Circulating Neutrophils in Septic Preterm Neonates: Comparison of Two Reference Ranges

William D. Engle, MD*; Charles R. Rosenfeld, MD*; Anna Mouzinho, MD; Richard C. Risser‡; Fiker Zeray, RN*; and Pablo J. Sanchez, MD*

ABSTRACT. Objective. To study the effect of sepsis on circulating neutrophils in very low birth weight neonates and to assess the usefulness of recently revised reference ranges for circulating neutrophils in the diagnosis of sepsis in this population by comparison with previously reported reference ranges.

Methods. Neutrophil parameters (absolute total neutrophils, absolute total immature neutrophils, and the immature:total neutrophil proportion) were analyzed retrospectively in 202 sepsis episodes in 192 neonates (birth weight = 1055 ± 246 g, X ± SD; estimated gestational age = 29 ± 2 weeks) between birth and 30 days of age. The percentage of values lying outside the reference ranges reported recently by Mouzinho et al32 and previously by Manroe et al24 were compared. To more accurately assess possible differences in specificity between the two reference ranges, neonates with early-onset group B streptococcal infection (n = 19) were compared with a matched control group (n = 51) using conditional logistic regression.

Results. Greater sensitivity was observed using the previous reference ranges of Manroe et al24 over the entire study period (0 to 720 hours) both for the initial and the second complete blood count (CBC). The previous reference ranges also were more sensitive than the revised ranges for the initial CBC at 0 to 72 and at 73 to 720 hours and for infections attributable to coagulase-negative staphylococci. However, specificity in neonates without group B streptococcal infection was significantly greater with the revised reference ranges compared with those of Manroe et al24 (initial CBC, 73% vs 45%; serial CBCs, 59% vs 10%).

Conclusion. The observed differences in sensitivities may be of limited clinical significance because very low birth weight infants often are begun on antibiotic therapy regardless of laboratory values. However, the striking differences in specificity using the revised reference ranges suggest that these ranges may be clinically useful in determining length of antimicrobial therapy in infants in whom cultures remain sterile. Pediatrics 1997;99(3).

ABBREVIATIONS. VLBW, very low birth weight; CBC, complete blood count; BW, birth weight; GBS, group B streptococcal (infection); ATI, absolute total immature neutrophil count; ET, immature neutrophil:total neutrophil proportion; ATN, absolute total neutrophil count; PPV, positive predictive value; NPV, negative predictive value.

The timely diagnosis of sepsis in the very low birth weight (VLBW; ≤1500 g) neonate is critical because the illness can be rapidly progressive and in some instances fatal.1,2 Numerous investigators have evaluated the usefulness of various laboratory tests in the diagnosis of systemic infection in this population.3–6 These include determination of C-reactive protein,7 erythrocyte sedimentation rate,8 haptoglobin,9 orosomucoid,10 fibronectin,7 elastase-α1-proteinase inhibitor complex,11 C3d,12 endotoxin,13 acridine orange cytoplasm,14 and nitroblue tetrazolium reduction.15 Although multiple tests have been used together for this purpose, perhaps the single test of greatest utility in establishing a diagnosis of sepsis has been the complete blood count (CBC) and in particular the various neutrophil parameters.2,16–23 In studies reported in 1979,24 we established reference ranges for circulating neutrophils in neonates with postnatal age ≤30 days. Although the gestational age and birth weight (BW) of these neonates ranged from 29 to 44 weeks and from 860 to 5000 g, respectively, these data were obtained between 1974 and 1976, when the survival of preterm, VLBW neonates was substantially less than that observed more recently. In this report and others, neutropenia was associated with neonatal sepsis, especially attributable to group B streptococcus (GBS).25,26

Based on subsequent studies from our institution and elsewhere,27–30 it appeared, however, that many normal VLBW neonates were considered to be neutropenic using the references ranges of Manroe et al.24 More recently, we reported revised reference ranges for circulating neutrophils in VLBW neonates.32 Although the reference ranges for absolute total immature neutrophils (ATI) and the immature:total neutrophil proportion (IT) were unchanged, the reference ranges for absolute total neutrophils (ATN) differed from those previously reported. There was a broader distribution for ATN values during the first 72 hours after birth, primarily reflecting a markedly lower limit throughout this period of time and a shift in the peak upper range from 10 to 12 hours to 18 to 24 hours after birth (see Figure). Because more VLBW neonates would now have

