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Use of the Complete Blood Cell Count in Early-Onset Neonatal Sepsis

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Abstract

Background—Early-onset sepsis is an important cause of morbidity and mortality in neonates, and its diagnosis remains challenging. The complete blood cell count and differential have been previously evaluated as diagnostic tools for early-onset sepsis in small, single-center reports. We evaluated the diagnostic accuracy of the complete blood count and differential in early-onset sepsis in a large, multicenter population of neonates admitted to the neonatal intensive care unit.

Methods—Using a cohort of 166,092 neonates with suspected early-onset sepsis with cultures admitted to 293 neonatal intensive care units, we calculated odds ratios and receiver operating characteristic curves for complete blood cell count indices and prediction of a positive culture. We determined sensitivity, specificity, and likelihood ratios for various commonly used cut-off values from the complete blood cell count.

Results—Low white blood cell counts, low absolute neutrophil counts, and high immature-to-total neutrophil ratios were associated with increasing odds of infection (highest odds ratios: 5.38, 6.84, and 7.97, respectively). Specificity and negative predictive values were high (73.7–99.9% and >99.8%). However, sensitivities were low (0.3–54.5%) for all complete blood cell count indices analyzed.

Conclusion—Low white blood cell count, absolute neutrophil count, and high immature-to-total neutrophil ratio were associated with increasing odds of infection, but no complete blood cell count-derived index possesses the sensitivity to rule out reliably early-onset sepsis in neonates.

Keywords

neonatal; early-onset sepsis; blood cell count

Early-onset sepsis (EOS) causes substantial morbidity and mortality in affected neonates.^{1–4} The diagnostic standard for EOS is the blood culture. Because signs and symptoms of EOS are often subtle and non-specific, blood cultures are frequently obtained from neonates who do not have EOS.⁵ Blood culture sensitivity is often affected by the neonate's prior exposure

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Conflicts of Interest

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to antepartum and empirical antibiotics and the relatively small blood volumes (0.5–1.0 mL) obtained for culture.^{6,7} Blood cultures are also limited by the time needed from collection to isolation of the infecting organism, potentially resulting in a delay of appropriate antimicrobial therapy.

A sensitive diagnostic test may improve outcomes associated with EOS by decreasing this delay in treatment. Moreover, a test with high specificity is important to decrease exposure of unaffected neonates to broad-spectrum antibiotics and invasive procedures.^{8,9} Previous studies evaluating the use of the white blood cell count (WBC), WBC differential, and WBC indices for predicting EOS in neonates have shown variable test characteristics (see Table, Supplemental Digital Content 1, which lists previously published studies of complete blood cell count indices and early-onset sepsis).¹⁰ However, these studies were limited by relatively small sample size, lack of center diversity, and exclusion of extremely premature neonates.

We sought to determine the diagnostic utility of the complete blood cell (CBC) count for the diagnosis of EOS in neonates admitted to the neonatal intensive care unit (NICU) using a large contemporary database.

MATERIALS AND METHODS

Study Population

We obtained CBC counts and culture data from neonates admitted to 293 NICUs in the United States managed by the Pediatrix Medical Group from 1996–2009. The data were obtained from an administrative database that prospectively captures information from daily progress notes generated by clinicians using a computer-assisted tool on all neonates cared for by the Pediatrix Medical Group. Data on multiple aspects of care are entered into the system to generate admission notes, daily progress notes, procedure notes, and discharge summaries. Information is collected regarding maternal history and demographics, medications, laboratory results, culture results, diagnoses, and other aspects of clinical care.

Definitions

EOS was defined as a positive culture (blood, urine, or cerebrospinal fluid [CSF]) during the first 3 days of life. Neonates who did not have a culture obtained during the first 3 days of life were excluded from the analysis. We excluded sepsis episodes for organisms considered to be contaminants. When multiple cultures with the same organism were obtained within a 21-day period, they were considered to be a single infectious episode. Cultures positive with >1 organism were treated as separate positive cultures. If one of the organisms was considered to be a contaminant, we counted only the true organism as a positive culture and ignored the likely contaminant.

