Original Article

Risk factors and outcome of *Klebsiella* sepsis in neonates

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ABSTRACT

Background: *Klebsiella* is the most common organism isolated in early onset sepsis and causes outbreaks in neonatal intensive care unit (NICU). No clear risk factors for *Klebsiella* sepsis have been documented. **Objective:** The objective of the study was to study the risk factors, clinical profile, and outcome of *Klebsiella* in neonatal sepsis. **Materials and Methods:** A retrospective observational study was done at an extramural tertiary care center from January to December 2017. After getting Institutional Ethics Committee approval, data were collected from hospital records of admitted neonates whose blood culture was positive for *Klebsiella*. Detailed antenatal and natal history including birth weight, Apgar score, sex, and age was taken. Data on ventilator support, continuous positive airway pressure, intravenous fluids, enteral and parenteral nutrition, central line, and surgical procedure were collected. **Results:** Of the total of 1852 blood cultures sent, 308 (16.63%) showed growth. Altogether, 63 (20.45%) cases with *Klebsiella* growth were included in the study, of which 40 were male and 23 were female (1.7:1). *Klebsiella* was isolated in 25 (62.5%) who died. Birth weight was 2.152±0.752 g for babies who died and 2.613±0.525 g among discharged. Mortality was high in males 18 (72%) as compared to females 7 (28%), in low birth weight babies 32 (63.69 %), with thrombocytopenia 18 (80%), and those on invasive mode of ventilation. By regression analysis, it was found that duration of days of NICU stay, shock, invasive ventilation, umbilical venous, and arterial catheterization were identified as the factors that influence outcome in *Klebsiella* sepsis. **Conclusion:** High index of suspicion, initiating early and appropriate antibiotic therapy, antibiotic stewardship, and environmental cleaning improve the outcome. With emerging drug resistance, prevention of sepsis by infection control measures is needed.

Key words: Invasive ventilation, *Klebsiella*, Meropenem, Umbilical venous catheterization

Sepsis is the leading cause of morbidity and mortality among neonates worldwide [1]. Hospital-based studies suggest an incidence of 30 per 1000 live births [2], whereas the incidence of 2.7–17% was seen in community-based studies [2-4]. The National Neonatal Perinatal Database of India showed the incidence of culture-proven sepsis cases as 8.5 per 1000 live births [2]. If sepsis manifests within the first 72 h of life, it is termed as early-onset sepsis (EOS) and after 7 days, it is late-onset sepsis (LOS). Maternal genitourinary tract is predominantly colonized by Gram-negative bacteria which is a proven risk factor for EOS. Risk factors for EOS are chorioamnionitis, maternal intrapartum fever, prematurity, prolonged rupture of membranes, and inadequate intrapartum antibiotic prophylaxis [5]. Nosocomial infections, prematurity, prolonged hospitalizations, use of central lines, parenteral feeding, and mechanical ventilation are considered as risk factor for LOS [6]. *Klebsiella* is a Gram-negative, encapsulated, non-motile, lactose fermenting, and facultative anaerobic bacillus and is the most common organism isolated in EOS [1,7,8]. It is known to cause pneumonia, meningitis, and septicemia. Capsule or slime layer protects *Klebsiella* from host defenses, which is used for its serologic identification. The unique ability of *Klebsiella* to survive in the hospital environment and rapid spread in neonatal intensive care unit (NICU) results in outbreaks [9]. Carbapenem-resistant *Enterobacteriaceae* are known to cause invasive infections and have high mortality rates. These organisms carry genes conferring high level of resistance to penicillin, carbapenems, and other antimicrobials often leaving with limited therapeutic options. The aim of the present study was to assess the risk factors, clinical profile, and outcomes of *Klebsiella* in neonatal sepsis (NS).

