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Can we rely on the neutrophil left shift for the diagnosis of neonatal sepsis? Need for re-evaluation

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ABSTRACT

Background: Neonatal sepsis cause significant morbidities and mortality among affected neonates. The gold standard for its diagnosis is the blood culture. However, its usefulness is limited by many factors. A rapid diagnostic test with high sensitivity and specificity is needed for rapid identification of neonatal sepsis without exposing unaffected neonates to antibiotic therapy. The accuracy of immature neutrophil count for the diagnosis of neonatal sepsis is controversial.

Objective: Being rapid, simple and readily available, this study aimed to re-evaluate the usefulness of neutrophil left shift for the diagnosis of neonatal sepsis and assess its prognostic value in reflecting the patients' outcome.

Methods: This prospective cross-sectional study included 285 neonates admitted to the neonatal intensive care unit, Cairo University. Demographic, clinical and laboratory data were collected including complete blood pictures with manual differentials and blood culture results. The diagnostic accuracy of neutrophil left shift was done through applying multiple logistic regression and receiver operating characteristic [ROC] curve.

Results: Among the study group, 61.4% had definite sepsis while 12.3% had probable sepsis. The median immature to total neutrophil ratio (I/T ratio) was 0.25, IQR 0.21, range 0.03–0.8. I/T ratio $\geq$ 0.2 was present in 65.6% of the patients and had significantly increased odds of infection, sensitivity (82.4%), specificity (81.3%), positive predictive value (92.5%) and negative predictive value (62.2%). By plotting neutrophil left shift against blood culture, total white blood cell count (WBC) and platelet count in a ROC curve and calculating areas under the curve (AUC), it proved to be a good diagnostic test (AUC: 0.861) while total WBC count (AUC: 0.515) and platelet count (AUC: 0.366) had poor diagnostic accuracy.

Conclusion: Neutrophil left shift is a rapid, simple and readily available test that has a reasonable positive predictive value and specificity which denotes its usefulness in the early diagnosis of neonatal sepsis as well as in decreasing the exposure of non-septic neonates to antimicrobial therapy.

Introduction

Band cells are neutrophils that have not reached full maturation and are characterized by absence of complete separation of the lobes which gives its nucleus a characteristic horse-shoe shape with a uniform thickness. Other immature neutrophil forms include promyelocytes, myelocytes and metamyelocytes. On stimulation by proinflammatory cytokines and catecholamines, the bone marrow releases bands and other immature forms into the circulation.[1,2]

Increased immature neutrophil count in blood was often used as a clinical marker of sepsis. In 2005, the pediatric consensus definition of sepsis (SIRS) included the presence of immature neutrophils >10%. However, this definition was intended for all children <18 years old and term neonates ($\geq$37 weeks gestation) while preterm neonates (<37 weeks gestation) were excluded.[3] Thereafter, clinicians used band counts >10% as an indicator of sepsis.[1]

Recently, the diagnostic accuracy of immature neutrophil count as an indicator of sepsis has become controversial, being affected by many factors other than infection including clinical situations as hemolysis, hemorrhage, perinatal asphyxia, maternal hypertension and therapeutic interventions as parenteral nutrition, corticosteroids and surgery.[4,5] Moreover, van der Meer and colleagues[6] reported wide inter and intralaboratory variation and

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interpretations for band forms leading to limitation in the use of I/T ratio as a criterion for definion.

Neonatal sepsis cause significant morbidities and mortality among affected neonates. Unfortunately, its clinical presentation is often nonspecific. The gold standard for its diagnosis is the blood culture. However, its usefulness is limited by the time needed from collection until the infecting organism is isolated, leading to a delay in starting the appropriate antibiotic regimen. Also, its sensitivity is often affected by prior exposure of the neonate to empirical antibiotics as well as its relatively small blood volumes which may affect its reliability for organism isolation.[7,8] Moreover, sepsis cannot always be excluded with a negative blood culture. On the contrary, isolation of an organism in a blood culture may reflect asymptomatic bacteremia or contamination.[9]

Hence, there is still a need for a diagnostic test with high sensitivity, to help improve outcome of septic neonates by alleviating the delay in treatment, and high specificity, to decrease exposure of non-septic neonates to empirical antibiotic therapy.[9] The accuracy of several biomarkers for diagnosing sepsis, as interleukins (IL6, IL8), CD64, tumour necrosis factor alpha in the early, procalcitonin in the middle and C reactive protein in the late phases of sepsis, have been studied and seemed promising. Unfortunately, these biomarkers are costly and/or not readily available in developing countries.[10]

Aim of the work

Being cheap, simple, rapid and readily available, we aimed at re-evaluating the usefulness of the neutrophil left shift for the diagnosis of neonatal sepsis and assessing its prognostic value in reflecting the patients' outcome.

