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Late Onset Gram Negative Infection in Inborn Neonates - Experience of A Tertiary Care Centre

Dr Amit Kumar [1], Dr Girijanand Jha [2], Dr Binod Kumar Singh [3], Dr Saroj Kumar [4], Dr Sujit Kumar [5]

[1] *Senior Resident, Deptt of Pediatrics, N.M.C.H, Patna.*
[2]*Senior Resident, Deptt of Pediatrics, N.M.C.H, Patna.*
[3]*Professor & HOD, Deptt of Pediatrics, N.M.C.H, Patna.*
[4]*Assistant Professor, Deptt of Pediatrics, N.M.C.H, Patna.*
[5]*Associate Professor, Deptt of Pediatrics, N.M.C.H, Patna.*
Corresponding Author: Dr Girijanand Jha,

Abstract:
Aim & Objective: *To study the incidence, mortality and risk factors of late onset neonatal sepsis caused by gram negative bacteria (late onset gram negative sepsis or LOGNS) in inborn babies.*
Design and setting: *Retrospective case control study at NICU of NMCH Patna from November 2017 to April 2019 (1.5 years).*
Participants: *Inborn infants with evidence of invasive infection caused by Gram negative bacteria presenting at 72 hours or more of life .Controls were infants with no evidence of invasive infection by gram negative organism at 72 hours of age and beyond, matched for gestational age and time of presentation at our NICU.*
Main outcomes measured: *incidence, risk factors and mortality data.*
Results: *67 neonates with LOGNS were identified of which 44 were inborn and included in our study. The majority of infants with LOGNS were VLBW. The incidence of LOGNS was 4.8 per 100 NICU admissions at our hospital. Klebsiella spp was the commonest organism followed closely by E. coli and Pseudomonas spp. There was no significant difference between cases and controls regarding maternal risk factors, gestational age or birth weight.There was a significant association in univariate analysis between the occurrence of LOGNS and mechanical ventilation as well as its duration, parenteral nutrition for >7 days, delayed commencement of enteral feeds (mean delay of > 7 days), presence of a central venous catheter and occurrence of NEC. However, in multivariate analysis, only the duration of Mechanical ventilation remained significantly associated with LOGNS.*

Keywords*: Blood culture, gram negative bacteria, late onset neonatal sepsis, late onset gram negative sepsis, mechanical ventilation, neonatal intensive care unit, parenteral nutrition.*

Abbreviations*: GA: gestational age; LONS: Late onset neonatal sepsis; LOGNS: late onset gram negative sepsis; NEC: necrotizing enterocolitis; NCPAP: nasal continuous positive airway pressure; NICU: neonatal intensive care unit; TPN: total Parenteral nutrition; ROM: rupture of membranes; VLBW: very low birth weight;*

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I. Introduction

Every year about 7.6 million children die before reaching their 5th birthday and of these 64% die of infectious causes[1], majority of which are preventable[2]. Neonatal period constitutes only the first 28 days of life and yet it accounts for 40% of all deaths in children under five years of age.[3] In 2010, neonatal conditions accounted for 3.07 million deaths worldwide and among the many neonatal conditions, the three major contributors were (in order of magnitude) prematurity, birth asphyxia, and neonatal infections.[4,5,6] Despite advances in maternal and neonatal care, infections remain a frequent and important cause of neonatal and infant morbidity and mortality. In developing countries where neonatal sepsis is responsible for about 30-50% of the total neonatal deaths.[7,8]

Neonatal sepsis is a clinical syndrome characterized by signs and symptoms of infection with or without accompanying bacteremia in the first month of life. Neonatal sepsis can be classified into two major categories depending up on the onset of symptoms: Early onset neonatal sepsis (EONS) presenting within 72 hours of age and Late onset neonatal sepsis (LONS) that presents after 72 hours of age. LONS is a significant phenomenon in NICU, wreaking havoc on approx 25% of VLBW babies resulting in mortality or significant

morbidity in many of them.[9] Review of literature revealed that over the last twenty years, the relative contribution of gram negative organisms to late onset sepsis has increased considerably, more than 2.5 times in some studies.[10] In cases of LOGNS, the mortality is high and there exists an inverse relationship between its occurrence and gestational age and birth weight.[11]

Premature infants are at particular risk of LONS because of their immunological issues, relatively thinner skin barrier and increased requirement of devices as well procedures for supporting life in the first few days. The source of infection is from the community or health- care. The most common pathogens are Staphylococcus aureus, coagulase negative staphylococcus aureus (CONS) and gram negative rods.[12]

There have been many studies for determination of risk factors of LONS, including aspects of both maternal and neonatal care. But many of these factors were common associations of prematurity, thereby making it difficult to draw conclusions regarding causality. Through this study we tried to identify potential risk factors for LOGNS, thereby providing suggestions for further opportunities for prevention of LOGNS.

