CHALLENGES IN TREATMENT STRATEGIES FOR MANAGEMENT OF NEONATAL SEPSIS

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Abstract

Background: *Neonatal sepsis is an important cause of morbidity and mortality in newborns. The symptoms and signs of neonatal sepsis are often non-specific and similar to other common neonatal diseases, investigation results are also non-specific and low sensitivity of blood culture also causes diagnostic dilemma and often empirical antibiotic treatment is given. This is why, there is challenges in making the diagnosis and treating neonatal sepsis.*

Objectives: *To find the etiology, sensitivity and specificity of clinical features and investigations and optimal and effective treatment for neonatal sepsis.*

Materials and methods: *The study was a prospective study done in the neonatal ward of a tertiary hospital in Bangladesh; total 100 neonates diagnosed as neonatal sepsis, were enrolled in this study. All study subjects were fully evaluated clinically, thoroughly investigated and properly treated as per protocol.*

Results: *The sensitivity and specificity of clinical features and investigations were statistically significant (i.e. p <0.05) and etiologic agents were isolated by urine culture and sensitivity to antibiotics were shown and outcome measure e.g. mortality was 22% (OR 3.54; 95% CI 2.04-6.13; P <0.05).*

Conclusion: *There are challenges in making diagnosis and treating neonatal sepsis, yet sincere approach to diagnosis and rational and appropriate use of antibiotics along with necessary adjuvant therapy can mitigate the challenges.*

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Introduction

Globally bacterial infection (sepsis, meningitis, pneumonia etc.) is a leading cause of 2.9 million neonatal deaths every year.[1] Strategies to reduce preventable infection-related neonatal deaths by 2030 to meet the WHO Sustainable Development Goal (SDG) is a global health priority. Neonates are especially vulnerable to sepsis due to perinatal exposure to infective agents, compromised immune system and maternal and neonatal risk factors.[1] In recent years neonatal mortality has decreased at much lower rates, and currently represents 40% of all childhood mortality.[2] Three-fourths of these deaths occur in the first week of life.[3] Neonatal sepsis is the third leading cause of neonatal mortality, only behind to prematurity and perinatal asphyxia.[4] is responsible for 13% of all neonatal mortality, and 42% of deaths in the first week of life.[5,6] In developing countries, clinically diagnosed sepsis is present in 49–170 per 1000 live births, culture-proven sepsis in 16 per 1000 live births and neonatal meningitis in 0.8–6.1 per 1000 live births.[7] Infants with neonatal infections are more likely to have adverse neuro-developmental outcomes at follow up, including cerebral palsy, lower mental and psychomotor development index scores, visual impairment and impaired growth.[8,9]

Risk factors for early-onset neonatal sepsis (EOS) include prematurity, immunologic immaturity, maternal Group B streptococcal (GBS) colonization, prolonged rupture of membranes, and maternal intra-amniotic infection.[10] Intra-partum antimicrobial prophylaxis administered to GBS-colonized women has reduced the burden of disease associated with early onset GBS invasive infections.[11] Late-onset neonatal sepsis (LOS)

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attributable to Gram-positive organisms, including coagulase negative Staphylococci and Staphylococcus aureus, is associated with increased morbidity and mortality among premature infants.[11] Invasive candidiasis is an emerging cause of late-onset sepsis, especially among infants who receive broad spectrum antimicrobial agents.[12]

Despite recent medical advances have improved neonatal care, yet many challenges remain in the diagnosis and management of neonatal infections.[13] The diagnosis of neonatal sepsis is complicated by the non-specific signs and symptoms of sepsis, low sensitivity of the gold standard blood culture test (particularly following intra-partum antibiotic prophylaxis), delayed availability of culture results (approximately 48–72 hours after blood collection) and the frequent presence of noninfectious conditions that resemble sepsis, especially in preterm infants, and by the absence of optimal diagnostic tests.[14] Since neonatal sepsis is a high-risk disease, especially in preterm infants, clinicians are compelled to empirically administer antibiotics to infants with risk factors and/or signs of suspected sepsis.[15] Unfortunately, both broad-spectrum antibiotics and prolonged treatment with empirical antibiotics are associated with adverse outcomes and increased antimicrobial resistance.[16] Given current challenges with diagnosis, and the high mortality and morbidity associated with neonatal sepsis, particularly in low-income countries, there is a need to develop novel approaches for identifying neonates at greatest risk.[17] Although there are challenges in making the diagnosis and providing appropriate treatment for neonatal sepsis, we need to overcome those obstacles with rational approach to investigate and manage neonatal sepsis. The objective of this prospective study was to find out the etiology, sensitivity and specificity of the clinical features and investigations and optimal and effective treatment for neonatal sepsis.