From the Departments of *Pediatrics and ‡Academic Computing, University of Texas Southwestern Medical Center, Dallas, TX 75235–9063. Presented in part at the Annual Meeting of the American Pediatric Society/Society for Pediatric Research, San Diego, CA, May 8, 1995. Dr Ana Mouzinho was a visiting Research Scientist from Portugal. Reprint requests to (W.D.E.) University of Texas Southwestern Medical Center at Dallas, Department of Pediatrics, 5323 Harry Hines Blvd, Dallas, TX 75235–9063. PEDIATRICS (ISSN 0031 4005). Copyright © 1997 by the American Academy of Pediatrics.

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ATN values that would fall into the normal range, we hypothesized that the usefulness of peripheral neutrophil values in helping to establish a diagnosis of sepsis in this population might be diminished. To address this concern, we analyzed circulating neutrophil values obtained from 192 VLBW neonates born between 1987 and 1993 with proven sepsis in the first postnatal month. Neutrophil values were examined using the reference ranges of Manroe et al.24 as well as those of Mouzinho et al.32 to assess differences in sensitivity between the two methods. In addition, a subset of the population [19 infants with early-onset (0 to 72 hours) GBS infection] was compared with a matched control group to assess differences in specificity between the reference ranges of Manroe et al.24 and Mouzinho et al.32

METHODS

Subjects

The study population consisted of 192 VLBW neonates delivered at Parkland Memorial Hospital between January 1, 1987 and December 31, 1993 who had a positive bacterial or fungal isolate from blood and/or cerebrospinal fluid in the first month of life (Table 1). The 192 study infants had a total of 202 episodes of culture-proven sepsis identified by prospective surveillance and they represented 11% of the 1732 neonates with BW <1500 g. The dotted lines depict the reference range of Manroe et al24 For the latter, the minimum value of 1750 total neutrophils/mm3 is established by 72 hours of age; a stable maximum value of 5400 neutrophils/mm3 is reached at 120 hours.

Figure. Reference ranges for total neutrophil values in the first 60 hours after birth. The solid lines depict the boundaries of the revised reference range of Mouzinho et al25 in infants <1500 g. The dotted lines depict the reference range of Manroe et al24 For the latter, the minimum value of 1750 total neutrophils/mm3 is established by 72 hours of age; a stable maximum value of 5400 neutrophils/mm3 is reached at 120 hours.

Table 1. Characterization of Study Population

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<thead>
<tr>
<th></th>
<th>Early-onset GBS</th>
<th>Matched Controls</th>
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<tbody>
<tr>
<td>Number of infants</td>
<td>19</td>
<td>51</td>
</tr>
<tr>
<td>Birth weight (g)*</td>
<td>1019 ± 267</td>
<td>1057 ± 270</td>
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<tr>
<td>Gestational age (wk)*</td>
<td>28.5 ± 2.5</td>
<td>28.6 ± 2.6</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Males</td>
<td>5 (26)†</td>
<td>14 (27)</td>
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<tr>
<td>Females</td>
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<tr>
<td>African-American</td>
<td>14 (74)</td>
<td>39 (76)</td>
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<td>Latin-American</td>
<td>2 (10.5)</td>
<td>6 (12)</td>
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<tr>
<td>White</td>
<td>2 (10.5)</td>
<td>6 (12)</td>
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<td>Asian</td>
<td>1 (5)</td>
<td>0 (0)</td>
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<tr>
<td>Clinical</td>
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<tr>
<td>Maternal PIH‡</td>
<td>2 (11)</td>
<td>11 (22)</td>
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<tr>
<td>5-min Apgar score ≤5</td>
<td>8 (42)</td>
<td>10 (20)</td>
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<td>Respiratory distress syndrome</td>
<td>9 (47)</td>
<td>35 (69)</td>
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<td>Mechanical ventilation</td>
<td>14 (74)</td>
<td>36 (71)</td>
</tr>
<tr>
<td>Apnea of prematurity</td>
<td>10 (53)</td>
<td>37 (73)</td>
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* Values are presented as means ± SD.
† Numbers in parentheses are percentages (except for range).
‡ Pregnancy-induced hypertension.

Table 2. Neutrophils With Early-onset Group B Streptococcal (GBS) Sepsis and Their Matched Controls

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§ THIS INDICATES THAT AT LEAST ONE ABNORMAL VALUE WAS PRESENT FROM ATN, ATI AND I:T VALUES.

