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Interpreting Complete Blood Counts Soon After Birth in Newborns at Risk for Sepsis

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Abstract

BACKGROUND—A complete blood count (CBC) with white blood cell differential is commonly ordered to evaluate newborns at risk for sepsis.

OBJECTIVES—To quantify how well components of the CBC predict sepsis in the first 72 hours after birth.

METHODS—For this retrospective cross-sectional study we identified 67 623 term and late-preterm (≥ 34 weeks gestation) newborns from 12 northern California Kaiser hospitals and 1 Boston, Massachusetts hospital who had a CBC and blood culture within 1 hour of each other at < 72 hours of age. We compared CBC results among newborns whose blood cultures were and were not positive and quantified discrimination by using receiver operating characteristic curves and likelihood ratios.

RESULTS—Blood cultures of 245 infants (3.6 of 1000 tested newborns) were positive. Mean white blood cell (WBC) counts and mean absolute neutrophil counts (ANCs) were lower, and mean proportions of immature neutrophils were higher in newborns with infection; platelet counts did not differ. Discrimination improved with age in the first few hours, especially for WBC counts and ANCs (eg, the area under the receiver operating characteristic curve for WBC counts was 0.52 at < 1 hour and 0.87 at ≥ 4 hours). Both WBC counts and ANCs were most informative when very low (eg, the likelihood ratio for $\text{ANC} < 1000$ was 115 at ≥ 4 hours). No test was very sensitive; the lowest likelihood ratio (for WBC count $\geq 20\,000$ at ≥ 4 hours) was 0.16.

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CONCLUSION—Optimal interpretation of the CBC requires using interval likelihood ratios for the newborn's age in hours.

Keywords

complete blood count; sepsis; bacteremia; neutrophils; leukocytes; sensitivity; likelihood ratios; newborn

The evaluation of newborns for possible early-onset sepsis is difficult because risk factors for infection are common and early signs and symptoms are nonspecific. When newborns are symptomatic or have significant risk factors, a complete blood count (CBC) is commonly used to help assess the likelihood of infection and the need for antibiotics. In fact, Centers for Disease Control and Prevention guidelines for the prevention of early-onset group B *Streptococcal* infection,¹ endorsed by the American Academy of Pediatrics,² recommend a CBC for certain high-risk infants, such as those whose mothers were positive for group B *Streptococcus* (GBS) but were not adequately treated with antibiotics.

The Centers for Disease Control and Prevention recommendations do not provide guidance on how to use the results of the CBC to estimate the likelihood of infection. Published reference ranges vary widely for components of the CBC, including the total white blood cell (WBC) count, the absolute neutrophil count (ANC), and the proportion of total neutrophils that are immature (I/T).^{3–7} Total and differential white blood cell counts are affected by many factors besides infection, including infant age in hours,^{3–6} the method of blood sampling,^{8–10} the method of delivery,^{11–13} maternal hypertension,^{4,14,15} and the infant's gender.¹² It is not surprising that many different values for the sensitivity and specificity of different components of the CBC as predictors of infection have been published, depending on the population studied and what levels of these tests were considered "abnormal."

A significant limitation of previous studies is that they have generally dichotomized each of the CBC results (ie, classified results as normal or abnormal). In addition to the problem of inconsistency of such classification systems across studies and populations, this wastes information by failing to quantify the difference between borderline and profoundly abnormal results.¹⁶ Most studies have had small numbers of subjects with culture-confirmed infections, leading to imprecise estimates of test characteristics. Finally, whether or how to take into account factors other than infection that affect white blood cell counts has not been evaluated. For the current study we took advantage of information systems available in the Northern California Kaiser Permanente Medical Care Program (KPMCP) and Brigham and Women's Hospital (BWH) to investigate (1) whether accounting for other predictors of WBC count, ANC, and I/T, such as type of delivery, maternal hypertension, and infant gender, would improve performance of these tests for predicting infection, (2) interval likelihood ratios (LRs)¹⁶ for various ranges of normal and abnormal results, and (3) how these LR vary with age at the time of the CBC.

