation of the computerized medical prescription. The restricted use antimicrobials undergo additional control, being released only after approval by the HICC and analysis by the pharmacist.

#### **Diagnostic support laboratory (DSL)**

**Area (square meter)**

28m<sup>2</sup>

**Computers**

3 units

**Standardization of sample collection, preservation and transportation:** the collection of biological material is done by the nursing team or by the medical team depending on the target anatomical site. The guidelines for

Collection fee;

Daily delivery of partial/total cultures;

Contamination index;

Report on frequency of isolation of multi-drug resistant pathogens, by

**Softwares**

MATRIX, MV 2000i, MV SOUL

preparation, collection and transportation of the sample to the laboratory are made by the microbiology team. type of sample and resistance mechanism;  
Compulsory notification.

**Equipaments**

Stove, autoclave, microscope, refrigerator, cold room, Bunsen burner, centrifuge, laminar flow hood, vortex, automated microbiology equipment: VITEK and BACTALERT

**Microscopic examination and staining:** direct tests may be performed without staining, Gram staining or other stains.

**Human Resources\***

33 clinical pathology technicians

5 laboratory analysts

3 microbiology analysts

3 administrative assistants

2 general services assistants

1 pathologist

1 coordinator

**Culture, isolation and identification:** clinical material will be evaluated with the microscopy results, directing the seeding procedures in specific media. The growth of microorganisms in the different culture media used provides the first information for their identification. Automated methods generally use the same tests as manual identification and increase the number of tests and can characterize with greater certainty and better discrimination of unusual genera and species.

**Sensitivity profile:** antimicrobial sensitivity tests are performed according to the CLSI criteria.

**Disclosure of results of sensitivity profile:** performed through partial and final reports, for decision making by the clinical staff and re-

evaluation of the empirical therapy in force.

**Analysis of changes in the sensitivity profile and investigation of multidrug-resistant microorganisms:** analyses of the frequency of appearance of multidrug-resistant pathogens, as well as identification of resistance mechanisms are shared with the HICC to feed back the management systems of antimicrobial use in the hospital.

\*In the Human Resources section, the total number of professionals in the HICC, HP and DSL departments was highlighted.

## II - Checklist of the essential elements

### Core elements of hospital antibiotic stewardship programs: assessment tool

Hospital Leadership Commitment	YES	NO
Does the hospital have a formal, written policy of support from senior hospital management in efforts to improve antimicrobial use in the institution?	X	
Does the policy ensure that staff in departments/sectors have sufficient time to contribute to activities related to antimicrobial use management?		X
Are there goals related to the control of antimicrobial use in the Hospital's Strategic Plan?	X	
Is there support for the training and continuing education of the hospital's health professionals on topics related to infection control, microbial resistance and management of antimicrobial use?	X	
Does the institution have a microbiology laboratory?	X	

Does the microbiology laboratory have automated systems for identification (or Maldi-TOF) or sensitivity testing (fusion disc or other tests that determine the minimum inhibitory concentration - MIC) and agility in providing culture/antibiogram results within 72 hours?	X	
Does the Hospital have an Antimicrobial Use Management Program?	X	
Are there human, financial and IT resources necessary to implement the Antimicrobial Use Management Program in the hospital?	X	
Do the components of the operational team have a specific time frame defined for the execution of the Program's actions?		X
<b>DEFINITION OF RESPONSIBILITY</b>	<b>YES</b>	<b>NO</b>
Is there a team of professionals responsible for controlling the use of antimicrobials in the hospital?	X	
If there is an Antimicrobial Stewardship Program in place:		
Has an operational team responsible for designing and implementing the Program been formally appointed?		X
Is there an appointed operational team leader who is responsible for the implementation and results of the hospital's Program?		X
Is the Program operational leader an infectious disease infectologist, a clinical pharmacist or other professional with expertise in infectious diseases?		X
Is there an appointed clinical pharmacist responsible for working towards managing the use of antimicrobials in the hospital?		X
Is the Program management team interdisciplinary?		X
Indicate the people below who are part of the program management team:		X
( ) Clinician ( ) Nurse ( ) Infectologist ( ) Clinical Pharmacist ( ) Microbiologist ( ) CCIH representative ( ) Quality control representative ( ) Microbiology laboratory representative ( )		

Pharmacy and Therapeutics Commission representative ( ) IT  
Technology representative ( ) Others

**EDUCATION** **YES** **NO**

Does the hospital have a continuing education program for its professionals aimed at increasing awareness of the use of antimicrobials? **X**

Does the hospital have an education program for patients and accompanying persons/caregivers on the correct use of antimicrobials? **X**

**DEVELOPMENT OF ACTIONS TO IMPROVE ANTIMICROBIAL PRESCRIBING**

**POLICIES** **YES** **NO**

Does the hospital have protocols for the main clinical syndromes, based on national guidelines and local epidemiological and microbiological profiles, to assist in the selection of antimicrobials for common clinical conditions? **X**

Are the protocols widely disseminated to all stakeholders and are professionals properly trained in their adoption? **X**

Does the hospital have an institutional policy that requires prescribers to document the dose, duration, and indication of all prescribed antimicrobials in the prescription? **X**

**STRATEGIC ACTIONS FOR THE MANAGEMENT OF ANTIMICROBIAL USE** **YES** **NO**

Is there a data collection tool for managing the use of antimicrobials? If yes, which ones? **X**

Is there a database for managing the use of antimicrobials? If yes, which? **X**

Does a physician or pharmacist review prescriptions for specific antimicrobial agents (i.e. prospective audit) in the hospital? **X**

Are prescribers informed about the compliance of their prescriptions after the audit has taken place? **X**

Does the hospital have a form-based restriction system for specific antimicrobials?	X	
Does the hospital have a pre-authorization system for specific antibiotics?	X	
Does the hospital reviewed of planned outpatient parenteral antibiotic therapy (OPAT)?	X	
Does the hospital pharmacy perform antimicrobial dose adjustments in cases of organic dysfunction of the patient?	X	
Is antimicrobial dose optimization (pharmacokinetics / pharmacodynamics) performed to optimize the treatment of microorganisms with reduced sensitivity?		X
Are there automatic alerts in situations where therapy is unnecessarily duplicated?	X	
Does the hospital have automatic time-sensitive stop orders for specific antimicrobial prescriptions, especially antibiotics administered for surgical prophylaxis?		X
Does the hospital perform de-escalation of antimicrobials when indicated?	X	
Does the hospital perform culture-guided antimicrobial therapy?	X	
Does the hospital perform serum monitoring? If yes, which?	X	
Does the hospital perform antimicrobial use management using biomarkers? If yes, which?		X
Does the hospital have protocols for treating the following infections and syndromes?		
Community acquired pneumonia	X	
Lower urinary tract infection	X	
Skin and soft tissue infection	X	
Pyelonephritis	X	
Surgical prophylaxis	X	
Sepsis	X	

