UNIVERSIDADE FEDERAL DE UBERLÂNDIA
Instituto de Ciências Biomédicas
Programa de Pós-Graduação em Imunologia e Parasitologia Aplicadas

ESTUDO MULTICÊNTRICO DE INFECÇÃO DE CORRENTE SANGUÍNEA E PNEUMONIA NOSOCOMIAL EM PACIENTES INTERNADOS EM UTI's DE ADULTOS NO ESTADO DE MINAS GERAIS

Elias Rodrigues de Almeida Júnior

Uberlândia - MG
Setembro - 2021

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“O êxito está em ter êxito e não em ter condições de êxito. Condições de palácio tem qualquer terra larga, mas onde estará o palácio se não o fizerem ali?”

Fernando Pessoa

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RESUMO

Introdução: Existe falta de estudos multicêntricos reconhecendo a importância das infecções relacionadas à assistência à saúde (IRAS) nas unidades de terapia intensiva (UTIs) brasileiras. Essas infecções graves correspondem ao evento adverso mais recorrente em hospitais de todo o mundo e representam um importante problema de saúde pública. Neste estudo, nós descrevemos o peso das pneumonias nosocomiais e de infecções de corrente sanguínea (ICSs), as tendências das infecções associadas a dispositivos invasivos, bem como a prevalência e etiologia das infecções polimicrobianas nesse cenário.

Objetivos: Fornecer um quadro atualizado de prevalência de IRAS, infecções associadas a dispositivos invasivos e infecções polimicrobianas, bem como identificar variáveis associadas ao risco de desenvolvimento dessas infecções graves.

Metodologia: Inquéritos de prevalência pontual de um dia foram realizados por meio de protocolos padronizados em 35 UTIs de adultos (médico-cirúrgicas e coronarianas) de 8 mesorregiões do estado de Minas Gerais, Brasil. Os prontuários médicos de pacientes internados elegíveis foram revisados no dia da pesquisa para coletar dados sobre características demográficas, taxas de IRAS presentes no momento da pesquisa, uso de dispositivos invasivos, o tempo de internação de 374 pacientes e os perfis bacterianos, além de todos os dados relevantes associados com epidemiologia dessas infecções. Um estudo pareado de caso-controle foi realizado em um total de 66 pares para ICS e 115 pares para pneumonia de acordo com os critérios de seleção desenvolvidos, e os dados sobre infecções associadas a dispositivos invasivos foram analisados para revelar os padrões de uso de dispositivos invasivos associados a essas infecções.

Resultados: No total, 171 pacientes (45,7%) tiveram pelo menos uma IRAS, sendo a maioria (78,4%) adquirida na UTI. Esses pacientes apresentaram um total de 240 infecções; incluindo 123 pneumonia (51,3%) e 66 ICS (27,5%), e 78,9% e 80,3%, respectivamente, foram adquiridas na UTI. A etiologia dessas infecções foi predominada por bactérias Gram-negativas versus bactérias Gram-positivas (48,9% versus 43,3%), com destaque para *Acinetobacter baumannii* (13,7%) e *Pseudomonas aeruginosa* (12,8%). Entre as infecções associadas a dispositivos invasivos (42,5%), houve 78,8% de infecções de corrente sanguínea associadas a cateter (ICSAC), 71,5% de pneumonias associadas à ventilação (PAVs) e 54,2% de infecções do trato urinário associadas a cateteres (ITUAC). As frequências de uso dos dispositivos invasivos foram 70,1% para cateter venoso central (CVC), 48,9% para ventilação mecânica (VM) e 64,4% para cateter vesical de demora (CVD). Os patógenos mais frequentes associados as

infecções associadas a dispositivos invasivos foram *Pseudomonas aeruginosa* (14,7%) e *Acinetobacter baumanni* (15,7%).

Conclusão: Nós podemos confirmar uma alta carga de IRAS graves adquiridas em UTIs, bem como altas frequências de uso de dispositivos invasivos em UTIs adultas brasileiras, em comparação com os achados de outros países de baixa e média renda. E infelizmente, uma frequência de 23.8% de infecções foram polimicrobianas com 41.2% sendo por bacilos Gram-negativos. Esses dados podem ser utilizados para um melhor planejamento dos programas de vigilância de infecção hospitalar em nossos hospitais.

Palavras-chave: Infecções relacionadas à assistência à saúde; Estudo multicêntrico; Unidades de terapia intensiva; Infecção de corrente sanguínea; Pneumonia; Dispositivo invasivo; Infecções polimicrobianas.

ABSTRACT

Introduction: There is a lack of multi-centre reports acknowledging the importance of healthcare-associated infections (HAIs) in Brazilian intensive care units (ICUs). These severe infections correspond to the most recurrent adverse event in hospitals worldwide and represent an important public health problem. In this study we described the burden of nosocomial pneumonias and bloodstream infection (BSIs), the trends in device-associated healthcare-associated infections (DA-HAIs), as well as the prevalence and etiology of polymicrobial infections in this scenario.

Aim: To provide an up-to-date picture of the burden of HAIs, DA-HAIs, and polymicrobial infections, as well as to identify variables associated with the risk of development of these severe infections.

Methodology: 24-hour point-prevalence surveys were conducted using standardized protocols in 35 adult (medical-surgical and coronary) ICUs from 8 mesoregions of Minas Gerais State, Brazil. Medical records of eligible inpatients were reviewed on the survey day to collect data regarding demographic characteristics, HAI rates present at the time of the survey, device use, length of stay from 374 patients and bacterial profiles, and all relevant data associated with the epidemiology of these infections. A matched-pairs case-control study was performed on a total of 66 pairs for BSI and 115 pairs for pneumonia according to the selection criteria developed, and the data regarding DA-HAIs were analyzed to disclose patterns of invasive device use associated with these infections.

Results: Overall 171 patients (45.7%) had at least one HAI, with most (78.4%) acquired in the ICU. These patients presented a total of 240 infections; including 123 pneumonia (51.3%) and 66 BSI (27.5%), and 78.9% and 80.3%, respectively, were acquired in the ICU. The etiology of them was predominated by Gram-negative bacteria versus Gram-positive bacteria (48.9% versus 43.3%), highlighting *Acinetobacter baumannii* (13.7%) and *Pseudomonas aeruginosa* (12.8%). Among the DA-HAIs (42.5%), there were 78.8% of central line-associated bloodstream infections (CLABSIs), 71.5% of ventilator-associated pneumonias (VAPs) and 54.2% of catheter-associated urinary tract infections (CAUTIs). The invasive devices frequencies were 70.1% for central venous catheter (CVC), 48.9% for mechanical ventilation (MV) and 64.4% for indwelling urinary catheters (IUC). The most frequent pathogens associated with DA-HAIs were *Pseudomonas aeruginosa* (14.7%) and *Acinetobacter baumanni* (15.7%).

Conclusion: We can endorse a high severe ICU-acquired HAIs burden as well as high frequencies of medical invasive device use in Brazilian adult ICUs when compared with findings from other low- and middle-income countries. And unfortunately, polymicrobial infections presented a frequency of 23.8%, with 41.2% caused by Gram-negative bacilli. These data can be utilized for better planning of nosocomial infection surveillance programs in our hospitals.

Keywords: Healthcare-associated infection; Multi-centric study; Intensive care units; Bloodstream infection; Pneumonia; Medical device; Polymicrobial infections.

LISTA DE ABREVIATURAS, SIGLAS E SÍMBOLOS

ANVISA	Agência Nacional de Vigilância Sanitária
BGN	Bacilo Gram-negativo
BSI	Bloodstream Infection
CAUTI	Catheter-associated urinary tract infection
CDC	Centers for Diseases Control and Prevention
CI	Confidence Interval
CLABSI	Central line-associated bloodstream infection
CNNI	Coagulase-negative staphylococci non-identified
CC17	Complexo clonal 17
CVC	Cateter venoso central/Central venous catheter
DDD	Dose diária definida
et al.	E colaboradores
EUA	Estados Unidos da América
HAI	Healthcare-associated Infection
HC-UFU	Hospital de Clínicas da Universidade Federal de Uberlândia
ICS	Infecção da Corrente Sanguínea
IRAS	Infecção relacionada à assistência de saúde
ICU	Intensive Care Unit
IUC	Indwelling urinary catheter
KPC	*Klebsiella pneumoniae* carbapenemase
LBA	Lavado bronco-alveolar
LOS	Length of Stay
Micromol	Laboratório de Microbiologia Molecular
MRSA	*Staphylococcus aureus* resistente a meticilina
MV	Mechanical Ventilation
N	Number
NG/ET	Nasogastric/enteral tube
NHSN	National Healthcare Safety Network
NTH	Non-teaching hospital
OMS	Organização Mundial de Saúde
PAV	Pneumonia Associada à Ventilação Mecânica

OR	Odds ratio
p	Probabilidade de significância
PBP2a	Proteína de ligação à penicilina 2a
PBP5	Proteína de ligação à penicilina 5
PVL	Panton-Valentine leucocidina
SARA	Síndrome da Angústia Respiratória Aguda
SD	Standard deviation
sp.	Espécie
spp.	Espécies
ST	Sequence Types
TH	Teaching hospital
UFC/ml	Unidade de formação de colônias por mililitro
UFU	Universidade Federal de Uberlândia
UTI	Unidade de Terapia Intensiva
VAP	Ventilator-associated pneumonia
VRE	Enterococcus resistentes à vancomicina
vs.	Versus
WHO	World health organization
α	Alfa
β	Beta
µl	Microlitro
ºC	Grau Celsius
≥	Maior ou igual
±	Mais ou menos
<	Menor
≤	Menor ou igual

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APRESENTAÇÃO

No Brasil, assim como em vários outros países de baixa e média renda, as infecções relacionadas à assistência à saúde (IRAS) correspondem ao evento adverso mais recorrente e representam uma das principais ameaças à segurança dos pacientes em unidades de terapia intensiva (UTIs) (ROSENTHAL et al., 2010; ESTEBAN et al., 2007; VINCENT et al., 2009). Também, são responsáveis por maiores taxas de morbidade, mortalidade, tempo de permanência na UTI e maiores custos, especialmente devido a ineficiência de políticas públicas de prevenção e controle dessas infecções graves nesses países (WHO, 2016; FORTALEZA et al., 2017; LU et al., 2018).

De acordo com a literatura científica, cerca de 20,0% a 30,0% dos pacientes internados em UTIs no Brasil desenvolvem IRAS (PADOVEZE; FORTALEZA, 2014; FORTALEZA et al., 2017) com alta incidência de infecções de corrente sanguínea (ICS) e pneumonia (LU et al., 2018). Além disso, essas infecções graves geralmente são causadas por microrganismos resistentes aos antimicrobianos e se assemelham quanto aos fatores de risco relacionados, tempo de internação, maiores taxas de mortalidade e custos (WHO, 2016; VILAR-COMPTE; CAMACHOORTIZ; PONCE-DE-LEON, 2017). Sendo assim, sua epidemiologia se tornou um grande problema global.

Nos últimos anos, a equipe do Laboratório de Microbiologia Molecular (Micromol) da Universidade Federal de Uberlândia (UFU) tem focado os estudos em pesquisas voltadas para o conhecimento da epidemiologia de IRAS, principalmente aquelas causadas por patógenos pertencentes de fenótipos resistentes e multirresistentes. Neste contexto, estão sendo realizados estudos multicêntricos no estado de Minas Gerais, bem como em outras regiões do país, apoiados por agências de fomento, com o objetivo principal de quantificar o impacto de IRAS e a magnitude dessas infecções em UTIs de adultos causadas por microrganismos multirresistentes. Com o intuito de ampliar a pesquisa, a partir de um banco de dados preexistente, a proposta desse trabalho foi determinar o cenário das ICS e de pneumonias nosocomiais e sua etiologia em UTIs de adultos clínico/cirúrgicas e cardiológicas do estado de Minas Gerais considerando que essas infecções estão entre as mais graves, com pior prognóstico e são de grande importância no nosso país. Adicionalmente, temos como objetivo analisar o uso de dispositivos invasivos bem como as infecções de etiologia polimicrobianas.

Estudos epidemiológicos relacionados às ICS e pneumonias em UTIs de adulto de hospitais de referência, universitários ou não, têm sito publicados em países desenvolvidos, entretanto, permanecem escassos os resultados de estudos multicêntricos brasileiros, revelando

a falta de dados e trabalhos de boa qualidade a fim de suprir e complementar o conhecimento a respeito de um tema extremamente relevante nacional e internacionalmente. Dessa forma, o desenvolvimento dessa pesquisa e seus frutos chegam para integrar o cenário dos estudos das IRAS e inspirar novas pesquisas similares de modo a complementar e beneficiar o estudo dessas infecções graves tão importantes globalmente.

O desafio, nessa proposta, é obter dados que contribuam para o conhecimento e controle dessas infecções, sua etiologia e o uso de antimicrobianos no ambiente hospitalar. Devido a importância do tema, os conhecimentos produzidos resultarão em publicações em revistas de impacto e resumos em congresso.

Esta dissertação foi subdividida em 5 capítulos, conforme apresentado a seguir:

1. **Capítulo 1 – Fundamentação teórica -** Apresenta uma revisão de literatura atualizada sobre aspectos epidemiológicos das IRAS, especialmente ICS e pneumonias nosocomiais.

2. **Capítulo 2 – Artigo 1.** Alarming Results from a Multi-Centric Surveillance of Nosocomial Bloodstream Infections and Pneumonia Trials in Brazilian Adult Intensive Care Units **-** Artigo submetido e em revisão no periódico **"Journal of Medical Microbiology**", apresentando resultados sobre aspectos epidemiológicos de pneumonia nosocomial e infecção de corrente sanguínea em pacientes internados em UTIs mistas de adultos de hospitais universitários e não universitários no estado de Minas Gerais;

3. **Capítulo 3 – Artigo 2.** Multi-Center Study of Prevalence and Risk Factors of Device-Associated Healthcare-Associated Infections in 35 Brazilian Adult Intensive Care Units **-** Artigo submetido no periódico **"Epidemiology and Health"** com descrição da distribuição de IRAS associadas a dispositivos invasivos, especialmente as pneumonias associadas a ventilação, as infecções de corrente sanguínea associadas ao cateter central e as infecções do trato urinário associadas ao cateter vesical;

4. **Capítulo 4 – Artigo 3.** Prevalence and Microbiology of Adult Intensive Care Unit-Acquired Polymicrobial Infections **-** Artigo com descrição de aspectos de prevalência e etiologia de IRAS mono e polimicrobianas.

5. **Capítulo 5 – Considerações finais.** Apresenta as principais conquistas obtidas com o estudo, suas contribuições e aplicabilidade dos resultados da pesquisa.

Capítulo 1

Fundamentação Teórica

1.1 Infecção relacionada à assistência à saúde

As infecções relacionadas à assistência à saúde (IRAS) correspondem ao evento adverso mais recorrente em hospitais em todo o mundo (VINCENT et al., 2009; CARDOSO et al., 2014), e representam um problema de saúde pública importante em razão do aumento nos gastos, tempo de internação, morbidade e mortalidade (ANVISA, 2013), principalmente em países em desenvolvimento, como o Brasil, onde as políticas públicas de prevenção e controle dessas infecções são, por vezes, ineficazes, apesar de evidências científicas comprovarem seu crescente aumento nas últimas décadas (FORTALEZA et al., 2017; VILAR-COMPTE; CAMACHO-ORTIZ; PONCE-DE-LEÓN, 2017). Ainda assim, as IRAS não recebem a atenção compatível com o seu impacto sobre a saúde (NOGUEIRA JUNIOR et al., 2014; PADOVEZE; FORTALEZA, 2014).

Um estudo realizado no período de 2011 a 2013, em 152 hospitais de diferentes tamanhos, em 10 estados localizados nas cinco macrorregiões do Brasil, evidenciou taxas de prevalência geral de IRAS de 10,8%, sendo que na região norte do Brasil foi relatado maior predomínio de pacientes com IRAS (12,2%), seguindo-se pelas regiões centro-oeste (11,3%), sudeste (10,2%), nordeste (9,3%) e sul (8,3%). Esses dados confirmam que as IRAS precisam receber tratamento prioritário nas pautas de saúde púbica do Brasil, assim como em outros países em desenvolvimento (FORTALEZA et al., 2017). Infelizmente, com o passar dos anos, cada vez mais, os recursos para a saúde no país vêm oscilando significativamente, e esse fator, aliado a má gestão, compromete a qualidade do atendimento.

Adicionalmente, o estudo multi-hospitalar realizado por Braga e colaboradores (2019) nas unidades de terapia intensiva (UTIs) de adultos de 28 hospitais localizados no estado de Minas Gerais, mostrou prevalência maior de IRAS (51,2%) quando comparada com UTIs de hospitais dos Estados Unidos da América (EUA) (6,1%) e Europa (48,4%), mas semelhante a de outros estudos brasileiros (RICHARDS et al., 2000; ALBERTI et al., 2002; LISBOA et al., 2007; VINCENT et al., 2009; SILVA et al., 2012; BRAGA et al., 2018).

As UTIs são consideradas centros de emergência e disseminação de microrganismos resistentes aos antimicrobianos, uma vez que apresentam pacientes mais graves, em uso intenso de dispositivos invasivos e antimicrobianos (RICHARDS; THURSKY; BUISING, 2003; YLIPALOSAARI et al., 2006). Nessas unidades ocorre uma alta frequência de contato profissional-paciente, favorecendo a disseminação de patógenos epidemiologicamente importantes, explicada pela baixa adesão à higienização das mãos, bem como a sobrecarga de

trabalho dos profissionais de saúde, aliada ainda a diversos problemas estruturais (ALP et al., 2011; MOREIRA et al., 2013; ALP; DAMANI, 2015).

Segundo a World Health Organization (WHO) (2011) as IRAS acometem cerca de 30% dos pacientes internados em UTIs, diferentes de outras unidades hospitalares, cuja frequência está em torno de 10%. Entre os fatores de risco que contribuem para esta alta frequência de IRAS em UTIs, estão: scores de gravidade clínica aguda e crônica mais significativos, imunocomprometimento, maior utilização de procedimentos invasivos, e utilização de antimicrobianos (especialmente os de amplo espectro) antes e durante a internação na unidade. (ALP; DAMANI, 2015; BONTEN, 2012).

Atualmente, de modo geral, na maioria dos hospitais, as infecções mais frequentes são as do trato urinário (LO et al., 2008; GOULD et al., 2017). Entretanto, nas UTIs, as mais frequentes são as pneumonias, seguindo-se das infecções de corrente sanguínea (ICS), sítio cirúrgico e do trato urinário, e estas infecções estão especialmente relacionadas ao uso de dispositivos invasivos, como ventilação mecânica (pneumonia), cateter venoso central (CVC) (corrente sanguínea) e sonda vesical (trato urinário) (VINCENT et al., 2009; ADOGI et al., 2010; SILVA et al., 2012; ZARAGOZA; RAMÍREZ; LÓPEZ-PUEYO, 2014).

Corroborando esses dados, o estudo multicêntrico realizado nas UTIs mineiras mencionado anteriormente reforçou a pneumonia como o tipo de infecção mais frequente, seguido pela ICS e do trato urinário, que juntas representaram 90,8% das infecções hospitalares detectadas (BRAGA et al., 2018).

A utilização de critérios microbiológicos no diagnóstico de IRAS além dos exames clínicos e de imagem (no caso das pneumonias), é extremamente importante pois eleva a segurança no momento de escolha da terapia inicial e da adequação da terapia definitiva, resultando em um melhor prognóstico para o paciente (ALLEGRANZI et al., 2011; KOLLEF; BURNHAM, 2017). Em alguns estudos multicêntricos realizados nos EUA e na Europa (RICHARDS et al., 2000; VINCENT et al., 1995) cerca de dois terços das infecções em pacientes críticos adultos apresentam resultados de culturas microbiológicas. No Brasil, assim como em outros países em desenvolvimento, essa frequência é menor em função da escassez de laboratórios vinculados aos hospitais ou falta de terceirização deste serviço, além da não realização de testes de suscetibilidade “in vitro”, o que acaba dificultando a terapia empírica adequada e contribuindo para o uso excessivo de antimicrobianos, resultando na seleção de microrganismos multirresistentes nas UTIs (ALLEGRANZI et al., 2011; VILAR-COMPTE; CAMACHO-ORTIZ; PONCE-DE-LEÓN, 2017).

Sabino e colaboradores (2018) realizaram um estudo na UTI de adultos do Hospital de Clínicas da Universidade Federal de Uberlândia (HC-UFU) e constataram incidência de 56,1% de IRAS provocadas por bacilos Gram-negativos (BGN), seguido por microrganismos Gram-positivos (33,7 %), este último correspondendo ao causador da maioria dos episódios de sepse (55%). Além disso, o mesmo estudo divulgou um percentual de 60% de amostras de BGN resistentes aos antimicrobianos. Nesse contexto, é nítida a importância da resistência bacteriana, principalmente por estar associada a um tempo de internação maior, maiores custos hospitalares e altos índices de morbidade e mortalidade nos pacientes críticos internados em UTIs (OLIVEIRA et al., 2012; DUDECK et al., 2013; ALP; DAMANI, 2015).

Entre os potenciais determinantes das elevadas taxas de IRAS em países com menos recursos financeiros para as necessidades dos programas de controle de infecções, incluem-se: inexistência de "guidelines/orientações" locais e nacionais, ambientes inapropriados quanto a limpeza e higiene, infraestrutura precária, insuficiência de materiais de consumo, conhecimento e aplicações precárias de condições básicas para o controle destas infecções, número insuficiente de enfermeiros, resultando numa baixa relação enfermeiro-paciente, superlotação das UTIs, além da utilização prolongada e elevada de procedimentos invasivos, bem como de antimicrobianos (ROSENTHAL, 2012; ALEGRANZI, 2011). Merece também ser destacada a falta de conhecimento dos profissionais de saúde para a identificação de fatores de risco para as infecções, sobretudo quanto a higienização das mãos, respeito das precauções por contato, e a utilização de máscaras, luvas e outros equipamentos de proteção, que são ocasionalmente não respeitados em virtude da ausência de recursos e insumos básicos nas UTIs (VILAR-COMPTE; CAMACHO-ORTIZ; PONCE-DE-LEÓN, 2017). Infelizmente, a corrupção política também é um problema alarmante nestes países, onde profissionais administrativos infligem dano adicional através do "roubo" e desvio dos recursos já precários destinados ao controle destas infecções, resultando em um grande impacto no controle e prevenção das IRAS (VILAR-COMPTE; CAMACHO-ORTIZ; PONCE-DE-LEÓN, 2017).

Infecções polimicrobianas são aquelas causadas por mais de um microrganismo no mesmo sítio de infecção e são ainda mais problemáticas, com escores de gravidade clínica mais elevados, maior duração do tempo de internação e taxas de mortalidade ainda mais altas em infecções graves como as ICS (WANG et al., 2020, ZHENG et al., 2020). A variedade de patógenos que podem estar envolvidos nesse tipo de infecção é um desafio adicional para o tratamento antimicrobiano adequado nesses pacientes (FERRER et al., 2015), e, infelizmente, amplos estudos multicêntricos sobre a temática ainda são escassos em países em desenvolvimento.

Seguindo esse pensamento, é fundamental a implementação de medidas de prevenção e controle de todas as IRAS, de modo a alcançar desfechos positivos na saúde e melhorar a segurança da assistência aos pacientes críticos. Para chegar nesse resultado é indispensável o envolvimento de todos os setores governamentais e profissionais, traçando estratégias bem definidas, estimulando a higienização adequada das mãos, observação contínua dos pacientes de risco, respeito das precauções padrão para a redução de transmissão cruzada, assim como estabelecer uma vigilância de controle de infecção hospitalar competente (ANVISA, 2013; DELLINGER et al., 2013).

1.1.1 Infecções de Corrente Sanguínea

A ICS é definida como uma infecção decorrente da difusão de um microrganismo na corrente sanguínea, classificando-se em primária, definida pelo uso de CVC, cultura de ponta de cateter positiva ou aquelas de origem desconhecida, e as denominadas secundárias, onde o foco da infecção se localiza em outros sítios que não o sistema vascular-circulatório (pulmão, trato urinário, sítio cirúrgico e outros, por exemplo) (MAYER et al., 2012). Há variação na distribuição, a maioria (cerca de 70%) das ICS são usualmente secundárias, com predomínio em países em desenvolvimento, já as primárias são mais frequentes nos países desenvolvidos (LAUPLAND et al., 2002; VALLÉS; FERRER, 2009; VALLÉS et al., 2011; ZARKOTOU et al., 2011).

