Characterisation and antimicrobial resistance of sepsis pathogens in neonates born in tertiary care centres in Delhi, India: a cohort study

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Summary

Background Sepsis is one of the most common causes of neonatal deaths globally. Most sepsis-related deaths occur in low-income and middle-income countries, where the epidemiology of neonatal sepsis remains poorly understood. Most of these countries lack proper surveillance networks, hampering accurate assessment of the burden of sepsis, implementation of preventive measures, and investment in research. We report results of neonates born in hospital from a multicentre collaboration on neonatal sepsis.

Methods In this cohort study, dedicated research teams prospectively followed up neonates born in one of three tertiary care centres in Delhi, India (Vardhaman Mahavir Medical College, Maulana Azad Medical College, and All India Institute of Medical Sciences [coordinating centre]) and subsequently admitted to the intensive care unit. Neonates were followed up daily until discharge or death. On clinical suspicion, neonates underwent sepsis work-up including blood cultures. The isolated organisms were identified and tested for antimicrobial susceptibility. We defined Gram-negative isolates resistant to any three of five antibiotic classes (extended-spectrum cephalosporins, carbapenems, aminoglycosides, fluoroquinolones, and piperacillin-tazobactam) as multidrug resistant.

Findings 13 530 neonates of 88 636 livebirths were enrolled between July 18, 2011, and Feb 28, 2014. The incidence of total sepsis was 14·3% (95% CI 13·8–14·9) and of culture-positive sepsis was 6·2% (5·8–6·6). Nearly two-thirds of total episodes occurred at or before 72 h of life (defined as early onset; 1351 [83%] of 1980). Two-thirds (645 [64%]) of 1005 isolates were Gram-negative including, *Acinetobacter* spp (22%), *Klebsiella* spp (17%), and *Escherichia coli* (14%). The pathogen mix in early-onset sepsis did not differ from that of late-onset sepsis (ie, after 72 h). High rates of multidrug resistance were observed in *Acinetobacter* spp (181/222, 82%), *Klebsiella* spp (91/169, 54%), and *Escherichia coli* (52/137, 38%) isolates. Meticillin resistance prevailed in 61% (85/140) of coagulase-negative staphylococci and 38% (43/114) of *Staphylococcus aureus* isolates. Nearly a quarter of the deaths were attributable to sepsis. The population-attributable risks of mortality were 8·6% in culture-negative sepsis, 15·7% in culture-positive sepsis by multidrug-resistant organisms, and 12·0% in culture-positive sepsis by non-multidrug-resistant organisms.

Interpretation The high incidence of sepsis and alarming degree of antimicrobial resistance among pathogens in neonates born in tertiary hospitals underscore the need to understand the pathogenesis of early-onset sepsis and to devise measures to prevent it in low-income and middle-income countries.

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See **Comment** page e676

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Introduction

Sepsis is one of the three most common causes of neonatal deaths globally.[1] Most infection-related deaths in the neonatal period occur in low-income and middle-income countries due to poor hygiene and suboptimal practices for infection control. A significant proportion of these deaths are caused by multidrug-resistant pathogens.[2] Despite the massive burden, few high-quality data about neonatal sepsis are available from these countries.[2,3]

The currently available multisite studies on sepsis are from well-established surveillance networks in high-income countries such as the USA,[4] the UK,[5] and Germany.[6] Such infection surveillance networks are a rarity in low-income and middle-income countries;[3] the few available ones have used passive surveillance (eg, the National Neonatal Perinatal Database [NNPD][7] and the Asia-Pacific Neonatal Infections Study [APNIS][8]). Most of the other studies from low-income and middle-income countries are typically from a single site, retrospective, or have relied on routine laboratory reports.[9–12] They often lack rigorous data collection and reporting methods, and run the risk of misclassification and underestimation or overestimation of the incidence of sepsis.[13–15]

The paucity of high-quality data has undermined the recognition of neonatal sepsis as an area of serious concern in public health, the implementation of measures aimed at improvement of health-systems,[3,13,14] and investments in research and innovation in low-income and middle-income countries.[14] In this study, we report data for incidence, profile of organisms, and

