Original Article

Mortality profile and incidence of deaths due to neonatal sepsis in an urban tertiary care center in South India: A retrospective study

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ABSTRACT

Background: The neonatal mortality rate is a key outcome indicator for newborn care and directly reflects prenatal, intrapartum, and neonatal care. **Objective:** Primary objective was to assess the neonatal mortality profile, incidence of neonatal sepsis among total neonatal deaths and pattern of antimicrobial resistance. **Methodology:** This was a retrospective descriptive study done at a tertiary care center. All neonatal deaths from January 2014 to December 2014 were reviewed, and primary causes of mortality, incidence of sepsis among neonatal deaths and pattern of antimicrobial resistance were analyzed. **Results:** Common causes of neonatal mortality were sepsis, respiratory distress syndrome, congenital malformations, asphyxia, extreme preterm, meconium aspiration syndrome. Case fatality rate was high in extreme preterm neonates (82%), followed by respiratory distress syndrome (29%), congenital malformations (29%), sepsis (25%), asphyxia (25%). In our study incidence of neonatal sepsis among total neonatal deaths was about 20.5%. *Staphylococcus aureus* (60%) and *Klebsiella pneumoniae* (23%) were predominant organisms. Highest case fatality rate was associated with *K. pneumoniae* sepsis about 60%, followed by *Escherichia coli* sepsis (54%) and *Acinetobacter* sepsis (50%). Multidrug resistance is an emerging problem, especially in *Acinetobacter* sepsis. **Conclusion:** Sepsis still remains the leading cause of death in developing countries. *S. aureus* was the most common predominant organism; of this, two-thirds were methicillin-resistant *S. aureus*. About 90% of *K. pneumoniae* were resistant to extended-spectrum cephalosporins**.** Multidrug resistance is an emerging problem, especially in *Acinetobacter* sepsis.

Key words: *Antimicrobial resistance, Mortality, Sepsis*

About 0.76 million neonates die every year in India, the highest for any country in the world. The NMR has declined from 44 per 1000 live births in 2000 to 29 per 1000 live births in 2012, but the rate of decline has been slow and lags behind that of infant mortality rate [1]. 70% of infant deaths occur in neonatal period [1]. The NMR is a key outcome indicator for newborn care and directly reflects prenatal, intrapartum, and neonatal care. This neonatal mortality rate in India is 28/1000 live births and in Tamil Nadu, it is 15/1000 live births. Current early neonatal mortality rate in India is 22/1000 live births and in Tamil Nadu, it is 11/1000 live births [2]. Sepsis is one of the common preventable causes of neonatal death globally. The most sepsis-related deaths occur in low-income and middle-income countries, where the epidemiology of neonatal sepsis remains poorly understood [3]. This study was conducted to illustrate the neonatal mortality profile. Secondary objectives were to assess incidence of sepsis and its contribution to neonatal mortality. The common bacterial agents associated with neonatal sepsis and their antibiotic susceptibility pattern was also analyzed. This will pave the way for initiation of quality improvement measures to reduce the deaths due to neonatal sepsis in the unit.

MATERIALS AND METHODS

This was a retrospective study conducted at a tertiary care outborn neonatal unit in South India. Hospital records of all neonatal deaths (term and preterm) during the period of January 2014 to December 2014 were scrutinized from the medical records department, and admission details of all neonates were obtained. The primary cause of mortality, incidence of deaths due to sepsis and pattern of antimicrobial resistance was analyzed.

Neonatal deaths were classified based on WHO, ICD-10 version: 2010 criteria as neonatal sepsis, birth asphyxia, prematurity, respiratory distress syndrome (RDS), transient tachypnea of newborn, pneumonia, meningitis, neonatal jaundice, meconium aspiration syndrome (MAS), acute kidney injury (AKI), intraventricular hemorrhage (IVH), neonatal hypoglycemia, congenital malformations (congenital diaphragmatic hernia, tracheoesophageal fistula , congenital heart disease , and any other diagnosis. Neonatal deaths were then stratified into four birth weight and gestational age categories to study birth weight and gestational age specific mortality.

