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Original Article

Role of Neutrophil CD64 in the Diagnosis of Neonatal Sepsis

Adel Moideen[1], Ayesha Erum Hadi[2], Apurv Barche[3], Sneha Jaganathan Andrade[3], Aditya Verma[3], Leslie Edward Lewis[3], Jayashree Purkayastha[3]

[1]Department of Nephrology, University of Toronto, Toronto, Ontario, Canada
[2]Department of Radiodiagnosis, McMaster University, Hamilton, Ontario, Canada
[3]Department of Paediatrics, Kasturba Medical College Manipal, Manipal Academy of Higher Education (MAHE) Karnataka - 576104, India.

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***Corresponding Author**
Jayashree Purkayastha
Professor,
Department of Paediatrics,
Kasturba Medical College Manipal,
Manipal Academy of Higher Education (MAHE)
Karnataka - 576104, India.
Email: jayashreepurkayastha@yahoo.com

Abstract

Introduction: Neutrophil surface CD64 (Cluster of differentiation 64), the high-affinity Fc receptor, is quantitatively up-regulated during infection and sepsis. The diagnostic utility of NCD64 as a reliable marker of neonatal sepsis has not been explored so far. Hence this study has been conducted to compare NCD64 with other currently used infection markers including total leucocyte count, platelet count, absolute neutrophil count (ANC), band:neutrophil ratio and highly sensitive C reactive protein (hs-CRP).

Methods: Consecutively born neonates between March 2014 to November 2014 were enrolled with documented sepsis (n = 81), clinical sepsis (n = 35), and no sepsis (n = 87). NCD64 was analyzed by flow cytometry.

Results: Sepsis episodes had a higher median CD64 index of 10.35 (Range: 15.88, 6.87) as against 2.97 (Range: 5.53, 1.64) in the control group ($p < 0.001$). The percentage of NCD64 positive cells was also significantly higher in the sepsis group compared to the control group (63.90 ± 2.67 vs 15.07 ± 1.95; $p = 0.001$). In the ROC curve analysis NCD64, percentage of NCD64 positive cells had the highest AUC (AUC-0.914) using a cutoff of 28.01%, followed by CD64 mean fluorescence intensity (MFI) with an AUC of 0.850 using a cutoff of 5.54. NCD64 was significantly elevated in the groups with documented and clinical sepsis ($p < 0.001$).

Conclusions: NCD64 is a highly sensitive marker for neonatal sepsis. Prospective studies incorporating NCD64 into a sepsis scoring system are warranted.

Introduction

Neonatal sepsis is a clinical syndrome of bacteremia with systemic signs and symptoms of infection with in the first 28 days of life. In a country like India and other developing countries, neonatal sepsis is the single most important cause of neonatal deaths in the community, accounting for over half of them. Successful treatment depends on early initiation of appropriate antibiotic therapy, but early diagnosis of neonatal bacterial

infections is difficult because clinical signs are non-specific and may initially be subtle.[1,2]

Neonatal sepsis is categorized as early or late onset. Although advances in neonatal intensive care have led to improved survival of very low birth weight (VLBW) infants, late-onset sepsis continues to be an important cause of morbidity and mortality.[3-5] Very few modalities are available for investigating neonatal sepsis. As such, positive blood cultures still remain the gold standard for the diagnosis of sepsis, but many times the cultures may be negative even in a symptomatic neonate. When blood culture is negative we have to depend on other parameters for the diagnosis of neonatal sepsis. These tests should be fast and reliable. One of these is neutrophil CD64 which is supposed to be very specific for neonatal sepsis. CD64 (Cluster of differentiation 64) is a type of integral membrane glycoprotein known as an Fc receptor that binds monomeric IgG-type antibodies with high affinity; more commonly known as Fc-gamma receptor 1 (FcγR1).[6] It is expressed at low concentration on the surface of non-activated neutrophils making normal ranges easy to define and independent of ethnic background, genetic influences or gender.[6] Its up-regulation is induced by granulocyte colony stimulating factor (G-CSF) and interferon gamma (INF-γ) within four to six hours of stimulation, five to 10 fold increase during sepsis, under the influence of inflammatory cytokines; this increase in surface density occurs in a graded manner dependent on the intensity of the cytokine stimulus.[6]

The purpose of this study was to measure the Neutrophil CD64 in blood as an adjunct to our previously validated hematologic scoring system for detecting neonatal sepsis.

