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ANÁLISE DA RELAÇÃO COLONIZAÇÃO E INFECÇÃO POR ENTEROBACTÉRIAS RESISTENTES AOS CARBAPENÊMICOS

MABEL DUARTE ALVES GOMIDES

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Tese apresentada ao Programa de Pós-Graduação em Ciências da Saúde da faculdade de Medicina da Universidade Federal de Uberlândia, como requisito parcial para obtenção do título de Doutor em Ciências da Saúde.

Área de concentração: Ciências da Saúde.

Orientador:
Prof. Dr. Anderson Luiz Ferreira

Coorientador:
Prof. Dr. Geraldo Sadoyama

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(autor desconhecido)

RESUMO

Introdução: As colonizações e infecções por enterobacteriáceas resistentes aos carbapenêmicos (CRE - *carbapenem-resistant Enterobacteriaceae*) têm aumentado de forma ameaçadora, com predomínio da *Klebsiella pneumoniae* resistente aos carbapenêmicos (CRKP - *carbapenem-resistant Klebsiella pneumoniae*), apesar da implementação das medidas de controle e prevenção. Consequentemente, tem sido observado aumento na incidência de infecções relacionadas à assistência à saúde (IRAS), morbimortalidade e tempo de hospitalização. A colonização por CRE e fatores de risco, como: pacientes graves, internação prolongada, dispositivos invasivos e exposição prévia aos antibióticos, podem favorecer a infecções invasivas por CRE. A disseminação da CRE ocorre, principalmente, em ambientes hospitalares, por transmissão cruzada entre pacientes e profissionais de saúde ou em ambientes contaminados. A colonização representa um risco na disseminação das CRE, e a detecção isolada das infecções é, apenas, a ponta do iceberg. Portanto, a vigilância ativa é uma importante estratégia para a detecção de CRE, e permite controlar a propagação dessas bactérias resistentes. **Objetivos:** Objetivou-se demonstrar a importância do protocolo de vigilância ativa CRE e avaliar as taxas e prevalências, os fatores de risco e a mortalidade nos colonizados e infectados por CRKP, além de traçar um perfil da colonização, infecção e mortalidade, ao longo de cinco anos. **Material e Métodos:** Realizou-se um estudo observacional e retrospectivo em hospital público, no sudeste do Brasil. Foram analisados um total de 1.920 pacientes maiores de 12 anos, internados na unidade de terapia intensiva (UTI), de janeiro/2014 a dezembro/2018. Todos os pacientes foram submetidos ao protocolo de vigilância ativa com teste de triagem para CRE, por meio de swab retal. **Resultados:** Entre todos os 1.920 pacientes, a média de idade foi de 52,42 ± 19,34 anos (variação de 13 a 97 anos), com predomínio do sexo masculino (65,31%). sobre o sexo feminino (1,88:1). A alta (68,12%) foi um desfecho mais predominante do que a morte (2,13:1). O escore SAPS II variou de 16 a 131 (média 62,19 ± 18,73). O tempo médio de internação foi de 21,03 ± 18,12 dias (intervalo de 1 a 175 dias). Os testes de triagem CRE foram positivos em 10,91% das coletas de swab retal com 13,66% de coletas positivas nos mesmos pacientes. A análise de prevalência da colonização, infecção e mortalidade para CRE, com predomínio para CRKP, foi

elevada na UTI. Observou-se uma chance elevada (OR 7,967) de pacientes colonizados evoluírem com infecção invasiva para CRE. Os fatores de risco mais prevalentes para os colonizados por CRE e infectados por CRKP foram traqueostomia e exposição prévia aos antibióticos. **Conclusões:** A detecção de pacientes colonizados para CRE, por meio dos testes de triagem, mostrou ser um importante instrumento no controle de infecções e colonizações. Visto que permite a implantação precoce de medidas que controlam a propagação de bactérias resistentes. Contudo, ao longo dos cinco anos, demonstrou-se que as taxas e prevalências de CRE nos pacientes colonizados e infectados por CRKP mantiveram-se elevadas. Ressalta-se, portanto, a necessidade de reavaliar o protocolo de vigilância ativa de CRE, desta UTI, além do excesso de coletas de triagem e uso empírico de antibióticos.

Palavras-chave: *Klebsiella pneumoniae*; Infecções Nosocomiais; Unidade de Terapia Intensiva; Vigilância; Controle de Infecções; Antibióticos.

ABSTRACT

Introduction: The Colonization and infections by carbapenem-resistant Enterobacteriaceae (CRE) have increased in a threatening manner, with a predominance of carbapenem-resistant Klebsiella pneumoniae (CRKP), despite the implementation of control and prevention measures. Consequently, there is an increase in the incidence of healthcare-associated infections (HAI), morbidity and mortality, and long-term hospital stay. CRE colonization along with other risk factors, such as critically ill patients, long-term hospital stay, invasive devices, and previous antibiotic exposure can result in CRE invasive infections. Transmission of CRE occurs mainly within hospital environments, especially in ICU, due to cross-transmission between patients and healthcare professionals, or through contaminated environments. Colonization represents a CRE dissemination threat, and the isolated detection of infections is only the “tip of the iceberg”. Therefore, active surveillance is an important strategy for CRE detection and allows to obtain control of the spread of these resistant bacteria. **Objectives:** This study aimed to demonstrate the importance of active CRE surveillance protocols and to assess rates and prevalence, risk factors, and mortality in colonized and CRKP infected patients. This study also aims to outline a colonization, infection, and mortality profile over a five-year time. **Material and Methods:** Retrospective, observational study of a public tertiary hospital in southeastern Brazil. A total of 1,920 patients older than 12 years were analyzed, admitted to an intensive care unit (ICU) from January 2014 to December 2018. All patients were submitted to the active surveillance protocol with a CRE screening test through a rectal swab. **Results:** Among all 1,920 patients, the mean age was 52.42 ±19.34 years (range 13–97 years), and there was a predominance of the male (65.31%). over the females (1.88:1) sex. Discharge (68.12%) was a more predominant outcome than death (2.13:1). The SAPS II score ranged from 16 to 131 (mean 62.19 ±18.73). The mean length of hospital stay was 21.03 ±18.12 days (range 1 – 175 days). CRE screening tests were positive in 10.91% of rectal swab collections with 13.66% of positive collections in the same patients. The analysis of the prevalence of colonization, infection, and mortality for CRE, with a predominance of CRKP, was high in the ICU. A high chance (OR 7.967) of colonized patients evolve to a CRE invasive infection was observed. The most

prevalent risk factors for CRE colonized and CRKP infected were tracheostomy and previous antibiotic exposure. **Conclusion:** Detection of CRE colonized patients, through screening tests, proved to be an important instrument in the control of infections and colonization. Since it allows the early implementation of measures that control the spread of resistant bacteria. However, over the five years, it has been shown that the rates and prevalence of CRE in the colonized and infected with CRKP patients remained high. Therefore, the need to reevaluate the active surveillance protocol of this ICU is highlighted, in addition to the excess of screening collections and empirical use of antibiotics.

Keywords: *Klebsiella pneumoniae*; Health Care Associated Infections; Intensive Care Units; Surveillance; Infection control; Anti-Bacterial Agents

LISTA DE ABREVIATURAS E SIGLAS

MDR - multidrug-resistant

IRAS - infecções relacionadas à assistência à saúde

ESBL - extended-spectrum β-lactamase

VRE - vancomycin-resistence *Enterococcus*

CRE - carbapenem-resistant *Enterobacteriaceae*

UTI - unidade de terapia intensiva

BGN - bactéria gram-negativa

CDC – Centers for Disease Control and Prevention

EUA - Estados Unidos da América

XDR - extensively drug-resistant

PDR - pandrug-resistant

AmpC – *3´5´-adenosina-monofosfato-cíclico type β-lactamase*

KPC - *Klebsiella pneumoniae* carbapenemase

NDM - *New Delhi metallo-β-lactamase*

VIM - *Verona integron-encoded metallo-β-lactamase*

OXA beta-lactamases - *β-oxacillinase*

OXA-48 – *Carbapenem-hydrolyzing oxacillinase-48*

IOM - Institute of Medicine

IMP – *Imipenemase metallo-β-lactamase*

SUMÁRIO

1 INTRODUÇÃO

As bactérias resistentes a múltiplas drogas (MDR - *Multidrug-resistant*) têm causado grande impacto na saúde pública, nos últimos anos, com prevalência mundialmente elevada nas infecções relacionadas à assistência à saúde (IRAS) (CASTANHEIRA et al., 2017; DAVIDO et al., 2018; RUPPÉ; WOERTHER; BARBIER, 2015; SHIELDS et al., 2017; SMIBERT et al., 2019; TRAN et al., 2019). Entre as causas de infecção, as bactérias gram-negativas (BGN) são responsáveis por mais de 30% das infecções hospitalares, e pelo menos 70% das infecções nas unidades de terapia intensiva (UTI) (LI et al., 2019b; PELEG; HOOPER, 2010; TZOUVELEKIS et al., 2012), sendo 10 a 13% de bactérias MDR (CASTANHEIRA et al., 2017; LI et al., 2019b).

As BGN MDR apresentam capacidade de regulação dos genes com uma infidade de mecanismos de resistência que podem ser múltiplos, contra o mesmo antibiótico, ou único, contra múltiplos antibióticos (CASTANHEIRA et al., 2017; LI et al., 2019a; PELEG; HOOPER, 2010). As opções terapêuticas para os pacientes com infecções por bactérias MDR são limitadas (SAMPAIO; GALES, 2016). Além, do uso indiscriminado de antibióticos de largo espectro, no meio hospitalar, favorecendo o desenvolvimento da colonização por vantagem competitiva, por supressão da microbiota natural e pelo crescimento da resistência antimicrobiana por pressão seletiva (PELEG; HOOPER, 2010; SIEGEL et al., 2007b).

Com isso, a disseminação de bactérias MDR pode ocorrer a partir do ambiente hospitalar e se espalhar para a comunidade, ou pode ser introduzida no ambiente hospitalar com a admissão de um novo paciente colonizado e/ou infectado, proveniente da comunidade, ou ainda, e mais frequentemente, de outra instituição (TRAN et al., 2019). A identificação precoce e o isolamento desses pacientes são primordiais para evitar a disseminação dos agentes citados (POGORZELSKA; STONE; LARSON, 2012; TRAN et al., 2019).

Entre BGN MDR, destacam-se as bactérias produtoras de β-lactamases de espectro estendido (ESBL - *extended-spectrum β-lactamase*) e as bactérias resistentes aos carbapenêmicos, como os bacilos não fermentadores e as enterobacteriáceas (CRE - *carbapenem-resistant Enterobacteriaceae*) (ALP; AKOVA,

2017; DAVIDO et al., 2018; TRAN et al., 2019).

As CRE apresentam elevadas taxas de resistência aos antibióticos de primeira linha, o que aumenta as taxas de morbimortalidade pela restrição de antibacterianos disponíveis para a prática clínica (CASTANHEIRA et al., 2017; DAVIDO et al., 2018; LI et al., 2019b; RUPPÉ; WOERTHER; BARBIER, 2015; SABET et al., 2018; SHIELDS et al., 2017). A persistência da bactéria ativa, sem o tratamento eficaz, facilita a disseminação da resistência bacteriana, principalmente a carbapenemase. (LI et al., 2019b; SABET et al., 2018; SHIELDS et al., 2017).

A infecção relacionada à assistência, causada por CRE, pode ocorrer de forma endógena, oriunda da translocação de bactérias da microbiota intestinal, ou exógena, por meio de transmissão cruzada, pelo contato nos cuidados assistenciais de saúde (ALP; AKOVA, 2017; MCCONVILLE et al., 2017; PITTET; DONALDSON, 2005; RUPPÉ; WOERTHER; BARBIER, 2015). Existe uma correspondência expressiva entre os pacientes colonizados por CRE, sob cuidados de saúde, e o risco de desenvolverem infecção, inclusive com aumento na mortalidade (TRAN et al., 2019).

As IRAS causadas pelas CRE são comumente graves e de difícil controle pelas poucas opções terapêuticas, e são frequentes nas UTI (CASTANHEIRA et al., 2017; LI et al., 2019b; LOHO; DHARMAYANTI, 2015; RUPPÉ; WOERTHER; BARBIER, 2015; SHIELDS et al., 2017). Por isso, essas infecções merecem a atenção especial dos serviços de saúde, voltada para as medidas preventivas (CASTANHEIRA et al., 2017).

As infecções por CRE acometem, preferencialmente, pacientes de maior gravidade e suscetíveis às situações de risco, como comorbidades, cirurgias e uso de imunossupressores e dispositivos invasivos de longa permanência (CENTERS FOR DISEASE CONTROL AND PREVENTION, 2009; COLPAN et al., 2005; CORREA; FORTALEZA, 2019; FRENCH et al., 2017; LI et al., 2019b; TRAN et al., 2019; WANG et al., 2016).

A transmissão das CRE ocorre em qualquer situação de assistência à saúde, embora seja mais frequente em instituições de cuidados intensivos, devido à presença de pacientes mais vulneráveis à colonização e infecção (SIEGEL et al., 2007a; TRAN et al., 2019).

As evidências epidemiológicas sugerem que o principal modo de transmissão cruzada de bactérias entre pessoas, seja por meio do contato com as mãos (LI et al., 2019a). AS mãos são facilmente contaminadas durante a processo de prestação de cuidados ou no contato com sujidades das superfícies do ambiente hospitalar (LI et al., 2019a; SIEGEL et al., 2007a).

A detecção de pacientes colonizados e infectados são as duas principais abordagens para o controle da propagação das CRE (NORDMANN et al., 2012). Sabe-se que a colonização por CRE pode preceder a infecção, e os portadores, especialmente os assintomáticos, podem servir como um importante reservatório para disseminação horizontal, sustentando esses microrganismos dentro dos ambientes hospitalares (ZHAO et al., 2014).

A prevenção e a vigilância de CRE necessitam de políticas estratégicas apropriadas e efetivas, além de recursos para a prevenção e controle de infecção para auxiliar na redução da incidência de IRAS por bactérias resistentes (MOURIK, 2018; SIEGEL et al., 2007a). Os países subdesenvolvidos apresentam limitados recursos para vigilância, necessitando de muita cooperação na prevenção e controle para reduzir a disseminação de BGN MDR (TRAN et al., 2019).

Em decorrência da ampla disseminação de CRE, houve a necessidade do Centro de Controle e Prevenção de Doenças dos Estados Unidos da América (CDC – *Centers for Disease Control and Prevention*) divulgar normas de prevenções para os pacientes infectados ou colonizados por bactérias resistentes, como: isolamento do paciente, cuidados por equipe exclusiva e controle no uso de antibióticos. Essas medidas têm por finalidade evitar a propagação de bactérias multidrogas resistentes no intrahospitalar (CENTERS FOR DISEASE CONTROL AND PREVENTION, 2009; CENTERS FOR DISEASE CONTROL AND PREVENTION, 2013).

No entanto, ressalta-se a higiene das mãos como base de qualquer estratégia de prevenção de infecção, e que deve estar combinanda com a detecção dos colonizados por testes de triagem, limpeza dos equipamentos e ambientes, uso de banhos de clorexidina e educação e treinamento de pessoal (DA SILVA; TRAEBERT; GALATO, 2012; DAVIDO et al., 2018; DERDE et al., 2014).

Para uma gestão de infecção hospitalar adequada é necessário a conscientização sobre os fatores de risco, a adesão às medidas preventivas e a

padronização do uso de antibióticos de acordo com dados microbiológicos conhecidos (PELEG; HOOPER, 2010; SABET et al., 2018).

Outras medidas estratégicas de controle e prevenção seriam a descolonização e o uso de terapias combinadas como alternativas eficazes nas infecções resistentes, com maiores taxas de sobrevida em relação à monoterapia, apesar do mau prognóstico e eficácia e segurança incerta (ALP; AKOVA, 2017; RAPP; URBAN, 2012; SMIBERT et al., 2019).

A descolonização ainda não estão bem estabelecidas uma vez que as recaídas são frequentes, mas a falta de tratamento demonstra uma colonização prolongada entre os portadores (DAVIDO et al., 2018). Entre as descolonizações, destaca-se o transplante de microbiota fecal, com resultados aparentemente promissores, apesar da durabilidade duvidosa (BAR-YOSEPH et al., 2016).

