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Original Research Article

Burden of *Klebsiella pneumoniae* in late onset neonatal sepsis in a tertiary care hospital in Western Maharashtra

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ABSTRACT

Background: *Klebsiella pneumoniae* is a notorious superbug that is rapidly becoming the most common nosocomial pathogen to be isolated from intensive care settings.
Objective: To determine the burden of *Klebsiella pneumoniae* and associated risk factors of late onset sepsis among neonates admitted into neonatal intensive care unit (NICU).
Materials and Methods: A prospective study was conducted among 200 neonates admitted into the NICU of Sassoon General Hospital from January 1, 2019 to December 31, 2019. Neonates <28 days of age exhibiting clinical signs and symptoms of sepsis >72hrs after birth were included in the study. A detailed case history format of patient information was prepared. Blood sample was subjected to identification by culture and real time polymerase chain reaction (RT-PCR). Neonates who were positive by blood culture were confirmed as having sepsis.
Results: Frequency of *Klebsiella pneumoniae* was 33.3% by blood culture and 38.1% by RT-PCR. Most of the septic neonates were males (n=6; 60%), formula fed (n=7; 70%), extremely low birth weight (n=6; 60%), delivered through caesarean section (n=6, 60%) and were preterm (n=7; 70%). Mortality was seen in 2 (20%) cases. All the isolates were sensitive to meropenem, piperacillin + tazobactam, amikacin, polymyxin B and colistin.
Conclusion: Occurrence of *Klebsiella pneumoniae* was 33.3% in late onset neonatal sepsis by blood culture. Low birth weight, formula feeding, prematurity and caesarean section were associated with a higher risk of sepsis in these patients. Antimicrobial stewardship and hospital infection control measures are need of the hour in preventing late onset neonatal sepsis.

1. Introduction

Neonatal sepsis is the third leading cause of neonatal mortality and a major public health problem especially in developing countries.[1] The incidence of neonatal sepsis as per data from National Neonatal-Perinatal Database (2002-2003) is 30/1000 live births and *Klebsiella pneumoniae* was found to be the most common organism.[2,3] The 'Levels and Trends in Child Mortality report, 2019' estimates the global rate of neonatal deaths as 17 per 1000 live births.[4,5] Neonatal sepsis is more common in developing countries than developed nations due to unsafe delivery practices, lack of proper education regarding institutional deliveries, faulty infant registration and surveillance systems.[6]

Neonatal sepsis has been classified as Early onset (<72hours) and Late onset (>72 hours) sepsis (LOS) depending on the time of presentation of the first clinical signs and symptoms after birth. According to the National Nosocomial Infection Surveillance System report, the rate of nosocomial infections is 14.5 per 1000 patients.[6]

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The risk of nosocomial infections in neonates is mainly affected by invasive procedures, prematurity and duration of stay at the hospital.[7] Preterm and low birth weight infants bear the maximum brunt of nosocomial sepsis due to impaired immune responses. They are likely to have adverse neurodevelopmental outcomes at follow up including cerebral palsy, lower psychomotor development scores and impaired growth.[8]

Klebsiella pneumoniae (KP) is an important pathogen of neonatal sepsis accounting for 4-9% cases in developed countries and 16-28% cases in developing countries.[9] It is Gram-negative, non-motile, usually encapsulated and belongs to Enterobacteriaceae family. The classic strains (c-KP) cause neonatal sepsis, pneumonia and other nosocomial infections in the immunocompromised while the hypervirulent strains (hv-KP) cause meningitis and abscesses in healthy patients.[10]

Extended spectrum beta lactamase (ESBL) positive KP strains are now increasingly being isolated especially in intensive care units. This is due to its ability to acquire antibiotic resistance determinants in gut which increases with longer hospital stays and use of invasive devices both a common feature of late onset neonatal sepsis. Due to this, it belongs to 'critical category' of World Health Organization (WHO) global priority pathogen list and also part of the ESKAPE group of nosocomial pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa, Enterobacter spp*).[11,12]

The clinical course of sepsis in Neonatal Intensive Care Unit (NICU) can turn out to be fulminant leading to septic shock, disseminated intravascular coagulation and death within hours of onset. Blood culture, the current gold standard often remains negative owing to the small volume obtained from neonates and/ or prior use of antibiotics. Often, the results of blood culture require 48-72hrs and samples are generally incubated for 5 days until they show a positive signal in the continuous monitoring systems. Owing to their rapidity and sensitivity, molecular techniques such as real time polymerase chain reaction (RT-PCR) are acquiring importance in the detection of bacterial DNA directly from the blood samples.