Coagulase-negative *Staphylococcus* (CoNS) infections were divided into 3 categories: definite, probable, and possible. We defined a definite CoNS infection as 2 positive cultures drawn on the same day; probable CoNS infection as 2 positive cultures within a 4-day period, 3 positive cultures within a 7-day period, or 4 positive cultures within a 10-day period; and possible CoNS infection as a culture positive for CoNS that did not meet criteria for definite or probable CoNS sepsis. Only definite and probable CoNS infections were included in the analysis. We excluded all negative cultures obtained after a positive culture in the same patient given the likelihood of a false-negative result. If multiple cultures were obtained on the same day, we kept 1 entry, in order of preference, positive culture vs. negative culture and blood vs. urine vs. CSF culture.

We collected demographic data including: sex, race, birth weight, gestational age at birth (GA), inborn status, Apgar score at 1 and 5 minutes, level of respiratory support on day of life 1, and exposure to antenatal antibiotics and steroids. If 1 CBC counts were obtained on the same day for a patient, we included the highest value for WBC count, absolute neutrophil count (ANC), immature-to-total neutrophil ratio (I/T ratio), and platelet count for that day. We included CBC counts obtained on the day of culture or on the day prior to culture if no CBC count was obtained on the day of culture. Means of CBC count indices were compared between neonates with positive and negative cultures using t-tests with $P < 0.05$ considered statistically significant.

Statistical analysis

The association of CBC count indices (WBC count, ANC, I/T ratio, and platelet count) with culture results was determined using logistic regression with and without controlling for GA as a predictor variable. For each regression, we divided the WBC counts, ANC, I/T ratio, and platelet counts into 5% increments (vintiles). We obtained odds ratios (OR) for each vintile compared with the median vintile. We reported OR with 95% confidence intervals (CI). Given that the majority of CBC counts were drawn on day of life 1 (defined as the date of birth), we repeated the same regressions limiting the CBC count data to day of life 3 to evaluate whether these associations persisted over time. To evaluate whether CBC count indices were more strongly associated with blood cultures, we repeated our regressions including only blood cultures in the analysis.

We calculated sensitivities, specificities, positive and negative predictive values, and positive and negative likelihood ratios for previously defined diagnostic cut-off values of WBC counts, ANC, I/T ratio, and platelet counts at various gestational ages.^{11,12} Finally, we determined the area under the receiver operating characteristic (ROC) curves for WBC counts, ANC, I/T ratio, and platelet counts for each GA category and the entire cohort. For WBC counts, we calculated the ROC curves for WBC counts $> 20,000/\text{mm}^3$ and WBC counts $< 5000/\text{mm}^3$. We multiplied values for ANC, WBC counts < 5000 , and platelet counts by (-1) to generate positive ROC curves. We conducted the analysis with STATA 10 (College Station, TX). This study was approved by the Duke Institutional Review Board.

RESULTS

We identified 166,092 neonates with 171,376 cultures: 168,604 (98.4%) blood cultures, 274 (0.2%) urine cultures, and 2498 (1.5%) CSF cultures. The mean GA and birth weight of all neonates was 34.6 weeks (5th, 95th percentile: 27, 40) and 2420 g (860, 3960), respectively. Fifty-six percent of the neonates were male, 92% were inborn, and 56% were white. There were 2177 (1.3%) positive cultures in 2164 neonates (1.3%). Of these, 2001 (91.9%) were from blood, 146 (6.7%) from urine, and 30 (1.4%) from CSF (see Table, Supplemental Digital Content 2, which displays organism by culture site). The following cultures were excluded from the analysis as their organisms were considered to be contaminants: non-speciated streptococci (n=322), *Bacillus* sp. (n=90), *Corynebacterium* sp. (n=36), diphtheroids sp. (n=35), Gram-positive rods (not including *Listeria* sp.) (n=50), *Lactobacillus* sp. (n=1), *Micrococcus* sp. (n=46), *Stomatococcus* sp. (n=1), and *Bacteroides* sp. (n=5).

