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EDITORIAL

The global threat of antimicrobial resistance - The need for standardized surveillance tools to define burden and develop interventions☆,☆☆

A ameaça global da resistência antimicrobiana - A necessidade de instrumentos de vigilância padronizados para definir carga e desenvolver intervenções

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Anti-microbial resistance (AMR) is one the biggest issues the medical community is currently facing, as evidenced by the increasing prevalence of pan-resistant strains. In addition to treatment options, AMR also has major financial and economical implications. It has been estimated that up to 50% of antimicrobial use is inappropriate; each year approximately 2 million people in the US are infected with a resistant organism.[1] Up to 23,000 yearly deaths are reportedly caused directly by such infections.[1] The situation is further complicated in low-income countries by lack of effective surveillance systems, laboratory diagnostics, and access to appropriate antimicrobials in the face of financial limitations.

The emergence of MDR Gram-negative bacterial (GNB) resistance is particularly of concern, especially in intensive care units (ICUs) and immunocompromised patients, as there are often limited treatment options available and second-line treatments usually have unfavorable pharmacokinetic and pharmacodynamics profiles, which has been linked to adverse outcomes.[2] Intensive care units have a disproportionately high incidence of nosocomial infections relative to the number of patients, and this incidence continues to rapidly rise.[3,4] For example, in ICUs in the United States, the prevalence of MDR pathogens such as vancomycin-resistant *Enterococci* (VRE) and carbapenem-resistant *Acinetobacter baumannii* has risen to 33.3% and 30%, respectively.[5] Most of these infections are catheter-related blood stream infections (CRBSI) and ventilator-associated pneumonia (VAP).[6,7] In addition, medical equipment is also a risk factor for horizontal transmission of nosocomial organisms.[8] The high incidence of resistance may be due to the high burden of antimicrobial use in this population, causing selective pressure. The European point prevalence survey of antimicrobial use conducted by the Antibiotic Resistance and Prescribing in European Children (ARPEC) group reported a significantly higher prevalence of antibiotic use in intensive care and hematology–oncology wards.[9]

In Brazil and Latin America, the frequency of Gram-negative bacilli in hospital-acquired bloodstream infections surpasses those of Gram-positive, with a significant proportion of multi-resistant infections.

In a multicenter study evaluating nosocomial bloodstream infections (NBSIs) in Brazil, Pereira et al. found

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342 clinically significant episodes in pediatric patients (≤16 years). 96% of BSIs were monomicrobial. Gram-negative organisms caused 49.0% of these NBSIs, Gram-positive organisms caused 42.6%, and fungi caused 8.4%. The most common pathogens were coagulase-negative staphylococci (CoNS) (21.3%), *Klebsiella* spp. (15.7%), *Staphylococcus aureus* (10.6%), and *Acinetobacter* spp. (9.2%). The crude mortality was 21.6% (74 of 342). 45% of NBSIs occurred in a pediatric or neonatal ICU. The most frequent underlying conditions were malignancy, in 95 patients (27.8%). In this study, the prevalence of antibiotic-resistant Gram-negative bacteria was very high, especially *Pseudomonas aeruginosa* and *A. baumannii*. Carbapenem-resistance rates as high as 40% for *Acinetobacter* spp. and 23% for *P. aeruginosa* were observed, among the highest described in the literature for the pediatric population.[10]

In 2007, Arnoni et al. reported the Gram-negative profile of infections in a pediatric center in Brazil and found that 47.8% were multidrug-resistant, 54.2% were *Klebsiella* spp. Extended spectrum β-lactamase producers and 36.4% were imipenem-resistant *P. aeruginosa*. The mortality rate was 36.9% in the studied cases, and was significantly higher in the group of patients with multidrug resistant infections.[11]

This retrospective study by Costa et al.[12] provides valuable pediatric data on AMR rates in this vulnerable cohort with hematological malignancies in an intensive care setting, which has not previously been reported. It found a high burden of GNB infection in this cohort, with MDR-GNB accounting for just under half of the cases. The most common MDR-GNB pathogens were *A. baumannii* (17%), *Stenotrophomonas maltophilia* (15%), Enterobacter spp. (15%), and *K. pneumonia* (15%). The frequency of resistance amongst these pathogens ranged from 18.5% up to 50%. *P. aeruginosa* was the most commonly found non MDR-GNB pathogen (41%). In both MDR-GNB and non MDR-GNB groups, bacteria were isolated most frequently from the tracheal aspirate, followed by blood and urine cultures. Solid CNS tumors were the most frequent underlying condition in both these groups.