As infecções por CRE em pacientes de UTI aumentam o tempo de internação, os custos do tratamento e as taxas de morbimortalidade dos pacientes (TZOUVELEKIS et al., 2012; ZHAO et al., 2014). O que torna necessário a adoção de protocolos de vigilância e medidas de isolamento para o controle de surtos infecciosos nos ambientes hospitalares.

O presente estudo justifica-se, cientificamente, pela relevância das colonizações e infecções por CRE, pois representam preocupação e desafio no controle da disseminação, no tratamento das infecções, com limitadas opções terapêuticas, e pelas elevadas taxas de mortalidade (BRACCO et al., 2013; NORDMANN, 2014; ZHAO et al., 2014).

Frente a isso, o presente estudo busca responder à seguinte pergunta de pesquisa: “Qual a importância da implantação do protocolo de vigilância ativa por meio de testes de triagem para rastreamento de pacientes colonizados por CRE nos ambientes de maior risco, como a UTI”?

2 FUNDAMENTAÇÃO TEÓRICA

2.1 Enterobacteriáceas resistentes aos carbapenêmicos (CRE - carbapenem-resistant Enterobacteriaceae)

As BGN são responsáveis por muitas infecções hospitalares, sendo a família Enterobacteriaceae a mais frequente (WORLD HEALTH ORGANIZATION, 2008). As enterobactérias habitam o trato gastrointestinal e urinário do homem formando uma microbiota natural ou um importante reservatório de resistências bacterianas com chance de disseminar para o meio ou causar infecção (MARTIN et al., 2017; MCCONVILLE et al., 2017; RUPPÉ; WOERTHER; BARBIER, 2015). As enterobactérias representam um dos principais patógenos causadores infecções hospitalares e da comunidade (BAR-YOSEPH et al., 2016; BRACCO et al., 2013; DIENSTMANN et al., 2010; NORDMANN et al., 2012; NORDMANN, 2014; RUPPÉ; WOERTHER; BARBIER, 2015).

Todas as espécies da família Enterobacteriaceae têm sido implicadas nas infecções da corrente sanguínea, do trato urinário, do trato respiratório inferior, principalmente, associado à ventilação mecânica e do intra-abdominal (LI et al., 2019b; PELEG; HOOPER, 2010; SCHWABER; CARMELI, 2008; TACCONELLI et al., 2014). Apesar disso, destaca-se a *Escherichia coli* como causa frequente de infecções do trato urinário e a *Klebsiella spp.* e *Enterobacter spp.* como importantes causas de pneumonia (DIENSTMANN et al., 2010; LI et al., 2019a; TACCONELLI et al., 2014).

A emergência de enterobactérias resistentes, principalmente pela produção de ESBL e de mecanismos de multirresistências para carbapenêmicos, tem sido considerada um problema grave, que requer atenção imediata, devido à fácil disseminação e dificuldades terapêuticas (LI et al., 2019b; PELEG; HOOPER, 2010; TRAN et al., 2019).

As CRE apresentam incidência crescente em âmbito mundial e expressivas diferenças entre regiões (BERRY et al., 2019; FRIEDMAN et al., 2017). As enterobactérias resistentes podem ser transmitidas no meio dos cuidados de saúde ou na comunidade e os pacientes hospitalizados são os mais susceptíveis à adquirir as colonizações e/ou infecções (FRENCH et al., 2017).

Os processos infecciosos por CRE são muito graves e representam uma grande ameaça à vida do paciente, devido à capacidade de disseminação e baixa resposta aos antibióticos (FRENCH et al., 2017; RAMAN et al., 2015; TABAH et al., 2012; THADEN et al., 2017). A dificuldade terapêutica aumenta o tempo de permanência no hospital e o risco de mortalidade (26 a 70%) (BERRY et al., 2019; FRENCH et al., 2017; FRIEDMAN et al., 2017; MCCONVILLE et al., 2017; PELEG; HOOPER, 2010). Consequentemente, há um aumento nos custos hospitalares decorrentes do consumo de medicamentos, do suporte clínico, da monitorização invasiva e dos programas de prevenção (MÜLLER et al., 2015; RAMAN et al., 2015; THADEN et al., 2017).

2.1.1 Resistência antibiótica

A resistência aos antibióticos emergiu em virtude de mutações bacteriana ou seleção das cepas mutantes por vantagem competitiva (BUSH; JACOBY, 2010; CAI et al., 2017; SIEGEL et al., 2007b). Geralmente, ocorrem por consequência do uso indiscriminado ou não otimizado de antibióticos profiláticos e terapêuticos nos hospitais, na comunidade e na agricultura (DERDE et al., 2014; NORDMANN et al., 2012; NODMANN, 2014; TZOUVELEKIS et al., 2012; ZHAO et al., 2014).

A pressão seletiva de genes de multirresistência ocorre, sobretudo, nos ambientes hospitalares, sendo as UTI os locais de maior ocorrência (NORDMANN, 2014; SAMPAIO; GALES, 2016). Isso ocorre pelo fato de admitirem pacientes de elevada gravidade e com vários fatores de risco para infecção e colonização (LOHO; DHARMAYANTI, 2015; SIEGEL et al., 2007a). Entre os fatores, destacam-se os dispositivos invasivos de demora, que são uma porta de entrada para infecções graves (POGORZELSKA; STONE; LARSON, 2012).

As BGN apresentam vários mecanismos de resistência aos antibióticos que são adquiridos por seleção natural, decorrente de pressão do meio, de mutação, de transdução por meio de bacteriófago e da conjugação direta de plasmídeo por pontes citoplasmáticas para diferentes classes de antibióticos (BUSH; JACOBY, 2010; PELEG; HOOPER, 2010; RAMAN et al., 2015; RAPP; URBAN, 2012; THADEN et al., 2017).

As resistências antimicrobianas foram definidas como: MDR para microrganismos não suscetíveis a ≥ 1 agente em ≥ 3 categorias antibióticos; XDR (*Extensively drug-resistant*) para bactérias não suscetíveis a ≥ 1 agente em todas as categorias, exceto ≤ 2; e PDR (*Pandrug-resistant*) para bactérias não suscetíveis a todos os agentes antibióticos (MAGIORAKOS et al., 2012; THADEN et al., 2017). O aumento das enterobactérias com fenótipos MDR tem sido observado, com comprometimento dos programas de tratamento para as infecções graves (CASTANHEIRA et al., 2017).

Em geral, as taxas de resistência foram elevadas nas IRAS com padrões de MDR (47,8%) em relação a XDR (20,5%) e PDR (0,4%) (TABAH et al., 2012). Apesar da limitação de antibióticos disponíveis para tratamento das bactérias resistentes de qualquer padrão, não foi observado o aumento da mortalidade ligada diretamente à resistência, mas houve um aumento da mortalidade relacionado ao tratamento incorreto (MAGIORAKOS et al., 2012; TABAH et al., 2012; THADEN et al., 2017).

As BGN resistentes a múltiplas drogas emergiram há décadas, inicialmente por genes codificadores da perda de porinas associadas à produção de ESBL ou da combinação ocasional de impermeabilidade da membrana pela β-lactamases cromossômicas (AmpC - 3´5´-adenosina-monofosfato-cíclico *type β-lactamase*) (BRACCO et al., 2013; NORDMANN et al., 2012, SCHWABER; CARMELI, 2008; TABAH et al., 2012). Esse fator confere resistência a ampicilina, amoxicilina, outras penicilinas e cefalosporinas, exceto as de quarta geração (BUSH; JACOBY, 2010; DIENSTMANN et al., 2010).

Em decorrência desses fatos, os antibióticos das classes das Piperacilinas/Tazobactam, Carbapenêmicos e Glicopeptídeos foram amplamente utilizados como as únicas alternativas terapêuticas, tanto nas terapias empíricas como nas IRAS de causa confirmada em culturas (SCHWABER; CARMELI, 2008; TABAH et al., 2012). Com isso, no início dos anos de 2000, houve progressão no perfil de resistência das bactérias gram-negativas, inclusive das enterobactérias, com manifestação de resistência aos carbapenêmicos, como o Imipenem, Meropenem, Doripenem ou Ertapenem (CORREA; FORTALEZA, 2019; SCHWABER; CARMELI, 2008; TISCHENDORF; DE AVILA; SAFDAR, 2016).

A resistência aos carbapenêmicos emerge da produção de cabapenemases, que são β-lactamases capazes de hidrolisar penicilinas, cefalosporinas, monobactâmicos e carbapenêmicos (BUSH; JACOBY, 2010; NORDMANN et al., 2012; PELEG; HOOPER, 2010; SCHWABER; CARMELI, 2008). São reconhecidas, mundialmente, três classes principais de carbapenemases nas CRE, como β-lactamase ambler de classe A: carbapenemases do tipo KPC (*Klebsiella pneumoniae* carbapenemase); classe B: metalo-β-lactamases, incluindo as NDM (*New Delhi metallo-β-lactamase*) e VIM (*Verona integron-encoded metallo-β-lactamase*); e classe D: OXA (*β-oxacilinase*)- *type carbapenemases*, sendo a OXA-48 (*Carbapenem-hydrolyzing oxacillinase-48*) a mais frequente em enterobactérias (BUSH; JACOBY, 2010; MARQUES et al., 2015; NORDMANN, 2014; PELEG; HOOPER, 2010; RAPP; URBAN, 2012; SCHWABER; CARMELI, 2008).

As β-lactamases ambler de classe A incluem, entre outros, a bactéria *Klebsiella pneumoniae carbapenemase* (KPC), sendo mais prevalentes em plasmídeos de *Klebsiella pneumoniae* e constituindo um importante mecanismo de resistência no contexto hospitalar dos países (BUSH; JACOBY, 2010; CASTANHEIRA et al., 2017; MARTIN et al., 2017; NORDMANN, 2014).

Os genes responsáveis pela codificação das carbapenemases estão incorporados no cromossomo da bactéria ou em pequenas moléculas de DNA circular, extracromossômicas e móveis, como plasmídeos ou transposons (MARQUES et al., 2015; MARTIN et al., 2017; RAPP; URBAN, 2012). Estes são facilmente transportados e podem ser difundidos entre cepas de mesma espécies e gêneros, esclarecendo a disseminação entre gram-negativos (MARTIN et al., 2017; PELEG; HOOPER, 2010; SCHWABER; CARMELI, 2008). As bactérias que recebem estes plasmídeos podem ser portadoras de fatores de virulência e apresentar outros mecanismos de resistência, o que resulta em infecções graves por germes XDR (SCHWABER; CARMELI, 2008; TABAH et al., 2012).

A resistência aos carbapenêmicos tem surgido em diversas enterobactérias, como *Klebsiella pneumoniae*, *Escherichia coli*, *Klebsiella oxytoca*, *Enterobacter cloacae*, *Citrobacter freundii* e *Enterobacter aerogenes* (MCCONVILLE et al., 2017; TISCHENDORF; DE AVILA; SAFDAR, 2016). Dentre essas cepas, a espécie de enterobactéria e a classe de resistência mais comum, em todo o mundo, é a

Klebsiella pneumoniae produtora de KPC, encontrada nos Estados Unidos, Israel, China, Europa e América do Sul, inclusive no Brasil, com taxa de resistência de 27,1% (LIN et al., 2013; MARTIN et al., 2017; MCCONVILLE et al., 2017; PELEG; HOOPER, 2010; SAMPAIO; GALES, 2016; TISCHENDORF; DE AVILA; SAFDAR, 2016).

2.1.2 Infecção e Colonização

As doenças ou síndromes infecciosas são caracterizadas pela presença de sinais e sintomas decorrentes de estímulos dos mediadores pró-inflamatórios, ativados pelos danos da invasão, multiplicação ou ação de produtos tóxicos dos agentes infecciosos no hospedeiro (LOHO; DHARMAYANTI, 2015).

Os processos infecciosos localizam-se, principalmente, no trato respiratório inferior, pneumonias ou traqueobronquites (25% dos casos nas UTI); infecções do trato geniturinário (40% das IRAS); infecções primárias de corrente sanguínea, sepse e choque séptico; e os sítios cirúrgicos (GOTO et al., 2016; HAQUE et al., 2018; PELEG; HOOPER, 2010; TABAH et al., 2012). Visto que, as IRAS são comumente causadas por BGN e estão associadas à maior gravidade, pior prognóstico e elevado risco de mortalidade (FORTALEZA et al., 2017; HAQUE et al., 2018; MAGILL et al., 2014; PELEG; HOOPER, 2010; RAMAN et al., 2015; VAN MOURIK et al., 2018).

Estes sítios de infecção estão mais propensos a serem comprometidos quando associados aos dispositivos (21 a 26% dos casos), isto é, pneumonia associada à ventilação mecânica, infecção de corrente sanguínea associada ao cateter venoso central, infecção do trato geniturinário associada à sonda vesical de demora (aumenta a bacteriúria em 5 a 10% por dia) e infecção do sítio cirúrgico associada aos drenos e cateteres (GOTO et al., 2016; HAQUE et al., 2018; MAGILL et al., 2014; PELEG; HOOPER, 2010).

As infecções associadas aos dispositivos ainda representam mais da metade dos casos de infecção, quando comparados às não relacionadas aos dispositivos, apesar das fortes campanhas de prevenção em favor da retirada precoce dos dispositivos (MAGILL et al., 2014).

Em situações particulares, as IRAS causadas por CRE apresentam vários fatores de risco reconhecidos, compreendendo as doenças críticas, colonizações, internações prolongadas em UTI - prévias ou entre setores do hospital - exposição prévia aos antibióticos, transplante de órgãos ou célula-tronco, uso de dispositivos invasivos e equipamentos endoscópicos contaminados (FRENCH et al., 2017; LOHO; DHARMAYANTI, 2015).

Os pacientes colonizados por CRE são importantes fatores de risco para infecção sistêmica, podendo ocorrer em 16,5% a 73% dos casos ou serem fontes de contaminação para outros pacientes (CORREA; FORTALEZA, 2019; FRENCH et al., 2017; MCCONVILLE et al., 2017; SCHECHNER et al., 2013; RUPPÉ; WOERTHER; BARBIER, 2015; WANG et al., 2016).

Os fatores predisponentes para a colonização por CRE dos pacientes são ainda controversos, mas parecem estar relacionados com o desequilíbrio da microbiota natural e aumento da carga bacteriana, sendo o trato gastrointestinal um dos principais reservatórios endógenos, ou com a transferência cruzada de bactérias resistentes entre pacientes e profissionais de saúde (CORREA; FORTALEZA, 2019; TISCHENDORF; DE AVILA; SAFDAR, 2016).

Os pacientes colonizados são portadores por tempo prolongado e apresentam elevadas chances de contaminação do meio hospitalar e da comunidade em geral, além da predisposição de desenvolverem infecção invasiva a qualquer momento (CORREA; FORTALEZA, 2019; RUPPÉ; WOERTHER; BARBIER, 2015; SCHWABER; CARMELI, 2008; TISCHENDORF; DE AVILA; SAFDAR, 2016).

Além disso, as colonizações são mais prevalentes no paciente diabético, internação prolongada e/ou na UTI, exposição prévia aos antibióticos e uso de cateter venoso central e/ou ventilação mecânica (LIN et al., 2013; SCHECHNER et al., 2013). A identificação desses fatores de riscos auxilia na prevenção e no tratamento de pacientes colonizados que desenvolvem infecções, pois as taxas de mortalidade são elevadas e variam de 26% a 41% (MCCONVILLE et al., 2017; SCHECHNER et al., 2013).

A dificuldade da detecção precoce e as limitações terapêuticas são causas que favorecem a rápida propagação da bactéria, com elevado risco de surtos de infecção em ambientes fechados, como as UTI (BURNS et al., 2013; FRENCH et al.,

2017). Portanto, os testes de triagens de protocolos de vigilância podem ser utilizados de forma sistemática em situações específicas com a finalidade de conhecimento epidemiológico e prevenção de transmissão (BURNS et al., 2012; LOHO; DHARMAYANTI, 2015).

A prevalência da colonização em áreas endêmicas de CRE está em torno de 3 a 7%, o que fortalece a necessidade de busca ativa por cultura de vigilância e medidas de controle para os casos confirmados, como o isolamento de contato e higiene frequente das mãos (BURNS et al., 2012; CORREA; FORTALEZA, 2019; DERDE et al., 2014; FRENCH et al., 2017; HUSSEIN et al., 2017; MCCONVILLE et al., 2017; TISCHENDORF; DE AVILA; SAFDAR, 2016).