Of all patients with positive cultures, 60% had a WBC count between $5000/\text{mm}^3$ and $19,000/\text{mm}^3$, 87% had an ANC $< 1500/\text{mm}^3$, 82% had a platelet count between $150,000/\text{mm}^3$ and $400,000/\text{mm}^3$, and 31% had an I/T ratio < 0.2 (Table 1).

Low WBC counts, low ANCs, high I/T ratios, and low platelet counts were associated with increased odds of EOS (Figure 1). However, a high WBC count was not associated with

increased odds of infection. Controlling for GA, we observed similar results. The first (WBC count $<5500/\text{mm}^3$) through fourth vintiles (WBC count $<8800/\text{mm}^3$) were associated with increased odds of EOS—OR 8.80 (95% CI 6.29–11.20), OR 3.30 (95% CI 2.53–4.29), OR 1.94 (95% CI 1.46–2.57), and OR 1.53 (95% CI 1.13–2.06), respectively. ANC's below the sixth vintile were associated with EOS, with the strongest association observed for the first vintile (ANC $<1533/\text{mm}^3$) OR—10.74 (95% CI 7.76–15.06). We observed significant association with EOS for I/T ratios above the sixteenth vintile (>0.24) and for platelet counts below the second vintile ($<147,000/\text{mm}^3$).

Limiting the analysis to CBC counts from day of life 3 did not significantly alter the results. For WBC counts, only the first (WBC count $<5500/\text{mm}^3$) and second vintiles (WBC count $<6900/\text{mm}^3$) were associated with increased risk of EOS. For ANC, the first and second vintiles, corresponding to a maximum ANC of $1530/\text{mm}^3$ and $2280/\text{mm}^3$, respectively, were associated with EOS. I/T ratios above the nineteenth (I/T >0.37) and twentieth (I/T >0.51) vintiles were associated with increased EOS, but we observed no relationship between platelet count and EOS on day of life 3.

When limiting the analysis to blood cultures only, we observed similar results. The first, second, and third vintiles of WBC were associated with increased odds of bacteremia (OR 5.37 [95% CI 4.25–6.81], OR 2.20 [95% CI 1.70–2.86], and OR 1.43 [95% CI 1.08–1.89], respectively). ANC values below the fifth vintile ($<3504/\text{mm}^3$) were also associated with increased odds of bacteremia, as were I/T ratios above the sixteenth vintile (>0.24) and platelet counts below the third vintile ($<148,000/\text{mm}^3$).

The sensitivity for EOS based on previously described cut-offs was low for all indices, with the highest value observed for an I/T ratio >0.20 in neonates <34 weeks GA (65.1%) (see Table, Supplemental Digital Content 3, which shows test characteristics of various WBC, ANC, I/T ratio, and platelet count values). Specificity was generally high, with the lowest value observed for a WBC count $>20,000/\text{mm}^3$ in neonates >36 weeks GA (61.9%). We observed the highest positive likelihood ratios (+LR) with an ANC $<100/\text{mm}^3$ in neonates >36 weeks GA (+LR=229) and lowest +LR for WBC counts $>50,000/\text{mm}^3$ in neonates >36 weeks GA (+LR=0.3). Negative likelihood ratios were lowest for I/T ratios >0.20 and >0.25 in neonates <34 weeks GA (0.5) and highest for WBC count $>20,000/\text{mm}^3$ in neonates >36 weeks GA (1.2).

The area under the ROC curve (AUC) was similar for CBC indices across GA categories. AUCs were highest for WBC counts $<5000/\text{mm}^3$ (AUC=0.668) and I/T ratio (AUC=0.686). They were lower for ANC (AUC=0.586), platelet counts (AUC=0.554), and for WBC counts $>20,000/\text{mm}^3$ (AUC=0.525). These trends were preserved when repeating the ROC curves separately by GA categories.