II. Aims & Objectives

Aim: To study the pattern of LOGNS in inborn neonates at our NICU.
Objective: To study the incidence, mortality, causative agents, maternal and neonatal risk factors for LOGNS in our NICU.

III. Methodology

Study setting: NICU of N.M.C.H Patna
Study duration: 1.5 years, from November 2017- April 19.
Study design: Retrospective case control study.

Inclusion criteria: LOGNS was defined as the positive culture of a gram negative organism in a neonate of age more than 72 hours at the time of presentation of features of sepsis. Data was collected from NICU microbiology data-base. If a neonate had more than one episode of LOGNS, only the first episode was included in our study. Controls were matched according to gestational age (within 2 weeks bands, e.g. 26-28 weeks etc) and time of admission to the neonatal unit. A neonate was enrolled as a control only when it stayed for more than 72 hours in our NICU and didn't suffer from a gram negative sepsis during their stay. Only inborn babies were included in our study to eliminate confounding factors due to prevalent practices at other hospitals.

Data collection: Data was collected from hospital records using a standardized proforma. Information was sought about basic demographic, clinical and outcome details as well as information on possible risk factors for infection, which was collected from recorded cases of LOGNS. Maternal risk data included chorioamnionitis, maternal fever within two weeks before delivery, antenatal steroids and duration of rupture of membranes. Neonatal risk data included ventilation type and duration, age at commencement of enteral feeds, parenteral nutrition and duration, central line use and duration, injectable antibiotic use, and the presence of necrotising enterocolitis (NEC).

For cases, the exposure duration for these risk factors was taken from the day 1 of admission to the day of first positive culture growth of a gram negative organism. For controls, this duration was taken from the day 1 of their NICU admission to the day of positive culture growth of their matched cases.

Data analysis: Data was analysed using SPSS version 18 for windows. Categorical variables were compared using chi square test and continuous variables by student's t- test or Mann Whitney's test as applicable. A backward stepwise (conditional) multivariate logistic regression analysis was performed to identify the relationship between variables. For both uni- and multi-variate analysis, P value less than 5% was taken as significant.

IV. Result

Of 94 neonates identified with gram negative infection, 27 had early onset sepsis and 23 were out born. So, 44 neonates were included as cases. The incidence of LOGNS came out to be 4.8 per 100 NICU admissions and in 8.1 % of inborn VLBW admissions. The median age at presentation was 7.2 days (S.D= 1.8 days). Death occurred in 14 (31.8%) cases, where LOGNS was the primary cause of death in 12 (27.3%). Overall mortality in control group was 17% (n=15; p= 0.07 for difference of deaths between the two groups).

Table 1: Basic characteristics of cases & controls

Characteristics	**Cases(N=44)**	**Controls (N=88)**
Mean GA (weeks)	29.1	29.4
GA <32 weeks	33 (75%)	67 (76.1%)
Median weight on admission (g)	1132	1092
VLBW	34 (72.3%)	65 (73.9%)
Male %	27 (61.4%)	58 (65.9%)
IUGR	9 (20.5%)	16(18.2%)

On performing t tests and chi square tests as required, we found no statistically significant difference between the cases and controls in basic characteristics as detailed in table 1.

Table 2: Comparison of maternal risk factors

Characteristics	**Cases (N=44)**	**Controls (N=88)**	**P value**
Clinical chorioamnionitis	15 (34.1%)	33 (37.5%)	0.70
Maternal fever (14 days before delivery)	6 (13.6%)	9 (10.2%)	0.56
ROM >18 hours	10 (22.7%)	22 (25%)	0.77
Antenatal steroids	29 (65.9%)	51 (57.9%)	0.38

Again, no significant difference was found between the cases and controls.

Among the organisms isolated, Klebsiella spp was the commonest (n=18, 40.9%), followed by E. coli (n=10, 22.7%), Pseudomonas aeruginosa (n=8, 18.2%), Acinetobacter spp (n=4, 9.1%), Serratia spp (n=2, 4.6%), and Citrobacter spp (n=1, 2.3%), Enterobacter spp (n=1, 2.3%).

Table 3: Potential risk factors for LOGNS

Parameter	**Cases N=44**	**Controls N=88**	**P value**
Mechanical ventilation	32 (72.7%)	40 (45.5%)	0.003
Mean days on ventilator	6.9	4.7	0.007
NCPAP	16 (36.4%)	45 (51.2%)	0.11
Mean days on NCPAP	4.3	5.8	0.06
Parenteral nutrition for >7 days	23 (52.3%)	29 (32.9%)	0.03
Mean age of starting enteral feeds	7.6	5.3	0.01
Central line	35 (79.5%)	54 (61.3%)	0.03
Mean days of central line	8.7	6.9	0.045
NEC	11 (25%)	8 (9.1%)	0.02
Prior Antibiotic use	13 (29.5%)	21 (23.9%)	0.49

6 neonates among the cases of LOGNS also had evidence of meningitis (all 6 had CSF abnormality and 1 also had growth of E .coli in CSF culture) & were treated accordingly.