PATIENTS AND METHODS

The study was approved by the KPMCP, BWH, and the University of California, San Francisco, institutional review boards for the protection of human subjects.

We obtained data for this cross-sectional study from KPMCP and BWH demographic, laboratory, and hospitalization databases. We queried microbiology databases to identify all infants for whom a blood culture was obtained at <72 hours of age. We kept the first positive blood culture for infants with positive cultures, and the first blood culture for other

infants, and then matched all blood cultures by date and time to the (single) CBC obtained closest in time to the blood culture for each infant.

Study Subjects

Newborn infants were eligible for the study if (1) they were born between January 1, 1995, and September 30, 2007, at a KPMCP hospital that had at least 100 total births in that time period, or at the BWH from January 1, 1993, through December 31, 2007, (2) their estimated gestational age was ≥ 34 weeks, and (3) they had a CBC and blood culture drawn within 1 hour of one another at < 72 hours of age. CBCs and blood cultures were drawn according to the protocols and clinical judgment of clinicians at each site; the timing was often based on convenience (eg, when the infant was in the nursery) as well as medical indications. In many cases, the infants were asymptomatic and the tests were obtained because of maternal risk factors.

Predictor Variables

We obtained maternal data from the electronic record, including method of delivery (vaginal versus cesarean) and diagnoses of preeclampsia (International Classification of Diseases, Ninth Revision¹⁷ codes 642.3– 642.7) and chorioamnionitis (code 658.4X). Except for the infants with positive blood cultures whose paper medical charts we reviewed, we did not have data on other maternal risk factors (eg, fever or length of rupture of membranes) or infant symptoms for this study because these were not yet in an electronic medical chart. CBCs were completed with Beckman-Coulter (Brea, CA) or Sysmex (Munderlein, IL) hematology analyzers at KPMCP hospitals and an Advia 120 automated hematology analyzer (Siemens USA, Deerfield, IL) at the BWH. The differential WBC count, which allowed estimation of the ANC and I/T, was estimated manually with a mean of 100.0 cells (SD: 0.9) to allow for identification of bands. The ANC was calculated as the automated estimate of the WBC count $\times$ (% segmented neutrophils + % bands)/100. I/T was calculated as the total number of immature neutrophils (promyelocytes, myelocytes, metamyelocytes, and bands) divided by the total number of cells in the neutrophilic cell line (immature plus segmented neutrophils).

Outcome Variables

We classified all blood cultures as positive or not without regard for CBC results by using an algorithm based primarily on the organism risk category and the time to culture positivity.¹⁸ Three infants whose blood cultures only grew coagulase-negative *Staphylococcus* were included because they had significant symptoms. Three blood cultures were positive for more than 1 organism.

Statistical Analysis

We compared demographic and clinical characteristics of infants with and without infection by using t tests or χ^2 tests as appropriate. To determine if adjusting the WBC count, ANC, and I/T for other variables would improve discrimination, we estimated predicted values of these tests using multiple linear regression models on the infants who did not have infection. Models included age (using linear splines with knots at 3, 6, 9, 12, and 24 hours), age squared, birth weight (in 5 categories), gender, birth facility, year of birth, maternal preeclampsia, cesarean delivery, and 5-minute Apgar score (dichotomized at < 7). We subtracted these predicted values from observed values and visually inspected receiver operating characteristic (ROC) curves for these residuals and raw test results to ensure that their slopes were monotonically decreasing. We then compared the ability of the residuals with the raw test results to discriminate between newborns who did and did not have infections by comparing areas under ROC curves in 3 time periods.

We estimated percentiles according to age for the WBC count, ANC, and I/T using quantile regression (the `qreg` procedure in Stata [Stata Corp, College Station, TX]) for tests performed at <24 hours after birth, with terms for age, age squared, and linear splines with knots at 3, 6, 9, and 12 hours.

To estimate LRs for the WBC count, ANC, and I/T, we selected cutoffs that were round numbers and that generated 5 strata with approximately equal numbers of cases. We chose this method rather than identifying inflection points in observed ROC curves to avoid overfitting. We similarly stratified according to age at the time of sampling. We estimated LRs as the proportion of bacteremia cases, with each result divided by the proportion of noncases with that result.¹⁶ We performed all analyses by using Stata/SE 11, supplemented by a Stata algorithm that we developed to calculate interval LRs (available from the authors).

