

## The Predictive Value of Micro-Erythrocyte Sedimentation Rate in Neonatal Sepsis in a Low Resource Country

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### Abstract

**Background:** Neonatal sepsis is a major cause of morbidity and mortality in developing countries. Blood culture which is the gold standard for confirmation of sepsis has a low yield and does not provide rapid diagnosis. In addition, it is relatively costly and requires skilled workers and laboratory equipments that are scarce and space in between low resource settings. Therefore, there is need for other rapid screening tests, so that prompt intervention can be instituted. There is therefore need for other rapid screening or diagnostic tests. This study was therefore carried out to determine the predictive value of micro-erythrocyte sedimentation rate (mini-ESR) in the diagnosis of neonatal sepsis.

**Methods:** A prospective study was carried out from July to December 2007. Blood was obtained from 406 neonates with suspicion of sepsis for the estimation of mini-ESR, blood culture, full blood count and blood film. Blood culture was used as gold standard for the diagnosis of neonatal sepsis.

**Results:** Two hundred and fifty one (61.8%) neonates had elevated mini-ESR while 169 (41.6%) had positive blood culture. The prevalence of neonatal sepsis was 33.1%. The sensitivity, specificity, positive and negative predictive values of mini-ESR using blood culture as gold standard were 75.7%, 48.1%, 51.0% and 73.5% respectively. Combination of mini-ESR with band forms had high sensitivity and negative predictive values of 95.9% and 94.2% respectively.

**Conclusion:** Mini-ESR can be combined with band forms as screening tools for neonatal sepsis.

**Keywords:** Predictive value; Mini-ESR; Neonatal sepsis; Low resource country

### Introduction

Sepsis remains a significant cause of neonatal morbidity and mortality despite the use of potent antibiotics and intensive supportive care [1,2]. The World Health Organization estimates that 5 million neonates die each year and that nearly all (98%) of these deaths occur in developing countries with infections being the single most important cause [3].

Early diagnosis of neonatal sepsis (NNS) has remained a frustrating experience even in the developed countries [4]. Prompt and correct diagnosis of NNS is difficult because of its subtle and non-specific symptoms and signs [5,6]. The gold standard for diagnosis is blood culture but has a high cost and delay of at least 48 hours before preliminary results are gotten [6]. The yield of blood culture is between 30%-70% and thus some neonates with sepsis may go undetected [7]. In addition, the inability to adequately exclude the diagnosis of neonatal sepsis early usually results in unnecessary and prolonged exposure of neonates to antibiotics. Hence simple, quick, inexpensive laboratory test which may assist the clinician in the diagnosis of sepsis (or its exclusion) would ensure early treatment and prevent unnecessary antibiotic therapy. The micro-erythrocyte sedimentation rate (mini-ESR) is a test that involves the use of micro-hematocrit capillary tube to measure the distance that erythrocytes have fallen after one hour in a vertical column of anti-coagulated blood under gravity [8,9]. It is a simple inexpensive bedside test which requires a small volume of blood and less skill. The use of mini-ESR as a rapid test would reduce unnecessary and prolonged exposure of neonates to antibiotics and can serve as a preliminary step in diagnosis of NNS [10].

### Aim

To determine the predictive value of Mini-ESR in neonatal sepsis by making comparison of its Sensitivity, Specificity, Positive and Negative Predictive Values with that of blood culture which is gold standard.

### Materials and Methods

It was a prospective study carried out between 1st July and 31st December, 2007 in the Special Care Baby Unit (SCBU) of University of Port Harcourt Teaching Hospital. The hospital which is situated in Port Harcourt, the metropolitan centre of the crude oil rich Niger Delta region of Nigeria, serves as a referral and regional neonatal care centre.

All newborns aged 0-28 days admitted during the period of study with one or more symptoms/signs suggestive of sepsis or risk factors for sepsis were recruited into the study. For every neonate recruited, mini-ESR was estimated with capillary blood obtained by heel prick, collected in a standard 75 millimeter heparinised micro-hematocrit tube with internal diameter of 1.1 millimeters. Air was not allowed to interrupt the column of blood to avoid false normal result and one end of the tube was sealed with 2-3 millimeter of clay. The capillary tubes were placed on vertical lines drawn on a wall of each ward using 45 degree set square (rule). The capillary tubes were anchored firmly with adhesive at the base of the tubes with the names of the patients and time of blood collection stated. Alarm clocks were used to ensure that the one hour sedimentation period was maintained; thereafter the distance from the highest point of the plasma column to the meniscus of the packed red cell column (height of the plasma column) of each tube was

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measured with a rule. Mini-ESR was said to be elevated if the height of plasma column measured was greater than the sum of the age in days and a constant (3) for neonates aged 0-14 days; and greater than 15 mm/hr for neonates aged 15-28 days [10,11].