Meningitis	X	
Empiric treatment for oxacillin-resistant <i>Staphylococcus aureus</i>	X	
<i>Clostridium difficile</i> infection - CDI	X	
Laboratory confirmed bloodstream infections	X	
<b>PROGRAM MONITORING PROCESS / USE AND CONSUMPTION INDICATORS</b>	<b>YES</b>	<b>NO</b>
Does your Antimicrobial Stewardship Program monitor adherence to documentation policies (dose, duration and indication)?	X	
Does your Program monitor adherence to the institution's clinical protocols?	X	
Does the hospital monitor antimicrobial prescriptions with suspension/revision?	X	
The hospital monitors antimicrobial use (consumption) on the units or in the institution by one of the following measures:		
By the average amount, in grams, of antimicrobials used per patient (Defined Daily Dose - DDD)?	X	
By the counts of antimicrobial (s) administered to patients per day (Days of Therapy - DOT)?		X
By the number of days the patient receives antimicrobial(s) regardless of the number of drugs (Length of therapy - LOT)?		X
<b>RESULT INDICATORS / OUTCOME</b>	<b>YES</b>	<b>NO</b>
Does the hospital track <i>C. difficile</i> infection rates?	X	
Does the hospital monitor costs on antimicrobial consumption?	X	
<b>DISSEMINATION OF RESULTS</b>	<b>YES</b>	<b>NO</b>
Has the updated antimicrobial sensitivity profile been disseminated to prescribers in your hospital?	X	
Have prescribers received direct and personalized communication on how they can improve their antimicrobial prescribing?	X	

If the Hospital has an Antimicrobial Stewardship Program

Do you periodically disseminate the results of the Program to all professionals in the Hospital?	X
Does your Program operational team disseminate specific reports on antimicrobial use to prescribers?	X
Is information on antimicrobial use and microbial resistance regularly passed to all sectors of the hospital relevant to the Program?	X
Have the results, objectives and targets been disseminated to senior hospital management and all sectors involved in the Program?	X

Artigo 2: *Antimicrobial Stewardship Program: impact of COVID-19 in time series of antibacterial use and microbial resistance in a public teaching hospital*, a ser submetido ao periódico *The Lancet Regional Health – Americas* (ISSN 2667-193X), sem fator de impacto no momento

\**The Lancet Regional Health – Americas* é uma nova revista de acesso aberto, lançada em 2021, parte da iniciativa global da Lancet de defender a qualidade e o acesso aos cuidados de saúde em todas as regiões do mundo. O Fator de Impacto mede o número médio de citações recebidas em um determinado ano por artigos publicados na revista durante os dois anos anteriores.

**Antimicrobial Stewardship Program: impact of COVID-19 in time series of antibacterial use and microbial resistance in a public teaching hospital**

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## SUMMARY

**Background:** Antimicrobial resistance (AMR) is considered one of the main global challenges in public health. This study aimed to analyse the antibacterial consumption (ATBc), and the incidence of multidrug-resistant organisms (MDRO) in a Brazilian teaching hospital. **Method:** The ATBc was measured by defined daily doses (DDD) calculated per 1000 patient-days. The incidence of MDRO was collected from the hospital infection control committee (HICC) specialized reports. Changes in ATBc and MDRO incidence over time was explained by the composite annual growth rate (CAGR) that is presented by the average yearly change as a proportion (%) of the consumption in the starting year. The ESKAPE is an acronym for six highly virulent and antibacterial-resistant bacterial pathogens, on which we focused. **Findings:** Daptomycin and linezolid had the a positive increase in consumption during the study period (39.4 and 27.7%, respectively), followed by the polymyxins (9.8%). The MDRO of the ESKAPE group with the highest variation in the period were *Staphylococcus (aureus, coagulase-negative, sp)* (29.2%), *Enterococcus (faecium, faecalis, sp)* (27.8%) and *Acinetobacter (baumannii, sp)* (18.4%). Other MDRO, outside the ESKAPE group, had significant variation, such as *Providencia sp* (51.2%) and *Clostridioides difficile* (37.7%). **Interpretation:** The COVID-19 pandemic may have reinforced the deterioration of the scenario of accelerating AMR increase. This warrants further surveillance data investigations to assess the pandemic's impact on AMR epidemiological trends. **Funding:** This study was partially financed by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001. No other funding was received.

**Keywords:** Antimicrobial Stewardship; Drug Utilization Review; Drug Resistance, Microbial; Outcome Assessment, Health Care; Pharmacoepidemiology; COVID-19.

## INTRODUCTION

Antimicrobial resistance (AMR) is considered one of the main global challenges in public health nowadays (HOFER, 2019) due to its potential impact on human and animal health, as well as a significant increase in healthcare costs (BRASIL, 2021a; WHO, 2017, 2021b). AMR is a natural evolutionary phenomenon for microorganisms that can be accelerated by inappropriate human practices, such as excessive use of antimicrobials (JINDAL; PANDYA; KHAN, 2015). To reduce the pace of AMR emergence, multiple actions need to be adopted, such as the provision of basic sanitation, clean water, rigorous protocols to guide the rational use of antimicrobials, investments in public health and more homogeneous regulatory policies across the globe - both in public and private sectors (HOFER, 2019).

Antimicrobial Stewardship Programs (ASP) represent a useful strategy consisting of actions to promote the responsible use of antimicrobials (PEREZ et al., 2020). Several metrics have been proposed to adequately monitor ASP performance, regarding process and outcome measures, such as: quality of antimicrobials use, microbial resistance, *Clostridioides difficile* infection rates, length of hospital stay, readmission rates, mortality estimates and costs (BRASIL, 2017a).

The emergence of COVID-19 at the end of 2019 brought a global health emergency, overstressing healthcare systems, and represented an additional challenge to planning actions to reduce the AMR emergence. Hospital infection control and ASP activities were impacted and weakened during the COVID-19 pandemic (FUKUSHIGE et al., 2022). Several factors contributed, such as the burden on health services, complexity of care in the context of the new disease, structural difficulties of services to accommodate patients, changes in hygiene and cleaning procedures, and expansion of the professional staff without proper training for the care of critically ill patients (OPAS, 2021).

Trends in antimicrobial use during the pandemic were heterogeneous when compared at the community and hospital level (FUKUSHIGE et al., 2022). Despite the low incidence of secondary bacterial infections, nearly three-quarters of all COVID-19 patients were treated with at least one antimicrobial, especially in the early phase of the pandemic (KARIYAWASAM et al., 2022; RUSSELL et al., 2021). Antibacterial use was reported in approximately 60% of patients diagnosed with COVID-19, although bacterial infection rates in these patients were around 5% (KARIYAWASAM et al., 2022). At the

hospital level, an upward trend in antimicrobial use was recorded during the pandemic, which may also be related to the discontinuation of ASP. Together, these factors contributed to the increase in inappropriate use of antibiotics (FUKUSHIGE et al., 2022).

