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Review Article

Carbapenem-Resistant Infections in Neonates and Children in Latin America: A Literature Review

Gabriella Shanks[1]* and Louis Grandjean[2]

[1]*Charité–Universitätsmedizin Berlin, Institute of Tropical Medicine and International Health, Berlin, Germany;* [2]*Institute of Child Health, University College London, London, United Kingdom*

Abstract. Carbapenems are broad-spectrum beta-lactam antibiotics that are increasingly being used worldwide to treat multidrug-resistant infections, but since their introduction, carbapenem resistance has emerged. This phenomenon has been well documented in the adult population, but there is a paucity of evidence from the neonatal and pediatric populations. A literature search of carbapenem-resistant infections in Latin American neonates and children was conducted via PubMed/Medline and SCOPUS: 551 titles were screened, and 17 articles were included in the review. The most commonly reported predominant isolate was *Klebsiella pneumoniae* (11 of 17 studies). Genotypic data were available in 10 of 17 studies, and the *KPC* gene was the most commonly reported resistance gene. The mortality rate ranged from 13% to 52.6%. Carbapenem-resistant infections are prevalent in children and neonates in Latin America and are associated with high rates of mortality, highlighting the need for enhanced antimicrobial stewardship and surveillance within these populations.

INTRODUCTION

The rise of antimicrobial resistance (AMR) poses a global threat to humanity. In response, the WHO published the Global Action Plan Initiative on Antimicrobial Resistance in 2015, advocating for national action plans to be developed using a One Health approach.[1] Carbapenem antibiotics have gained widespread use because of the emergence of extended-spectrum beta-lactamases and cephalosporinases, but their frequent usage has led to the emergence of novel resistance mechanisms, including that of carbapenemases. They have therefore been classified in the Watch/Reserve section of the WHO AWaRE list, which is a classification tool used to promote antimicrobial stewardship.[2] Concerns about carbapenem-resistant organisms (CROs) are especially heightened in low- and middle-income countries (LMICs) because of several factors, including inadequate antimicrobial stewardship practice, lack of rapid diagnostic testing leading to prolonged use of broad-spectrum antimicrobials, and the widespread availability of over-the-counter antimicrobial agents.[3] A recent systematic review highlighted high AMR rates across the Americas, particularly within LMICs.[4] The increasing prevalence of carbapenem-resistant infections has been well documented within the adult population. There is less published evidence available for pediatric and neonatal populations, but existing studies do indicate that infections due to CROs can result in high rates of morbidity and mortality, particularly within the neonatal population.[5,6] This literature review aims to summarize available evidence on CRO infections in the pediatric and neonatal population of Latin America.

MATERIALS AND METHODS

Carbapenem resistance was defined as resistance to meropenem, imipenem, or ertapenem based on Clinical and Laboratory Standards Institute guidance. Neonates were defined as 0–30 days old, and pediatric individuals were defined as 0–18 years old. PubMed/Medline and SCOPUS were searched using the following search terms: "(extended spectrum beta-lactamase OR extended-spectrum beta-lactamase OR carbapenemases OR carbapenemase OR ESBL OR beta-lactamases OR beta-lactamase OR carbapenem resistance OR carbapenem-resistance OR carbapenem-resistant) AND (Latin America OR latin america OR Bolivia OR "Bolivia" OR paraguay OR uruguay OR brazil OR colombia OR peru OR patagonia OR mexico OR el salvador OR belize OR panama OR costa rica OR honduras OR guatemala OR nicaragua OR argentina OR chile OR venezuela OR ecuador OR guyana OR suriname) NOT (africa or asia or europe or australasia or oceana or North America) AND (children OR child OR pediatric OR adolescent) NOT (meat OR poultry)." The included articles were based on research carried out within Latin America.

The PRISMA 2020 checklist was used to structure the literature review and to select relevant data on CRO infection in the neonatal/pediatric population in Latin America. Identified journals were assessed for duplicates, which were excluded. Journal titles were then screened based on specific inclusion and exclusion criteria (Supplemental Table 1). Abstracts and then full-text articles were then reviewed according to these criteria (Supplemental Figure 1). The review focused on studies which report clinical data on pediatric/neonatal CRO infections, risk factors for infection, in vitro resistance data and resistance mechanisms, the prevalence of CRO infection, and mortality. Data from the selected articles were recorded using a data capture sheet with predefined variables (Supplemental Tables 2 and 3).

RESULTS

Seventeen studies met the inclusion criteria and were included in this review.[6–23] The dates of publication ranged from 2007 to 2023, the earliest period of study was 2001–2003, and the latest was 2016–2021.[8,22] Four of 17 studies were written in Spanish, and the rest were written in English. Participant age was accessible in 13 of 17 included studies, with 11 studies reporting a median age below 5 years and 9 of these reporting a median age below 2 years. Data on sex were available in 13 studies, and the majority in 9 of these

* Address correspondence to Gabriella Shanks, Charité–Universitätsmedizin Berlin, Institute of Tropical Medicine and International Health, Berlin, Germany. E-mails: gabriella.shanks@charite.de or gabriella.shanks1@nhs.net

studies reported the majority of participants as male (range, 51.54–79%). The average number of participants per study was 146.56 (range, 19–599). Of 17 studies, 7 reported data on infection due to CROs, whereas 10 studies included both infection and colonization data.