Methods

This study was a prospective study done in the Neonatal ward in the Sher-e-Bangla Medical College, Barishal from July 2016 to December 2016. Total 100 neonates were enrolled in this study. The aim of the study was to find out the etiology, sensitivity and specificity of the clinical features and the investigations, and optimal and effective management of neonatal sepsis. The study population was enrolled after obtaining informed written consent of the parents. Both extramural and intramural neonates admitted with the history suggestive of neonatal sepsis, were included in this study irrespective of gestational age, birth weight, sex, post natal age and ethnicity. Neonates diagnosed with perinatal asphyxia, early prematurity (<34 wk gestation) and very low birth weight (VLBW) (<1500 gm), inborn error of metabolism, genetic or chromosomal disorders and congenital anomalies were excluded from this study. All the enrolled newborns were fully clinically evaluated, appropriately investigated and properly treated as per protocol. Test used for screening were (1) Total leukocyte count <5000 or >20,000/cmm, (2) Neutropenia /Neutrophilia (age adjusted count, described by Monroe et al 1979), (3) Immature to total neutrophil (I.T. ratio >0.2), (4) C-reactive protein positive (CRP) (i.e. value > 10 mg/L), (5) platelet counts <50,000/mm.[8]

For isolation of the invading micro-organisms, we performed urine and cerebro-spinal fluid (CSF) culture as appropriate; blood culture was not available, which was a limitation. Data were collected and were analyzed by SPSS version 16; continuous variables were analyzed by student's *t* test and categorical variables were by chai-square test and statistical analysis was considered significant, if p value was less than 0.05.

Results

In this prospective study, total 100 neonates were enrolled with suspected neonatal sepsis. The clinical data e.g. birth weight, gestational age, sex ratio, mode of delivery, place of delivery etc. among the study population, were as shown in table – 1.

Table – 1

Base-line clinical data in study population.

Clinical parameter	n=100 (mean±S.D.)
Birth weight (gm)	2456±124
Gestational age (weeks)	36.28±1.6
Male/female ratio	53/47
Mode of delivery (vaginal/cesarean)	64/36
Place of delivery (home/hospital)	58/42

Sensitivity and specificity of the clinical features of neonatal sepsis were shown in table – 2.

Table – II

Sensitivity and specificity of the clinical features of neonatal sepsis.

Clinical feature	Sensitivity	Specificity	P value
Reluctance to feed	52 %	46 %	<0.05
Lethargy	42 %	48 %	<0.05
Hypotonia	38 %	44 %	<0.05
Poor reflexes	54 %	56 %	<0.05
Feed intolerance	36 %	42 %	<0.05
Hypothermia	34 %	38 %	<0.05
Apnea	44 %	46 %	<0.05
Respiratory distress	32 %	42 %	<0.05

Sensitivity and specificity of the investigations of neonatal sepsis were shown in table – 3.

Table - III

Sensitivity and specificity of the investigations of neonatal sepsis.

Investigations	Sensitivity	Specificity	P value
Culture of urine	04 %	12 %	<0.05
Culture of CSF	00 %	00 %	-
Neutropenia	24 %	38 %	<0.05
I/T ratio	36 %	42%	<0.05
Thrombocytopenia	34 %	36 %	<0.05
C reactive protein	52 %	48 %	<0.05
X ray chest (opacity)	24 %	28 %	<0.05

I/T ratio = Immature to total leucocyte ratio

In this prospective study, the study population were evaluated by urine and CSF culture as appropriate; CSF culture yielded no positive results. Etiologic organisms were found in positive urine culture, the result is as shown in table IV.

Table – IV

Etiologic agents found in culture of urine in Neonatal sepsis.

