International Journal of Research in Medical Sciences
Qazi M et al. Int J Res Med Sci. 2019 May;7(5):1909-1913
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20191699

Original Research Article

Risk factors and outcome of *Klebsiella pneumonia* sepsis among newborns in Northern India

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Received: 15 March 2019
Revised: 31 March 2019
Accepted: 08 April 2019

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ABSTRACT

Background: The increasing clinical incidence of antibiotic-resistant bacteria is a major global health care issue. Among MDR pathogens, *Klebsiella pneumoniae* (KP) is one of the world's most dangerous superbugs; and becoming resistant to virtually every antibiotic available today. The objective were to study the clinical characteristics of neonatal sepsis caused by KP and the antibiotic sensitivity pattern of *Klebsiella pneumoniae* in a neonatal intensive care unit (NICU) in northern india.
Methods: This observational study was conducted with neonates who were admitted in NICU of Government Medical College (GMC) Jammu (Jammu and Kashmir) India and whose blood culture showed growth of KP in a study period of 1 year between 1st January 2018 to 31st December 2018. The data was entered into a register and presented by descriptive statistics.
Results: Twenty four neonates were included in the study. The clinical presentations include refusal of feed (83.3%), lethargy (79.2%), respiratory distress (70.8%), shock (70.8%), fever (37.5%) or hypothermia (58.3%), apnea (29.2%) and abdominal distension (33.3%). Most common perinatal risk factor was prolonged labor (>24 h) seen in 79.2% of cases. C-reactive protein (CRP) level was positive in 95% of the cases. The mortality was 25%. KP strains were sensitive to colistin, polymyxin B, cotrimoxazole and tetracyclines.
Conclusions: The clinical manifestations of neonatal sepsis caused by KP are usually non-specific. CRP detection is valuable for early diagnosis of sepsis. Neonatal sepsis persists as a cause of mortality in this region. Regular antimicrobial surveillance for empirical treatment remains an important component of neonatal care.

Keywords: Drug sensitivity, *Klebsiella pneumoniae*

INTRODUCTION

Sepsis is a significant cause of morbidity and mortality in neonates.[1] Neonatal sepsis (NS) is defined as a disseminated disease with positive blood culture during the first month of life and is more common in developing countries compared with developed countries.[2,3] Sepsis with Gram negative microorganisms is increasingly reported nowadays particularly in Asian countries.[4,5] The inadvertent use of broad-spectrum antibiotics has led to the emergence of multidrug resistant Gram-negative bacteria.[6] Klebsiella species are of significant importance in this regard.[7] This microorganism accounts for NS in 4-9% of cases in developed countries and 16-28% in developing countries.[8-11] KP belongs to the family of Enterobacteriaceae. There are "classic" and hypervirulent strains of *K. pneumoniae*.[12] "Classic" non-virulent K. pneumoniae (c-KP) strains are usually associated with

pneumonia, urinary tract infection, nosocomial infections and neonatal sepsis in immunocompromised patients.[13] C-KP can cause NS outbreaks in hospitals and ICU.[14,15] C-KP strains have recently gained notoriety due to their propensity to acquire antimicrobial resistance. Within the last few decades, extended-spectrum b-lactamase (ESBL)-positive KP isolates have been recovered worldwide, especially in intensive care units (ICU).[16] The prevalence of ESBL-producing strains of KP is 23% in the USA and up to 85-100% in some European countries.[17] Hypervirulent strains of KP (hv-KP) were first recognized in Taiwan in the last twentieth century and caused liver abscesses, meningitis and endophthalmitis in previously healthy adult patients.[18-20] Currently, hv-KP strains are being spread in different parts of the world.[21,22] High virulence of hv-KP is associated mainly with enhanced capsule production, that can be triggered by a regulator of the mucoid phenotype (rmpA) gene and mucoviscosity associated gene A (magA).[12,22] In addition to c-KP and hv-KP, in recent years the third type of KP was detected, which characterized by a combination of antibiotic resistance and hypervirulence.[21,23,24] The prevalence of antibiotic resistance in hv-KP isolates is rare compared with the high prevalence of antibiotic resistant c-KP isolates.[25]

A report in 2016 showed that in China 12.6% of hv-KP isolates from several invasive infections produced ESBL.[26] The role of virulent strains of K. pneumoniae (including hv-KP) in neonatal infections is unknown. This study was undertaken to monitor temporal change in prevalence of *K. pneumoniae* as a causative organism for neonatal infections and its antimicrobial sensitivity patterns from blood cultures of neonates admitted in NICU in GMC Jammu (Jammu and Kashmir) India.

