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Risk factors and outcome of *Klebsiella pneumoniae* sepsis among Newborns.

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Abstract

The present study was conducted to identify the risk factors, antibiotic susceptibility pattern and outcome of neonatal *Klebsiella pneumoniae* sepsis. All admitted neonates with clinically suspected sepsis underwent blood culture. Babies with positve blood culture were included in the study. Detailed antenatal, natal and neonatal treatment histories including the outcome were noted. Among 120 clinically suspected cases of neonatal sepsis, 50 (41.6%) had a positive blood culture, out of which 33 (27.5%) were due to *Klebsiella pneumoniae*. Neonates with birth weight ≤ 2.5 Kg, preterm neonates, inborn babies and neonates with early-onset sepsis were found to have higher risk for infection by *Klebsiella pneumoniae* based on univariate analysis. Regression analysis identified neonates with birth weight ≤ 2.5 Kg and inborn babies to be at higher risk of developing Klebsiella infection. All Klebsiella pneumoniae isolates were sensitive to meropenam.

Keywords: *Klebsiella pneumoniae*, Neonatal sepsis, Risk factors, Outcome

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Introduction

Sepsis is a common cause for admission to neonatal units and is a leading cause of morbidity and mortality among neonates worldwide [1]. The National Neonatal Perinatal Database of India, reveals an incidence of 8.5 culture proven cases of sepsis per 1,000 live births [2]. Neonatal sepsis is generally categorized as early or late onset. Early-onset neonatal sepsis occurs within first 72 hours of life, while the late-onset neonatal sepsis after 72 hours of life. In general, gram negative bacteria are the predominant causes of neonatal sepsis and among them *Klebsiella pneumoniae* is the most common pathogen, especially in developing countries [1, 3- 5]. Therefore, there is a need to study the risk factors for neonatal sepsis caused by locally prevalent *Klebsiella pneumoniae* strains and its outcome. We performed this study to determine the various risk factors associated with neonatal sepsis caused by *Klebsiella pneumoniae*, its sensitivity pattern and outcome.

Material and Methods

A prospective observational study was conducted at our tertiary care teaching hospital. This study was approved by the Institute's research and ethical committee and informed consent was obtained from each patient's next of kin. During a period of two years, all inborn and outborn babies clinically suspected to have sepsis were evaluated. Blood culture was performed for all those neonates. The babies for whom the blood culture was negative were excluded from the study. The neonates with blood culture positive for *Klebsiella pneumoniae* were considered as cases and those positive for other pathogens were considered as controls. The antibiotic susceptibility of all the *Klebsiella pneumoniae* isolated was determined by the Kirby-Bauer disk diffusion method according to Clinical Laboratory Standards Institute guidelines [6]. All the *Klebsiella pneumoniae* isolates were also tested for extended spectrum β-lactamase (ESBL) by combination disk method using both cefotaxime and ceftazidime, alone and in combination with clavulanic acid [6]. Double-disk test using both cefotaxime and ceftazidime, alone and in combination with clavulanic acid, was performed for detection of extended spectrum β-lactamase (ESBL) in *Klebsiella pneumoniae*, according to CLSI guidelines. In this test, an overnight culture suspension of the test isolate adjusted to 0.5 McFarland standard was inoculated using a sterile cotton swab on the surface of a Mueller Hinton Agar. The Cefotaxime (30 µg) and cefotaxime-clavulanic acid (30 µg/ 10 µg) disks were placed 20 mm apart on the agar. Similarly, the ceftazidime (30 µg) and ceftazidime-clavulanic acid (30 µg/ 10 µg) disks were placed 20 mm apart. After incubating overnight at 37^{0}C, a ≥ 5-mm in-

crease in the zone diameter for either antimicrobial agent tested in combination with clavulanic acid vs. its zone when tested alone was interpreted as positive for ESBL production. *Escherichia coli* ATCC 25922 and *Staphylococcus aureus* ATCC 25923 were used for quality control of Kirby-Bauer disk diffusion method. *Klebsiella pneumoniae* ATCC 700603 and *Escherichia coli* ATCC 25922 were used for quality control of ESBL testing.