The study's most significant finding was the association of MDR-GNB infection with hospital-acquired infections (HAIs) and hematological disease ($p = 0.015$, $p = 0.021$, respectively). Other significant findings were the notably higher rate of MDR-GNB infection in patients who received inappropriate initial antibiotic therapy or delayed treatment.

The overall prevalence rate of 46.5% of MDR-GNB organisms in the study is similar to that found in a retrospective observational study from a tertiary hospital in Rome (39%).[13] Although the patient groups in these studies were not entirely similar, they were comparable in that 86.3% subjects had an underlying condition. However, the frequencies of MDR, such as *Escherichia coli*, *Klebsiella pneumoniae* and *A. baumannii* (50%, 46.6%, and 36.4%, respectively), were significantly lower than resource-limited intensive care or sepsis cohorts. Le Doare et al. observed that 66.8% of all isolates were GNB in resource poor settings; *K. pneumoniae* was the predominant pathogen, accounting for approximately half of the isolates and demonstrating the highest overall resistance (50–84.4% to third generation cephalosporins).[14] Similarly, Cai et al. reported Gram-negative organisms as responsible for 65.5% cases of VAP in PICU patients from Wuhan, China. MDR *A. baumannii* was responsible for more than 50% of these infections; over 70% strains were carbapenem- and cephalosporin-resistant.[15] A small prospective Thai study in PICU patients also demonstrated that approximately half of HAIs were due to MDR-GNB organisms, in particular *A. baumannii* and *Pseudomonas* spp., all of which were carbapenem-resistant.[16] This study also found stay of more than seven days in PICU to be an independent risk factor for MDR-HAI.[16] Several previous studies have also demonstrated the association between prior antibiotic use and infection with drug-resistant organisms, especially Gram-negative bacteria.[17,18] An association between emergence of resistant organisms and use of particular antibiotic agents more commonly has also been found in longitudinal time-series analyses.[19]

Berezin et al. reviewed GNB in PICU and neonatal ICU (NICU) set-ups in Latin America,[20] however, only six of the 12 included studies reported susceptibility data, suggesting the general paucity of surveillance data from the region. One study reported 64% of *K. pneumoniae* isolates were resistant to third-generation cephalosporins, but all *K. pneumoniae* and 80% of *P. aeruginosa* were susceptible to carbapenems, which differed from the findings of Costa et al.[12] In general, the review found a higher rate of HAI in children admitted to PICU in Latin America when compared to similar European and North American settings. There was a wide variability in frequency of GNB, depending on the region, although the commonest organisms were similar (i.e., *K. pneumoniae*, *E. coli*, and *P. aeruginosa*), with only sporadic cases of *Acinetobacter* but with a high level of MDR.

Given the national and regional variations of resistance patterns, as indicated by previous studies, as well as likelihood of admissions to such centers occurring from different parts of the country, larger prevalence studies are required to enhance understanding of resistance patterns. Long term outcome in these patients, taking into account the prognosis of underlying malignancies, would also add to the understanding of the implications of infection with MDR-GNB.

The WHO six-point package, issued to combat AMR at the World Health Day 2011, emphasized need for financial commitment, strengthening surveillance, access to quality medicines, stewardship, infection control, and promoting research into new ways of combating infectious diseases.[21] The GARPEC project is one such initiative that aims to promote collaborative research and collection and sharing data between participants at a regional and global level in order to accumulate an evidence base for developing appropriate stewardship programs based on antibiotic prescribing patterns and resistance surveillance data. International collaboration on standardised surveillace efforts linked with evidence based interventions will be key in overcoming this impending threat to international child health.

Conflicts of interest

The authors declare no conflicts of interest.

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