Methods

In this prospective observational study, all neonates presenting with clinical features suggestive of sepsis at the neonatal intensive care unit of a tertiary care hospital from March 2014 to November 2014 were eligible for inclusion. Neonates who had received antibiotic therapy for > 72 hours were excluded. Informed consent was taken from all parents prior to the inclusion in the study. This study was approved by the Research Ethics Board of the institution. Neonates were selected for the study if they had two or more of the following clinical features:[7] Respiratory changes- tachypnea, apnea, increased ventilatory support, or desaturation; Cardiovascular changes - heart rate variability, pallor, decreased perfusion or hypotension; Metabolic changes - hypothermia, hyperthermia, feed intolerance, glucose instability (Hypo / hyperglycemia), or unexplained metabolic acidosis; Neurologic changes - lethargy, poor suck, convulsion, hypotonia or decreased activity; Skin infections - abscess, pyoderma, bruising.

As part of the evaluation, detailed history with clinical examination was done and demographic, clinical and laboratory data were collected for all the neonates. In all the cases, neonatal details like date of birth, gestational age, gender and birth weight were collected. Antenatal details including parity, gestational age, presence of maternal fever, prolonged rupture of membranes (PROM), chorioamnionitis, urinary tract infection (UTI) and pretreatment with antimicrobials whenever relevant were collected. Mode of delivery, place of birth, resuscitation methods and Apgar score were recorded. Blood was drawn for a complete blood count along with blood culture, CRP, NCD64 and CD64 index. Neonatal age at the time of obtaining blood culture, physical examination details and antibiotic pretreatment were also recorded. All blood cultures were collected by using standard sterile techniques. The Bactec microbial detection system (Becton-Dickinson, Sparks, MD) was used to detect positive blood cultures. The details of the organism isolated and the timing of the positive signal were obtained from the microbiology department. Each positive blood culture result was grouped as either drawn < 72 hours (Early onset) or ≥ 72 hours of life (Late-onset). Other investigations like urine routine, chest X-ray and cerebrospinal fluid (CSF) study were done as and when required. Accordingly, neonates were grouped as blood culture positive and negative sepsis, and no sepsis and were followed up.

The following hematological criteria were used as indicators of sepsis: TLC: < 5,000 / cu.mm or > 20,000 / cu.mm, ANC: Considered low if below normal for age as per the Manroe's chart for term and Mouzinho's chart for VLBW infants, I:T ratio: > 0.3 in term and > 0.2 in preterms, platelet count: < 1,50,000/ cu.mm. Measurement of NCD64 index: 50 µL of heparinised whole blood was incubated for 30 minutes at room temperature with a saturating amount of phycoerythrin conjugated NCD64 in dark condition. This was followed by ammonium chloride-based red cell lysis (For 12 - 15 mins). The counting beads were added to the sample and mixed thoroughly. Sample was acquired in FACS Calibur using Cell quest pro software. A minimum of 10,000 cells data was saved. The saved data was analysed. The study data was processed using SPSS V16.0. For the analysis of baseline characteristics of study group, descriptive statistics was used. Median values were described with interquartile range of 75th percentile - 25th percentile. For the variables following normal distribution curve, mean and standard error mean were computed. The chi-square test was used in the analysis of categorical variables between groups. Receiver operating characteristic curves were generated and analyzed for the area under the curve (AUC). Significance was assessed at 5% level of significance. A p-value of < 0.05 was considered statistically significant.

Results

We included 116 neonates who had clinical features of sepsis, after excluding 40 neonates who had received antibiotics for > 72 hours prior to admission. Of the enrolled 116 neonates, blood culture was positive in 81 neonates (Documented sepsis) and 35 were grouped as culture negative sepsis (Clinical sepsis). The blood culture positive and negative groups were further sub-grouped as early onset sepsis (EOS) and late onset sepsis (LOS). Healthy term and preterm neonates for whom blood was drawn for routine serum bilirubin estimation, with no evidence of sepsis were selected as controls. Flowchart (Figure 1) shows the study recruitment done.