DISCUSSION

A missed diagnosis of EOS can be catastrophic due to the high morbidity and mortality associated with the disease,^{1–3} and, as a result, empirical antibiotics are frequently administered to neonates with suspected EOS. However, the majority ($>98\%$) of these neonates have negative blood cultures, resulting in widespread exposure to antimicrobials, need for intravenous access, and frequent admission to intensive care nurseries.^{8,13}

In this study, we present the largest series of CBC counts in neonates with EOS admitted to the NICU. We found that low, but not high, WBC counts were associated with EOS. Specificity was high for WBC counts $<5000/\text{mm}^3$ and WBC counts $<1000/\text{mm}^3$, but sensitivity was poor. In addition, 60% (1315/2177) of subjects with a positive culture had a “normal” WBC count ($5000/\text{mm}^3$ – $19,999/\text{mm}^3$). However, when all 4 CBC count indices

were normal on the same day, only 0.6% of patients (330/52,368) had a positive culture result. This is similar to findings in a previous study of 376 neonates with clinical suspicion of sepsis and an 8% rate of confirmed infection, where a WBC count $<5000/\text{mm}^3$ was found to have a specificity of 94% but a sensitivity of only 50%.¹³ In a study of 287 neonates with prenatal risk factors or clinical suspicion of sepsis and 9% positive cultures, the authors observed equally low sensitivity (44%) and positive predictive value (36%) but high specificity (92%) and high negative predictive value (94%) for abnormal WBC counts ($<5000/\text{mm}^3$ or $>25,000/\text{mm}^3$, $30,000/\text{mm}^3$, and $21,000/\text{mm}^3$ at birth, 24 hours, and 48 hours of life, respectively).¹⁴

In our study, +LR were high for low WBC counts $<1000/\text{mm}^3$ and $<5000/\text{mm}^3$ but much lower for high WBC counts. Assuming a pretest probability of positive culture of 5% in a neonate <34 weeks GA, the post-test probability of a positive culture given a WBC count $>50,000/\text{mm}^3$ is only 11.5% (+LR=2.3). Similarly, in a cohort of 245 neonates 34 weeks gestation, +LRs were lower for WBC counts $>20,000/\text{mm}^3$ (1.20, 0.77, and 0.16 when drawn at <1 , 1–3, and 4 hours, respectively), while they were significantly higher for WBC counts $<5000/\text{mm}^3$ (27.6 and 80.5 when drawn at 1–3 and 4 hours, respectively).¹⁵

In addition to WBC counts, ANC, I/T ratio, and platelet counts are also widely used as potential markers of infection.¹⁶ In a prospective study of 150 neonates 32–38 weeks GA with EOS, the sensitivity of an ANC $<8000/\text{mm}^3$ was 76%, and the negative predictive value was 94%.¹⁷ In this study, all 150 neonates were included based on clinical suspicion of infection, likely contributing to an increased incidence of positive cultures (14%) compared with only 1.3% observed in our population. With this lower incidence of positive culture, and using lower ANC cut-offs, we found much lower sensitivities and similarly high negative predictive values. An ANC $<1000/\text{mm}^3$ had a +LR of 7.5, 33.5, and 115 when drawn at <1 , 1–3, and 4 hours, respectively, in patients 34 weeks with positive culture results.¹⁵ However, only 14% of neonates with EOS had an ANC $<1000/\text{mm}^3$, while 27% had an ANC $>10,000/\text{mm}^3$.

In a single-center, prospective study of 169 neonates with GA <32 weeks or clinically symptomatic presentation and an 8% cumulative incidence of positive cultures, an I/T ratio >0.20 had a sensitivity of 73%.¹⁸ In that study, however, the mean I/T ratio of neonates without sepsis was 0.6, compared with 0.16 in our cohort.¹⁸ In our study, elevated I/T ratios (>0.2 , >0.25 , >0.5) had low sensitivities (54.6%, 47.9%, 21.9%, respectively) comparable to a prior multi-center report.¹¹ These I/T cut-offs were associated with relatively high specificities (73.7%, 81.7%, 95.7%, respectively) and negative predictive values (99.2%, 99.2%, 99.0%, respectively), but positive predictive values were low (2.5%, 3.2%, 6.0%, respectively) in the setting of a low overall proportion of positive cultures in our study.^{14,19} Recently, increasing I/T ratios were shown to have increasing +LR values, highest for a cut-off >0.60 at 4 hours (10.7) in 245 neonates with culture-proven sepsis.¹⁵ Again, this is comparable to our findings, where elevated I/T ratios had increasing +LR.

