International Journal of Infectious Diseases 17 (2013) e961–e965

Contents lists available at SciVerse ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

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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ARTICLE INFO

Article history:
Received 19 September 2012
Received in revised form 2 April 2013
Accepted 5 April 2013

Corresponding Editor: Ziad Memish, Riyadh, Saudi Arabia

Keywords:
Late-onset *Klebsiella pneumoniae*
Incidence
NICU
Carbapenem resistance
Pakistan

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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1201-9712/$36.00 – see front matter
http://dx.doi.org/10.1016/j.ijid.2013.04.007

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

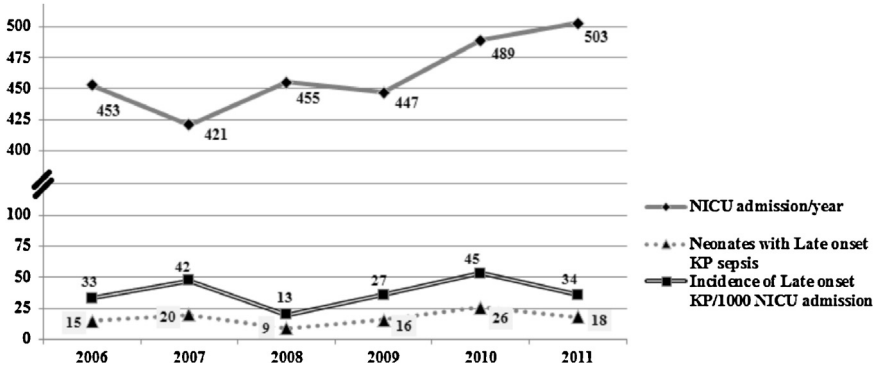

Figure 1. Annual incidence of late-onset *Klebsiella pneumoniae* per 1000 NICU admissions (KP, *Klebsiella pneumoniae*; NICU, neonatal intensive care unit).

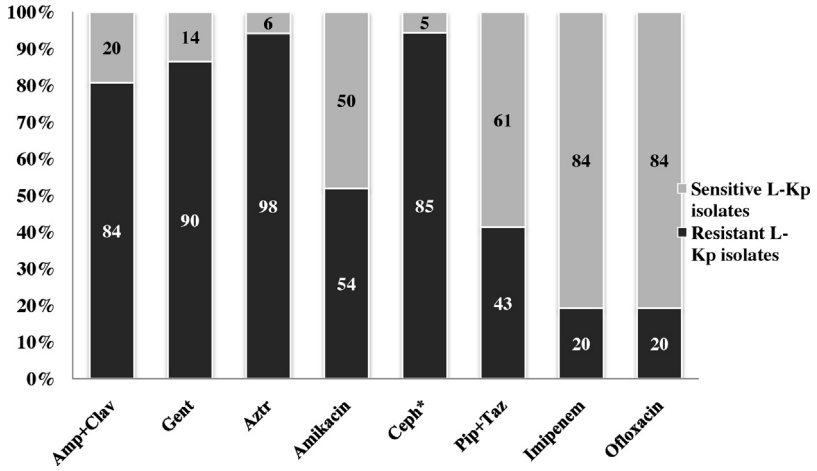

Figure 2. Overall antibiotic resistance pattern of late-onset *Klebsiella pneumoniae* isolates in the NICU cohort. *Ceph: antibiotic susceptibility was checked with ceftriaxone, cefuroxime, and cefixime. Abbreviations: Amp+Clav, ampicillin + clavulanic acid; Gent, gentamicin; Aztr, aztreonam; Ceph, cephalosporin; Pip+Taz, piperacillin + tazobactam.

cephalosporin (Figure 2). Late-onset *K. pneumoniae* strains were susceptible to fluoroquinolones and carbapenems, however only half of the late-onset *K. pneumoniae* strains were susceptible to amikacin. A trend of increasing resistance to all antibiotics was seen (Figure 3). CR *K. pneumoniae* isolates were first isolated in 2008. In 2011, three-quarters (72%; n = 13) of late-onset *K. pneumoniae* were CR *K. pneumoniae*. Late-onset *K. pneumoniae* remained susceptible to fluoroquinolones. Two of the 17 neonates who died had a CR *K. pneumoniae*, leading to CR *K. pneumoniae* case fatality rate of 12%.

Table 1 compares the discharge status of neonates with late-onset *K. pneumoniae* sepsis and the risk factors for mortality. Having an extremely low birth weight (p = 0.01, AOR 6.1, 95% CI 0.8–44.4), being a male (p = 0.06, AOR 9.2, 95% CI 1.3–66.9), having severe thrombocytopenia (p = 0.07, AOR 3.9, 95% CI 1.2–13.0), and failure to achieve microbiological clearance (mean 4 ± 2 days) ($p <$ 0.001, AOR 19.6, 95% CI 4.0–98.0) were significantly associated with mortality. The choice of antibiotic management had no significant association with the outcome. Most children had received mechanical ventilation, had a central line, and had received TPN for their management; however these variables were not significant in the final model. Eleven neonates (65%) did not achieve microbiological clearance after 96 h and died.