O CVC é um dispositivo muito utilizado em UTIs e pode ser inserido em um vaso sanguíneo de grosso calibre como a veia subclávia, a veia jugular interna e a veia femoral, com o objetivo de infundir medicações, nutrição parenteral, transfusão sanguínea, ou produtos sanguíneos como derivados do plasma e concentrados de plaquetas, e outros fluidos agressivos para vasos periféricos como medicações vasoativas e quimioterápicos (GOMINET et al., 2017). O CVC também pode ser usado para realizar hemodiálise, obter saturação venosa central de oxigênio e medir a pressão venosa central (MERMEL, 2000; GOMINET et al., 2017)

No contexto da ICS associada ao uso do CVC, duas situações principais podem resultar no desenvolvimento da infecção, uma delas é a colonização extraluminal do local de inserção do cateter pela própria microbiota da pele dos pacientes ou a partir da contaminação cruzada trazendo microrganismos das mãos mal higienizadas dos profissionais de saúde (CARRARA, 2016; ANVISA, 2017). Outro cenário é denominado de colonização intraluminal, que, em decorrência do manuseio inapropriado no momento da inserção do cateter, ou até mesmo da

infusão de soluções contaminadas, os microrganismos adentram a corrente sanguínea e provocam essa infecção grave (CARRARA, 2016; ANVISA, 2017).

Além disso, a formação de biofilmes está muito correlacionada à ICS associada ao uso de CVC (GOMINET et al., 2017). O biofilme é um aglomerado de microrganismos em uma superfície envoltos por uma matriz extracelular autoproduzida (COSTERTON et al., 1999). A contaminação da superfície do cateter pode ter origem a partir da microbiota da pele ou da contaminação cruzada no momento da inserção ou do manuseio do dispositivo, o interior do lúmen do cateter pode ser contaminado a partir da infecção hematogênica de outro sítio infeccioso ou com uma infusão de fluidos não estéreis (RAAD et al., 1993). Os microrganismos aderem ao cateter e facilitam a chegada de outros patógenos, se multiplicam e produzem mais da matriz extracelular que segura o biofilme no lugar e leva a ligação irreversível ao CVC (FLEMMING; WINGENDER, 2010). Essa matriz extracelular é composta principalmente de água, polissacarídeos, DNA extracelular e lipídeos, e promove estabilidade mecânica para o biofilme, melhora a aderência ao cateter e protege os microrganismos contra agressões externas, antibióticos e até mesmo a resposta imune dos pacientes (DONLAN, 2001; FLEMMING; WINGENDER, 2010).

A ICS está incluída entre as complicações infecciosas mais graves decorrentes de hospitalização e cuidados médicos (ANVISA, 2013) e associada com a alta taxa de mortalidade nessas unidades (MICEK et al., 2005; SABATIER; PEREDO; VALLÉS; FERRER, 2009; MASEDA et al., 2011; GAHLOT et al., 2014). Nas últimas décadas, foi observado aumento na incidência dessas infecções, refletindo, entre outros fatores, a difícil implementação de técnicas básicas de prevenção e controle de infecção (SABATIER; PEREDO; VALLÉS; FERRER, 2009; MASEDA et al., 2011), e a rotineira utilização de procedimentos médicos invasivos (NNIS, 2001; DIEKEMA et al., 2003), particularmente o uso de dispositivos intravasculares e a presença de ventilação mecânica, considerados fatores de risco importantes (LEÃO et al., 2007).

De acordo com o National Healthcare Safety Network (NHSN) (2021a), a ICS associada ao uso do CVC é a principal causa de infecção em UTI. Em UTIs dos EUA ocorrem aproximadamente 30.000 novos casos dessas infecções a cada ano (NHSN, 2021b), resultando no aumento do tempo de internação de 10 a 20 dias e custos aproximados de US$ 30.000 por paciente (CDC, 2011; WEAVER et al., 2014).

Quanto à etiologia, os microrganismos mais isolados de ICS associadas ao CVC são os cocos Gram-positivos, incluindo *Staphylococcus spp*. coagulase negativa, *Staphylococcus aureus* e *Enterococcus spp.*, com presença significativa de cepas mais resistentes aos

antibióticos como por exemplo o *Staphylococcus aureus* resistentes à meticilina. Porém, em países em desenvolvimento, como o Brasil, os BGN são mais associados a essas infecções, destacando as espécies *Klebsiella pneumoniae* e *Escherichia coli* resistentes a cefalosporinas de amplo espectro (CDC, 2011; TUON et al., 2012; DRASKOVIĆ et al., 2014) e, na última década, daqueles resistentes a carbapenêmicos (ROSENTHAL et al., 2012). Entretanto, nas ICS secundárias prevalecem os BGN, sobretudo *Acinetobacter baumannii*, *Pseudomonas aeruginosa* e *Klebsiella pneumoniae,* (DIEKEMA et al., 2004; DOYLE et al., 2011), com a participação expressiva tanto em países desenvolvidos quanto em desenvolvimento dos seguintes fenótipos: *Escherichia coli* e *Klebsiella pneumoniae* resistentes a cefalosporinas de amplo espectro (WEINER et al., 2016; BRAGA et al., 2018). Atualmente, a emergência em UTIs de fenótipos resistentes é ainda mais expressiva entre os BGN não fermentadores, destacando-se a participação de *Pseudomonas aeruginosa* e *Acinetobacter baumannii* resistentes a carbapenêmicos (HIDRON et al., 2008; WEINER et al., 2016).

Além das bactérias, ICS devido a fungos leveduriformes, destacando-se aqueles do gênero *Candida,* aparecem entre os agentes etiológicos mais frequentes dessas infecções. As candideminas estão associadas a um pior prognóstico e a fatores de risco como: gravidade da doença, tempo de internação mais prolongado e o uso indiscriminado de antibióticos (LEE et al., 2018; MEJIA-CHEW et al., 2019).

1.1.2 Pneumonia

Pacientes internados em UTIs geralmente são afetados por diversas comorbidades, uso extensivo de antimicrobianos e de dispositivos invasivos como a ventilação mecânica, o que pode facilitar a colonização do trato respiratório superior com organismos virulentos, e alguns desses patógenos como *Streptococcus pneumoniae*, *Haemophilus influenzae* e certos BGNs adentram o trato respiratório inferior através da aspiração de secreções da orofaringe (LANKS et al., 2019). Essa aspiração pode ocorrer até mesmo em pacientes com quadros clínicos não muito graves, mas nesse caso a progressão para pneumonia seria rara, e evolução para pneumonia depende do patógeno e do volume de secreção aspirado, da frequência de aspiração e da virulência dos microrganismos em relação ao sistema imune do paciente (SCHELD, 1991; LANKS et al., 2019).

A pneumonia de origem hospitalar é definida como aquela que se desenvolve após um período maior ou igual a 48 horas da admissão, e é a infecção mais comum em UTIs, com os pacientes submetidos à ventilação mecânica como a população de maior risco (JOSEPH et al.,

2010a). Esta síndrome está associada com um aumento significativo no tempo de internação, morbidade, mortalidade e custos (KLOMPAS; PLATT, 2007; SAFDAR et al., 2005), e sua frequência varia de 6 a 52% nessas unidades (JOSEPH et al., 2010ª; BOUADMA et al., 2010; CHAN; GRAVES; DELLIT, 2010).

Os indicadores epidemiológicos evidenciaram que os valores são mais altos nos países em desenvolvimento como o Brasil quando comparado com UTIs dos EUA, correspondendo a 13,6 por 1000 ventiladores-dia e 3,3 por 1000 ventiladores-dia, respectivamente (LEYLABADLO et al., 2017; POURMAND et al., 2017; ROSENTHAL et al., 2010).

A pneumonia associada a ventilação mecânica (PAV) é definida como pneumonia que ocorre 48 horas ou mais após a intubação endotraqueal, com infiltrado radiológico novo e/ou progressivo e pelo menos duas das seguintes características: escarro purulento, temperatura corporal superior a 38ºC ou inferior a 35ºC, contagem de leucócitos superior a 10000/µl ou inferior a 3000/µl, e cultura positiva do aspirado endotraqueal (contagem $\geq 10^6$ UFC/ml) (KOLLEF; BURNHAM, 2017).

A PAV pode ser classificada em precoce ou tardia, a precoce geralmente apresenta melhor prognóstico clínico e ocorre nos primeiros 4 dias de uso de ventilação mecânica, já a tardia acontece após o quinto dia e é acompanhada de maiores taxas de morbidade e mortalidade (JOSEPH et al., 2010b). Os microrganismos *Staphylococcus aureus*, *Streptococcus pneumoniae* e *Haemophilus influenzae* estão muito presentes na PAV precoce, já a tardia tem como principais agentes etiológicos *Pseudomonas aeruginosa*, *Acinetobacter baumannii* e *Klebsiella* spp. e *Staphylococcus aureus* resistente a meticilina (MRSA) (HUNTER, 2006).

É comum que os pacientes internados em UTIs passem por modificações da microbiota normal, inclusive a do trato respiratório, com a adição de BGNs como *Acinetobacter baumannii, Pseudomonas aeruginosa*, e Gram-positivos como MRSA (BASSI et al., 2010). A colonização com esses patógenos é um grande fator de risco para o desenvolvimento de PAV e geralmente acontece a partir de 5 a 7 dias de hospitalização, e é agravada pela utilização de antimicrobianos e dispositivos invasivos dentro da unidade (RELLO et al., 2002; KIENINGER; LIPSETT, 2009). Além disso, a utilização de tubo endotraqueal é conhecida por comprometer os mecanismos de defesa naturais dos pacientes além de facilitar a aspiração de secreção do trato respiratório superior para os pulmões, contribuindo para o desenvolvimento de pneumonia (KIENINGER; LIPSETT, 2009).

Além da prótese ventilatória, outros fatores de risco estão associados a essa infecção, incluindo escores de gravidade clínica aguda mais significativos, presença de comorbidades, pacientes imunocomprometidos, trauma, cirurgia, uso de dispositivos invasivos, corticoides e

antibióticos, além do prolongado período de internação (HUGONNET; UÇKAY; PITTET, 2007; JOSEPH et al., 2010b; SANDIUMENGE; RELLO, 2012). Também, a administração de terapia antibiótica inicial e empírica inapropriada pode contribuir para o agravamento do estado clínico do paciente e aumento do tempo de internação (ARTHUR et al., 2016; GARNACHO-MONTERO et al., 2007). Um estudo realizado na UTI de adultos do HC-UFU, identificou como fatores de risco independentes para o desenvolvimento de PAV o tempo de utilização de ventilação mecânica maior que 7 dias, além do uso de traqueostomia e uso de mais de 3 antimicrobianos (ROCHA et al., 2008).

Os principais agentes etiológicos das PAVs são *Staphylococcus aureus, Pseudomonas aeruginosa, Acinetobacter baumannii* e *Klebsiella pneumoniae*. (HUNTER, 2012; PITTET; DONALDSON, 2006). Estudos mais recentes relatam que entre os patógenos responsáveis por essas infecções estão *Acinetobacter baumannii* e *Pseudomonas aeruginosa* como os mais frequentes e predominam nos países em desenvolvimento, bem como em países da América do Norte e Europa, principalmente aqueles resistentes aos carbapenêmicos e as cefalosporinas de amplo espectro (ARABI et al., 2008; HIDRON et al., 2008; PELEG; HOOPER, 2010).

De acordo com Zilberberg e Shorr (2010), o diagnóstico de pneumonia requer sinais e sintomas, critérios clínicos, radiológicos e microbiológicos. O diagnóstico microbiológico baseia-se na contagem de microrganismo no lavado bronco-alveolar (LBA) acima de 10^4 UFC/ml (PELEG; HOOPER, 2010). Em países em desenvolvimento, a utilização de critérios microbiológicos é menos utilizada, e baseia-se usualmente na contagem de bactérias no aspirado endotraqueal (maior que 10^6 UFC/ml) (PELEG; HOOPER, 2010). Os critérios clínicos e radiológicos são inespecíficos pois podem ser provocados por outras doenças pulmonares como síndrome da angústia respiratória (SARA), trombo embolia e infarto pulmonar (KIENINGER; LIPSETT, 2009), então o mais recomendado para o diagnóstico é o uso de critérios microbiológicos por serem específicos e permitir o isolamento do agente etiológico, além de definir o perfil de susceptibilidade e resistência aos antimicrobianos, permitindo uma adequação da terapia antibiótica e um melhor prognóstico para o paciente (BONTEN, 2011).

Em função da gravidade das PAVs e da susceptibilidade dos pacientes, o tratamento deve ser iniciado rapidamente após o diagnóstico, e geralmente, esse tratamento é empírico com antimicrobianos de amplo espectro até que o diagnóstico microbiológico seja concluído (ALP; DAMANI, 2015; VILAR-COMPTE; CAMACHO-ORTIZ; PONCE-DE-LEÓN, 2017). Quando o agente causal é definido, é importante o de-escalonamento da terapia antibiótica, passando esta a ser dirigida especificamente ao fenótipo encontrado. Esse procedimento é importante pois limita o risco de superinfecções, diminui a seleção de microrganismos

resistentes bem como os custos associados (KOLLEF et al., 1999; RELLO et al., 2004; MICEK et al., 2004; NIEDERMAN, 2006; NIEDERMAN; SOULOUNTSI, 2011).

A partir desse levantamento, se torna evidente a necessidade de estudos esclarecedores sobre a epidemiologia de PAVs com o objetivo de dar embasamento sobre esse problema de saúde pública tão importante em países em desenvolvimento como o Brasil, de modo a auxiliar no conhecimento do impacto negativo para a segurança dos pacientes e estimular a implementação de políticas públicas de controle dessa infecção.

1.2 Consumo de antimicrobianos e multirresistência

Atualmente a preocupação quanto ao aumento da resistência antimicrobiana entre os BGNs vem aumentando, pois em muitas situações não existe opção de tratamento dentre os antibióticos disponíveis (MARCHAIM; KAYE, 2017). Além disso, a resistência e multirresistência bacterianas e o atraso no início da terapia antimicrobiana apropriada em pacientes com IRAS está intimamente relacionado a maior mortalidade (CAIN et al., 2015; SARAVU et al., 2015).

Magiorakos et al. (2012) definiram microrganismo multirresistente como um microrganismo não suscetível a pelo menos um agente em três ou mais classes de antimicrobianos. E devido ao uso irresponsável e inapropriado dos antimicrobianos, muitas vezes ocorre a disseminação e transmissão desses patógenos multirresistentes, especialmente pelo mau controle de infecções e falha de políticas públicas e práticas de prevenção (HIJAZI, 2019), e no cenário brasileiro, essa problemática é ainda mais importante pela alta densidade de uso de antimicrobianos, especialmente carbapenêmicos e fluoroquinolonas (PORTO et al., 2013; DANTAS et al, 2014). Um estudo brasileiro observou um consumo de antibióticos de 52.2% em pacientes hospitalizados, onde a região Nordeste obteve a maior prevalência de uso de antibióticos (60.4%) (PORTO et al., 2020). Quando comparamos esses resultados com estudos em países desenvolvidos, como a Itália, percebemos um consumo de antibióticos menor com cerca de 44% dos pacientes hospitalizados recebendo terapia antimicrobiana (VICENTINI et al., 2020).

O consumo de antibióticos é medido utilizando unidades de referência como a dose diária definida (DDD) (GRAU et al., 2013). A Organização Mundial da Saúde (OMS) determina a DDD de cada antimicrobiano anualmente, tornando possível comparar a frequência de microrganismos e seus fenótipos de resistência (WHO, 2019). Diversos estudos já demonstraram que o número do DDD/1000 pacientes-dia é uma unidade de medida relevante

para comparar o consumo de antimicrobianos entre diferentes regiões (WU et al, 2017; PITIRIGA et al., 2018). Na Inglaterra, por exemplo, um estudo demonstrou o consumo médio de antimicrobianos da classe dos carbapenêmicos de 224.2 DDD/1000 pacientes-dia (SINGH et al., 2015), já no Brasil, o consumo da mesma classe encontrado por Rossi et al. (2016) foi de 389.3 DDD/1000 pacientes-dia.

Nos dias atuais, em alguns casos as IRAS causadas por microrganismos multirresistentes são tratadas por antimicrobianos de amplo espectro, o que pode favorecer um pior prognóstico para o paciente, além de facilitar esses microrganismos a se tornarem endêmicos nas unidades críticas de saúde, acarretando em um problema de saúde global (VALLÉS et al., 2011; CHMIELARCZYK et al., 2018; MARCHAIM; KAYE, 2017). Nos países em desenvolvimento como o Brasil, o cenário é ainda mais problemático, com maiores taxas de infecção provocadas por patógenos multirresistentes, uso inapropriado e indiscriminado de antibióticos de amplo espectro de forma empírica, associado a escassez de laboratórios de microbiologia e de recursos humanos e financeiros (VILAR-COMPTE; CAMACHOORTIZ; PONCE-DE-LEON, 2017).

A problemática atual de altas taxas de IRAS provocadas por microrganismos multirresistentes é agravada pela falta de novos antimicrobianos, o que aumenta ainda mais as taxas de resistência na ausência de novos medicamentos (BOUCHER et al., 2009; PELEG; HOOPER, 2010). Além disso, as IRAS causadas por BGN multirresistentes representa um grande fator de risco e preditor de mortalidade (VARDARKAS et al., 2013), e o atraso no início do tratamento está associado com aumento do tempo de hospitalização, pior prognóstico e maiores taxas de óbito (ZILBERBERG et al., 2008; MICEK et al., 2012; BATTLE et al., 2017).

A alta frequência de microrganismos hospitalares multirresistentes principalmente nas UTIs passou a ser considerada um problema de saúde global, atraindo atenção de órgãos governamentais nacionais e internacionais (HAMBRAEUS, 2006; BIEDENBACH; MOET; JONES, 2004). Embora a presença e a transmissão desses microrganismos sejam documentadas mais frequentemente nas últimas décadas, especialmente em países de baixa e média renda, no Brasil, o problema é ainda mais significativo principalmente devido à falta de documentação científica multicêntrica aliada à pouca eficácia das políticas de prevenção e controle existentes. Complicando ainda mais a situação, os recursos financeiros são limitados e existe o uso pouco criterioso e excessivo de antimicrobianos associados à falta de laboratórios de microbiologia. (GISKE et al., 2008; SCHWABER; CARMELI, 2009; ALLEGRANZI et al., 2011; VILAR-COMPTE; CAMACHO-ORTIZ; PONCE-DE-LEÓN, 2017).

A literatura tem revelado que os principais agentes bacterianos do ambiente hospitalar vêm sofrendo modificações ao longo dos anos devido, principalmente, ao uso indiscriminado de antibióticos, o que favorece o desenvolvimento de mecanismos de resistência cada vez mais elaborados, contribuindo para a permanência e adaptação desses patógenos nos hospitais (DORON; DAVIDSON, 2011; RUIZ, 2018).

É consenso que a resistência bacteriana tem sido um importante fator na elevação dos índices de mortalidade em pacientes críticos, e aliado a isso, nas últimas décadas, tem-se observado o aumento expressivo da incidência de IRAS provocadas por BGN multirresistentes, destacando-se *Klebsiella pneumoniae* e *Acinetobacter baumannii*, que possuem capacidade de adquirir e/ou desenvolver resistência a quase todos antimicrobianos disponíveis para tratamento, através da transferência horizontal de genes ou por mutações em genes cromossomais (GOOTZ, 2010; TANWAR, 2014; HOU, 2015). Esses microrganismos passaram também a ser motivo de preocupação devido às opções terapêuticas limitadas e muitas vezes, indisponíveis, o que resulta em maiores chances de terapia empírica inapropriada, que associada à demora no escalonamento do antimicrobiano após confirmação microbiológica, tem reflexos no prognóstico e nos custos (ZILBERBERG et al., 2014; DAIKOS et al., 2014).

Os BGNs possuem diversos mecanismos de resistência, como por exemplo a presença de enzimas carbapenemases que hidrolisam imipenem, meropenem e outras penicilinas e cefalosporinas (QUEENAN; BUSH, 2007; BERTONCHELI; HÖRNER, 2008). Esse mecanismo de resistência pode ser facilmente disseminado por meio de elementos genéticos móveis (plasmídeos) (GOOTZ et al., 2009), e uma das principais carbapenemases é a *Klebsiella pneumoniae* carbapenemase (KPC), que se encontra disseminada mundialmente (RUIZ-GARBAJOSA et al., 2013). A KPC pode ser encontrada em mais de 115 *Sequence Types* (STs) (CHEN et al., 2014), e, no Brasil os clones mais frequentemente encontrados incluem o ST437 e ST11 (ANDRADE et al., 2011; NICOLETTI et al., 2012).

Outros BGNs importantes como o *Acinetobacter baumannii* apresentam como mecanismo de resistência diversos mecanismos: modificações de sítios alvo das drogas, inativação enzimática, efluxo ativo e diminuição do influxo de medicamentos, sendo o mecanismo de resistência mais relevante, a produção de β-lactamases adquiridas, incluindo serina e metalo- β-lactamases, as quais conferem resistência aos carbapenêmicos. (CHAKRAVARTY, 2020). Alteração na permeabilidade das proteínas de membrana externa (PME) ou porinas, e a hiper expressão de bombas de efluxo também são mecanismos importantes, além de mutações em genes cromossomais e aquisição horizontal de genes de resistência (ASIF; ALVI; REHMAN, 2018).

Embora os BGN apresentem grande destaque no momento em relação a etiologia das IRAS no Brasil, os cocos Gram-positivos, especialmente *Staphylococcus* spp. e *Enterococcus* spp., incluindo os multirresistentes, também são importantes no ambiente hospitalar, levando a uma restrição importante das opções terapêuticas (ALLEN, 2005; DHILLON; CLARK, 2009; VINCENT et al., 2009;). Entre os fenótipos de destaque estão o MRSA e *Enterococcus* resistentes à vancomicina (VRE) e sua incidência varia muito entre os países e regiões (NATIONAL NOSOCOMIAL INFECTION SURVEILLANCE, 2000; HIDRON et al., 2008; WEINER et al., 2016).

A epidemiologia do *Staphylococcus aureus* é dinâmica e tem sido foco de muitos estudos ao longo dos anos, e o MRSA sempre foi um problema clínico e epidemiológico nos países desenvolvidos, representando um desafio às práticas de controle e prevenção de infecção (WEINER et al., 2016). Hoje, no Brasil, esse fenótipo representa uma frequência de 5 a 7,5% na maioria dos hospitais (DAMACENO et al., 2015; VELOSO et al., 2019).

O MRSA é resistente à meticilina através da aquisição horizontal do gene *mecA* que codifica a proteína de ligação à penicilina 2a (PBP2a), uma transpeptidase com baixa afinidade pela maioria dos antibióticos β-lactâmicos, conferindo resistência a praticamente todos antibióticos dessa classe (VESTERGAARD et al., 2019). O gene *mecA* está presente em uma família de elementos genéticos chamados SCC*mec* e muitas vezes carregam genes adicionais que também conferem resistência a outros antibióticos (KATAMAYA et al., 2000; ITO et al., 2001). Na última década o MRSA permaneceu sendo cada vez mais relatado no Brasil, com clones mais comuns no ambiente hospitalar sendo aqueles carregando os SCC*mec* tipos II, III e IV (CHAMON et al., 2017; CAVALCANTE et al., 2017; PEREIRA-FRANCHI et al., 2019), sendo o SCC*mec* tipo II e tipo IV os clones mais prevalentes, com alguns adquirindo capacidade de produzir α-hemolisina, a citotoxina Panton-Valentine leucocidina (PVL), e biofilme (CAVALCANTE et al., 2017; DUARTE et al., 2018).

Já o VRE tem sua importância justificada por sua resistência intrínseca a muitos antibióticos utilizados para o tratamento das infeções associadas, a resistência intrínseca mais importante observada nos *Enterococcus* é a resistência aos aminoglicosídeos, aos glicopeptídeos, e resistência a ampicilina induzida por enzimas β-lactamases (RAZA et al., 2018) e esses patógenos possuem grande relevância epidemiologica no Brasil, por exemplo, a resistência dos enterococos à vancomicina aumentou de 4,4% em 2003 para 27,0% em 2013 (GALES et al, 2009; JONES et al., 2013).