Table 1. Comparison of AUC values of various hematological parameters from Receiver Operating Characteristic (ROC) curves

Variable	AUC Mean ± SE (95% Confidence interval)
Platelet	0.721 ± 0.036 (0.650 - 0.792)
ANC	0.645 ± 0.038 (0.570 - 0.720)
I:T ratio	0.645 ± 0.038 (0.570 - 0.720)
hs-CRP	0.826 ± 0.028 (0.771 - 0.882)
CD64 MFI	0.850 ± 0.039 (0.791 - 0.908)
% NCD64 positive cells	1.914 ± 0.019 (0.878 - 0.951)

Figure 1. Study flow chart

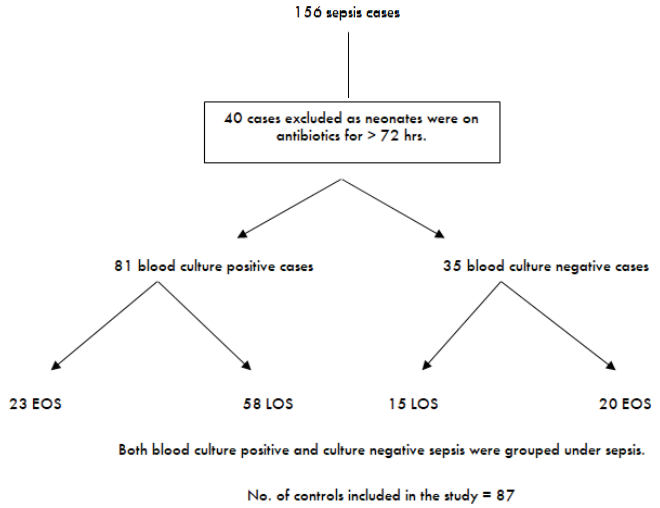


Table 2. Baseline characteristics of study population

Variable	Sepsis (Cases) N = 116	No sepsis (Controls) N = 87
Sex – Male Female	84 (72.4%) 32 (27.6%)	55 (63.2%) 32 (36.8%)
Singleton Multiple	112 (96.6%) 4 (3.4%)	84 (96.6%) 3 (3.4%)
Age at sepsis evaluation: (Mean ± SEM, weeks)	35.99 ± 0.43	35.53 ± 0.39
Inborn Outborn	22 (19%) 94 (81%)	41 (47.1%) 46 (52.9%)
Gestation: Preterm (≤ 33 weeks) Late preterm (34 - 36 weeks) Term (≥ 37 weeks)	 26 (22.4%) 18 (15.5%) 72 (62.1%)	 24 (27.6%) 19 (21.8%) 44 (50.6%)
Mode of delivery: Vaginal Assisted vaginal LSCS	 (37.9%) 44 (3.4%) 4 (58.6%) 68	 24 (27.6%) 3 (3.4%) 60 (69.0%)
Age at sepsis evaluation: < 72 hrs > 72 hrs	 (32.8%) 38 (67.2%) 78	 72 (82.8%) 15 (17.2%)
Asphyxia: Present Absent	(19%) 22 (81%) 94	10 (11.5%) 77 (88.5%)
PROM: Present Absent	(16.4%) 19 (83.6%) 97	18 (20.7%) 69 (79.3%)

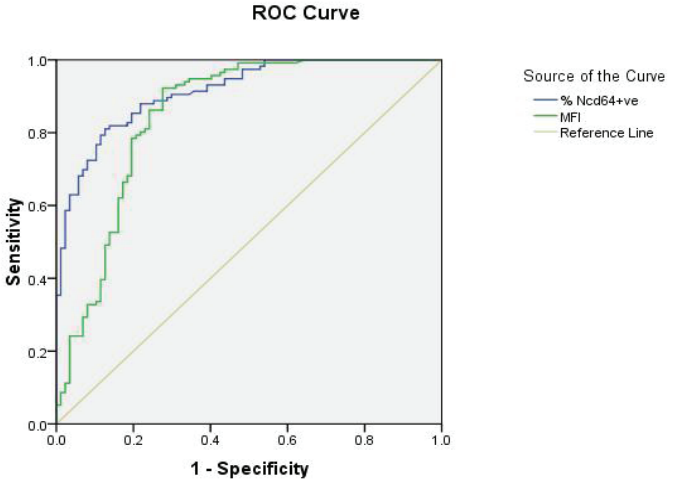
Blood culture yield in the early onset sepsis group was 60.5% as against the blood culture yield of 74.4% in the late onset sepsis group. Of 116 septic neonates, pathogenic organisms could be isolated from 81 (70%) cases: 19 - Coagulase-negative staphylococcus (CONS), 19 - Klebsiella pneumoniae, nine - Candida, seven - Enterobacter, six – Escherichia coli, five - Burkholderia, three - Methicillin resistant staphylococcus aureus (MRSA), three - Streptococcus, two - Pseudomonas, one - non fermenting gram negative bacilli (NFGNB), two - Serratia, two - Staphylococcus aureus, one - Acinetobacter and one - Kodamea spp. On the basis of the sepsis scoring system using hematologic variables, septic neonates (n = 116) were characterized by significantly higher white blood cell counts, ANC's and immature / total neutrophil ratios, compared with the control group (n = 87), as well as lower platelet counts ($p < 0.05$ for all comparisons) (Table 3).