4. Discussion

K. pneumoniae is a recognized cause of neonatal septicemia worldwide.[1] Our late-onset *K. pneumoniae* neonatal sepsis rate was high (37/1000 NICU admissions), with increasing drug resistance over the years. In 2010, there was high rate of nosocomial infections in the NICU and the infection control team performed surveillance cultures. No specific source was identified; however *K. pneumoniae* was identified from a number of environment surfaces and therefore the NICU was closed for terminal disinfection. At the same time, hand washing certification of the NICU staff was performed, along with education on strict barrier nursing and reinforcement of gown and glove precautions for suspected or culture-proven septic neonates. Routine surveillance of hand hygiene in the NICU indicated an increase in hand washing compliance from 60% to 100% after these measures. The nurse to patient ratio in our NICU remained unchanged (12 neonates/4–5 nurses). The current recommendations for the prevention of CR *K. pneumoniae* outbreaks include contact precautions for infected or colonized patients and active surveillance in high-risk units.

Seasonal variations in infections by some pathogenic Gram-negative organisms have been observed. The incidence is highest in the summer months and the proposed hypothesis

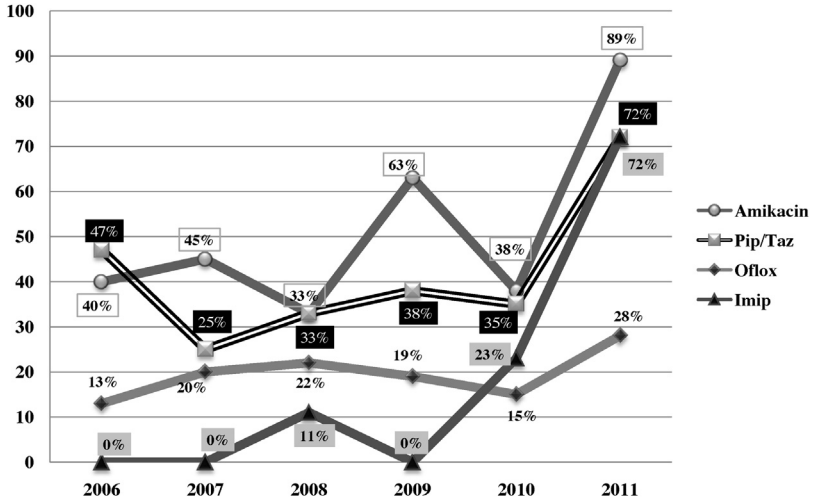

Figure 3. Annual antibiotic resistance pattern for late-onset *Klebsiella pneumoniae* isolates from the neonatal cohort. Abbreviations: Pip/Taz, piperacillin + tazobactam; Oflox, ofloxacin; Imip, imipenem.

Table 1
Risk factors associated with mortality in neonates who developed late-onset *Klebsiella pneumoniae* neonatal sepsis in the NICU

Variables	Discharged (n = 87)	Died (n = 17)	p-Value	OR (95% CI)	AOR[a] (95% CI)
Neonatal features					
Age[b] (days) (mean ± SD)	3.5 ± 5	2.2 ± 3	0.78	0.9 (0.7–1.3)	
Gestational age (weeks) (mean ± SD)	31 ± 3	29 ± 3	0.02	0.7 (0.6–0.9)	0.8 (0.6–1.1)
Premature (%)[c]	57 (66%)	11 (65%)	0.94	0.9 (0.3–2.9)	
Weight (kg) (mean ± SD)	2 ± 0.9	1.8 ± 0.9	0.30	0.7 (0.4–1.3)	
ELBW	7 (8%)	5 (29%)	0.01	4.7 (1.3–17.5)	6.1 (0.8–44.4)
Male (%)	50 (57%)	14 (82%)	0.06	3.0 (0.9–9.5)	9.2 (1.3–66.9)
Ventilated (%)	53 (61%)	16 (94%)	0.01	10.2 (1.3–80.9)	
Central line (%)	61 (70%)	14 (82%)	0.40	2.0 (0.5–7.5)	
Hospitalization day at *K. pneumoniae* sepsis[d] (mean ± SD)	9.4 ± 9	10 ± 13	0.80	1.0 (0.9–1.0)	
TPN received (%)	71 (82%)	17 (100%)	0.07	1.2 (1.1–1.4)	
TPN duration (days) (mean ± SD)	12 ± 11	15 ± 15	0.90	1.0 (0.9–1.0)	
Laboratory investigations[e]					
WBC (10^9/l)	14 ± 9	10 ± 5	0.05	0.9 (0.8–0.9)	
Neutrophils (%)	61 ± 19	62 ± 25	0.90	1.1 (0.9–1.3)	
Platelets (10^9/l)	164 ± 200	70 ± 63	0.03	1.0 (0.9–1.0)	
Severe thrombocytopenia[f]	22 (25%)	8 (47%)	0.07	2.6 (0.9–7.6)	3.9 (1.2–13.0)
C-reactive protein	7.0 ± 6	9.3 ± 6.7	0.22	1.0 (0.9–1.2)	1.2 (1.0–1.4)
Late-onset *K. pneumoniae* antimicrobial susceptibility					
Amikacin	45 (52%)	5 (29%)	0.09	2.6 (0.8–8.0)	1.2 (0.2–6.0)
Piperacillin + tazobactam	50 (57%)	11 (61%)	0.60	0.7 (0.3–2.2)	
Fluoroquinolones	70 (80%)	14 (82%)	1.0	0.9 (0.2–3.4)	
Carbapenem	69 (79%)	15 (88%)	0.52	0.5 (0.1–2.4)	
Length of hospital stay (days) (mean ± SD)	26 ± 18	25 ± 19	0.83	0.9 (0.9–1.0)	
Microbiological clearance achieved (%)	79 (91%)	6 (35%)	<0.001	18.1 (5.3–62.1)	19.6 (4.0–98.0)