A detailed antenatal, natal and postnatal history was taken. The birth weight, sex and day of onset of sepsis were noted. Details regarding risk factors such as ventilator support, CPAP, central line and exchange transfusion prior to onset of sepsis were also noted.

Data entry and analysis were done using SPSS for Windows Version SPSS 16.0 (SPSS Inc, Chicago, IL, USA). Means and standard deviations (SD) were calculated as required for numerical variables. The Chi-square test or Fisher's exact test was used to compare two groups. We confirmed the results of these tests with logistic regression analysis. This was necessary to avoid producing spuriously significant results with multiple comparisons. Results of the logistic regression analysis were reported as adjusted odd ratios with their 95% confidence intervals. All*P* values<0.05 were considered statistically significant.

Results

During the study period there were a total of 120 clinically suspected cases of neonatal sepsis. Of the 120 neonates, only 50 (41.6%) had a positive blood culture result. The mean birth weight of the babies was 2.16 ± 0.65 Kg (1.2 - 3.4) and the mean postnatal age was 3.46 ± 5.41 days (1- 26). The male to female ratio was 3:2. Of the 50 culture-proven cases of neonatal sepsis, 33 were positive for *Klebsiella pneumoniae*, while the remaining 17 were positive for other pathogens including Coagulase negative Staphylococci (6), *Enterobacter* spp. (3), *Acinetobacter* spp. (3), Streptococcus pneumonia (2), *Escherichia coli* (1), *Pseudomonas stutzeri* (1), Group B *Streptococcus* (1). Of the 33 *Klebsiella pneumoniae* isolates, 18 (54.5%) were ESBL producers. The antibiotic susceptibility pattern of the non-ESBL producing and ESBL producing *Klebsiella pneumoniae* are summarized in Table 1. The prevalence of ESBL producing *Klebsiella pneumoniae* among inborn and outborn neonates was 64% -(16 out of 25) and 25% (2 out of 8), respectively (*P* < 0.1015). The prevalence of ESBL producing *Klebsiella pneumoniae* during May-June 2006 was 83.3% (15 of 18), while during the rest of the study period it was 20% (3 of 15) (*P* value 0.0010).

***Table 1**. Antibiotic susceptibility pattern of the 33 Klebsiella pneumoniae isolates*

Antibiotic	**Non-ESBL-producers, n = 15 (45.5 %)**	**ESBL-producers, n = 18 (54.5%)**
	No. of susceptible isolates (%)	**No. of susceptible isolates (%)**
Ampicillin	0 (0)	0 (0)
Gentamicin	0 (0)	0 (0)
Amikacin	13 (86.7)	14 (77.8)
Chloramphenicol	5 (33.3)	3 (16.7)
Ciprofloxacin	4 (26.7)	2 (11.1)
Ceftriaxone	1 (6.7)	0 (0)
Meropenem	15 (100)	18 (100)

**All ESBL-producing isolates were considered resistant to penicillins and oxyiminocephalosporins, according to CLSI guidelines.*

***Table 2.** Univariate analysis of risk factors for Klebsiella pneumoniae infection*

Parameter	***Klebsiella pneumoniae*** (n = 33) (%)	**Other infections** (n = 17) (%)	**Relative risk** (95% confidence limits)	***P* value**
PROM > 24 hrs	4 (12.1)	1 (5.9)	1.24 (0.76 to 2.02)	0.6497
Birth weight ≤ 2.5 Kg	25 (75.8)	5 (29.4)	2.08 (1.19 to 3.65)	0.0042
Preterm	20 (60.6)	3 (17.6)	1.81 (1.18 to 2.75)	0.0097
Inborn	25 (75.8)	6 (35.3)	1.92 (1.10 to 3.34)	0.0129
Male sex	21 (63.6)	9 (52.9)	1.17 (0.76 to 1.79)	0.6697
Early-onset	29 (87.9)	10 (58.8)	2.04 (0.92 to 4.57)	0.0303
Ventilation	11 (33.3)	2 (11.8)	1.42 (1.00 to 2.03)	0.1729
CPAP	6 (18.2)	3 (17.6)	1.01 (0.61 to 1.69)	1.0000
Central line	2 (6.1)	0 (0)	1.55 (1.26 to 1.91)	0.5420
Exchange transfusion	2 (6.1)	0 (0)	1.55 (1.26 to 1.91)	0.5420