There is a paucity of reports on the burden of *Klebsiella pneumoniae* in late onset neonatal sepsis in the NICU. Accordingly, this study was undertaken to determine the frequency of *Klebsiella pneumoniae*, antibiotic resistance profile, risk factors and evaluate clinical outcome of the affected neonates.

2. Materials and Methods

2.1. Ethical approval

This study was approved by the Institutional Ethics Committee of BJGMC and Sassoon General Hospital, Pune, Maharashtra [Ref No.: BJGMC/IEC/Pharmac/D- 1018156-156]

2.2. Study setting

A prospective laboratory based study was conducted in the Department of Microbiology, BJGMC, Pune over a period of 1 year from January 2019 – December 2019. The study population consisted of 200 neonates with clinical sepsis >72hrs after birth in the hospital. Neonates who developed clinical signs of sepsis within 72hrs of birth and referred cases of neonatal sepsis from other hospitals were excluded from the study.

2.3. Study procedure

Written informed consent was taken from the guardians and a standardised case report format was prepared. Details regarding birth weight, type of delivery, feeding practice, gestational age, mortality, primary diagnosis and clinical findings were taken. A septic work up was undertaken before commencing antibiotics from neonates which showed signs of clinical sepsis such as presence of fever, poor feeding, respiratory distress, seizures, lethargy. It included at least a venepuncture for complete blood count, total leucocyte count, C-reactive protein (CRP) and blood culture with additional investigations depending upon the clinical presentation.

One microliter of whole blood sample was collected in BD BACTEC Peds Plus^{TM}/F bottles for blood culture in BD BACTEC 9120 equipment and at the same time 500μl of blood was collected in EDTA vials which was used for identification by real time PCR.

2.4. Data analysis for blood culture

When a flash positive BACTEC bottle was identified then it was plated on Blood agar and MacConkey agar. Blood agar plates were incubated under 5% CO_2 in McIntosh and Filde's jar and MacConkey agar plates were incubated aerobically at 37°C in incubator for 24 hours. On the following day if growth was present, the organisms were identified through gram staining and standard biochemical tests.[13] Antimicrobial susceptibility testing (AST) was performed by Kirby-Bauer disc diffusion method as per latest Clinical and Laboratory Standards Institute (CLSI) guidelines.[14] Antibiotic discs (Hi- Media) were used and for quality control of AST E.coli ATCC 25922, S.aureus ATCC 25923, Enterococcus faecalis ATCC 29212 was used. Flash negative BACTEC bottle was identified after 7 days and discarded. The sample was reported as no growth.

2.5. Data analysis for RT-PCR

For Real Time multiplex PCR, TRUPCR® Neonatal Sepsis Detection kit (3B BlackBio Biotech India Ltd)

was used. The manufacturer's instructions were followed and the protocol described was used for reaction preparation, program setup, channel selection and result analysis. The following organisms were present in this panel: Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Escherichia coli. Cut off for this assay is 36 C_T value. The reactions were performed under standard thermocycling conditions of HiMedia Insta Q96® Plus Real Time PCR Machine (HiMedia Laboratories, Pvt. Ltd. Mumbai, Maharashtra, India). The melting curves were generated to verify the specificity of the amplicons in the positive and negative control and consequently analysed in the equipment software (Insta Q96™, HiMedia).

Positive and Negative controls were checked before analysing the samples. Samples whose C_T value was ≤36 were considered positive for that particular pathogen and those whose C_T value was >36 were considered negative for that particular pathogen. The results of RT-PCR were compared with blood culture, the gold standard.

3. Results

The study comprised of 200 neonates who met the inclusion criteria and had clinical sepsis. During this period 30 (15%) neonates were positive by blood culture and 42 (21%) by RT-PCR. Out of these gram negative bacilli were identified from 28 (93.3%) neonates by blood culture and 38 (90.4%) by RT-PCR. Ten (33.3%) neonates were positive for KP by blood culture and 16 (38.1%) by RT-PCR. Clinical characteristics of neonates identified with KP are shown in Table 1.

Of the 10 KP positive neonates, 6 (60%) were males, 7 (70%) were preterm, 6 (60%) were delivered through caesarean section, 7 (70%) were on formula feed, 6 (60%) were extremely low birth weight (weight <1kg), RDS was seen in 8 (80%), seizures in 6 (60%) and 2 (20%) had died (Table 1).

