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Evaluation and Role of Basic Hematological Scoring System in Early detection of Neonatal Sepsis

Dr. K N Mishra[1], Dr. Randhir Kumar Mishra[2*]

[1] Professor & HOD, Department of Pediatrics, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India

[2] Junior Resident, Department of Pediatrics, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India

[*] Corresponding Author: Dr. Randhir Kumar Mishra

Abstract

Neonatal sepsis has subtle and varied clinical presentation in the initial stages. Aggressive approach to diagnosis and management is the principle determinant of the prognosis. Early diagnosis of neonatal sepsis is the corner stone to reduce the case fatality rate. Blood culture to identify the organism is the gold standard for the diagnosis. However, the yield is low due to several reasons such as low inoculum in the sample sent, inability of the laboratory to identify all the organisms and prior antibiotic usage.1 Added to this is the delay in obtaining the results. The earliest result will be available after 48 hours of incubation of the blood sample. This period could be too late for the clinician to initiate any useful treatment.

The present study was done in SNCU of Department of Pediatrics, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India. Total 50 neonates having positive indications for the sepsis were included in the present study. Score of ≤ 2 is considered as lower risk; score 3-4 as moderate risk; and score ≥ 5 as higher risk for developing sepsis. Minimum score that can be obtained is 0 and maximum score up to 7.

Neonatal sepsis is a life-threatening yet treatable condition. Non- infectious disorders may produce haematological changes similar to those seen with infection, thereby compromising the specificity and positive predictive value of the screening tests. The feasibility and the cost effectiveness of Haematological scoring system increase the usefulness of this test. Modified haematological score improves the specificity and likelihood ratios without decreasing the sensitivity in neonatal sepsis. Hence it can be concluded that the hematologic scoring system are useful test to distinguish the infected from non-infected infants. These are simple, quick, cost effective and readily available tool with high sensitivity and specificity in the early diagnosis of neonatal sepsis.

Keywords: Haematological scoring system (HSS), Blood culture, Neonatal septicemia, etc

Introduction

Neonatal sepsis is a clinical syndrome of bacteremia characterized by systemic signs and symptoms of infection in the first month of life. Neonatal sepsis encompasses systemic 3 infections of the newborn including septicemia, meningitis, pneumonia, arthritis, osteomyelitis and urinary tract infection of the newborn. Sepsis is the commonest cause of neonatal mortality and is probably responsible for 30- 50% of the total neonatal deaths each year in developing countries [1, 2]. It is estimated that 20% of all neonates develop sepsis and approximately 1% die of sepsis related causes [2]. Sepsis related mortality is largely preventable with rational antimicrobial therapy with aggressive supportive care.

According to recent data from National Neonatal Perinatal Database (NNPD) 2000, the incidence of neonatal sepsis has been reported to be 38 per 1000 intramural live births in tertiary care institutions [3]. Septicemia was the commonest clinical category with an incidence of 24 per 1000 live births. Meningitis was diagnosed in 0.5 per 1000 live births. Neonatal sepsis was one of the common causes of neonatal mortality contributing to 23% of all neonatal deaths [3]. Klebsiella pneumoniae was the most frequently isolated pathogen (31.2%), followed by Staphylococcus aureus (17.5%) among the intramural live births. Among extramural babies admitted for neonatal problems, Klebsiella pneumoniae was the commonest organism (36.4%), followed by Staphylococcus aureus (14.3%) and Pseudomonas (13.2%).

Neonatal sepsis can be divided into two main classes depending on the onset of symptoms related to sepsis [4].

Early onset sepsis: Early onset sepsis usually presents within the first 72 hours of life. In severe cases, the neonate may be symptomatic in utero (fetal tachycardia, poor beat to beat variability) or within a few hours after birth. The source of infection is generally the maternal genital tract. Clinically, neonates usually present with respiratory distress and pneumonia. Presence of some perinatal risk factors has been associated with an increased risk of early onset sepsis. Recommendations from developed countries suggest that presence of ≥2 risk factors should be considered an indication for starting antibiotics. However the main organism is group B streptococci (GBS) which is not a problem in our neonatal intensive care units. Hence, their recommendations may not be applicable to our setting. Since definitive data for our setting is lacking, an empirical approach has been recommended. Presence of the following high-risk factors has been associated with an increased risk of early onset sepsis [4, 5].

