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Trends in antibiotic susceptibility and incidence of late-onset *Klebsiella pneumoniae* neonatal sepsis over a six-year period in a neonatal intensive care unit in Karachi, Pakistan

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SUMMARY

Introduction: The incidence, change in antibiotic susceptibility, and risk factors associated with mortality of late-onset *Klebsiella pneumoniae* sepsis during 2006–2011, in a neonatal intensive care unit (NICU) of a developing country, were analyzed.

Methods: The medical records of neonates with a discharge diagnosis of sepsis due to late-onset *K. pneumoniae* were retrieved. Demographic features, gestational age, date and year of admission, antibiotic susceptibility of isolates, and discharge status were recorded. The late-onset *K. pneumoniae* incidence per 1000 NICU admissions and risk factors for mortality due to late-onset *K. pneumoniae* sepsis are reported.

Results: During the period 2006–2011, 104 of 2768 neonates developed late-onset *K. pneumoniae* sepsis. The overall incidence of late-onset *K. pneumoniae* sepsis was 3.7% (37/1000 NICU admissions), with the highest annual incidence being 53/1000 in 2010. Most cases were males (n = 64; 62%) and most were premature and very low birth weight (n = 68; 65%). More than 80% of isolates were resistant to ampicillin + clavulanic acid, gentamicin, aztreonam, and cephalosporins. An increasing trend of resistance to amikacin, fluoroquinolones, piperacillin/tazobactam, and imipenem was observed. In 2011, three-quarters (72%; n = 13) of late-onset K. pneumoniae were CR *K. pneumoniae*. Seventeen (16%) neonates died. Being male (p = 0.06, adjusted odds ratio (AOR) 9.2, 95% confidence interval (CI) 1.3–66.9), having an extremely low birth weight (p = 0.01, AOR 6.1, 95% CI 0.8–44.4), having severe thrombocytopenia (p = 0.07, AOR 3.9, 95% CI 1.2–13.0), and failure to achieve microbiological clearance ($p < 0.001$, AOR 19.6, 95% CI 4.0–98.0) were significantly associated with mortality due to late-onset *K. pneumoniae* sepsis.

Conclusion: There has been a rise in carbapenem-resistant strains of late-onset *K. pneumoniae*, associated with an increased mortality and limited antibacterial choices. Antimicrobial stewardship and rigorous infection control measures seem to be the only way to limit the spread of these strains.

1. Introduction

Gram-negative organisms are the major pathogens of neonatal sepsis in developing countries.[1] Prematurity, low birth weight, and prolonged hospitalization are the predisposing factors for neonatal sepsis.[2,3] *Klebsiella pneumoniae* is an important pathogen of community-acquired and nosocomial neonatal infections,[1] with case fatality varying from 18% to 68%.[4,5] Drug-resistant *K. pneumoniae* has surfaced as an important pathogen in recent years and has serious implications because of the limited antibiotic choices, increased hospital expenditure, and poor neonatal outcome.[2] A high rate (47%) of cephalosporin resistance has previously been reported from our institute.[4–6] Carbapenems (i.e., imipenem and meropenem) were among the first-line agents used against multidrug-resistant Gram-negative pathogens prior to the emergence of carbapenem-resistant *K. pneumoniae* (CR *K. pneumoniae*) globally. Carbapenem resistance is conferred through the expression of carbapenemases, encoded by mobile genes facilitating rapid horizontal spread. The emergence of these strains has further limited the antibiotic options.[7,8] Carbapenemases are classified as class A (KPC carbapenemases), class B (metallo-beta-lactamases), or class D (OXA-type carbapenemases).[9] CR *K. pneumoniae* is associated with high morbidity and mortality in neonates, the critically ill and immunocompromised, and in children exposed to invasive procedures.[10,11] Polymyxin and fluoroquinolones are the only available options against these

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multidrug-resistant strains.[6,12] Data on the frequency and antimicrobial susceptibility pattern of late-onset neonatal *K. pneumoniae* from developing countries and Pakistan are limited. We report the incidence, change in antibiotic susceptibility, and risk factors associated with mortality of late-onset *K. pneumoniae* neonatal sepsis during 2006–2011 in the neonatal intensive care unit (NICU) of a tertiary care hospital in Pakistan.

2. Materials and methods

We retrospectively reviewed the charts of all neonates with a discharge diagnosis of *K. pneumoniae* sepsis from the NICU of the Aga Khan University Hospital (AKUH), Karachi from January 2006 to December 2011. Medical records were retrieved using the hospital information system and International Classification of Diseases (ICD) codes (ICD9 CM 482.0, 041.3, and 320.82; *K. pneumoniae* pneumonia, *Klebsiella* infection, Gram-negative meningitis, respectively) and the internal birth registry of the NICU, which holds the records of all birth and discharge diagnoses. Only those with late-onset *K. pneumoniae* isolated from the blood stream (with or without meningitis) were selected and analyzed.