The increase in ATBc resulting from the pandemic jeopardizes the progress achieved in combating AMR. It is mandatory to reverse this damage and continue to make progress in antimicrobial stewardship. However, the initiatives are still heterogeneous among high-, middle- and low-income countries (COX et al., 2017), and data are still scarce. Such information is critical to support the implementation of effective measures and interventions (FUKUSHIGE et al., 2022).

By October 2022, according to Our World in Data, Brazil ranked the 15th in the world for proportionate deaths from COVID-19, with 3,221 deaths per million inhabitants (DONG; DU; GARDNER, 2020). In this context, it would be relevant to discuss pre- and post-pandemic ASP outcomes, and explore potential impacts on antimicrobial consumption and AMR. Thus, regarding the wide use of antimicrobials in COVID-19 patients, even with no confirmed secondary infections, and the high number of cases and deaths in Brazil, the study aimed to analyse the consumption of antibacterial, and the epidemiological distribution of multidrug-resistant organisms (MDRO) in a Brazilian teaching hospital from 2015 to 2021.

## **METHODS**

### **Study area**

The study setting was a general public teaching hospital which belongs to the Brazilian Unified Health System. This 392-bed hospital is a referral center for more than 1.2 million people living in the region of Belo Horizonte, Minas Gerais State, in Southeast Brazil. The hospital provides care for about 50 thousand patients per year, encompassing medium and high complexity assistance for clinical, surgical and polytrauma emergencies, as well as maternal and child care. The population assisted is mainly adults and has a heterogeneous profile.

The antimicrobial formulary, including the standardised drugs, is available in the computerized physician order entry (CPOE). The computer system requires the record of the reason for indication of all antimicrobials prescribed. Reserve antimicrobials, broad-spectrum and/or high-cost antimicrobials are dispensed only after review by a clinical pharmacist and by the hospital infection control committee (HICC). The main strategies for infection control focused on AMR at the hospital of study involve active search, antimicrobial evaluation, analysis and dissemination of epidemiological results and technical visits.

### **Study design**

This study was a time series using data collected retrospectively from January 2021 to December 2021. This time series was performed by analyzing aggregated data available in the hospital database. The Institutional Ethics Committee approved the study protocol of the Universidade Federal de Minas Gerais (CAAE 54060321.8.0000.5149). The informed consent form was waived because there was no recruitment of individual participants.

### **Data source**

Medication consumption data were obtained by means of HP reports issued via computerized management software - MV 2000i<sup>®</sup>/MV Soul<sup>®</sup>. Microbial resistance data were obtained from the laboratory management software - Matrix<sup>®</sup>.

### **Definition of variables – antibacterial consumption**

The consumption of antibacterial agents and the frequency of MDRO were variables of interest in this study. The consumption of antimicrobials was measured by defined daily doses (DDD), the metrics adopted by the HICC, following the guidelines proposed by WHO (WHO, 2022). DDD was calculated per 1000 patient-days, and the latest ATC/DDD index was applied for the study period. Data on antimicrobial consumption was collected from reports and calculated by subtracting the number of antimicrobial units dispensed less the number of antimicrobial units returned to the hospital pharmacy. Data on antimicrobial consumption was extracted from MV 2000i<sup>®</sup>, MV Soul<sup>®</sup> and Matrix<sup>®</sup> softwares. Afterwards, data were tabulated in a Microsoft Office Excel (2003) spreadsheet and plotted serially over the years, monthly, from January 2015 to December 2021. The antibacterial agents of interest in this study were those antibacterials standardized in the hospital and listed by the Brazilian Health Regulatory Agency (Anvisa) with mandatory monitoring for hospitals providing intensive care. Data on antibacterials were presented by drug (categorised by 2021 ATC code and 2021 AWaRe classification) and then by therapeutic class (ATC 2021 classification).

### **Definition of variables – MDRO**

The results for all microbiological cultures (including clinical and surveillance cultures) were manually recorded in the hospital management software by the HICC nurses to guide the healthcare team on specific procedures required by patients, such as contact precautions. There was no change in the surveillance criteria during the period of study. Thus, the incidence of MDRO was collected from the HICC specialized reports and then exported to a Microsoft Excel (2003) spreadsheet. The definition of MDRO was the resistance of microorganisms to three or more classes of tested antimicrobials (BRASIL, 2021a). Data on MDRO were classified according to the list proposed by WHO that mentions the global priority pathogens. The group designated by the acronym ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter species*) was assigned with the highest priority status due to its significant threat to humans (MANCUSO et al., 2021). Inconclusive results were excluded from the sample, encompassing microorganisms categorized in the laboratory database as “other Gram-

positive”, "other Gram-negative", "other", "missed test", “toxin for *C. difficile* negative or indeterminate” or "under identification". The other microorganisms, not belonging to the ESKAPE group, were categorised as Non-ESKAPE. The flowchart detailing the study design is depicted in Figure 1.