1. Febrile illness in the mother within 2 weeks prior to delivery
2. Prolonged rupture of membranes >24 hours.
3. Foul smelling and/ or meconium stained liquor amnii.
4. Low birth weight (<2500 grams) or preterm baby

5. More than 3 vaginal examinations during labour
6. Prolonged and difficult delivery with instrumentation
7. Perinatal asphyxia (Apgar score<4 at 1 minute or age) or difficult resuscitation Neonates with presence of foul smelling liquor or three of the above mentioned risk factors should be considered to have early onset sepsis and treated with antibiotics. Presence of ≥2 risk factors should be investigated with a septic screen and treated accordingly.

Late onset sepsis: Late onset sepsis usually presents after 72 hours of age. The source of infection is either nosocomial or community-acquired and neonates usually present with septicemia, pneumonia or meningitis [6, 7]. Various factors that predispose to an increased risk of nosocomial sepsis include NICU admissions, low birth weight, prematurity, invasive procedures, parenteral fluid therapy, ventilation and use of stock solutions. Factors that may increase risk of community-acquired late onset sepsis include poor hygiene, poor cord care, bottle-feeding and prelacteal feeds. Breast-feeding, on the other hand, prevents infection in neonates.

Sepsis is a life-threatening condition that arises when the body's response to infection causes injury to its own tissues and organs. Common signs and symptoms include fever, increased heart rate, increased breathing rate, and confusion. There may also be symptoms related to a specific infection, such as a cough with pneumonia, or painful urination with a kidney infection. In the very young, old, and people with a weakened immune system, there may be no symptoms of a specific infection and the body temperature may be low or normal, rather than high. Severe sepsis is sepsis causing poor organ function or insufficient blood flow. Insufficient blood flow may be evident by low blood pressure, high blood lactate, or low urine output. Septic shock is low blood pressure due to sepsis that does not improve after fluid replacement [8].

Sepsis is caused by an inflammatory immune response triggered by an infection. Most commonly, the infection is bacterial, but it may also be fungal, viral, or protozoan. Common locations for the primary infection include the lungs, brain, urinary tract, skin, and abdominal organs. Risk factors include very young age, older age, a weakened immune system from conditions such as cancer or diabetes, major trauma, or burns. An older method of diagnosis was based on meeting at least two systemic inflammatory response syndrome (SIRS) criteria due to a presumed infection. In 2016, SIRS was replaced with a shortened sequential organ failure assessment score (SOFA score) known as the quick SOFA score (qSOFA) which is two of the following three: increased breathing rate, change in level of consciousness, and low blood pressure. Blood cultures are recommended preferably before antibiotics are started, however, infection of the blood is not required for the diagnosis. Medical imaging should be used to look for the possible location of infection [8]. Other potential causes of similar signs and symptoms include anaphylaxis, adrenal insufficiency, low blood volume, heart failure, and pulmonary embolism [9].

Sepsis is usually treated with intravenous fluids and antibiotics. Typically, antibiotics are given as soon as possible. Often, ongoing care is performed in an intensive care unit. If fluid replacement is not enough to maintain blood pressure, medications that raise blood pressure may be used. Mechanical ventilation and dialysis may be needed to support the function of the lungs and kidneys, respectively. To guide treatment, a central venous catheter and an arterial catheter may be placed for access to the bloodstream. Other measurements such as cardiac output and superior vena cava oxygen saturation may be used. People with sepsis need preventive measures for deep vein thrombosis, stress ulcers and pressure ulcers, unless other conditions prevent such interventions. Some might benefit from tight control of blood sugar levels with insulin [8]. The use of corticosteroids is controversial, with some reviews finding benefit and others not.

