

Original Article

Phenotypical profile of colistin and tigecycline resistance in a public hospital in Brazil

Perfil fenotípico de resistência à colistina e tigeciclina em um hospital público no Brasil

Perfil fenotípico de resistencia a la colistina y tigeciclina en un hospital público de Brasil

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RESUMO

Justificativa e objetivos: Infecções Relacionadas à Assistência à Saúde (IRAS) causadas por bacilos Gram negativos multirresistentes (BGN-MDR) são consideradas um problema de saúde pública e um impacto nas taxas de mortalidade nas Unidades de Terapia Intensiva (UTI). O objetivo deste estudo foi verificar o perfil fenotípico de resistência à colistina e à tigeciclina, consideradas como último recurso terapêutico aos BGN-MDR. **Métodos:** Os dados foram coletados nas fichas de busca ativa do serviço de controle de infecções e prontuários médicos de pacientes internados em duas UTI de um hospital público de Joinville, entre janeiro de 2016 e junho de 2017. **Resultados:** Ocorreram 256 IRAS por BGN, acometendo principalmente o gênero masculino (62%), com mediana de idade de 65 anos. Entre os BGN, 37% expressaram MDR; sendo as espécies mais frequentes: *Klebsiella pneumoniae* (47%), *Acinetobacter baumannii* (23%) e *Stenotrophomonas maltophilia* (11%). A resistência de BGN-MDR a colistina e tigeciclina foi de 5% e de 12%, respectivamente; 5% dos isolados foram resistentes aos dois antibióticos. A taxa de óbito entre os pacientes com IRAS por BGN-MDR resistentes à colistina foi mais alta (60%) que aquelas à tigeciclina (45%). **Conclusão:** *K. pneumoniae* e *A. baumannii* produtores de carbapenemases, resistentes a colistina e tigeciclina prevaleceram entre os BGN-MDR, e estiveram associadas à maioria dos óbitos. Essas observações, junto com o alto uso de carbapenêmicos na terapia empírica, mostra a necessidade do uso racional de antimicrobianos.

Descritores: Resistência microbiana a medicamentos. Colistina. Infecção hospitalar. Enterobacteriaceae. Carbapenêmicos.

ABSTRACT

Introduction and objectives: Healthcare-associated Infections (HAI) caused by multidrug-resistant Gram-negative bacteria (MDR-GNB) are considered a public health problem and influence mortality rates in Intensive Care Units (ICU). The aim of this study was to verify the phenotypic profile of colistin and tigecycline, considered the last antimicrobial choice to treat MDR-GNB infections. **Methods:** Data were collected on the active search records of the infection prevention and control services and medical records of patients admitted to two ICU at a public hospital in Joinville, Brazil, between January 2016 and June 2017. **Results:** There

were 256 HAI caused by GNB, mainly affecting males (62%), with 65 years as the median age. Among GNBs, 37% expressed MDR; the most frequent species were: *Klebsiella pneumoniae* (47%), *Acinetobacter baumannii* (23%) and *Stenotrophomonas maltophilia* (11%). MDR-GNB resistance to colistin and tigecycline was 5% and 12%, respectively; 5% of isolates were resistant to both antibiotics. Death rate among patients with HAI caused by colistin-resistant MDR-GNB was higher (60%) than those to tigecycline (45%). **Conclusion:** Colistin and tigecycline-resistant carbapenemase-producing *K. pneumoniae* and *A. baumannii*, prevailed among MDR-GNB, and were associated with most deaths. These observations, alongside the high use of carbapenems in empirical therapy, show the need for rational use of antimicrobials.

Keywords: Drug Resistance. Colistin. Healthcare-associated Infections. Enterobacteriaceae. Carbapenems