Em relação aos β-lactâmicos, a resistência se deve à mutação ou super produção de proteína de ligação à penicilina 5 (PBP5), já a resistência aos aminoglicosídeos é resultado

da absorção mais lenta do antibiótico (SOOD et al., 2008; RAZA et al., 2018). A vancomicina atua na superfície externa da membrana plasmática das bactérias inibindo a síntese do peptideoglicano, se ligando em determinada região do precursor do peptideoglicano e bloqueando a ação de enzimas envolvidas na síntese da parede celular (COURVALIN, 2006). A resistência à vancomicina acontece a partir da produção de precursores de baixa afinidade e eliminação dos precursores de alta afinidade, reprogramando a síntese do peptideoglicano e diminuindo a afinidade desses precursores com a vancomicina, e consequentemente promovendo resistência (PÉRICHON; COURVALIN, 2009). O VRE pode adquirir resistência a partir da mutação do DNA próprio ou da aquisição de material genético de outros microrganismos (SOOD et al., 2008).

A resistência à vancomicina é mediada pelos genes *VanA* e *VanB* que ocorrem frequentemente no VRE e os dois tipos são carregados pelos transposons Tn*1546* e Tn*1547* (CATTOIR; GIARD, 2014). No Brasil, diversos estudos evidenciaram isolados de VRE contendo o gene *VanA* (RESENDE et a., 2014), e estudos de epidemiologia molecular vêm mostrando uma propagação global de clones de alto risco, facilitando a aquisição cumulativa de resistência aos antibióticos, características de virulência e a habilidade de adquirir elementos genéticos por transferência horizontal (RESENDE et a., 2014). Alguns estudos identificaram os *Sequence Types* ST*192*, ST*412* e S*T478*, pertencentes ao Complexo Clonal 17 (CC17) como os clones prevalentes em ambiente hospitalar brasileiro (SILVA et al., 2012; PRADO et al., 2016).

Nesse contexto, além de evidências da importância de todos esses fenótipos, descritos na literatura através dos diversos estudos epidemiológicos abordados anteriormente, a comunidade científica em todo o mundo vem utilizando com sucesso métodos de tipagem molecular para a investigação desses microrganismos, sua participação e transmissão durante os surtos hospitalares, evidenciando de forma mais precisa toda circulação e emergência de novos fenótipos (PRADO et al., 2016). Esses métodos auxiliam no esclarecimento dos principais reservatórios desses microrganismos, e como consequência, as estratégias de prevenção e controle são aprimoradas.

1.3 Referências

AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA. **Medidas de Prevenção de Infecção Relacionada à Assistência à Saúde**. Série segurança do paciente e qualidade em serviços de saúde. Brasília, DF: Ministério da saúde: p. 1-122, 2017. Disponível em: http://www.riocomsaude.rj.gov.br/Publico/MostrarArquivo.aspx?C=pCiWUy84%2BR0%3D. Acesso em: 04 jul. 2021.

AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA. **Medidas de Prevenção de Infecção Relacionada à Assistência à Saúde**. Volume 4, Série Segurança do Paciente e Qualidade em Serviços de Saúde, Brasília, DF: Ministério da saúde: p. 1-92, 2013. Disponível em: https://segurancadopaciente.com.br/wp-content/uploads/2015/09/ebook-anvisa-04-medidas-de-prevencao-de-de-infeccao-relacionada-a-assistencia-a-saude.pdf. Acesso em: 12 jul. 2021.

AGODI, A. et al. Building a benchmark through active surveillance of intensive care unit-acquired infections: the Italian network SPIN-UTI. **The Journal of Hospital Infection**, Nova Iorque, v. 74, n. 3, p. 258-265, 2010. https://doi:10.1016/j.jhin.2009.08.015

ALBERTI, C. et al. Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. **Intensive Care Medicine**, Berlim, v. 28, n. 2, p. 108-121, 2002. https://doi.org/10.1007/s00134-001-1143-z

ALLEGRANZI, B. et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. **The Lancet**, Londres, v. 377, n. 9761, p. 228-241, 2011. https://doi:10.1016/S0140-6736(10)61458-4

ALLEN, S. Prevention and control of infection in the ICU. **Current Anaesthesia & Critical Care**, [s. l.], v. 16, n. 4, p. 191-199, 2005. https://doi.org/10.1016/j.cacc.2006.01.003

ALP, E. et al. Infection control practice in countries with limited resources. **Annals of Clinical Microbiology and Antimicrobials**, Londres, v. 10, n. 36, 2011. https://doi:10.1186/1476-0711-10-36

ALP, E.; DAMANI, N. Healthcare-associated infections in intensive care units: epidemiology and infection control in low-to-middle income countries. **Journal of Infection in Developing Countries**, v. 9, n. 10, p. 1040-1045, 2015. https://doi.org/10.3855/jidc.6832

ANDRADE, L.N. et al. Dissemination of blaKPC-2 by the Spread of Klebsiella pneumoniae Clonal Complex 258 Clones (ST258, ST11, ST437) and Plasmids (IncFII, IncN, IncL/M) among Enterobacteriaceae Species in Brazil. **Antimicrobial Agents and Chemotherapy**, v. 55, n. 7, p. 3579–3583, 2011. https://doi.org/10.1128/AAC.01783-10

ARABI, Y. et al. Ventilator-associated pneumonia in adults in developing countries: a systematic review. **International journal of infectious diseases: IJID**: official publication of the International Society for Infectious Diseases, v. 12, n. 5, p. 505–12, 2008. https://doi.org/10.1016/j.ijid.2008.02.010

ARTHUR, L. E. et al. Antibiotics for ventilator-associated pneumonia. **The Cochrane database of systematic reviews**, v. 10, n. 10, p. CD004267, 2016. https://doi.org/10.1002/14651858.CD004267.pub4

ASIF, M.; ALVI, I.A.; REHMAN, S.U. Insight into Acinetobacter baumannii: pathogenesis, global resistance, mechanisms of resistance, treatment options, and alternative modalities. **Infection and Drug Resistance**, v. 11, p. 1249, 2018. https://doi.org/10.2147/IDR.S166750

BASSI, G.L. et al. Do guidelines change outcomes in ventilator-associated pneumonia? **Current Opinion in Infectious Diseases**, v. 23, p. 171-77, 2010. https://doi.org/10.1097/QCO.0b013e328337241a.

BATTLE, S. E. et al. Association between inappropriate empirical antimicrobial therapy and hospital length of stay in Gram-negative bloodstream infections: stratification by prognosis. **The Journal of Antimicrobial Chemotherapy**, Inglaterra, v. 72, n. 1, p. 299-304, 2017. https://doi.org/10.1093/jac/dkw402

BERTONCHELI, C.M.; HÖRNER, R. A review on metallo-β-lactamases. **Revista Brasileira de Ciências Farmacêuticas**, v. 44, n. 4, p. 577-599, 2008. http://dx.doi.org/10.1590/S1516-93322008000400005

BIEDENBACH, D. J.; MOET, G. J.; JONES, R. N. Occurrence and antimicrobial resistance pattern comparisons among bloodstream infection isolates from the SENTRY Antimicrobial Surveillance Program (1997-2002). **Diagnostic Microbiology and Infectious Disease**, Nova Iorque, v. 50, n. 1, p. 59-69, 2004. https://doi.org/10.1016/j.diagmicrobio.2004.05.003

BONTEN. M.J. Ventilator-Associated Pneumonia: Preventing the Inevitable. **Clinical Infectious Diseases**, v. 52, p. 115-21, 2011. https://doi.org/10.1093/cid/ciq075.

BONTEN, M. J. Colonization pressure: a critical parameter in the epidemiology of antibiotic-resistant bacteria. **Critical Care**, v. 16, n. 4, p. 142, 2012. https://doi.org/10.1186/cc11417

BOUADMA, L. et al. A multifaceted program to prevent ventilator-associated pneumonia: Impact on compliance with preventive measures. **Critical Care Medicine**, v. 38, n. 3, p. 789–796, 2010. https://doi.org/10.1097/CCM.0b013e3181ce21af

BOUCHER, H. W. et al. Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America. **Clinical Infectious Diseases**, v. 48, n. 1, p. 1-12, 2009. https://doi.org/10.1086/595011

BRAGA, I.A. et al. Multi-hospital point prevalence study of healthcare-associated infections in 28 adult intensive care units in Brazil. **Journal Of Hospital Infection**, v. 99, n. 3, p.318-324, 2018. http://dx.doi.org/10.1016/j.jhin.2018.03.003

CAIN, S. E. et al. Stratification of the Impact of Inappropriate Empirical Antimicrobial Therapy for Gram-Negative Bloodstream Infections by Predicted Prognosis. **Antimicrobial Agents and Chemoterapy**, v. 59, n. 1, p. 245-250, 2015. https://doi.org/10.1128/AAC.03935-14

CARDOSO, T. et al. Classification of healthcare-associated infection: a systematic review 10 year after the first proposal. **BMC Medicine**, Londres, v. 12, n. 1, p. 40, 2014. https://doi.org/10.1186/1741-7015-12-40

CARRARA, D. Fisiopatogenia das infecções associadas a cateter intravascular: o papel do biofilme. In: SILVA, A. A.; FEIJÓ, D. F.; LESSA, S. S. **Infecção da corrente sanguínea associada ao uso de cateteres vasculares**. 4º ed. São Paulo: APECIH, 2016. cap. 3, p.35-44.

CATTOIR, V.; GIARD, J.C. Antibiotic resistance in Enterococcus faecium clinical isolates. **Expert Review of Anti-infective Therapy**. v. 12, p. 239-48, 2014. https://doi.org/10.1586/14787210.2014.870886

CAVALCANTE, M. V. et al. Characteristics of methicillin-resistant Staphylococcus aureus in patients on admission to a teaching hospital in Rio de Janeiro, Brazil. **American Journal of Infection Control**, v. 45, n. 11, p. 1190–1193, 2017.

CDC, Center for Disease Control and Prevetion. **Guideline for the Prevention of Intravascular Catheter-Related Infections**, Atlanta, 2011. Disponível em: https://www.cdc.gov/infectioncontrol/pdf/guidelines/bsi-guidelines-H.pdf. Acesso em: 20 maio 2021.

CHAKRAVARTY, B. Genetic mechanisms of antibiotic resistance and virulence in Acinetobacter baumannii: background, challenges and future prospects. **Molecular Biology Reports**, v. 47, p. 4037-4046, 2020. https://doi.org/10.1007/s11033-020-05389-4

CHAMON, R. C. et al. Complete substitution of the Brazilian endemic clone by other methicillin-resistant Staphylococcus aureus lineages in two public hospitals in Rio de Janeiro, Brazil. **Brazilian Journal of Infectious Diseases**, v. 21, n. 2, p. 185–189, 2017. https://doi.org/10.1016/j.bjid.2016.09.015

CHAN, J. D.; GRAVES, J. A.; DELLIT, T. H. Antimicrobial treatment and clinical outcomes of carbapenem-resistant Acinetobacter baumannii ventilator-associated pneumonia. **Journal of intensive care medicine**, v. 25, n. 6, p. 343–8, 2010. https://doi.org/10.1177/0885066610377975

CHEN, L., et al., Carbapenemase-producing Klebsiella pneumoniae: molecular and genetic decoding. **Trends in Microbiology**, v.22, n.12, p. 686-696, 2014. https://doi.org/10.1016/j.tim.2014.09.003

CHMIELARCZYK, A. et al. Severe infections caused by multidrug-resistant nonfermentative southern Poland. **Advances in clinical and experimental medicine**, v. 27, n. 3, p. 401-407, 2018. https://doi.org/10.17219/acem/68545

COSTERTON, J.W.; STEWART, P.S.; GREENBERG, E.P. Bacterial biofilms: a common cause of persistent infections. **Science**, v.284, n.5418, p.1318-22, 1999. https://doi.org/10.1126/science.284.5418.1318

COURVALIN, P. Vancomycin Resistance in Gram-Positive Cocci. **Clinical Infectious Diseases**, v.42, p.25-34, 2006. https://doi.org/10.1086/491711.

DAIKOS, G. L. et al. Carbapenemase-producing Klebsiella pneumoniae bloodstream infections: lowering mortality by antibiotic combination schemes and the role of carbapenems. **Antimicrobial Agents and Chemotherapy**, Washington, v. 58, n. 4, p. 2322-2328, 2014. https://doi.org/10.1128/AAC.02166-13

DAMACENO, Q.; NICOLI, J.R.; OLIVEIRA, A. Variability of cutaneous and nasal population levels between patients colonized and infected by multidrug-resistant bacteria in two Brazilian intensive care units. **SAGE Open Medicine**, v. 3, 2015. https://doi.org/10.1177/2050312114566668

DANTAS, R.C. et al. Pseudomonas aeruginosa bacteraemia: independent risk factors for mortality and impact of resistance on outcome. **Journal of Medical Microbiology**, v.63, n.12, p.1679-1687, 2014. https://doi.org/10.1099/jmm.0.073262-0

DELLINGER, R. P. et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. **Critical Care Medicine**, Berlim, v. 41, n. 2, p. 580-637, 2013. https://doi:10.1097/CCM.0b013e31827e83af

DHILLON, R.; CLARK, J. Infection in the intensive care unit (ICU). **Current Anaesthesia & Critical Care**, v. 20, n. 4, p. 175-182, 2009. https://doi.org/10.1016/j.cacc.2009.01.003

DIEKEMA, D. J. et al. Antimicrobial resistance trends and outbreak frequency in United States hospitals. **Clinical Infectious Diseases**, v. 38, n. 1, p. 78-85, 2004. https://doi.org/10.1086/380457

DIEKEMA, D. J. et al. Epidemiology and outcome of nosocomial and community-onset bloodstream infection. **Journal of Clinical Microbiology**, v. 41, n. 8, p. 3655-3660, 2003. https://doi.org/10.1128/JCM.41.8.3655-3660.2003

DONLAN, R.M. Biofilms and device-associated infections. **Emerging Infectious Diseases**, v.7, p.277-81, 2001. https://doi.org/10.3201/eid0702.010226

DORON, S.; DAVIDSON, L. E. Antimicrobial stewardship. **Mayo Clinic Proceedings**, v. 86, n. 11, p. 1113-1123, 2011. https://doi.org/10.4065/mcp.2011.0358

DOYLE, J. S. et al. Epidemiology of infections acquired in intensive care units. **Seminars in Respiratory and Critical Care Medicine**, v. 32, n. 2, p. 115-138, 2011. https://doi.org/10.1055/s-0031-1275525

DRASKOVIĆ, B. et al. Infections associated with the central venous catheters. **Srpski Arhiv Celokupno Lekarstvo,** Belgrade, v. 142, n. 3, p. 261-266, 2014. https://doi.org/10.2298/sarh1404261d

DUARTE, E. R. et al. Disseminated clonal complex 5 (CC5) methicillin-resistant Staphylococcus aureus SCCmec type ii in a tertiary hospital of southern Brazil. **Revista do Instituto de Medicina Tropical de São Paulo**, v. 60, p. 5–9, 2018. https://doi.org/10.1590/S1678-9946201860032

DUDECK, M. A. et al. National Healthcare Safety Network (NHSN) report, data summary for 2012, device-associated module. **American Journal of Infection Control**, San Luis, v. 41 n. 12, 2013, p. 1148 1166. http://dx.doi.org/10.1016/j.ajic.2013.09.002

ESTEBAN, A. et al. Sepsis incidence and outcome: Contrasting the intensive care unit with the hospital ward. **Critical Care Medicine**, v.35, p.1284-1289, 2007. https://doi.org/10.1097/01.CCM.0000260960.94300.DE.

FERRER, M. et al. Polymicrobial intensive care unit-acquired pneumonia: prevalence, microbiology and outcome. **Critical Care**, v. 19, n. 1, p. 450, 2015. https://doi.org/10.1186/s13054-015-1165-5

FLEMMING, H-C.; WINGENDER, J. The biofilm matrix. **Nature Reviews Microbiology**, v. 8, p. 623-33, 2010. https://doi.org/10.1038/nrmicro2415

FORTALEZA, C. M. C. B. et al. Multi-state survey of healthcare-associated infections in acute care hospitals in Brazil. **Journal of Hospital Infection**, v. 96, n. 2, p. 139-144, 2017. https://doi.org/10.1016/j.jhin.2017.03.024

GAHLOT, R. et al. Catheter-related bloodstream infections. **International Journal of Critical Illness and Injury Science**, v. 4, n. 2, p. 162–167, 2014. https://doi.org/10.4103/2229-5151.134184

GALES, A. C. et al. Antimicrobial susceptibility of gram-positive bacteria isolated in Brazilian hospitals 87 participating in the SENTRY Program (2005-2008). **Brazilian Journal of Infectious Diseases**, v.13, p.90-98, 2009. https://doi.org/10.1590/S1413-86702009000200004

GARNACHO-MONTERO, J. et al. Optimal management therapy for Pseudomonas aeruginosa ventilator-associated pneumonia: an observational, multicenter study comparing monotherapy with combination antibiotic therapy. **Critical care medicine**, v. 35, n. 8, p. 1888–95, 2007. https://doi.org/10.1097/01.CCM.0000275389.31974.22

GISKE, C. G. et al. Clinical and economic impact of common multidrug-resistant Gram-negative bacilli. **Antimicrobial Agents and Chemotherapy**, Washington, v. 52, n. 3, p. 813-821, 2008. https://doi:10.1128/AAC.01169-07

GOMINET, M. et al. Central venous catheters and biofilms: where do we stand in 2017? **APMIS**, v. 125, p.365-75, 2017. https://doi.org/10.1111/apm.12665.

GOOTZ, T. D. The global problem of antibiotic resistance. **Critical Reviews in Immunology**, Boca Raton, v. 30, n. 1, p. 79-93, 2010. https://doi.org/10.1615/CritRevImmunol.v30.i1.60

GOOTZ, T.D., et al. Genetic organization of transposase regions surrounding blaKPC carbapenemase genes on plasmids from Klebsiella strains isolated in a New York City hospital. **Antimicrobial Agents and Chemotherapy**, v. 53, n. 5, p. 1998-2004, 2009. https://doi.org/10.1128/AAC.01355-08

GOULD, C. V. et al. **Guideline for prevention of catheter-associated urinary tract infection 2009**. Disponível em: https://www.cdc.gov/infectioncontrol/pdf/guidelines/cauti-guidelines-H.pdf. Acesso em 07 jan 2021.

GRAU, S. et al. How to measure and monitor antimicrobial consumption and resistance. **Enfermedades Infecciosas y Microbiologia Clinica**, v. 31, p. 16-24, 2013. https://doi.org/10.1016/S0213-005X(13)70128-9

HAMBRAEUS, A. Lowbury Lecture 2005: infection control from a global perspective. **Journal of Hospital Infection**, Nova Iorque, v. 64, n. 3, p. 217-223, 2006. https://doi.org/10.1016/j.jhin.2006.07.003

HIDRON, A. I. et al. Antimicrobial-Resistant Pathogens Associated with Healthcare-Associated Infections: Annual Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. **Infection Control & Hospital Epidemiology**, v. 29, n. 11, p. 996–1011, 2008.https://doi.org/10.1086/591861

HIJAZI, K.; JOSHI, C.; GOULD, I.M. Challenges and opportunities for antimicrobial stewardship in resource-rich and resource-limited countries. **Expert Review of Anti-infective Therapy**, v. 17, n. 8, p. 621-634, 2019. https://doi.org/10.1080/14787210.2019.1640602

HOU, X. H. Molecular characterization of multidrug-resistant Klebsiella pneumoniae isolates. **Brazilian Journal of Microbiology**, Rio de Janeiro, v. 46, n. 3, p. 759-768, 2015. https://doi.org/10.1590/S1517-838246320140138

HUGONNET, S.; UÇKAY, I.; PITTET, D. Staffing level: a determinant of late-onset ventilator-associated pneumonia. **Critical care**, Londres, v. 11, n. 4, p. 80, 2007. https://doi.org/10.1186/cc5974

HUNTER, J.D. Ventilator associated pneumonia. **Postgraduate Medical Journal**, v. 82, p.172-8, 2006. https://doi.org/10.1136/pgmj.2005.036905.

HUNTER, J. D. Ventilator associated pneumonia. **BMJ**, v. 344, n. 29, p. 3325–3325, 2012. https://doi.org/10.1136/bmj.e3325

ITO, T. et al. Structural comparison of three types of staphylococcal cassette chromosome mec integrated in the chromosome in methicillinresistant Staphylococcus aureus. **Antimicrobial Agents Chemotherapy**, v.45, p.1323– 1336, 2001. http://dx.doi.org/10.1128/AAC.45.5.1323-1336.2001

JONES, R.N. et al. Susceptibility rates in Latin American nations: report from a regional resistance surveillance program (2011). **Brazilian Journal of Infectious Diseases**, v.17, n.6, p.672-681, 2013. https://doi.org/10.1016/j.bjid.2013.07.002

JOSEPH, N.M. et al. Ventilator-associated pneumonia: role of colonizers and value of routine endotracheal aspirate cultures. **International Journal of Infectious Diseases**, v.14, p.7239, 2010a..https://doi.org/10.1016/j.ijid.2010.02.2248.

JOSEPH, N. M. et al. Role of intensive care unit environment and health-care workers in transmission of ventilator-associated pneumonia. **Journal of infection in developing countries**, v. 4, n. 5, p. 282–91, 2010b. https://doi.org/10.3855/jidc.800

KATAYAMA, Y.; ITO, T.; HIRAMATSU, K. A new class of genetic element, staphylococcus cassette chromosome mec, encodes methicillin resistance in Staphylococcus aureus. **Antimicrobial Agents Chemotherapy**, v.44, p.1549–1555, 2000. http://dx.doi.org/10.1128/AAC.44.6.1549-1555.2000.

KIENINGER, A.N.; LIPSETT, P.A. Hospital-Acquired Pneumonia: Pathophysiology, Diagnosis, and Treatment. **Surgical Clinics of North America**, v. 89, p.439-61, 2009. https://doi.org/10.1016/j.suc.2008.11.001.

KLOMPAS, M. PLATT, R. Ventilator-associated pneumonia-the wrong quality measure for benchmarking. **Annals of Internal Medicine**, v.147, n.11, p. 803-5, 2007.

KOLLEF, M. BURNHAM, C-A. Ventilator-Associated Pneumonia: The Role of Emerging Diagnostic Technologies. **Seminars in Respiratory and Critical Care Medicine**, v. 38, p.253-63, 2017. https://doi.org/10.1055/s-0037-1599224.

KOLLEF, M. H. et al. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. **Chest**, Chicago, v.115, n.2, p.462-474, 1999. https://doi.org/10.1378/chest.115.2.462

LANKS, C.W.; MUSANI, A.I.; HSIA, D.W. Community-acquired Pneumonia and Hospital-acquired Pneumonia. **Medical Clinics of North America**, v.103, p.487-501, 2019. https://doi.org/10.1016/j.mcna.2018.12.008.

LAUPLAND, K. B. et al. Population-based assessment of intensive care unit-acquired bloodstream infections in adults: Incidence, risk factors, and associated mortality rate. **Critical Care Medicine**, v. 30, n. 11, p. 2462-2467, 2002.https://doi.org/10.1097/00003246-200211000-00010

LEAO, L.A.N.O. et al. Fenotipagem de bactérias isoladas em hemoculturas de pacientes críticos. **Revista da Sociedade Brasileira de Medicina Tropical**, v. 40, n. 5, p. 537-540, 2007. https://doi.org/10.1590/S0037-86822007000500009

LEE, R. et al. Impact of Infectious Disease Consultation on Clinical Management and Mortality in Patients With Candidemia. **Clinical Infectious Diseases**, v. 68, n. 9, p.1585-1587, 2018. http://dx.doi.org/10.1093/cid/ciy849.

LEYLABADLO, H. E. et al. Extended-Spectrum Beta-Lactamase Producing Gram Negative Bacteria In Iran: A Review. **African journal of infectious diseases**, v. 11, n. 2, p. 39–53, 2017. https://doi.org/10.21010/ajid.v11i2.6

LISBOA, T. et al. Prevalência de infecção nosocomial em unidades de terapia intensiva do Rio Grande do Sul. **Revista Brasileira de Terapia Intensiva**, v.19, n.4, 2007. http://dx.doi.org/10.1590/S0103-507X2007000400002

LO, E. et al. Strategies to prevent catheter-associated urinary tract infections in acute care hospitals. **Infection Control and Hospital Epidemiology**, v.29, n.1, p. 41-50, 2008. https://doi.org/10.1086/591066

LÜ, Y. et al. A multi-center nested case-control study on hospitalization costs and length of stay due to healthcare-associated infection. **Antimicrobial Resistance and Infection Control**, v.7, p.99, 2018. https://doi.org/10.1186/s13756-018-0386-1.