The median platelet count was 172 ix 10^9/L in both the groups. CRP was deranged in 60% of blood culture positive neonates and 62.5% of the RT-PCR positive neonates. The median showed that values of ANC, I: T ratio and Band forms were normal in both the groups.(Table 2)

In this study, KP was resistant to gentamicin (60%), ciprofloxacin (80%), ceftriaxone (80%), ampicillin + clavulanic acid (100%), tetracycline (70%), ceftazidime (70%), ceftazidime + clavulanic acid (70%) and cefepime (80%). All the isolates were sensitive to amikacin, meropenem, piperacillin + tazobactam, polymyxin B and colistin.(Table 3)

4. Discussion

KP is an opportunistic pathogen causing both community and hospital acquired infections.[15] It can cause outbreaks in NICUs due to its ability to harbour numerous plasmids, which increases its survival in environment and the human gut.[10] This leads to rapid acquisition of antimicrobial resistance by the organism. The frequency of KP in our study was 33.3% by blood culture. Hassuna NA et al observed 15.3% while Jatsho J et al observed 27% KP isolates in their study.[16,17]

KP is a recognised cause of late onset neonatal sepsis worldwide.[4,17,18] Table 1 shows that majority of the neonates were males (60%) which is due to the fact that males are immunologically weaker at birth (gene responsible for immunoglobulin synthesis is located on X chromosome) and also due to gender bias in seeking healthcare.[18,19] Jatsho J et al also reported 52.3% of males in their study.[19]

Also, 70% of the neonates were preterm (<37 weeks). These findings are consistent with Saleem AF et al (65%) and Qazi M et al (50%).[18,20] Most of the neonates were low for birth weight in our study (median weight-965grams). We also reported 60% extremely low for birth weight (<1 kg) neonates. Premature and low birth weight neonates are more prone to KP infections as they require longer hospital stays, use of invasive devices and mechanical ventilation which increases the risk of KP colonization from the environment.[4,19] KP can survive in hospital settings and spreads rapidly leading to outbreaks.[20] Jatsho J et al noted that preterm neonates had low IgG levels which acted as stress factors leading to poor adaptation to extra uterine life, increasing susceptibility to nosocomial infections.[19] Shitaye D et al observed that prematurity is an important risk factor for neonatal sepsis irrespective of the causative pathogen.[21]

It was also noted that 60% of the neonates were delivered through caesarean section which is more commonly associated with LOS than vaginal delivery.[22] Caesarean section interferes with the normal colonization process and low birth weight infants are shown to have delayed colonization as well as less diversity of the gut microbiota.[22] This increases their chances of acquiring nosocomial infections from the environment.

Exclusive breast feeding was only seen in 3 (30%) neonates which explains the high burden of nosocomial sepsis in our study. Breast milk has numerous benefits in promotion of neonatal immune functions and can reduce risk of LOS by three folds.[23]

Mortality was 20% in our study. This is consistent with findings by Qazi M et al (25%) and Mai JY et al (21%).[20,24] However, a larger sample size is needed to prove a significant increase in mortality due to KP.

Table 2 Shows the laboratory characteristics of the KP septic neonates. The median platelet count was 172x 10^9/L in both the groups. CRP was deranged in 60% of BC positive neonates and 62.5% in RT-PCR positive neonates. The median showed that values of TLC, platelets, ANC, I: T ratio and Band forms were normal in both the groups.

Table 1: Showing clinical characteristics of *Klebsiella pneumoniae* infected neonates

Factors	Blood culture positive (N=10)	Real time PCR positive (N=16)
Age at onset (in days)[a]	13 (5-22)	11 (5-22)
Sex of baby [b]		
Male	6 (60%)	10 (62.5%)
Female	4 (40%)	6 (37.5%)
Gestational age [b]		
Term	3 (30%)	5 (31.3%)
Preterm	7 (70%)	11 (68.7%)
Mode of delivery [b]		
Normal Vaginal	4 (40%)	6 (37.5%)
Caesarean section	6 (60%)	10 (62.5%)
Type of breast-feeding [b]		
Exclusive	3 (30%)	5 (31.3%)
Formula feed	7 (70%)	11 (68.7%)
Birth weight (in grams) [a]	965 (770-1970)	965 (550-2100)
Extremely low birth weight [b]	6 (60%)	9 (56.2%)
Mortality [b]	2 (20%)	0
Temperature (°C) [a]	36.2 (36.2-37.2)	36.5 (36.2-37.2)
Respiratory distress (RDS) [b]	8 (80%)	12 (75%)
Neurological sequelae (Seizures) [b]	6 (60%)	10 (62.5%)

[a] Continuous variables are presented as median (median range).
[b] Categorical variables are presented as number (percent).