Research in context

Evidence before this study

We searched PubMed using the terms "sepsis" and "neonate" (from Jan 1, 2005 to Feb 29, 2016), and limited the search to studies from low-income and middle-income countries. Of the 1460 citations, we included 29 studies reporting data on predominantly (50% or more) neonates born in hospital, and had included at least 20 neonates with sepsis. We excluded studies with a community setting and those reporting data on only single organisms. Most studies were from a single centre (26) and had reported routine microbiology and clinical data (27). Generally, the quality of studies was low. The median number of neonates with sepsis was 84 (IQR 50–143). The incidence of culture-positive sepsis varied from 3·0 per 1000 livebirths to 54·9 per 1000 livebirths (six studies) and case fatality rate varied from 9% to 30% (7 studies). The proportion of early-onset sepsis (onset within 2–4 days after birth; seven studies) ranged from 10·4% to 85·0% of total neonatal sepsis. On enlisting the three most common pathogens in each study, we found *Klebsiella* spp (15 studies), *E coli* (10 studies), and *Staphylococcus aureus* (ten studies) to be the common isolates. *Acinetobacter* spp and group B streptococci were reported as one of three common pathogens in two and five studies, respectively. Pathogen profiles were similar between early-onset and late-onset sepsis (ten studies). The three Gram-negative pathogens—*Klebsiella* spp, *E coli*, and *Acinetobacter* spp—showed a high degree of resistance to commonly used antibiotics such as ampicillin (up to 100%, 100%, and 80%, respectively), cefotaxime (95%, 86%, and 75%), and gentamicin (91%, 79%, and 100%). Carbapenem resistance was reported in *Acinetobacter* spp (0–30%; four studies) and *E coli* (0–15%; four studies); of the five studies reporting data for carbapenem resistance in *Klebsiella* spp, none showed resistance to carbapenems.

Added value of this study

Our study fills a substantial significant gap in the understanding of epidemiology of sepsis in neonates in low-income and middle-income countries. We report a high burden of sepsis among neonates born in tertiary hospitals. Almost two-thirds of sepsis episodes occurred at or before 72 h of life and were caused by pathogens usually associated with nosocomial infections. *Acinetobacter* spp emerged as the most common pathogen. There was a high degree of antimicrobial resistance even to reserve antibiotics such as carbapenems. Approximately half of culture positive neonates died due to sepsis and a quarter of all the deaths were attributable to sepsis.

Implications of all the available evidence

The findings underscore the need to examine the disease biology of early-onset sepsis, including its association with obstetric and neonatal care practices around birth, and to design relevant strategies to prevent infections.

antimicrobial resistance from a prospective cohort study involving three major hospitals in Delhi, India.

Methods

Study design and participants

The Delhi Neonatal Infection Study (DeNIS) collaboration comprises investigators at three tertiary care neonatal units: Vardhaman Mahavir Medical College (VMMC), Maulana Azad Medical College (MAMC), and All India Institute of Medical Sciences (AIIMS; coordinating centre), and one extramural neonatal unit (Chacha Nehru Bal Chikitsalaya) in Delhi. This descriptive cohort study was done among neonates delivered in the tertiary care hospitals (data for Chacha Nehru will be reported separately; appendix p 3) and who required admission to the neonatal intensive care unit (NICU) for any indication during the study period. Neonates requiring rehospitalisation after initial discharge were excluded. The research staff tracked all NICU admissions and enrolled neonates after obtaining informed consent from parents. The research staff prospectively recorded potential maternal risk factors at birth and neonatal factors on a daily basis until discharge or death of the neonates (appendix pp 20–21).

See Online for appendix

The study was approved by the Institutional Ethics Committees of AIIMS, VMMC, and MAMC. Written informed consent was taken from the parents of enrolled neonates.

Procedures

All enrolled neonates were monitored daily for signs and symptoms of sepsis. Sepsis was suspected in the presence of perinatal risk factors or a set of clinical signs as per the Young Infant Study Algorithm.[16] The research nurses obtained blood and, if needed, cerebrospinal fluid samples under strict aseptic conditions and sent them for culture and sepsis screen (appendix p 6) before initiation of any antibiotic therapy. Lumbar puncture was done in all cases of suspected sepsis at one site and only when suspected of meningitis at the other two sites.

The clinical team initiated antibiotics according to the policy of each unit (appendix p 3). The research nurses recorded the age at suspicion of sepsis, investigations done, details of the antibiotics administered, and the clinical course of the baby on a daily basis.

Samples of blood and other body fluids were subcultured after overnight incubation in 5% sheep blood agar (BioMerieux, Marcy l'Etoile, France) and McConkey agar (Oxoid, Hampshire, UK; appendix p 22). Antimicrobial resistance of the isolates was determined as per Clinical and Laboratory Standards Institute guidelines (2011–13).[17–19] Antimicrobial resistance was reported as susceptible, intermediate, resistant, or not tested for each individual antibiotic. Additionally, the Gram-negative pathogens were classified based on their resistance (intermediate or resistant) to various antibiotic