RESUMEN

Justificación y objetivos: Las Infecciones nosocomiales (IH) causadas por bacilos Gram negativos multirresistentes (BGN-MDR) se consideran un problema de salud pública y un impacto en las tasas de mortalidad en las Unidades de Terapia Intensiva (UTI). El objetivo de este estudio fue verificar el perfil fenotípico de resistencia a la colistina y a la tigeciclina, consideradas como último recurso terapéutico a los BGN-MDR. **Métodos:** Los datos fueron recolectados en las fichas de búsqueda activa del servicio de control de infecciones y prontuarios médicos de pacientes internados en dos UTI de un hospital público de Joinville, entre enero de 2016 y junio de 2017. **Resultados:** Ocurrieron 256 IHs por BGN, que afectan principalmente al género masculino (62%), con mediana de edad de 65 años. Entre los BGN, el 37% expresó MDR; siendo las especies más frecuentes: *Klebsiella pneumoniae* (47%), *Acinetobacter baumannii* (23%) y *Stenotrophomonas maltophilia* (11%). La resistencia de BGN-MDR a la colistina y tigeciclina fue del 5% y del 12%, respectivamente; 5% de los aislados fueron resistentes a los dos antibióticos. La tasa de muerte entre los pacientes con IH causadas por los BGN-MDR resistentes la colistina fue más alta (60%) que aquellas a tigeciclina (45%). **Conclusión:** *K. pneumoniae* y *A. baumannii* productoras de carbapenemases, resistentes la colistina y la tigeciclina, fueron más frecuentes entre los BGN-MDR y su asociación estuvo presente en la mayoría de las muertes. Estas observaciones, junto con el alto uso de carbapenems en la terapia empírica, muestran la necesidad de un uso racional de los antimicrobianos.

Palabras Clave: Farmacorresistencia Microbiana. Colistina. Infección Hospitalaria. Enterobacteriaceae. Carbapenémicos

INTRODUCTION

The World Health Organization (WHO) recognizes that Healthcare-associated Infections (HAI) have a strong impact on patients' morbidity and mortality, quality of life and care services costs. The WHO also points out that about 7% of patients hospitalized in developed countries and 10% in developing countries acquire at least one episode of HAI during hospitalization, reaching a death rate of 10%.¹ The European Centre for Disease Prevention and Control (ECDC) data show that 4.5 million people acquire HAI in European hospitals annually, leading to an increase of 16 million days in hospitalization and

approximately 37,000 deaths per year.² A multicenter study in the United States of America (USA) estimated that these infections affect more than 1.7 million people/year, which are associated with 99,000 deaths annually.¹

In Brazil, 720,000 people on average are infected in hospitals per year; of these, 20% result in HAI-related deaths. These infections are more frequently in the ICU, with rates ranging from 5% to 35%, an associated mortality of 9% to 38%, reaching 60% as a direct cause of death, depending on the affected population.^{3,4}

Thus, it is worth mentioning the increase in antimicrobial resistance, especially of multidrug-resistant Gram-negative bacilli (MDR-GNB), the most common pathogens of infections, such as ventilator-associated pneumonia (VAP), urinary tract infections (UTI), primary bloodstream infections (BSI) and surgical site infections (SSI).⁵ Brazilian studies have shown that *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Enterobacter* sp, *Pseudomonas aeruginosa* and *Escherichia coli* are the main MDR-GNB involved in HAI. Treatment of these infections is hampered by the lack of alternatives, especially regarding the use of new antimicrobials, revealing a public health crisis^{6,7}.

By the end of the 20th century, following the increase in MDR-GNB, colistin and tigecycline were back to being used as the only therapeutic alternatives for infections caused by these bacteria.⁸ However, in 2016 China recorded the first colistin-resistant gene, mediated by plasmid, in *E. coli*, known as *mcr-1* (mobile colistin resistance gene).⁹ Since then, publications have shown the presence of *mcr-1* gene on several countries, including Brazil.¹⁰⁻

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A study conducted in Brazil reports that tigecycline was the main non-beta-lactam agent used to treat colistin-resistant *K. pneumoniae* isolates. However, isolates of *P. aeruginosa*, *Proteus* spp., *Providencia* spp. and *Morganella* spp., resistance-nodulation-cell division (RND) efflux pumps producers, were found to be tigecycline-resistant.⁸

Another aspect to be highlighted is the economic and care dimensions involved. MDR infections increase hospitalization time, number of diagnostic and therapeutic procedures, and may triple the expenses of care services, depending on the hospital care profile.^{3,4} The Centers for Disease Control and Prevention (CDC) estimated that each year in the USA at least 2 million people develop HAI by MDR bacteria and 23,000 deaths/year are directly associated, with an approximate cost of \$20 billion/year.¹³ In Europe, according to 2007 data, it was estimated that HAI caused by MDR bacteria resulted in 25,000 deaths annually, with a total cost of €1.555 million/year.²

The aim of this study was to evaluate the phenotypic profile of MDR-GNB related to colistin and tigecycline in patients with HAI, admitted in two ICU of a public hospital, located in northern Santa Catarina. The study of MDR-GNB resistance to these two antimicrobials can contribute to epidemiological data of HAI isolates in Brazilian ICU and improve the quality of care.