METHODS

We retrospectively collected the medical data of the neonates admitted in Government Medical College Jammu, Jammu and Kashmir, India from the department of Pediatrics and neonatology in one-year period between 1st January 2018 to 31st December 2018. Data was collected through the hospital record section (HRS) that generates daily reports. Subjects of the study were neonates (age under 28 days) who were admitted in NICU and whose blood cultures showed growth of KP.

Exclusion criteria

- Babies whose blood culture report showed growth of some other organism with Klebsiella.
- Babies who were admitted with severe sepsis because initial clinical features were missed.

Data analysis

The data was entered into a register and presented by descriptive statistics. All numeric values were expressed in exact number and percentages. Categorical variables were compared using X2 test. P <0.05 was considered as statistically significant.

RESULTS

Twenty four neonates were included in the study who were admitted in NICU of GMC Jammu, Jammu and Kashmir, India.12 (50%) were preterm very low birth weight babies, 03 (12.5%) were preterm low birth weight and 9 (37.5%) were term appropriate for gestational age babies. No baby was term, small for gestational age or preterm extremely low birth weight. 15 (62.5%) newborns were male and 9 (37.5%) were female. Of these 24 newborns, 8 (33.3%) were admitted due to perinatal asphyxia, 04 (16.7%) for meconium aspiration syndrome and 12 (50%) were preterm very low birth weight babies admitted for preterm care /weight gain/sepsis and necrotizing enterocolitis (NEC) management. All of them were admitted on day 1 of life. Most of the neonates develop symptoms on day 4 of life. Time of onset of symptoms is shown in Table 1.

Table 1: Time of onset of symptoms (n=24).

Age when symptoms occurred	Number	Percentage
Day 1 and Day 2	0	0
Day 3	6	25
Day 4	12	50
Day 5 to Day 7	4	16.7
After Day 7	2	8.3

Perinatal risk factors responsible are enumerated in Table 2 which shows that a very high proportion of the babies had these risk factors making them susceptible to sepsis. Prolonged labor (>24h) was most common risk factor seen in 79.2% of cases whereas unclean or >3 sterile vaginal examinations was least common risk factor seen in 16.7% of cases. There was a coexistence of more than one factor in many cases.

Table 2: Perinatal risk factors for NS.

Risk factors	Number	Percentage
Prolonged labor (>24 h)	19	79.2
Premature rupture of membrane (>18 h)	17	70.8
Maternal fever within 2 weeks (>38°C)	13	54.2
Foul-smelling liquor	12	50
Birth asphyxia	9	37.5
Unclean or >3 sterile vaginal examinations	4	16.7

The symptoms and signs of neonates with blood culture positive for KP are shown in Table 3. Refusal of feed (83.3%) was the most common presentation followed by lethargy (79.2%), respiratory distress (70.8%)/shock

(70.8%) whereas apnea (29.2%), gastrointestinal bleeding (25%) were the least common presentation.

Table 3: Symptoms/signs of neonates with blood culture positive for *Klebsiella pneumoniae* (n=24).

Symptom/sign	Number	Percentage
Refusal of feed	20	83.3
Lethargy	19	79.2
Respiratory distress	17	70.8
Shock	17	70.8
Convulsion	15	62.5
Hypothermia	14	58.3
Sclerema	10	41.7
Fever	9	37.5
Vomiting	8	33.3
Abdominal distension	8	33.3
Apnea	7	29.2
Gastrointestinal bleeding	6	25.0
Mottling	5	20.8

In this study KP was resistant to meropenem, vancomycin, aztreonam, amoxicillin clavulanate. cefotaxime/ceftriaxone and piperacillin-tazobactum had intermediate sensitivity whereas cotrimoxazole, colistin and polymyxin B were highly sensitive (Table 4). Regarding the outcome, 6 (25%) newborns expired and 18 (75%) recovered. Clinical improvement was assessed by commencement of feeding. On an average, feeds were started on day 4 of treatment. However, intravenous antibiotics to which the bacteria were sensitive were continued for 14 days.

Table 4: Drug sensitivity pattern of *Klebsiella pneumoniae*.

