Predictors of Neonatal Sepsis in Rural Karnataka, India

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Abstract

Neonatal sepsis can present with subtle signs but have a fulminant and fatal course if not recognised and treated early. Many practitioners in resource-poor settings are forced to empirically manage infants at risk for sepsis without access to blood cultures. We sought to identify predictors of poor outcomes in infants with suspected sepsis at a hospital in rural Karnataka, India. This was an observational study of infants aged zero to 30 days who were admitted from January to December 2011 with a diagnosis of presumed bacterial sepsis. We extracted perinatal risk factors, gestational age, birth weight, history and physical exam at the time of admission, white blood cell count, C-reactive protein, duration of hospitalisation, disposition, and blood culture results from medical charts. Poor outcome was defined as death, positive blood culture, hospitalisation greater than five days, or transfer to higher level of care. We calculated predictive values and odds ratio for each variable using univariate logistic regression. Seventy-nine infants were included; 58 (73.4%) experienced a poor outcome. Prematurity and temperature instability were significantly associated with poor outcome, with trends towards higher risk for those having very low birth weight, convulsions, a bulging fontanelle, or lethargy on admission. Nine blood cultures were positive, including seven with Staphylococcus. In a cohort of infants admitted for presumed sepsis in rural Karnataka, prematurity and temperature instability were associated with poor outcome. Larger studies are needed to evaluate bacterial aetiologies and to determine the optimal antibiotic regimen.

Key words Neonatal sepsis, predictors, bacterial pathogens

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INTRODUCTION

Every year, 1.2 million infants born in India die within the first month of life, accounting for 25-30% of neonatal deaths globally [1-2]. India has the highest absolute number of under-five deaths of any country, nearly half of which occur in the neonatal period with 25% estimated to result from bacterial infections [3-5]. Bacterial sepsis in neonates can present with subtle signs but have a fatal course, a tragic combination in settings where access to care and options for intervention are limited.

MATERIAL AND METHODS

We conducted a retrospective cohort study of all infants aged zero to 30 days who were admitted to the neonatal intensive care unit or ward from January to December 2011 for presumed neonatal sepsis. This study site was a referral hospital in rural southern India that has approximately 600 deliveries annually. Oxygen and bag-mask ventilation were available. Institutional review boards at both involved institutions approved this study. Consent was not obtained, as this was a retrospective cohort study.

Medical charts were reviewed for data on maternal and infant history, infant physical examination on admission, laboratory results, and duration and outcome of hospitalization. Data about the following variables were collected: perinatal risk factors (maternal fever, prolonged rupture of membranes); resuscitation at delivery; estimated gestational age (based on last menstrual period); duration of hospitalization; birth weight; temperature and respiratory rate on presentation; presence of retractions (in-drawing of chest wall), lethargy (defined as movement only with stimulation), convulsions, poor suck, grunting or nasal flaring, greater than ten pustules, and bulging fontanelle at any point during the first seven days of hospitalization; jaundice within 24 hr of life; C-reactive protein level and total white blood cell (WBC) count obtained within 48 hr of life; disposition (death, transfer to another facility for higher level of care, discharge home); blood culture results; and duration of hospitalisation. These variables were derived from IMNCI guidelines and other studies that have evaluated predictors of sepsis in similar populations [6,12-13]. Blood culture specimens were inoculated into blood and MacConkey agar plates. Antibiotic resistance patterns were studied by the Kirby Bauer disc diffusion technique.

"Poor outcome" was a composite endpoint that included death, growth of bacteria from blood cultures obtained during admission, hospitalisation greater than five days, or transfer to another facility for higher level of care. We calculated the positive predictive value (PPV), negative predictive value (NPV), and odds ratio with confidence intervals for each variable using univariate logistic regression. We also calculated the rate of positive blood cultures and the percentage of those positive cultures caused by each isolated pathogen.

RESULTS

Seventy-nine infants were admitted for suspected sepsis from January to December 2011. These infants had a median age of zero days (range: zero-30 days), birth weight of 2.5 kg (range: 1.3-3.8 kg) and gestational age of 38 weeks (range: 32-42 weeks)

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(Table 1). All infants were empirically treated with ampicillin and gentamicin as first line antibiotics. Eight infants were transitioned to second line antibiotics, including two that received piperacillin-tazobactam and six that received cefotaxime and amikacin.