Risk factors associated with CRO infection were identified in 9 of 17 studies, and these included previous antibiotic use, particularly beta-lactams, carbapenem, and vancomycin. Comorbidities such as chronic lung disease, chronic renal disease, and immunodeficiency were noted in five studies. Admission to the intensive care unit and the use of central venous catheters (CVCs) were both linked to a higher risk of CRO infection; one study reported utilization of CVCs in 85% of patients with CRO infections. The most common pathogens were *Klebsiella pneumoniae, Escherichia coli, Acinetobacter baumannii*, and *Pseudomonas aeruginosa*.[7,8,11,15,17–19,22,23]

The mechanism of carbapenem resistance was reported in 7 of 17 studies. A study from Anzoátegui State, Venezuela, reported that all included *K. pneumoniae* isolates ($n = 19$) contained *KPC-2* and *VIM-2* genes. Polymerase chain reaction (PCR) amplification and sequencing produced "identical profiles" from all of these strains, and plasmid DNA analysis revealed some "similarly sized plasmids" that were present in "almost all of the 19 isolates."[21] Another study also based in Medellín, Colombia, reported the presence of a *KPC* carbapenemase in 85.7% of included *K. pneumoniae* isolates ($n = 24$); 87.5% of the 24 included isolates contained a *KPC-2* gene, and the remaining 12% contained a *KPC-3* gene. Three *P. aeruginosa* isolates contained *VIM-2*, and one *Enterobacter cloacae* isolate had *KPC-3*.[11] In Cochabamba, Bolivia, all carbapenem-resistant *Acinetobacter* species contained the *OXA-23* gene. However Southern blotting confirmed that the location of the genes was chromosomal rather than on a plasmid.[13] A study based in San José, Costa Rica, reported that 8 of 32 included *P. aeruginosa* isolates found in hospital-acquired infections harbored genes coding for carbapenem resistance (25%), 4 of 8 strains contained *VIM-2* and *IMP-18* alleles, and the remaining 4 contained only the *VIM-2* gene.[16] In Corrientes, Argentina, PCR sequencing was performed on 22 isolates of *K. pneumoniae*, and 100% were found to contain a *KPC* gene.[9] In Buenos Aires, Argentina, singleplex and multiplex PCRs were used to identify the resistance mechanism of various organisms with phenotypic carbapenem resistance, 80% of which were *K. pneumoniae*. The most common resistance gene identified was the *KPC* gene, which was in 74% of CROs.[23] In Saõ Paulo, Brazil, carbapenem-resistant *K. pneumoniae* isolates were sequenced ($n = 36$), and 72.2% were found to contain a *KPC* gene; the *KPC-2* gene was the only allele identified.[22]

The mortality rate from CRO infection was reported in 5 of 17 included studies. A study based in Sao Paulo, Brazil, reported a mortality rate of 50% in bloodstream infections secondary to CROs, which was significantly higher than that of non-CRO infections (36.9%, $P = 0.0130$).[8] A study from Medellín, Colombia, comparing clinical characteristics of children infected or colonized with carbapenem-resistant *K. pneumoniae* ($n = 34$) reported mortality rates of 38.2% for infection ($n = 13$) and 21.9% for colonization ($n = 12$, no statistical analysis included in the report).[15] Another study from Medellín, Colombia, reported data from five tertiary care hospitals and compared outcomes from infection with various carbapenem-resistant gram-negative bacilli. This study reported a mortality rate of 16.4% in patients infected with carbapenem-resistant *K. pneumoniae*, *P. aeruginosa*, or *E. coli* ($n = 9$). *Pseudomonas aeruginosa* was the most lethal organism included, with a mortality rate of 18.2% (no statistical analysis data related to mortality rate included).[11] A study from Guatemala City, Guatemala, assessed clinical outcomes relating to infection in 99 patients with carbapenem-resistant bacterial organisms. The most prevalent resistant organism was *K. pneumoniae* (25% of included isolates), 62% of which were resistant to imipenem. The mortality rate reported was 20%, but no data on specific causative organisms were included (nor was there any statistical analysis).[19] A study based in Buenos Aires, Argentina, compared clinical outcomes of bloodstream infections due to carbapenem-resistant and carbapenem-sensitive gram-negative bacteria, and mortality rates were 13% and 5.5%, respectively ($P = 0.15$).[23]

DISCUSSION

The Latin American Network for Antimicrobial Resistance Surveillance, established in 1996 by the Pan American Health Organization and the WHO, involves 20 countries with National Reference Laboratories that collect AMR data. However, data submission is inconsistent, and data on clinical outcomes are lacking as well as differentiation between adult and pediatric infections.[24] The WHO's Global Antimicrobial Resistance and Use Surveillance System (GLASS), which receives surveillance data from 172 participating countries, reported increasing rates of carbapenem resistance in certain organisms by a variety of different mechanisms (including *A. baumannii* and *K. pneumoniae*), importantly referring to potential selection bias and differences in surveillance coverage.[25]