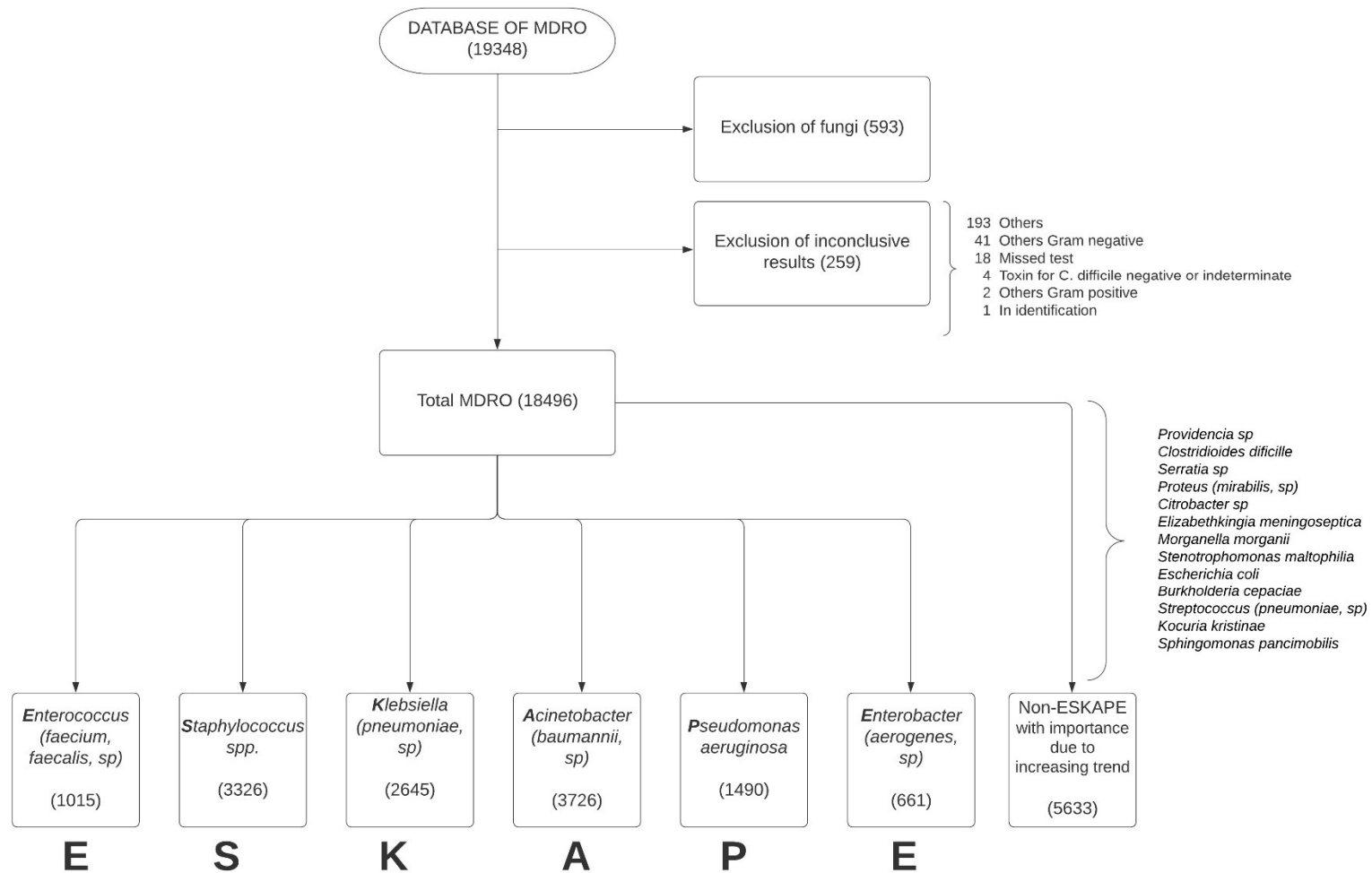


Figure 1- Protocol Design - Inclusion and Exclusion Criteria (ESKAPE group: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* species. Abbreviation: MDRO, multidrug-resistant organisms.

The compound annual growth rate (CAGR) was used to calculate the annual changes in antimicrobial consumption and the incidence of MDRO pathogens. The first calculation of CAGR was obtained by using the RRI function of Microsoft Excel<sup>®</sup> (2003) subtracting the last year of the study (2021) to the first year (2015), corresponding to the notation CAGR<sub>t</sub>. The second calculation of CAGR was obtained by the same function (TAXAJURO) subtracting the last year (2021) until the first year before the pandemic (2019), corresponding to the notation CAGR<sub>p</sub>. Delta coefficient ( $\Delta$ ) was calculated by subtracting CAGR<sub>p</sub> by CAGR<sub>t</sub>. All statistical analyses were performed using R statistical software (version 4.0; R Foundation for Statistical Computing, Vienna, Austria). The study was conducted and reported according to the guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE-AMS) reporting epidemiological studies focused on the relationship between MDRO and antimicrobial use.

## RESULTS

The CAGR<sub>t</sub> revealed four antibacterials with an increasing consumption trend (ceftriaxone, piperacillin-tazobactam, levofloxacin oral, and ampicillin-sulbactam), two with a decreasing trend (daptomycin and ceftazidime) and 11 with a stable trend, as detailed in Table 1. The consumption of polymyxin E could not be estimated because of null DDD in the first year of analysis.

Overall, the results for CAGR<sub>p</sub> revealed seven antimicrobials with an upward consumption trend (daptomycin, linezolid parenteral, levofloxacin parenteral, tigecycline, vancomycin, ceftriaxone, piperacillin-tazobactam), two with a downward trend (ciprofloxacin parenteral and ceftazidime) and eight with a stable trend. The variation of DDD per 1000 patient-days by each antimicrobial assessed across years is also presented in Table 1.

Polymyxin E, also called colistin, was not included in antimicrobial hospital formulary at the beginning of this time series. However, due to market fluctuations, and drug shortage of polymyxin B, colistin came to be incorporated as a therapeutic alternative and therefore could be monitored for DDD results until 2020. The DDD of polymyxins showed a downward trend in the total period, revealed by CAGR<sub>t</sub>=-5.0%, but an upward trend in the pandemic period CAGR<sub>p</sub>=4.8%, resulting in an increase in consumption of 9.8 %.

Table 1 - Variation of the DDD (defined daily dose) per 1000 patient-days of antibacterials

ATC code	AWaRe Classification (2021)	Defined daily dose (DDD) per 1000 patient-days	2015	2016	2017	2018	2019	2020	2021	Time Series	CAGRt	CAGRp	Δ
J01XB01	Reserve	Polymyxin E - Colistin	0.0	0.0	0.0	0.0	0.0	33.5	111.6		N/A	N/A	N/A
J01XX09	Reserve	Daptomycin	140.7	72.2	38.6	26.8	8.7	18.4	11.4		-30.2%	9.2%	39.4%
J01XX08	Reserve	Linezolid parenteral	36.8	78.9	53.0	39.2	16.9	39.7	34.5		-0.9%	26.7%	27.7%
J01MA12	Watch	Parenteral levofloxacin	60.0	64.8	72.1	43.7	57.1	43.2	85.6		5.2%	14.5%	9.2%
J01GB06	Access	Amikacin	222.3	75.6	84.5	119.1	143.6	101.5	154.6		-5.1%	2.5%	7.5%
J01AA12	Reserve	Tigecycline	88.1	100.7	78.5	86.0	81.3	92.5	105.9		2.7%	9.2%	6.5%
J01XA01	Watch	Vancomycin	558.0	537.2	473.3	535.7	525.2	558.8	687.1		3.0%	9.4%	6.4%
J01DD04	Watch	Ceftriaxone	790.9	757.5	891.5	855.3	986.5	1450.4	1521.3		9.8%	15.5%	5.7%
J01DE01	Watch	Cefepime	450.3	458.2	401.1	454.7	416.2	412.4	455.5		0.2%	3.1%	2.9%
J01CR05	Watch	Piperacillin-tazobactam	296.1	327.1	493.8	428.2	442.6	517.2	654.5		12.0%	13.9%	1.9%
J01XB02	Reserve	Polymyxin B	426.8	383.6	338.5	299.8	258.8	291.4	186.3		-11.2%	-10.4%	0.8%
J01DH02	Watch	Meropenem	769.6	854.0	812.5	924.0	909.5	934.9	966.5		3.3%	2.0%	-1.3%
J01XA02	Watch	Teicoplanin	315.1	331.9	329.7	308.0	242.8	291.0	181.3		-7.6%	-9.3%	-1.7%
J01MA02	Watch	Ciprofloxacin oral	139.5	142.1	123.2	162.5	117.6	63.7	82.3		-7.3%	-11.2%	-4.0%
J01MA02	Watch	Parenteral ciprofloxacin	129.9	68.4	78.1	95.3	76.4	39.5	28.3		-19.6%	-28.2%	-8.6%
J01MA12	Watch	Levofloxacin oral	98.6	208.9	209.4	344.7	371.0	232.5	267.0		15.3%	-10.4%	-25.7%
J01DD02	Watch	Ceftazidime	95.8	82.5	46.1	91.7	146.0	66.5	9.5		-28.1%	-59.8%	-31.7%
J01CR01	Access	Ampicillin-sulbactam	2.06	24.4	20.2	27.4	16.0	21.5	15.7		33.7%	-0.6%	-34.3%

ATC Code - Tool for drug utilization monitoring and research in order to improve quality of drug use

AWaRe Classification - Tool for monitoring antibiotic consumption, defining targets and monitoring the effects of stewardship policies that aim to optimize antibiotic use and curb antimicrobial resistance

DDD - Defined daily dose is the assumed average maintenance dose per day for a drug used for its main indication in adults

CAGRt - Compound Annual Growth Rate the total period (2015 to 2021)

CAGRp - Compound Annual Growth Rate the pandemic period (2019 to 2021)

Δ - Variation of CAGRp-C.