We found platelet counts to be less helpful in the setting of EOS evaluation, with a small increase in the odds of infection with low platelet counts. This is similar to results from a previous study of 356 neonates, where a platelet count $<100,000/\text{mm}^3$ and $<150,000/\text{mm}^3$ had low sensitivity (14% and 32%) and positive predictive value (14% and 13%).²⁰

Strengths of our study include the large cohort size, detailed data on CBC count indices, and complete culture results. Our study is limited by the retrospective nature of the analysis. These data are not from a prospective clinical trial that has undergone the scrutiny of independent monitoring, but rather are derived from electronic documentation. In addition, our dataset lacked information on prior antibiotic exposures (antepartum and empirical)

before cultures were obtained, which might lead to falsely negative culture results. Also, maternal risk factors such as hypertension and preeclampsia, which are known to cause neonatal neutropenia and thrombocytopenia unrelated to infection, are not reliably available in the database and were thus not accounted for in the analysis.²¹ Our description of the urine culture results was limited by the absence of information on colony count. In addition, we did not have information on the time at which CBC counts were obtained and were, therefore, not able to use previously defined, time-sensitive CBC index cut-offs or repeat CBC count analyses on the same day.^{22,23} In instances where >1 CBC count was obtained on the same day, we retained only the highest values of CBC count indices for the analysis as we did not have information on time of day in the data. Lastly, this sample represents only neonates admitted to a NICU rather than the population of all neonates evaluated with a CBC count, and we have no information on whether infants were symptomatic at the time of their evaluation.

In summary, although low WBC counts and ANCs and high I/T ratios are associated with infection, low sensitivities for CBC count cut-offs make these indices poor diagnostic markers to rule out infection. Thus, obtaining a CBC solely for the purpose of ruling out EOS in neonates is not supported, and empiric antibiotic therapy will remain necessary in a large number of neonates with clinical suspicion of EOS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

Association between complete blood cell count indices and early-onset sepsis. **A.** WBC vintiles and ORs; **B.** ANC vintiles and ORs; **C.** I/T ratio vintiles and ORs; **D.** Platelet vintiles and ORs. CBC indicates complete blood cell; EOS, early-onset sepsis (< 72 hours); WBC, white blood cell; ANC, absolute neutrophil count; I/T ratio, immature-to-total neutrophil ratio; OR, odds ratio.

TABLE 1

Means and 95% Confidence Intervals for CBC Count Indices by Culture Results and Day of Life

	Positive culture	Negative culture
WBC, /mm ³		
Day 1	12,849 (12,252–13,447)	15,058 (15,007–15,109)
Day 2	14,658 (13,686–15,631)	18,093 (17,972–18,214)
Day 3	13,365 (11,801–14,929)	15,367 (15,114–15,619)
ANC, /mm ³		
Day 1	6496 (6082–6910)	7976 (7937–8014)
Day 2	9693 (8930–10,457)	11,742 (11,646–11,838)
Day 3	8768 (7564–9971)	9780 (9595–9965)
I/T ratio		
Day 1	0.32 (0.30–0.33)	0.16 (0.16–0.16)
Day 2	0.30 (0.28–0.33)	0.16 (0.16–0.16)
Day 3	0.21 (0.17–0.24)	0.13 (0.13–0.14)
Platelet count, /mm ³		
Day 1	226,504 (221,778–231,231)	238,158 (237,680–238,635)
Day 2	224,174 (216,307–232,040)	236,723 (235,659–237,787)
Day 3	212,189 (197,169–227,210)	236,977 (234,667–239,287)

CBC indicates complete blood cell; WBC, white blood cell; ANC, absolute neutrophil count; I/T, immature-to-total neutrophils.