Table 2: Showing laboratory characteristics of *Klebsiella pneumoniae* infected neonates

Factors	Blood culture positive (N=10)	Real time PCR positive (N=16)
Total Leucocyte Count (mm^3) [a] (TLC)	5000 (5000-20000)	10000 (5000-25000)
Platelet ($\times 10^9$/L) [a]	172 (10-319)	172 (10-447)
Absolute Neutrophil count (μl) [a] (ANC)	2250 (2250-17500)	6400 (2250-17500)
White blood cell count ($\times 10^3/\mu$l) [a] (WBC)	8.7 (8-9.7)	8.4 (7-12)
Immature: Total Neutrophil Ratio [a] (I:T)	0.05 (0.01-0.16)	0.12 (0.04-0.2)
Band Forms (%) [a]	5.5 (1-10)	7.5 (5-10)
C-Reactive Protein (CRP) [b]	6 (60%)	10 (62.5%)

[a] Continuous variables are presented as median (median range).
[b] Categorical variables are presented as number (percent).

Table 3: Showing percentage of resistant *Klebsiella pneumoniae* isolates

Antibiotics	K. pneumoniae (N = 10)
Ampicillin	10 (100%) [a]
Amikacin	0
Gentamicin	6 (60%)
Ciprofloxacin	8 (80%)
Ceftriaxone	8 (80%)
Ampicillin + Clavulanic acid	10 (100%)
Tetracycline	7 (70%)
Meropenem	0
Ceftazidime	7 (70%)
Ceftazidime + Clavulanic acid	7 (70%)
Cefepime	8 (80%)
Piperacillin + Tazobactam	0
Polymyxin B	0
Colistin	0

[a] Data are presented as number (percentage of total) unless otherwise indicated

High or low WBC, high ANC, high I: T ratio and low platelet count are associated with LOS.[9] Elevation of CRP is seen with most systemic infections. However, it is also raised in trauma, tissue necrosis, inflammatory processes, advanced cancer. CRP has poor predictive value for sepsis diagnosis but has a good prognostic value for successful treatment.[25,26] Individual laboratory parameters are very non-specific hence they should be used in combination with clinical signs and culture report.

ESBL producing KP sepsis is on the rise worldwide with isolates from NICU contributing the maximum cases.[27–29]

Table 3 shows that all KP isolates were sensitive to carbapenem (meropenem) in our study. Similar observations were made by Khan E et al and Bhat YR et al where ESBL KP isolates were sensitive to carbapenems.[30,31] KP was seen sensitive to piperacillin + tazobactam, colistin and polymixin B in our study. However, Qazi M et al reported a high level of carbapenem resistance (100%) in their study.[20] Carbepenem resistant KP can be treated with polymyxin, tigecycline or a combination of antibiotics coupled with removal of invasive devices.[18,32] Zea-Vera A et al stated that late onset sepsis pathogens are more resistant to antibiotics than early onset sepsis pathogens.[9]

The frequency of KP in our study was 33.3% by BC and 38.1% by RT-PCR. This is because RT-PCR has higher sensitivity than BC. Due to the small volume of blood collected for culture, low-level bacteraemia or antibiotic therapy prior to sample collection in the neonates, they could not be picked up by blood culture. Thus, a negative BC does not necessarily imply the absence of bacterial sepsis in a neonate, which makes it important to implement molecular techniques like RT-PCR that are more specific and aid in faster diagnosis.[33] Hence, in NICU settings where antibiograms are periodically done and the antibiotic sensitivity pattern is consistent for a particular organism, molecular techniques such as RT-PCR can be used to implement empirical antibiotics for a particular organism in the absence of a positive blood culture.

5. Conclusion

The high burden of *Klebsiella pneumoniae* LOS (33.3%) emphasizes the need for infection control in the NICU. Low birth weight, formula feeding, prematurity and caesarean section were associated with a higher risk of sepsis in these patients. Efforts have been laid to improve adherence to antimicrobial stewardship guidelines and prevent irrational use of antibiotics in the unit. These include training and implementation of infection control practices, reinforcement of WHO's five moments of hand hygiene and aseptic techniques for invasive procedures.

6. Conflicts of Interest

The authors declare no potential conflict of interest with respect to research, authorship, and/or publication of this article.

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