RESULTS

Of the 550 367 infants eligible for the study on the basis of their hospital, year of birth, and gestational age, we identified 311 (0.57 of 1000 live births) with positive blood cultures as defined above. We included in this study the subset of 67 623 infants (12.3% of the 550 367 eligible newborns) who had a CBC performed within 1 hour of a blood culture, including 245 of the 311 whose blood culture was positive (3.6 of 1000 infants who received CBCs).

Characteristics of the newborns included in the study and the proportions with documented infections are shown in Table 1. The majority of infants had white mothers, were born at Kaiser, were ≥ 39 weeks' gestation, and had their CBCs measured in the first 8 hours after birth. Infants were at higher risk of infection if they were born by cesarean delivery, born in the earlier years of the study, had 5-minute Apgar scores of <7, or had their CBCs measured at <1 hour of age.

The organism most commonly identified in the positive cultures (Table 2) was GBS (56%), followed by *Escherichia coli* (22%) and *Enterococcus faecalis* (4%). The proportion with GBS infections was lower at BWH (49% vs 59%) and declined over the years of the study, from 67% of infections to 37%. As a result, the proportion of infections caused by *E coli* increased slightly (from 19% to 28%), although the rate of *E coli* infections in each time period was similar.

Results for components of the CBC are shown in Fig 1. Because 95% of the infants with infections had their CBCs measured at <24 hours, we restricted the figures to that time period. The figures show a bimodal distribution in timing of CBCs, with the first peak shortly after birth, and a second peak at ~4 hours. The median WBC count and ANC values rise after birth, peak at 6 to 8 hours, and then decline slightly during the next 18 hours. In contrast, the median I/T declines slightly and approximately linearly during the first day. Among newborns with infection, mean WBC counts were 29% lower, mean ANC were 39% lower, and I/Ts were 133% higher than in newborns without infection; platelet counts did not differ significantly.

Because the WBC count, ANC, and I/T may be influenced by many factors other than sepsis, we created new variables for each test that corresponded to the difference between that test result and what would be predicted on the basis of other factors available in this data set that were known or observed to influence test results (see "Methods"). Resulting areas under ROC curves, stratified according to age, are shown in Table 3. Overall and for each age stratum, the differences in predictive ability with and without the additional factors were generally small in practical and statistical terms; we therefore elected to continue with raw test results for the remaining analyses.

There was a dramatic improvement in the discrimination of WBC count, ANC, and I/T during the first 4 hours after birth (Fig 2, which includes all of the data, not just results from the first 24 hours). This occurred similarly for GBS and non-GBS infections; sample sizes were not sufficient to consider other organisms separately. The platelet count did not predict infection, regardless of age. Both the WBC counts and ANCs provided little information about infection risk in the first hour, with only very low counts being informative. The WBC counts and ANCs improved significantly at 1 to 4 hours, and improved more at ≥ 4 hours. In contrast, I/T did provide some information in the first hour, although it also discriminated better after 4 hours. The slopes of all ROC curves monotonically decrease until close to the upper right corner, where the slope increases a little, but remains <1 . Because the slope of the ROC curve is equal to the LR, this shows that both WBC counts and ANCs were associated with a higher risk of infection only when they were low. For both WBC counts and ANCs, however, very high values, although not worrisome, are also not reassuring. The LR for WBC count $> 30\,000$ for all ages was 0.844 and the LR for ANC $> 25\,000$ for all ages was 0.935).

LRs for WBC counts, ANCs, and I/T at <1 hour, 1 to <4 hours, and ≥ 4 hours are shown in Table 4 (we present point estimates of LRs; 95% confidence intervals are available on request). LRs for platelet counts are not shown; whether dichotomized at 150 or divided into 5 categories, no level of the platelet count had an LR significantly different from 1. The lowest LRs for the other tests, corresponding to the most normal results at ≥ 4 hours of age, are in the range of 0.15 to 0.3, which reflects the limited sensitivity of these tests for diagnosing sepsis, and hence their limited ability to be reassuring. In contrast, the LRs for the most abnormal tests are high, in the range of 50 to 120 for the lowest values of the WBC count and ANC.