Table 3. Haematological profile of cases and controls

Variable	Sepsis (Cases) N = 116 Median (75^{th}, 25^{th} IQR)	No sepsis (Controls) N = 87 Median (75^{th}, 25^{th} IQR)	p value
Hemoglobin (gm / dL)	14.7 (17.07, 12.55)	16.2 (18.2, 14.40)	0.006
Total count (cu. mm)	9700 (16700, 5853)	12900 (18900, 9738)	0.001
ANC (cu. mm)	3810 (8197.50,1795.50)	6365 (11300, 3870)	0.001
Platelet count (Lakhs / cu.mm)	1.03 (2.63, 0.34),	2.36 (2.86, 1.75)	0.001
I:T ratio	0.115 (0.33, 0.00)	0.00 (0.10, 0.00)	0.002
hs-CRP (mg / L)	47.5 (120.82, 9.2)	4.5 (8.90, 1.1)	0.001
CD64 MFI	10.35 (15.88, 6.87)	2.97 (5.53, 1.64)	0.001

There was statistically significant difference in the hs-CRP levels in the sepsis group compared to the control group (47.5 with range: 120.8 - 9.2 vs 4.5 with range: 8.9 - 1.1; $p = 0.001$). Those with sepsis also demonstrated significantly higher CD64 MFI (Mean Fluorescence Intensity) values than those with no sepsis (10.35 with range: 6.87-15.88 vs 2.97 with range 1.64 - 5.53; $p = 0.001$) (Table 3).

Figure 2. ROC curves for percentage NCD64 positive cells and CD64 index



The mean time taken for hs-CRP, NCD64 and blood culture positivity was analysed and it was observed that mean time taken for hs-CRP positivity was 0.798 ± 0.33 hours which was the least, followed by NCD64 (2.802 ± 0.038 hours). Mean time taken for blood culture positivity was 55.315 ± 3.022 hours which was significantly longer. As treatment cannot be withheld in a neonate with suspected sepsis waiting for blood culture report, the role of hs-CRP and NCD64 becomes important as they give faster clue with regard to sepsis. In the receiver operating characteristic curves for the various hematologic parameters (hs-CRP and NCD64) percentage of NCD64 positive cells had the highest AUC (AUC-0.914) using a cutoff of 28.01%, followed by CD64 MFI with an AUC of 0.850 using a cutoff of 5.54.

Table 4. Sensitivity, specificity, PPV and NPV of various sepsis markers using optimal cutoff values

A	B	C	D	E
TLC	21	99	96	48
ANC	25	93	83	48
Platelet	62	83	83	62
I:T ratio	36	89	81	51
hs-CRP	75	83	85	71
CD64 MFI	86	76	83	81
% nCD64 positive cells	85	81	85	81

Note: A = Variable, B = Sensitivity (%), C = Specificity (%), D = Positive predictive value (%), E = Negative predictive value (%)

The assessment of individual markers indicated that NCD64 has the highest overall sensitivity and negative predictive value (NPV) for the prediction of sepsis. We chose the calculated cutoff value of 28.01% NCD64 positive cells and CD64 MFI of 5.54 to be the optimal point, as it would permit a very high sensitivity (86%) and NPV (81%) and simultaneously be able to maintain an acceptable specificity > 75%. The cutoff value CRP ≥ 10 mg / L currently adopted in the neonatal unit provided only a sensitivity and specificity of 75% and 83% respectively. Thus, neutrophil CD64 and hs-CRP could be used in conjunction for early detection of sepsis owing to its faster result. NCD64 index at a cut-off value of ≥ 5.54 was positive in 86% of blood culture positive neonates (p value - 0.001) while at a cut-off value of 28.01% NCD64 positive cells, blood culture positive neonates were 83% (p value - 0.001). CD64 index at a cut-off value of ≥ 5.54 was able to detect 85% of EOS and 87% of LOS neonates while at a cut-off value of 28.01% NCD64 positive cells,72% EOS and 91% of LOS neonates were detected.