Predominant carbapenem resistance mechanisms have been shown to vary depending on geographical region: Southeast Asia reports higher rates of *NDM* and other *MBL* carbapenemases, whereas in Europe, *KPC* and *OXA-48* are the predominant carbapenemases.[26,27] High percentages of *KPC* in *K. pneumoniae* and *OXA* enzymes in *A. baumannii* have been identified in studies from Latin America.[28,29] This review similarly demonstrates geographical differences in the prevalence and mechanism of carbapenem-resistant infections. In a study based in Venezuela, 100% of carbapenem-resistant *K. pneumoniae* isolates contained *VIM* and *KPC* carbapenemase genes, whereas in Guatemala, *NDM* production in *K. pneumoniae* was found in 94% of resistant isolates.[19,21] A study in Bolivia reported a significant prevalence of multidrug-resistant *A. baumannii* isolates, 100% of which were due to *OXA-23*-like carbapenemase, raising concerns about this organism's potential to cause severe untreatable infections in young patients.[13] These variations in the predominant organism and resistance mechanism emphasize the critical need for enhanced local, national, and international surveillance efforts.

No studies from several countries, including Peru, Belize, and Ecuador, were identified by the literature search, highlighting gaps in available data for pediatric and neonatal patients (Supplemental Figure 2). We acknowledge the publication after our literature search of a surveillance study

from Peru that includes data on neonatal and pediatric resistant gram-negative bloodstream infections.[30]

A high incidence of carbapenem-resistant infections is demonstrated within the included studies, with increasing rates over time. For example, a study based in Guatemala City, Guatemala, reported a shift from 0% to 57% carbapenem resistance in *K. pneumoniae* isolates between 2005 and 2019, respectively, with similar trends observed in *A. baumannii* isolates.[19]

The prevalence of carbapenem-resistant infections is increasing globally for both adults and children, but there are important differences between the two cohorts.[5] Studies from China and the United States revealed significant differences in the predominant resistance mechanism between adults and children; for instance, a study based in China found that *NDM* was the most common carbapenemase produced in children infected with CROs, compared with *KPC* in adults, whereas a study reporting data from 18 sites in the United States found that carbapenem resistance in children was less likely to be caused by carbapenemase production than that in adults.[31,32]

Comparing challenges related to carbapenem-resistant infection between adults and children involves recognizing shared and unique aspects between each population. For example, adults and children may both be subject to excessive antibiotic exposure, which contributes to the development of carbapenem resistance. Similarly, infection control practices to reduce nosocomial transmission are important in both groups. Pediatric and neonatal populations are usually not included in clinical trials researching novel combination antibiotics; therefore, pharmacokinetic/pharmacodynamic (PKPD) data are usually extrapolated from adult data.[33] Greater variability in PKPD is evident within the pediatric and especially the neonatal cohort than within adults; this may reduce the reliability of extrapolation of adult antimicrobial data to the pediatric population, resulting in antibiotic misuse or over- or underdosage. Furthermore, diagnostic challenges arise when AMR diagnostic tools are not validated for use in the pediatric population.[34]

Previous antibiotic use, especially of beta-lactams, including carbapenems, and comorbidities such as chronic illnesses are significant risk factors for carbapenem-resistant infections; these risk factors are consistent with existing adult data.[35] Global antibiotic consumption increased by 65% between 2000 and 2015, and carbapenem resistance will likely become more prevalent in adult and pediatric populations as consumption continues to rise.[36]

This review included studies in English and Spanish only, identifying a potential selection bias against Brazilian studies written in Portuguese. However, only one article was excluded for this reason. The selected articles are likely to represent data from areas with adequate laboratory resources to perform processes such as DNA sequencing, which may not recognize or represent low-resource settings with a high burden of disease. These areas should be brought to the attention of key stakeholders. Multifaceted strategies, including antimicrobial stewardship programs and enhanced surveillance, are crucial in combating carbapenem resistance. A study based in the United States used surveillance data obtained from seven participating sites to demonstrate a falling incidence of CRO infection between 2016 and 2020, highlighting that the enhanced surveillance of CROs allowed for the timely implementation of prevention measures and continued focus on antimicrobial stewardship with effective results.[37] Local stewardship initiatives and global surveillance programs like WHO GLASS play important roles in guiding effective antimicrobial use and monitoring resistance trends.

CONCLUSION

This literature review has summarized the available evidence of carbapenem-resistant infection in pediatric and neonatal populations in Latin America. Mortality rates are exceedingly high among neonates and children, emphasizing the severity of these infections and the urgency for effective treatment strategies. Moving forward, surveillance of AMR within the pediatric population should be included and prioritized in national screening programs and globally where possible, and stakeholders should endeavor to ensure that surveillance data represent low-resource settings, where there is high burden of disease.

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Current contact information: Gabriella Shanks, Royal London Hospital, London, United Kingdon, E-mail: gabriella.shanks1@nhs.net. Louis Grandjean, Institute of Child Health, University College London, London, United Kingdon, E-mail: l.grandjean@ucl.ac.uk.

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