Fifty-eight infants (73.4%) experienced the poor outcome. Among these, 55 (70%) were hospitalised more than five days, eight (10%) required escalation in antibiotic therapy, two (3%) were advised to transfer to higher level of care, nine (11%) had a positive blood culture, and three (4%) died. The majority of prolonged hospitalisations were for continuation of intravenous antibiotics for suspected or culture-proven sepsis (n=51). Other causes included prematurity (n=12), hyperbilirubinemia requiring phototherapy (n=6), hypoglycaemic seizures (n=1), hypothermia (n=1), and apnoea (n=1). Temperature instability, defined as temperature <35.5°C or >37.5°C on admission (OR 10.27), and prematurity, defined as gestational age less than 38 weeks (OR 4.32), were significantly associated with poor outcome (Table 2). Very low birth weight (VLBW), convulsions, a bulging fontanelle, and lethargy on admission trended toward risk for poor outcome. Tachypnea, poor suck, low birth weight (LBW), abnormal WBC count (<5 or >20,000/mm3), and CRP positivity (>7 mg/L) were not associated with poor outcome. Temperature instability, VLBW, convulsions, bulging fontanelle, and lethargy had a PPV of greater than 90%. All variables had a NPV of less than 35%.

Among the 79 infants in this study, blood cultures were obtained in 55 (69.6%). All blood cultures were obtained prior to administration of antibiotics. Nine (16.4%) of these cultures were positive. Pathogens isolated included Staphylococcus (n=7), Pseudomonas (n=1), and Klebsiella (n=1) (Table 3). None of these pathogens were speciated secondary to resource limitations at the laboratory where testing was completed. Notably, all Staphylococcus spp. (species) were cloxacillin-resistant.

Table 1 – Patient characteristics

	Number	Percent
Gestational Age		
=38 weeks	57	72.2%
<38 weeks	22	27.8%
Birth Weight		
=2.5 kg	43	54.4%
=1.5 kg and <2.5 kg	28	35.4%
<1.5 kg	5	6.3%
Unspecified	3	3.8%
Other		
Temperature instability	21	27.3%
Prematurity	22	27.8%
Convulsions	6	7.8%
Bulging fontanelle	1	1.3%
Lethargy	11	14.7%
Tachypnea	38	48.7%
Poor suck	33	42.9%
CRP positive (>7 mg/L)	24[a]	34.3%
WBC <5 or >20,000/mm^3	7[b]	10.5%

[a]Data missing for 9 infants
[b]Data missing for 6 infants

DISCUSSION

In this study of infants treated empirically for sepsis, 73.4% of infants experienced a poor outcome despite receiving empiric antibiotic therapy upon admission; however, only 16% of infants had blood cultures were positive and 4% died. Other studies in similar populations have shown higher blood culture positivity rates of 25-29% [10,14] and mortality rates of 3-32% [8,9,12]. The lower rate of documented bacteraemia in our study may be related to our small study size, or technical issues with the blood culture techniques. For example, all cultures were transported 55 kilometres to a larger laboratory, which may have altered growth. Additionally, our yield may have been negatively affected by obtaining only one culture per infant. One study reported that 28% of positive cultures became positive only on subsequent subcultures [15]. However, the low mortality rate (4%) in our study arguably suggests it is unlikely that much larger numbers of infants had bacteraemia. Conversely, it may be that conservative admission criteria at the study hospital meant that many infants without sepsis were being admitted due to prematurity or other isolated clinical signs concerning for sepsis.

While our small study was limited in its power to evaluate predictors of poor outcomes, temperature instability and prematurity were associated with significantly elevated risk. The results are in accordance with many other studies in resource-limited settings that identify prematurity [8-9] and temperature instability [6,8,10-11] as predictive of poor outcomes and add to mounting data suggesting that strategies to reduce neonatal mortality must focus on reducing the incidence of and complications from premature deliveries. Such strategies include maximising access to prenatal care, administering antenatal corticosteroids to women at risk for preterm delivery in the prenatal period, improving infection control efforts within hospitals, considering empiric antibiotic therapy for high risk mothers and infants, and promoting Kangaroo care and

Table 2: Predictors of Neonatal Sepsis

Predictor	PPV	NPV	Odds Ratio (a)
Temperature instability	95.2%	33.9%	10.27 (1.28-82.47)
Prematurity	86.4%	31.6%	4.32 (1.01-30.05)
VLBW (<1.5 kg)	100.0%	34.9%	Infinity (0.58-infinity)
Convulsions	100.0%	28.2%	Infinity (0.56-infinity)
Bulging fontanelle	100.0%	27.0%	Infinity (0.02-infinity)
Lethargy	90.9%	28.1%	4.13 (0.49-34.55)
LBW (<2.5 kg)	78.6%	34.9%	1.95 (0.65-6.28)
Tachypnea	76.3%	30.0%	1.38 (0.50-3.79)
Poor suck	78.8%	27.3%	1.30 (0.46-3.67)
CRP positive (>7 mg/L)	75.0%	21.7%	1.10 (0.33-3.65)
WBC <5 or >20,000/mm3	71.4%	21.7%	0.76 (0.13-4.36)