N/A = Not applicable. Trend analyses was not performed and CAGR not calculated because of missing data, changes in the type of data or change in data process

Time-serie red and black dots indicate maximal and minimal values in the time interval

Antibacterial consumption assessment grouped by class showed a downward trend before the pandemic for “other antibacterials” (CAGR<sub>t</sub>=-17.6%), “polymyxins” (CAGR<sub>t</sub>=-5.0), “other aminoglycosides” (CAGR<sub>t</sub>=-5.1), “tetracyclines” (CAGR<sub>t</sub>=2.7), “glycopeptide antibacterials” (CAGR<sub>t</sub>=-0.1), and “fourth-generation cephalosporins” (CAGR<sub>t</sub>=0.2). . The class “combinations of penicillins, including beta-lactamase inhibitors and “carbapenems” showed an increasing trend. The other classes revealed a stable trend in consumption. The variation of DDD by each antibacterials class assessed across years is detailed in Table 2.

Regarding the occurrence of MDRO, among the pathogens included in the ESKAPE group, *Acinetobacter (baumanii, sp)*, *Pseudomonas aeruginosa* and *Enterobacter (aerogenes, sp)* presented a decreasing trend in CAGRt. Upon evaluating CAGR<sub>p</sub>, the incidence of *Staphylococcus (aureus, coagulase-negative, sp)* and *Enterococcus (faecium, faecalis, sp)* tended to increase (CAGR<sub>p</sub>=49.6% and 47.6%, respectively). The evaluation of the variation between CACR<sub>t</sub> and CAGR<sub>p</sub> for the MDROs showed the most significant increase in the trend for *Enterococcus (faecium, faecalis, sp)*, *Staphylococcus (aureus, coagulase-negative, sp)*, and *Acinetobacter*

Table 2 - Variation of the DDD (defined daily dose) per 1000 patient-days of of the therapeutic classes (ATC Classification,2021)

Classification	Name	2015	2016	2017	2018	2019	2020	2021	Time Series	CAGR
Antibiotics	Linezolid + Daptomycin	177.5	151.2	91.6	66.1	25.7	58.1	45.8		-17.6%
	Polymyxin E (Colistin) + Polymyxin B	426.8	383.6	338.5	299.8	258.8	325.0	297.9		-5.0%
Aminoglycosides	Amikacin	222.3	75.6	84.5	119.1	143.6	101.5	154.6		-5.1%
	Tigecycline	88.1	100.7	78.5	86.0	81.3	92.5	105.9		2.7%
Antibacterials	Vancomycin + Teicoplanin	873.2	869.1	803.0	843.6	767.9	849.9	868.3		-0.1%
Anti-cephalosporins	Cefepime	450.3	458.2	401.1	454.7	416.2	412.4	455.5		0.2%
Anti-cephalosporins	Ceftazidime + Ceftriaxone	886.7	840.1	937.7	947.0	1132.5	1516.9	1530.8		8.1%
Penicillins, including beta-lactams	Ampicillin-sulbactam + Piperacillin-tazobactam	298.2	351.4	514.0	455.5	458.6	538.8	670.3		12.3%
	Meropenem	769.6	854.0	812.5	924.0	909.5	934.9	966.5		3.3%
	Ciprofloxacin + Levofloxacin	428.0	484.2	482.7	646.1	622.1	378.9	463.2		1.1%

Drug utilization monitoring and research in order to improve quality of drug use

Name of the substance (normally the INN name) or the name of the ATC level.

DDD: the assumed average maintenance dose per day for a drug used for its main indication in adults

CAGR<sub>t</sub>: Compound Annual Growth Rate the total period (2015 to 2021)

CAGR<sub>p</sub>: Compound Annual Growth Rate the pandemic period (2019 to 2021)






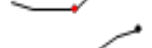

CACR<sub>t</sub>

When the analysis was not performed and CAGR not calculated because of missing data, changes in the type of data or change in data process

▲ and ▼ indicate maximal and minimal values in the time interval

(*baumanii, sp*). Detailed data on MDRO results across years is presented in Table 3.

**Table 3 - Variation of the multidrug-resistant organism grouped according to the WHO list of global priority pathogens**

Multidrug-resistant organism (MDRO)	2015	2016	2017	2018	2019	2020	2021	Time Series	CAGRt	CAGRp	Δ
<i>Enterococcus (faecium, faecalis, sp)</i>	132	132	83	45	94	227	302		12.6%	47.6%	35.0%
<i>Staphylococcus (aureus, coagulase-negative, sp)</i>	399	240	152	147	333	941	1114		15.8%	49.6%	33.8%
<i>Acinetobacter (baumannii, sp)</i>	852	793	499	329	352	351	550		-6.1%	16.0%	22.1%
Non-ESKAPE	350	202	317	394	842	1798	1730		25.6%	27.1%	1.5%
<i>Pseudomonas aeruginosa</i>	183	143	140	139	248	326	311		7.9%	7.8%	0.0%
<i>Klebsiella (pneumoniae, sp)</i>	156	170	258	370	393	579	719		24.4%	22.3%	-2.1%
<i>Enterobacter (aerogenes, sp)</i>	65	73	80	62	98	168	115		8.5%	5.5%	-3.0%

CAGRt - Compound Annual Growth Rate the total period (2015 to 2021)

CAGRp - Compound Annual Growth Rate the pandemic period (2019 to 2021)

Δ – Variation of CAGRp-CAGRt

N/A = Not applicable. Trend analyses was not performed and CAGR not calculated because of missing data, changes in the type of data or change in data process

Time-serie red and black dots indicate maximal and minimal values in the time interval

The ESKAPE group: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter species*.

Non-ESKAPE – represents all other MDROs identified, with importance due to the increasing trend

MDRO - Multidrug-resistant organism

WHO - World Health Organization

The quantitative of "Non-ESKAPE" MDRO increased considerably in the pandemic years, ranging from 17% of MDRO in 2015 to approximately 45% in 2020 and 35% in 2021. Data on "Non-ESKAPE" is presented in Figure 2 and detailed in Table 4. In this context, the largest increase in incidence was of the bacteria of the genus *Providencia* ( $\Delta=57.0\%$ ), followed by *Clostridioides difficile* ( $\Delta=35.7\%$ ). Detailed data on "Non-ESKAPE" MDRO results across years is presented in Table 4.