2.1.3 Transmissão

A disseminação de CRE, por todo o mundo, apresenta resultados desastrosos para a saúde pública, justamente pelas dificuldades terapêuticas e elevado potencial de difusão de clones bacterianos capazes de transportar diversos plasmídeos (ALBIGER et al., 2015; CORREA; FORTALEZA, 2019; HUSSEIN et al., 2017; LIN et al., 2013; MARTIN et al., 2017; MÜLLER et al., 2015). Esse potencial de dispersão dos plasmídeos e capacidade de virulência de determinados clones bacterianos predispõe a surtos generalizados e complexos dentro e entre países (MARTIN et al., 2017; PIRES et al., 2016).

De acordo com ampla evidência epidemiológica, a transmissão bacteriana nos ambientes de saúde pode ser controlada de dois modos diferentes, o horizontal e o vertical, sendo um horizontal, por meio de prática padrão de higiene das mãos, impedindo a disseminação cruzada entre pessoas (GOTO et al., 2016; MÜLLER et al., 2015). O vertical seria por meio da vigilância ativa de patógenos específicos permitindo o isolamento de contato de pacientes colonizados ou infectados com outras pessoas (GOTO et al., 2016; MÜLLER et al., 2015).

Múltiplos fatores favorecem a rápida disseminação de bactérias MDR, como o tratamento com antibióticos sem eficácia terapêutica para bactérias resistentes ou de amplo espectro para pacientes com infecções sensíveis (RAMAN et al., 2015). Esses fatores culminaram em um ciclo vicioso que envolve o aumento da resistência

antimicrobiana, com a perda de eficácia dos antibióticos desenvolvidos no último século e a redução nas indústrias farmacêuticas de novos medicamentos (PELEG; HOOPER, 2010; RAMAN et al., 2015).

A facilidade de disseminação e persistência de bactérias resistentes são determinadas pela disponibilidade e vulnerabilidade do paciente, por pressão seletiva exercida pelos antibacterianos, pelo número de paciente colonizados ou infectados e pelo impacto da implementação e aderência da prevenção (BERRY et al., 2019; NORDMANN, 2014; SAMPAIO; GALES, 2016; TISCHENDORF; DE AVILA; SAFDAR, 2016). Isso pode ocorrer em qualquer serviço de saúde, embora seja mais frequente em instituições de cuidados intensivos, justamente por apresentarem pacientes mais vulneráveis à colonização e infecção (MÜLLER et al., 2015; RUPPÉ; WOERTHER; BARBIER, 2015; WANG et al., 2016).

2.2 Infecções Relacionadas à Assistência à Saúde (IRAS)

As IRAS são uma das complicações ou eventos adversos mais comuns em ambientes intra-hospitalares ou em qualquer outro estabelecimento de saúde, que ocorrem tanto por interação entre pacientes como pelos profissionais da área de saúde no exercício de suas atividades (CENTERS FOR DISEASE CONTROL AND PREVENTION, 2007; WORLD HEALTH ORGANIZATION, 2008). Por definição, as IRAS comprometem indivíduos após 48 horas ou mais da admissão nos estabelecimentos de saúde ou em até 30 dias após a alta (ALLEGRANZI et al., 2011; PITTET; DONALDSON, 2005).

As taxas de IRAS têm aumentado de forma ameaçadora em todo o mundo, afetando milhares de pessoas durante à assistência à saúde, especialmente em países emergentes (MCCONVILLE et al., 2017; PELEG; HOOPER, 2010; PITTET et al., 2008).

A infecção no intra-hospitalar pode ser adquirida pela contaminação cruzada entre pacientes, no ambiente hospitalar, nas intervenções médicas, como procedimentos cirúrgicos e implantes de dispositivos invasivos, ou por meio de mecanismos intrínsecos, provenientes da microbiota do paciente colonizada por cepas resistentes (GOTO et al., 2016; HAQUE et al., 2018; PITTET; DONALDSON,

2005).

As IRAS podem ser polimicrobianas, entretanto, em sua maioria são monomicrobianas com predomínio de bactérias gram-negativas, principalmente por MDR (CAI et al., 2017; GOTO et al., 2016; TABAH et al., 2012). Entre as bactérias gram-negativas, as enterobactérias se destacam pela elevada frequência (ALLEGRANZI et al., 2011; RAMAN et al., 2015; RUIZ et al., 2010). Enquanto nas IRAS, as espécies de enterobactérias mais frequentes (27% de todos os patógenos) e relevantes (70% dos gram-negativos) são a *Escherichia coli, Klebsiella pneumoniae e Pseudomonas aeruginosas* (RAMAN et al., 2015; SCHWABER; CARMELI, 2008).

Nas IRAS, as enterobactérias podem causar infecções que comprometem o trato respiratório inferior, a corrente sanguínea, o trato urinário, o intra-abdominal e o sítio cirúrgico (FORTALEZA et al., 2017; PELEG; HOOPER, 2010; RAMAN et al., 2015; RUIZ et al., 2010). E estão frequentemente relacionadas aos dispositivos médicos invasivos ou procedimentos cirúrgicos (VAN MOURIK et al., 2018).

Geralmente, as IRAS por CRE são doenças complexas que dependem de elevado consumo de materiais e de assistência especializada, além de favorecer a internação prolongada (HAQUE et al., 2018). Esses fatores, associados ao elevado número de casos de IRAS, incrementam os custos com a assistência à saúde em todo o mundo (CAI et al., 2017; HAQUE et al., 2018; PELEG; HOOPER, 2010; THADEN et al., 2017). Mesmo com muito investimento em tratamento e prevenção, ainda são muitos os danos irreparáveis, além de elevado risco de vida (HAQUE et al., 2018; PELEG; HOOPER, 2010).

Estima-se que pelo menos 20 a 30% das IRAS são evitáveis com medidas simples de prevenção, como a prática efetiva de higiene das mãos com substância à base de álcool (ARANAZ-ANDRÉS et al., 2008; HAQUE et al., 2018; PELEG; HOOPER, 2010; PITTET; DONALDSON, 2005; WANG et al., 2016). Essa atitude, isoladamente, pode resguardar vidas, além de diminuir a morbidade e os gastos com saúde, entretanto, a atuação prática depende dos assistentes de saúde (HAQUE et al., 2018).

O grande desafio das IRAS está na aplicação das estratégias de vigilância dos programas de controle de infecção, com medidas intervencionistas adequadas e

padronizadas aos sistemas de cuidados de saúde, reduzindo as complicações referente aos atendimentos dos pacientes e às mortes inesperadas (CENTERS FOR DISEASE CONTROL AND PREVENTION, 2015) PITTET; DONALDSON, 2005; VAN MOURIK et al., 2018).

Esse cenário desafiador para a saúde pública tem gerado muita preocupação com relação à segurança do paciente (CAI et al., 2017; PELEG; HOOPER, 2010; PITTET et al., 2008; WANG et al., 2016). Por isso, a precaução de danos potencialmente evitáveis tem se tornado uma prioridade de investimento na política de saúde pública, que busca divulgar a necessidade de adoção de medidas preventivas e de vigilância (HAQUE et al., 2018; VAN MOURIK et al., 2018; WANG et al., 2016).

2.2.1 Epidemiologia

As IRAS são consideradas prioridades em saúde pública, pois correspondem de 5% a 35% de todas as infecções, com taxas de infecções nosocomiais (18 a 54%) e surtos hospitalares (aproximadamente 90%) muito elevados, principalmente em pacientes com grande vulnerabilidade (COLPAN et al., 2005; VAN MOURIK, 2018; FORTALEZA et al., 2017). Segundo Aranaz-Andrés, et al. (2008), as IRAS correspondem a 25,3% de todos os eventos adversos, sendo responsável, em parte, pelo aumento do tempo de permanência e internações adicionais.

A incidência de IRAS é avaliada considerando os fatores ambientais, como desinfecção, esterilização, medidas diárias de higiene e área de isolamento; aspectos relacionados ao paciente, como idade, comorbidades e imunossupressão; e período de internação (WANG et al., 2016).

As CRE emergiram nos últimos anos e se disseminaram rapidamente pelo mundo, causando IRAS com incidência (13,2% a 89%) e mortalidade (44% a 70%) elevadas, além de aumento no tempo de internação e nos custos com a saúde, o que ameaça a segurança dos pacientes (ALBIGER et al., 2015; CORREA; FORTALEZA, 2019; FRENCH et al., 2017; HUSSEIN et al., 2017; MCCONVILLE et al., 2017; MÜLLER et al., 2015; PIRES et al., 2016; SCHWABER; CARMELI, 2008; THADEN et al., 2017; TISCHENDORF; DE AVILA; SAFDAR, 2016).

As infecções hospitalares são graves por apresentarem prevalência aumentada de bactérias resistentes e acometererm pacientes criticamente enfermos com necessidades de cateteres invasivos, ventilação mecânica, uso de antibióticos de largo espectro e longos períodos de internação (HAQUE et al., 2018; MCCONVILLE et al., 2017). A maioria dos pacientes com IRAS estão nas UTI, onde apresentam taxas de incidência (60% dos casos) e mortalidade (10 a 40% dos casos) elevadas (TABAH et al., 2012; WORLD HEALTH ORGANIZATION, 2008).

A taxa de mortalidade de IRAS depende de fatores como diagnóstico precoce e controle da infecção, comorbidade dos pacientes, tempo e escolha apropriada de antimicrobianos, avanços tecnológicos na assistência médica, tempo de hospitalização em UTI e mecanismos de resistência das bactérias (DA SILVA; TRAEBERT; GALATO, 2012; FORTALEZA et al., 2017; TABAH et al., 2012; WANG et al., 2016).

2.2.2 Fatores de Risco

Nas IRAS são muitos os fatores que aumentam a probabilidade de ocorrência de uma doença ou agravo à saúde, como idade, sexo, local de infecção, tipo de internação, internações prévias ou atuais em áreas de saúde ou em UTI e exposições aos antibióticos (COLPAN et al., 2005; PELEG; HOOPER, 2010; WANG et al., 2016).

Os principais fatores de risco que tornam os pacientes suscetíveis e vulneráveis à infecção nosocomial e à colonização são: doenças crônicas (diabetes mellitus, câncer, enfisema, insuficiência cardíaca, trauma, queimaduras, desnutrição, etc), idade avançada, terapia imunossupressora e/ou antibiótica prévia, cirurgias recente, dispositivos invasivos (ventilação mecânica, cateteres venosos centrais e de hemodiálise, sondas enterais e urinários e tubos endotraqueais), internações prolongadas e/ou em UTI (FRENCH et al., 2017; CORREA; FORTALEZA, 2019; LINARES et al., 2008; RUIZ et al., 2010; TRAN et al., 2019; WU et al., 2016).

As internações nas UTI apresentam maior incidência de IRAS em relação aos outros setores do hospital, provavelmente pela admissão de pacientes graves com necessidade de monitorização invasiva e exposição aos cuidados dos profissionais

de saúde (MCCONVILLE et al., 2017). Essas condições tornam os pacientes suscetíveis às bactérias multirresistentes, o que exige da equipe atenção criteriosa para uma identificação precoce dos processos infeciosos, a fim de minimizar os danos e os riscos (MCCONVILLE et al., 2017; WU et al., 2016).

A mortalidade aumentou significativamente nos pacientes com fatores de risco, como idade avançada, local de infecção e internação na terapia intensiva (COLPAN et al., 2005; WANG et al., 2016). Para os pacientes internados em terapia intensiva, o risco de morte ocorre mais pelas complicações infecciosas do que pelas doenças agudas que motivaram a hospitalização (GOTO et al., 2016; HAQUE et al., 2018).

2.3 Prevenção e Controle

A vigilância epidemiológica constitui-se de um conjunto de ações como coleta, análise e interpretação contínua e sistemática dos dados (HAQUE et al., 2018; SCHNEIDER et al., 2019; TACCONELLI et al., 2014). Essa proporciona conhecimento, detecção ou prevenção de qualquer mudança nos fatores determinantes e condicionantes de saúde individual ou coletiva, que são essenciais para o planejamento, a implementação e a avaliação das práticas de saúde (HAQUE et al., 2018; SCHNEIDER et al., 2019; TACCONELLI et al., 2014).

A prevenção e o controle da disseminação de bactérias MDR na assistência à saúde partem de premissas de resguardar a vida e minimizar os danos que levam a morbidades e incapacidades a longo prazo (MÜLLER et al., 2015; PITTET et al., 2008; SCHNEIDER et al., 2019).

As medidas de vigilância ativa buscam controlar a transmissão das infecções por meio dos testes de triagens nos pacientes de alto risco para colonização, isolamento de contato de pacientes infectados ou colonizados e a boa prática de higiene das mãos (GOTO et al., 2016). Enquanto, as medidas preventivas para IRAS abordam ações relacionadas com a higiene das mãos, limpeza dos ambientes e equipamentos, banhos de clorexidina e administração otimizada de antibióticos nas práticas hospitalares, na comunidade e na agropecuária (MÜLLER et al., 2015; RUPPÉ; WOERTHER; BARBIER, 2015).

Essa medidas precisam ser proativas e atuar entre fronteiras, tanto na detecção de bactérias MDR quanto nos cuidados preventivos, com finalidade de reduzir as taxas de infecções no meio hospitalar e minimizar seleção e disseminação de resistência antimicrobiana (FRIEDMAN et al., 2017; MCCONVILLE et al., 2017; MÜLLER et al., 2015).

A adequação da gestão de infecção hospitalar depende da conscientização a esses fatores de risco e da adesão às medidas preventivas estratégicas básicas, como a higiene das mãos (DA SILVA; TRAEBERT; GALATO, 2012; DERDE et al., 2014; HAQUE et al., 2018; HUSSEIN et al., 2017; TACCONELLI et al., 2014; WANG et al., 2016). Essas ações são prioridades e exigem, das agências de saúde, estratégias apropriadas para redução da incidência de infecções (SCHNEIDER et al., 2019; HAQUE et al., 2018; VAN MOURIK et al., 2018).

Contudo, a implementação destas medidas é muito complexa em qualquer lugar no mundo, pois envolve ações das políticas de saúde pública voltadas para a educação e treinamento de pessoal, além de padronização das medidas (MÜLLER et al., 2015; PITTET et al., 2008; SCHNEIDER et al., 2019).

As medidas de controle e prevenção necessitam, regularmente, de avaliações e ajustes de conduta, além de liderança administrativa, científica e comprometimento de recursos para esses fins (HAQUE et al., 2018; MOURIK, 2018; SCHNEIDER et al., 2019). Dependem também de ações de cultura de segurança com esforços multidisciplinares e de apoio direto de líderes e equipes (GOMIDES et al., 2019; GOTO et al., 2016; RAMAN et al., 2015).

Vários países, principalmente aqueles em desenvolvimento, como o Brasil, necessitam, urgentemente de adesão a essas medidas (MCCONVILLE et al., 2017; SAMPAIO; GALES, 2016).

2.4 Tratamento

As infecções graves, por bactérias resistentes aos antibióticos, apresentam elevada mortalidade e prolongamento no tempo de internação, principalmente em decorrência da escolha inadequada, atraso no início do antibiótico, uso de terapia não combinada e rápida infusão dos antibióticos (RAMAN et al., 2015; THADEN et

al., 2017; WU et al., 2016). A fim de minimizar esses efeitos adversos, recomenda-se um estudo do perfil de resistência antimicrobiana de cada instituição, com padronização da dispensação dos antibióticos, além da otimização das doses e tempo de infusão e de tratamento, (PELEG; HOOPER, 2010; RAMAN et al., 2015; RUPPÉ; WOERTHER; BARBIER, 2015).

As taxas de resistência aos carbapenêmicos encontram-se elevadas, variando em até 67,3%, principalmente no transplante de órgão sólidos e de medula óssea, nos tratamentos quimioterápicos agressivos, nos procedimentos cirúrgicos eletivos ou nas infecções adquiridas na comunidade (HUSSEIN et al., 2017; SAMPAIO; GALES, 2016; SCHWABER; CARMELI, 2008; WU et al., 2016). Portanto, restringir o uso de antibiótico de amplo espectro tem a finalidade de minimizar a propagação global da resistência antimicrobiana (FRENCH et al., 2017; PELEG; HOOPER, 2010; RAMAN et al., 2015).