Both culture positive and culture negative sepsis were included. Following protocols were followed in our unit: Blood culture was

collected before starting antibiotics and repeat cultures were done whenever there was a clinical deterioration. 1 ml of blood was added to the bottle containing 20 ml of brain heart infusion broth. Culture bottles were incubated aerobically at 37°C for 7 days. Subculture was done on sheep blood agar and MacConkey agar routinely after 48 h and 7 days. The isolates were identified based on standard bacteriological techniques.

Data were analyzed using Statistical Package for Social Science Program Version 20.0. Descriptive statistics measures such as mean, standard deviation, rate and proportions were calculated. Chi-square test/Fischer exact test was used for analysis of categorical variables. Other statistical tests used were percentages and proportions. Institutional Ethical Committee approval was obtained.

RESULTS

There were 605 (18%) neonatal deaths among 3366 admissions during this period. 10.5% had prolonged rupture of membranes (PROM) for more than 24 h, 12.5% was born through meconium-stained amniotic fluid (MSAF). 38% were delivered by cesarean section, and 22% required resuscitation at birth. Mean birth weight was 2067±859 g, and mean gestational age was 34±4.7 w. Mean temperature on admission was 36.2±0.8°C. 98.5% of the neonates received intravenous fluids and 96% required invasive mechanical ventilation and 52% were boys (Table 1).

Common causes of neonatal mortality were sepsis, RDS, congenital malformations, asphyxia, extreme preterm, and MAS. Other causes of mortality were necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPL), AKI, IVH, meningitis, and neonatal jaundice. Case fatality rate was high in extreme preterm neonates (82%), followed by RDS (29%), congenital malformations (29%), sepsis (25%), and asphyxia (25%). According to ICD-10 criteria, among 605 neonatal deaths, proportion of deaths due to sepsis was (20.5%), RDS (18.5%), congenital malformations (17%), asphyxia (16.5%), extreme preterm (7.5%), MAS (5%), pneumonia (8%), NEC (2%), BPD (0.6%), AKI (1%), IVH (1%), meningitis (1.3%), neonatal jaundice (0.5%), and hemolytic disease of newborn (0.5%). The cause of mortality is significantly associated with case fatality proportion among the neonates, with a highly significant ($p<0.001$). Highest case fatality rate was among extreme preterm neonates (Table 2).

Analyzing the deaths based on birth weight and gestational age showed about 80% of the neonates <1000 g and <28 w of gestation expired (Table 3). In our study, the incidence of neonatal sepsis among total neonatal deaths was about 20.5%. Incidence of early-onset sepsis and late-onset sepsis was about 44% and 56%, respectively. Culture positive late-onset sepsis was higher (54%) compared to culture positive early-onset sepsis (48%).

Common organisms isolated in this study were *Staphylococcus aureus* (60%) and *Klebsiella pneumoniae* (23%), followed by *Escherichia coli* (9%), *Acinetobacter* (4%), and *Enterococcus* (4%). Highest case fatality rate of about 60% was associated with *Klebsiella* sepsis, followed by *E. coli* (54%) and *Acinetobacter* sepsis (50%) (Table 4). Among Gram-negative organisms, 86% of Klebsiella, and 100% of Acinetobacter isolated were resistant to extended-spectrum Cephalosporins, and 33% of them were multidrug-resistant (MDR). Among Gram-positive organisms, 67% of *S. aureus,* and 83% of *Enterococcus* showed resistance to Oxacillin. Most of the *S. aureus* isolated were sensitive to vancomycin, and only one of the *Enterococci* isolated was resistant to vancomycin (Table 5).