Table 3. *Logistic regression analysis of risk factors for Klebsiella pneumoniae infection*

	***P* value**	**Adjusted Odds ratio**	**95% confidence interval**	
			Lower	**Upper**
Birth weight ≤ 2.5 Kg	0.033	14.487	1.234	170.045
Preterm	0.401	2.596	.281	24.020
Inborn	0.039	14.965	1.154	194.087
Early-onset	0.696	1.630	.141	18.838

Therefore, an outbreak of ESBL producing *Klebsiella pneumoniae* was suspected during May-June 2006. The outbreak investigations carried out failed to identify the source. Majority of the *Klebsiella pneumoniae* isolated during that period had a similar antibiogram and were ESBL producers.

Neonates with birth weight ≤ 2.5 Kg, preterm neonates, inborn babies and neonates with early-onset sepsis were found to have higher risk for infection by *Klebsiella pneumoniae* based on univariate analysis (Table 2). However, logistic regression analysis performed to avoid spuriously significant results showed only neonates with birth weight ≤ 2.5 Kg and inborn babies were at higher risk of infection by *Klebsiella pneumoniae* (Table 3).

Sixteen (48.5%) of the 33 neonates with *Klebsiella pneumoniae* infection died, while only 4 (23.5%) of the 17 neonates with other infections succumbed to the illness ($P < 0.1610$). The mortality rate was slightly more among neonates infected with ESBL-producing *Klebsiella pneumoniae* (55.5%) compared to those with ESBL-negative *Klebsiella pneumoniae* (40.0%) ($P < 0.5888$).

Discussion

Klebsiella pneumoniae is the most commonly reported cause of neonatal sepsis in several studies from developing countries [3- 5]. There are also frequent reports of outbreaks of neonatal sepsis due to *Klebsiella pneumoniae* in nursery and NICUs [7]. In the present study an outbreak was suspected during May-June 2006 in NICU due to the sudden increase in occurrence of ESBL producing *Klebsiella pneumoniae* with similar antibiogram. However molecular typing was not performed to determine whether a particular strain was circulating in the NICU, due to the lack of facilities. The NICU was temporarily closed and was fumigated, following which the incidence of ESBL producing *Klebsiella pneumoniae* drastically reduced. We assessed the various risk factors for

Klebsiella pneumoniae infection. We noted that neonates with birth weight ≤ 2.5 Kg and inborn babies were at higher risk for infection by *Klebsiella pneumoniae*. Gene rally, rate of infection is inversely related to birth weight [8]. This explains why neonates with birth weight ≤ 2.5 Kg were at increased risk for *Klebsiella pneumoniae* infection. Therefore, prevention, early recognition and early therapy for neonatal sepsis in the low birth weight babies is critical in decreasing the mortality. Similarly, the inborn babies had increased risk for *Klebsiella pneumoniae* infection because of the ability of this pathogen to survive in the hospital environment and spread rapidly resulting in outbreaks [9]. Although preterm neonates were observed to be at increased risk for *Klebsiella pneumoniae* infection by univariate analysis, the logistic regression analysis failed to prove it as a significant risk factor. This could be due to the general increase in the risk of the preterm neonates for infections by pathogens other than *Klebsiella pneumoniae*. In a study by Shitaye et al, prematurity was observed to be a common risk factor for neonatal sepsis irrespective of the pathogen [10].

We observed a relatively high mortality rate among neonates with *Klebsiella pneumoniae* infection. However, it was not statistically significant. Our failure to prove a significant increase in mortality could be due to the small sample size, which is a limitation of this study. We also noted that the mortality rate was slightly more among neonates infected with ESBL-producing *Klebsiella pneumoniae*. Other studies also have documented a high rate of mortality in patients infected by ESBL-producing *Klebsiella pneumoniae* [9, 11].