Entre as classes de antibióticos utilizados nos casos de IRAS por CRE, destacam-se as polimixinas (colistina e polimixina B) como um antibiótico de resgate, apesar da farmacocinética imprópria, da nefrotoxicidade, e da chance de resistência (PELEG; HOOPER, 2010; RAPP; URBAN, 2012; SHIELDS et al., 2017).

O elevado consumo dessa classe de antibióticos, devido ao aumento na taxa de resistência aos carbapenêmicos, favoreceu o surgimento de cepas resistentes com fortes possibilidades de surtos por enterobactérias XDR (ALBIGER et al., 2015; HUSSEIN et al., 2017; SAMPAIO; GALES, 2016).

Novos medicamentos com atividade antibacteriana para CRE foram liberados, tais como doripenem e tigeciclina, com ampla atividade em infecções de tecidos moles e intra-abdominais (PELEG; HOOPER, 2010; WU et al., 2016). Além dos medicamentos que foram desenvolvidos em associações a outros preexistentes, como a ceftazidima-avibactan, com resultados promissores no manejo destas bactérias multirresistentes (RUPPÉ; WOERTHER; BARBIER, 2015).

2.5 Segurança do Paciente

A segurança do paciente, segundo as definições do *Institute of Medicine* (IOM), depende do aumento da probabilidade de desfechos desejados (AGÊNCIA

NACIONAL DE VIGILÂNCIA SANITÁRIA, 2013; KOHN; CORRIGAN; DONALDSON, 2000). Portanto, essa segurança fica ameaçada em área endêmica para CRE, pela rápida disseminação da bactéria e gravidade do processo infeccioso (RAMAN et al., 2015).

A necessidade de redução dos danos preveníveis ao paciente, durante o processo de assistência à saúde (WORLD HEALTH ORGANIZATION, 2008), resultou em várias campanhas mundiais focadas na higiene das mãos, nos cuidados que podem prevenir IRAS e nas medidas para evitar a resistência aos antibióticos (CENTERS FOR DISEASE CONTROL AND PREVENTION, 2009).

As medidas preventivas são baseadas num conjunto de ações e melhorias contínuas do ambiente, além do controle de riscos (MAGILL et al., 2014; PITTET; DONALDSON, 2005). Destacando, como seguir corretamente as normas de higiene das mãos, prescrição e administração da quimioprofilaxia antibiótica, detecção e compreensão da epidemiologia das IRAS, uso adequado de equipamentos e uma boa prática clínica (WORLD HEALTH ORGANIZATION, 2008).

Os sistemas de vigilância e as modificações nas políticas são necessários para redução das taxas de infecções hospitalares, uma vez que 20% a 30% de todas as IRAS são, provavelmente, evitáveis (RAMAN et al., 2015).

Portando, a adoção da segurança clínica, estruturada em três pilares, como: identificação de propedêutica mais segura e eficiente, garantia de implementação efetiva e condução sem erros, seriam medidas plausíveis para se obter uma assistência à saúde de alta qualidade (ARANAZ-ANDRÉS et al., 2008).

3 OBJETIVOS

3.1. Geral

Objetiva-se com o presente estudo estabelecer a prevalência de colonização e/ou infecção por CRE com seus fatores de risco e taxas de mortalidade em pacientes críticos.

3.2. Específicos

São objetivos específicos desta pesquisa:

3.2.1 Artigo 1

- Demonstrar a importância da cultura de vigilância;
- Analisar a relação entre colonização e infecção por CRE;
- Determinar os fatores de risco associados a colonização e infecção;
- Verificar o risco de mortalidade relacionada às espécies de bactérias, à exposição prévia de antibióticos e colonização por CRE.

3.2.2 Artigo 2

- Avaliar o resultado das ações do protocolo de detecção e prevenção de CRKP através das taxas e prevalências de infecção, colonização e mortalidade;
- Determinar os fatores de risco para as infecções por CRKP;
- Verificar o risco de mortalidade do CRKP.

4 ARTIGOS

4.1 Artigo 1

Title: The impact of carbapenem-resistant Enterobacteriaceae surveillance screening in a critically ill patient, a nested control case study

4.2 Artigo 2

Title: Outcomes of Infection and Carbapenem-resistant *Klebsiella pneumoniae* Mortality: An Observational Study on Detection and Prevention Protocol in Intensive Care Unit

ARTIGO 1

TITLE PAGE

Title: The impact of carbapenem-resistant Enterobacteriaceae surveillance screening in a critically ill patient, a nested control case study

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ABSTRACT

Background: Carbapenem-resistant Enterobacteriaceae (CRE) colonization is an important cause of healthcare-associated infections (HAI), morbimortality, and long-term hospital stay. This study aimed to demonstrate the importance of CRE surveillance screening and to evaluate the prevalence of invasive infections, risk factors, and mortality risk in the colonized. **Methods:** A retrospective observational case-control study nested analyzed 1,920 patients from the CRE screening surveillance protocol, admitted to the adult ICU in southeastern Brazil, from January / 2014 to December / 2018. **Results:** There were 297 (15.47%) colonized patients, with one for every six patients. In these colonized, 20.54% presented invasive infection, with 79.31% of Klebsiella pneumoniae. The colonization-infection ratio demonstrated the important role of surveillance screening. The mortality risk was significantly higher among the colonized, colonized-infected, Enterobacter cloacae colonization, and previous cephalosporins exposure. **Conclusions:** The early detection of colonization through CRE surveillance screening proved an important tool to contain the CRE spread. However, observation over the years has not shown effective control of colonization and infection. CRE colonization and colonization-infection were highly prevalent, as well as mortality rates. In short, active CRE surveillance screening is essential, but its impact depends on effective actions in the implementation of preventive measures and feedbacks between the teams.

Keywords: Carbapenem-Resistant Enterobacteriaceae; Health Care Associated Infections; Intensive Care Units; Surveillance; Anti-Infective Agents.

INTRODUCTION

The carbapenem-resistant Enterobacteriaceae (CRE) Colonization is an important cause of infection and one of the main foci of dissemination both in the hospital and in the community [1,2].

The CRE dissemination occurred alarmingly around worldwide due to the low response to available therapies and the difficult management of empirical antibiotics [3,4]. Consequently, there was a high prevalence of colonization and infection by CRE, followed by a serious threat to the exercise of public health, there was a high prevalence of CRE colonization and infection with serious threats to the exercise of public health [5-10].

The gastrointestinal tract's microbiota is the main CRE reservoir in asymptomatic carriers, followed by the oropharynx, skin, and urine [11,12]. These reservoirs are colonization focus considered essentials in the CRE spread inside and outside the hospital environment [11,13-16].

The antimicrobial resistance genes for enterobacteria emerged in the past two decades [2,7,9], due to the competitive selection pressure caused by the wide use of broad-spectrum antibiotics, especially in intensive care units (ICU) and long-stay hospitals [1,6,8,11,17,18].

Health units have individual microbial biosystems because they use specific antibiotic dispensing rules, but not optimized, for each type of infection, providing high rates of resistance to third-generation cephalosporins (10 to 97%) [13,17] For this reason, the presence of bacteria with multiple resistance in healthcare-associated infections (HAI) is more relevant [8,13,19-22].

CRE colonization can be acquired directly after antibiotics exposure or due to

cross-transmission between patients and healthcare professionals [2,14]. The patients most susceptible to CRE colonization are the severely ill and with comorbidities, invasive devices, previous antimicrobial exposure, and long-term hospitalization [8,9,22,23].

The active surveillance screening to CRE is an important mechanism for interrupting the spread process [4,24]. It allows early implantation of protective measures through contact isolation, positively impacting public health [9,23,25]. According to the CDC, rectal swab detection is considered a preferable surveillance screening method [25].

The patients CRE colonized have a high probability of developing a subsequent infection which may be associated with bacteremia, and to cause high morbidity, and mortality (30 to 75%) [7,8,10,17,24,26-28].

The CRE HAI are serious because frequently presented failures therapeutic, which result in long-term hospital stays, and increased hospital costs [10,13-15].

According to updated data from the Centers for Disease Control and Prevention (CDC), mortality caused by antimicrobial-resistant infections has decreased in the United States between 2013 and 2019 [29]. However, the number of registered infections caused by resistant bacteria is still high, with over 2.8 million cases/year and 35,000 deaths/year [29].

This research aimed to demonstrate the importance of CRE active surveillance screening in the ICU and to verify the prevalence of CRE invasive infections between CRE-colonized and control patients. Besides, to determine the risk factors and mortality rates related to strains, previous antibiotics exposure, and type of CRE colonization.

METHODS

Study Design

A retrospective observational nested case-control cohort study on CRE colonized patients was carried out in an adult ICU with 30 beds of a public tertiary hospital in southeastern Brazil.

The study included patients over 12 years old, hospitalized in adult ICU, from January 2014 to December 2018. They were subjected to the CRE detection and prevention protocol, decided by the Hospital Infection Control Commission (CCIH), in April 2011 (Minutes 09/2011). The resolution follows guidelines from the Brazilian National Health Surveillance Agency (ANVISA) [30], and antimicrobial resistance criteria from the World Health Organization (WHO) [31], and the Center for Disease Control and Prevention (CDC) [25]. The CRE measures protocol determines the detection with surveillance screening by rectal swab collections at admission and weekly. Besides, prevention measures as strict contact isolation in a properly identified private room, rapid and safe de-hospitalization of patients, restricted use of probes and catheters, protection, and hygiene of health professionals, cleaning of the environment and rational dispensing of antibiotics.

This research was approved by the Research Ethics Committee (CEP) under number 1.638.131.

Data Collection

The CRE surveillance protocol records, from the period 2012 to 2018, were collected adding up to a total of 2,126 records. After review, patients who were discharged or died before the first rectal swab collection, as well as those who had

incomplete or double-filled records were excluded.

The final analysis of the protocol sheets allowed to include 1,920 patients from the CRE surveillance protocol, from January 2014 to December 2018. The demographic, clinical, and microbiological data from the individual records were collected. Such as identification record, age, sex, clinical diagnosis of admission, disease severity score (SAPS II - Score Simplified Acute Physiology), presence of invasive devices, identification of enterobacteria and other microorganisms, antimicrobials used, results of rectal swabs for CRE, and dates of admission and outcome, discharge, or death.

The patients' record provided information regarding the length of ICU stay, long-term mechanical ventilation (over 10 days), long-term hemodialysis catheters (over 15 days), antibiotics exposure 30 days before the colonization and/or infection, and late death (30 days after admission). Some of the variables were stratified according to observed averages, such as younger (13 to 54 years old) and older (55 to 97 years old) age groups, low (16 to 62) or high (63 to 217) disease severity scores (SAPS II), and short-term (1 to 21 days) or long-term (22 to 175 days) ICU stay.

The infected patients were clinically diagnosed and tested positive for CRE cultures, according to the CDC's National Healthcare Safety Network (CDC/NHSN's) infection guidelines [32]. The clinical and surveillance culture samples were subjected to identification and susceptibility tests using VITEK2's automated system (BioMérieux, France) according to Clinical and Laboratory Standard Institute (CLSI) guidelines [33].

Statistical Analysis

The clinical data were registered in frequency and the continuous variables normally distributed were expressed as mean with standard deviation and compared by the *Student* t-test. The Shapiro-Wilk test determined the normality of quantitative variables. Pearson's chi-square test ($\chi 2$) or Fisher's exact test analyzed the colonized and non-colonized samples for infection and determined the risk factors for colonization. The risk factors that were statistically relevant ($p < 0.05$) were submitted to the multivariate logistic regression test to determine the effect of all risk factors on the colonized and controls, and to the multinomial logistic regression test to determine the influence of factors on colonized and colonized-infected by CRE in relation to controls. Multiple Cox regression, the Kaplan-Meier method, and the log-rank test were used to estimate survival by comparing curves among the colonized, colonized-infected, and control groups. Multiple Cox regression was also used to calculate the proportional hazards of CRE microorganism colonization and previous antibiotic exposure to colonization. All analyses adopted a significance level (α) less than 5% (p-value <0.05). The strength of association between the explanatory variables and the response was assessed by calculating the OR with a 95% confidence interval (95% CI). The statistical tests were carried out in the SPSS (Statistical Package for Social Sciences) software for Windows, version 21.0 (IBM-SPSS Inc, Armonk, NY).

RESULTS

Among all 1,920 patients, males predominated (65.31%) over females (1.88:1), with a mean age of 52.42 ±19.34 years old (range from 13 to 97 years old). Discharge (68.12%) was a more predominant outcome than death (31.87%). SAPS ranged from 16 to 131, with a mean of 62.19 ±18.73. The mean length of hospital

stay was 21.03 ±18.12 days (variation of 1 to 175 days).

A total of 3,154 rectal swabs were collected. From those, 2,807 were negative for CRE in 1,623 patients, with a range of 1 to 15 swabs/patient (mean of 1.74), and 344 were positive (10.91%) in 297 patients, with a range of 1 to 3 positive swabs/patient (mean of 1.16). *Klebsiella pneumoniae* predominated (83.16%) among patients, followed by *Enterobacter cloacae* (9.76%), *Escherichia coli* (4.38%), *Enterobacter aerogenes* (1.34%), *Serratia marcescens* (0.67%), *Enterobacter gergoviae* (0.34%), and *Serratia fonticola* (0.34%). Three patients had 2 rectal swabs with isolated CRE with different microorganisms. The first swab identified *Klebsiella pneumoniae,* and the second swab showed two *Enterobacter cloacae* and one *Serratia fonticola*.

Patients were categorized into two samples: 297 (15.47%) colonized patients, including the colonized-infected (positive surveillance screening), and 1,623 (84.53%) control patients, non-colonized for CRE (negative surveillance screening). In colonized and control patients, respectively, males predominated (66.32% and 65.12%) over females (1.97:1 and 1.87:1) and the discharge (67.34% and 68.26%) in relation to deaths (2.06: 1 and 2.15: 1). The sample of colonized CRE showed statistically significant differences in relation to the control for the SAPS mean 65.54 ± 17.96 (p 0.01), with a range from 16 to 127, and length of hospital stay of 33.40 ± 24.47 days (p <0.001), with an interval of 3 to 175 days. The mean age was of 53.85 ± 19.37 years (p 0.167), range from 14 to 97 years, without statistical difference.

The CRE invasive infections were present in 61 (20.54%) of the 297 colonized patients and in 51 (3.14%) of the 1,623 control patients. Among the colonized-infected, the following strains of CRE predominated in different collection sites: *K.*

144 *pneumoniae* (81.96%) in urine, blood, tracheobronchial secretion, tissue secretion; *E.*
145 *cloacae* (16.39%) in blood, central venous catheter tip, and tissue secretion; *E. coli*
146 (4.92%) in urine and blood. The other CRE, included *S. mascescens* (1.64%) in
147 urine, *E. aerogenes* (1.64%) in blood, and *E. gergoviae* (1.72%) in tracheobronchial
148 secretion, were not statistically different compared to the control. Clinical infections
149 caused by two strains in different cultures were identified in four patients colonized by
150 *K. pneumoniae*. In that case, two patients had *K. pneumoniae* with *E. cloacae*; one
151 patient had *K. pneumoniae* with *E. coli*; and the other had *K. pneumoniae* with *E.*
152 *aerogenes*. In one patient colonized by *E. coli* was identified an invasive infection by
153 *E. coli* with *E. cloacae*.
154 The colonization and infection relation over years of this research
155 demonstrated a high detection, such as in 2014 one infected for 3.5 cases, 2015 [1
156 for 2.4]; 2016 [1 to 3.6]; 2017 [1 to 8.3] and 2018 [1 to 7.2]. Thus, it was possible to
157 make an analysis of the colonized and infected ratio for each year of this research
158 (Figure 1).
159 CRE clinical invasive infection with by the same colonization microorganisms
160 occurred in 53 (17.84%) of the 297 colonized patients, of which 48 (90.56%) were K.
161 pneumoniae. Pearson's chi-square test ($\chi 2$) or Fisher's exact test of colonized and
162 CRE infected patients demonstrated an association of the variables with a high
163 chance of patients colonized by CRE presenting infection with these strains (Table 1).
164 The independent variables were analyzed using Pearson's chi-square test ($\chi 2$)
165 or Fisher's exact test to check the risk factors for colonization, followed by a
166 multivariate logistic regression analysis of the variables that showed a statistically
167 significant difference ($p < 0.05$) (Table 2).