Table 1: Baseline characteristics of the study subjects

Variables	Number (%) of neonates (n=605)
Neonatal variables	
Birth weight, g*	2067 (859)
Gestation, weeks*	34 (4.7)
Sex	
Boys	315 (52)
Girls	290 (48)
Intravenous fluids	596 (98.5)
Mechanical ventilation	582 (96.1)
Maternal variables	
Positive-pressure ventilation	136 (22.4)
Temperature on admission*	36.2 (0.8)
Prolonged rupture of membranes (>24 h)	64 (10.5)
Meconium stained amniotic fluid	76 (12.5)
Cesarean delivery	232 (38.3)

*Values are represented as mean±SD, SD: Standard deviation

Table 2: Neonatal mortality profile

Cause of mortality*	Admitted n (%)	Case fatality n (%)
Sepsis	499 (15)	124 (25)
Respiratory distress syndrome	388 (11.5)	112 (29)
Asphyxia	406 (12)	100 (25)
Congenital malformations	350 (10.4)	102 (29)
Extreme preterm	56 (1.7)	46 (82)
Meconium aspiration syndrome	143 (4.2)	31 (22)
Others	1524 (45.2)	90 (6)

*p<0.001 (Chi-square test)

Table 3: Mortality profile based on birth weight and gestational age

	Total admissions	Neonatal deaths	Neonatal deaths (%)
Body weight* (g)			
<1000	58	46	79
1001-1499	379	138	36
1500-2499	1036	196	19
>2500	1893	225	12
Gestational age # (week)			
<28	56	46	82
28-33+6	368	132	36
34-36+6	1044	185	18
>37	1898	242	13

*p<0.001 (Chi-square test), #p<0.001 (Chi-square test)

Table 4: Profile of bacterial isolates and their case fatality rates

Organisms	Number of isolates (n=300) %	Number of deaths (n=124) case fatality rates %
Gram-negative*		
E. coli	26 (9)	14 (54)
Klebsiella	70 (23)	42 (60)
Acinetobacter	12 (4)	6 (50)
Gram-positive#		
S. aureus	180 (60)	6 (3)
Enterococcus	12 (4)	2 (17)

*p=0.876 (Fishers exact test), #p=0.081 (Fisher's exact test). *E. coli: Escherichia coli, S. aureus: Staphylococcus aureus*

Table 5: Antimicrobial resistance pattern

Organisms	Number of resistant isolates n (%)
Gram-negative	
E. coli	
ES cephalosporins	0/26 (0)
Carbapenems	0/26 (0)
MDR	0/26 (0)
Klebsiella	
ES cephalosporins	60/70 (86)
Carbapenems	0/70 (0)
MDR	0/70 (0)
Acinetobacter	
ES cephalosporins	12/12 (100)
Carbapenems	4/12 (33)
MDR	4/12 (33)
Gram-positive	
Staphylococcus aureus	
Oxacillin	120/180 (67)
Vancomycin	0/180 (0)
Enterococcus	
Oxacillin	12/12 (100)
Vancomycin	1/12 (8)

E. coli: Escherichia coli, MDR: Multidrug-resistant

DISCUSSION

In our study, sepsis was the most common cause of neonatal death followed by RDS, congenital malformations and asphyxia. Overall mortality rate during the study period was 18%. Li Liu et al. showed preterm birth complications (14.1%), intrapartum-related complications (9.4%), and sepsis or meningitis (5.2%) as the leading cause of neonatal deaths [4]. Blandina et al. had shown an overall mortality of 10.7% over a period of 10 years and leading causes of death were birth asphyxia (n=245, 45.7%), prematurity (n=188, 35.1%), congenital malformations (n=49, 9.1%), and infections (n=46, 8.6%) [5]. Million deaths study collaborators showed that three common causes of neonatal mortality were prematurity and low birth weight (0.33 million), neonatal infections (0.27 million), and birth asphyxia (0.19 million) [6]. In a study by Saminathan et al., common causes of neonatal mortality were perinatal asphyxia, followed by prematurity and RDS [7].

According to NNPD report 2002-2003 [8], among the extramural admissions, most common primary cause of death was sepsis (37.6 %), followed by prematurity and related complications in 19.3% and birth asphyxia in 18.5%, which was similar to our study. Still sepsis is the leading cause of death in developing countries, whereas extreme prematurity is the leading cause of death in developed countries. According to UNICEF, globally, the main causes of neonatal deaths were preterm birth complications (35%), intrapartum-related complications (24%), and sepsis (15%) [9].