MAGIORAKOS, A.-P. et al. Multidrug-resistant, extensively drug-resistant and pandrugresistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. **Clinical Microbiology and Infection**, v.18, n.3, p. 268-281, 2012. https://doi.org/10.1111/j.1469-0691.2011.03570.x

MARCHAIM, D.; KAYE, K Infection and antimicrobial resistance in the intensive care unit: Epidemiology and prevention. **UpToDate**, 2017. Disponível em: < https://www.uptodate.com/contents/infections-and-antimicrobial-resistance-in-theintensive-care-unit-epidemiology-and-prevention?search=infections-and-antimicrobialresistance-in-the-&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2> Acesso em: 18 jul 2020.

MASEDA G. E. et al. Update on catheter related bloodstream infections in ICU patients. **Enfermidades Infecciosas e Microbiologia Clinica**, v. 29, n. 4, p.10-15, 2011.

MAYER, J. et al. Agreement in Classifying Bloodstream Infections Among Multiple reviewers conducting surveillance. **Clinical Infectious Diseases**, v.55, n.3, p.364 -70, 2012. https://doi.org/10.1093/cid/cis410

MEJIA-CHEW, C. et al. Effect of infectious disease consultation on mortality and treatment of patients with candida bloodstream infections: a retrospective, cohort study. **The Lancet Infectious Diseases**, v.19, n.12, p.1336-1344, 2019.http://dx.doi.org/10.1016/s1473-3099(19)30405-0.

MERMEL, L.A. Prevention of intravascular catheter-related infections. **Annals of Internal Medicine**, v.132, p.391-402, 2000.

MICEK S. et al. An institutional perspective on the impact of recent antibiotic exposure on length of stay and hospital costs for patients with gram-negative sepsis. **Infectious Diseases**, Inglaterra, v. 12, p. 56, 2012. https://doi.org/10.1186/1471- 2334-12-56

MICEK, S. T. et al. A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. **Chest**, Chicago, v. 125, n. 5, p. 1791-1799, 2004. https://doi.org/10.1378/chest.125.5.1791

MICEK, S.T. et al. Pseudomonas aeruginosa Bloodstream Infection: Importance of Appropriate Initial Antimicrobial Treatment. **Antimicrobial Agents and Chemotherapy**, v. 49, n. 4, p. 1306-1311, 2005. https://doi.org/10.1128/AAC.49.4.1306-1311.2005

MOREIRA, M. R. et al. Antimicrobial use, incidence, etiology and resistance patterns in bacteria causing ventilator-associated pneumonia in a clinical-surgical intensive care unit. **Revista da Sociedade Brasileira de Medicina Tropical**, Rio de Janeiro, v. 46, n. 1, p. 39-44, 2013. https://doi.org/10.1590/0037-868216722013

NATIONAL NOSOCOMIAL INFECTIONS SURVEILLANCE SYSTEM. Report, data summary from January 1992-April 2000. **American Journal of Infection Control**, St. Louis, v. 28, n. 6, p. 429-448, 2000. https://doi.org/10.1067/mic.2000.110544

NHSN, National Healthcare Safety Network. **NHSN Bloodstream infection event**, Atlanta, 2021a. Disponível em: https://www.cdc.gov/nhsn/pdfs/pscmanual/4psc_clabscurrent.pdf. Acesso em 14 mar 2021.

NHSN, National Healthcare Safety Network. **Patient Safety Component Manual**, Atlanta, 2021b. Disponível em: https://www.cdc.gov/nhsn/pdfs/pscmanual/pcsmanual_current.pdf. Acesso em 14 mar 2021.

NICOLETTI, A.G., et al., Clonal Complex 258, the Most Frequently Found Multilocus Sequence Type Complex in KPC-2-Producing Klebsiella pneumoniae Isolated in Brazilian Hospitals. **Antimicrobial Agents and Chemotherapy**, v.56, n.8, p.4563–4564, 2012. https://doi.org/10.1128/AAC.00219-12

NIEDERMAN, M.S. De-escalation therapy in ventilator-associated pneumonia. **Current Opinion in Critical Care**, Philadelphia, v. 12, n. 5, p. 452-457, 2006. https://doi.org/10.1097/01.ccx.0000244126.84989.a2

NIEDERMAN, M. S.; SOULOUNTSI, V. De-escalation therapy: is it valuable for the management of ventilator-associated pneumonia? **Clinics in Chest Medicine**, Philadelphia, v.32, n.3, p. 517-534, 2011. https://doi.org/10.1016/j.ccm.2011.05.009

NNIS, National Nosocomial Infection Surveillance System Report, Data summary from January 1992 – June 2001, issued August 2001. **American Journal of Infection Control**, v. 29, n. 6, p. 404-421, 2001. https://doi.org/10.1067/mic.2001.119952

NOGUEIRA JUNIOR, C. et al. Characterization of epidemiological surveillance systems for healthcare-associated infections (HAI) in the world and challenges for Brazil. **Cadernos de Saúde Pública**, Rio de Janeiro, v. 30, n. 1, p. 11-20, 2014. http://dx.doi.org/10.1590/0102-311X00044113

OLIVEIRA, A. C. et al. Infecções relacionadas à assistência em saúde e gravidade clínica em uma unidade de terapia intensiva. **Revista Gaúcha de Enfermagem**, Porto Alegre, v. 33, n. 3, 2012. http://dx.doi.org/10.1590/S1983-14472012000300012

PADOVEZE, M. C.; FORTALEZA, C. M. C. B. Healthcare-associated infections: challenges to public health in Brazil. **Revista Saúde Pública**, São Paulo, v. 48, n. 6, p. 996-1001, 2014. https://doi:10.1016/j.jhin.2007.07.007

PELEG, A.Y.; HOOPER, D.C. Hospital-acquired infections due to Gram-negative bacteria. **The New England Journal of Medicine**, v. 362, n. 19, p. 1804-1813, 2010. https://doi.org/10.1056/NEJMra0904124

PEREIRA FRANCHI, M.R.N. et al. Molecular epidemiology of MRSA in the Brazilian primary health care system. **Tropical Medicine & International Health**, v.24, n.3, p. 339–347, 2019. https://doi.org/10.1111/tmi.13192

PÉRICHON, B.; COURVALIN, P. VanA-Type Vancomycin-Resistant Staphylococcus aureus. **Antimicrobial Agents Chemotherapy**, v.53, p.4580-7, 2009. https://doi.org/10.1128/AAC.00346-09.

PITIRIGA, V. et al. Antimicrobial stewardship program in a Greek hospital: implementing a mandatory prescription form and prospective audits. **Future Microbiology**, v.13, n.8, p.889-896, 2018. https://doi.org/10.2217/fmb-2018-0020

PITTET, D.; DONALDSON, L. Challenging the world: Patient safety and health care-associated infection. **International Journal for Quality in Health Care**, v. 18, n. 1, p. 4–8, 2006. https://doi.org/10.1093/intqhc/mzi093

PORTO, A.M.P. et al. Global point prevalence survey of antimicrobial consumption in Brazialian hospitals. **Journal of Hospital Infection**, v.104, n.2, p.165-171, 2020. https://doi.org/ 10.1016/j.jhin.2019.10.016

PORTO, J.P. et al. Active surveillance to determine the impact of methicillin resistance on mortality in patients with bacteremia and influences of the use of antibiotics on the development of MRSA infection. **Revista da Sociedade Brasileira de Medicina Tropical**, v.46, n.6, p.713-718, 2013. https://doi.org/10.1590/0037-8682-0199-2013

POURMAND, A. et al. Emerging trends in antibiotic resistance: Implications for emergency medicine. **The American Journal of Emergency Medicine**, v. 35, n. 8, p. 1172–1176, 2017. https://doi.org/10.1016/j.ajem.2017.03.010

PRADO, G.V.B. et al. Virulence and resistance pattern of a novel sequence type of linezolid-resistant Enterococcus faecium identified by whole-genome sequencing. **Journal of Global Antimicrobial Resistance**, v. 6, p.27-31, 2016. https://doi.org/10.1016/j.jgar.2016.02.002

QUEENAN, A.M.; BUSH, K. Carbapenemases: the versatile beta-lactamases. **Clinical Microbiology Reviews**, v. 20, n. 3, p. 440-58, 2007. https://doi.org/10.1128/CMR.00001-07

RAAD, I. et al. Ultrastructural analysis of indwelling vascular catheters: a quantitative relationship between luminal colonization and duration of placement. **Journal of Infectious Diseases**, v.168, n.2, p.400-7, 1993. https://doi.org/10.1093/infdis/168.2.400[

RAZA, T. et al. Vancomycin resistant Enterococci: A brief review. **Journal of Pakistan Medical Association**, v.68, n.5, p.768-72, 2018.

RELLO, J. et al. Epidemiology and Outcomes of Ventilator-Associated Pneumonia in a Large US Database. **Chest**, v.122, p.2115-21, 2002. https://doi.org/10.1378/chest.122.6.2115.

RELLO, J. et al. De-escalation therapy in ventilator-associated pneumonia. **Critical Care Medicine**, New York, v. 32, n. 11, p. 2183-2190, 2004. https://doi.org/10.1097/01.CCM.0000145997.10438.28

RESENDE, M. et al. Emergence of vanA vancomycin-resistant Enterococcus faecium in a hospital in Porto Alegre, South Brazil. **Journal of Infection in Developing Countries**., v.8, p.160-7, 2014. https://doi.org/10.3855/jidc.4126

RICHARDS, M. J. et al. Nosocomial infections in combined medical-surgical intensive care units in the United States. **Infection Control and Hospital Epidemiology**, Thorofare, v. 21, n. 8, p. 510-515, 2000. https://doi.org/10.1086/501795

RICHARDS, M.; THURSKY, K.; BUISING, K. Epidemiology, prevalence, and sites of infections in intensive care units. **Seminars in Respiratory and Critical Care Medicine**, Nova Iorque, v. 24, n. 1, p. 3-22, 2003. https://doi:10.1055/s-2003-37913

ROCHA, L.A. et al. Ventilator-associated pneumonia in an adult clinical-surgical intensive care unit of a Brazilian university hospital: incidence, risk factors, etiology, and antibiotic resistance. **Brazilian Journal of Infectious Diseases**, v.12, p.80-5, 2008. https://doi.org/10.1590/S1413-86702008000100017.

ROSENTHAL, V. D. et al. International Nosocomial Infection Control Consortium (INICC) report, data summary of 36 countries, for 2004-2009. **American Journal of Infection Control**, v. 40, n. 5, p. 396-407, 2012.https://doi.org/10.1016/j.ajic.2011.05.020

ROSENTHAL, V. D. et al. International Nosocomial Infection Control Consortium (INICC) report, data summary for 2003-2008, issued June 2009. **American Journal of Infection Control**, v. 38, n. 2, 2010. https://doi.org/10.1016/j.ajic.2009.12.004

ROSSI, I. et al. Outbreaks of colistin-resistant and colistin-susceptible KPC-producing Klebsiella pneumoniae in a Brazilian intensive care unit. **Journal of Hospital Infection**, v.94, n.4, p.322-329, 2016. https://doi.org/10.1016/j.jhin.2016.08.019

RUIZ, J. et al. Antimicrobial stewardship programme in critical care medicine: A prospective interventional study. **Medicina Intensiva**, v. 42, n. 5 p. 266-273, 2018. https://doi.org/10.1016/j.medine.2017.07.004

RUIZ-GARBAJOSA, P., et al., Multiclonal dispersal of KPC genes following the emergence of non-ST258 KPC- producing Klebsiella pneumoniae clones in Madrid, Spain**. The Journal of Antimicrobial Chemotherapy**, v. 68, n. 11, p. 2487-2492, 2013. https://doi.org/10.1093/jac/dkt237

SABATIER, C.; PEREDO, R.; VALLÉS, J. Bacterial bloodstream infections in critical patients. **Medicina Intensiva**, v.33, n.7, p.336-345, 2009. https://doi.org/10.1016/j.medin.2008.08.001

SABINO, S. S. Infecções hospitalares por micro-organismos resistentes aos antimicrobianos em pacientes internados na unidade de terapia intensiva de adultos em um hospital terciário de Minas Gerais: incidência, etiologia, fatores de risco, evolução e custos. 2018. 73 f. Dissertação (Mestrado) – Universidade Federal de Uberlândia, Uberlândia, 2018.

SAFDAR, N. et al. Clinical and economic consequences of ventilator-associated pneumonia: A systematic review. **Critical Care Medicine**, v.33, n.10, p.2184 2193, 2005. http://dx.doi.org/10.1097/01.ccm.0000181731.53912.d9.

SANDIUMENGE, A.; RELLO, J. Ventilator-associated pneumonia caused by ESKAPE organisms. **Current Opinion in Pulmonary Medicine**, v.18, n.3, p.187–193, 2012. https://doi.org/10.1097/MCP.0b013e328351f974

SARAVU, K. et al. Clinic-microbiological profile and outcomes of nosocomial sepsis in an Indian tertiary care hospital – a prospective cohort study. **Pathogens and global health**, Ingalaterra, v.109, n.5, p.228-35, 2015.https://doi.org/10.1179/2047773215Y.0000000026

SCHELD, W.M. Developments in the pathogenesis, diagnosis and treatment of nosocomial pneumonia. **Surgery Gynecology and Obstetrics Archives**, v.172, p.42-53, 1991.

SCHWABER, M. J.; CARMELI, Y. The effect of antimicrobial resistance on patient outcomes: importance of proper evaluation of appropriate therapy. **Critical Care**, Londres, v.13, n.1, p.106, 2009. https://doi.org/10.1186/cc7136

SILVA, L.P.P. et al. Genetic features and molecular epidemiology of Enterococcus faecium isolated in two university hospitals in Brazil. **Diagnostic Microbiology and Infectious Disease**., v.74, p.267-71, 2012a. https://doi.org/10.1016/j.diagmicrobio.2012.07.012

SILVA, E. et al. Prevalence and outcomes of infections in Brazilian ICUs: a subanalysis of EPIC II study. **Revista Brasileira de Terapia Intensiva**, São Paulo, v.24, n.2, p.143-150, 2012b. http://dx.doi.org/10.1590/S0103-507X2012000200008

SINGH, S. et al. A three-point time series study of antibiotic usage on an intensive care unit, following an antibiotic stewardship programme, after an outbreak of multi-resistant

Acinetobacter baumannii. **European Journal of Clinical Microbiology & Infectious Diseases**, v.34, n.9, p.1893-1900, 2015. https://doi.org/10.1007/s10096-015-2429-3

SOOD, S. et al. Enterococcal infections & antimicrobial resistance**. Indian Journal of Medical Research**, v. 128, n.2, p.111-21, 2008.

TANWAR, J. et al. Multidrug resistance: an emerging crisis. **Interdisciplinary Perspectives on Infectious Diseases**, Cairo, p. 1–7, 2014. https://doi.org/10.1155/2014/541340

TUON, F.F.; GORTZ, L.W.; ROCHA, J.L. Risk factors for pan-resistant Pseudomonas aeruginosa bacteremia and the adequacy of antibiotic therapy, **Brazillian Journal of Infectious Disease**, v.16, n.4, p.351-356, 2012. https://doi.org/10.1016/j.bjid.2012.06.009

VALLÉS, J. et al. Health-care-associated bloodstream infections at admission to the ICU. **Chest**, v.139, n. 4, p.810-815, 2011. https://doi.org/10.1378/chest.10-1715

VALLÉS, J.; FERRER, R. Bloodstream Infection in the ICU**. Infectious Disease Clinics of North America**, v.23, n.3, p.557-569, 2009. https://doi.org/10.1016/j.idc.2009.04.005

VARDAKAS, K.Z. et al. Predictors of mortality in patients with infections due to multi-drug resistant Gram-negative bacteria: the study, the patient, the bug or the drug? **The Journal of Infection**, Inglaterra, v.66, n.5, p.401-14, 2013.https://doi.org/10.1016/j.jinf.2012.10.028

VELOSO, J.O. et al. Methicillin-resistant and vancomycin-intermediate Staphylococcus aureus colonizing patients and intensive care unit environment: virulence profile and genetic variability. **APMIS**, v.127, p.717-26, 2019. https://doi.org/10.1111/apm.12989

VESTERGAARD, M.; FREES, D.; INGMER, H. Antibiotic Resistance and the MRSA Problem. **Microbiol Spectrum**, v.7, n.2, 2019;7. https://doi.org/10.1128/microbiolspec.GPP3-0057-2018

VICENTINI, C. et al. Point prevalence data on antimicrobial usage in Italian acute-care hospitals: Evaluation and comparison of results from two national surveys (2011– 2016). **Infection Control & Hospital Epidemiology**, v.41, n.5, p.579-584, 2020. https://doi.org/10.1017/ice.2020.18

VILAR-COMPTE, D.; CAMACHO-ORTIZ, A.; PONCE-DE-LEÓN, S. Infection control in limited resources countries: Challenges and priorities. **Current Infectious Disease Reports**, Filadélfia, v.19, n. 5, p. 20, 2017. https://doi.org/10.1007/s11908-017-0572-y

VINCENT, J.L. et al. The prevalence of nosocomial infection in intensive care units in europe. Results of the european prevalence of infection in intensive care (Epic) study. Epic international advisory committee. **JAMA**, v.274, p.639-644, 1995.

VINCENT, J. L. et al. International study of the prevalence and outcomes of infection in intensive care units. **Journal of the American Medical Association**, Chicago, v.302, n.21, p.2323-2329, 2009. https://doi.org/10.1001/jama.2009.1754

WANG, Y.-C. et al. Is Polymicrobial Bacteremia an Independent Risk Factor for Mortality in Acinetobacter baumannii Bacteremia? **Journal of Clinical Medicine**, v.9, n.1, p.153, 2020. https://doi.org/10.3390/jcm9010153

WEAVER, S. J.; WEEKS, K.; PHAM, J. C. on the CUSP: stop BSI: evaluating the relationship between central line–associated bloodstream infection rate and patient safety climate profile. **American Journal of Infection Control**, San Luis, v.42, n.10, p.203-208, 2014. https://doi.org/10.1016/j.ajic.2014.05.020

WEINER, L. M. et al. Antimicrobial-resistant pathogens associated with healthcareassociated infections: Summary of data reported to the national healthcare safety network at the centers for disease control and prevention, 2011-2014. **Infection Control and Hospital Epidemiology**, Thorofare, v.37, n.11, p.1288-1301, 2016. http://dx.doi.org/10.1017/ice.2016.174

WORLD HEALTH ORGANIZATION. **Collaborating Centre for Drug Statistics Methodology**. ATC Index with DDDs. Oslo, Norway: WHO; 2019. Disponível em: https://www.whocc.no/atc_ddd_index/. Acesso 15 fev 2021

WORLD HEALTH ORGANIZATION. **Health care-associated infections Fact Sheet**. Geneva: WHO; 2016. Disponível em: https://www.who.int/gpsc/country_work/gpsc_ccisc_fact_sheet_en.pdf. Acesso em 30 nov 2020.

WORLD HEALTH ORGANIZATION. **Report on the Burden of Endemic Healthcare-associated Infection Worldwide**. Geneva: WHO, 2011. Disponível em: https://apps.who.int/iris/bitstream/handle/10665/80135/9789241501507_eng.pdf;jsessionid=76FC27C7595E2DAF355DA9EBF4435E6A?sequence=1. Acesso em 12 dez 2020.

WU, C.T. et al. Decreased antimicrobial resistance and defined daily doses after implementation of a clinical culture-guided antimicrobial stewardship program in a local hospital. **Journal of Microbiology, Immunology and Infection**, v.50, n.6, p.846-856, 2017. https://doi.org/10.1016/j.jmii.2015.10.006

YLIPALOSAARI, P., et al. Intensive care acquired infection is an independent risk factor for hospital mortality: a prospective cohort study. **Critical Care**, Londres, v.10, n.2, p.66, 2006. https://doi.org/10.1186/cc4902

ZARAGOZA, R.; RAMÍREZ, P.; LÓPES-PUEYO, M. Infección nosocomial em las unidades de cuidados intensivos. **Enfermedades Infecciosas y Microbiología Clínica**, v.32, n.5, p.320-327, 2014. https://doi.org/10.1016/j.eimc.2014.02.006

ZARKOTOU, O. et al. Predictors of mortality in patients with bloodstream infections caused by KPC-producing Klebsiella pneumoniae and impact of appropriate antimicrobial treatment. **Clinical Microbiology and Infection**, v.17, n.12, p.1798-1803, 2011. https://doi.org/10.1111/j.1469-0691.2011.03514.x

ZHENG, C. et al. Clinical characteristics and risk factors of polymicrobial Staphylococcus aureus bloodstream infections. **Antimicrobial Resistance & Infection Control**, v.9, n.1, p.76, 2020. https://doi.org/10.1186/s13756-020-00741-6

ZILBERBERG, M.D. et al. Antimicrobial Therapy Escalation and Hospital Mortality Among Patients with Health-Care-Associated Pneumonia: A Single-Center Experience. **Chest**, v.134, n.5, p.963-968, 2008. https://doi.org/10.1378/chest.08-0842

ZILBERBERG, M. D. et al. Multi-drug resistance, inappropriate initial antibiotic therapy and mortality in Gram-negative severe sepsis and septic shock: a retrospective cohort study. **Critical Care**, London, v.18, p.1-13, 2014. https://doi.org/10.1186/s13054-014-0596-8

ZILBERBERG, M. D.; SHORR, A. F. Ventilator-associated pneumonia: the clinical pulmonar infection score as a surrogate for diagnostics and outcome. **Clinical Infectious Diseases**, v.51, n.1, p.131-5, 2010. https://doi.org/10.1086/653062

Capítulo 2

Alarming Results from a Multi-Centric Surveillance of Nosocomial Bloodstream Infections and Pneumonia Trials in Brazilian Adult Intensive Care Units

ALARMING RESULTS FROM A MULTI-CENTRIC SURVEILLANCE OF NOSOCOMIAL BLOODSTREAM INFECTIONS AND PNEUMONIA TRIALS IN BRAZILIAN ADULT INTENSIVE CARE UNITS

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Keywords: Healthcare-associated infection; Multi-centric study; Intensive care units; Epidemiology; Bloodstream infection; Pneumonia.

2.1 ABSTRACT

Introduction: Healthcare-associated infections (HAIs) correspond to the most recurrent adverse event in hospitals worldwide and represent an important public health problem.

Gap statement: There is a paucity of multi-centric data describing severe HAIs as bloodstream infection (BSI) and pneumonia in Brazil.

Aim: To provide an up-to-date picture of the extent and patterns of HAI in adult Intensive Care Units (ICUs), as well as to identify variables associated with the risk of development of severe infections.

Methodology: Point-prevalence surveys were conducted using standardized protocols in 35 ICUs from Minas Gerais State, Brazil. Medical records of eligible inpatients at or before 8 am on the survey day were reviewed to identify HAIs present at the time of the survey. A matched-pairs case-control study was performed on a total of 66 pairs for BSI and 115 pairs for pneumonia according to the selection criteria developed.

Results: Overall 171 patients (45.7%) had at least one HAI, with most (78.4%) acquired in the ICU. These patients presented a total of 240 infections; including 123 pneumonia (51.3%) and 66 BSI (27.5%), and 78.9% and 80.3%, respectively, were acquired in the ICU. The etiology of them was starred by Gram-negative bacteria versus Gram-positive bacteria (48.9% versus 43.3%), highlighting *Acinetobacter baumannii* (13.7%) and *Pseudomonas aeruginosa* (12.8%). One striking observation of our data was the higher prevalence of *Staphylococcus aureus* (14.5%) and coagulase-negative staphylococci (10.2%) observed in the total of HAI.

Conclusion: A high severe ICU-acquired HAIs burden was found when compared with findings from other low- and middle-income countries. These data can be utilized for better planning of nosocomial infection surveillance programs in our hospitals.

2.2 INTRODUCTION

Healthcare-associated infections (HAIs) correspond to the most recurrent adverse event in hospitals worldwide representing an important public health problem [1-3], but only a few large epidemiologic studies of nosocomial infections in Intensive care Units (ICUs) have been carried out in low- and middle-income countries, such as Brazil, meaning that these infections do not receive the attention compatible with their impact on health, especially at developing countries [4-8].

