What's New about Antimicrobial Resistance in Pediatric Infectious Diseases?

Vikram S Kumar

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Source: Sands K, Carvalho MJ, Portal E, Thomson K, Dyer C, Akpulu C, Andrews R, Ferreira A, Gillespie D, Hender T, Hood K, Mathias J, Milton R, Nieto M, Taiyari K, Chan GJ, Bekele D, Solomon S, Basu S, Chattopadhyay P, Walsh TR. Characterization of antimicrobial-resistant gram-negative bacteria that cause neonatal sepsis in seven low- and middle-income countries. *Nat Microbiol* 2021;*6*(4):512–523. DOI: 10.1038/s41564-021-00870-7

The Burden of Antibiotic Resistance in Neonates from Developing Societies (BARNARDS) network was initiated to characterize the cause and burden of antimicrobial resistance in neonatal sepsis for seven low- or middle-income countries in Africa and South Asia. A total of 36,285 neonates were enrolled in the BARNARDS study between November 2015 and December 2017, of whom 2,483 were diagnosed with culture-confirmed sepsis. *Klebsiella pneumoniae* (*K. pneumoniae*) was the main cause of neonatal sepsis, with *Serratia marcescens*, *Klebsiella michiganensis*, *Escherichia coli* (*E. coli*), and *Enterobacter cloacae* (*E. cloacae*) complex also detected. Enterobacterales (*K. pneumoniae, E. coli*, and *E. cloacae*) harbored multiple cephalosporin and carbapenem-resistance genes. All isolated pathogens were resistant to multiple antibiotic classes, including those used to treat neonatal sepsis. Also in the study, intraspecies diversity of *K. pneumoniae* and *E. coli* indicated that multiple antibiotic-resistant lineages cause neonatal sepsis.

Source: Johnson J, Robinson ML, Rajput UC, Valvi C, Kinikar A, Parikh TB, Vaidya U, Malwade S, Agarkhedkar S, Randive B, Kadam A, Smith RM, Westercamp M, Mave V, Gupta A, Milstone AM, & Manabe YC. High burden of bloodstream infections associated with antimicrobial resistance and mortality in the neonatal intensive care unit in Pune, India. *Clin Infect Dis* 2021;*73*(2):271–280. DOI: 10.1093/cid/ciaa554

The authors performed a prospective cohort study in three tertiary neonatal intensive care units in Pune, India, to understand and describe the epidemiology of neonatal bloodstream infections (BSIs). Early-onset BSI was defined as BSI on day of life (DOL) 0–2 and late-onset BSI on DOL 3 or later. The majority of BSIs were caused by gram-negative bacteria (GNB) (58%)—among GNB, 61 (45%) were resistant to carbapenems. *Klebsiella* spp. ($n = 53$, 23%) were the most common cause of BSI. Nonlow birth weight neonates with late-onset BSI had the greatest excess in mortality. In summary, in the cohort studied, neonatal BSIs were most commonly caused by GNB, with a high prevalence of antimicrobial resistance (AMR), and were associated with high mortality, even in term neonates.

Source: Mogasale VV, Saldanha P, Pai V, Rekha PD, Mogasale V. A descriptive analysis of antimicrobial resistance patterns of WHO priority pathogens isolated in children from a tertiary care hospital in India. *Sci Rep* 2021;*11*(1):5116. DOI: 10.1038/s41598-021-84293-8

The World Health Organization (WHO) has articulated a priority pathogens list (PPL) to provide strategic direction to research and develop new antimicrobials. In this study, AMR patterns of WHO-PPL in a tertiary healthcare facility in Southern India were explored to understand the local priority pathogens. Culture reports of laboratory specimens from pediatric patients were extracted. The antimicrobial susceptibility patterns for selected antimicrobials on the WHO-PPL were analyzed and reported. Of 12,256 culture specimens screened, 2,335 (19%) showed culture positivity, of which 1,556 (66.6%) were organisms from the WHO-PPL. *E. coli* was the most common organism isolated (37%), followed by *Staphylococcus aureus* (*S. aureus*)(16%). A total of 72% of *E. coli* were extended-spectrum beta-lactamases (ESBL) producers, 55% of Enterobacteriaceae were resistant to third generation cephalosporins due to ESBL, and 53% of *S. aureus* were methicillin-resistant. The analysis showed AMR trends and prevalence patterns in the study setting and the WHO-PPL document are not fully comparable. This kind of local priority difference needs to be recognized in local policies and practices.