MATERIALS AND METHODS

A retrospective observational study was done at a tertiary care center from January to December 2017. The study was conducted in an extramural unit. After getting Institutional Ethical Committee

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approval, data were collected from hospital records of admitted neonates whose blood culture was positive for *Klebsiella*. All babies who had lethal congenital anomaly, polymicrobial growth, and those taken against the medical advice were excluded from the study. Consent could not be obtained as the data were collected from hospital records retrospectively. All neonates who satisfied the inclusion criteria during the study period were included in the study; hence, the sample size was not calculated. A detailed antenatal history including age of mother, parity, history of fever, urinary tract infection, and risk factors for chorioamnionitis was taken. Natal history including mode of delivery, Apgar score, birth weight, sex, age of baby on admission to NICU, and other factors was taken. Data of ventilator support, continuous positive airway pressure, intravenous fluids, enteral and parenteral nutrition, central line, and any surgical procedure were recorded.

Data entry and analysis were done using SPSS for Windows software. Appropriate statistical method was used to analyze factors influencing outcome of death or discharge among neonates with proven *Klebsiella* sepsis. Categorical data were represented in the form of frequencies and proportions. Continuous data were represented as mean and standard deviation. Chi-square was used for categorical variables as the test of significance. Independent t-test or Mann–Whitney U-test was used as the test of significance to identify the mean difference between two groups compared with discharged and mortality cases. Wilcoxon rank-sum test and Kruskal–Wallis test were used for skewed continuous variable. Univariate analysis and regression analysis were used to identify relationship between variables. $p<0.05$ was considered as statistically significant.

RESULTS

A total of 1852 samples were sent for blood cultures among 1073 neonates admitted. Altogether, 308 (16.63%) had growth in blood culture, 96 (8.94%) neonates died during the study period with 40 (41%) because of sepsis. *Klebsiella* was isolated in 63 (20.45%) cases, *Candida* in 40 (12.9%), *E. coli* in 25 (8.1%), and *Acinetobacter* in 20 (6.49%) cases. Finally, 63 (2.3%) cases positive for *Klebsiella* were included in the study, of which 40 were male and 23 female (1.7:1). There were 38 (60.3%) cases discharged and mortality was seen in 25 (39.6%) neonates. Birth weight was 2.152±0.752 g for babies who died and 2.613±0.525 g among discharged. Low birth weight was associated with higher mortality which was not statistically significant.

Maternal age was <30 years in 61 (96.8%) cases and more than 30 years in 2 (3.17%) cases. There was no statistically significant association with order of pregnancy and outcome in neonate (p=0.762) (Table 1).

A total of 18 (28.5%) neonates did not cry immediately at birth of which 7 (11.1%) were discharged and 11 (17.4%) died. There was no statistically significant association between birth weight and outcome in neonate. Duration of NICU stay varied from 3 to 7 days and 50 neonates stayed for more than 7 days which was statistically significant (Table 2).

Invasive ventilation was done for 37 (58.7%) neonates, of which 15 (25.3%) got discharged and 21 (33.3%) died which was statistically significant. Among the 27 (42.7%) babies who had umbilical venous catheterization, 11 (17.4%) were discharged and 16 (25.3%) died. This was statistically significant. There was no statistically significant association between abnormal total count, abnormal C-reactive protein (CRP), and thrombocytopenia (Table 2).

Although the isolated *Klebsiella* was multidrug resistant, it was highly sensitive to meropenem and colistin (Fig. 1).

DISCUSSION

Klebsiella is the most common organism to be isolated in NS [7,8] and has been reported to cause outbreak of NS in NICU [10]. *Klebsiella* was isolated as the cause of sepsis in 17% of cases with mortality of 56% in DeNIS study which was done in three tertiary care centers in Delhi, India [11]. In the present study, *Klebsiella* was isolated in 63 (20.45%) cases and mortality was seen in 25 (62.5%). Clinical features such as lethargy, fever, and refusal of feeds are non-specific and do not aid in diagnosis of sepsis [12]. In a study by Shitaye *et al*., it was found that prematurity was a common risk factor for NS [8].