According to scientific literature, around 20.0% - 30.0% of ICU hospitalized patients in Brazil develop HAI [6, 9], with a high incidence of bloodstream infections (BSIs) and pneumonia [10, 11]. Additionally, there is a connection between these severe infections usually due to antimicrobial-resistant pathogens and various risk factors including longer hospital length of stay (LOS), higher mortality rates and incremental costs [11-14]. It is fundamental to mention that, in recent years, there has been a significant increase of HAIs rates of infections caused by multi-resistant Gram-negative microorganisms, with emphasis on *Klebsiella pneumoniae* and *Acinetobacter baumanni,* due to the higher ability to develop resistance to all antimicrobials available for treatment and resulting in more morbidity, inappropriate antibiotic therapy and higher costs. Their epidemiology has become a major global problem [15, 16].

Given absence of multi-centric national data about BSI and pneumonia and the lack of resources necessary for an incidence study, we aimed to provide an up-to-date, picture of the extent and patterns of these infections in patients cared for in adult ICUs. Additionally, we aimed to identify risk factors associated with their development.

2.3 METHODS

Participating hospitals

The 28 participating hospitals were selected by multistage stratified random sampling to have representatives in all macrogeographical regions of Minas Gerais State, Brazil. It was included five large university hospitals and 23 regional hospitals. All patient data were anonymized and collected. Hospitals from the following eight meso-regions were included: Campo das Vertentes, Metropolitana de Belo Horizonte, Norte de minas, Oeste de Minas, Sul/sudoeste de Minas, Triângulo Mineiro/Alto Paranaíba, Vale do Rio Doce and Zona da Mata

[17], and an agreement was signed with each participating hospital representant giving authorization to perform the research.

Study design and data collection

This was an observational, cross-sectional, 24-hour point prevalence study design that was executed with visits to 35 adult ICUs (28 medical– surgical ICUs, and seven Coronary ICUs) in each participating hospital by a trained nurse responsible for the data collection. We obtained consent from all individuals to participate in the study.

The patients form included the following data: (1) hospitals demographics (characteristics of the hospital and the ICU); (2) patient demographics and other risk factors (age, sex, date of hospital and ICU admission, reason for admission, and primary diagnoses and comorbidities); (3) data about infections (episodes of HAI, microbiological culture results, antibiotic exposure, etc.).

This stage of the research was performed between February and December 2016, and all HAIs assessed in this study were from ICUs inpatients, meaning that only patients interned in adult ICUs on the day of the survey were evaluated and that the hospital-acquired HAIs included only those patients cared for in these units.

Definitions

HAIs were defined following the National Healthcare Safety Network (NHSN) and the Agência Nacional de Vigilância Sanitária (ANVISA) guidelines [10,18]. The ANVISA guidelines complemented the definition of HAIs to include in the characterization of bloodstream infections, those clinically diagnosed patients without laboratory confirmation.

Case-control study

This was a matched-pairs case-control study and was performed to a total of 66 pairs (66 patients with BSI vs 66 without BSI), and 115 pairs (115 patients with pneumonia vs 115 without pneumonia) according to the selection criteria used.

Cases were defined as those patients diagnosed with bloodstream infection or pneumonia either by the attending physician or by the Hospital Infection Control Service physician, according to medical records observed on the day of the inquire and it should be

emphasized that we performed one matched-case study for patients with BSI, and another independent matched-case study for patients with pneumonia.

Controls were defined as patients that did not present BSI or pneumonia on the matching day. One control was selected for each case and matched by the following characteristics: cause of hospitalization, age, sex, and time of risk. It was considered a variation of ± 10 years for the age matching. The duration of risk was the total LOS before the matching day for control patients and before infection diagnosis for case patients and the difference between the risk duration of the control patients was ± 10 days in relation to the case-patients.

Ethical approval

The study was approved by the Research Ethics Committee of the Federal University of Uberlandia, Minas Gerais, and ethical approval was granted under Protocol Number 239/11. In all stages of the study, the principles of confidentiality and non-maleficence were applied. The hospitals and patients' identities were confidential.

Statistical analysis

The data were generated with descriptive statistics according to the type of variable. A value of $p \leq 0.05$ was considered significant. The normality of the data was tested with the Shapiro-Wilk and Kolmogorov Smirnov tests. For quantitative variables, Student's t-test was used for parametric distributions and the Mann-Whitney U-Test for non-parametric distributions. For categorical data, the chi-square or Fisher's exact test was used as appropriate. Statistical analyzes were performed using the Graph-PadPrism program version 8 (Graph-Pad Software, San Diego, CA). The multivariate analysis was performed using multiple logistic regression and the values were included for variables with significant statistics (p <0.05), using the Bioestat® software version 5.3 [19].

2.4 RESULTS

The prevalence of HAIs in the hospitals of eight meso-regions of Minas Gerais state, Brazil, is presented in **Table I**. In total, the 28 hospitals had 374 occupied ICU beds, and on the day of the survey around half of the patients 171/374 (45.7%) were infected, with most (78.4%) of the HAI acquired in the ICU. These patients with HAI had a total of 240 infections; including

123 pneumonia (51.3%) and 66 BSI (27.5%), with 78.9% and 80.3% respectively, acquired in the ICU.

Among these patients, the risk factors for patients with BSI and pneumonia by matching cases and controls are presented in **Table II**. The overall success rates of the variables used to match the cases and controls were 81.8% and 78.7%, respectively. The biggest success rate achieved was 89.4% for the cause of hospitalization variable in the BSI matched pairs, and the smallest was 71.2% for the time of risk variable in the same group.

The matched case-control study of risk factors among patients of the ICU with BSI and pneumonia showed that significant difference ($p<0,05$) was observed in relation to the classical risk factors described in national and international literature and are among them: length of hospitalization in ICU, use of a central venous catheter (CVC) for 7 days or over, mechanical ventilation, antimicrobial therapy, the use of carbapenem, cephalosporin (3^{rd} or 4^{th} generation) and polymyxin. **(Tables III and IV)**

However, concerning the use of wide-spectrum cephalosporins in BSI patients and these cephalosporins, polymyxin and initial empirical antimicrobial therapy to pneumonia patients, these characteristics were independently associated with a higher risk of acquisition of infections, when compared with the pairs among patients with these infections. The risk factors independently associated with BSI and pneumonia, respectively are shown in **Tables III** and **IV**.

The most common organisms recovered inside and outside the ICU are listed in **Table V**. Overall, 141 isolated organisms were identified in infected patients with 82.9% acquired in the ICU. The most common micro-organisms causing HAI in ICUs were *Staphylococcus aureus* (14.5%), *Acinetobacter baumannii* (13.7%) and *Pseudomonas aeruginosa* (12.8%). In total 43 organisms were identified in patients with BSI, and 46 in those with pneumonia acquired in ICUs, and the most frequent isolates were coagulase-negative staphylococci non-identified (CNNI) (25.6%) and *Pseudomonas aeruginosa* (30.4%), respectively.

Highlighting data related to adult coronary ICUs, of 22.5% of patients with HAIs, 11/16 (68.8%) and 05/16 (31.2%), were infections acquired in and out the ICU, respectively, and of all HAIs, 37.5% were BSI and 50% pneumonia, with 18.7% due to *Staphylococcus aureus* and these organisms too represented a majority of cases of BSI. No patients with pneumonia presented microbiological criteria for diagnostic (Data not shown).

2.5 DISCUSSION

Importantly, this study reveals that the prevalence of HAI is very high with one in every 2.19 critical adult inpatients has at least one infection. Furthermore, our results reveal a substantial burden of HAI in medical/surgical and coronary ICUs, with greater frequencies of BSIs (38.6%) and pneumonia (71.9%). Globally, the prevalence of HAI across the various hospitals ranged from 26.2% to 83.3%, with a higher proportion of these infections found in medium-size university hospitals with ≤200 beds. The Brazilian rapidly escalating prevalence of HAI in ICUs is currently frightening, and our results were similar to other previous studies reporting a high burden of these infections in tertiary care hospitals in low- and middle-income countries [6, 9, 20]. Literature is emphatic when it shows that in countries like Brazil the rates of ICU-acquired infections are at least two to three times higher than in high-income countries [13, 21].

This study accentuates that pneumonia and BSI are the most frequent types of HAI in our critical patients, corroborating other previous reports [6, 22-24]. We observed the highest prevalence of HAI (66.6%), as well as of BSI (25.0%) in the northern region of the state at the Norte de minas mesoregion, and pneumonia (50.0%) at the Zona da Mata mesoregion in the southeastern of Minas Gerais. This can be associated with the first zone as one of the lowest gross domestic products in the state as well as having lower income [25, 26].

Although there is a plethora of studies about the risk factors for nosocomial infections [12, 27, 28], in our observations, patients with BSI and pneumonia in comparison with controls presented longer ICU-LOS, higher use of invasive devices as CVC and mechanical ventilation, as well as more use of antimicrobials, especially carbapenems and cephalosporins (3^{rd} or 4^{th} generation) as risk factors results, similar to recently published reports [29-32], revealing an increase in the prevalence of these severe infectious syndromes, reflecting among other factors, the difficult implementation of infection control technics [28, 33]. In addition, empirical initial antimicrobial therapy also behaved as an important characteristic associated with nosocomial pneumonia in our study. The impact of antibiotic-resistance on initially appropriate antibiotic therapy is an important determinant of inappropriate therapy, and is associated with an increase in the risk of hospital mortality given the paucity of therapies to cover multidrug-resistant Gram-negative bacteria [34-36].

Based on infections with microbiological criteria, an important finding was that the etiology of these infections was starred by Gram-negative organisms versus Gram-positive organisms, respectively 48.9% versus 43.3%, highlighting *Acinetobacter baumannii* and

Pseudomonas aeruginosa isolates, likewise other scientific reports worldwide especially in developing countries such as Brazil [15, 22, 37]. But one striking observation of our results is the higher prevalence of *Staphylococcus aureus* and coagulase-negative microorganisms observed in the total of HAI, as well as in all infections acquired outside the ICU. Although recently, other studies have seen swings in the pathogen pattern towards *Staphylococcus aureus* infections [20, 38], currently Gram-negative pathogens are still the most common agents of these infections as seen in our study. Presence and transmission of these microorganisms in an ICU setting, especially multidrug-resistant bacteria, represent a significant problem mainly in countries with limited resources due to higher morbidity, mortality and costs [4]. The reality of these countries presents a lack of multi-centric scientific documentation coupled with low efficiency of prevention and transmission control policies, limited financial resources and excessive indiscriminate use of antimicrobials, associated with a scarcity of microbiology laboratories [4, 14, 39, 40]. All these factors combined justify and contribute to the high rates of severe HAIs observed in this study.

From all that has been said, we can reach a fundamental conclusion: HAIs challenges public health in Brazil, and is related to high mortality, morbidity, use of invasive devices and inappropriate antibiotic therapy besides the acute clinical serious diseases usually observed in patients cared in these critical units. This point-prevalence multi-centric study provides important data on HAI, mainly BSI and pneumonia in Brazilian ICUs with high rates mainly caused by Gram-negative microorganisms.

Author contributions

Conceptualization: E.R.A.J., P.P.G.F., R.M.R. Methodology: E.R.A.J., I.A.B., R.M.R. Formal analysis: E.R.A.J. Investigation: E.R.A.J., I.A.B. Writing – original draft preparation: E.R.A.J. Writing – review and editing: P.P.G.F., R.M.R. Supervision: P.P.G.F., R.M.R. Project administration: P.P.G.F., R.M.R. Funding acquisition: P.P.G.F., R.M.R.

Conflicts of interest

All authors declare that they have no conflict of interest regarding this study.

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2.6 REFERENCES

1. **Esteban A, Frutos-Vivar F, Ferguson ND, Peñuelas O, Lorente JÁ, et al**. Sepsis incidence and outcome: Contrasting the intensive care unit with the hospital ward*: Critical Care Medicine 2007;35:1284–1289. https://doi.org/10.1097/01.CCM.0000260960.94300.DE.

2. **Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, et al**. Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care: Critical Care Medicine 2001;29:1303–1310. https://doi.org/10.1097/00003246-200107000-00002.

3. **Vincent J-L**. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009;302:2323. https://doi.org/10.1001/jama.2009.1754.

4. **Allegranzi B, Bagheri Nejad S, Combescure C, Graafmans W, Attar H, et al**. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. Lancet 2011;377:228–241. https://doi.org/10.1016/S0140-6736(10)61458-4.

5. **Weinshel K, Dramowski A, Hajdu Á, Jacob S, Khanal B, et al**. Gap analysis of infection control practices in low- and middle-income countries. Infection Control & Hospital Epidemiology 2015;36:1208–1214. https://doi.org/10.1017/ice.2015.160.

6. **Fortaleza CMCB, Padoveze MC, Kiffer CRV, Barth AL, Carneiro IC do RS, et al**. Multi-state survey of healthcare-associated infections in acute care hospitals in Brazil. Journal of Hospital Infection 2017;96:139–144. https://doi.org/10.1016/j.jhin.2017.03.024.

7. **Nogueira Junior C, Mello DS de, Padoveze MC, Boszczowski I, Levin AS, et al**. Characterization of epidemiological surveillance systems for healthcare-associated infections (Hai) in the world and challenges for Brazil. Cadernos de Saúde Pública 2014;30:11–20. https://doi.org/10.1590/0102-311X00044113.

8. **Padoveze MC, Fortaleza CMCB, Padoveze MC, Fortaleza CMCB**. Healthcare-associated infections: challenges to public health in Brazil. Revista de Saúde Pública 2014;48:995–1001. https://doi.org/10.1590/s0034-8910.2014048004825.

9. **Prade S, Oliveira S, Rodriguez R, Nunes F, Netto E, et al**. Estudo brasileiro da magnitude das infecções hospitalares em hospital terciário. Revista de Controle de Infecção Hospitalar 1995;2:11–24.

10. **BRASIL**. Agência Nacional de Vigilância Sanitária (ANVISA). Critérios diagnósticos de infecções relacionadas à assistência à saúde. 1st ed. Brasil. Available from:http://bvsms.saude.gov.br/bvs/publicacoes/criterios_diagnosticos_infeccoes_assistencia_saude.pdf. Published 2013.

11**. Lü Y, Cai MH, Cheng J, Zou K, Xiang Q, et al**. A multi-center nested case-control study on hospitalization costs and length of stay due to healthcare-associated infection. Antimicrobial Resistance and Infection Control 2018;7:99. https://doi.org/10.1186/s13756-018-0386-1.

12. **Gahlot R, Nigam C, Kumar V, Yadav G, Anupurba S**. Catheter-related bloodstream infections. International Jourbal of Critical Illness and Injury Science 2014;4:162–167. https://doi.org/10.4103/2229-5151.134184.

13. **World Health Organization**. Health care-associated infections fact sheet. Geneva: WHO. Available from: http://www.who.int/gpsc/country_work/gpsc_ccisc_fact_sheet_en.pdf. Published 2016.

14. **Vilar-Compte D, Camacho-Ortiz A, Ponce-de-León S**. Infection control in limited resources countries: challenges and priorities. Current Infectious Disease Reports 2017;19:20. https://doi.org/10.1007/s11908-017-0572-y.

15. **Tuon FF, Gortz LW, Rocha JL**. Risk factors for pan-resistant Pseudomonas aeruginosa bacteremia and the adequacy of antibiotic therapy. Brazilian Journal of Infectious Diseases 2012;16:351–356. https://doi.org/10.1016/j.bjid.2012.06.009.

16. **Peleg AY, Hooper DC**. Hospital-acquired infections due to gram-negative bacteria. New England Journal of Medicine 2010;362:1804–1813. https://doi.org/10.1056/NEJMra0904124.

17. **IBGE** – Instituto Brasileiro de Geografia e Estatística. Tabelas da Divisão Territorial Brasileira. Available from: https://www.ibge.gov.br/geociencias/organizacao-do-territorio/estrutura-territorial/23701-divisao-territorial-brasileira.html?edicao=30111&t=acesso-ao-produto; Published 2020.

18. **Horan TC, Andrus M, Dudeck MA**. CDC/NHSN surveillance definition of healthcare-associated infection and criteria for specific types of infections in the acute care setting. American Jourbal of Infection Control 2008;36:309-332. 10.1016/j.ajic.2008.03.002

19. **Ayres M, Ayres Jr M, Ayres DL, Santos AAS**. Bioestat 5.0 – Statistical Applications in Areas of Biological and Medical Sciences. Belém/PA: Sociedade Civil Mamirauá; Brasília: Ministério da Ciência e Tecnologia. Version 5.3 [software]. Available from: https://www.mamiraua.org.br/downloads/programas/. Brazilian. Published 2007.

20. **Braga IA, Campos PA, Gontijo-Filho PP, Ribas RM**. Multi-hospital point prevalence study of healthcare-associated infections in 28 adult intensive care units in Brazil. Journal of Hospital Infection 2018;99:318-324. https://doi.org/10.1016/j.jhin.2018.03.003

21. **World Health Organization**. Report on the Burden of Endemic Healthcare-associated Infection Worldwide. Geneva: WHO. Available from: https://apps.who.int/iris/bitstream/handle/10665/80135/9789241501507_eng.pdf;jsessionid=76FC27C7595E2DAF355DA9EBF4435E6A?sequence=1. Published 2011.

22. **Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, et al**. The prevalence of nosocomial infection in intensive care units in europe. Results of the european prevalence of infection in intensive care (Epic) study. Epic international advisory committee. JAMA 1995;274:639–644.

23. **Ponce de León-Rosales SP, Molinar-Ramos F, Domínguez-Cherit G, Rangel-Frausto MS, Vázquez-Ramos VG**. Prevalence of infections in intensive care units in Mexico: a multicenter study. Critical Care Medicine 2000;28:1316–1321. https://doi.org/10.1097/00003246-200005000-00010.

24. **Cairns S, Reilly J, Booth M**. Prevalence of healthcare-associated infection in Scottish intensive care units. Journal of Hospital Infection 2010;76:308–310. https://doi.org/10.1016/j.jhin.2010.05.010.

25. **BRASIL**. Ministério da Educação (MEC). Mapa de demanda por educação profissional. 1st ed. Brasília, Brasil. Available from: http://portal.mec.gov.br/novoscaminhos/arquivos/arquivos-mapa/relatorio_final_bahia.pdf. Published 2020.

26. **BRASIL**. Instituto Brasileiro de Geografia e Estatística (IBGE). Sistemas de Contas Regionais. 12th ed. Rio de Janeiro, Brasil. Available from: https://biblioteca.ibge.gov.br/visualizacao/livros/liv101765_informativo.pdf. Published 2018.

27. **Klompas M, Platt R**. Ventilator-associated pneumonia--the wrong quality measure for benchmarking. Annals of Internal Medicine 2007;147:803–805. https://doi.org/10.7326/0003-4819-147-11-200712040-00013.

28. **Maseda GE, Alvarez J, Garnacho-Montero J, Jerez V, Lorente L, et al**. Update on catheter related bloodstream infections in ICU patients. Enfermidades Infecciosas e Microbiologia Clinica 2011;29:10-15.

29. **Leão LSN de O, Passos XS, Reis C, Valadão LMA, Silva M do RR, et al**. Fenotipagem de bactérias isoladas em hemoculturas de pacientes críticos. Revista da Sociedade Brasileira de Medicina Tropical 2007;40:537–540. https://doi.org/10.1590/S0037-86822007000500009.

30. **Hugonnet S, Uçkay I, Pittet D**. Staffing level: a determinant of late-onset ventilator-associated pneumonia. Critical Care 2007;11:80. https://doi.org/10.1186/cc5974.

31. **Joseph NM, Sistla S, Dutta TK, Badhe AS, Parija SC**. Ventilator-associated pneumonia: role of colonizers and value of routine endotracheal aspirate cultures. International Journal of Infectious Diseases 2010;14:723-729. https://doi.org/10.1016/j.ijid.2010.02.2248.

32. **Sandiumenge A, Rello J**. Ventilator-associated pneumonia caused by ESKAPE organisms: cause, clinical features, and management. Current Opinion on Pulmonary Medicine 2012;18:187–193. https://doi.org/10.1097/MCP.0b013e328351f974.

33. **Sabatier C, Peredo R, Vallés J**. Bacteriemia en el paciente crítico. Medicina Intensiva 2009;33:336–345.

34. **Arthur LE, Kizor RS, Selim AG, van Driel ML, Seoane L**. Antibiotics for ventilator-associated pneumonia. Cochrane Database of Systematic Reviews;2016. Epub ahead of print 20 October 2016. DOI: 10.1002/14651858.CD004267.pub4. https://doi.org/10.1002/14651858.CD004267.pub4.

35. **Garnacho-Montero J, Sa-Borges M, Sole-Violan J, Barcenilla F, Escoresca-Ortega A, et al**. Optimal management therapy for Pseudomonas aeruginosa ventilator-associated pneumonia: an observational, multicenter study comparing monotherapy with combination antibiotic therapy. Critical Care Medicine 2007;35:1888–1895. https://doi.org/10.1097/01.CCM.0000275389.31974.22.

36. **Zilberberg MD, Shorr AF, Micek ST, Vazquez-Guillamet C, Kollef MH**. Multi-drug resistance, inappropriate initial antibiotic therapy and mortality in Gram-negative severe sepsis and septic shock: a retrospective cohort study. Critical Care 2014;18:596. https://doi.org/10.1186/s13054-014-0596-8.

37. **Silva E, Dalfior Junior L, Fernandes H da S, Moreno R, Vincent J-L**. Prevalence and outcomes of infections in Brazilian ICUs: a subanalysis of EPIC II study. Rev Bras Ter Intensiva 2012;24:143–150.

38. **Weiner-Lastinger LM, Abner S, Edwards JR, Kallen AJ, Karlsson M, et al**. Antimicrobial-resistant pathogens associated with adult healthcare-associated infections: Summary of data reported to the National Healthcare Safety Network, 2015-2017. Infection Control & Hospital Epidemiology 2020;41:1–18. https://doi.org/10.1017/ice.2019.296.

39. **Giske CG, Monnet DL, Cars O, Carmeli Y**. Resistance on behalf of R-A on A. Clinical and economic impact of common multidrug-resistant gram-negative bacilli. Antimicrobial Agents and Chemotherapy 2008;52:813–821. https://doi.org/10.1128/AAC.01169-07.

40**. Schwaber MJ, Carmeli Y**. The effect of antimicrobial resistance on patient outcomes: importance of proper evaluation of appropriate therapy. Critical Care 2009;13:106. https://doi.org/10.1186/cc7136.

Table I

Point - prevalence of healthcare-associated infections in adult intensive care units of hospitals in different meso-regions of Minas Gerais state, Brazil

Meso-region	Hospitals (N)	Patients with ICU-acquired HAI N (%)	Patients with HAI acquired in medical/surgical ICUs N (%)	Patients with HAI acquired in coronay ICUS N (%)	Patients with BSI / ICU-acquired N (%)	Patients with Pneumonia / ICU-acquired N (%)
Campo das Vertentes	2	4 (57.1)	4 (100.0)	-	1 (14.3) / 0 (0.0)	6 (85.7) / 4 (66.7)
Metropolitana de Belo Horizonte	3	8 (57.1)	6 (75.0)	2 (25.0)	8 (57.1) / 4 (50.0)	8 (57.1) / 5 (62.5)
Norte de Minas	2	13 (81.2)	10 (76.9)	3 (23.1)	6 (37.5) / 5 (83.3)	8 (50.0) / 6 (75.0)
Oeste de Minas	1	4 (100.0)	4 (100.0)	-	-	3 (75.0) / 3 (100.0)
Sul/sudoeste de Minas	5	17 (65.4)	15 (88.2)	2 (11.8)	2 (7.7) / 1 (50.0)	22 (84.6) / 14 (63.6)
Triângulo Mineiro/Alto Paranaíba	11	73 (82.9)	69 (94.5)	4 (5.5)	43 (48.9) / 37 (86.0)	64 (72.7) / 54 (84.4)
Vale do Rio Doce	2	5 (100.0)	5 (100.0)	-	2 (40.0) / 2 (100.0)	2 (40.0) / 2 (100.0)
Zona da Mata	2	10 (90.9)	10 (100.0)	-	4 (36.4) /4 (100.0)	10 (90.9) / 9 (90.0)
Total	**28**	**134 (78.4)**	**123 (91.8)**	**11 (8.2)**	**66 (38.6) / 53 (80.3)**	**123 (71.9) / 97 (78.9)**

ICU, Intensive care unit; HAI, Healthcare-associated infection; BSI, Bloodstream infection.