DISCUSSION

This large study of components of the CBC as predictors of bacterial infection in newborns provides several results that should be clinically useful in the early evaluation of newborns for possible infection. First, although many factors other than infection affect WBC values in the first several hours after birth, adjusting a normal range to account for these factors led to little improvement in the discrimination of the components of the CBC. Second, the usefulness of the CBC in distinguishing between infants who do and do not have infections increases dramatically during the first 4 hours after birth. Third, rather than attempting to dichotomize CBC results into those in and outside of a “normal range,” it is more informative to use the age-specific LRs associated with intervals of specific test results. Finally, related to this last point, in this age group using a normal range with upper limits for the WBC count and ANC will lead to newborns with high WBC count and ANC being labeled as having “abnormal” results, when in fact only low WBC count and ANC are associated with increased likelihood of infection.

Our results confirm and extend those of previous studies. Multiple studies have shown that the WBC count and ANC increase rapidly during the first 6 hours, leveling off thereafter.^{3–5,12} Our fifth and 50th percentiles closely match those for term infants reported by Schmutz et al,¹² who used a similar design by using data systems at Intermountain Health care. Our finding that the test characteristics of the CBC improve with age is in agreement with studies that reveal poor performance of the CBC when it is used primarily in young (<4 hours old) infants,^{5,7,19–21} including some who specifically show improvement with later CBCs.^{19,20}

Our study has important limitations. First, this is a study of early-onset sepsis in term and late-preterm infants. Most (75%) of the CBCs were obtained in the first 8 hours after birth,

including 54% obtained in the first 4 hours. In older infants, not only low but also high WBC counts and ANC's (and low platelet counts) may be suggestive of infection. Thus, these results should not be generalized to infants older than ~12 hours of age. Similarly, WBC counts and ANC's are normally lower in more premature infants¹²; this would presumably worsen discrimination in that group.

Second, this study included only infants who had CBCs and blood cultures measured by their treating clinicians, either because of risk factors for infection or symptoms. As a result, odds ratios reported in Table 1 should not be used to infer risk relationships in the general population of infants. For example, although preterm delivery is a risk factor for infection in newborns,^{22–24} the fact that preterm infants were more likely to be selected for CBCs and blood cultures masked the relationship between gestational age and infection in this study, as evidenced by the odds ratio of 0.61 for infants with a gestational age of 34 to 36⁶/7 weeks compared with infants with a gestational age of ≥39 weeks.

Third, although this was a large study, the need to stratify on both age at the time of the CBC and intervals of test results meant that each LR we reported was based on a smaller sample size, leading in some cases to wide confidence intervals around the LRs. Because of this need to stratify according to age, we were unable to estimate joint LRs for specific combinations of CBC results (eg, an LR for an ANC of 2000 to 4999 in an infant with an I/T of 0.3–0.44). Although it may be tempting to use the product of the interval LRs for each test in Table 4 as a joint LR, this approach may not be valid because (particularly in the case of the WBC count and ANC) the tests cannot be assumed to be independent.

Finally, it is possible that the LRs for these tests vary not only with the age of the infant but also with the distribution of organisms,²⁵ gestational age, and other risk factors, and level of symptoms in those with infection. Thus, optimal prediction of sepsis will require additional studies to better define these relationships and at least a moderately complicated algorithm that would best be implemented within an electronic medical chart. In future analyses we plan to explore the best way to combine results of clinical and laboratory data to estimate the probability of sepsis, and how the process might be automated.

CONCLUSIONS AND CLINICAL IMPLICATIONS

Although additional refinements are needed, this study has important clinical implications. Perhaps most importantly, results of the CBC can provide more information about the risk of sepsis after the first few hours after birth. If the intent of drawing a CBC is to use that information to make clinical decisions regarding the likelihood of infection, for example, whether to initiate empiric antibiotic therapy, then delaying the CBC for a few hours may be advisable. On the other hand, if an infant's risk factors or symptoms are sufficiently worrisome to draw a CBC and blood culture before ~4 hours of age, it may be prudent to start antibiotics at the same time, rather than waiting for the results of the initial CBC.