Discussion

It is difficult to recognize the neonates with sepsis before receipt of the blood culture results and this remains a challenge. Currently blood culture is the most effective method for diagnosing neonatal sepsis. However, the sensitivity of this method is low and using it as a gold standard in the diagnosis of septicemia is met with many difficulties. A study by Magudumana et al showed that fewer than 10% of neonates evaluated and treated for sepsis had blood culture positive sepsis.[8] As there is a possibility of sepsis even in the absence of negative blood culture results (for example, if the neonate had been exposed to antibiotics in utero), clinicians may opt to continue antibiotic treatment on the basis of the clinical profile.

There are a variety of rapid tests which are helpful for screening of neonatal sepsis. White blood cell count and differential count, acute phase reactants like CRP, micro ESR, agglutination tests, pro-inflammatory and anti-inflammatory cytokine level estimation, DNA sequence test like polymerase chain reaction (PCR), are used depending on their sensitivity and specificity. Leucopenia (< 5000 / cu. mm) is more specific for neonatal sepsis.[9] Absolute neutropenia (< 1000 / cu.mm) is more predictive of neonatal sepsis than neutrophilia.[10] A hematologic scoring system has been introduced by Rodwell et al in 1988 by using seven hematological parameters.[11] Among the various cytokines studied, interleukin-6 (IL-6) has emerged as an early marker of neonatal sepsis. The cutoff values for IL-6 to diagnose sepsis ranges between 18 to 31 pg / ml.[8,12-14] Serial measurement of CRP is probably of more value than expensive and time consuming determination of IL-6 plasma concentration in the evaluation of neonatal sepsis.[15] One of the newer acute phase markers of infection is procalcitonin (PCT), the pro-hormone of calcitonin, which occurs in very low concentrations in the serum of healthy people.[16] Recently numerous cell surface antigens have been studied as potentially promising biomarkers of infection, including CD11b, CD69 and CD64.[17]

There is a significant increase in the CD64 expression on the surface of neutrophils in response to bacterial infection in neonates, similar to that seen in older children as well as adults.[18] The quantification of NCD64 is rapid (< 60 minutes) and only minimal blood volume is used. For the present study, no additional blood was drawn from neonates. NCD64 is constitutively expressed on antigen presenting cells (Monocytes, macrophages and dentritic cells), to a lesser extent to eosinophils, but only to a very low extent on resting neutrophils.[6,19-21] Several studies have indicated that quantification of the neutrophil / polymorphonuclear cell (PMN) NCD64 is a worthwhile candidate for evaluation as a more sensitive and specific indicator of sepsis than the other available diagnostics tests. Majority of the studies have shown that NCD64 has high diagnostic specificity and sensitivity.[22-24] Therefore, we focused on NCD64 as a diagnostic adjunct to

standard hematologic indices in our study. A smaller study in critically ill neonates and infants by Groselj-Grenc et al used the standardized CD64 index for the first time and demonstrated its superiority over all other infection markers. They also pesented evidence that NCD64 was the best individual marker for bacterial sepsis in children.[25] Bhandari et al[26] conducted the third largest study in neonates with suspected sepsis and also these authors found that CD64 index had the best diagnostic performance for culture-positive sepsis compared with all traditional hematologic assays. The study by Bhandari et al showed a sensitivity of 70% and a specificity of 62% with a cutoff value of 2.30.[26] In another study performed over 100 patients in NICU, the NCD64 index was found again to be the best with the highest sensitivity, with no difference between NCD64 and MFI.[27] In the present study, we found that NCD64 positive cells and NCD64 index had the highest AUC, compared to the other routinely used hematologic parameters. Here, the cutoff CD64 index of 5.54 by itself yielded a sensitivity of 86% and a specificity of 76% for diagnosing sepsis. NCD64 index could detect 85% of early onset sepsis neonates and 87% of late onset sepsis neonates. In addition, the results of CD64 are available in a much shorter time than blood culture results which could reduce the injudicious use of antibiotics. However, ours is a relatively smaller study and hence larger, multicentric studies are warranted to implement it in neonatal sepsis. However critical issues like availability at all centers and cost must be evaluated carefully.

Conclusions

The NCD64 index and percentage of NCD64 positive cells were significantly elevated during neonatal sepsis episodes and were the most diagnostic and faster measure of confirmed sepsis. It also additionally identifies a separate group among culture-negative sick neonates and may be useful to guide early antibiotic administration.

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