AOR, adjusted odds ratio; CI, confidence interval; ELBW, extremely low birth weight; NICU, neonatal intensive care unit; OR, odds ratio; SD, standard deviation; TPN, total parenteral nutrition; WBC, white blood cells.
[a] AOR: univariate p-value <0.25 taken into account for multivariate analysis.
[b] Age at the time of NICU admission.
[c] Premature: gestational age <37 weeks.
[d] Day of hospital admission when the positive late-onset *K. pneumoniae* culture was sent.
[e] Laboratory investigations when the neonate become symptomatic and bacterial culture was positive for late-onset *K. pneumoniae*.
[f] Platelet count <50 × 10^9/l.

is differences in their colonization rates. Our neonatal late-onset *K. pneumoniae* rates were high during the summer months, a finding consistent with those of previously published studies.[19,20] The majority of neonates in our study were male. The same has been reported previously.[3,21] This could be due to a gender bias in health-seeking practices in this part of the world.[22] Moreover, the ESBL phenotype of *K. pneumoniae* has been reported more frequently in males.[6] Immaturity of the immune system in premature neonates predisposes them to nosocomial infections.[1,12] Most of the neonates in our study were premature, however this had no significant association with mortality (Table 1).

An increase in ESBL-producing *K. pneumoniae* sepsis has been reported worldwide,[1,23] and the NICU contributes most cases.[24] These ESBL-producing *K. pneumoniae* are usually sensitive to carbapenems.[6,25] Our late-onset *K. pneumoniae* isolates showed a multidrug resistance pattern with a rise in carbapenem resistance (Figure 3). There are few therapeutic options available against CR *K. pneumoniae*: imipenem or meropenem (if the minimum inhibitory concentration (MIC) is ≤1 μg/ml), polymyxin, tigecycline, or a combination of antibiotics associated with the removal of invasive devices.[26] Polymyxin B is one of the few antibiotics that can be used for the treatment of CR *K. pneumoniae* and other multidrug-resistant Gram-negative pathogens.[2,12,27] CR *K. pneumoniae* is associated with a high mortality.[28] Eleven neonates did not achieve microbiological clearance and died while on treatment, however only two of them had CR *K. pneumoniae*. CR *K. pneumoniae* is associated with an increased mortality worldwide;[26,28] our CR *K. pneumoniae* case fatality rate was 20%.

This was a single-center study and therefore results should be generalized with caution. Because of the retrospective design we were limited by the completeness of documentation; some information was missing. Our late-onset *K. pneumoniae* rate could be high as we had an outbreak in 2010, and during outbreaks the spread is clonal; however there were cases during the whole study duration. This is the first study from Pakistan reporting the clinical characteristics and outcomes in neonates with resistant *K. pneumoniae* infections.

In conclusion, our study showed an increasing incidence and antibiotic resistance of late-onset *K. pneumoniae* isolates in the NICU over the 6-year study period. KPC is a severe threat to the healthcare system and calls for stringent standard infection control practices in healthcare settings, with antibiotic stewardship to control the injudicious use of antibiotics for neonatal sepsis.

Acknowledgement

Drs Ali Faisal Saleem and Farah Naz Qamar received research training support from the National Institute of Health's Fogarty International Center (1 D43 TW007585-01). Drs Sarah Kiani, Muhammad Mohsin, and Mutahera Mazhar are thanked for their help with the data collection.

Conflict of interest: No conflict of interest to declare.

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