8 COMPARISON OF THE SENSITIVITY OF THE REVISED REFERENCE RANGE 32 AND THAT OF MANROE ET AL.24 FOR NEUTROPHIL VALUES IN VLBW NEONATES.

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18 ON THE TWO SETS OF REFERENCE RANGES WERE COMPAARED USING McNEMAR'S TEST CONSIDERING THE CASES AND MATCHED CONTROLS, RESPECT-

18 TO REPORTING PPV AND NPV DIRECTLY FROM A CASE-CONTROL

18 TOTAL NUMBER OF INFANTS WITH ABNORMAL

18 ON THE FIRST 30 DAYS OF LIFE. THIRTY-TWO OF THESE WERE

18 ON THE TWO SETS OF REFERENCE RANGES WERE COMPAARED USING McNEMAR'S TEST CONSIDERING THE CASES AND MATCHED CONTROLS, RESPECT-

17 TABLE 3. COMPARISON OF THE SENSITIVITY OF THE REVISED REFERENCE RANGE 32 AND THAT OF MANROE ET AL24 FOR NEUTROPHIL VALUES IN VLBW NEONATES WITH PROVEN SEPSIS

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that of Mouzinho et al\textsuperscript{32} (73\% and 84\%, respectively). These differences were significant by McNemar's test ($P < .001$ for initial neutrophil values and $P = .008$ for the second CBC). A similar difference in sensitivity for any abnormality also was noted between the new and old reference ranges for the initial CBC both at 0 to 72 hours ($P = .031$) and at 73 to 720 hours ($P = .002$) (Table 3). However, there were no significant differences between reference ranges for neutrophilic parameters in the second CBC, or when any neutrophil abnormalities from both the first and second CBCs were considered for either early-onset or late-onset sepsis episodes.

Among the 19 cases of early-onset GBS infection, no neonate demonstrated neutrophilia with either of the ATN reference ranges, and the occurrence of neutropenia was ~70\% lower with the revised compared with the previous reference ranges. Using the reference ranges of Mouzinho et al, at least one neutrophil value was abnormal in 58\% and 88\% of first and second CBCs, respectively (Table 3). This did not differ significantly from that seen with the values reported by Manroe et al\textsuperscript{24} 74\% and 94\%, respectively. Among the 16 infants who had both a first and second CBC performed, comparison of earlier and later neutrophil values failed to show differential sensitivity, regardless of which reference ranges were used.

Because only 3 cases of sepsis attributable to coagulase-negative staphylococci occurred in the first 72 hours, data are reported for only those sepsis episodes ($n = 78$) that occurred from 73 to 720 hours (Table 3). With the ATN reference range of Mouzinho et al,\textsuperscript{32} at least one neutrophil value was abnormal in 76\% and 87\% of first and second CBCs, respectively, as compared with 85\% and 90\%, respectively, using the range of Manroe et al. The difference in sensitivity was only significant for the first CBC ($P = .016$). There also was no difference in the sensitivities when abnormalities on either the first or second CBC were considered, 84\% and 95\%, respectively.

Only 3 cases of sepsis attributable to Gram-negative organisms occurred in the first 72 hours; therefore, data are reported only for the 26 late-onset episodes. As seen in Table 3, the percentage of abnormal neutrophil values was identical using either reference range, ie, $\geq 89\%$. Furthermore, the sensitivities using both first and second CBCs were 100\% with either ATN reference ranges.

**Analysis of Specificity**

Results of the comparison between neonates with early-onset GBS infection and their matched, uninfected controls permit an assessment of specificity; these data are presented in Table 4. When the first CBC was examined, ATN and ATI values, whether assessed quantitatively (cells/mm\textsuperscript{3}) or qualitatively (ie, the relative number within vs outside the reference range), did not differ between GBS cases and controls. Although the quantitative difference in the initial I:T proportion between cases and controls was of marginal significance ($P = .06$), there was a highly significant difference ($P = .002$) when the I:T proportion was assessed qualitatively, ie, 58\% of the cases were outside the I:T reference range as compared with 14\% of the matched controls.