Table II
Success rate of paired variables for risk factors in patients with nosocomial infections through a case-control study

Variables	Bloodstream infection				Pneumonia			
	Total pairs (N)	**Achieved pairs (N)**	**Achieved Success (%)**	***P****	**Total pairs (N)**	**Achieved pairs (N)**	**Achieved Success (%)**	***P****
Cause of hospitalization	66	59	89.4	>0.9999[a]	115	99	86.1	>0.9999[a]
Sex	66	53	80.3	>0.9999[a]	115	92	80.0	>0.9999[a]
Age	66	56	84.8	0.9516[b]	115	88	76.5	0.8809[c]
Time of risk	66	47	71.2	0.8081[c]	115	83	72.2	0.0596 [c]
Total	264	216	81.8		460	362	78.7	

[a]Chi-squared Test; [b]Student's T-Test; [c]Mann-Whitney U-Test
* $P \leq 0.05$ was considered to indicate statistical significance.

Table III
Characteristics, use of invasive procedures and use of antimicrobials in a case-control study of paired patients with bloodstream infection in adult intensive care units in the state of Minas Gerais, Brazil

Characteristics	All N=374 (%)	Total of paired patients N=132 (%)	Paired Patients (BSI)		Univariate analysis (*p*)	Multivariate analysis		
			Case N=66 (%)	Control N=66 (%)		OR	95% CI	*p*
Lenght of hospitalization in ICU, mean; days (range) ± SD	10.9 (1 - 120) ± 13.4	13.3 (1 - 75) ± 12.3	16.1 (1 – 66) ± 12.2	10.5 (1 - 75) ± 11.9	**0,0002**[a]	1.0319	1.00 - 1.07	0.0872
Underlying conditions:								
Diabetes mellitus	147 (39.3)	50 (37.9)	22 (33.3)	28 (42.4)	0,2817[b]	-	-	-
Neoplasia	46 (12.3)	8 (6.1)	3 (4.5)	5 (7.6)	0,7179[c]	-	-	-
Chronic lung disease	44 (11.8)	16 (12.1)	10 (15.1)	6 (9.1)	0,2861[b]	-	-	-
Chronic kidney disease	45 (12.0)	15 (11.4)	10 (15.1)	5 (7.6)	0,1703[b]	-	-	-
Chronic heart disease	141 (37.7)	45 (34.1)	18 (27.3)	27 (40.9)	0,0984[b]	-	-	-
Neurological disorders	35 (9.3)	13 (9.8)	5 (7.6)	8 (12.1)	0,3809[b]	-	-	-
Hospital management and invasive procedures:						-	-	-
Central Venous Catheter	262 (70.0)	102 (77.3)	52 (78.8)	50 (75.7)	0,6779[b]	-	-	-
CVC use ≥ 7 days	122 (32.6)	49 (37.1)	30 (45.4)	19 (28.8)	**0,0475**[b]	0.6595	0.26 - 1.67	0.3788
Urinary Catheter	241 (64.4)	85 (64.4)	44 (66.6)	41 (62.1)	0,5855[b]	-	-	-
Mechanical ventilation	183 (48.9)	78 (59.1)	48 (72.7)	30 (45.4)	**0,0014**[b]	0.7611	0.31 - 1.85	0.5466
Antimicrobial therapy:	198 (52.9)	95 (71.9)	66 (100.0)	29 (43.9)	**<0,0001**[b]	0.6560	0.22 - 1.99	0.4559
Carbapenem	86 (22.9)	44 (33.3)	35 (53.0)	9 (13.6)	**<0,0001**[b]	1.3015	0.49 - 3.49	0.6005
Cephalosporin (3rd or 4th generation)	69 (18.4)	30 (22.7)	20 (30.3)	10 (15.1)	**0,0378**[b]	3.9352	1.28 - 12.10	**0.0168**
Fluoroquinolones	16 (4.3)	9 (6.8)	6 (9.1)	3 (4.5)	0,4922[c]	-	-	-
Aminoglycoside	7 (1.9)	4 (3.0)	2 (3.0)	2 (3.0)	>0,9999[c]	-	-	-
Polymyxin	18 (4.8)	16 (12.1)	13 (19.7)	3 (4.5)	**0,0077**[b]	1.4806	0.45 - 4.82	0.5148
Empirical antimicrobial therapy	95 (25.4)	30 (22.7)	14 (21.2)	16 (24.2)	0,6779 [b]	-	-	-

BSI, bloodstream infection; OR, odds ratio; CI, confidence interval; SD, standard deviation; ICU, intensive care unit; CVC, central venous catheter.
[a]Mann-Whitney U-Test; [b]Chi-squared Test; [c]Fisher's exact test
* $P \leq 0.05$ was considered to indicate statistical significance.

Table IV
Characteristics, use of invasive procedures and use of antimicrobials in a case-control study of paired patients with pneumonia in adult intensive care units in the state of Minas Gerais, Brazil

Characteristics	Total of paired patients N= 230 (%)	Paired Patients Pneumonia		Univariate analysis (*p*)	Multivariate analysis		
		Case N= 115 (%)	Control N= 115 (%)		OR	95% CI	*p*
Lenght of hospitalization in ICU, mean; days (range) ± SD	11.4 (1 - 94) ± 11.2	14.1 (1 - 54) ± 10.6	8.7 (1 - 94) ± 11.2	**<0,0001[a]**	1.0054	0.98 a 1.03	0.6748
Underlying conditions:							
Diabetes mellitus	88 (38.3)	42 (36.5)	46 (40.0)	0,5874[b]	-	-	-
Neoplasia	30 (13.0)	17 (14.8)	13 (11.3)	0,4335[b]	-	-	-
Chronic lung disease	33 (14.3)	23 (20.0)	10 (8.7)	**0,0145[b]**	1.2081	0.54 a 2.69	0.6442
Chronic kidney disease	30 (13.0)	17 (14.8)	13 (11.3)	0,4335[b]	-	-	-
Chronic heart disease	67 (29.1)	31 (26.9)	36 (31.3)	0,4681[b]	-	-	-
Neurological disorders	25 (10.9)	11 (9.6)	14 (12.2)	0,5251[b]	-	-	-
Hospital management and invasive procedures:							
Urinary Catheter	155 (67.4)	83 (72.2)	72 (62.6)	0,1218[b]	-	-	-
Mechanical ventilation	136 (59.1)	83 (72.2)	53 (46.1)	**<0,0001[b]**	1.5619	0.87 a 2.80	0.1333
Antimicrobial therapy:	152 (66.1)	115 (100.0)	37 (32.2)	**<0,0001[b]**	0.9639	0.34 a 2.72	0.9445
Carbapenem	74 (32.2)	58 (50.4)	16 (13.9)	**<0,0001[b]**	1.8313	0.73 a 4.60	0.1981
Cephalosporin (3rd or 4th generation)	51 (22.2)	37 (32.2)	14 (12.2)	**0,0003[b]**	2.6183	1.01 a 6.82	**0.0487**
Fluoroquinolones	12 (5.2)	11 (9.6)	1 (0.9)	**0,0030[b]**	1.1487	0.29 a 4.56	0.8437
Aminoglycoside	3 (1.3)	1 (0.9)	2 (1.7)	>0,9999[c]	-	-	-
Polymyxin	16 (6.9)	12 (10.4)	4 (3.5)	**0,0381[b]**	8.5523	1.65 a 44.32	**0.0106**
Empirical antimicrobial therapy	80 (34.8)	68 (59.1)	12 (10.4)	**<0,0001[b]**	0.3248	0.16 a 0.66	**0.0018**

OR, odds ratio; CI, confidence interval; SD, standard deviation; ICU, intensive care unit.
[a]Mann-Whitney U-Test; [b]Chi-squared Test; [c]Fisher's exact test
* $P \leq 0.05$ was considered to indicate statistical significance

Table V

Organisms responsible for HAIs acquired in or out the mixed medical-surgical ICUs

	Total of HAI N (%)		BSI N (%)		Pneumonia N (%)	
ICU-acquired:						
Number of organisms identified	117		43		46	
Organism (frequency)	*Staphylococcus aureus*	*17* (14.5)	CNNI	11 (25.6)	*Pseudomonas aeruginosa*	14 (30.4)
	Acinetobacter baumannii	*16* (13.7)	*Staphylococcus aureus*	5 (11.6)	*Acinetobacter baumannii*	12 (26.1)
	Pseudomonas aeruginosa	*15* (12.8)	*Klebsiella pneumoniae*	5 (11.6)	*Staphylococcus aureus*	10 (21.7)
	CNNI	12 (10.2)	*Acinetobacter baumannii*	4 (9.3)	*Stenotrophomonas maltophilia*	3 (6.5)
	Escherichia coli	*11* (9.4)	*Escherichia coli*	4 (9.3)	*Klebsiella pneumoniae*	2 (4.3)
	Candida albicans	*11* (9.4)	*Staphylococcus epidermidis*	3 (6.9)	*Staphylococcus epidermidis*	2 (4.3)
	Klebsiella pneumoniae	*9* (7.7)	*Staphylococcus haemolyticus*	3 (6.9)	*Candida albicans*	1 (2.2)
	Enterococcus faecalis	5 (4.3)	*Staphylococcus hominis*	3 (6.9)	Others	2 (4.3)
	Staphylococcus epidermidis	5 (4.3)	*Enterococcus faecalis*	2 (4.7)	-	-
	Staphylococcus hominis	*3* (2.6)	Others	3 (6.9)	-	-
	Stenotrophomonas maltophilia	3 (2.6)	-	-	-	-
	Staphylococcus haemolyticus	*3* (2.6)	-	-	-	-
	Others	*7* (5.9)	-	-	-	-
Acquired outside the ICU:						
Number of organisms identified	24		12		8	
Organism (frequency)	*Staphylococcus aureus*	*8* (33.3)	*Staphylococcus aureus*	4 (33.3)	*Staphylococcus aureus*	3 (37.5)
	CNNI	4 (16.7)	CNNI	3 (25.0)	*Pseudomonas aeruginosa*	1 (12.5)
	Pseudomonas aeruginosa	*3* (12.5)	*Pseudomonas aeruginosa*	2 (16.7)	CNNI	1 (12.5)
	Klebsiella pneumoniae	*2* (8.3)	*Staphylococcus epidermidis*	2 (16.7)	*Klebsiella pneumoniae*	1 (12.5)
	Staphylococcus epidermidis	2 (8.3)	*Escherichia coli*	1 (8.3)	*Stenotrophomonas maltophilia*	1 (12.5)
	Escherichia coli	*2* (8.3)	-	-	Others	1 (12.5)
	Stenotrophomonas maltophilia	1 (4.2)	-	-	-	-
	Others	*2* (8.3)	-	-	-	-

HAI, Healthcare-associated infection; BSI, bloodstream infection; CNNI, coagulase-negative staphylococci non-identified. Others - *Enterobacter spp.; Proteus mirabilis; Serratia spp.; Citrobacter freundii; Streptococcus spp.*

Capítulo 3

Multi-Center Study of Prevalence and Risk Factors of Device-Associated Healthcare-Associated Infections in 35 Brazilian Adult Intensive Care Units

MULTI-CENTER STUDY OF PREVALENCE AND RISK FACTORS OF DEVICE-ASSOCIATED HEALTHCARE-ASSOCIATED INFECTIONS IN 35 BRAZILIAN ADULT INTENSIVE CARE UNITS

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Running title: Device-associated Healthcare-associated Infections Burden in Brazil

3.1 ABSTRACT

Objectives: In Brazilian intensive care units (ICUs) as in other countries, device-associated healthcare-associated infections (DA-HAIs) are critical for patients' outcomes. In this study we aimed to report the trends in DA-HAIs and invasive device use using data from a multi-centre prevalence survey.

Methods: A DA-HAI multi-centre one-day point prevalence surveillance study was conducted in 35 adult ICUs in Brazilian hospitals. We collected prospective data regarding device use, DA-HAI rates, length of stay from 374 patients as well as bacterial agents and antibiotic-profiles. HAI definitions were those applied by the attending physician or by the Hospital Infection Control Service physician.

Results: Among the DA-HAIs (42.5%), most (78.8%) were central line-associated bloodstream infections (CLABSIs), and/or ventilator-associated pneumonias (VAPs) (71.5%) followed by catheter-associated urinary tract infections (CAUTIs) (54.2%). The invasive devices frequencies were 70.1% for central venous catheter (CVC), 48.9% for mechanical ventilation (MV) and 64.4% for indwelling urinary catheters (IUC). These DA-HAI rates observed in this study were very high, and the most frequent pathogens were *Pseudomonas aeruginosa* (14.7%) and *Acinetobacter baumanni* (15.7%).

Conclusions: We confirm a high DA-HAI burden in Brazilian adult ICUs, indicating a big threat to critical patients' safety.

Keywords: Healthcare-associated infection, Multi-center study, Intensive care units, Medical device

3.2 INTRODUCTION

In Brazil, as well as in several other low- and middle-income countries, device-associated health care-associated infections (DA-HAIs) represent one of the main threats to patients' safety in intensive care units (ICUs) [1-3], and are responsible for higher rates of morbidity, mortality, ICU length of stay (LOS) and higher costs, especially because of the lower efficiency of public policies towards prevention and control of these severe infections in these countries [4-6].

Upon extensive examination of literature, we can assert that there is a shortage of national surveillance systems as well as comprehensive prevalence surveys about DA-HAI rates and that these studies are important to portray a detailed picture of the problem and encourage the use of better infection control practices. In this context, central line-associated bloodstream infection (CLABSI), ventilator-associated pneumonia (VAP) and catheter-associated urinary tract infection (CAUTIs) represent a substantial portion of HAIs, besides VAP and CLABSI figuring among the main causes of morbidity, mortality, and higher costs in ICUs [7-10].

Worsening this scenario, invasive devices may serve as reservoirs for multidrug-resistant microorganisms such as *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* [10,11]. One of the main strategies reported in scientific literature to control and lower the risk of these infections is the reduction of the length of duration of invasive devices utilization, since the longer, a patient is in contact with the device, the higher is the risk of acquiring DA-HAIs [12], and for both patients' safety and economic purposes, surveillance studies like this one are fundamental to provide better knowledge to develop both HAI and DA-HAI reduction and control practices [13].

To address this knowledge gap in developing countries such as Brazil, we began an effort in 2016 to develop and conduct this multi-center survey to estimate the prevalence of DA-HAI, the distribution of these infections according to the infection site and pathogen. Accordingly, this study aims to disclose the prevalence of invasive devices, as well as to determine the distribution of DA-HAIs (VAP, CLABSI and CAUTI), and to identify microorganisms associated with these infections in 35 adults medical-surgical and coronary Brazilian ICUs.

3.3 MATERIALS AND METHODS

Survey design and participating hospitals

A one-day point prevalence study conducted throughout the year 2016 was performed in 35 adult ICUs located within eight meso-regions of Minas Gerais State: 28 medical-surgical ICUs, and 7 coronary ICUs. The participation of the hospitals was voluntary. The institutions were categorized as teaching (TH) and non-teaching (NTH) affiliated, and by size comprising <200 beds, 201 - 400 beds and > 400 beds (data not shown). The visits for data collection were scheduled according to each hospital's availability.

Data collection and analysis

One team received training on prevalence survey enquiry and data-collection procedures, and the hospital's medical records were reviewed to collect hospitals characteristics and patients' demographics and other patients and unit risk factors data from inpatients. This study assessed hospital and ICUs characteristics, patients' age, sex, date of hospital and ICU admission, cause of hospitalization, comorbidities, episodes of HAI, use of invasive devices, DA-HAIs, among other aspects. Data on antimicrobial therapy and microbiological culture results were also reviewed retrospectively from medical records.

All collected data were included in electronic spreadsheets to later obtain overall HAI prevalence and patterns of invasive devices in the different hospitals stratified by hospital category (TH or NTH), nosocomial infections aetiology and their association with DA-HAI.

Definitions

HAI. HAI was defined as hospital-acquired infection which was not present at the admission day, in patients with signs and symptoms of infection appearing after 48 hours of hospitalization. These criteria were determined following the National Healthcare Safety Network (NHSN) and the Agência Nacional de Vigilância Sanitária (ANVISA) guidelines [14,15].

Ventilator-associated pneumonia (VAP). VAP was indicated as pneumonia arising ≥48 hours after endotracheal intubation in patients with chest radiograph presenting new or

progressive infiltrate and at least two of the following criteria: purulent sputum, body temperature above 38°C or below 35°C, leukocyte count above 10.000/µl or below 3.000/µl, and microbiological isolates from positive tracheal aspirate culture ($\geq 10^5$ cfu/ml) [16,17].

Central line-associated bloodstream infection (CLABSI). CLABSI was defined when a patient was using CVC ≥48 hours and presented a positive blood culture, and presenting at least one of the following clinical criteria without any other recognized cause: body temperature above 38ºC and hypotension or oliguria [18,19].

Catheter-associated urinary tract infection (CAUTI). CAUTI was defined to patients in the use of indwelling urinary catheter and at least one of the following criteria without any other recognized cause: body temperature above 38°C, urgency, dysuria, suprapubic tenderness and positive uroculture ($\geq 10^5$ cfu/ml) with no more than two microorganism's species isolated [14,20].

Ethics Statement

Research Ethics Committee of the Federal University of Uberlandia, Minas Gerais, approved the study under protocol number 239/11. Both patients and hospitals' identities were classified, and all aspects of the study followed the principles of confidentiality and non-maleficence.

Statistical analysis

Data were assessed with descriptive statistics considering a value of $p \leq 0.05$ as statistically significant. Both Shapiro-Wilk and Kolmogorov Smirnov tests were applied to test the normality of the data and to determine whether to use parametric or non-parametric tests according to each quantitative distribution. Chi-square or Fisher's exact tests were used to assess categorical data as appropriate. All analyses were performed with the Graph-PadPrism program version 8 (Graph-Pad Software, San Diego, CA). To evaluate variables that showed $p \leq 0.05$ in the univariate analyses of invasive devices associated with the occurrence of severe HAI, a multiple logistic regression model was performed using the Bioestat® software version 5.3 [21] to assess the influence of each independent variable on the risk of acquiring HAIs.

3.4 RESULTS

Overall, twenty-eight hospitals participated in this study, representing eight meso-regions of Minas Gerais State, and data were collected from 35 ICUs. There were 458 patient beds across all ICUs with 374 (81.7%) of the beds accommodating patients at the time of the surveillance. The total device prevalence rate by hospital category (teaching and non-teaching affiliated) and by patients with HAI are presented in **Table 1**.

In total, the major devices (CVC, IUC, Nasogastric/enteral tube (NG/ET) and MV) were presented in most of the patients, respectively, 70.1%, 64.4%, 49.7% and 48.9%, likewise in both groups of hospitals (TH and NTH), with similar results specifically 74.5% and 66.8% (CVC), 63.1% and 65.4% (IUC), 47.8% and 51.2% (NG/ET) and 56.1% and 43.8% (MV) respectively, as well as for most of the infected patients with rates of CVC, IUC, NG/ET and MV of 84.2%, 70.8%, 71.9% and 67.3% respectively. In general, this study discloses that 992 invasive devices were being used at the time of the survey, with most (59.1%) featured in patients with HAI. **(Table 1)**

A summary of patients with invasive devices and their concomitant use are presented in **Fig. 1**. The more frequently observed combinations were CVC and IUC, with 204 combinations considering all patients included in the survey **(Fig.1A**), and 111 combinations in those with HAI **(Fig.1B**). When it comes to the simultaneous use of the four most frequent invasive devices, in total (31.6%, 118/374) patients presented this sort of combination, and (43.9%) of the infected ones were also using all of these devices. Highlighting the simultaneous use of CVC and MV devices, in total and regarding the infected patients, (44.9%, 168/374) and (62.6%, 107/171) respectively, were using both devices.

We observed that both pneumonia and BSI were the most common infection in our patients, with a prevalence of (71.9%, 123/171) and (38.6%, 66/171) respectively. Some contrasting eye-catching data was the longer ICU-LOS observed on infected patients about patients without infections (14.1 days vs 8.2 days), as well as the longer LOS before ICU admission (6.2 days vs 4.5 days). The risk factors that presented significant difference (p<0,05) were: LOS before ICU, ICU-LOS, chronic lung disease, chronic kidney disease, and most importantly the length of use of invasive devices as CVC, IUC, NG/ET and MV. However, of these risk factors, after the multivariate analysis, only the length of use of MV remained as the only characteristic that was independently associated with a higher risk of acquisition of HAIs. **(Table II)**

The risk of acquiring pneumonia and BSI in patients with MV and CVC as risk factors are presented in Table III. The relationship between pneumonia or BSI with the use of CVC, as well as BSI with the use of MV could not be reliably evaluated due to the lower frequency of these events on infected patients compared with patients without infection. Nevertheless, we observed that the length of the utilization of both invasive devices was independently associated with the development of pneumonia and BSI, respectively, when compared with the controls, with means of 14.8 days vs 7.8 days (BSI, p= 0.0223) and 13.5 days vs 5.5 days (Pneumonia, p<0,0001). **(Table III)**

Table IV shows the distribution of 141 isolated pathogens involved in HAIs with 102 of them involved in device-associated infections. Among the DA-HAI related pathogens, the most frequent organisms were *Staphylococcus aureus* (16.7%), followed by *Acinetobacter baumanni* (15.7%), *Pseudomonas aeruginosa* (14.7%), and CNNI (9.8%), indicating that Gram-negative bacteria were the most common organisms. *Pseudomonas aeruginosa* (28.6%) and *Acinetobacter baumanni* (24.5%) were the most frequent organisms isolated from tracheal aspirate in patients with VAP. Coagulase-negative staphylococci non-identified (CNNI) (24.4%) was the most common organism from positive hemocultures found in patients with CLABSI, and *Candida albicans* (41.7%) from patients with CAUTI.

3.5 DISCUSSION

Several studies have highlighted DA-HAIs as important causes of morbidity and mortality, and an important element in the increasing healthcare costs in low- to middle-income countries like Brazil [22-24]. In this regard, here, we tracked the burden of invasive device utilization in health care-associated infections in adult ICUs among several Brazilian hospitals based on findings from point-prevalence surveys performed in 2016.

Some studies performed in developing countries have highlighted that these complications are among the biggest concerns in the hospital setting [24,25]. An important finding of our study is that we were able to identify a prevalence of DA-HAIs significantly higher than other recent analogous studies carried out in Latin America [26,27]. We observed a high prevalence of invasive device use and a longer duration of device utilization in infected patients.

Here, the overall prevalence of DA-HAI was 42.5% (159/374), accounting for 92.9% of all the infected patients. The overall prevalence of CLABSI was 78.8% (52/66), nearly 5-fold higher than what has been reported in similar ICUs [27]. The overall rates of VAP and CAUTI

among the infected patients were 71.5% (88/123) and 54.2% (13/24), respectively, which is higher than what we can find in other reports around the world, with findings of about 6 to 50% of VAP, and up to 13% of CAUTI affecting ICU inpatients [27,28].

The higher rates of DA-HAIs in ICUs from low- and middle-income countries have many plausible explanations, like low adherence to infection control practices, lower hand hygiene compliance, hospital overcrowding, lack of medical supplies, nursing work overload as well as the common ICU circumstances in these countries altogether [29-31]. In this study, we identified that the longer duration of use of MV was an independent risk factor associated with the development of nosocomial infections. We also detected an important influence of invasive device use, duration of device use and duration of hospitalization in the ICUs and before ICU admission on patients with HAI, which corroborates with other previous reports [32,33].

From the infections with microbiological criteria, most remarkably, infections caused by Gram-negative bacteria presented higher prevalence than Gram-positive pathogens (49.0% vs. 38.2%), and mainly *Pseudomonas aeruginosa* (14.7%) and *Acinetobacter baumannii* (15.7%) were also more common in our ICUs and other reports [27,30,34]. A rising number of scientific studies have shown that in Brazil and other low- to middle-income countries, there is a predominance of Gram-negative microorganisms causing HAI specially in ICUs [34-36]. These are bad indicators considering the increase of multiple antibiotic resistance observed in this group of pathogens [37]. Unfortunately, worsening this situation, in these critical units, the use of antimicrobials is excessive and inappropriate most of the time [38]. In this scenario, studies have shown that the lack of microbiology laboratories associated with little multi-centre scientific literature, poor public health policies and insufficient financial resources in developing countries may contribute to the significant DA-HAI rates observed in this study [31,38].