METHODS

This study was conducted between January 2016 and June 2017 at the Hans Dieter Schmidt Regional Hospital in Joinville, Santa Catarina, a public hospital with 242 beds, of which 20 are general and cardiac ICU. Information was collected in the active search records of the infection prevention and control services and medical records. All patients aged 18 years or older, with ICU-acquired HAI, after 72 hours of hospitalization, were included in the study. The HAI were defined according to the *National Healthcare Safety Network* criteria.¹⁴ The variables studied were: age, gender; HAI types: ventilator-associated pneumonia (VAP) or not; primary bloodstream infection related to central vascular catheter (BSI-CVC) and urinary tract infection associated with urinary catheter (UTI-UC); ICU stay, isolated microorganisms and antimicrobial susceptibility profile.

The Clinical and Laboratory Standards Institute (CLSI) recommendations were adopted to determine the phenotypic profile; for identification of colistin and tigecycline resistance, the reference was Technical Note No. 01/2013 of Anvisa.¹⁵⁻¹⁷ The criteria proposed by Magiorakos et al. were adopted to define MDR-GNB.¹⁸

Data was plotted in a Microsoft Office[®] Excel table and later analyzed descriptively. The study was approved by the Research Ethics Committees of the Universidade Regional de Joinville (Univille), according to Protocol No. 1599756 and the Hans Dieter Schmidt Regional Hospital under Protocol No. 1613535.

RESULTS

During the study period, 1,545 patients were admitted to the ICU, of which 275 developed one or more episodes of HAI, totaling 478 (31%) cases. Of these, 21% (101/478) were diagnosed only by clinical criteria, without culture confirmation; 79% (377/478) of the cases were confirmed by microbiological culture.

Regarding the patients' profile, men were the most affected – 62% (171/275), whereas women accounted for 38% (104/275) of the cases. The median age was 65 years and median ICU stay was 23 days.

Of the 478 identified HAI, 377 had microorganisms growth, GNB being the more frequent (68%; 256/377), followed by Gram-positive cocci (18%; 67/377), fungi (12%; 47/377) and others (2%; 7/377). Among the GNB, *K. pneumoniae* prevailed in – 26% (66/256) of isolates, *P. aeruginosa* – 20% (52/256) and *A. baumannii* – 13% (33/256); with lowest percentage of *E. coli* and *Enterobacter cloacae* complex, both with – 8% (20/256), *Proteus mirabilis* – 6% (15/256), *Serratia marcescens* – 5% (13/256), *Enterobacter aerogenes* and *Stenotrophomonas maltophilia*, both – 4% (10/256), *Burkholderia cepacia* complex – 2% (7/256), and others (4%; 10/256).

Of the 256 GNB associated with HAI, 37% (95/256) met the criteria for MDR. Of the 95 pathogens with MDR phenotypic profile, the most frequent species were: *K. pneumoniae* – 47% (45/95) followed by *A. baumannii* with – 23% (22/92) and *S. maltophilia* – 11% (10/95). On the other hand, lower indices of *P. aeruginosa* – 8% (8/95), *B. cepacia* complex – 7% (7/95), *E. cloacae* complex – 2% (2/95) and *E. aerogenes* – 1% (1/95) were observed.

Among MDR-GNB, 67% (64/95) of the isolates were resistant to carbapenems, with higher prevalence of *K. pneumoniae* – 48% (31/64) and *A. baumannii* – 34% (22/64), followed by *P. aeruginosa* – 13% (08/64), *E. cloacae* complex – 3% (2/64) and *E. aerogenes* – 2% (1/64).

Frequency of MDR-GNB was higher in VAP (57%), then UTI-UC (24%) and BIS-CVC (19%). MDR-GNB with phenotypic resistance to colistin (5%) prevailed in UTIs and BIS. Of the 12% MDR-GNB expressing phenotypic resistance to tigecycline, 64% derived from VAP and 36% from UTI; 5% of these isolates were resistant to all tested antimicrobials, as detailed in Table 1.