AKUH is a tertiary care hospital with a 12-bed, level III NICU (equipped with 10 conventional ventilators, two continuous positive airway pressure (CPAP) drivers, and a high-frequency oscillatory ventilator) providing all neonatal services except extracorporeal membrane oxygenation (ECMO) and hemodialysis. The NICU admits approximately 460 neonates annually. Extremely low birth weight neonates comprise 18% of the total admissions. There are four levels of care in our NICU: level 1 has five beds for neonates born within the institution; level 2 has five beds for neonates admitted via the emergency room or referred from other hospitals; levels 3 and 4 are isolation rooms.

Admissions to the NICU come from two sources: (1) those born in the hospital, and (2) those admitted through the emergency room or transferred from other hospitals. The empiric antibiotic policy of the unit recommends ampicillin and gentamicin for those born in the hospital, while cefotaxime plus amikacin is used for referrals, based on local epidemiological data suggesting a high prevalence of resistant Gram-negative organisms in public sector hospitals.[13] Clinical and Laboratory Standards Institute (CLSI) guidelines for the identification of *K. pneumoniae* are followed at the AKUH laboratory.[14] The strains of *K. pneumoniae* were referred to as extended-spectrum beta-lactamase (ESBL) if they were resistant to cephalosporin, monobactams, and penicillin,[15,16] and as CR *K. pneumoniae* if they were resistant to carbapenems (e.g., meropenem and imipenem).[9] A blood stream infection (BSI) occurring after 72 h of life was termed as 'late-onset' and usually related to infection acquired at home or from the hospital environment, as mentioned.[1,17] Microbiological clearance was defined as two or more consecutive negative blood cultures, with no subsequent positive cultures.[18]

2.1. Statistical analysis

The data were analyzed using SPSS version 20 (IBM SPSS, IBM Corp., Armonk, NY, USA). Demographic features including age (in days) at time of admission, weight (kg), gender, year of admission, gestational age, day of admission at the time of positive *K. pneumoniae*, laboratory parameters (i.e., complete blood count and C-reactive protein), antibiotic susceptibility of late-onset *K. pneumoniae* isolates, time to microbiological clearance, and discharge status (dead or alive at discharge) were recorded. Means and standard deviations are reported for continuous variables (i.e., gestational age, weight, and duration of total parenteral nutrition (TPN)) and frequencies and percentages are reported for categorical variables (i.e., extremely low birth weight (weight less $\leq$1000 g), gender, and antibiotic susceptibility pattern). The annual late-onset *K. pneumoniae* incidence in the NICU is presented per 1000 NICU admissions, and antibiotic susceptibilities are reported. Logistic regression was applied to determine the independent risk factors for mortality. A p-value of <0.25 was considered significant at the univariate level. All variables found significant at the univariate level were entered into a multivariable model and adjusted odds ratios (AOR) and 95% confidence intervals (CI) are reported.

2.2. Ethical approval

The study was approved by the ethics review committee (1951-Ped-ERC-11) of the Aga Khan University, Karachi, Pakistan.

3. Results

A total of 104 out of 2768 NICU admissions were identified with late-onset *K. pneumoniae* sepsis during the period 2006–2011. The incidence was 3.7% (37/1000 NICU admissions; standard error 2.3); the annual incidence is shown in Figure 1. The highest incidence of late-onset *K. pneumoniae* was in the year 2010: 53/1000 NICU admissions. Most of the neonates developed late-onset *K. pneumoniae* during the months of May–August (n = 41; 41%). Most were males (62%; n = 64); two-thirds (n = 69; 66%) had a central line and three-quarters (n = 75; 72%) were ventilated. Sixty-eight (65%) neonates were premature (mean gestational age 30.8 $\pm$ 3 weeks). The mean age at the time of NICU admission was 4.9 $\pm$ 4 days (for referred newborns). Seventeen neonates (16%) died; 9 were born in the hospital (53%).

Overall more than 80% of late-onset *K. pneumoniae* isolates were resistant to ampicillin–sulbactam, gentamicin, aztreonam, and

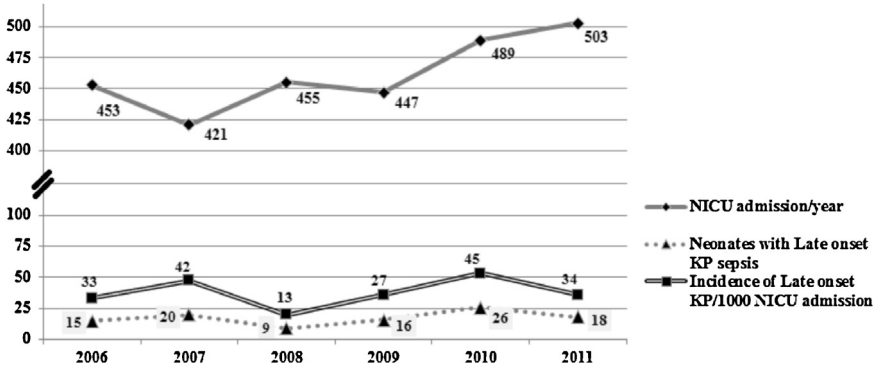

Figure 1. Annual incidence of late-onset *Klebsiella pneumoniae* per 1000 NICU admissions (KP, *Klebsiella pneumoniae*; NICU, neonatal intensive care unit).