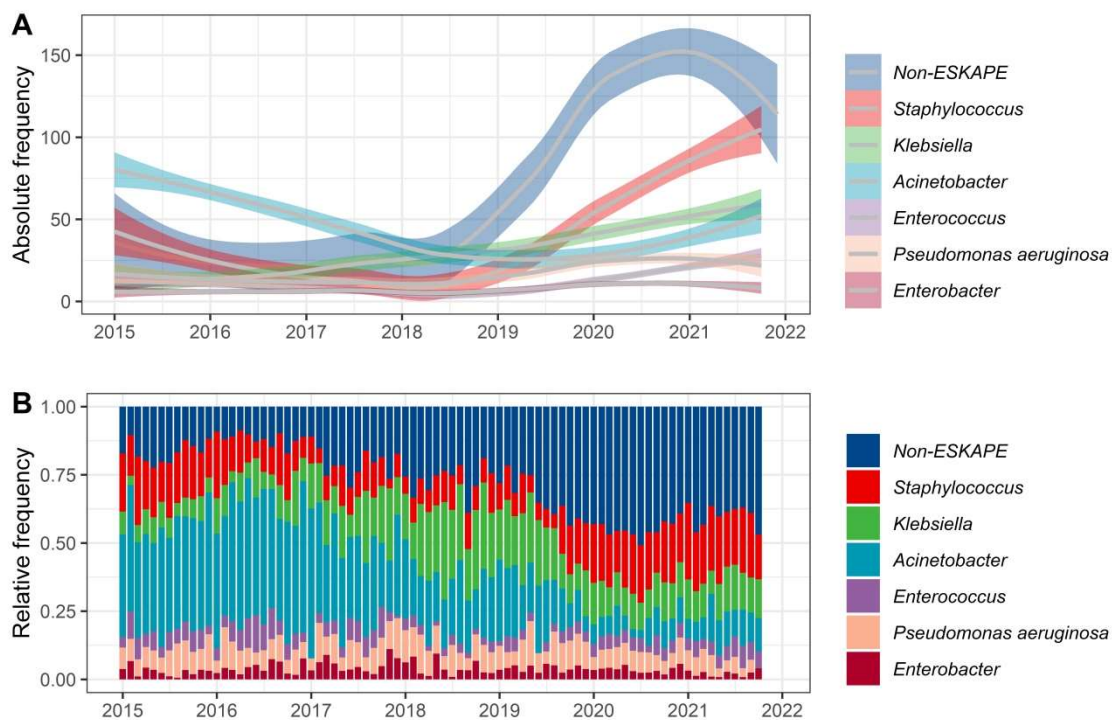


Figure 2 - Absolute and relative frequency of incidence of multidrug-resistant organisms (MDRO).

The ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species).

Table 4 - Discrimination of pathogens MDRO categorized as "Non-ESKAPE"

"Non-ESKAPE" Multidrug-resistant organism	2015	2016	2017	2018	2019	2020	2021	Time Series	CAGRt	CAGRp	$\Delta$
<i>Providencia sp</i>	25	5	4	15	4	15	13		-8.9%	48.1%	57.0%
<i>Clostridioides difficile</i>	15	11	0	0	6	14	15		0.0%	35.7%	35.7%
<i>Serratia sp</i>	88	4	68	100	80	162	146		7.5%	22.2%	14.7%
<i>Proteus (mirabilis, sp)</i>	71	51	45	57	89	181	221		17.6%	35.4%	17.8%
<i>Citrobacter sp</i>	15	5	11	7	23	61	54		20.1%	32.9%	12.8%
<i>Elizabethkingia meningoseptica</i>	0	0	0	1	0	0	0		0.0%	0.0%	0.0%
<i>Morganella morganii</i>	10	10	10	6	25	73	60		29.2%	33.9%	4.7%
<i>Stenotrophomonas maltophilia</i>	22	20	19	27	33	25	39		8.5%	5.7%	-2.8%
<i>Escherichia coli</i>	83	84	157	178	556	1136	1063		43.9%	24.1%	-19.8%
<i>Burkholderia cepaciae</i>	13	10	3	3	12	14	1		-30.7%	-56.3%	-25.6%
<i>Streptococcus (pneumoniae, sp)</i>	0	0	0	0	14	117	117		N/A	N/A	N/A
<i>Kocuria kristinae</i>	6	1	0	0	0	0	0		N/A	N/A	N/A
<i>Sphingomonas pancimobilis</i>	2	1	0	0	0	0	1		N/A	N/A	N/A

CAGRt - Compound Annual Growth Rate the total period (2015 to 2021)

CAGRp - Compound Annual Growth Rate the pandemic period (2019 to 2021)

$\Delta$  – Variation of CAGRp-CAGRt

N/A = Not applicable. Trend analyses was not performed and CAGR not calculated because of missing data, changes in the type of data or change in data process

Time-serie red and black dots indicate maximal and minimal values in the time interval

The ESKAPE group: *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter species*.

Non-ESKAPE – represents all other MDROs identified, with importance due to the increasing trend

MDRO - Multidrug-resistant organism

WHO - World Health Organization

## DISCUSSION

In this seven-year retrospective study assessing important ASP metrics, there was a change in the trend for ATBc, and in the incidence of MDRO with the occurrence of the COVID-19 pandemic. Three of the ten antibacterial classes monitored had their trends altered by the pandemic, represented by an increase in lipopeptides and oxazolidinones and a decrease in quinolones. Two of the six microorganisms of the ESKAPE group increased their incidence considerably – *Enterococcus spp* and *Staphylococcus spp*.

The increase in the consumption of antimicrobials has been previously highlighted in healthcare contexts with a low rate of bacterial co-infections in patients with COVID-19, which has been paradoxically related to excessive prescription of antibacterials (LUCIEN et al., 2021; WEINER-LASTINGER et al., 2022). However, such findings are limited to single-center retrospective studies and deserve further investigations. A systematic review with meta-analysis reported an estimated incidence of 7-8% of hospitalized patients in general hospitals and 14% of intensive care unit (ICU) patients diagnosed with secondary infection (sepsis, nosocomial pneumonia). However, 72% of COVID-19 patients received broad-spectrum antibacterials (LANSBURY et al., 2020).

The classes with the highest variation in ATBc were the lipopeptides and the oxazolidinones, represented by daptomycin and linezolid, respectively. These antimicrobials were selected for reserved use in the hospital of study, being indicated for infections caused by vancomycin-resistant enterococci (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA) in patients allergic to glycopeptides (vancomycin or teicoplanin), and patients with renal or hematological dysfunction (leucopenia). This increase may suggest an increased prevalence of VRE and MRSA, which other authors have pointed out in the same period (O'TOOLE, 2021; POLLY et al., 2022). However, further investigations should confirm this hypothesis since the method employed in the present study categorized the MDROs with no specification of the resistance mechanisms involved.