Of the GBS-infected neonates, 58\% had $\geq 1$ abnormality in neutrophil values detected on the first CBC using the data of Mouzinho et al\textsuperscript{32} vs 27\% of controls ($P = .03$). Corresponding percentages using the reference ranges of Manroe et al\textsuperscript{24} (74\% vs 55\%, respectively) are not significantly different. Thus specificity for the initial CBC using the reference ranges of Mouzinho et al\textsuperscript{32} was significantly greater than that of Manroe et al\textsuperscript{24} 73\% vs 45\% ($P = .003$ by McNemar’s test).

When we analyzed serial CBC data using the presence of $\geq 1$ abnormality, there was no significant difference in sensitivity between the two reference ranges (100\% for Manroe et al\textsuperscript{24} 94\% for Mouzinho et al\textsuperscript{32}; $P = 1.0$). However, as shown in Table 4, the specificity was significantly better using the data of Mouzinho et al\textsuperscript{32} vs Manroe et al\textsuperscript{24} 59\% (100\% - 41\%) vs 10\% (100\% - 90\%) ($P < .0001$).

Considerig the reference ranges of Mouzinho et al\textsuperscript{32} and estimating prevalence of early-onset GBS at 1\%, the PPV and NPV for the initial CBC were 2.1\% and 99.4\%, respectively. Corresponding values for the Manroe et al\textsuperscript{24} reference ranges were 1.3\% and 99.3\%. When serial counts were used, the PPV and NPV for the Mouzinho et al\textsuperscript{32} reference ranges were 1.5\% and 99.7\%, respectively; corresponding values for Manroe et al\textsuperscript{24} were 1.1\% and 100\%, respectively.

**DISCUSSION**

Sepsis in the VLBW neonate can be a devastating problem, leading to considerable morbidity and mortality.\textsuperscript{1,2} The inability to adequately exclude the diagnosis of neonatal sepsis, on the other hand, can result in unnecessary and prolonged exposure to antibiotics. Thus, laboratory tests that assist the clinician in the diagnosis of infection in VLBW neonates have

| TABLE 4. Comparison of Neutrophil Indices in Neonates With Proven Early-onset Group B Streptococcal Sepsis and Matched, Uninfected Control Neonates |
|---------------------------------|------------------|------------------|
|                                | GBS (n = 19)    | Control (n = 51) |
| A. Analysis of first CBC        |                  |                  |
| ATN (cells/mm\textsuperscript{3}) | 2118 ± 1441*   | 3044 ± 2729 .20  |
| ATI (cells/mm\textsuperscript{3}) | 315 ± 330      | 251 ± 519 .72    |
| I:T                             | 0.25 ± .26      | 0.10 ± .22 .06    |
| ATN                             |                  |                  |
| Outside Mouzinho reference range | 16‡             | 20 §             |
| Outside Manroe reference range  | 58               | 51 §             |
| B. Analysis of serial CBC†      |                  |                  |
| ≥1 Abnormality                  |                  |                  |
| Mouzinho reference range        | 58               | 27 §             |
| Manroe reference range          | 74               | 55 §             |

* Values are means ± SD.
† Values are percentages.
‡ GBS n = 16; control group n = 39.
considerable relevance. In 1979, we\textsuperscript{24} reported reference ranges for circulating neutrophils in neonates ≤30 days and demonstrated their utility in confirming the presence or absence of neonatal sepsis.\textsuperscript{23,25,27} More recently, we and others\textsuperscript{27-31} observed the frequent occurrence of neutropenia in otherwise healthy VLBW neonates when the 1979 reference ranges were used. Because of these findings, we examined the reference ranges for circulating neutrophils in VLBW neonates ≤30 days, a group of neonates whose survival had increased significantly over the ensuing 14 to 15 years.\textsuperscript{32} In this study, we observed a broader distribution for ATN values in the first 72 hours after birth. Thus, although we revised these reference ranges, those for ATI and I:T values were unchanged. Because of the small number of infants with sepsis in that study,\textsuperscript{32} no conclusions regarding the usefulness of the revised reference ranges in the diagnosis of infection could be made. Thus, we undertook the present study to assess whether there are differences in the usefulness of the previous\textsuperscript{24} and revised\textsuperscript{32} reference ranges reported by us in establishing or ruling out a diagnosis of sepsis in the VLBW neonate.