In our study, all isolated *Klebsiella pneumoniae* organisms were uniformly sensitive to meropenem. In other similar studies also *Klebsiella pneumoniae* were observed to be highly sensitive to meropenem, which suggests that meropenem has an important role in the treatment of infections by multi-drug resistant *Klebsiella pneumoniae* [9, 12, 13]. Therefore, meropenem should be considered for empirical therapy in all suspected, proven cases or during an outbreak of Klebsiella sepsis till antibiotic sensitivity pattern is available.

In conclusion, *Klebsiella pneumoniae* was significantly associated with sepsis occurring among inborn babies and those with birth weight ≤ 2.5 Kg. As *Klebsiella pneumoniae* is known to cause outbreaks among inborn babies in neonatal units, infection control measures should be

strictly practiced. Similarly, adequate care of the low birth weight babies is of utmost importance to prevent infection by *Klebsiella pneumoniae*. A relatively high mortality rate among neonates with *Klebsiella pneumoniae* emphasizes the importance of adequately treating this infection. Meropenem should be considered for suspected or proven cases of Klebsiella sepsis.

References

1. Kaistha N, Mehta M, Singla N, Garg R, Chander J. Neonatal septicemia isolates and resistance patterns in a tertiary care hospital of North India. J Infect Dev Ctries 2009; 4: 55-7.
2. National Neonatal Perinatal Database. NNPD report 2002-03. http://www newbornwhocc org/pdf/nnpd_-report_2002-03 PDF 2005
3. Waliullah MS, Islam MN, Siddika M, Hossain MK, Hossain MA. Risk factors, clinical manifestation and bacteriological profile of neonatal sepsis in a tertiary level pediatric hospital. Mymensingh Med J 2009; 18: S66-S72.
4. Iregbu KC, Elegba OY, Babaniyi IB. Bacteriological profile of neonatal septicaemia in a tertiary hospital in Nigeria. Afr Health Sci 2006; 6: 151-154.
5. Shitaye D, Asrat D, Woldeamanuel Y, Worku B. Risk factors and etiology of neonatal sepsis in Tikur Anbessa University Hospital, Ethiopia. Ethiop Med J 2010; 48: 11-21.
6. Clinical Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. Twentieth informational supplement ed. CLSI document M100-S20. CLSI: Wayne, PA; 2010.
7. Banerjee M, Sahu K, Bhattacharya S, Adhya S, Bhowmick P, Chakraborty P. Outbreak of neonatal septicemia with multidrug resistant Klebsiella pneumoniae. Indian J Pediatr 1993; 60: 25-27.
8. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics 2002; 110: 285-291.
9. Harish BN, Menezes GA, Shekatkar S, Parija SC. Extended-spectrum beta-lactamase-producing Klebsiella pneumoniae from blood culture. J Med Microbiol 2007; 56: 999-1000.
10. Shitaye D, Asrat D, Woldeamanuel Y, Worku B. Risk factors and etiology of neonatal sepsis in Tikur Anbessa University Hospital, Ethiopia. Ethiop Med J 2010; 48: 11-21.
11. Szilagyi E, Fuzi M, Borocz K, Kurcz A, Toth A, Nagy K. Risk factors and outcomes for bloodstream infections with extended-spectrum beta -lactamase-producing Klebsiella pneumoniae ; Findings of the nosocomial surveillance system in Hungary. Acta Microbiol Immunol Hung 2009; 56: 251-262.
12. Serefhanoglu K, Turan H, Timurkaynak FE, Arslan H. Bloodstream infections caused by ESBL-producing E. coli and K. pneumoniae: risk factors for multidrug-resistance. Braz J Infect Dis 2009; 13: 403-407.
13. Taneja N, Rao P, Arora J, Dogra A. Occurrence of ESBL and Amp-C beta-lactamases and susceptibility to newer antimicrobial agents in complicated UTI. Indian J Med Res 2008; 127: 85-88.

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