Our results suggest that a longer duration of use of CVC and MV are undoubtedly associated with the acquisition of BSI and pneumonia, respectively, same as in other studies [39,40]. Interesting enough, the use of invasive devices itself seems to not represent such a precise foolproof risk factor to develop HAIs, but the general duration of use of these devices seems to be the key to the issue. Other studies have also suggested that the risk of acquisition of infections increases as a patient spends more time in use of invasive devices [12,39].

Measures to help reduce the risk of acquisition of DA-HAIs in ICUs from low- to middle-income countries need to be adopted and targeted more quickly to help reduce DA-HAI

rates to the minimum possible level. Unfortunately, our data only represented the typical adult ICU situation in Brazil, and it is important to disclose some limitations. Although this is a multi-centre study, our hospital sample was limited to few hospitals that may not be representative of all of Brazil. Additionally, rates per 1,000 device-days were not demonstrated.

To conclude, the data reported in this study strengthen the fact that intense invasive device use and high rates of DA-HAIs caused by Gram-negative pathogens must be regarded and taken seriously in our country. These infections pose an important risk in Brazilian ICUs, and directly impact patient safety and outcomes. Surveillance of nosocomial infections is a necessary first step toward reducing the risk of infection among patients treated in Brazilian hospitals particularly those due to antibiotic-resistant pathogens, and the next step is to apply infection control practices that have been well shown in the scientific scenario to prevent nosocomial infections.

ETHICS STATEMENT

Research Ethics Committee of the Federal University of Uberlandia, Minas Gerais, approved the study under protocol number 239/11. Both patients and hospitals' identities were classified, and all aspects of the study followed the principles of confidentiality and non-maleficence.

SUPPLEMENTARY MATERIALS

None

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare for this study.

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AUTHOR CONTRIBUTIONS

Conceptualization: ERAJ, PPGF, RMR. Methodology: ERAJ, IAB, RMR. Formal analysis: ERAJ. Data curation: ERAJ, IAB. Writing – original draft: ERAJ. Writing – review & editing: ERAJ, PPGF, RMR. Project administration: PPGF, RMR. Funding acquisition: PPGF, RMR.

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3.6 REFERENCES

1. Burke JP. Infection control — a problem for patient safety. New England Journal of Medicine. 2003;348(7):651–6.

2. Rosenthal VD, Guzman S, Orellano PW. Nosocomial infections in medical-surgical intensive care units in Argentina: Attributable mortality and length of stay. American Journal of Infection Control 2003;31(5):291–5.

3. Vincent J-L. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009;302(21):2323.

4. Fortaleza CMCB, Padoveze MC, Kiffer CRV, Barth AL, Carneiro IC do RS, Giamberardino HIG, et al. Multi-state survey of healthcare-associated infections in acute care hospitals in Brazil. Journal of Hospital Infection 2017;96(2):139–44.

5. World Health Organization. Health care-associated infections fact sheet. Geneva: WHO. 2016 [cited 2021 Jun 8]. Available from: http://www.who.int/gpsc/country_work/gpsc_ccisc_fact_sheet_en.pdf.

6. Lü Y, Cai MH, Cheng J, Zou K, Xiang Q, Wu JY, et al. A multi-center nested case-control study on hospitalization costs and length of stay due to healthcare-associated infection. Antimicrob Resistance and Infection Control 2018;7(1):99.

7. Rosenthal VD, Maki DG, Jamulitrat S, Medeiros EA, Todi SK, Gomez DY, et al. International Nosocomial Infection Control Consortium (Inicc) report, data summary for 2003-2008, issued June 2009. American Journal of Infection Control 2010;38(2):95-104.e2.

8. Singh S, Chaturvedi R, Garg SM, Datta R, Kumar A. Incidence of healthcare associated infection in the surgical ICU of a tertiary care hospital. Medical Journal Armed Forces India 2013;69(2):124–9.

9. Alp E, Damani N. Healthcare-associated infections in Intensive Care Units: epidemiology and infection control in low-to-middle income countries. Journal of Infection in Developing Countries 2015;9(10):1040–5.

10. Khan ID, Basu A, Kiran S, Trivedi S, Pandit P, Chattoraj A. Device-Associated Healthcare-Associated Infections (Da-hai) and the caveat of multiresistance in a multidisciplinary intensive care unit. Medical Journal Armed Forces India 2017;73(3):222–31.

11. Mitchell BG, Ferguson JK, Anderson M, Sear J, Barnett A. Length of stay and mortality associated with healthcare-associated urinary tract infections: a multi-state model. Journal of Hospital Infection 2016;93(1):92–9.

12. Gould CV, Umscheid CA, Agarwal RK, Kuntz G, Pegues DA, Healthcare Infection Control Practices Advisory Committee (HICPAC). Guideline for prevention of catheter-associated urinary tract infections 2009. Infection Control & Hospital Epidemiology 2010;31(4):319–26.

13. Sydnor ERM, Perl TM. Hospital epidemiology and infection control in acute-care settings. Clinal Microbiology Reviews. 2011;24(1):141–73.

14. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care–associated infection and criteria for specific types of infections in the acute care setting. American Journal of Infection Control 2008;36(5):309–32.

15. Brasil. Agência Nacional de Vigilância Sanitária (ANVISA). Critérios diagnósticos de infecções relacionadas à assistência à saúde. 2013 [cited 2021 Jun 14]. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/criterios_diagnosticos_infeccoes_assistencia_saude.pdf.

16. Skrupky LP, McConnell K, Dallas J, Kollef MH. A comparison of ventilator-associated pneumonia rates as identified according to the National Healthcare Safety Network and American College of Chest Physicians criteria*: Critical Care Medicine 2012;40(1):281–4.

17. Kollef M, Burnham C-A. Ventilator-associated pneumonia: the role of emerging diagnostic technologies. Seminars in Respiratory Critical Care Medicine. 2017;38(03):253–63.

18. Centers for Disease Control and Prevention. National Healthcare Safety Network (NHSN) patient safety component manual. 2017 [cited 2021 Jun 14]. Available from: https://www.cdc.gov/nhsn/pdfs/pscmanual/pcsmanual_current.pdf.

19. Mayer J, Greene T, Howell J, Ying J, Rubin MA, Trick WE, et al. Agreement in classifying bloodstream infections among multiple reviewers conducting surveillance. Clinical Infectious Diseases 2012;55(3):364–70.

20. Aubron C, Suzuki S, Glassford NJ, Garcia-Alvarez M, Howden BP, Bellomo R. The epidemiology of bacteriuria and candiduria in critically ill patients. Epidemiology and Infection. 2015;143(3):653–62.

21. Ayres M, Ayres JM, Ayres DL, Santos AAS. Bioestat 5.0 – Statistical Applications in Areas of Biological and Medical Sciences. Brasília: Ministério da Ciência e Tecnologia. Version 5.3 [software]; 2007 [cited 2021 Jul 3]. Available from: https://www.mamiraua.org.br/downloads/programas/.%20Brazilian.

22. Rosenthal V. The attributable cost, length of hospital stay, and mortality of central line-associated bloodstream infection in intensive care departments in Argentina: A prospective, matched analysis. American Journal of Infection Control 2003;31(8):475–80.

23. Higuera F, Rangel-Frausto MS, Rosenthal VD, Soto JM, Castañon J, Franco G, et al. Attributable cost and length of stay for patients with central venous catheter—associated bloodstream infection in mexico city intensive care units a prospective, matched analysis. Infection Control & Hospital Epidemiology 2007;28(1):31–5.

24. Mehta A, Rosenthal VD, Mehta Y, Chakravarthy M, Todi SK, Sen N, et al. Device-associated nosocomial infection rates in intensive care units of seven Indian cities. Findings of the International Nosocomial Infection Control Consortium (Inicc). Journal of Hospital Infection 2007;67(2):168–74.

25. Rosenthal VD, Guzman S, Migone O, Safdar N. The attributable cost and length of hospital stay because of nosocomial pneumonia in intensive care units in 3 hospitals in Argentina: A prospective, matched analysis. American Journal of Infection Control 2005;33(3):157–61.

26. Rosenthal VD, Maki DG, Mehta Y, Leblebicioglu H, Memish ZA, Al-Mousa HH, et al. International Nosocomial Infection Control Consortiu (Inicc) report, data summary of 43 countries for 2007-2012. Device-associated module. American Journal of Infection Control 2014;42(9):942–56.

27. Rosenthal VD, Al-Abdely HM, El-Kholy AA, AlKhawaja SAA, Leblebicioglu H, Mehta Y, et al. International Nosocomial Infection Control Consortium report, data summary of 50 countries for 2010-2015: Device-associated module. American Journal of Infection Control 2016;44(12):1495–504.

28. Joseph NM, Sistla S, Dutta TK, Badhe AS, Parija SC. Ventilator-associated pneumonia: A review. European Journal of Internal Medicine 2010;21(5):360–8.

29. Chandra PN, Milind K. Lapses in measures recommended for preventing hospital-acquired infection. Journal of Hospital Infection 2001;47(3):218–22.

30. Tao L, Hu B, Rosenthal VD, Gao X, He L. Device-associated infection rates in 398 intensive care units in Shanghai, China: International Nosocomial Infection Control Consortium (Inicc) findings. International Journal of Infectious Diseases 2011;15(11):774–80.

31. Allegranzi B, Nejad SB, Combescure C, Graafmans W, Attar H, Donaldson L, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. The Lancet 2011;377(9761):228–41.

32. Vincent J-L, Sakr Y, Singer M, Martin-Loeches I, Machado FR, Marshall JC, et al. Prevalence and outcomes of infection among patients in intensive care units in 2017. JAMA 2020;323(15):1478.

33. Kumar S, Sen P, Gaind R, Verma PK, Gupta P, Suri PR, et al. Prospective surveillance of device-associated health care–associated infection in an intensive care unit of a tertiary care hospital in New Delhi, India. American Journal of Infection Control 2018;46(2):202–6.

34. Navoa-Ng JA, Berba R, Galapia YA, Rosenthal VD, Villanueva VD, Tolentino MCV, et al. Device-associated infections rates in adult, pediatric, and neonatal intensive care units of hospitals in the Philippines: International Nosocomial Infection Control Consortium (Inicc) findings. American Journal of Infection Control 2011;39(7):548–54.

35. Zorgani A, Abofayed A, Glia A, Albarbar A, Hanish S. Prevalence of device-associated nosocomial infections caused by gram-negative bacteria in a trauma intensive care unit in libya. Oman Medical Journal. 2015;30(4):270–5.

36. Braga IA, Campos PA, Gontijo-Filho PP, Ribas RM. Multi-hospital point prevalence study of healthcare-associated infections in 28 adult intensive care units in Brazil. Journal of Hospital Infection 2018;99(3):318–24.

37. Marchaim D, Kaye K. Infection and antimicrobial resistance in the intensive care unit: Epidemiology and prevention. UpToDate; 2017 [cited 2021 Aug 5]. Available from: https://www.uptodate.com/contents/infections-and-antimicrobial-resistance-in-the-intensive-care-unit-epidemiology-and-prevention.

38. Vilar-Compte D, Camacho-Ortiz A, Ponce-de-León S. Infection control in limited resources countries: challenges and priorities. Current Infectious Disease Reports. 2017;19(5):20.

39. Couto RC, Pedrosa TMG, Tofani C de P, Pedroso ERP. Risk factors for nosocomial infection in a neonatal intensive care unit. Infection Control & Hospital Epidemiology. 2006;27(6):571–5.

40. Xu Y, Lai C, Xu G, Meng W, Zhang J, Hou H, et al. Risk factors of ventilator-associated pneumonia in elderly patients receiving mechanical ventilation. Clinical Interventions in Aging. 2019;14:1027–38.

Table I. Overall device prevalence by hospital category and by patients with healthcare-associated infections

Invasive Devices	Overall Prevalence N= 374 (%)	Hospital category		Patients with HAI N =171 (%)
		Teaching hospitals N=157 (%)	Non-teaching hospitals N=217 (%)	
Central Venous Catheter	262 (70.1)	117 (74.5)	145 (66.8)	144 (84.2)
Indwelling Urinary Catheter	241 (64.4)	99 (63.1)	142 (65.4)	121 (70.8)
Nasogastric/enteral Tube	186 (49.7)	75 (47.8)	111 (51.2)	123 (71.9)
Mechanical Ventilation	183 (48.9)	88 (56.1)	95 (43.8)	115 (67.3)
Tracheostomy	64 (17.1)	29 (18.5)	35 (16.1)	49 (28.7)
Dialysis Catheter	31 (8.3)	16 (10.2)	15 (6.9)	23 (13.5)
Others	25 (6.7)	10 (6.4)	15 (6.9)	11 (6.4)
Total	992 (100.0)	434/992 (43.8)	558/992 (56.2)	586/992 (59.1)

HAI, Healthcare-associated Infection; Others: parental nutrition, artificial cardiac pacemaker, various types of drains, and all other devices but the ones listed here.

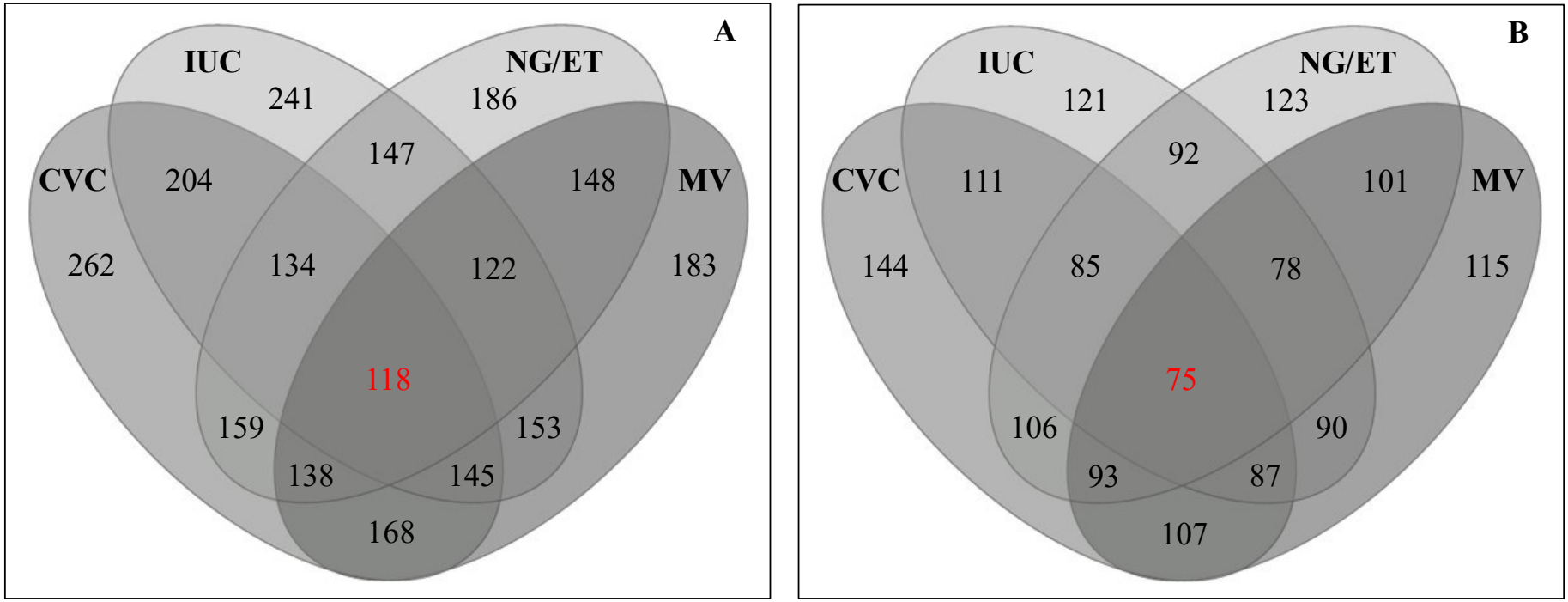

Figure 1: Four sets Venn Diagram of the most frequent invasive devices and their concomitant use from the overall 374 patients prevalence survey (A) and 171 patients with HAI (B)
CVC, Central Venous Catheter; IUC, Indwelling Urinary Catheter; NG/ET, Nasogastric/enteral tube; MV, Mechanical Ventilation.

Table II. Characteristics of patients with and without healthcare-associated Infections and their use of invasive devices

Characteristics	Patients with HAI N=171 (%)	Patients without HAI N= 203 (%)	*P*	Multivariate Analysis		Patients with pneumonia N= 123 (%)	Patients with BSI N= 66 (%)	Patients with UTI N= 24 (%)	Patients with SSI N=20 (%)
				OR (95%CI)	*P*				
Sex:					-				
Male	98 (57.3)	110 (54.2)	0.5448[a]	-	-	74 (60.2)	37 (56.1)	9 (37.5)	9 (45.0)
Female	73 (42.7)	93 (45.8)	0.5448[a]	-	-	49 (39.8)	29 (43.9)	15 (62.5)	11 (55.0)
Age, mean [range] ± SD	58.1 [15 – 97] ± 19.6	59.7 [12 – 95] ± 18.7	0.3462[b]	-	-	58.2 [15 – 97] ± 20.0	58.1 [15 – 93] ± 20.1	58.1 [21 – 82] ± 16.3	51.7 [15 – 80] ±16.3
LOS before ICU, mean days [range] ± SD	6.2 [0 – 53] ± 10.6	4.5 [0 – 112] ± 11.4	**0.0002**[b]	1.0075 (0.98 a 1.03)	0.5260	5.8 [0 – 53] ± 10.5	9.3 [0 – 53] ± 13.4	4.3 [0 – 23] ± 5.9	4.8 [0 – 32] ± 8.5
ICU LOS, mean days [range] ± SD	14.1 [1 – 66] ± 11.1	8.2 [1 – 120] ± 14.2	**<0.0001**[b]	1.0255 (1.00 a 1.05)	0.0595	13.8 [1 – 54] ± 10.4	16.1 [1 – 66] ± 12.2	20.4 [5 – 44] ± 10.9	11.4 [1 – 30] ± 8.7
Cause of hospitalization:				-	-				
Clinical	144 (84.2)	184 (90.6)	0.0593[a]	-	-	103 (83.7)	54 (81.8)	20 (83.3)	15 (75.0)
Surgical	1 (0.6)	1 (0.5)	>0.9999[c]	-	-	-	-	-	1 (5.0)
Trauma	26 (15.2)	18 (8.9)	0.0581[a]	-	-	20 (16.3)	12 (18.2)	4 (16.7)	4 (20.0)
Underlying conditions:				-	-				
Diabetes mellitus	65 (38.0)	82 (40.4)	0.6384[a]	-	-	44 (35.8)	22 (33.3)	11 (45.8)	5 (25.0)
Neoplasia	22 (12.9)	19 (9.4)	0.2797[a]	-	-	15 (12.2)	3 (4.5)	2 (8.3)	2 (10.0)
Chronic lung disease	27 (15.8)	17 (8.4)	**0.0266**[a]	1.8707 (0.94 a 3.72)	0.0737	23 (18.7)	10 (15.2)	4 (16.7)	2 (10.0)
Chronic kidney disease	27 (15.8)	18 (8.9)	**0.0404**[a]	1.6132 (0.82 a 3.19)	0.1690	18 (14.6)	10 (15.2)	5 (20.8)	1 (5.0)
Chronic heart disease	45 (26.3)	96 (47.3)	<0.0001[a]	-	-	33 (26.8)	18 (27.3)	7 (29.2)	6 (30.0)
Neurological disorders	15 (8.8)	20 (9.9)	0.7208[a]	-	-	12 (9.8)	5 (7.6)	2 (8.3)	-
Assessed patients using invasive devices:	147 (85.9)	192 (94.6)		-	-	103 (83.7)	53 (80.3)	21 (87.5)	18 (90.0)
Days with CVC, device days, mean ± SD	1612, 12.8 ± 9.8	996, 9.0 ± 15.9	**<0.0001**[b]	0.9802 (0.95 a 1.01)	0.2428	1116, 12.6 ± 8.9	629, 14.8 ± 12.3	217, 12.8 ± 8.4	211, 12.4 ± 10.8
Days with IUC, device days, mean ± SD	1455, 14.1 ± 11.1	741, 6.8 ± 8.9	**<0.0001**[b]	1.0271 (0.99 a 1.07)	0.1961	1049, 13.8 ± 10.8	587, 16.3 ± 13.3	135, 11.3 ± 8.7	153, 11.8 ± 9.6
Days with NG/ET, device days, mean ± SD	1485, 14.4 ± 12.1	747, 12.9 ± 18.9	**<0.0001**[b]	0.9917 (0.96 a 1.02)	0.6202	971, 13.1 ± 9.9	661, 17.8 ± 14.8	205, 15.8 ± 10.6	80, 11.4 ± 12.5
Days of MV, device days, mean ± SD	1386, 14.1 ± 11.4	460, 7.2 ± 7.5	**<0.0001**[b]	1.0886 (1.05 a 1.13)	**< 0.0001**	979, 13.4 ± 10.8	655, 16.8 ± 13.4	220, 14.7 ± 9.5	101, 12.6 ± 11.5

HAI, Healthcare-associated Infection; BSI, bloodstream infection; UTI, urinary tract infection; SSI, surgical site infection; SI, skin infection; ICU, intensive care unit; SD, standard deviation; LOS, length of stay; CVC, Central Venous Catheter; IUC, Indwelling Urinary Catheter; NG/ET, Nasogastric/enteral tube; MV, Mechanical Ventilation.

[a]Chi-squared Test; [b]Mann-Whitney U Test; [c]Fisher's exact test

* $P \leq 0.05$ was considered to indicate statistical significance.

Table III. Risk of acquiring Pneumonia and BSI in patients in use of invasive devices

Variable	Value	P	Multivariate Analysis	
			OR (95%CI)	P
CVC use				
Pneumonia	103	<0.0001[a]	1.3948 (0.75 a 2.61)	0.2966
No pneumonia	155			
BSI	52	<0.0001[a]	1.1113 (0.52 a 2.36)	0.7834
No BSI	210			
MV use				
Pneumonia	88	0.4643[a]	-	-
No pneumonia	95			
BSI	48	<0.0001[a]	6.3780 (2.85 a 14.30)	< 0.0001
No BSI	135			
Duration of CVC use, days, mean ± SD				
BSI	14.8 ± 12.3	**0.0009[b]**	1.0298 (1.00 a 1.06)	**0.0293**
No BSI	7.8 ± 12.2			
Duration of MV use, days, mean ± SD				
Pneumonia	13.4 ± 10.8	**0.0015[b]**	1.1175 (1.07 a 1.16)	**< 0.0001**
No pneumonia	5.5 ± 9.3			

HAI, Healthcare-associated Infection; CVC, Central Venous Catheter; MV, Mechanical Ventilation;
[a]Chi-squared Test; [b]Mann-Whitney U Test;
* $P \leq 0.05$ was considered to indicate statistical significance.

Table IV. Distribution of DA-HAIs and related microorganisms in the participating ICUs

Microorganisms	Overall N (%)	DA-HAI related N (%)	VAP N (%)	CLABSI N (%)	CAUTI N (%)
Number of organisms identified	141	102	49	41	12
Gram-negative:					
Pseudomonas aeruginosa	18 (12.8)	15 (14.7)	14 (28.6)	1 (2.4)	-
Acinetobacter baumannii	16 (11.3)	16 (15.7)	12 (24.5)	4 (9.8)	-
Escherichia coli	13 (9.2)	8 (7.8)	-	4 (9.8)	4 (33.3)
Klebsiella pneumoniae	11 (7.8)	7 (6.9)	3 (6.1)	2 (4.9)	2 (16.7)
Stenotrophomonas maltophilia	4 (2.8)	4 (3.9)	4 (8.2)	-	-
Gram-positive:					
Staphylococcus aureus	25 (17.7)	17 (16.7)	11 (22.4)	6 (14.6)	-
CNNI	16 (11.3)	10 (9.8)	-	10 (24.4)	-
Staphylococcus epidermidis	7 (4.9)	6 (5.9)	1 (2.1)	5 (12.2)	-
Enterococcus faecalis	5 (3.5)	1 (0.9)	-	1 (2.4)	-
Staphylococcus hominis	3 (2.1)	2 (1.9)	-	2 (4.9)	-
Staphylococcus haemolyticus	3 (2.1)	3 (2.9)	-	3 (7.3)	-
Fungi:					
Candida albicans	11 (7.8)	6 (5.9)	1 (2.1)	-	5 (41.7)
Others	9 (6.4)	7 (6.9)	3 (6.1)	3 (7.3)	1 (8.3)

DA-HAI, Device-associated healthcare-associated infection; VAP, ventilator-associated pneumonia; CLABSI, central line-associated bloodstream infection; CAUTI, catheter-associated urinary tract infection; CNNI, coagulase-negative staphylococci non-identified. Others - *Enterobacter spp.; Proteus mirabilis; Serratia spp.; Citrobacter freundii; Streptococcus spp.*

Capítulo 4

Prevalence and Microbiology of Adult Intensive Care Unit-Acquired Polymicrobial Infections

PREVALENCE AND MICROBIOLOGY OF ADULT INTENSIVE CARE UNIT-ACQUIRED POLYMICROBIAL INFECTIONS

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4.1 ABSTRACT

Introduction: The frequency and clinical significance of polymicrobial healthcare-associated infections (HAIs) in critical patients are poorly understood. The main aim of the present study is to describe the prevalence, risk factors, clinical characteristics and the microbiology of polymicrobial versus monomicrobial infections.