Disease severity partly determines the outcome. The risk of death from sepsis is as high as 30%, from severe sepsis as high as 50%, and from septic shock as high as 80%. The number of cases worldwide is unknown as there is little data from the developing world. Estimates suggest sepsis affects millions of people a year. In the developed world approximately 0.2 to 3 people per 1000 are affected by sepsis yearly, resulting in about a million cases per year in the United States. Rates of disease have been increasing [8]. Sepsis is more common among males than females. The medical condition has been described since the time of Hippocrates. The terms "septicemia" and "blood poisoning" have been used in various ways and are no longer recommended [10].

Early diagnosis is necessary to properly manage sepsis, as initiation of rapid therapy is key to reducing deaths from severe sepsis [8]. Some hospitals use alerts generated from electronic health records to bring attention to potential cases as early as possible.

Within the first three hours of suspected sepsis, diagnostic studies should include white blood cell counts, measuring serum lactate, and obtaining appropriate cultures before starting antibiotics, so long as this does not delay their use by more than 45 minutes. To identify the causative organism (s), at least two sets of blood cultures using bottles with media for aerobic and anaerobic organisms should be obtained, with at least one drawn through the skin and one drawn through each vascular access device (such as an IV catheter) in place more than 48 hours [8]. Bacteria are present in the blood in only about 30% of cases. Another possible method of detection is by polymerase chain reaction. If other sources of infection are suspected, cultures of these sources, such as urine, cerebrospinal fluid, wounds, or respiratory secretions, also should be obtained, as long as this does not delay the use of antibiotics [8].

Within six hours, if blood pressure remains low despite initial fluid resuscitation of 30 ml/kg, or if initial lactate is ≥ 4 mmol/l (36 mg/dl), central venous pressure and central venous oxygen saturation should be measured. Lactate should be re-measured if the initial lactate was elevated [8]. Evidence for point of care lactate measurement over usual methods of measurement, however, is poor [11].

Within twelve hours, it is essential to diagnose or exclude any source of infection that would require emergent source control, such as necrotizing soft tissue infection, infection causing inflammation of the abdominal cavity lining, infection of the bile duct, or intestinal infarction [8]. A pierced internal organ (free air on abdominal x-ray or CT scan), an abnormal chest x-ray consistent with pneumonia (with focal opacification), or petechiae, purpura, or purpura fulminans may be evident of infection.

Two sets of blood cultures (aerobic and anaerobic) should be taken without delaying the initiation of antibiotics.

Cultures from other sites such as respiratory secretions, urine, wounds, cerebrospinal fluid, and catheter insertion sites (in-situ more than 48 hours) can be taken if infections from these sites are suspected. In severe sepsis and septic shock, broad-spectrum antibiotics (usually two, a β-lactam antibiotic with broad coverage, or broad-spectrum carbapenem combined with fluoroquinolones, macrolides, or aminoglycosides) are recommended. However, combination of antibiotics is not recommended for the treatment of sepsis but without shock and immunocompromised persons unless the combination is used to broaden the anti-bacterial activity. The choice of antibiotics is important in determining the survival of the person. Some recommend they be given within one hour of making the diagnosis, stating that for every hour of delay in the administration of antibiotics, there is an associated 6% rise in mortality. Others did not find a benefit with early administration [12].

Neonatal sepsis has subtle and varied clinical presentation in the initial stages. Aggressive approach to diagnosis and management is the principle determinant of the prognosis. Early diagnosis of neonatal sepsis is the corner stone to reduce the case fatality rate. Blood culture to identify the organism is the gold standard for the diagnosis. However, the yield is low due to several reasons such as low inoculum in the sample sent, inability of the laboratory to identify all the organisms and prior antibiotic usage.1 Added to this is the delay in obtaining the results. The earliest result will be available after 48 hours of incubation of the blood sample. This period could be too late for the clinician to initiate any useful treatment.

Methodology

The present study was planned in SNCU of Department of Pediatrics, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India. Total 50 neonates having positive indications for the sepsis were included in the present study. Score of ≤ 2 is considered as lower risk; score 3-4 as moderate risk; and score ≥ 5 as higher risk for developing sepsis. Minimum score that can be obtained is 0 and maximum score up to 7.