Among infants for whom a decision to start antibiotics can be deferred until after 4 hours of age, the CBC is more likely to be helpful. However, most of these infants will have CBC results with modest LRs, in the range of 0.2 to 5. Thus, even when the CBC is optimally interpreted, decisions about antibiotic treatment should remain highly dependent on maternal risk factors and newborn symptoms of infection.⁵ Future approaches to the sepsis evaluation will require models that are explicit about how multiple information sources (maternal risk factors, newborn clinical examinations, and laboratory test results) are integrated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

CBC	complete blood count GBS—group B <i>Streptococcus</i>
WBC	white blood cell
ANC	absolute neutrophil count
I/T	proportion of neutrophils that are immature
KPMCP	Northern California Kaiser Permanente Medical Care Program
BWH	Brigham and Women's Hospital
LR	likelihood ratio
ROC	receiver operating characteristic

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WHAT'S KNOWN ON THIS SUBJECT

Components of the complete blood count (CBC) provide information about the likelihood of sepsis in newborns, but previous studies have used varying definitions of abnormal and yielded inconsistent results.

WHAT THIS STUDY ADDS

White blood cell counts and absolute neutrophil counts increase the probability of sepsis only when they are low. The informativeness of the CBC increases with age and when interval likelihood ratios are used rather than a “normal” range.

FIGURE 1.

Test results according to age for complete blood counts performed at <24 hours. A, WBC count according to age; B, ANC according to age; C, I/T according to age; D, platelet count according to age. All counts are thousands per microliter. Cases are shown as red diamonds; only a 20% random sample of the newborns with no infection is shown. Lines indicate the results of quantile regressions at the 1%, 10%, 50%, 90%, and 99% points of the distributions. A larger version of this figure is available online as Supplemental Figure 1.

FIGURE 2. ROC curves for WBC counts (A), ANC (B), I/T ratio (C), and platelet counts (D) performed at <72 hours according to age at the time of the CBC.

TABLE 1

Demographic and Clinical Characteristics of the Study Subjects

	Confirmed Infection	No Confirmed Infection	Infection Risk per 1000	Bivariate Odds Ratio	P
Entire study, <i>n</i>	245	67 378	3.6	—	—
Maternal characteristics					
Age, mean $\pm$ SD, y	29.7 $\pm$ 6.6	29.8 $\pm$ 6.1	—	—	.8
Race, <i>n</i>					
White	119	33 112	3.6	1.00	—
Black	20	6530	3.1	0.85	.51
Asian	41	9398	4.3	1.21	.29
Hispanic	54	13 984	3.8	1.07	.66
Other/unknown	11	4354	2.5	0.70	.26
Delivery, <i>n</i>					
Vaginal	151	46 982	3.1	1.00	—
Cesarean	94	20 383	4.6	1.43	.006
Newborn characteristics					
Year of birth, <i>n</i>					
1993–1997	76	13 413	5.6	2.75	<.001
1998–2002	109	24 855	4.4	2.13	<.001
2003–2007	60	29 110	2.1	1.00	—
Hospital/health care system of birth, <i>n</i>					
KPMCP	164	47 214	3.5	1.00	—
BWH	81	20 164	4.0	1.07	.29
Gender, <i>n</i>					
Female	108	29 988	3.6	1.00	—
Male	137	37 390	3.7	1.02	.89
Gestational age, mean $\pm$ SD, wk					
34 to <37 wk, <i>n</i>	29	11 364	2.5	0.67	.05
37 to <39 wk, <i>n</i>	54	13 260	4.1	1.07	.65
$\geq$ 39 wk, <i>n</i>	162	42 754	3.8	1.00	—
Birth weight, mean $\pm$ SD, kg	3.43 $\pm$.56	3.34 $\pm$.65	—	—	.05