In the present study, PROM, abnormal APGAR, shock, invasive ventilation, CRP, thrombocytopenia, umbilical venous and arterial catheterization, failure to attain full feeds, and total

Table 1: Maternal risk factors

Variable	Total (63)		Discharge (38)		Death (25)		p-value
	n	%	n	%	n	%	
Primipara	35	55.5	20	31.7	15	23.8	0.762
Parity ≥2	28	44.4	18	28.5	10	15.8	
Number of PV examination – once	24	38.09	16	25.4	8	12.7	
Number of PV examination ≥2 times	20	31.7	11	17.4	9	14.3	
Maternal fever	3	4.76	-	-	3	4.76	
Antenatal antibiotics	21	33.3	12	19.04	9	14.3	0.716
Vaginal delivery	43	68.2	23	36.5	20	31.7	
LSCS	20	31.7	16	25.4	4	6.34	
PROM	7	11.1	2	3.17	5	7.93	0.103
Prolonged labor	6	9.52	2	3.17	4	6.34	

Table 2: Risk factors in neonates

Variable	Total (63)		Discharge (38)		Death (25)		p-value
	n	%	n	%	n	%	
Did not cry at birth	18	28.5	7	11.1	11	17.4	0.028
Birth weight							
<1500 g	11	17.4	4	6.34	7	11.1	0.185
1500–2490 g	21	33.3	13	20.6	8	12.7	
>2500 g	31	49.2	21	33.3	10	15.8	
NICU stay (days)							
<3	1	1.58	1	1.58	-	-	0.008
3–7	12	19.04	3	4.76	9	14.3	
>7	50	79.3	34	54	16	25.3	
Clinical presentation							
Fever	10	15.8	9	14.3	1	1.58	0.74
Lethargy	41	65	23	36.5	18	28.5	0.350
Irritable cry	25	39.6	15	23.8	10	15.8	0.967
Refusal of feed	34	54	27	42.8	17	27	0.796
Seizure	22	35	14	22.2	8	12.7	0.693
Arthritis	5	7.93	4	6.34	1	1.58	0.640
Ventilation requirement							
Mechanical ventilation	37	58.7	16	25.3	21	33.3	0.001
Non-invasive ventilation	21	33.3	12	19.1	9	14.2	0.716
Continuous positive airway pressure	18	28.5	10	15.8	8	12.7	0.25
Invasive procedures							
Umbilical artery catheterization	10	15.8	1	1.58	9	14.3	0.001
Umbilical venous catheterization	27	42.7	11	17.4	16	25.3	0.006
Peripheral inserted central catheters	16	25.3	8	12.7	8	12.7	0.329
Total parenteral nutrition	58	92	34	53.9	24	38.1	0.640
Surgery	30	47.6	20	31.7	10	15.8	0.326
Laboratory investigations							
Abnormal total count	21	33.3	11	17.4	10	15.8	0.533
Thrombocytopenia	46	73	25	39.6	21	33.3	0.318
Abnormal C-reactive protein	59	93.6	35	55.5	24	38.1	0.107
CSF culture positive	9	14.2	5	7.93	4	6.34	0.126

number of NICU stay were identified as factors influencing the outcome in the univariate analysis. In the present study, regression analysis identified number of days of NICU stay, shock, invasive ventilation, and umbilical catheterization influenced outcome. In all sick neonates, umbilical venous catheterization was done and if necessary umbilical arterial cauterization was done.

In a study done by Bhatt *et al*., neonates, prematurity, birth weight ≤2500 g, and inborn babies (as compared to out born babies) were risk factors for EOS using univariate analysis [13]. Furthermore, regression analysis identified birth weight ≤2500 g and inborn babies had higher risk of developing *Klebsiella* infection [13]. In the study done by Qazi *et al*. in North India, it was found that birth weight ≤2500 g and inborn babies were the risk factors for *Klebsiella* sepsis [14]. Similar results were seen in our study where mortality was in high in low birth weight babies.