Neonatal septicemia was diagnosed as per the clinical criteria given by Vergnano *et al.* [13]. Blood sample (0.5 to 2 ml) was collected with all aseptic precaution and was inoculated into blood culture bottle BactT/Alert® PF (BIOMERIEUX, INC. Durhams, NC 27704) containing 20 ml of broth.

Clinical data involved initial demographic data of all the subjects were obtained from the admission record. Babies who had hemogram done at the time of admission as the baseline investigation and did not develop any sepsis with in next 72 hours were considered as normal or no sepsis group.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study:

Inclusion Criteria

Maternal fever (>38^0C); Premature rupture of membranes (PROM) > 12 hours; More than 3 vaginal examinations after rupture of membranes; Foul-smelling liquor; Meconium stained liquor; Maternal UTI within 2 weeks prior to delivery; Prolonged and difficult delivery with instrumentation.

Exclusion Criteria

New born babies with gestational age < 28 weeks; Neonates with birth weight less than <1000 gm; Neonates with lethal congenital anomalies; Still born and fetal deaths; Post-dated and postmature neonates.

Table 1: Haematological scoring system

Criteria	Abnormality	Score
Total leukocyte count (cells/cumm)	<5000	1
	>20,000	
ANC (cells/cumm)	<1800	1
Immature neutrophil count (cells/cumm)	<1200	1
I:T	≥0.2	1
I:M	≥0.3	1
Platelet count (cells/cumm)	<150,000	1
Degenerative changes in neutrophils	Toxic granules	1
	Cytoplasmic	
	Vacuoles	

I: T – Immature to total neutrophils ratio; I: M – Immature to mature neutrophils ratio; ANC – Absolute neutrophil count

Results and Discussion

Neonatal Sepsis is a devastating condition with a case fatality rate ranging from 30 to 50%.15, 16 early recognition and treatment can reduce the case related mortality to 10%. Blood culture which is the gold standard for diagnosis is difficult to obtain and has a very low sensitivity due to various preanalytical and analytical issues and is not available during the therapeutic window [14]. PCR for detection of antigen is currently gaining acceptance but are quite expensive [15]. CRP and Procalcitonin are biochemical markers of neonatal sepsis in routine use which has better value in following the progress of the disease [16].

Complete blood count and peripheral blood picture is an early and commonly sought investigations by the clinicians when sepsis is suspected in neonates. Changes in various components of blood count and blood picture makes it one of the dependable early aid to diagnosis and management of neonatal sepsis. Rodwell suggested a comprehensive scoring system using blood counts and blood picture. The diagnostic usefulness of Rodwell's hematological scoring system and its individual components have been extensively studied and found invaluable [17].

Risk factors from mothers and babies were found in all neonates with proven sepsis. Results of this study was similar with the theory declaring that neonates with suspected sepsis showed clinical manifestations and had risk factors from mothers or babies; or had no clinical manifestations but had risk factors from the mother or the baby. Risk factors from mothers included premature or prolonged (>18 hours) rupture of membranes, maternal peripartum fever, foul-smelling or cloudy amnion fluid, and multiple gestation. Risk factors from baby included prematurity, low birth weight, asphyxia neonatorum, required intubation or resuscitation, and invasive procedures [18, 19].

Table 2: Age & Sex with Culture results

Culture Observations	Preterm	Term	Total
Positive	10	6	16
Negative	3	31	34
Total	13	37	50

Table 3: Haematological scoring system

Haematological scoring system	Culture Positive	Culture Negative	Total
0-2	0	7	7
3-4	2	25	27
More than 5	16	0	16
Total	18	32	50

Table 4: Haematological scoring system comparison with C-reactive protein

Haematological scoring system	C-reactive protein Reactive	C-reactive protein Non-Reactive	Total
0-2	0	8	8
3-4	17	8	25
More than 5	15	2	17
Total	32	18	50