Drug sensitivity to Klebsiella	Number	Percentage
Colistin	23	95.8
Polymyxin B	22	91.7
Cotrimoxazole	18	75
Tetracyclines	17	70.8
Chloramphenicol	11	45.8
Piperacillin-tazobactum	10	41.6
Gatifloxacin	9	37.5
Linezolid	9	37.5
Cefepime	6	25
Cefotaxime/ceftriaxone	2	8.3
Meropenem/imipenem	0	0
Amikacin	0	0
Vancomycin	0	0
Amoxicillin clavulanate	0	0
Cefuroxime sodium	0	0
Aztreonam	0	0

DISCUSSION

KP is the most commonly reported cause of neonatal sepsis in several studies from developing countries.[27-29] There are also frequent reports of outbreaks of neonatal sepsis due to KP in nursery and NICUs.[30] However molecular typing was not performed in our study to determine whether a particular strain was circulating in the NICU due to the lack of facilities. In a previous study, neonatal sepsis caused by KP has been shown to present with non-specific features like fever or hypothermia, tachypnoea, apnoea and feed intolerance consistent with our study.[31] We assessed the various risk factors for KP infection. We noted that neonates with birth weight ≤2.5Kg and inborn babies were at higher risk for infection by KP. Generally, rate of infection is inversely related to birth weight.[8] This explains why neonates with birth weight ≤2.5Kg were at increased risk for KP 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 KP infection because of the ability of this pathogen to survive in the hospital environment and spread rapidly resulting in outbreaks.[32] Although preterm neonates were observed to be at increased risk for KP infection. This could be due to the general increase in the risk of the preterm neonates for infections by pathogens other than KP. In a study by Shitaye et al, prematurity was observed to be a common risk factor for neonatal sepsis irrespective of the pathogen.[29] Most children developed symptoms on day 3 (25%) or day 4 (50%). The mortality (25%) is almost the same or slightly higher than that found in other studies.[31,33] Our failure to prove a significant increase in mortality could be due to the small sample size, which is a limitation of this study.

In other studies, KP were observed to be sensitive to meropenem which is quite opposite to our study.[32,34,35] KP organisms were highly sensitive to colistin/polymyxin B and resistant to meropenem. Currently available studies on multidrug resistant Klebsiella are predominantly based on intensive care units. There is a paucity of information about outbreaks in neonatal units.[36] Hence, we describe the clinical features and drug sensitivity pattern of *Klebsiella pneumoniae* infection in a neonatal intensive care unit in Northern india.

This study has several limitations. The retrospective design based on existing patient registers or databases cannot exclude the possibility of confounding that may have affected these results. Accuracy and variability in the quality of documentation among different health care personnel it was not feasible to ensure with retrospective audit of databases.

This study had 3 major limitations. First, there was intermittent stock-out of some antibiotic disks, leading to inconsistent reporting of antibiograms. Second, the isolates per species of organism were not enough for every bacteria, as CLSI recommends a minimum of 10 isolates per species of organism for an antibiogram to be

very effective.[37] Third, small sample size which is another limitation.

CONCLUSION

Every attempt should be made to obtain specimens for culture and sensitivity testing prior to initiating antibiotics. Empirical antibiotic therapy should be based on knowledge of likely pathogens for the site of infection, information from patient history (e.g. recent hospitalizations, work-related exposure, travel and pets), and local susceptibility.

All patients receiving antibiotics should be monitored for resolution of infectious signs and symptoms (e.g. decreasing temperature and white blood cell count) and adverse drug events. Clinicians should work towards optimizing antibiotic use through antibiotic stewardship programs and interventions, which help to ensure that patients get the right antibiotics at the right time for the right duration. A number of evidences from researches across the globe prove that multi drug resistant bacteria are emerging worldwide causing many public health problems and challenges to healthcare.

Based on the result from our pooled data, we can conclude that currently we have only few antibiotics that are effective to treat KP.

Recommendations

Promising future strategies to combat resistance requires additional societal investment in basic and applied research and policy activities. These interventions include preventing infections from occurring in the first place, encouraging new economic models that spur investment in anti-infective treatments, slowing the spread of resistance in order to prolong the useful lives of antibiotics, discovering new ways to directly attack microbes in a manner that does not drive resistance and altering host-microbe interactions in order to modify disease without directly attacking microbes.[38]

A more innovative form of stewardship is the development of therapies that do not drive resistance and hence the genomic revolution and the use of bacteriophages has been promising in the last one decade studies.[39]

ACKNOWLEDGEMENTS

Authors would like to thank all the staff of the hospital record room for their help and co-operation in completing this small piece of work.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Qazi M, Saqib N, Raina R. Risk factors and outcome of *Klebsiella pneumonia* sepsis among newborns in Northern India. Int J Res Med Sci 2019;7:1909-13.