Table 1 – MDR-GNB frequency and colistin and/or tigecycline resistance profile according to HAI

| MDR-GNB distribution | VAP | UTI | BIS | Total |
|--|---------|---------|---------|---------|
| | n (%) | n (%) | n (%) | n (%) |
| MDR-GNB | 54 (57) | 23 (24) | 18 (19) | 95 (37) |
| Colistin-resistant MDR-GNB | 1 (20) | 2 (40) | 2 (40) | 5 (5) |
| Tigecycline-resistant MDR-GNB | 7 (64) | 4 (36) | 0 | 11 (12) |
| Tigecycline and colistin-resistant MDR-GNB | 2 (40) | 2 (40) | 1 (20) | 5 (5) |

HAI: Healthcare-associated Infection; GNB: Gram-negative Bacilli; MDR: Multidrug-resistant; VAP: Ventilator-associated Pneumonia; UTI: Urinary Tract Infection; BIS: Primary Bloodstream Infection.

MDR-GBN *K. pneumoniae* isolates showed greater phenotypic resistance to colistin or tigecycline, 80% and 45.5%, respectively; 45.5% of isolates *A. baumannii* were resistant to tigecycline. Resistance to both antibiotics was observed in *K. pneumoniae* (80%) and *E. aerogenes* (20%), as detailed in Table 2.

Table 2 – Distribution of bacterial species with phenotypic profile resistant to colistin and/or tigecycline

| MDR-GBN | Antimicrobials | | |
|---------------------------|----------------|----------|-------------|
| | Pol | Tig | Pol and Tig |
| | n (%) | n (%) | n (%) |
| <i>K. pneumoniae</i> | 4 (80) | 5 (45.5) | 4 (80) |
| <i>A. baumannii</i> | – | 5 (45.5) | – |
| <i>P. aeruginosa</i> | 1 (20) | – | – |
| <i>E. aerogenes</i> | – | – | 1 (20) |
| <i>E. cloacae</i> complex | – | 1 (9) | – |

GNB Gram-negative Bacilli; MDR: Multidrug-resistant; n: Number of isolates; Tig: Tigecycline; Pol: Polymyxin; R: Resistant; S: Sensitive; –: Untested

Regarding use of antimicrobials prior to the HAI diagnosis, of the five patients with polymyxin and tigecycline resistant isolates, one patient with *K. pneumoniae* infection did not use antimicrobials and four received empirical therapy. Of these, three patients with *K. pneumoniae* were treated with monotherapy (two cases with carbapenem and one with ampicillin/sulbactam) and the patient with *E. aerogenes* isolate received combined therapy (carbapenem + ampicillin/sulbactam). No patient received empirical therapy with polymyxin or tigecycline.

Concerning the clinical outcome of patients with MDR-GBN HAIs, hospital discharge occurred in 38% (36/95) and death in 62% (59/95) of cases. Death rate among patients with HAI caused by colistin-resistant MDR-GBN was higher – 60% (3/5) – than those resistant to tigecycline – 45% (5/11). Of the five patients who developed pan-resistant GNB infection, 80% (4/5) died, three cases associated with *K. pneumoniae* and one *E. aerogenes*.

DISCUSSION

This study identified a 31% prevalence of HAI in the ICU, like other Brazilian studies that report rates ranging from 5% to 51.2%, with associated mortality of 9% to 38%, reaching 60% as a direct cause of death, depending on the affected population.^{3,4,19}

Men aged 65 years (as the median) were the most affected – 60% –, and the median length stay in the ICU was 23 days. A study stated that age, gender, length of stay in the ICU, use of invasive devices, severity and comorbidity of patients are associated with increased mortality from MDR bacteria.⁷

Data obtained in this study demonstrates that of the isolated GNB, 37% were MDR-GNB and, of these, the species *K. pneumonia* (47%) and *A. baumannii* (23%) showed resistance to most tested antimicrobials, including carbapenems. Higher results were observed in a tertiary hospital ICU in northern Brazil, where 84% of *K. pneumoniae* isolates were classified as MDR, including carbapenems. The study also found that 100% of these isolates were ESBL and carbapenemase producers.¹⁹ According to the ECDC surveillance report, carbapenems resistance rates recorded in 2018, when compared to 2016, show an increase in *A. baumannii* (68% vs. 64%) and *Klebsiella* spp. (11% vs. 8%) species.²⁰