The standard criterion for sepsis in neonates is defined as the presence of bacterial infection documented by positive blood culture [12]. As such, all babies with suggestive signs and symptoms who had their mini-ESR done also had two milliliters of venous blood collected from a peripheral vein for blood culture after adequate skin preparation and before the commencement of antibiotics. The blood was aseptically introduced into aerobic and anaerobic culture media. The blood culture specimens were processed according to standard methods in the microbiology laboratory of UPTH [13]. Inoculated blood culture media were considered negative if there was no growth after continuous incubation for up to 7 days, subcultures being made each day. Antibiotic sensitivity was done using Kirby-Bauer disc diffusion method [13].

Full blood count was also done in the Hematology Laboratory for all neonates recruited for the estimation of packed cell volume, total leukocyte count, platelet count, neutrophil count and blood film for band forms. Full blood count was suggestive of sepsis if the total leukocyte count was greater than  $20 \times 10^9/L$  or less than  $5 \times 10^9/L$ , [5] Platelet count less than  $100 \times 10^9/L$ , [14] neutrophil count greater than 75% or less than 40% of the total leukocyte count and the presence of more than 20% band forms in the peripheral blood film [15].

The clinical details and results of laboratory investigations were recorded in a proforma.

Comparison between the mini-ESR and blood culture was done as follows:

True positive → Elevated mini-ESR in neonates with positive blood culture.

False positive → Elevated mini-ESR in neonates with negative blood culture.

True Negative → Normal mini-ESR in neonates with negative blood culture.

False negative → Normal mini-ESR in neonates with positive blood culture.

The sensitivity, specificity, positive and negative predictive values of mini-ESR compared to blood culture was calculated using the formulae: [16]

$$\text{Sensitivity} = \frac{\text{True Positives (TP)}}{\text{True Positive (TP) + False Negatives (FN)}} \times 100\%$$

$$\text{Specificity} = \frac{\text{True Negatives (TN)}}{\text{True Negatives (TN) + False Positives (FP)}} \times 100\%$$

$$\text{Positive predictive value} = \frac{\text{True Positives (TP)}}{\text{True Positives (TP) + False Positives (FP)}} \times 100\%$$

$$\text{Negative Predictive Value} = \frac{\text{True Negatives (TN)}}{\text{True Negatives (TN) + False Negatives (FN)}} \times 100\%$$

The results were analyzed using the statistical package, SPSS version 14.0 and Epi-info version 6.04.

## Results

Of the 511 neonates admitted into the SCBU, 406 met study criteria and were recruited. Two hundred and sixty four (65.0%) were males and 142 (35.0%) females with mean birth weight of  $2.8 \pm 0.9$  kg and a mean gestational age of  $36.7 \pm 3.6$  weeks. One hundred and sixty nine neonates had positive blood culture giving a prevalence rate of 33.1% for sepsis.

The proportion of neonates with True Positive, False Positive, True Negative and False Negative Mini- ESR using Blood Culture as Gold Standard is shown in Table 1.

Using the data in Table 1, the sensitivity, specificity, positive and negative predictive values of mini-ESR were calculated to be 75.7%, 48.1%, 51.0% and 73.5% respectively (Table 2). It also show that when mini ESR was combined with levels of band forms, the sensitivity and negative predictive value of increased to 95.9% and 94.2% respectively.

## Discussion

The present study showed that mini-ESR correctly identified 128 out of 169 neonates who had blood culture proven sepsis, giving a sensitivity of 75.7%. This implies that about three quarters of neonates with suspected sepsis will be correctly diagnosed with the mini-ESR. This value is comparable with the 79% reported by Misra et al. [17] and

Mini-ESR	Blood culture		Total
	No Positive	No Negative	
Elevated	128 (TP)	123 (FP)	251
Normal	41 (FN)	114 (TN)	155
Total	169	237	406

Key:  
 TP = True positive  
 TN = True negative  
 FP = False positive  
 FN = False negative

**Table 1:** Proportion of Neonates with True Positive, True Negative, False Positive and False Negative Mini-ESR using Blood Culture as Gold Standard.

Haematological Parameters	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Band forms	87.6	100.0	100.0	91.9
<b>Mini-ESR</b>	<b>75.7</b>	<b>48.1</b>	<b>51.0</b>	<b>73.5</b>
Platelet count $< 100 \times 10^9/L$	18.9	88.2	53.3	60.4
TLC $> 20 \times 10^9/L$	10.5	88.9	38.1	60.6
TLC $< 5 \times 10^9/L$	9.9	98.1	78.9	60.6
Mini-ESR+ Band forms	95.9	48.1	56.8	94.2
Mini-ESR + TLC $> 20 \times 10^9/L$	86.0	41.9	50.8	80.9
Mini-ESR + Platelet count ( $< 100 \times 10^9/L$ )	81.1	44.3	50.9	76.6
Mini-ESR + TLC $< 5 \times 10^9/L$	74.4	43.9	35.8	80.4

Key:  
 PPV= Positive predictive value  
 NPV= Negative predictive value  
 TLC= Total leukocyte count

**Table 2:** Sensitivity, Specificity, Positive and Negative Predictive Values of Mini-ESR in isolation and in combination with some Haematological Parameters using Blood Culture as Gold Standard.