Polymixins represented another class with increasing in consumption that was analyzed by the combined data for the consumption of polymyxin B and colistin. According to HICC statistical analyses, the standard empiric regimen aiming to cover 95% of the most prevalent potential pathogens in the intensive care unit (ICU) of the

studied hospital was the triple association of meropenem, vancomycin and polymyxin. Polymyxins are active against a large portion of the gram-negative bacilli of clinical relevance, especially *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Enterobacter spp.*, *Klebsiella pneumoniae*, and *Escherichia coli*. These same microorganisms also showed an upward trend in other studies (DE CARVALHO et al., 2022; MAURER; HOGAN; WALKER, 2021; RUSSO et al., 2022). With no availability of polymyxin, colistin had been used during specific periods, and without both, the drug of choice was tigecycline, administered in double doses. Inappropriate drug replacements have been reported as a consequence of drug shortage with a potential impact on the quality and safety of drug therapy (SHUKAR et al., 2021).

Studies have demonstrated a sustained increase in the spread of multidrug-resistant bacteria, endorsing the framing of reliable and comparable methods for generating data on AMR globally (O'NEILL, 2016; WHO, 2021b). The microorganisms considered a global priority by WHO were also the most prevalent MDRO in the hospital of study. The upward trend was intensified during the pandemic for *Staphylococcus (aureus, negative coagulase, sp)*, which is in line with reports from other countries (CULTRERA et al., 2021; SAINI et al., 2021). *Enterococcus (faecium, faecalis, sp)* also significantly increased during the pandemic. Viral infections are suspected of altering the bacterial microbiome, which benefits the growth of *Enterococcus* and increases intestinal permeability, favoring the development of invasive infections (TOC et al., 2022). The third highest variation among the MDRO was related to *Acinetobacter (baumanii, sp)*, an opportunistic pathogen, highly prevalent in ventilator-associated pneumonia and bloodstream infections, with increased incidence during the COVID-19 pandemic also reported in several countries (LUCIEN et al., 2021; RANGEL; CHAGAS; DE-SIMONE, 2021; RUSSO et al., 2022). The cytokine storm generated in response to the viral infection required clinical management with immunosuppressive drugs, such as corticoids. The immunosuppression could facilitate the proliferation of opportunistic pathogens, such as *Acinetobacter (baumanii, sp)*, and this assumption needs clarification.

Part of the burden imposed by the COVID-19 pandemic was related to the overload on healthcare systems, which surely had repercussions on infection prevention and control routines in institutions (5). The hospital structure could also influence the incidence of healthcare-associated infections (HCAI) and work processes, as proposed by Donabedian (23). Some of the changes in the structure and processes were observed worldwide, such as the limited supply of personal protective equipment and medicines,

such as polymyxins, changes in cleaning and procedures of the environment disinfection, difficulty in allocating patients to private rooms/cohort units, among other factors (BRASIL, 2021a; MAURER; HOGAN; WALKER, 2021). This multifactorial impact on structure and work processes may explain the registered increase in the incidence of *C. difficile*, recognized as a marker of antibacterial overuse and easily transmissible by spores.

The strengths of our study include a long-term computerized database with no missing data since 2015 regarding outcomes recommended for ASP follow-up. We did not find a large study with comparative information covering the period before and during the COVID-19 pandemic. Our data provide helpful information for a better understanding of how antimicrobial consumption and resistance have evolved in a public hospital in a middle-income country. The results of this study suggest that further studies should be carried out and signal priorities for actions to improve healthcare practices for infection control in the studied hospital. A legacy of this study is the systematization of a tool to continue monitoring the DDD and the incidence of MDRO, in a more automated way, facilitating the work of the HICC, hospital pharmacy and the ASP operational team.

Drug utilization studies should consider the COVID-19 pandemic if they aim to measure the impact of changes in policy or prescribing that overlaps with the pandemic. We suggest to either account for these changes by comparing to historical controls or when contextualizing drug utilization shifts during this time period, interpreting that it could be due to the COVID-19 pandemic.

There are some limitations to be addressed. Firstly, it is a single-center study, hindering the possibility to generalize the findings to our country. And finally, although the microorganisms were classified as MDRO, their resistance profile was not determined in this study.

## CONCLUSION

This study allowed the analyses of the consumption of antimicrobials and the distribution of the main MDROs from 2015 to 2021 in a public teaching hospital in Brazil. There was a significant increase in the consumption of “other antibacterials” (daptomycin and linezolid) and polymyxins. *Staphylococcus (aureus, negative coagulase, sp)*, *Enterococcus (faecium, faecalis, sp)* and *Acinetobacter (baumanii, sp)* had the highest upward tendency in the hospital of study during the COVID-19 pandemic. Further deterioration in the scenario of accelerating AMR increase may be associated with the occurrence of the pandemic. This warrants further investigations of surveillance data to assess the AMR epidemiological trends and establish strategies to mitigate the problem.

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**Conflicts of Interest**

The authors declare no conflict of interest.

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**Author's contributions**

AFM, MAPM and CMB designed the study. BCFD assisted with data collection. RPS carried out the statistical analyses. EML, MHNGA, LRV, CDCA and AFFS participated in data interpretation. AFM drafted the manuscript. All authors critically reviewed the text and approved the final version of the manuscript.

## 5 CONSIDERAÇÕES FINAIS

Esse trabalho explorou a dinâmica de enfrentamento da RMM em um hospital público brasileiro, dada a lacuna científica nas publicações dessa temática em países de baixa-média renda. Para compreender o impacto da utilização de antimicrobianos sobre a RMM, definiu-se cinco objetivos específicos. O primeiro, pretendia caracterizar o ASP, avaliando a estrutura física, os principais processos de trabalho para o gerenciamento de antimicrobianos e levantar os indicadores monitorados na instituição. O segundo e o terceiro, visavam calcular o consumo de antimicrobianos e avaliar a tendência de evolução temporal desse uso. O quarto objetivo, pretendia avaliar a tendência de evolução temporal de aparecimento de MDRO, e por fim, estas métricas seriam correlacionadas.

A análise permitiu concluir que embora o hospital atenda a um alto percentual das ações exigidas para um ASP, ficou evidente que a instituição não emprega o arcabouço clássico de “estrutura, processos e resultados” para conduzir o Programa. Quanto as métricas de consumo de antimicrobianos, concentramos a análise nos antibacterianos, indicando significativo aumento no consumo de lipopeptídeos (daptomicina), oxazolidinonas (linezolida) e polipeptídeos (polimixina B e colistina). Os patógenos do grupo ESKAPE, são aqueles de maior prioridade, a nível mundial, para pesquisa e desenvolvimento, conforme publicações da OMS. Como esperado, as bactérias do grupo ESKAPE também protagonizaram a lista de MDRO nesta instituição. O *Staphylococcus (aureus, coagulase negativa, sp)*, *Enterococcus (faecium, faecalis, sp)* e *Acinetobacter (baumanii, sp)* tiveram a mais expressiva tendência de aumento, durante a pandemia da COVID-19.