Table 5: Sensitivity, specificity, Positive predictive value (PPV), and Negative predictive value (NPV)

	Sensitivity %	Specificity %	PPV %	NPV %
Total leukocyte count	63	76	45	88
Absolute neutrophil count	47	90	44	90
Immature to total neutrophil ratio	93	91	92	94
Immature to mature neutrophil ratio	92	95	93	94
Platelet	55	54	57	56

Early diagnosis of neonatal septicemia is still a great challenge. For early diagnosis of neonatal septicemia a hematologic scoring system (HSS) of Rodwell are preferable because it includes all parameters. Haematological parameters should accurately predict the presence or absence of infection and be reliable [20]. The HSS assigns a score of 1 for each of seven hematologic findings and shown to be significantly ($P<0.005$) associated with sepsis. There is one exception, an abnormal total PMN count is assigned a score of 2 rather than 1 if no mature PMNs are seen on the blood smear [21].

Septic marker examination such as CRP, cytokine, and procalcitonin levels in the establishment of early diagnosis of neonatal sepsis will give better value if the results are combined each other, but all those examinations are expensive and not available in every health centre [22, 23]. The utilization of HSS in early diagnosis of neonatal sepsis is more simple, cheaper, and faster examination than other septic markers and available in every health centre [24, 27].

Ghosh *et al.* and Narasimha *et al.* reported that Immature PMN count and I: T PMN ratio is sensitive indicator of neonatal sepsis. Degenerative changes in the PMNs made no significant contribution in the diagnosis, in this study [28, 29]. Presence of toxic granules indicates the production of unusual PMNs during infection and stress induced leucopoiesis. They are never seen in healthy babies. Their presence invariably indicates sepsis, but their count is not always increased. Thrombocytopenia was frequently associated with sepsis and indicated poor prognosis. This is thought to be due to increased platelet destruction, sequestration secondary to infections, failure in platelet production due to reduced megakaryocytes or damaging effects of endotoxin [30, 31].

Higher the score on HSS, more are the chances of sepsis. The simplification and standardization of the interpretation of this global test is still required. Variety of other rapid detection methods of microorganisms, like DNA probes, automated blood culture system and fluorometric detection systems are also available globally, but HSS can still be used as a screening test for diagnosing sepsis and to differentiate infected neonates from the non-infected ones. Furthermore, the sensitivity and the specificity of the test are also high, with certainty of sepsis increasing with the score [32].

Murphy *et al.* reported on 100% sensitivity and 100% negative predictive value of two normal white blood cell counts (WBC) within 8 to 12 hours and a negative blood culture at 24 hours for ruling out early onset sepsis in the neonate [33]. Measurement of immature neutrophil granulocytes has been considered to be a helpful early indicator of various infectious conditions and has a long clinical tradition in the diagnosis of bacterial sepsis in neonates [34].

As no single individual haematological parameter is superior in comparison to another in predicting neonatal sepsis, a combination of these parameters in the form of HSS has been recommended. Hematologic scoring system (HSS) should improve the efficiency of the CBC as a screening test for sepsis until a reliable diagnostic test is available. The HSS has practical advantages; it is applicable to all infants, including those who have received antibiotic therapy prior to evaluation and simplifies the interpretation of hematologic profile.

The limitation of our study was the possibility of difficulty in blood sampling of neonates for blood culture examination. This was due to that all of our subjects came with clinical manifestations, however positive blood culture results were found only in 10 neonates.

Conclusion

Neonatal sepsis is a life-threatening condition if not treated aggressively. Non- infectious disorders may produce haematological changes similar to those seen with infection, thereby compromising the specificity and positive predictive value of the screening tests. The feasibility and the cost effectiveness of Haematological scoring system increase the usefulness of this test. Modified haematological score improves the specificity and likelihood ratios without decreasing the sensitivity in neonatal sepsis. Hence it can be concluded that the hematologic scoring system are useful test to distinguish the infected from non-infected infants. These are simple, quick, cost effective and readily available tool with high sensitivity and specificity in the early diagnosis of neonatal sepsis.

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