Source: Enane LA, Christenson JC. Global emerging resistance in pediatric infections with TB, HIV, and gram-negative pathogens. *Paediatr Int Child Health* 2021;41(1):65–75. DOI: 10.1080/20469047.2020.1853350

Global burdens of drug-resistant tuberculosis (DR-TB), human immunodeficiency virus (HIV), and gram-negative pathogens have a particular impact on pediatric age groups, necessitating a pediatric-focused agenda to address emerging resistance. Challenges include the diagnosis and identification of resistant infections, limited access to novel antimicrobials

Department of Pediatrics, Subbaiah Institute of Medical Sciences, Pediatric generalist, Sarji Hospital, Shivamogga, Karnataka, India

Corresponding Author: Vikram S Kumar, Professor, Department of Pediatrics, Subbaiah Institute of Medical Sciences, Pediatric generalist, Sarji Hospital, Shivamogga, Karnataka, India, Phone: +91 9241495056, e-mail: vikramskumar@yahoo.co.in

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or pediatric-friendly formulations, limited access to research and clinical trials, and implementation challenges related to prevention and successful completion of treatment. In this review, the particular complexities of emerging resistance in TB, HIV, and gram-negative pathogens in children, with attention to both clinical and public health challenges, are highlighted. Key principles of a pediatric-focused agenda to address antimicrobial resistance are outlined. They include quality of care, increasing equitable access to key diagnostics, expanding antimicrobial stewardship and infection prevention across global settings, and health system strengthening. The study states that increased access to research studies, including clinical trials, was needed. Further study and implementation of care models and strategies for the child- or adolescent-centered management of infections such as HIV and TB can critically improve outcomes and avoid the development of resistance. As the current global pandemic of a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), threatens to disrupt health systems and services for vulnerable populations, the authors conclude that this is a critical time to mitigate against a potential surge in the incidence of resistant infections.

Source: Antimicrobial Resistance Collaborators (2022). Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet (London, England)* 2022;*99*(10325):629–655. DOI: 10.1016/S0140-6736(21)02724-0

This study presents the most comprehensive estimates of AMR burden to date. The authors estimated deaths and disability-adjusted life-years attributable to and associated with bacterial AMR for 23 pathogens and 88 pathogen–drug combinations in 204 countries and territories in 2019. They obtained data from systematic literature reviews, hospital systems, surveillance systems, and other sources, covering 471 million individual records or isolates and 7,585 study location years. On the basis of the available predictive statistical models, there were an estimated 4.95 million (3.62–6.57) deaths associated with bacterial AMR in 2019, including 1.27 million (95% UI 0.911–1.71) deaths attributable to bacterial AMR. At the regional level, the researchers estimated the all-age death rate attributable to resistance to be highest in Western sub-Saharan Africa, at 27.3 deaths per 1,00,000 (20.9–35.3), and lowest in Australasia, at 6.5 deaths (4.3–9.4) per 1,00,000. Lower respiratory infections accounted for >1.5 million deaths associated with resistance in 2019, making it the most burdensome infectious syndrome. The six leading pathogens for deaths associated with resistance (*E. coli*, followed by *S. aureus*, *K. pneumoniae*, *Streptococcus pneumoniae*, *A. baumannii*, and *Pseudomonas aeruginosa*) were responsible for 9,29,000 (6,60,000–1,270,000) deaths attributable to AMR and 3.57 million (2.62–4.78) deaths associated with AMR in 2019. One pathogen–drug combination, methicillin-resistant *S. aureus*, caused >1,00,000 deaths attributable to AMR in 2019, while six more each caused 50,000–1,00,000 deaths—multidrug resistant excluding extensively DR-TB, third-generation cephalosporin-resistant *E. coli*, carbapenem-resistant *A. baumannii*, fluoroquinolone-resistant *E. coli*, carbapenem-resistant *K. pneumoniae*, and third-generation cephalosporin-resistant *K. pneumonia*.