Etiologic agent	1st antibiotic	2nd antibiotic	3rd antibiotic
E. coli	Gentamicin	Ceftazidim	Meropenem
Klebshiella	Ceftazidim	Amikacin	Meropenem
Pseudomonas	Ceftazidim	Gentamicin	Meropenem
Proteus	Ceftazidim	Gentamicin	Meropenem

In this study seventy eight neonates were improved from neonatal sepsis and discharged; however, 22 newborns died of sepsis. Outcome measures were evaluated as shown in table 5.

Table – V

Outcome measures in Neonatal sepsis.

Outcome	n (%)	Odds ratio	95% C.I.	P value
Mortality	22 (22%)	3.54	2.04 – 6.13	<0.05
Improved	78 (78%)	3.53	2.05 – 6.20	<0.05

Discussion

Neonatal sepsis is not always very much straight forward in clinical presentation for diagnosis and often difficult to treat with empirical antibiotic therapy.[17,18] The symptoms and signs of sepsis in newborns are mostly nonspecific, low sensitivity/specificity of investigations result and availability, low sensitivity and delay in blood culture result often poses serious difficulty in making proper diagnosis and ideal antibiotic choice for treatment of neonatal sepsis is often a problem.[19]

In this prospective study, the population has mean birth weight 2456 (±124) gm, gestational age 36.28 (±1.6) weeks and male, female ratio 53%/47%. The sensitivity and specificity pattern of the clinical features of neonatal sepsis were as follows: reluctance to feed (52% vs. 46%, p<0.05), lethargy (42% vs. 48%, p<0.05), hypotonia (38% vs. 44%., p<0.05), poor reflexes (54% vs. 56%, p <0.05), feed intolerance (36% vs. 42%, p<0.05), hypothermia (34% vs. 38%, p<0.05), apnea (44% vs. 46%, p<0.05) and respiratory distress (32% vs. 42%, p<0.05). Sepsis share a similar clinical presentation to other common conditions e.g. perinatal asphyxia, extreme prematurity, inborn error of metabolism etc. in the neonatal period. Auxiliary tests are paramount for its diagnosis.[12] The World Health Organization identified seven clinical signs—difficulty in feeding, convulsions, movement only when stimulated, respiratory rate >60 per min, severe chest indrawing and axillary temperature >37.5°C or <35.5 °C—that should prompt neonatal referral to a hospital.[12] Other authors have also included cyanosis and grunting.[11]

The sensitivity and specificity of investigation results were as follows: urine C/S (04% vs. 12%, p < 0.05), neutropenia (24% vs. 38%, p < 0.05), I/T ratio (36% vs. 42%, p < 0.05), thrombocytopenia (34% vs. 36%, p < 0.05), CRP (C reactive protein) (52% vs. 48%, p < 0.05) and X ray chest (24% vs. 28%, p < 0.05). In complete blood cell count, low values of white blood cells, low values of absolute neutrophil counts and high immature/total ratio (I/T ratio) are associated with early-onset sepsis.[5] In this type of sepsis, high values of white blood cells and absolute neutrophil counts are not informative.[4] High or low white blood cells counts, high absolute neutrophil counts, high immature/total ratio and low platelet counts are associated with late-onset sepsis.[5] Despite their association with infection, all of these findings have low sensitivities.[4,5] The results of investigations of this study were similar to the study by SK Anwer et al., where the sensitivity and specificity of investigations were as follows: abnormal neutrophil count (61.90% vs. 51.72%), I/T ratio (i.e. e"0.2) (30.89% vs. 65.51%), thrombocytopenia (i.e.d"150000/mm^3) (52.38% vs. 60.06%), and CRP (66.66% vs. 48.27%).[20] However, N Kumar et al. evaluated the diagnostic role of presepsin and its comparison with C-reactive protein (CRP) and Procalcitonin (PCT) and found sensitivity of CRP, PCT and presepsin was 80.5%, 80.5%, 97.6% and specificity was 97.5%, 80.5%, 95.1% respectively. PCT and CRP were comparable as diagnostic markers of neonatal sepsis.[21] Presepsin, in comparison with CRP and PCT has better sensitivity and negative predictive value (NPV).[21] In the study by M Adib et al., at a cut-off value, 12 mg/l, CRP was found to have a sensitivity of 45%, specificity of 95%, positive predictive value (PPV) of 30%, negative predictive value (NPV) of 30% for the diagnosis

of neonatal sepsis and also found 70% sensitivity, 80% specificity, 80% PPV and 75% NPV for procalcitonin as a marker for the early diagnosis of neonatal sepsis.[22]