	Confirmed Infection	No Confirmed Infection	Infection Risk per 1000	Bivariate Odds Ratio	P
5-minute Apgar score, <i>n</i>					
<7	33	2389	13.6	7.67	<.001
7–10	212	64 989	3.3	1.00	—
Age at CBC paired with blood count, <i>n</i>					
<1 h	64	10 150	6.3	2.29	<.001
1 to <4 h	91	32 992	2.8	1.00	—
4 to <8 h	55	13 216	4.1	1.51	.02
8 to <24 h	19	7307	2.6	0.94	.82
24 to <48 h	14	2837	4.9	1.79	.04
<48 h	2	876	2.3	0.83	.79

Totals in the “confirmed infection” and “no confirmed infection” columns by demographic and clinical characteristics do not always add to the entire-study totals because of differences in the (small) amounts of missing data for each variable.

TABLE 2

Distribution of Organisms for Infection Cases

Organism	KPMCP, <i>n</i>	%	BWH, <i>n</i>	%	1993-1997, <i>n</i>	%	1998-2002, <i>n</i>	%	2003-2007, <i>n</i>	%	Total, <i>N</i>	Total %
GBS	97	59	40	49	51	67	64	59	22	37	137	56
<i>E coli</i>	39	24	14	17	15	20	21	19	17	28	53	22
Other	24	15	20	25	8	11	18	17	18	30	44	18
<i>Enterococcus</i> species	4	2	7	9	2	3	6	6	3	5	11	4
Total	164	100	81	100	76	100	109	100	60	100	245	100

TABLE 3

Area Under the ROC Curve (95% CI) for Raw WBC Count and Residual Variables, Defined as the Difference Between Values Observed and Those Predicted From Age, Gender, Delivery Method, and Other Predictors

	Total	Age, h		
		<1	1–3.99	≥4
WBC count	0.71	0.52	0.64	0.87
WBC count-residual	0.70	0.55	0.66	0.87
<i>P</i> for difference	.84	.003	.15	.88
ANC	0.73	0.55	0.68	0.85
ANC-residual	0.71	0.57	0.68	0.84
<i>P</i> for difference	.01	.14	.86	.51
I/T	0.76	0.73	0.73	0.82
I/T-residual	0.76	0.70	0.72	0.85
<i>P</i> for difference	.79	.10	.81	.01

Values were estimated by using all of the newborns with confirmed infections and a 30% random sample of those with no confirmed infection (total sample size: 20 152); larger samples of the noninfected newborns could not be accommodated computationally.

LRs for Components of the CBC According to Age at the Time of Testing Among Newborns With CBC and Blood Cultures Performed at <72 Hours of Age

TABLE 4

	Age at Time of CBC, h				No. With Infection, Total	% of Those With Infection With Result	% of Those Without Infection With Result
	<1	1-3.99	≥4				
Total No. with infection	64	91	90		245		
% of all with infection	26	37	37		100		
	LR	LR	LR				
WBCs, × 103/μL							
0-4.99	a	27.6	80.5		46	19	0.5
5-9.99	1.4	2.4	6.4		53	22	7.6
10-14.99	1.1	0.65	1.0		53	22	25
15-19.99	0.73	0.64	0.41		45	18	31
<20	1.2	0.77	0.16		48	20	35
ANC, × 103/μL)							
0-0.99	7.5	33.5	115		35	14	0.4
1-1.99	2.3	9.3	51.7		30	12	1.1
2-4.99	1.0	1.1	6.9		44	18	9.6
5-9.99	0.89	0.92	0.64		70	29	33.7
<10	0.93	0.55	0.31		65	27	55.3
I/T							
0-0.1499	0.45	0.46	0.25		61	25	66
0.15-0.299	1.3	1.2	1.2		69	28	23
0.3-0.4499	1.4	2.9	3.1		44	18	7
0.45-0.599	4.8	3.3	8.8		37	15	3
<0.6	6.1	8.4	10.7		33	15	2

95% confidence intervals for LRs are available from the authors on request.

^aThe point estimate of this LR was 0, but there were only 56 infants in this cell.