Comparing data from the ECDC report with that published by Anvisa in 2017, higher carbapenem resistance rates were observed in *A. baumannii* (85%) and *P. aeruginosa* (42.9%); among enterobacteria, the prevalence was *K. pneumoniae* (46.8%), *Enterobacter* spp. (18.2%) and *E. coli* (9.9%).²¹

Currently, international and Brazilian government health agencies warn about the growth of MDR-GNB infections, with a predominance of *P. aeruginosa*, *A. baumannii* and *K. pneumoniae*. This is a bleak scenario, especially when considering that most infections caused by these pathogens are severe and therapeutic options limited, leaving only colistin and/or tigecycline as a treatment choice.²²

This study also identified colistin (5%) and tigecycline (12%) resistance rates. Another study developed in the same hospital found 139 clinical of carbapenem-resistant *A. baumannii* (CRAb) isolates, from 2010 to 2013; and between 2010 and 2011, all CRAb were sensitive to tigecycline and colistin. In 2013, the first tigecycline-resistant CRAb isolates (5.7%) were identified, but still 100% sensitive to colistin.²³ Analyzed data from these surveys conclude that CRAb rates were 23%, however, resistance to tigecycline increased in 9% and remained 100% sensitive to colistin. A different situation was observed for colistin and tigecycline-resistant enterobacteria, especially *K. pneumoniae*, in which a resistance of 80% and 45.5% can be verified, respectively. A colistin resistance rate of 27.1% in *K. pneumoniae* was found

in São Paulo hospitals, with resistance to carbapenems and carbapenemase-producing *Klebsiella pneumoniae* (KPC).⁸

In this study, considering the potential of MDR bacteria, alongside other factors inherent to the patient and health care services, the *K. pneumoniae* species had the highest phenotypic profile of resistance to antimicrobials and was associated with the highest number of deaths. *K. pneumoniae* is considered the most frequent nosocomial pathogen in Brazilian hospitals, especially in the ICU, featuring in several outbreaks, besides its KPC-producing clone being endemic to the country.²¹

Carbapenems and ampicillin/sulbactam were the most used antimicrobials in patients who acquired HAIs by MDR-GNB. Results show that the use of carbapenems, piperacillin/tazobactam and aminoglycosides were risk factors for acquisition of ESBL-producing enterobacteria, as well as *P. aeruginosa* and *A. baumannii* MDR.²⁴ Data available in the literature point to the inappropriate use of antimicrobials as the leading cause of the onset and dissemination of MDR bacteria in the ICU.^{6,19,25}

Data obtained in this investigation, although referring to a single hospital, reveals the size of the MDR-GNB problem and the need for constant monitoring and control in hospitals, especially in the ICU. To study factors associated with these MDR-GNB is essential to determine dissemination and emergence of new clones, as well as for the rational use of antimicrobials because of current fragile therapeutic options. Barrier measures to prevent HAI acquisition and data providing colistin and tigecycline resistance rates assist clinicians and other health professionals decide the best therapeutic option, thus, ensuring better patient safety.

Comparative studies addressing epidemiological data of antimicrobial resistance phenotypic profile are limited, because of several antimicrobial standardizations in the definition of MDR, that is, according to gender and/or species. Few are the multicenter reports with HAI rates and the resistance profile of main ICU isolates in the Brazilian territory. Publications mostly deal with reports of a single place or region, representing partial aspects about the reality of the Brazilian ICU.

Colistin and tigecycline-resistant carbapenemase-producing *K. pneumoniae* and *A. baumannii* isolates prevailed among MDR-GNB and were associated with most deaths. These observations, together with the high use of carbapenems in empirical therapy, show the need for rational use of antimicrobials and increased actions to prevent and control HAI.

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Authors' contribution:

Roseneide Campos Deglmann: conceptualization, data analysis and interpretation; writing of the original draft and critical review; approval of the final version for publishing. Responsible for all aspects of the study that ensure accuracy and completeness to any part of the work.

Debora de Oliveira: conceptualization, data analysis and interpretation; writing of the original draft; approval of the final version for publishing.

Paulo Henrique Condeixa de França: conceptualization, data analysis and interpretation; writing of the original draft and critical review; approval of the final version for publishing. Responsible for all aspects of the study that ensure accuracy and completeness to any part of the work.