A single value of C-reactive protein (CRP) has low sensitivities, especially during the early stages of infection.[6,7] Taking serial determinations 24–48 h after the onset of symptoms achieves a sensitivity of 74–89% and specificity of 74–95%.[6,7] CRP values are also affected by premature rupture of membranes, maternal fever, meconium aspiration, fetal distress and the etiology of the infection.[10] Blood culture is the gold standard for the diagnosis of neonatal sepsis.[4] However, its positivity rate is low and is affected by blood volume inoculated, prenatal antibiotic use, level of bacteremia and laboratory capabilities.[5] In developing countries, culture-negative sepsis is responsible for the majority of episodes.[4] Currently, the recommended minimal blood volume for cultures in newborns is 1 ml, but most samples taken are of less than 0.5 ml.[5] One classic study, focusing on E. coli infection, found that neonates have high-colony-count bacteremia.[6] However, a more recent study including other common neonatal-sepsis pathogens found that 68% of septic infants have low-level bacteremia (d"10 Colony-forming units (CFU)/ml) and 42% have counts d"1 CFU/ml.[7] In low-colony-count bacteremia, as many as 60% of cultures will be falsely negative with 0.5 ml sample volumes.[8] Multiple blood cultures could help increase the yield of this test.[9,10]

Table 4 showed that the various etiologic agents e.g. E coli, klebsheilla, pseudomonas and proteus etc. derived from urine C/S were sensitive to various antibiotics, such as gentamicin, amikacin, ceftazidim and meropenem. Table 5 shows the outcome of the study regarding neonatal septicemia, mortality was 22% (OR 3.54, 95% C.I. 2.04-6.13, P < 0.05) and cure rate was 78%, (OR 3.53, 95% C.I. 2.05-6.20, P < 0.05).

Clinical trials evaluating the treatment of neonatal sepsis failed to find an optimal antibiotic regimen.[10] The lack of an accepted definition of sepsis in neonates is one of the main obstacles.[12] Both the culture-proven sepsis and culture-negative sepsis require antibiotic therapy.[11] The knowledge of the most common pathogens and their antibiotic resistance patterns should guide the management of neonatal sepsis.[13,14] Almost all neonates in an NICU receive antibiotics during their hospitalization, but only 5% have a positive blood culture.[15] Most of the antibiotic courses are given empirically before 72 h of life, and 60% of these courses are prolonged for more than 48–72 h despite negative blood culture and a stable clinical condition.[15] Neonates with risk factors for early-onset sepsis or compatible clinical condition should receive prompt empiric antibiotic therapy.[13] Poupolo et al. developed a risk stratification tool to select neonates that need empiric therapy.[13] GBS and E. coli account for most episodes of early-onset sepsis in developed countries.[14] The combination of ampicillin and aminoglycosides should be the initial therapy for suspected early-onset sepsis.[15] This regimen has the additional advantage of having synergistic activity against GBS and Listeria monocytogenes.[16]

Every neonate with signs of late-onset sepsis should receive empiric antibiotic therapy.[13] In developed countries, almost three-fourths of CoNS isolated are resistant to methicillin.[15] Also, one-fourth of gram-negative pathogens are resistant to third-generation cephalosporins but only 10% are resistant to aminoglycosides.[15,17] Considering the high resistance to methicillin, some experts recommend using vancomycin plus an aminoglycoside as empiric therapy for late-onset sepsis.[13] However, CoNS infections are rarely fulminant and starting therapy with an anti-staphylococcal penicillin plus an aminoglycoside is a safe option.[14] Vancomycin should be reserved for confirmed cases of methicillin-resistant pathogens.[14] Newborn with risk factors for candida sepsis—central vascular access, endotracheal intubation, thrombocytopenia, exposure to broad-spectrum cephalosporins or carbapenems and extreme prematurity—should receive fungal empiric therapy.[16]

Conclusion

Though there are difficulties and challenges in making the diagnosis and providing management for neonatal sepsis, sincere efforts

and keen appropriate approach to reach the diagnosis are of paramount importance and rational use of appropriate antibiotics and adjuvant therapy are necessary for the management of neonatal sepsis.

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