The comparative analysis of risk factors between colonized and colonized-infected in relation to controls was carried out through the multinomial logistic regression of the risk variables with greater relevance in the univariate analysis (p <0.05) (Table 3).

A predominance of CRE strains in the invasive devices of colonized-infected patients was verified by multinomial logistic regression. The strains included *K. pneumoniae* in long-term hemodialysis catheters (OR [95%CI]: 2.387 [1.187-4.799] p 0.015), tracheotomy (3.262 [1.093-9.733] p 0.034), and long-term mechanical ventilation (5.931 [1.484-23.705] p 0.012). There was also *E. cloacae* in long-term hemodialysis catheters (4.624 [1.274-16.782] p 0.020).

A multiple Cox regression evaluated the survival rate during the colonization period among patients CRE-colonized by *K. pneumoniae* (OR [95%CI]: 2.206 [1.468-3.316] p <0.001), *E. cloacae* (5.173 [2.372-11.281] p <0.001), and other CRE (*E. aerogenes*, *E. coli*, *S. marcescens*, *E. gergoviae*, and *S. fonticola*). The other CRE bacteria were grouped since their individual analysis was statistically insignificant (1.398 [0.640-3.057] p 0.487) (Figure 2).

A multiple Cox regression was conducted to analyze the mortality risk in colonized patients with previous antibiotics exposure (Figure 3). The mortality of patients who were colonized 30 days after the use of the antibiotics showed statistically significant differences for the classes of aminopenicillins (OR [95%CI]: 3.452 [1.398-8.523] p <0.007) and other antibiotics classes grouped, such as carbapenems, cephalosporins, and fluoroquinolones (1.829 [1.078-3.102] p 0.025), compared to the control group.

The survival probability estimated by the Kaplan-Meier method demonstrated

higher mortality in colonized-infected and colonized patients compared to controls. Survival curves compared by the log-rank test demonstrated a statistically significant difference ($p < 0.001$) (Figure 4). Multiple Cox regression analyzed the death variable after 30 days of inpatient stay among the CRE-colonized. The results demonstrated a high mortality risk with significant statistical differences for the colonized (OR [95%CI]: 2.356 [1.547-3.587] $p < 0.001$) and colonized-infected (2.000 [1.187-3.368] $p < 0.001$).

DISCUSSION

Hospital environments can amplify the transmission of resistant strains by easy spread, increasing chances of infection-related morbidity and mortality, which threaten human health [34]

Patients colonized by multidrug-resistant bacteria are considered important reservoirs since they favor horizontal transmission of these microorganisms in hospitals [6,16]. In addition to the responsibility of healthcare teams, limited resources for CRE surveillance screening in underdeveloped countries is an additional concern for implementation measures of the infection control and prevention [35,36]. There is still no consensus in the literature about what would be the best method for detecting colonization, even though rectal swab collections are sensitive and have good correlation [15]. Therefore, it was considered the main screening method for active surveillance screening [25].

The positivity rate of CRE surveillance screening by rectal swab collections in the literature was 10.1%, with a predominance of *K. pneumoniae* (7.9% to 98.7%), followed by *E. cloacae* (22.0%), *E. coli* (20.0% to 82.1%), and other CRE (5.0%) [3,4,12,22,36-38]. In this study, CRE surveillance screening was carried out by rectal

swab with a positivity of 10.91% of collections and predominant strains were *K. pneumoniae* (84.17%), *E. cloacae* (9.76%), and *E. coli* (4.38%).

Interventionist measures by healthcare teams have been constant in multifaceted programs seeking control of CRE intra-hospital transmission [39]. The literature has shown colonization rates of 8.8% to 18.9% in inpatients staying in long-term units and 28% in transplant units [12,16,22,36]. This research highlights a high colonization rate (15.47%) in the sample, where identified the presence of at least 1 colonized patient for every 6 ICU inpatients.

The role of infection and colonization prevention goes beyond the identification of carriers through surveillance screening, it also depends on continuous efforts to achieve multi-professional adherence in protective isolation, hand hygiene, environmental cleaning, and appropriate antibiotic dispensation [2,25].

In 2016, in this ICU of the public hospital in southeastern Brazil, a study out on safety culture analysis, using the Safety Attitudes Questionnaire (SAQ) as an assessment tool of the multi-professional team, was carried [40]. The conclusion of the safety culture study demonstrated reliable and significant results in the safety perception, with attitudes weakened in the perception of management, working conditions, and communication failures [40]. This research observed relevant data on colonization and infection rates and demonstrated the great importance of surveillance screening to implement preventive measures early. Even so, the infection and colonization rates of this ICU were high during the research period.

Critically ill patients colonized are more prone to developing an invasive infection with broad resistance to available antibiotics [28]. However, the disease's severity varies according to the pathogen's virulence, the host's potential defense,

and exposure to medical procedures [12,22,41]. According to the literature, colonized have a high chance of developing an infection (OR 2.06 p 0.040) with rates ranging from 7.6 to 86.4% [3,7,10,12,26,27]. In infections of the colonized there was a predominance *K. pneumoniae*, followed by *E. coli*, *K. Oxytoca* and *E. cloacae* [3,4,6,9,12,16]. In this research, clinical CRE infection was present in 20.54% of colonized patients with an infection chance of 7.967 ($p < 0.001$). *K. pneumoniae*, followed by E. cloacae, predominated on urinary, bloodstream, lung, and tissue infections.

The risk factors that make the critical patient susceptible to colonization by CRE are several, such as tracheostomy (OR 4.8 p <0.0001), enteral feeding tube (OR 3.3 p 0,0001), long-term hospital stay (OR 3.8 p 0.045), previous carbapenems exposure (OR 2.54 p <0.05), and invasive procedures (OR 2.18 p <0.05) [4,6,9,12,22,25]. This research also revealed multiple risk factors for colonization, including long-term mechanical ventilation (OR 1.624 p 0.019) and previous exposure to aminopenicillins (OR 5.204 $p < 0.001$), carbapenems (OR 3.703 p 0.017), cephalosporins (OR 12.036 $p < 0.001$), and fluoroquinolones (OR 5.238 p 0.012).

CRE colonization is a pathogenic condition considered a strong determinant for the development of infection [3,6,22,26]. Some risk factors are facilitators in colonized patients, including previous use of antibiotics, such as fluoroquinolones (OR 3.04 p 0.037), mechanical ventilation, non-surgical invasive medical procedures (OR 2.18 p <0.05), endoscopy or colonoscopy (OR 3.7 p 0.02), previous hospitalizations, and long-term ICU stay (OR 7,45 p 0.023) [3,6,12,22,26,42]. This research found that risk factors for infection are similar to those for colonization but

more prevalent in long-term use of hemodialysis catheters (OR 2.490 [p 0.014]), long-term mechanical ventilation (OR 6.731 p 0.002), and previous exposure to antibiotics like aminopenicillins (8.745 p 0.001), carbapenems (OR 9.223 p 0.003), cephalosporins (OR 35.021 p < 0.001), and fluoroquinolones (OR 15.114 p 0.001).

The identification of modifiable risk factors and of the antimicrobial resistance profile in hospital units allows obtaining positive results of the protective measures with consequent reduction of the mortality [6,7,12]. Among the modifiable risk factors, the predominance of infection in invasive devices stands out in this research, such as by *K. pneumoniae* (81.96% of the colonized-infected) in long-term mechanical ventilation, tracheotomy, and long-term hemodialysis catheters; and by E. cloacae (16.39% of the colonized-infected) in long-term hemodialysis catheters, with a significantly higher mortality rate than that of other CRE.

The antibiotic dispensing programs are responsible for choosing the class, optimizing the dose, and delimiting the antibiotic use time [21,43]. These measures assist in the therapeutic responses of HAIs and in reducing the selection of drug-resistant microorganisms [44]. The importance of this appropriate control can be seen in the results of this research, in which the mortality risk was significantly higher in patients with previous aminopenicillins use and other antibiotic classes, such as carbapenems, cephalosporins, fluoroquinolones and polymyxins.

Among the most important adverse outcomes of the colonized patient, infection stands out and, on the other hand, mortality with variations in the literature from 27.5% to 41% [3,12,18]. This study observed higher mortality in the colonized-infected, followed by the colonized.

CONCLUSION

The early detection of colonization through the CRE active surveillance screening demonstrated to be an important tool for the implementation of the necessary measures to contain the spread of these multi-resistant microorganisms. However, observation over the years has not shown effective control of both colonization and infection. The colonized patients had a high chance of infection, and subsequently those colonized-infected had a higher risk of mortality. Colonization and colonization-infection presented known risk factors that can be modified through daily checking for infection signs in catheters, the daily awakening of the patients to disconnection the mechanical ventilation, early removal of the catheters and tubes, and antibiotic dispensing programs. In short, CRE active surveillance screening is essential, but its impact depends on effective actions in the implementation of preventive measures and feedbacks between the teams.

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[2]CONFLICT OF INTERESTS: No conflict

AUTHORS' CONTRIBUTION LIST

These authors contributed equally to this study:

(1) study conception and design, or data acquisition, or data analysis and interpretation; (2) writing the article or critical review for important scientific content; (3) final approval of the version to be submitted.

Mabel Duarte Alves Gomides e Geraldo Sadoyama.

These authors also contributed to this study:

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(3) final approval of the version to be submitted

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REFERENCES

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[2] **Conflict of interests:** Mabel Duarte Alves Gomides: No conflict; Astrídia Marília de Souza Fontes: No conflict; Amanda Oliveira Soares Monteiro Silveira: No conflict; Anderson Luiz Ferreira: No conflict; Geraldo Sadoyama: No conflict.

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TABLES

Table 1 – Bivariate analysis of the sample risk develop of invasive clinical CRE infection

Infection	CRE colonized N (%)	Controls N (%)	OR (95% CI)	p
Sim	61 (20.54)	51 (3.14)	7.967	
Não	236 (79.46)	1572 (96.86)	(5.361-	<0,001
Total	297	1623	11.841)	

CRE = *Carbapenem-resistant Enterobacteriaceae*, N = number of patients, OR = Odds Ratio, 95% CI = confidence interval, p = test significance

Table 2 – Bivariate and multivariate analysis of risk factors for CRE colonization in relation to non-colonized patients

Variables	CRE colonized N (%)	Non-colonized N (%)	Bivariate		Multivariate	
Total no. of patients	N 297 (15.47)	N 1623 (84.53)	OR (95% CI)	p	OR (95% CI)	p
Age range (55 to 97 years)	159 (53.54)	804 (49.54)	1.174 (0.916-1.504)	0.208	-	-
Gender (Males)	197 (66.33)	1057 (65.13)	0.948 (0.730-1.231)	0.740	-	-
SAPS (63 to 217)	172 (57.91)	759 (46.77)	1.566 (1.220-2.012)	0.001	0.733 (0.558-0.965)	0.027
ICU stays	175 (58.92)	500 (30.81)	3.222	<0.00	1.099	0.614

(22 to 175 days)			(2.499-4.154)	1	(0.762-1.585)	
Clinical diagnosis at ICU admission	N (%)	N (%)	OR (95% CI)	p	OR (95% CI)	p
Septic shock	26 (8.75)	134 (8.26)	1.066 (0.687-1.655)	0.733	-	-
Accute breathing insuffiency	30 (10.10)	123 (7.58)	1.370 (0.900-2.085)	0.161	-	-
Neoplasm	22 (7.41)	99 (6.10)	1.232 (0.762-1.989)	0.366	-	-
Postoperative	26 (8.75)	150 (9.24)	0.942 (0.609-1.457)	0.913	-	-
Lower levels of consciousness	43 (14.48)	270 (16.64)	0.848 (0.599-1.202)	0.393	-	-
Infectious Syndrome	16 (5.39)	51 (3.14)	1.755 (0.987-3.121)	0.059	-	-
Inflammatory Syndrome	18 (6.06)	95 (5.85)	1.038 (0.617-1.745)	0.893	-	-
Metabolic Syndrome	20 (6.73)	77 (4.74)	1.450 (0.872-2.410)	0.151	-	-
Trauma	96 (32.32)	624 (38.45)	0.765 (0.588-0.955)	0.050	-	-
Invasive devices	N (%)	N (%)	OR (95% CI)	p	OR (95% CI)	p
Central venous catheter	290 (97.64)	1474 (90.82)	4.188 (1.942-9.030)	<0.001	1.972 (0.863-4.507)	0.107
Long-term hemodialysis catheter	41 (13.80)	91 (5.61)	2,696 (1.822-3.989)	<0.001	1.225 (0.779-1.928)	0.379
Tracheostomy	210 (70.71)	638 (39.31)	3.727 (2.848-4.877)	<0.001	0.617 (0.406-0.939)	0.024
Long-term MV	218 (73.40)	710 (43.75)	3.548 (2.694-4.674)	<0.001	1.624 (1.085-2.430)	0.019
Long-term urethral catheter	282 (94.95)	1439 (88.66)	2.404 (1.399-4.131)	0.001	1.186 (0.646-2.177)	0.583
Enteral feeding tube	268 (90.24)	1266 (78.00)	2.606 (1.746-3.891)	<0.001	1.315 (0.848-2.038)	0.221
Long-term gastric tube	38 (12.79)	115 (7.09)	1.924 (1.303-2.841)	0.002	1.023 (0.664-1.575)	0.919

Previous antibiotics exposure	N (%)	N (%)	OR (95% CI)	p	OR (95% CI)	p
Aminopenicillins	14 (4.71)	10 (0.62)	7.980 (3.210-18.141)	<0.001	5.204 (2.244-12.066)	<0.001
Carbapenems	7 (2.36)	7 (0.43)	5.572 (1.940-16.005)	0.003	3.703 (1.259-10.893)	0.017
Cefalosporins	38 (12.79)	14 (0.86)	16.862 (9.011-31.555)	<0.001	12.036 (6.225-23.271)	<0.001
Fluoroquinolones	6 (2.02)	4 (0.25)	8.345 (2.341-29.755)	0.002	5.238 (1.443-19.009)	0.012

CRE = *Carbapenem-resistant Enterobacteriaceae*, N = number of patients, OR = Odds Ratio, 95% CI = confidence interval; p = test significance, SAPS = Score Simplified Acute Physiology, MV = MV = mechanical ventilation, ICU = intensive care unit.

Table 3 – Multinomial regression analysis of risk factors for colonization and colonization/infection by CRE as compared to controls

Variables	Colonized (N 236)			Colonized-infected (N 61)		
	OR	95% CI	p	OR	95% CI	p
SAPS (63 to 217)	1.433	1.070-1.921	0.016	1.127	0.638-1.990	0.681
Central venous catheter	2.061	0.859-4.946	0.105	1.467	0.175-12.296	0.724
Long-term hemodialysis catheter	0.980	0.588-1.632	0.937	2.490	1.206-5.141	0.014
Tracheostomy	1.472	0.935-2.316	0.095	2.703	0.976-7.489	0.056
Long-term MV	1.329	0.864-2.044	0.196	6.731	2.008-22.556	0.002
Long-term urethral catheter	1.067	0.576-1.975	0.836	2.756	0.448-31.467	0.222
Enteral feeding tube	1.348	0.847-2.148	0.208	1.098	0.364-3.313	0.868
Long-term gastric tube	0.873	0.536-1.421	0.585	1.621	0.797-3.296	0.182
Aminopenicillins	4.513	1.820-11.189	0.001	8.745	2.473-30.918	0.001
Carbapenems	2.565	0.728-9.034	0.143	9.223	2.125-40.037	0.003
Cefalosporins	8.363	4.085-17.122	<0.001	35.021	14.224-86.222	<0.001

Fluoroquinolones	3.230	0.708-14.742	0.130	15.114	3.012-75.842	0.001
Long- term ICU stays	1.365	0.914-2.038	0.128	0.447	0.209-0.955	0.038

CRE = *Carbapenem-resistant Enterobacteriaceae*, N = number of patients, OR = Odds Ratio, 95% CI = confidence interval; p = test significance, SAPS = Score Simplified Acute Physiology, MV = MV = mechanical ventilation, ICU = intensive care unit, N controls = 1623.