Subjects and methods

Study population

Between October 2016 and June 2017, 285 neonates, admitted to the neonatal intensive care unit (NICU) of New children hospital, Cairo university, were enrolled in a prospective cross-sectional study. They were 163 males and 122 females The current study was approved by the ethical committee at Faculty of Medicine, Cairo University and there was no need for an informed consent from the patients' guardians as all investigations done were part of the routine investigations needed for patient assessment in NICU.

Data collection

Demographic, clinical and laboratory data were collected for all neonates under study. Data collected included; Gender, gestational age, age on admission, length of hospital stay, clinical signs suggestive of sepsis and the outcome of the patients. Results of complete blood counts with manual differentials done by an experienced hematologist and microbiological laboratory investigations [blood culture] were collected.

Laboratory investigations

Laboratory investigations were done on admission or as a part of sepsis screening on appearance of any early clinical signs suggestive of sepsis (Table 1).[11]

Blood films were prepared from peripheral blood samples, 1 ml, anticoagulated with EDTA and stained with Giemsa stain. Immature neutrophil forms were identified with their morphological characteristics: myelocytes, being large with oval or round nucleus and bluish pink cytoplasm, metamyelocytes being large with kidney shaped nucleus and pinkish blue cytoplasm and band cells being smaller with horse-shoe shaped nucleus of uniform thickness.[12]

Table 1
Early clinical signs suggestive of sepsis.

Lethargy	Blood pressure decreased by >10%
Irritability	HR >160 beats/min when quiet, not crying
Poor feeding	
Respiratory distress	HR <100 beats/min
Jaundice	Poor peripheral perfusion [capillary refill time >2 s]
Apnea	
Seizures	Sluggish neonatal reflexes
Mottling	Hepatosplenomegaly
Muscle tone &/or spontaneous movement reduced from baseline	
Temperature instability	
*Single temp >38 °C	
*Two consecutive temp <36 °C	

Blood cultures were done under complete aseptic technique using BACTEC (PEDs) pediatric bottles. Blood cultures were considered positive if it yielded an organism known for causing bacteremia. In case of organisms known as skin contaminants, the blood culture was considered positive if this organism was yielded in 2 consecutive blood cultures within 7 days period. Multidrug (MDR) strains are those resistant to $\geq$3 classes of antimicrobials.

Diagnosis of sepsis

Sepsis was diagnosed by positive blood cultures and/or clinical sepsis that was accompanied by laboratory findings suggestive of sepsis as leucopenia or leucocytosis, degenerative neutrophil changes as toxic granulation, vacuolation, Dohle bodies, and thrombocytopenia.

Calculation of neutrophil left shift

We calculated the I/T ratio by dividing the total immature neutrophil count (including bands, myelocytes and metamyelocytes) by total neutrophil count (both immature and mature).

Normal I/T ratio is up to 0.16 during the first 24 h and decreases to 0.12 starting the 5th postnatal day till the end of the neonatal period.[13,14] I/T ratio $\geq$ 0.2 is considered positive for sepsis. The study group was further classified according to the I/T ratio into normal (<0.2), moderate shift to the left (0.2–0.29) and severe shift to the left ($\geq$0.3).

Statistical analysis

Data were analyzed by the Statistical Package for the Social Sciences (SPSS), version 16 (SPSS Inc, Chicago). Descriptive data for continuous variables were presented as median, interquartile range, percentiles, mean ± SD, and range. Categorical variables were presented as frequencies and percentages. Spearman correlation coefficients were calculated to signify the association between I/T ratio and different variables. The diagnostic accuracy of neutrophil left shift evaluated against blood culture [diagnostic standard], total WBC count, and platelet count was assessed by creating receiver operating characteristic [ROC] curve and calculating areas under the curve [AUC]. Optimal cuttoff values, sensitivities and specificities were determined. Multiple logistic regression tests were used to evaluate the accuracy of different grades of neutrophil left shift for the diagnosis of neonatal sepsis, and for the prognosis of the patients' outcome.

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