Respiratory distress syndrome was the second most common cause of death in our study, and the case fatality rate was 29%. Blandina et al., in their study, reported RDS as the fourth common cause of death contributing to about 10% of total deaths with case fatality rate of about 52% [5]. Some specific and simple measures have been identified which could be implemented to reduce deaths related to low birth weight and preterm in low-income countries [9]. In all high-risk pregnancies to be delivered in a tertiary care center, prophylactic use of steroid during premature labor, early initiation of CPAP in labor room and early referral of these preterm neonates for surfactant therapy should be encouraged.

Case fatality rate among neonates with birth weight <1000 g was very high (79%) while it was 36% among neonates 1000-1500 g, 19% in 1500 to 2500 g, and 12% in neonates >2500 g. In our study, neonates with birth weight <2500 g constituted about 44% of total admissions and 63% of total deaths. According to Blandina et al., neonates with birth weight below 2500 g constituted 29% of all admissions and 52.1% of all deaths. Survival was strongly related to birth weight, with risks for mortality or major morbidity on an average doubling for each 20-25% decrease in birth weight [10].

Among neonatal deaths due to cultural positive sepsis, early-onset sepsis and late-onset sepsis contributed to about 48% and 54%, respectively. Sepsis is still the leading cause of neonatal deaths in developing countries, and this was reflected in our study tool. In our study, the common spectrum of organisms isolated were *S. aureus* (60%), and *K. pneumoniae* (23%), followed by *E. coli* (9%), *Acinetobacter* (4%), and *Enterococcus* (4%). Among culture positive cases, predominant organisms causing mortality were *K. pneumoniae* (60%) and *E. coli* (54%). Other organisms which caused neonatal deaths were *Acinetobacter* (50%), *Enterococcus* (17%), and *S. aureus* (3%). *K. pneumoniae* and other Gram-negative organisms were the common causes of sepsis in a study by Zakaria et al. [11]; however, in the developed countries, Group B *Streptococcus* and coagulase-negative staphylococci were the predominant causes of sepsis.

According to DeNIS study, the common pathogens implicated in early-onset sepsis include *E. coli*, group B streptococci, listeria monocytogenes, and *Enterococcus* spp. An antibiogram is an overall profile of antimicrobial susceptibility testing results of a specific microorganism to a battery of antimicrobial drugs [12]. Gram-negative isolates resistant to any three of five antibiotic classes (cephalosporins, carbapenems, aminoglycosides,

quinolones, and piperacillin-tazobactam) were categorized as MDR. Among Gram-negative organisms, 86% of *K. pneumoniae* and 100% of *Acinetobacter* showed resistance to extended-spectrum cephalosporins, and another 33 were MDR. *E. coli* was sensitive to first line drugs such as ciprofloxacin, amikacin and also to extended spectrum cephalosporins and carbapenems and none of the organisms was MDR. Ramesh et al., in their study had observed high rates of multidrug resistance in *Acinetobacter* spp. (82%), *Klebsiella* spp. (54%), and *E. coli* (38%) isolates [3].

This high degree of antimicrobial resistance among the Gram-negative organisms and the increasing burden of MDR *Acinetobacter* seen in our study is similar to that found in the DeNIS study [3]. Among Gram-positive organisms, majority of the *S. aureus* and all of the *Enterococcus* isolated were resistant to oxacillin. However, most of the organisms were sensitive to vancomycin. Vancomycin-resistant *Enterococci* were seen in only one isolate. Limitations of our study were that this was a retrospective study and predominantly, neonatal deaths were analyzed. Since our center is a tertiary care hospital and included only outborn neonates, the results may not be generalized to all hospitals or to the population.

CONCLUSION

In our study, sepsis was the most common cause of neonatal mortality. *S. aureus* was the most common organism isolated and majority was methicillin resistant. About 90% of *K. pneumoniae* were resistant to extended-spectrum cephalosporins and had a very high case fatality rate. Multidrug resistance is an emerging problem, especially in *Acinetobacter* sepsis.

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