FIGURES

Figure 1 - Analysis of infection rates prior to colonization and total colonized and infected.

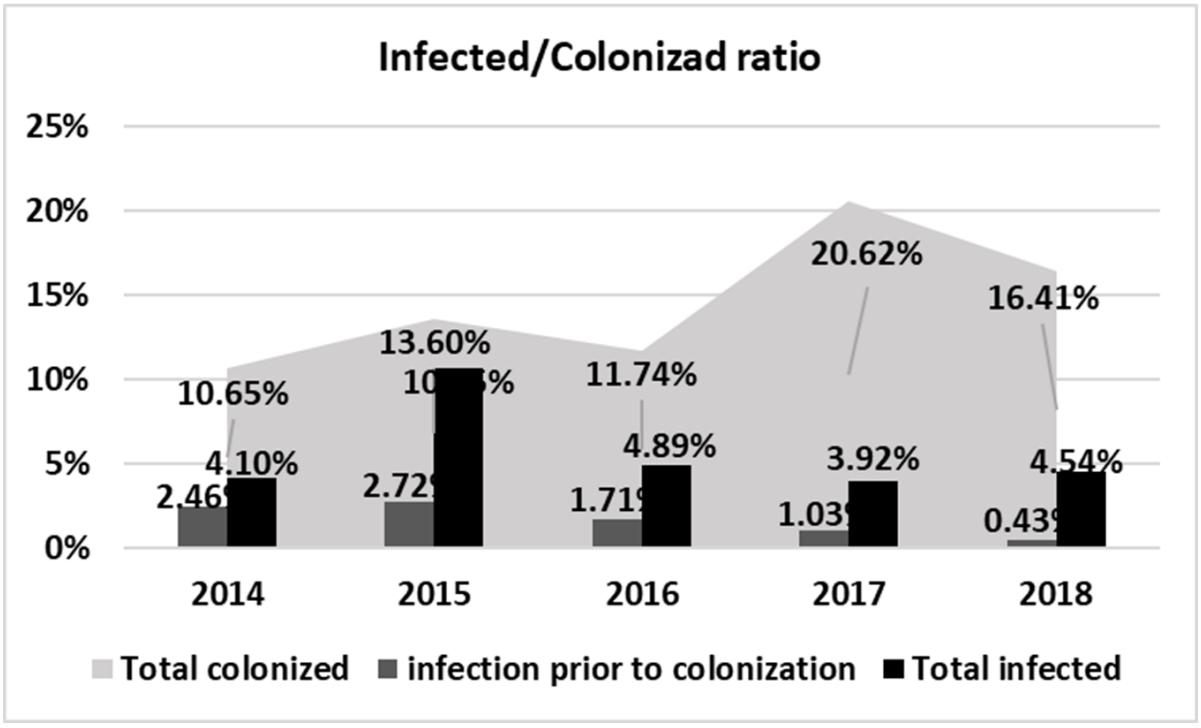


Figure 2 – Multiple Cox regression for analysis of the estimated survival in CRE colonized bacteria compared to controls

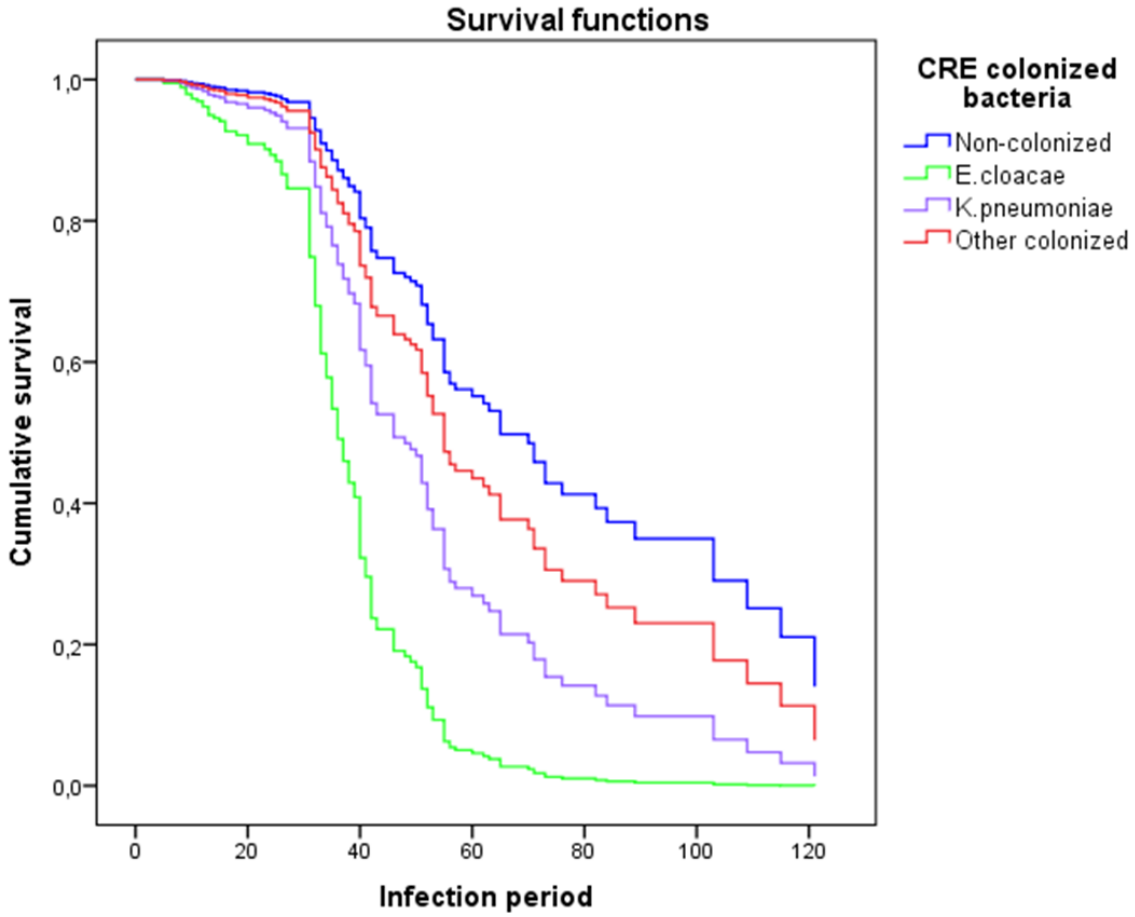


Figure 3 – Multiple Cox regression for analysis of risk estimation for previous antibiotics exposure in CRE colonized compared to controls

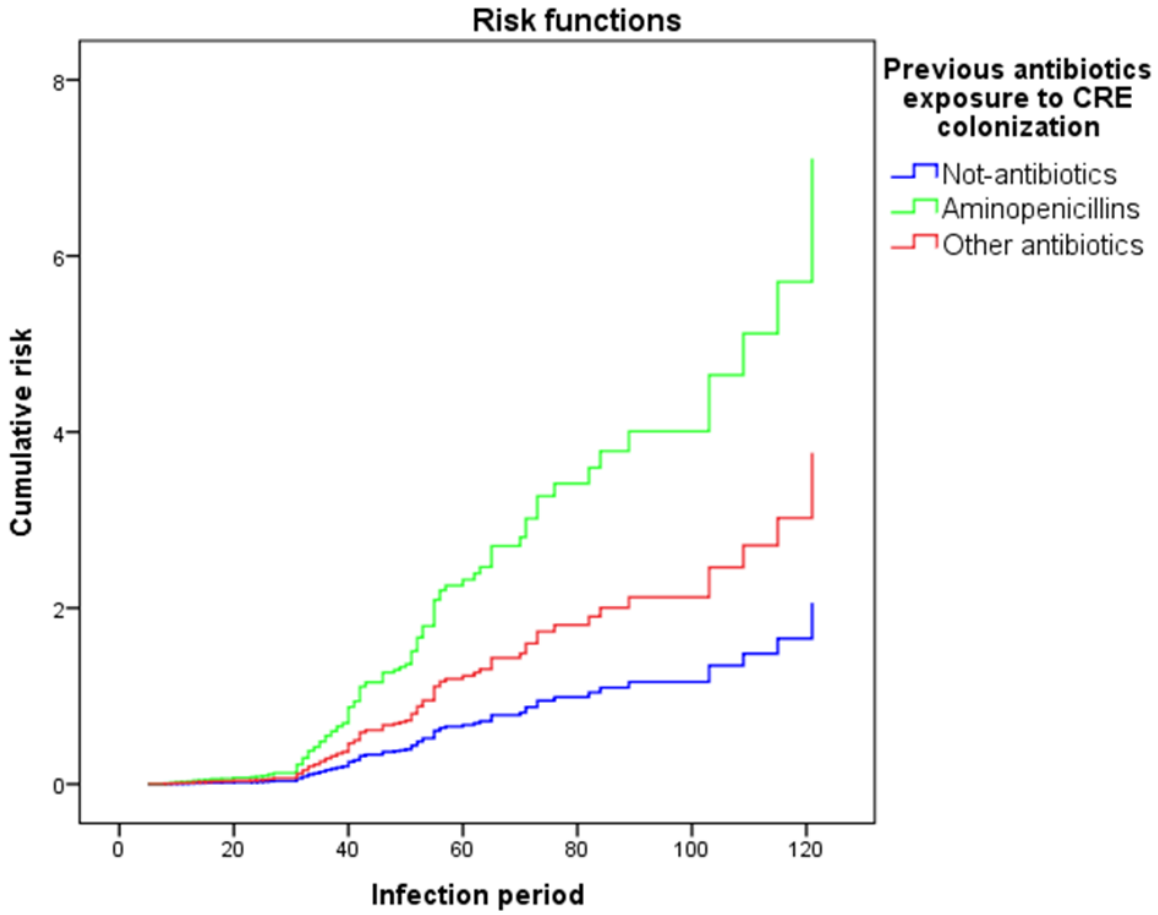
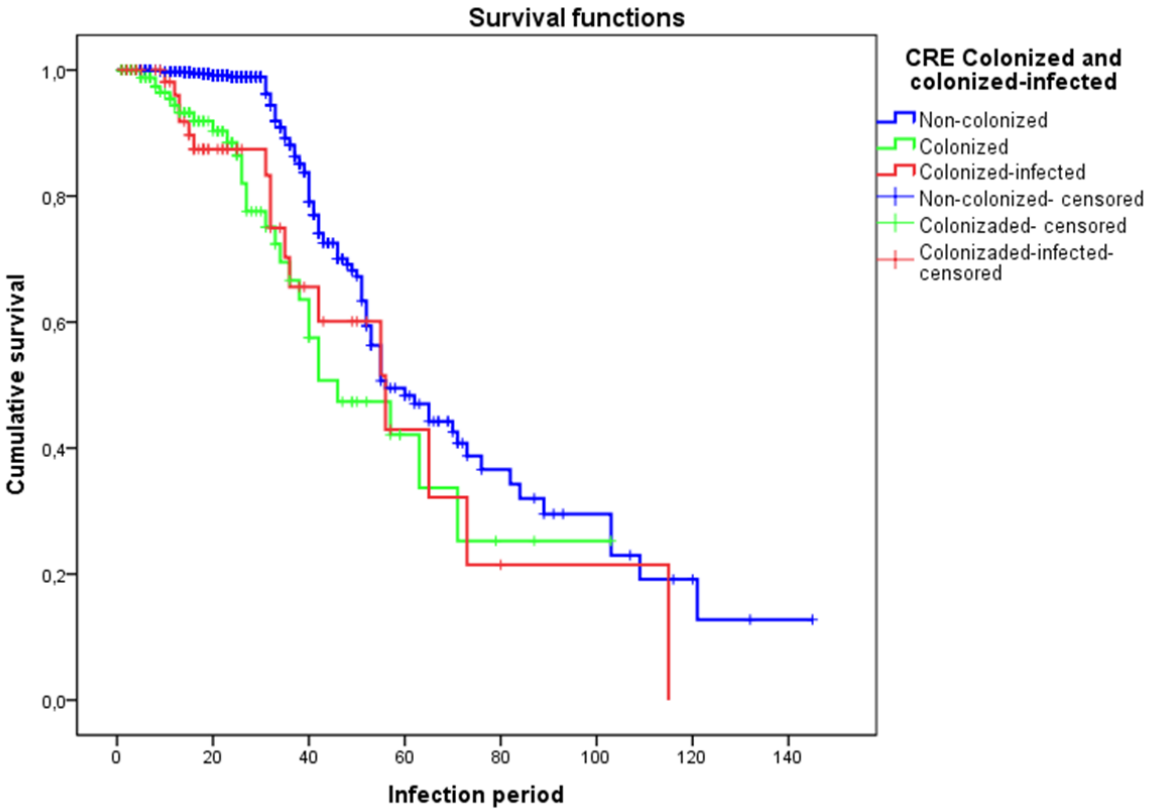


Figure 4 – Kaplan-Meier test for estimated survival of the colonized, colonized-infected patients in relation to control



ARTIGO 2

Title page

Title: Outcomes of Infection and Carbapenem-resistant *Klebsiella pneumoniae* Mortality: An Observational Study on Detection and Prevention Protocol in Intensive Care Unit

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Abbreviated title: Outcomes of Infection and Mortality in ICU

Word count: 2981 words

ABSTRACT

Objective: Evaluate the outcomes of infection and CRKP mortality based on the CRE detection and prevention protocol in the ICU, risk factors and mortality risk

Design. Retrospective observational nested case-control cohort study.

Setting. Adult ICU of a public tertiary hospital in southeastern Brazil.

Patients. 2,126 medical records of the CRE detection and prevention protocol admitted to the ICU, from 2012 to 2018, were collected. Clinical and microbiological data of 1,920 patients above 12 years old, from 2014 to 2018 were evaluated.

Methods: The data of the medical records included in the CRE detection and prevention protocol, as deliberated by the Hospital Infection Control Committee. It determines active surveillance screening, through weekly rectal swab collection.

Results: Samples of control patients (95.7%) and CRKP infected (4.3%) were analyzed for annual prevalence for colonization, infection, and mortality showed a CRKP clinical profile of the ICU. The main risk factors for CRKP infections were colonization (OR 4.283 [p<0,001]), and previous antibiotics exposure (OR 5.955 [p<0,001]). Antibiotics used prior to infection, such as aminopenicillins (OR 11.676 [p<0,001]) and cephalosporins (OR 8.707 [p<0,001]), demonstrated important effects for CRKP infection. CRKP mortality presented a high probability (OR 3.073 [p<0,01]) and the analysis of infection rates showed higher in patients with more than 30 days of hospitalization.

Conclusions: CRKP are important causes of infections and mortality in the ICU. The early detection of colonization through CRE surveillance screening along with clinical cultures proved to be decisive to outline a panorama of CRKP colonization and infection. These data are strategic for the early implementation of containing measures of the spread of resistant and preventive bacteria for new infections and colonizations. However, over the five years, it was observed that the rates and prevalence of CRKP infection and colonization remained high.

Keywords: Carbapenem-resistant *Enterobacteriaceae*; *Klebsiella pneumoniae*; Healthcare-associated Infections; Surveillance; Infection control; Anti- Bacterial Agents; Protocols.