Cases were more likely to receive ventilator support (72.7% vs 45.5%) and for a significant longer duration (mean duration 6.9 Vs 4.7 days). There was a significant delay in the time of initiation of enteral feeds in cases as compared to controls (7.6 vs 5.3 days). Cases were also more likely to have required parenteral nutrition for >7 days as compared to control (52.3% vs 32.9%)s. It was also found that more cases had central venous catheter at some time before first positive blood culture compared to controls (79.5% vs 61.3%) and for a significantly longer duration (mea duration 8.7 vs 6.9 days). Presence of features of NEC before sending blood culture was also more prevalent in cases than controls (25% vs 9.1%). Use of antibiotics prior to first positive blood culture & duration of NCPAP support wasn't found to be different between cases and controls.

On performing multivariate logistic regression analysis, we found that the duration of Mechanical ventilation at or before first positive culture remained independently associated with cases of LOGNS ($p < 5\%$).

V. Discussion

In the present study we have described the burden of LOGNS in a tertiary neonatal care with special emphasis to identify potential risk factors. In this case control design, where we matched controls to cases on gestational age, we have found that duration of mechanical ventilation is an independent risk factor for LOGNS. Considering the high proportion of control infants with risk factors potentially relevant to LOGNS susceptibility, the importance of our approach is quite evident.

Several studies have examined longitudinal data and estimated the incidence of LOGNS in neonatal units. Other studies have examined potential risk factors, but have focused mainly on outbreaks or as part of another trial. Graham et al[13] for example performed similar study in VLBW infants, but the study was part of a larger clinical trial looking at hand hygiene practices and so it was not adequately powered for this analysis.

Recently, some studies have described that intrapartum antibiotic prophylaxis has led to an increase in LONS. For instance, Glasgow et al[14] in their study found an increased incidence of LONS, mostly ampicillin resistant cases. However, longitudinal prospective surveillance by the Australian study group for neonatal infections failed to show such increase. Maternal steroid exposure has also been reported to increase the overall incidence of neonatal sepsis.[15] With this background we were tempted to assess the association between maternal risk factors and LOGNS. Considering that maternal risk factors are commoner among preterm pregnancies, we decided to match cases to controls on the basis of gestation and not weight. However, in our study we didn't find any association between incidence of LOGNS and maternal risk factors in the form of clinical chorioamnionitis, maternal fever, ROM more than 24 hour or antennal steroids use. Our results is supported by the similar findings of the National institute of child health and human development neonatal research network.[11]

Several studies have reported that mechanical ventilation, parenteral nutrition, NEC, deep venous catheterization etc are risk factors for LOGNS. We found the above risk factors to have an association with LOGNS in our study as well in univariate analysis. But in multivariate model, we found that duration of mechanical ventilation was an independent risk factor for LOGNS. These findings are in agreement with the study of Cordero et al who did a surveillance study on VAP in VLBW babies.[16] It is well known that endotracheal intubation and mechanical ventilation is an invasive procedure which though is an important intervention as well as a life saving measure, also predisposes to many complications, notably sepsis and ventilator associated pneumonia. There is good evidence[17] that minimizing the days of ventilator support as well as using less invasive modes of ventilation decreases the overall incidence of sepsis. This also reiterates that to decrease the incidence of sepsis in NICU[18], strict adherence to the aseptic measures, implementation of VAP care bundle and practicing proper hand hygiene without a fail is the need of the hour.

VI. Conclusions

LOGNS predominantly occurs in premature and VLBW babies. Maternal risk factors don't seem to be associated with an increased risk of LOGNS. Although many neonatal risk factors were seemingly associated in univariate analysis with LOGNS, they were perhaps reflection of their prevalence in the LBW population. In multivariate analysis only the duration of mechanical ventilation appears to be an independent risk factor for LOGNS.

VII. Limitations

There are a few limitations to our study. First, as we matched cases and controls on the basis of gestational age, we couldn't asses the importance of prematurity as a risk factor. However, this association is evident from a range of studies. Secondly, we couldn't study the risk factors for specific gram negative organisms because of relatively smaller number of individual pathogens. Third, we couldn't determine the type and amount of enteral feeds and so we were not able to assess the influence of breast milk, formula feeds or mixed feeding. Fourth, we don't have facilities for TPN (we give all parenteral supplementation except lipids), so we couldn't study the risks if any associated with TPN and development of LOGNS. Finally, as with any other case control study it is possible that the differences measured between cases and controls actually were other unmeasured factors in reality.

However, despite these limitations our study is among the very few studies of Eastern India to systematically analyze the risk factors for LOGNS caused by endemic Gram-negative bacteria in infants in the NICU. Through this study we tried to identify potential risk factors for LOGNS, thereby providing window for further opportunities for prevention of LOGNS

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Conflict of interest: None

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