71% by Akpede and Abiodun [18]. It is however higher than the 62.5% documented by Diwarker and Rosul G [19] and 14.3% by Zeeshan et al. [5]. These lower sensitivities could be attributed to the variation in the diagnostic criteria used in the different studies. The cut-off value in the present study was age dependent and corresponded to values above the 95th percentile for normal neonates as postulated by Adler and Denton [10]. The much lower sensitivity obtained by Zeeshan et al. [5] could be attributed to the high cut-off value of > 10 mm/hr used. This is because a high cut-off value would lead to fewer neonates testing positive for the disease condition and thus a lower sensitivity. The sensitivity obtained in the present study was lower than the 96.9% documented by Okolo et al. [20] in Benin who used mini-ESR values above the 95th percentile as defined by them (1.8-7.7 mm/hr) in a previous study of healthy Nigerian neonates [21]. Their cut-off was much lower than the 4.0-10.0 mm/hr value obtained by Adler and Denton [10] in Montreal, Canada which the present study used as cut-off. The lower mini-ESR used as reference by Okolo et al. [20] in their study, could therefore account for the much higher sensitivity obtained when compared with the present study.

Micro-Erythrocyte sedimentation rate was unable to identify 41 out of 169 neonates who had culture proven sepsis giving a specificity of 48.1%. This is at variance with the 60.9%, 75% and 90% reported by Diwarker and Rosul G [19], Zeeshan et al. [5] and Okolo et al. [20]. The variation in the specificity in the present study as compared to the latter studies [18-20] could be attributed to the different diagnostic criteria used as they had higher cut-off values compared to the present study.

The positive predictive value (PPV) of 51.0% obtained in the present study suggests that neonates with elevated mini-ESR have 51.0% probability of having sepsis. This value is much higher than the 13.8% reported by Zeeshan et al. [5]. This difference could be attributed to the disparity in the cut-off values used. The cut-off value of > 10 mm/hr used by Zeeshan et al. [5], which could be seen as being too high for younger babies, could possibly result in a much lower PPV with an increase in the specificity. The finding in the present study of a Negative Predictive Value (NPV) of 73.5% implies that neonates with normal mini-ESR have 73.5% probability that sepsis is absent. This value is comparable to the 75.5% reported by Zeeshan et al. [5]. It is however lower than the 90% reported by Okolo et al. [20] and 92% reported by Akpede and Abiodun [18]. In the latter study, [18] children aged 1 month to 5 years constituted the study population as opposed to the present study, where neonates aged 0-28 days made up the study population.

Interestingly, comparison of other haematological parameters (including mini-ESR) using blood culture as gold standard showed that the presence of band forms as defined in the methodology had the highest sensitivity of 87.6% followed by mini-ESR (75.7%). Band forms also had the best NPV of 91.9% followed also by mini-ESR (73.5%). This report is contrary to that documented by Okolo et al. [20] who observed a higher sensitivity and NPV of mini-ESR as compared to other haematological parameters. Thus, the mini-ESR which is a cheap, simple and readily available bedside test compares favourably with other haematological parameters which are expensive, requires skilled technicians and laboratory services, for the detection of neonatal sepsis. The mini-ESR would therefore be useful in resource poor centres where laboratory services may not be readily available, affordable and accessible.

When mini-ESR was used in combination with other haematological parameters, sensitivity and NPV increased considerably compared to

when used in isolation. This pattern was also noticed in other studies [5,20,22]. This study observed that mini-ESR in combination with band forms had the highest sensitivity of 95.9%. This therefore implies an enhancement in the identification of infected neonates as more than 95% of neonates with sepsis would be correctly diagnosed. This would thus facilitate early detection of sepsis and prompt treatment thereby reducing its morbidity and mortality. The high NPV of 94.2% observed with the same test combination would provide greater reassurance that sepsis is absent. The high NPV would therefore lead to a significant reduction in the use of antimicrobial agents thereby reducing cost, length of hospital stay as well as parental anxiety as it would permit the discontinuation of antibiotic therapy at the earliest possible time.

## Conclusion

The study concludes that although the micro-erythrocyte sedimentation rate has a high sensitivity in detecting neonates with sepsis, the sensitivity improved appreciably when it was combined with presence of band forms in blood films. Thus, Mini-ESR should be combined with band forms as screening tools in the diagnosis of neonatal sepsis.

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