INTRODUCTION

The carbapenem-resistant Klebsiella pneumoniae (CRKP) infections are the most frequent among the carbapenem-resistant enterobacteria (CRE) and are on the rise worldwide, despite the implementation of infection prevention and control (IPC) measurements.[1,2] The other bacteria as *Escherichia coli*, *Enterobacter sp.*, *Citrobacter sp.*, *Serratia marcescens*, and *Klebsiella oxytoca* are less frequencies.[1,3]

Klebsiella pneumoniae is commonly present in intestinal microbiota, and sometimes it acquires antimicrobial resistance genes from another bacterium or developed select after the use of broad-spectrum antibiotic exposure.[4,5] Antimicrobial resistance is more frequent in gram-negative bacteria, such as *Klebsiella pneumoniae*, commonly resistant to carbapenems and colistin.[6-8]

CRKP was isolated in the United States in 1996, and it easily spread worldwide through the public health care system and community due to its high dissemination capacity and few therapeutic options.[9-10] It is considered the most frequent species in most health services, especially in health units intensive care (ICU), and is related to catheter-associated bloodstream infections, urinary tract, mechanical ventilator-associated pulmonary, and the surgical site.[1,7,11-13] Among the highly relevant factors for the acquisition of resistance genes is the inappropriate antimicrobial treatment that allows the acquisition of resistance genes by colonizing bacteria.[3,14]

The CRKP are important causes of healthcare-associated infections (HAI) with high prevalence worldwide and related with significant morbidity and mortality, resulting in a long length of stay and high hospital costs.[1,2,4,5,7,9,15]

The transmission of resistant bacteria occurs predominantly inside the hospital environment and is responsible for HAI.[7] They are transmitted mainly through contact between patients and healthcare professionals or through contaminated surfaces and

fomites, or in rare cases, through an infected organ transplant.[7,16-19]

The critical patients are more susceptible to multidrug-resistant strains because they are exposed to several risk factors, such as invasive devices, long length of hospital stay, CRE colonization, and previous different antibiotics exposure.[5,20]

The multidrug-resistant strains, generally, have no response to conventional therapy with β-lactam class and other antimicrobials due to the various resistance mechanisms present among bacteria.[2,21] They can produce resistance through the hydrolysis of carbapenems in the acquisition of carbapenemase gene (Metallo-β-lactamases: VIM, IMP and NDM, and Oxa-48 types) or by not absorption these antibiotics due to quality change and/or quantity of porins.[21]

Despite the reports of strains resistant to all antimicrobials classes, most remain still susceptible to treatment with available drugs, such as polymyxin, tigecycline, fosfomycin, and aminoglycosides, or in combination with other antibiotics.[22] The development of new antibiotics of low toxicity and potentially effective in the control of these infections has not been as efficient as urgently needed to supplant antibiotic resistance acquisition.[7,22] Empirical antibiotic therapy with controlled dispensing by hospital infection control committees has been encouraged to ensure infection control and resistance mechanisms dissemination.[23]

The colonization represents a major threat to the increasing spread rates of bacterial resistance, with infections being just the “tip of the iceberg”.[24] Therefore, actives surveillance screening, especially in critical patient cases, are important strategies for preventing infections and control the spreading of resistance bacterial.[14,25,26,27] So, the detection of the carriers allows the early implementation of IPC measures.[14,26,27]

The IPC measures are highly effective in decrease the CRKP spread, including antimicrobial dispensing programs, contact isolations, hand hygiene practices, active surveillance screenings, and early infection detections.[12,27] These measures vary in different locations, which results in inconsistent responses, sometimes due to team resistance.[1]

The alternatives to standardize the results of IPC measures implementation the healthcare units include assessing the safety culture among teams and the interprofessional education associated with adaptive strategy and behavior change management processes.[1,28]

This study aimed to evaluate the outcomes of infection and CRKP mortality based on the CRE detection and prevention protocol in the ICU. In addition to assessing risk factors for CRKP infection and mortality risk.

This research contributes to the literature for demonstrating the importance of surveillance screening as a service routine and annual epidemiological profile to assess the results of prevention measures.

METHODS

Study Design

A retrospective observational nested case-control cohort study of CRKP infected patients was developed in the general adult intensive care unit (ICU), with 30 beds, of a public tertiary hospital in southeastern Brazil.

This research was approved by the Research Ethics Committee (CEP) (under number 1.638.131).

Study Setting

The data of this research were collected from medical records of patients admitted to the adult ICU included in the detection and prevention protocol, as deliberated by the April 2011 resolution of the Hospital Infection Control Committee (HICC) (Minute 09/2011). The protocol followed the guidelines established by the Brazilian National Health Surveillance Agency (ANVISA) and the guidelines on antimicrobial resistance established by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC).[5,29,30] The detection protocol determines active surveillance screening, through rectal swab collection on admission and on a weekly basis. And the CRE prevention measures include rigorous contact isolation in properly identified private rooms, restrict use of tubes and catheters, healthcare professionals' protection and hygiene, environmental cleaning, and proper antimicrobial dispensing.

Patients

2,126 medical records of the adult ICU patients, that made part of CRE detection and prevention protocol from 2012 to 2018, were collected. Patients above 12 years old admitted to the ICU with complete medical records were included. The duplicated and incomplete records, periods from 2012 to 2013 by collection irregularities, and discharge or death before the first swab collection were excluded.

The research evaluated clinical and microbiological data of 1,920 patients of the CRE detection and prevention protocol, from January 2014 to December 2018, that had the following data: medical history, age, sex, clinical diagnosis at admission, disease severity score (SAPS II), presence of invasive devices, enterobacteria and other microorganism identification, antimicrobials already used, rectal swab cultures for CRE, admission date, and discharge or death.

Patients CRE infected had their diagnosis updated based on clinical examination and positive CRE cultures according to the CDC/NHSN's (CDC's National Healthcare Safety Network) infection guidelines.[31]

ENVIRONMENTAL SAMPLING AND PROCESSING

The clinical culture samples (tissue and tracheobronchial secretion, blood, central venous catheter aspired blood, central venous catheter tip, urine, and cavity fluids, like liquor, pleural and ascitic fluids) and rectal swab were subjected to lab studies and clinical analysis at the hospital. The clinical and surveillance culture samples were subjected to identification and susceptibility tests using VITEK2's automated system (BioMérieux, France) according to CLSI (Clinical and Laboratory Standart Institute) guidelines, EDTA tests, and microdilution of polymyxins.[32]

DATA ANALYSIS

Some of the data were collected from detection and prevention protocol records, such as length of stay in the ICU, long-term hemodialysis catheter (more than 15 days), long-term mechanical ventilation (more than 10 days), long-term gastric tube (more than 10 days), colonization prior to infection, exposure to antimicrobials 30 days prior to infection, late death (30 days after hospitalization). Subsequently, the data were stratified according to young (13 to 54 years old) and old ranges (55 to 97 years old), and low (16 to 62) and high (63 to 217) SAPS, and short-term (1 to 21) and long-term (22 to 175 days) ICU hospitalization.

Statistical Analysis

The normally distributed continuous variables were expressed in mean and standard deviation and compared using the Student’s T-test. The Shapiro-Wilk test determined the normality of quantitative variables. Variables with non-normal distribution were expresses in medians (interquartile range). We performed a

bivariant analysis using Pearson's chi-squared test (x^2) or Fisher's exact test to determine the effect of each categorical variable with their respective significances. The multivariate logistic regression analysis was performed including risk factors that showed statistical significance (p (≤ 0.05) in the univariate analysis. A multinomial analysis was performed to determine the influence of different antibiotic classes in samples of CRKP patients, other CRE, and controls. The Kaplan-Meier test estimated the survival probability with death 30 days after hospitalization, considering the colonization period and death. The log-rank test compared the survival curves between patients infected with CRKP, other CREs, and control patients. The multiple Cox regression test measured the survival rate in relation to the proportional risk of CRKP patients, other CRE, and controls, as well as the proportional risk for CRKP infection 30 days after exposure to antibiotics. We adopted the significance level (α) of 5% in all analyses performed, that is, significant results showed a p-value lower than 5% (< 0,05). The strength of association between each explanatory variable and the response variable was assessed by the odds ratio (OR) with a 95% confidence interval (CI 95%). The statistical tests were carried out in the SPSS (Statistical Package for Social Sciences) software for Windows, version 21.0 (IBM-SPSS Inc, Armonk, NY).

RESULTS

In 5 years, were analyzed 1,920 medical records of adult patients admitted to the ICU that were part of the detection and prevention protocol for CRE with surveillance screening by weekly rectal swab during the hospital stay. There was a predominance of males (65.31%) compared with females (1.88:1), mean aged of 52.42 ± 19.34 years (range from 13 to 97 years). Hospital discharge was more

frequent (68.12%) than death (31.87%). The mean SAPS (Score Simplified Acute Physiology) was 62.19 ±18.73 (range from 16 to 131), and the length of ICU stay was 21.03 ±18.12 days (range from 1 to 175 days).

The samples included control patients (95.7%) and infected by CRKP (4.3%) with the following characteristics, respectively: predominance of males compared with females (1.87:1 and 2.07:1) and of the hospital discharges compared with death (2.19:1 and 1.18:1). The CRKP sample presented in relation to control statistically significant differences mean age of 57.58 ±19.19 years ($p < 0.05$), with a range of 16 to 90 years, and length of stay of 39.35 ±26.18 days ($p < 0.001$), with a range of 5 to 175 days, while SAPS of 64.90 ±21.57 ($p > 0.05$), with a range of 21 to 127, was not significant among the groups.

A total of 15,471 clinical cultures were collected, a mean of 8.06 per patient, with 125 (0,81%) positives for CRE at different sites, including tracheobronchial secretions, urine, blood, central venous catheter tip, central venous catheter aspirated blood, tissue secretion, and brain, thorax, and abdomen fluids. The active surveillance screenings for CRE identified 344 cultures positive of 3,154 rectal swab collections (10.91%) in 297 patients. Given that 47 cultures (13.66%) were positive again in 43 patients; twice in 39 patients and three times in four patients.

The most frequent strain was Klebsiella pneumoniae (71.53%) predominantly in tracheobronchial secretion, urine, and blood, followed by Enterobacter cloacae (14.28%) in central venous catheter aspirated blood and central venous catheter tip, then Escherichia coli (7.14%) in urine, Serratia marcescens (2.67%) in tracheobronchial and tissue secretions, and Enterobacter gergoviae (0.93%) in the tracheobronchial secretion. In five patients, we identified two positive cultures for different CRE, with *K. pneumoniae* associated with one *E. aerogenes*, two *E. cloacae*

and one *E. coli*, and one *E. cloacae* associated with *E. coli*.

To analyze CRKP colonization, infection, and mortality profiles were performed a bivariate analysis for each year of this research, which showed statistically significant differences in prevalence ratios for infection and colonization, and not significant for mortality (Fig 1).

The univariate analysis and multivariate logistic regression demonstrated which the risk factors for CRKP infection presented a statistically significant difference (Table 1).

To analyze the risk to be CRKP infected after 30 days the antibiotics exposure, were performed a multiple Cox regression and identified statistically significant differences for aminopenicillins classes (OR [95%CI]: 11.676 [5.843-23.334] p < 0.001) and cephalosporins (8.707 [5.068-14.960] p < 0.001). The individual analysis or in group (2,624 [0.931-7.399] p 0.068) of the other classes of antimicrobials, such as carbapenems, fluoroquinolones, and polymyxins, presented no statistical differences in relation to the control patients.

The previous antibiotics exposure proved to be an important risk factor for CRKP infection. Therefore, multinomial regression analyses were performed to compare the effect of the previously antibiotics used on the chance for CRKP infection and other CRE in relation to CRE non-infected patients (Table 2).

The survival probability was estimated by the Kaplan-Meier method using the time interval of colonization and infection within the length of stay, which showed higher mortality in CRKP patients compared to controls. The survival curves were compared by the log-rank test and showed a statistically significant difference (p < 0.001). The multiple Cox regression analyzed the proportional risk survival among CRKP infected patients, other CRE (E. aerogenes, E. cloacae, E. coli, E. gergoviae

and S. marcescens), and non-infected by CRE, present in clinical culture samples. Only patients infected with CRKP showed a statistically significant risk of mortality compared to control patients (OR [95%CI]: 3.073 [1.957-4.824] p <0.001). The individual or in group (1.067 [0.338-3.372] p 0.912) analysis of the bacteria E. aerogenes, E. cloacae, E. coli, E. gergoviae, and S. marcescens had no statistical significance.

For each year of research, the infection rate with more or less 30 days of length ICU stay and the mortality of CRKP were analyzed, in addition, the general mortality rate in the ICU (Fig 2).

DISCUSSION

The HAI caused by multi-drug resistant bacteria have become a serious public health problem since the availability of efficient antimicrobials is limited.[22] The difficulty to contain their spread through IPC measures has resulted in a high global prevalence rate and, consequently, in an economic threat and an important morbimortality cause.[6]

The resources to CRE active surveillance screening in developing countries are limited.[2] This brings additional concerns regarding the early implementation of preventive measures, in addition to the responsibility of the health teams, as it makes it difficult to control the spread of resistant bacteria. [3,7,25] In this study, CRE active surveillance screening, through rectal swabs, was implemented in 2011 with the creation of a CRE detection and prevention protocol in patients admitted to the ICU. In data analysis, it was observed that the routine of active surveillance screening was continued even in patients with positive detection, providing an increment in the healthcare costs for CRE detection.

The CRE strains have been difficult to control due to the significant increase in bacterial resistance mechanisms to antimicrobials and fast-spreading.[1,33] The literature shows a predominance of *K. pneumoniae*, followed by *E. cloacae*, *E. coli*, and *Proteus mirabilis*, and mainly from urine samples, respiratory cultures, blood, catheters, and wounds.[1,34-37] The current research revealed the predominance of CRKP in the ICU, mainly in the tracheobronchial secretion, urine, and blood cultures, followed by other carbapenem-resistant strains, such as *E. cloacae* in catheter aspired blood and *E. coli* in the urine.

In long-term care units, investigating the CRE load through clinical cultures reveals just "the tip of the iceberg", so it is extremely important to keep active surveillance screening, especially in patients with a CRE infection predisposition and colonization.[24] For that reason, surveillance screenings for resistant bacteria make it possible to build the CRE epidemiological profiles in healthcare units. [14,35] And, also, define antimicrobial susceptibility, favoring safe standardization of empirical therapies in severe situations.[14,35] In this study, the CRE detection protocol by surveillance screening, in the adult ICU, together with the clinical culture of infection, and data of mortality were fundamental for the composition of a CRKP epidemiological profile. This profile demonstrated a higher prevalence of colonization than infection, which presupposes success in the early implementation of preventive measures. However, the results show that variation over the years was discreet and there was no control over the infection and mortality.

The literature has demonstrated various risk factors for CRKP infections, such as long-term hospital of stay, previous antibiotics exposure, central venous catheter, enteral feeding tube, tracheostomy cannula, mechanical ventilation, and colonizations.[13,14,34,36,38] In turn, IPC measures for resistant bacteria, such as de-

hospitalization and early removal of invasive devices, decrease risk factors in the critically ill patients.[39] In agreement with some risk factors for CRKP infection, this study identified significant differences for tracheostomy, colonization, and previous antibiotics exposure, and older age groups.

In general, the use of antibiotics in the clinical practice has no standardization.[7,13] For this reason, prior exposure to multiple classes of broad-spectrum antimicrobials, such as fluoroquinolones, third- or fourth-generation cephalosporins, carbapenems, and aminopenicillins, may increase bacterial resistance.[13,38,39] As observed by some authors, that the CRKP infected showed an increase in mortality after aminoglycosides treatment.[7] In this study, the previous exposure to broad-spectrum antibiotics, especially aminopenicillins and cephalosporins, proved to be important risk factors for CRKP infections.

Early detection by surveillance screening and preventive measures, such as contact isolation, daily chlorhexidine bathing, hand hygiene, and environmental cleaning, aim to control the spreading of CRE and, consequently, minimize the risk of infection and mortality.[5] However, the applicability and results of IPC measures depend on well-structured and monitored healthcare professionals in prevention programs.[1] To reduce infection and mortality rates, it is necessary to follow a series of actions, such as well-executed prevention practices, sufficient financial resources, trust in protective measures, commitment of professionals, constant feedback, and regular updates.[40]

Yet, the authors' data reveal high CRKP invasive infection rates (6.2% to 30.0%) and mortality (30 to 70%) in many healthcare services.[2,7,15,22,38] In 2016, these authors carried out a study on safety culture in this ICU in order to assess the safety attitude among the multi-professional teams of coordinators, doctors, nurses,

nursing technicians, physiotherapists, psychologists, nutritionists and secretaries.[28] However, the result was not satisfactory, as it demonstrated a set with weakened attitudes in the perception of management, working conditions and communication failures.[28] The analysis of the current study raises a concern, as it demonstrates that the outcomes of infection (average of five years: 4.11% for <30 days and 9.74% for> 30 days) and CRKP mortality (average of five years: 44.18 %) remained high throughout the period, detecting discrepancy between the results and the actions of the CRE prevention protocol.