In the present report, the sensitivity for diagnosing neonatal sepsis is reduced using the more BW-specific ATN reference ranges of Mouzinho et al\textsuperscript{32} in certain circumstances. This might have been anticipated since Mouzinho et al\textsuperscript{32} observed a decrease in the lower limit of normal for ATN values throughout the first 60 hours after birth. Because GBS sepsis and pneumonia are most common during the first 72 hours after birth, one might expect that differences in the sensitivity of neutrophil values between the two reference ranges would be most apparent in these neonates in whom neutropenia has been shown to occur frequently.\textsuperscript{24-26} However, in the presence of early-onset GBS infection, at least one neutrophil value was abnormal in 58% to 74% of initial CBCs and 88% to 94% of second CBCs, the latter demonstrating the value of serial CBC determinations, and there was no significant difference in sensitivity between the reference ranges of Mouzinho et al\textsuperscript{32} and Manroe et al.\textsuperscript{24}

The occurrence of neutropenia in association with early-onset sepsis has been reported previously by us\textsuperscript{32} and others.\textsuperscript{3,26} Christensen\textsuperscript{35} has suggested that this is likely attributable to bone marrow depletion as well as a diminished capacity for accelerated neutrophil production by the preterm, VLBW neonate. This, however, appears to be limited to the first week after birth, because neutrophilia and elevated ATI and I:T values are commonly observed after that time.\textsuperscript{32} The current study, in which most instances of neutropenia occurred in the first 72 hours after birth, supports our previous observations. Furthermore, it is notable that late-onset infection with coagulase-negative staphylococci is rarely associated with neutropenia, whereas 15% to 20% of episodes of late-onset Gram-negative infection presented with or developed neutropenia. The reason for this difference is not known, but it may be related to the virulence of the infecting organism.

The differences in sensitivity that were observed between the two reference ranges may have limited clinical importance. For example, when all organisms were considered during the 73 to 720-hour period, the difference in sensitivity was minimal, 82% (Manroe et al\textsuperscript{23}) vs 77% (Mouzinho et al\textsuperscript{32}). However, the greater specificity shown for the Mouzinho et al\textsuperscript{32} reference ranges may be clinically relevant. We found that control neonates, matched with cases of early-onset GBS infection, were much less likely to have abnormal neutrophil values according to the Mouzinho et al\textsuperscript{32} reference ranges than with those of Manroe et al\textsuperscript{24} (first CBC, P = .004; serial CBCs, P < .0001). The enhanced specificity with the revised reference ranges shown for early-onset GBS sepsis, especially when considered in light of the very high sensitivity associated with serial neutrophil values, may be useful in determining the duration of treatment in neonates begun on antibiotics, but in whom cultures are either sterile or suggestive of contamination after 48 hours of treatment.

The results of this study provide support for the utility of assessing circulating neutrophil values in the diagnosis of sepsis in VLBW neonates, although not all investigators consider the laboratory differentiation of neutrophil values to be a reliable test in the neonate.\textsuperscript{36} In a large group of VLBW neonates with proven sepsis during a 7-year period, there was only a 6% and 11% likelihood of all neutrophil values being normal, using the reference ranges of Manroe et al\textsuperscript{24} and Mouzinho et al.\textsuperscript{32} Estimations of PPV and NPV indicated that PPV is fairly low while NPV is very high (90%-100%). As noted above, these values are dependent on prevalence, and thus in institutions with a higher prevalence of early-onset GBS, values for PPV and NPV can be different; as prevalence increases, PPV also increases but NPV decreases (if sensitivity and specificity are constant).

Antibiotic therapy should not be withheld in neonates considered at risk for sepsis while awaiting the results of an initial CBC, because these neutrophil values may frequently be normal. Indeed, this appears to reflect current practice in most nurseries. It is reassuring that completely normal neutrophil values on serial CBCs were unlikely to occur in septic VLBW neonates. Conversely, normal values were observed in the majority of matched-controls. Based on these findings and our experience, discontinuation of antibiotics after 48 hours\textsuperscript{37} seems appropriate in infants with normal serial neutrophil values (Mouzinho et al\textsuperscript{32} reference ranges) and clinical information suggesting the absence of infection. We conclude that the revised reference ranges of Mouzinho et al\textsuperscript{32} can be used to better assess circulating neutrophil values in the VLBW neonate with possible sepsis, generally by decreasing the number of false positives compared with the Manroe et al\textsuperscript{24} reference ranges.

ACKNOWLEDGMENTS

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REFERENCES


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