In Chandra *et al*. study performed at an intramural unit in Chennai, *Klebsiella* was seen in 110 (43%) cases of the samples sent for blood culture [15]. They also found that pregnancy-induced hypertension, PROM, abnormal Apgar, birth weight, shock, invasive ventilation, DIC, inotropes, blood products, abnormal total count, thrombocytopenia, and umbilical venous catheterization were initially identified as factors influencing the outcome by univariate analysis. However, regression analysis showed only thrombocytopenia and umbilical venous catheterization influenced outcome. In the study done by Hassuna *et al*. in Egypt, it was concluded that neonatal morality increased with decrease in birth weight and gestation. They also found thrombocytopenia in neonates who died of *Klebsiella* sepsis [16].

In the present study, *Klebsiella* showed varied sensitivity to all commonly used antibiotics and was sensitive to meropenem and colistin. It was found that even though *Klebsiella* was highly sensitive to meropenem and colistin, other factors also influenced the outcome. In both Bhatt *et al*. and Chandra *et al*. studies, similar sensitivity pattern of *Klebsiella* sensitive to meropenem was detected [13,15].

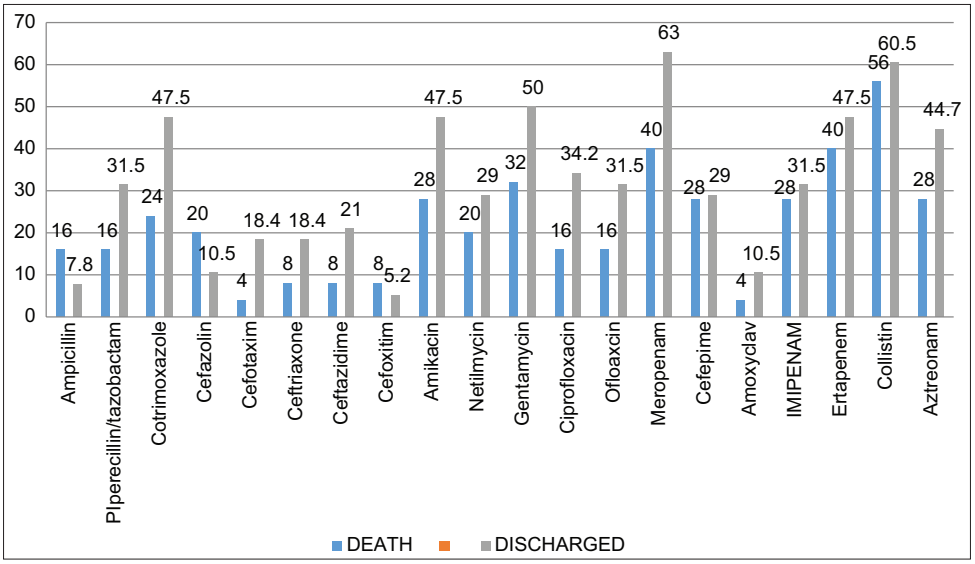

Figure 1: Antibiotic sensitivity pattern of Klebsiella

In this study, there is no single factor including prematurity, PROM, shock, and need for inotropes influencing the outbreak or outcome of *Klebsiella* sepsis. *Klebsiella* has as high as 40% mortality. It showed resistance to first-line antibiotics in NICU while showed sensitivity to meropenem and colistin. Usage of higher antibiotics in NICU must be strictly governed to prevent emergence of multidrug resistant *Klebsiella* [17,18]. Mortality was 25% in Qazi *et al*. study [14]. The study by Ghotaslou *et al*. also showed high mortality in NS [19].

Emphasis must be given to strict hand hygiene. Early and appropriate antibiotics must be started to control infection as no clear risk factors are documented determining the outcome in *Klebsiella* sepsis. Similar recommendations were done in the study by Zhou *et al*. who concluded contact precaution, environment disinfection, good compliance of hand hygiene, and single room isolation being critical in preventing transmission of carbapenemase-producing *Klebsiella pneumoniae* isolates [20]. The study had a few limitations. It was a retrospective study and the collection of data was from hospital records.