Methodology: We performed a 24-hour point prevalence study in 35 adult Intensive Care Units (ICUs) in Minas Gerais State, Brazil to collect data on HAI prevalence, patterns of monomicrobial and polymicrobial infections and their etiology.

Results: Among 171 (45.7%) patients with HAI, only 80 (46.8%) had microbiology confirmation, and of these patients, a total of 19 (23.8%) had polymicrobial infections. The most common sources of polymicrobial HAIs were pneumonia (16/19 patients, 84.2%) and bloodstream infection (BSI) (15/19 patients, 78.9%). *Staphylococcus aureus, Pseudomonas aeruginosa* and *Acinetobacter baumannii* were the most common isolated organisms in polymicrobial infections.

Conclusion: Polymicrobial infection occurred in approximately 1 in every 4 patients with microbiological criteria, including a great proportion of infections caused by Gram-negative bacteria associated with the use of polymyxin. These findings represent an important issue regarding patient's safety, specially concerning the low prevalence of microbiologic criteria and the relation between indiscriminate use of antimicrobials with worse prognosis and higher rates of HAIs.

Keywords: Healthcare-associated infection; Multi-centric study; Epidemiology; Polymicrobial infections.

4.2 INTRODUCTION

Infectious complications remain a major source of morbidity and mortality during hospitalization of critical patients worldwide (ABULHASAN et al., 2020), and in developing countries as Brazil, the frequency of ICU-acquired infections is at least 2 to 3 times higher than in high-income countries (WHO, 2016). Recent studies have shown that polymicrobial infections are increasingly being diagnosed in patients, with complex outcomes and difficult treatments (WANG et al., 2020), for instance, we can observe in some scientific reports high rates of polymicrobial severe HAIs, as 15.5% rates of polymicrobial bloodstream infection (BSI) in a Chinese study (ZHENG et al., 2020) vs 23.5% of the same infection in a Taiwanese hospital (WANG et al., 2020), and a prevalence if 16% of polymicrobial pneumonia in a multicenter Spanish study (FERRER et al., 2015).

The empirical and intense use of the most prescribed antibiotics associated with the current medical technology advances as the common use of invasive devices have modulated the hospital microbiota causing HAIs (HOU, 2015; WANG et al., 2020). In Brazil and in the world, the increasing use of antimicrobials not only selects resistant phenotypes, but also increases their dissemination in the environment, and scientific literature has shown that Gram-negative bacilli have been predominant in this scenario (FERRER et al., 2015; ROSSI et al., 2016; WANG et al., 2020).

In order to address this problem, we performed a prospective cohort study that enrolled patients with a microbiologically documented HAI. We compared the clinical characteristics, bacteriology and risk factors between patients with polymicrobial and monomicrobial infections. The specific aim was twofold. First, we aimed to characterize patients with polymicrobial HAIs and to identify clinical risks that are readily available in the ICU setting. Second, we aimed to characterize the bacteriology profile associated with monomicrobial and polymicrobial HAIs.

4.3 METHODOLOGY

Study design and population

A one-day point prevalence study was carried out in 35 adult ICUs located within 8 meso-regions of Minas Gerais state, Brazil: 2 ICUs in Campo das Vertentes, 5 ICUs in

Metropolitana de Belo Horizonte, 3 ICUs in Norte de minas, 1 ICUs in Oeste de Minas, 6 ICUs in Sul/sudoeste de Minas, 14 ICUs in Triângulo Mineiro/Alto Paranaíba, 2 ICUs in Vale do Rio Doce and 2 ICUs in Zona da Mata. Co-participating hospitals were selected at random, and the same methodology was applied by the same executing team. The data was obtained from medical records of all patients over 12 years of age admitted into the ICUs of participating hospitals and included: characteristics of hospital and ICU admission, demographics, comorbidities, risk factors, use of medical invasive devices, antimicrobial therapy, nosocomial infections prevalence and data on microbiological culture results.

The collected data were added to Excel software spreadsheets to access overall HAI prevalence, patterns of monomicrobial and polymicrobial infections and their etiology. All hospitals voluntarily participated in the study and the data collection procedures were scheduled conforming each hospital's availability.

Definitions

HAI was defined according to the Agência Nacional de Vigilância Sanitária (ANVISA) guidelines (ANVISA, 2013). We considered a monomicrobial infection if only one microorganism species was laboratory confirmed by the service physician or by the hospital's infection prevention and control team. In contrast, we considered a polymicrobial infection if more than one microorganism species was laboratory confirmed from the same site of infection (FERRER et al., 2015; WANG et al., 2020). Primary BSI was defined to those infections related to the use of central venous catheter (CVC) or when the source of infection could not be attributed to any known source, differently from secondary bacteremia, where the focus of infection is located in sites other than the vascular-circulatory system (lung, urinary tract, surgical site and others) (MAYER et al., 2012).

Ethical aspects

Data were collected under approval of the Research Ethics Committee of the Federal University of Uberlandia, Minas Gerais, according to protocol number 239/11.

Statistical analysis

Data were analyzed with Graph-PadPrism program version 8 (Graph-Pad Software, San Diego, CA), using descriptive statistics considering a value of $p \leq 0.05$ as statistically significant. All our data were quantitative variables, thus we performed Student's t-test for parametric distributions and Mann-Whitney U-Test for non-parametric distributions.

4.4 RESULTS

This study comprised a total of 374 patients, with 171 (45.7%) with HAI. Overall, only (80/171 patients, 46.8%) had microbiology confirmation on their infection diagnostic, and we separated them into 2 groups: polymicrobial infections and monomicrobial infections. Our patients' characteristics with their source of infection and their association between mono and polymicrobial HAIs are presented in **Table I**.

Among HAIs with microbiological criteria, this study found a proportion of 76.2% (61/80) of patients with monomicrobial infections and 23.8% (19/80) of patients with polymicrobial HAIs. Comparing to patients with monomicrobial HAIs, patients with polymicrobial HAIs presented higher proportions of chronic kidney disease, chronic heart disease, use of central venous catheter, mechanical ventilation, use of antimicrobial therapy, fluoroquinolones and polymyxin. The use of Polymyxin behaved as a significant risk factor for polymicrobial infection (P=0.0014), differently from use of urinary catheter which was more associated with monomicrobial infections (P=0.0373). The most common sources of polymicrobial HAIs were pneumonia (16/19 patients, 84.2%) and bacteremia (15/19 patients, 78.9%), followed by urinary tract infection (UTI) (6/19 patients, 31.6%). **(Table I)**.

We also found big proportions of severe infections as bacteremia (38.6%) and pneumonia (71.9%), with a greater proportion of primary bacteremia versus secondary bacteremia (68.2% vs 31.8%). Bacteremia was proportionally more present in polymicrobial infections but when stratified, primary bacteremia presented itself more associated with monomicrobial infections, and secondary bacteremia with polymicrobial infection. Both pneumonia and urinary tract infection were more associated with polymicrobial infections, differently from surgical site infections which were more associated with monomicrobial infections. Pneumonia behaved as an important risk factor for acquiring polymicrobial infections (P=0.0075) **(Table I)**.

Regarding the patients that had microbiological criteria for diagnostic, we found in total 141 microorganisms, with bigger prevalence of Gram-negative vs Gram positive bacteria (43.9% vs 41.8%). The most frequently isolated Gram-negative organisms among patients with polymicrobial HAI were *Pseudomonas aeruginosa* (36.4%) and *Acinetobacter baumannii* (21.2%), and the most common Gram-positive organism was *Staphylococcus aureus* (38.5%). Compared with monomicrobial HAIs, *Staphylococcus aureus, Pseudomonas aeruginosa,* CNNI*, Stenotrophomonas maltophilia*, *Enterococcus faecalis, Staphylococcus haemolyticus, Staphylococcus epidermidis* and *Staphylococcus hominis* are more likely isolated in polymicrobial HAIs **(Table II)**.

4.5 DISCUSSION

Using a point-prevalence design, we aimed to describe the prevalence, risk factors, clinical characteristics and microbiology of polymicrobial versus monomicrobial infections. In the primary analysis, polymicrobial etiology accounted for 23.8% cases of HAI in adult critical patients with positive microbiology, and except for polymyxin use in polymicrobial HAIs there was no other significant characteristic difference compared to patients with monomicrobial infections.

Information about polymicrobial HAI etiology in Brazil is much limited. One study that specifically addressed this issue found a higher proportion of polymicrobial etiology (25.0%) compared to the present report, and similar to our study, the authors showed presence of some important bacteria such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Staphylococcus aureus* (ROCHA et al., 2008). Indeed, a substantial proportion of Gram-negative isolates reported here were associated with polymicrobial infections.

These findings, along with the patient's characteristics have potential prognostic implications, especially combined with the high rates of Gram-negative bacteria causing these infections, representing a serious issue considering the increase of antimicrobial resistance observed in these group of pathogens, and the lack of resources in low- to middle-income countries like Brazil to handle the severity of infections caused by them (ALEGRANZI et al., 2011). For that reason, conducting studies about polymicrobial HAIs is of potential interest.

One of the key points observed in this study besides the great proportions of HAIs is the low percentage of patients who had microbiological criteria in their infection diagnose, only 46.8%. The extensive use of microbiological criteria is extremely important to increase safeness

when choosing the initial therapy, in addition, administration of inappropriate initial and empirical antimicrobial therapy can make it much difficult to implement an adequate antimicrobial therapy, resulting in a greater emergence of multidrug resistant pathogens in ICUs, contributing to the worsening of a patient's prognosis and increasing the length of hospital stay (ALLEGRANZI et al., 2011; VILAR-COMPTE; CAMACHO-ORTIZ; PONCE-DE-LEÓN, 2017).

A couple of scary but expected aspects of our study are the significant relation between polymyxin use and presence of pneumonia with the development of polymicrobial infections. The increasingly intense use of polymyxin has attracted health professional's attention, considering that it is one of the last antimicrobial treatment options for multidrug-resistant Gram-negative microorganisms, and a few reports have described colistin-resistant Klebsiella pneumoniae carbapenemase (KPC) outbreaks as consequences of that intense use (ROSSI et al., 2016; CHMIELARCZYK et al., 2018).

We also observed a high frequency of Gram-positive bacteria as *Staphylococcus aureus* and coagulase-negative microorganisms causing monomicrobial and polymicrobial HAIs which were also among the main pathogens found in a similar study (FERRER et al., 2015). This is a compelling result, whereas upon inspection of scientific literature we can perceive an ongoing switch concerning an increase of the prevalence of Gram-positive pathogens in the ICU scenario in developing countries (WEINER-LASTINGER et al., 2020).

This study has some limitations. Even it being of multi-center nature, our data was limited to hospitals from a single Bazilian state that may not represent the wholeness of Brazil, yet, our study has a huge importance in addressing Minas Gerais reality. In this manner we suggest new larger multi-center studies comprising the entire country to illustrate the burden of these severe infections and fulfill the gap in scientific literature concerning such an important issue.

In conclusion, the etiology of HAIs in 35 adult ICUs with microbiological confirmation pointed polymicrobial infections in 23.8% of the patients, with high ICU-LOS, medical invasive devices and use of antimicrobials. This epidemiologic prevalence report contributes with valuable data concerning the duality of monomicrobial and polymicrobial HAIs in Brazilian ICUs, showing high rates of Gram-negative bacilli causing mixed etiology infections.

4.6 REFERENCES

ABULHASAN, Y. B. et al. Health care-associated infections in a neurocritical care unit of a developing country. **Neurocritical Care**, v. 32, n. 3, p. 836–846, jun. 2020. https://doi.org/ 10.1007/s12028-019-00856-8

AGÊNCIA NACIONAL DE VIGILÂNCIA SANITÁRIA (ANVISA). **Critérios diagnósticos de infecções relacionadas à assistência à saúde**. 1a ed. Brasilia, Brasil, 2013. Disponível em: http://bvsms.saude.gov.br/bvs/publicacoes/criterios_diagnosticos_infeccoes_assistencia_saude.pdf. Acessado em 10 de agosto de 2021.

ALLEGRANZI, B. et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. **The Lancet**, v. 377, n. 9761, p. 228–241, jan. 2011. https://doi.org/10.1016/S0140-6736(10)61458-4.

CHMIELARCZYK, A. et al. Severe infections caused by multidrug-resistant nonfermentative southern Poland. **Advances in clinical and experimental medicine**, Polônia, v. 27, n. 3, p. 401-407, março, 2018. https://doi.org/10.17219/acem/68545

FERRER, M. et al. Polymicrobial intensive care unit-acquired pneumonia: prevalence, microbiology and outcome. **Critical Care**, v. 19, n. 1, p. 450, dez. 2015. https://doi.org/10.1186/s13054-015-1165-5

HOU, X. H. Molecular characterization of multidrug-resistant Klebsiella pneumoniae isolates. **Brazilian Journal of Microbiology**, Rio de Janeiro, v. 46, n. 3, p. 759-768, 2015. https:// doi: 10.1590/S1517-838246320140138

MAYER, J. et al. Agreement in Classifying Bloodstream Infections Among Multiple reviewers conducting surveillance. **Clinical Infectious Diseases**, v.55, n.3, p.364 -70, 2012.

ROCHA, L. DE A. DA et al. Ventilator-associated pneumonia in an adult clinical-surgical intensive care unit of a Brazilian university hospital: incidence, risk factors, etiology, and antibiotic resistance. **Brazilian Journal of Infectious Diseases**, v. 12, n. 1, p. 80–85, fev. 2008.

ROSSI, I. et al. Outbreaks of colistin-resistant and colistin-susceptible KPC-producing Klebsiella pneumoniae in a Brazilian intensive care unit. **Journal of Hospital Infection**, v. 94, n. 4, p. 322-329, 2016. https://doi.org/10.1016/j.jhin.2016.08.019

VILAR-COMPTE, D.; CAMACHO-ORTIZ, A.; PONCE-DE-LEÓN, S. Infection control in limited resources countries: Challenges and priorities. **Current Infectious Disease Reports**, Filadélfia, v.19, n. 5, p. 20, 2017. https://doi:10.1007/s11908-017-0572-y

WANG, Y.-C. et al. Is Polymicrobial Bacteremia an Independent Risk Factor for Mortality in Acinetobacter baumannii Bacteremia? **Journal of Clinical Medicine**, v. 9, n. 1, p. 153, 6 jan. 2020. https://doi.org/ 10.3390/jcm9010153

WEINER-LASTINGER, L. M. et al. Antimicrobial-resistant pathogens associated with adult healthcare-associated infections: Summary of data reported to the National Healthcare Safety Network, 2015–2017. **Infection Control & Hospital Epidemiology**, v. 41, n. 1, p. 1–18, jan. 2020. https://doi.org/10.1017/ice.2019.296.

WORLD HEALTH ORGANIZATION. **Health care-associated infections fact sheet**. Geneva, 2016. Disponível em: http://www.who.int/gpsc/country_work/gpsc_ccisc_fact_sheet_en.pdf. Acessado em 20 de agosto de de 2021.

ZHENG, C. et al. Clinical characteristics and risk factors of polymicrobial Staphylococcus aureus bloodstream infections. **Antimicrobial Resistance & Infection Control**, v. 9, n. 1, p. 76, dez. 2020. https://doi.org/10.1186/s13756-020-00741-6

Table I: Patient's characteristics, source of infection and their association between mono and polymicrobial HAIs among patients from adult ICUs in Minas Gerais, Brazil.

Characteristics	Patients with HAI N (%)	HAI with microbiological criteria N (%)	Monomicrobial infections N (%)	Polymicrobial infections N (%)	*P* value
Enrolled Patients, N	171 (45.7))	80 (46.8)	61 (76.2)	19 (23.8)	-
Age, mean [range] ± SD	58.1 [15 – 97] ± 19.6	56.8 [15 – 97] ± 19.4	57.5 [15 – 97] ± 19.4	54.8 [26 – 83] ± 19.9	0.6437[b]
Sex, male/female	98 (57.3) /73 (42.7)	47 (58.7) /33 (41.3)	32 (52.5) /29 (47.5)	15 (78.9) /4 (21.1)	**0.0425[a]**
ICU LOS, mean; days (range) ± SD	14.1 [1 – 66] ± 11.1	17.3 [1 – 66] ± 12.9	17.5 [1 – 66] ± 13.8	17.7 [5 – 44] ± 9.6	0.4569[a]
Diabetes mellitus	65 (38.0)	28 (35.0)	23 (37.7)	5 (26.3)	0.4208[a]
Neoplasia	22 (12.9)	5 (6.2)	5 (8.2)	0 (0.0)	-
Chronic lung disease	27 (15.8)	13 (16.2)	11 (18.0)	2 (10.5)	0.5094[a]
Chronic kidney disease	27 (15.8)	11 (13.7)	8 (13.1)	3 (15.8)	>0.9999[a]
Chronic heart disease	45 (26.3)	21 (26.2)	15 (24.6)	6 (31.6)	0.5605[a]
Neurological disorders	15 (8.8)	6 (7.5)	6 (9.8)	0 (0.0)	-
Using Central Venous Catheter	144 (84.2)	66 (82.5)	50 (81.9)	16 (84.2)	0.8300[a]
Using Urinary Catheter	121 (70.8)	50 (62.5)	42 (68.8)	8 (42.1)	**0.0373[a]**
Using Mechanical ventilation	115 (67.2)	60 (75.0)	45 (73.8)	15 (78.9)	0.6556[a]
Antimicrobial therapy:	169 (98.8)	79 (98.7)	60 (98.4)	19 (100.0)	0.5970[a]
Carbapenem	82 (47.9)	43 (53.7)	34 (55.7)	9 (47.4)	0.5298[a]
Cephalosporin (3rd or 4th generation)	49 (28.6)	22 (27.5)	17 (27.9)	5 (26.3)	0.9011[a]
Fluoroquinolones	15 (8.8)	7 (8.7)	4 (6.6)	3 (15.8)	0.2209[a]
Aminoglycoside	6 (3.5)	3 (3.7)	3 (4.9)	0 (0.0)	-
Polymyxin	18 (10.5)	14 (17.5)	6 (9.8)	8 (42.1)	**0.0014[a]**
Presence of bacteremia:	66 (38.6)	53 (66.2)	38 (62.3)	15 (78.9)	0.1851[a]
Primary bacteremia	45/66 (68.2)	44/53 (83.0)	32/38 (84.2)	12/15 (80.0)	0.4197[a]
Secondary bacteremia	21/66 (31.8)	9/53 (17.0)	6/38 (15.8)	3/15 (20.0)	0.4825[a]
Pneumonia	123 (71.9)	46 (57.5)	30 (49.2)	16 (84.2)	**0.0075[a]**
Urinary Tract Infection	24 (14.0)	23 (23.7)	17 (27.9)	6 (31.6)	0.7620[a]
Surgical Site Infection	20 (11.9)	8 (10.0)	7 (11.5)	1 (5.3)	0.4399[a]

HAI, Healthcare-associated Infection; OR, odds ratio; CI, confidence interval; SD, standard deviation; ICU, intensive care unit; LOS, length of stay.
[a]Mann-Whitney U-Test; [b]Student's T test. * $P \leq 0.05$ was considered to indicate statistical significance.

Table II. Microbiology of HAIs, sorted by monomicrobial and polymicrobial cases

Microorganism	Overall N (%)	Monomicrobial N (%)	Polymicrobial N (%)	*P* value
Number of organisms identified	141 (100.0)	61/141 (43.3)	80/141 (56.7)	
Gram-negative:	62/141 (43.9)	29/61 (47.5)	33/80 (41.2)	0.4961[a]
Pseudomonas aeruginosa	18/62 (29.0)	6/29 (20.7)	12/33 (36.4)	0.2625[a]
Acinetobacter baumannii	16/62 (25.8)	9/29 (31.0)	7/33 (21.2)	0.4009[a]
Escherichia coli	13/62 (20.9)	8/29 (27.6)	5/33 (15.2)	0.3492[a]
Klebsiella pneumoniae	11/62 (17.7)	6/29 (20.7)	5/33 (15.2)	0.7412[a]
Stenotrophomonas maltophilia	4/62 (6.4)	0/29 (0.0)	4/33 (12.1)	-
Gram-positive:	59/141 (41.8)	20/61 (32.8)	39/80 (48.7)	**0.0410[a]**
Staphylococcus aureus	25/59 (42.4)	10/20 (50.0)	15/39 (38.5)	0.4190[a]
CNNI	16/59 (27.1)	7/20 (35.0)	9/39 (23.1)	0.3658[a]
Staphylococcus epidermidis	7/59 (11.9)	2/20 (10.0)	5/39 (12.8)	>0.9999[a]
Enterococcus faecalis	5/59 (8.5)	0/20 (0.0)	5/39 (12.8)	-
Staphylococcus hominis	3/59 (5.1)	1/20 (5.0)	2/39 (5.1)	>0.9999[a]
Staphylococcus haemolyticus	3/59 (5.1)	0/20 (0.0)	3/39 (7.7)	-
Fungi:	-	-	-	-
Candida albicans	11/141 (7.8)	8/61 (13.1)	3/80 (3.7)	**0.0411[a]**
Others	9/141 (6.4)	4/61 (6.6)	5/80 (6.2)	>0.9999[a]

[a]Mann-Whitney U-Test; * $P \leq 0.05$ was considered to indicate statistical significance.

CNNI, coagulase-negative staphylococci non-identified. Others - *Enterobacter spp.; Proteus mirabilis; Serratia spp.; Citrobacter freundii; Streptococcus spp.*

Capítulo 5

Considerações finais

5.1 CONSIDERAÇÕES FINAIS

Os resultados desse estudo permitem melhor compreender o cenário das IRAS graves em pacientes adultos em UTIs clínico-cirúrgicas e coronarianas do Estado de Minas Gerais. Também, possibilitam avaliar o impacto da utilização de dispositivos invasivos como importantes fatores de risco para o desenvolvimento dessas infecções, assim como a alta frequência de uso desses dispositivos. Adicionalmente, os resultados obtidos permitiram as seguintes considerações:

i. Esse estudo observou frequências elevadas de pneumonia nosocomial e ICS nos pacientes internados em UTIs de adulto, significativamente associadas a fatores de risco clássicos como tempo de hospitalização na UTI, uso de CVC por 7 dias ou mais, uso de ventilação mecânica e terapia antimicrobiana;
ii. Relatamos uso extensivo de dispositivos médicos invasivos pelos pacientes internados em UTIs, especialemente os que apresentaram IRAS no dia da pesquisa;
iii. As investigações desse trabalho corroboram com achados similares em relação a etiologia dessas infecções, mais frequentemente causadas por BGNs, especialmente *Acinetobacter baumannii* e *Pseudomonas aeruginosa*, conhecidos por serem de difícil eliminação;
iv. Obtivemos um dado impressionante e comparável com outras pesquisas apontando um aumento do número de IRAS causadas por *Staphylococcus aureus* no Brasil;
v. Observamos uma baixa prevalência de critério microbiológico para diagnóstico de IRAS com participação expressiva de bacilos Gram-negativos nas infecções polimicrobianas;
vi. Por fim, observamos a necessidade urgente de desenvolvimento de políticas públicas de prevenção e vigilância mais eficazes de modo a controlar a disseminação de IRAS e melhorar o cenário da saúde e segurança dos pacientes no Brasil.