CONCLUSÕES

CRKP are important causes of infections and mortality in the adult ICU of a public tertiary hospital in southeastern Brazil. The early detection of colonization through surveillance screening for CRE along with clinical cultures showed to be fundamental for the composition of an epidemiological profile of colonization and infection. These data are strategic for the early implementation of containing measures of the spread of resistant and preventive bacteria for new infections and colonizations. However, over the five years of this research, it was observed that the rates and prevalence of CRKP infection and colonization remained high, demonstrating disagreement between the results and the actions of the CRE prevention protocol. Colonization and previous exposure to broad-spectrum antibiotics, mainly aminopenicillins and cephalosporins, proved to be important risk factors for CRKP infections. Based on the results of this ICU, it observed the need to reassess for the CRE detection and prevention protocol, with the purpose of reducing the excess of screening collections, implement measures for monitoring and evaluating preventive actions and standardizing the dispensing of antibiotics. The

authors consider it relevant to invest in improvements related to the patient safety culture among the teams associated with behavioral management.

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AUTHORSHIP AND MANUSCRIPT PREPARATION.

Manuscript preparation Mabel Duarte Alves Gomides was responsible for the study conception and design, data acquisition, data analysis and interpretation; writing the article or critical review for important scientific content; final approval of the version to be submitted.

Manuscript preparation. Astrídia Marilia de Souza Fontes participated in the study conception and design.

Manuscript preparation. Amanda Oliveira Soares Monteiro Silveira participated in the study conception and design and final approval of the version to be submitted

Manuscript preparation. Anderson Luiz Ferreira participated in the study conception and design and final approval of the version to be submitted.

Manuscript preparation. Geraldo Sadoyama participated in the study conception and design and interpretation; critical review for important scientific content; final approval of the version to be submitted

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TABLES

Table 1 – Analysis of risk factors for CRKP infections compared to CRKP non-infections

Variables	CRKP infections N (%)	CRKP non-infections N (%)	Univariate		Multivariate	
Total no. of patients	N 83 (4.3%)	N 1837 (95.7%)	OR (95% CI)	p	OR (95% CI)	p
Age range (55 to 97 years)	51 (61.45%)	912 (49.65%)	1.616 (1.029-2.539)	0.043	1.703 (1.029-2.818)	0.038
Gender (Males)	56 (67.47%)	1198 (65.22%)	1.106 (0.692-1.768)	0.725	-	-
SAPS (63 to 217)	43 (51.81%)	888 (48.34%)	1.149 (0.740-1.784)	0.575	-	-
Long-term ICU stays	57 (68.67%)	618 (33.64%)	4.324 (2.692-6.945)	<0.001	0.559 (0.287-1.089)	0.087
Colonization	50 (60.24%)	247 (13.45%)	9.753 (6.160-15.44)	<0.001	4.283 (2.553-7.185)	<0.001
Exposure to ATB	33 (39.76%)	65 (3.54%)	17.993 (10.86-29.79)	<0.001	5,955 (3,186-11,132)	<0.001
Invasive devices	N (%)	N (%)	OR	p	OR	p

			(95% CI)		(95% CI)	
CVC	80 (96.39%)	1684 (91.67%)	2.423 (0.756-7.763)	0.150	-	-
Long-term hemodialysis catheter	16 (19.28%)	116 (6.31%)	3.543 (1.990-6.308)	<0.001	1.364 (0.692-2.686)	0.370
Tracheostomy	72 (86.75%)	776 (42.24%)	8.949 (4.713-16.99)	<0.001	2.995 (1.215-7.381)	0.017
Long-term MV	72 (86.75%)	856 (46.60%)	7.501 (3.951-14.24)	<0.001	2.172 (0.919-5.135)	0.077
Long-term urethral catheter	80 (96.39%)	1641 (89.33%)	3.185 (0.996-10.18)	0.041	-	-
Enteral feeding tube	70 (84.34%)	1464 (79.70%)	1.372 (0.751-2.507)	0.400	-	-
Long-term gastric tube	18 (21.69%)	135 (7.35%)	3.491 (1.242-3.021	<0.001	1.778 (0.933-3.388	0.080
OTE failure	21 (25.30%)	112 (6.10%)	5.217 (2.013-6.055)	<0.001	1.607 (0.850-3.036)	0.144

CRKP = *carbapenem-resistant Klebsiella pneumoniae*, N = number of patients, OR = Odds Ratio, 95% CI = confidence interval; p = test significance, SAPS = Score Simplified Acute Physiology, CVC = central venous catheter, MV = mechanical ventilation, OTE = orotracheal extubation, ATB = antibiotics, ICU = intensive care unit.

Table 2 – Multinomial analysis of previous antimicrobials exposure in infections by CRKP and others CRE versus controls

Variables	CRKP infections (N 83)			Others CRE infections (N 29)		
	OR	95% CI	p	OR	95% CI	p
Aminopenicillins	31.971	13.307-76.810	<0.001	0.105	-	0.782
Carbapenems	21.009	6.720-65.683	<0.001	10.770	1.399-82.894	0.022
Cefalosporins	31.010	16.901-56.898	<0.001	5.017	1.009-24.948	0.049

CRKP = *carbapenem-resistant Klebsiella pneumoniae*, CRE = *Carbapenem-resistant Enterobacteriaceae*, N = number of patients, OR = Odds Ratio, 95% CI = confidence interval; p = test significance, N controls (not-infected by CRE) = 1808.

LEGENDS

Figure 1 – Analysis of the CRKP infection, mortality, and colonization prevalence ratio (OR [odds ratio])

Legends 1 – CRKP infection, colonization, and mortality (OR)

Figure 2 – Comparative analysis of CRKP infection and mortality rates and general

ICU mortality rate over 5-years

Legends 2 – CRKP infection and mortality rate and overall mortality rate in the ICU

FIGURES

Figure - 1

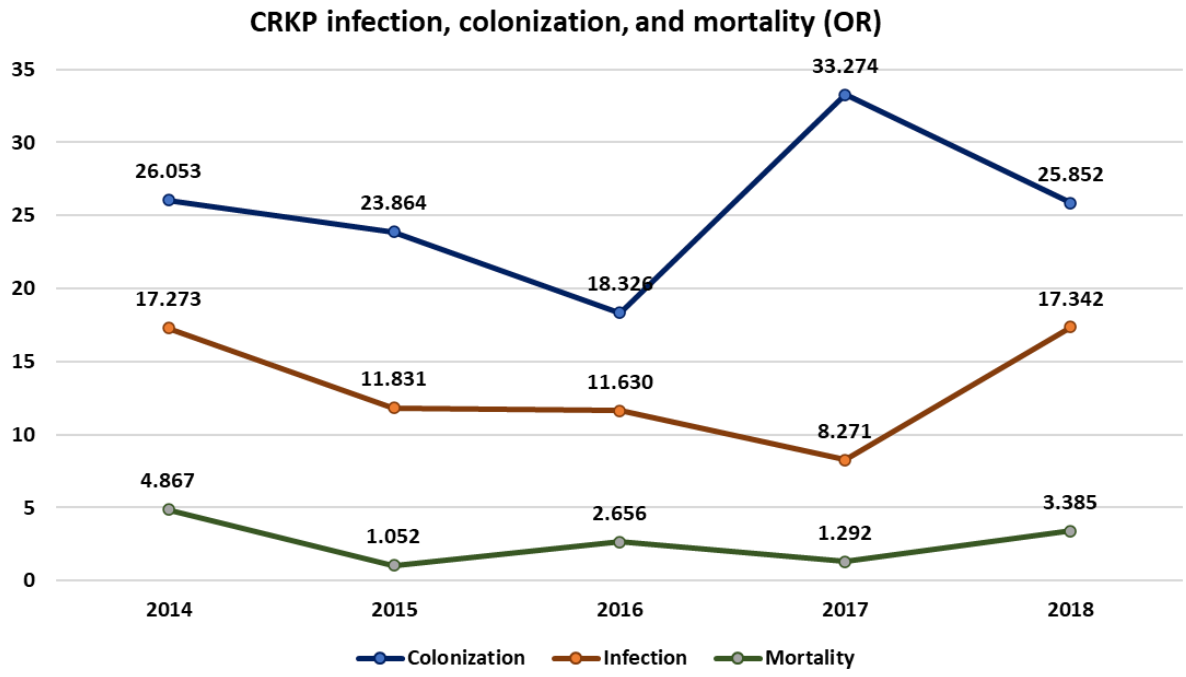
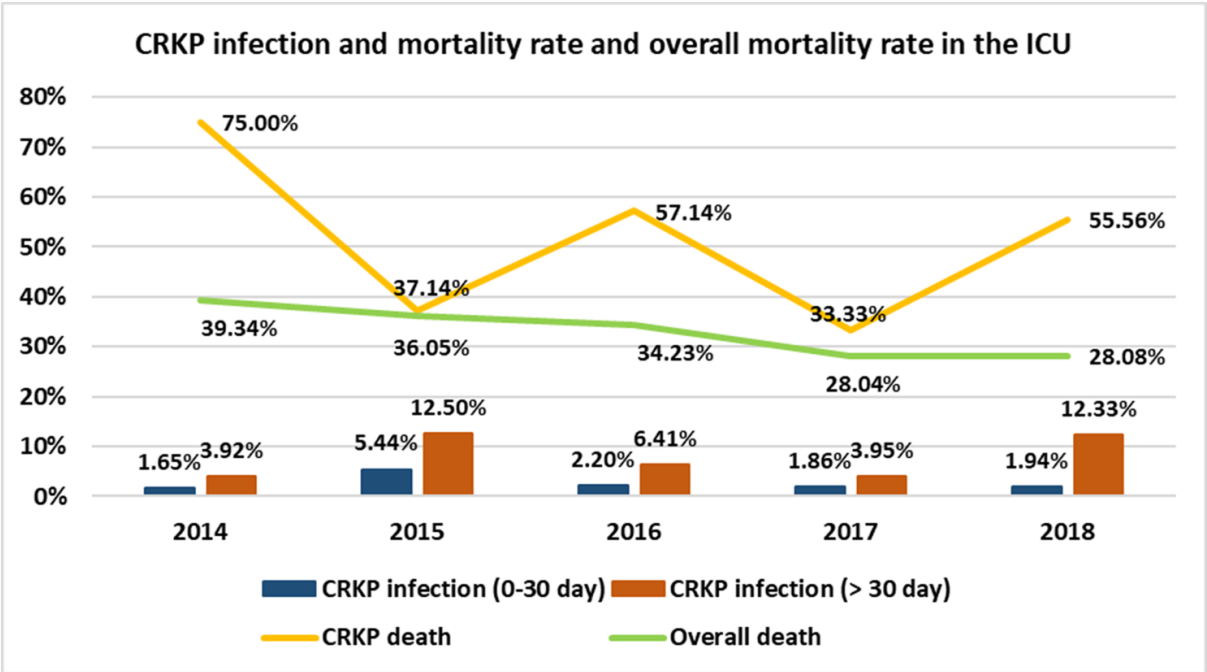


Figure - 2



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ANEXO I – Aprovação do Comitê de Ética em Pesquisa

UFU Comitê de Ética em Pesquisa — UNIVERSIDADE FEDERAL DE UBERLÂNDIA/MG — Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: "Analise da relação colonização e infecção por enterobactérias resistentes a carbapenêmicos e cultura de segurança em UTI de adultos"

Pesquisador: MABEL DUARTE ALVES GOMIDES

Área Temática:

Versão: 3

CAAE: 52659615.7.0000.5152

Instituição Proponente: Faculdade de Medicina

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.638.131

Apresentação do Projeto:

Emenda atual foi enviada pelos pesquisadores para atender à recomendação do CEP/UFU apontada no Parecer 1.595.823, de 14 de Junho de 2016, solicitando atualização do cronograma da pesquisa.

Objetivo da Pesquisa:

Os objetivos da pesquisa não foram alterados nesta Emenda.

O objetivo foi somente atualizar o cronograma.

Avaliação dos Riscos e Benefícios:

Os riscos e benefícios desta pesquisa não sofreram alterações com a presente emenda.

Comentários e Considerações sobre a Pesquisa:

Pesquisa pertinente. Considerações já foram feitas conforme o parecer 1.595.823, de 14 de Junho de 2016.

Considerações sobre os Termos de apresentação obrigatória:

Termos foram apresentados e a recomendação foi atendida.

Recomendações:

Sem recomendações.

Endereço: Av. João Naves de Ávila 2121- Bloco "1A", sala 224 - Campus Sta. Mônica
Bairro: Santa Mônica **CEP:** 38.408-144
UF: MG **Município:** UBERLANDIA
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UFU Comitê de Ética em Pesquisa — UNIVERSIDADE FEDERAL DE UBERLÂNDIA/MG — Plataforma Brasil

Continuação do Parecer: 1.638.131

Conclusões ou Pendências e Lista de Inadequações:

Os pesquisadores atualizaram o cronograma e encaminharam esta emenda, atendendo à recomendação do CEP/UFU.

Considerações Finais a critério do CEP:

Data para entrega de Relatório Parcial ao CEP/UFU: Janeiro de 2018.

Data para entrega de Relatório Parcial ao CEP/UFU: Janeiro de 2019.

Data para entrega de Relatório Parcial ao CEP/UFU: Janeiro de 2020.

Data para entrega de Relatório Final ao CEP/UFU: Janeiro de 2021.

OBS.: O CEP/UFU LEMBRA QUE QUALQUER MUDANÇA NO PROTOCOLO DEVE SER INFORMADA IMEDIATAMENTE AO CEP PARA FINS DE ANÁLISE E APROVAÇÃO DA MESMA.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_747484_E1.pdf	27/06/2016 09:33:49		Aceito
Outros	Justificativa.docx	27/06/2016 09:32:55	MABEL DUARTE ALVES GOMIDES	Aceito
Outros	RESPOSTA_DO_PARECER_CONSUBSTANCIADO.doc	01/06/2016 21:53:57	MABEL DUARTE ALVES GOMIDES	Aceito
Outros	TERMO_DE_CONSENTIMENTO_LIVRE_E_ESCLARECIDO_ESTUDO_PILOTO.doc	20/05/2016 20:55:55	MABEL DUARTE ALVES GOMIDES	Aceito
Brochura Pesquisa	PROJETO_DE_PESQUISA_PLATAFORMA_BRASIL.doc	20/05/2016 20:54:56	MABEL DUARTE ALVES GOMIDES	Aceito
Projeto Detalhado / Brochura Investigador	PROJETO_DETALHADO.doc	20/05/2016 20:53:35	MABEL DUARTE ALVES GOMIDES	Aceito
Outros	ASPECTOS_ETICOS.doc	21/01/2016 01:35:16	MABEL DUARTE ALVES GOMIDES	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TERMO_DE_CONSENTIMENTO_LIVRE_E_ESCLARECIDO.doc	21/01/2016 01:27:13	MABEL DUARTE ALVES GOMIDES	Aceito
Outros	Termo_de_Anuencia.pdf	19/01/2016 23:58:16	MABEL DUARTE ALVES GOMIDES	Aceito
Outros	SAQ_Short.pdf	19/01/2016 23:57:31	MABEL DUARTE ALVES GOMIDES	Aceito
Outros	Protocolo_do_Projeto_de_Pesquisa.	19/01/2016	MABEL DUARTE	Aceito

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Continuação do Parecer: 1.638.131

Outros	doc	23:55:35	ALVES GOMIDES	Aceito
Outros	Documento_de_Solicitacao_de_Autorizacao_de_Coleta_de_Dados_HC_UFU.pdf	19/01/2016 23:55:14	MABEL DUARTE ALVES GOMIDES	Aceito
Outros	DADOS_DO_PROJETO_DE_PESQUISA.doc	19/01/2016 23:53:52	MABEL DUARTE ALVES GOMIDES	Aceito
Outros	curriculo_lattes.doc	19/01/2016 23:53:13	MABEL DUARTE ALVES GOMIDES	Aceito
Declaração de Pesquisadores	TERMO_DE_COMPROMISSO_DA_EQUIPE_EXECUTORA.jpg	19/01/2016 23:45:26	MABEL DUARTE ALVES GOMIDES	Aceito
Declaração de Instituição e Infraestrutura	DECLARACAO_DA_INSTITUICAO_CO_PARTICIPANTE.pdf	19/01/2016 23:44:17	MABEL DUARTE ALVES GOMIDES	Aceito
Folha de Rosto	FOLHA_DE_ROSTO.pdf	19/01/2016 23:41:24	MABEL DUARTE ALVES GOMIDES	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

UBERLANDIA, 08 de Julho de 2016

Assinado por:
Sandra Terezinha de Farias Furtado
(Coordenador)