CONCLUSION

As clinical features cannot aid in diagnosis of sepsis investigations, high index of suspicion, initiating early and appropriate antibiotic therapy, antibiotic stewardship, and environmental cleaning improve the outcomes. With emerging drug resistance, prevention of sepsis by infection control measures is needed.

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. Report for the Year 2002-03. Available from: http://www.newbornwhocc.org/pdf/nnpd_report_2002-03.PDF. [Last accessed on 2018 Feb 02].
3. Bang AT, Bang RA, Baitule S, Deshmukh M, Reddy MH. Burden of morbidities and the unmet need for health care in rural neonates--a prospective observational study in Gadchiroli, India. Indian Pediatr 2001;38:952-65.
4. Zea-Vera A, Ochoa TJ. Challenges in the diagnosis and management of neonatal sepsis. J Trop Pediatr 2015;61:1-13.
5. Puopolo KM, Draper D, Wi S, Newman TB, Zupancic J, Lieberman E, *et al*. Estimating the probability of neonatal early-onset infection on the basis of maternal risk factors. Pediatrics 2011;128:e1155-63.
6. 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;110:285-91.
7. 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:S66-72.
8. 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.
9. Harish BN, Menezes GA, Shekatkar S, Parija SC. Extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* from blood culture. J Med Microbiol 2007;56:999-1000.
10. 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;60:25-7.
11. Investigators of the Delhi Neonatal Infection Study (DeNIS) Collaboration. Characterisation and antimicrobial resistance of sepsis pathogens in neonates born in tertiary care centres in Delhi, India: A cohort study. Lancet Glob Health 2016;4:e752-60.
12. Mai JY, Zhu ML, Chen C, He XL, Lin ZL. Clinical characteristics of neonatal *Klebsiella pneumoniae* sepsis and the antibiotic sensitivity pattern of strains. Zhongguo Dang Dai Er Ke Za Zhi 2010;12:700-3.
13. Zakariya BP, Vishnu Bhat B, Harish BN, Arun Babu T, Joseph NM. Risk factors and outcome of *Klebsiella pneumoniae* sepsis among newborns. Curr Pediatr Res 2012;16:115-8.
14. Qazi M, Saqib N, Raina R. Risk factors and outcome of *Klebsiella pneumoniae* sepsis among newborns in Northern India. Int J Res Med Sci 2019;7:1909-13.
15. Chandra NS, Sajjid M, Kamalrathnam CN, Prakash V. Study of clincial profile and outcome of *Klebsiella* sepsis in neonates at a tertiary care centre. Int J Contemp Pediatr 2019;6:2450-3.
16. Hassuna NA, AbdelAziz RA, Zakaria A, Abdelhakeem M. Extensively-drug resistant *Klebsiella pneumoniae* recovered from neonatal sepsis cases from a major NICU in Egypt. Front Microbiol 2020;11:1375.
17. Serefhanoglu K, Turan H, Timurkaynak FE, Arslan H. Bloodstream infections caused by ESBL-producing *Escherichia coli* and *Klebsiella*

pneumoniae: Risk factors for multidrug-resistance. Braz J Infect Dis 2009;13:403-7.
18. Taneja N, Rao P, Arora J, Dogra A. Occurrence of ESBL & Amp-C beta-lactamases & susceptibility to newer antimicrobial agents in complicated UTI. Indian J Med Res 2008;127:85-8.
19. Ghotaslou R, Ghorashi Z, Nahaei MR. *Klebsiella pneumoniae* in neonatal sepsis: A 3-year-study in the pediatric hospital of Tabriz, Iran. Jpn J Infect Dis 2007;60:126-8.
20. Zhou J, Li G, Ma X, Yang Q, Yi J. Outbreak of colonization by carbapenemase-producing *Klebsiella pneumoniae* in a neonatal intensive care unit: Investigation, control measures and assessment. Am J Infect Control 2015;43:1122-4.

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