É consenso de que um maior consumo de antimicrobianos, impacta no aparecimento da resistência microbiana a medicamentos, no entanto, permanece em aberto a compreensão do impacto da pandemia nesse processo. A correlação entre a série temporal da tendência de consumo de antimicrobianos e da tendência de aumento de MDRO, ainda está sendo explorada pelos pesquisadores por meio do modelo auto-regressivo integrado de médias móveis - ARIMA (1,1,1), sendo uma importante perspectiva futura para esta linha de pesquisa.

## 6 CONCLUSÃO

Este estudo descreveu a implementação do *Antimicrobial Stewardship Program* (ASP) em um hospital de ensino, aplicando a perspectiva Donabediana. Embora o hospital ainda não possua um modelo clássico de ASP, houve investimentos para melhorar a estrutura, processos e resultados, com o objetivo de cumprir as diretrizes internacionais dos ASPs. Além disso, se investigou a dinâmica entre consumo de antibacterianos e a emergência de resistência microbiana, discutindo a relação com a pandemia pela COVID-19. Verificou-se grande variação na tendência de consumo de linezolida, daptomicina e nas polimixinas. Além disso, *Staphylococcus (aureus, negative coagulase, sp)*, *Enterococcus (faecium, faecalis, sp)* e *Acinetobacter (baumannii, sp)* tiveram as maiores tendências de aumento, na instituição. A pandemia pode ter deteriorado ainda mais o cenário de aceleração do aumento da RMM. Isto justifica investigações adicionais dos dados de vigilância sobre as tendências epidemiológicas da RMM. Faz-se necessário dar continuidade a este estudo, e aprofundar nas análises de correlação entre consumo de antimicrobianos e resistência - métricas do ASP.

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**ANEXOS**

## ANEXO A – Aprovação do projeto no Comitê de Ética em Pesquisa da UFMG

LISTA DE PROJETOS DE PESQUISA:									
Tipo †	CAAE †	Versão †	Pesquisador Responsável †	Comitê de Ética †	Instituição †	Origem †	Última Avaliação †	Situação †	Ação
P	25655014.1.0000.5149	2	Maria Auxiliadora Parreiras Martins	5149 - Universidade Federal de Minas Gerais		PO	PO	Aprovado	 

UNIVERSIDADE FEDERAL DE  
MINAS GERAIS



### PARECER CONSUBSTANCIADO DO CEP

#### DADOS DO PROJETO DE PESQUISA

**Título da Pesquisa:** AVALIAÇÃO DO USO DE ANTIMICROBIANOS E RESISTÊNCIA MICROBIANA: ANÁLISE DE SÉRIES TEMPORAIS NO TRATAMENTO DE INFECÇÕES EM UM HOSPITAL PÚBLICO DE BELO HORIZONTE

**Pesquisador:** Maria Auxiliadora Parreiras Martins

**Área Temática:**

**Versão:** 2

**CAAE:** 54060321.8.0000.5149

**Instituição Proponente:** UNIVERSIDADE FEDERAL DE MINAS GERAIS

**Patrocinador Principal:** Financiamento Próprio

#### DADOS DO PARECER

**Número do Parecer:** 5.240.091

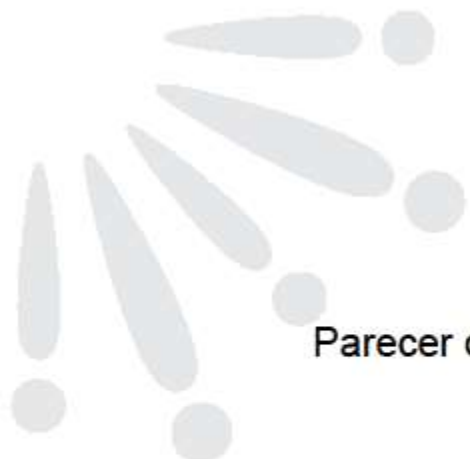
#### Apresentação do Projeto:

Segundo os investigadores:

A resistência microbiana é um dos principais desafios mundiais em saúde pública e tem aumentado gradualmente em todos os continentes. No Brasil vigora, desde 2017, a Diretriz Nacional para Elaboração de Programa de Gerenciamento do Uso de Antimicrobianos em Serviços de Saúde. Este documento recomenda como as instituições de saúde devem instrumentalizar as ações de combate à resistência microbiana, especialmente no que competem às ações para elaboração e implementação do programa de gerenciamento de uso de antimicrobianos em hospitais. A literatura destaca a necessidade de investimento em pesquisas que aperfeiçoem as métricas relacionadas ao Programa, além de elucidar e demonstrar as associações entre as intervenções e os desfechos mensurados. Assim, o objetivo desse estudo é avaliar o uso de antimicrobianos, por meio de medidas de consumo em gramas e dias de exposição, correlacionando ao aparecimento de resistência microbiana na instituição pesquisada. A unidade de estudo compreenderá todos os antimicrobianos utilizados no período de estudo, com recomendação de monitoramento nos hospitais com leitos de UTI conforme definição da ANVISA, padronizados na instituição em estudo, mensurados por meio do indicador de dose diária definida, dias de terapia e duração de terapia. Além disso, serão considerados os exames microbiológicos realizados no período de estudo para avaliação do perfil de susceptibilidade. Os

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## ANEXO B – Anuência da instituição em estudo



RGU ACO Ver. 05/2019

## Parecer de Projeto de Pesquisa

Belo Horizonte, 17 de março de 2021.

### Processo N°44/2020

**Título do Projeto:** "Avaliação do impacto da implantação de um programa de *Stewardship* em um Hospital de ensino".

**Equipe de pesquisadores:** Amanda Fonseca Medeiros (Farmácia/HRTN), Maria Auxiliadora Parreiras Martins (Profª FaFar/UFMG)

**Instituição envolvida:** Hospital Risoleta Tolentino Neves (Fundep/UFMG).

### Parecer

**A Comissão de Avaliação de Projetos de Pesquisa e Extensão (CAPPE/HRTN) posiciona-se favorável à realização do projeto de pesquisa no HRTN.**

A coleta de dados poderá ser iniciada após aprovação do projeto no CEP/UFMG.

**VIGÊNCIA DO PARECER:** Este Projeto tem validade de 05 (cinco) anos a partir da data do parecer final. O Relatório final das atividades com as publicações e produções científicas geradas a partir deste estudo deverá ser encaminhado ao NEPE após a conclusão do mesmo.

Rafael Calvão Barbuto

Coordenador do Núcleo de Ensino, Pesquisa e Extensão  
HRTN/FUNDEP/UFMG





## Building an Antimicrobial Stewardship Program: a narrative of six years under the Donabedian perspective

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