Source: Lai CC, Chen SY, Ko WC, Hsueh PR. Increased antimicrobial resistance during the COVID-19 pandemic. *Int J Antimicrob Agents* 2021;57(4):106324. DOI: 10.1016/j.ijantimicag.2021.106324

In addition to the SARS-CoV-2 infection itself, an increase in the incidence of antimicrobial resistance poses collateral damage to the current status of the coronavirus disease 2019 (COVID-19) pandemic. There has been a rapid increase in multidrug-resistant organisms (MDROs), including ESBL-producing *K. pneumoniae*, carbapenem-resistant New Delhi metallo-β-lactamase-producing Enterobacterales, *A. baumannii*, methicillin-resistant *S. aureus*, pan-echinocandin-resistant *Candida glabrata*, and multi-triazole-resistant *Aspergillus fumigatus*. The cause is multifactorial and is particularly related to high rates of antimicrobial agent utilization in COVID-19 patients with a relatively low rate of co- or secondary infection. This study along with many similar studies concludes that appropriate prescription and optimized use of antimicrobials according to the principles of antimicrobial stewardship as well as quality diagnosis and aggressive infection control measures may help prevent the occurrence of MDROs during this pandemic.

Source: Reyman M, van Houten MA, Watson RL, Chu MLJN, Arp K, de Waal WJ, Schiering I, Plötz FB, Willems RJL, van Schaik W, Sanders EAM, Bogaert D. Effects of early-life antibiotics on the developing infant gut microbiome and resistome: a randomized trial. *Nat Commun* 2022;13(1):893. DOI: 10.1038/s41467-022-28525-z

In this study, infants born at ≥36 weeks of gestational age, requiring broad-spectrum antibiotics for treatment of suspected early-onset neonatal sepsis (sEONS) in their first week of life were randomized 1:1:1 to receive three commonly prescribed intravenous antibiotic combinations, namely penicillin + gentamicin, co-amoxiclav + gentamicin, or amoxicillin + cefotaxime. The average antibiotic treatment duration was 48 hours. A subset of non-antibiotic-treated infants from a healthy birth cohort served as controls. Rectal swabs and/or feces were collected before and immediately after treatment, and at 1, 4, and 12 months of life. Microbiota was characterized by 16S ribosomal ribonucleic acid-based sequencing and a panel of 31 antimicrobial resistance genes was tested using a targeted quantitative polymerase chain reaction. Confirmatory shotgun metagenomic sequencing was executed on a subset of samples. The overall gut microbial community composition and antimicrobial resistance gene profile majorly shift directly following treatment and normalize over 12 months. The authors find a decreased abundance of Bifidobacterium spp. and an increased abundance of *Klebsiella* and *Enterococcus* spp. in the antibiotic-treated infants compared to controls. Amoxicillin + cefotaxime shows the largest effects on both microbial community composition and antimicrobial resistance gene profile, whereas penicillin + gentamicin exhibits the least effects. These data suggest that the choice of empirical antibiotics is relevant for adverse ecological side effects. Broad-spectrum antibiotics for sEONS may have pronounced effects on gut microbiome development and selection of antimicrobial resistance when administered in the 1st week of life, during the assembly phase of the neonatal microbiome.

Source: Song WM, Li YF, Liu YX, Liu Y, Yu CB, Liu JY, Li HC. Drug-resistant tuberculosis among children: a systematic review and meta-analysis. *Front Public Health* 2021;9:721817. DOI: 10.3389/fpubh.2021.721817

Drug-resistant tuberculosis (DR-TB), especially multidrug-resistant tuberculosis (MDR-TB) is a public health threat. Little is known about estimates of different profiles and rates of DR-TB among children globally. The authors did a systematic review and meta-analysis of observational studies reporting DR-TB among children. Publications reporting >60 children with bacteriologically confirmed TB and phenotypical drug susceptibility testing results were included.

Pooled proportions of MDR-TB and subanalysis by age subgroups, regions, and economical levels were performed.

The authors identified 4,063 studies, of which 37 were included. Of 23,652 pediatric TB patients, the proportions of DR-TB, MDR-TB, mono-resistant TB, polydrug-resistant TB, and extensively DR-TB were 13.59%, 3.72%, 6.07%, 1.61%, and 0.44%, respectively. The pooled proportion of MDR-TB among 23,652 children of 37 studies was 3.7%. The rate of MDR-TB was much lower in high-income countries (1.8%) than that in lower middle-income countries (6.3%) and upper middle-income countries (7.3%). More specifically, the rates of MDR-TB were 1.7% in the USA, 1.7% in the UK, 2.9% in India, 6.0% in South Africa, and 9.8% in China, respectively.

This meta-analysis concludes that the burden of DR-TB remains high in children, and there are potential associations between rates of pediatric MDR-TB and national economical levels. More interventions on child TB cases in low-income countries may be urgently needed in the future.

Orcid

Vikram S Kumar https://orcid.org/0000-0002-1369-7682