[a]Confidence interval

Table 3: Characteristics of Infants with Positive (+) Blood Cultures

	All infants with + blood cultures	*Staphylococcus*	*Pseudomonas*	*Klebsiella*
Premature	2 (22%)	2 (29%)	0	0
Temperature instability	5 (56%)	4 (44%)	1 (100%)	0
VLBW	0	0	0	0
Convulsions	2 (22%)	1 (14%)	1 (100%)	0
Bulging fontanelle	0	0	0	0
Lethargy	2 (22%)	1 (14%)	1 (100%)	0
= 2 clinical predictors	6 (67%)	5 (71%)	1 (100%)	0
= 3 clinical predictors	4 (44%)	3 (43%)	1 (100%)	0
Hospitalized >5 days	6 (67%)	5 (71%)	1 (100%)	0
Death	0	0	0	0
Transfer for higher LOC	0	0	0	0

breastfeeding.

During the intrapartum period, providers should provide aseptic delivery practices and sterile umbilical cord cutting to reduce infection risk in term and preterm infants. Further, administration of antibiotics to women with preterm prolonged rupture of membranes may decrease the incidence of neonatal infections by 32% [16-17]. Postnatally, close monitoring of premature infants and infants exhibiting temperature instability with a low threshold to start empiric antibiotic therapy and delayed discharge of premature infants may also decrease incidence of sepsis. Promotion of early and exclusive breastfeeding is desirable as breast milk contains lysozyme, secretory IgA, lactoferrin, and antimicrobial proteins and peptides, which inhibit the growth of gram-negative pathogens responsible for neonatal sepsis. [17-18] Kangaroo care, which involves skin-to-skin contact between mother and infant with frequent and exclusive breastfeeding, led to significant reduction in infection in LBW babies in hospital settings in a recent meta-analysis [19]. In addition, hospital policies to promote aseptic handling and hand washing are crucial to prevent nosocomial infections in neonates.

While the small size of our study limits our ability to precisely estimate the prevalence of bacteraemia, the isolates do provide a glimpse into the clinical epidemiology of neonatal sepsis in rural southern India. Staphylococcal species were the most common pathogens isolated in blood cultures, and all of these isolates were cloxacillin-resistant. Similarly, two prior Indian studies found that staphylococcal species accounted for 75-81% of positive blood cultures among neonates with suspected sepsis. The rate of S. aureus positivity versus coagulase-negative Staphylococcus varied considerably in these studies [15,20]. Among infants in our study who grew Staphylococcus spp., 71.4% had two or more clinical predictors of poor outcomes and 42.9% had three or more predictors. Further, 71.4% of these infants were hospitalized more than five days. Given our inability to speciate based on local resource limitations, these cloxacillin-resistant staphylococcal isolates could represent S. aureus, S. epidermidis, or another Staphylococcus spp. Although it is unclear what percentage represents true bacteraemia versus contamination, all of these agents are known pathogens in this population and many of the infants with positive cultures experienced poor outcomes. It is also notable that we obtained one isolate of Klebsiella spp. and Pseudomonas spp. Fortunately, both of these isolates were pan-sensitive in their antibiotic susceptibility profiles. However, it is crucial that local practitioners be aware of these organisms as potential pathogens given their propensity to acquire extended-spectrum beta-lactamase producing resistance patterns as has already been documented in a few larger Indian neonatal intensive care units [21-22].

Our study has several limitations. The small sample size limited our ability to evaluate predictor variables and capture rare outcomes. In addition, data were incomplete with one or more clinical or laboratory variables missing for 15.2% of infants. The inability to speciate blood cultures in our study made it difficult to rule out contamination as a possible cause of positive cultures, especially among staphylococcal isolates. Larger studies are needed to identify bacterial aetiologies of sepsis in Indian infants and to further investigate the prevalence of cloxacillin-resistant S. aureus.

CONCLUSIONS

In this study of newborns admitted for presumed bacterial sepsis in rural southern India, prematurity and temperature instability were associated with poor outcomes. Strategies to reduce both the incidence of premature birth and the risk of adverse consequences associated with prematurity will be critical in decreasing poor outcomes among infants in this setting. Staphylococcal species were the most common bacterial pathogens isolated in this study, but larger studies are needed to evaluate bacterial aetiologies of sepsis in this population and to determine the most appropriate empiric antibiotic regimen.

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