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Hematologic scoring system in early diagnosis of sepsis in neutropenic newborns

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The hematologic profiles of 1000 newborns were prospectively examined to identify infants with neutropenia ($N = 170$) according to the system of Manroe et al. (J Pediatr 1979;95:89–98) and to evaluate a hematologic scoring system (Rodwell et al. J Pediatr 1988;112:761–7) as a screening test for sepsis. Neutropenia was more commonly of noninfectious than infectious origin (83.5% *vs.* 16.5%; $P < 0.001$). On the initial test a positive screen (scores ≥3) identified 26 of 28 infants with sepsis or probable infection (sensitivity 93%; specificity 82%; positive and negative predictive values 50 and 98%, respectively). Corresponding values for an elevated immature:total neutrophil ratio were 100, 75, 43 and 100%. Overall mortality with neutropenia was 15% and was higher with an infectious than a noninfectious etiology (39% *vs.* 11%, $P < 0.001$) despite early antibiotic therapy. The combination of a neutrophil count ≤500/mm^3 and scores ≥3 or an elevated immature:total neutrophil ratio identified a poor prognostic group: 67% (8 of 12) and 70% (7 of 10) infants, respectively, with these findings died, 6 in the infected group. The hematologic scoring system or immature:total neutrophil ratio in combination with the degree of neutropenia provides valuable diagnostic and prognostic information which could be applied to identification of possible candidates for granulocyte transfusions or other experimental treatments.

INTRODUCTION

The management of neutropenic newborns may pose a serious clinical dilemma. In the majority of cases neutropenia is of noninfectious etiology and warrants conservative management.[1, 2] In contrast neutropenia of infectious origin may represent depletion of the neutrophil bone marrow storage pool (NBMSP) for which early diagnosis and aggressive therapy are critical for survival.[3, 4] The degree of neutropenia does not correlate with the depletion of the NBMSP,[3, 4] and in a recent study the immature:total neutrophil (I:T) ratio was of no value in identification of infants with sepsis.[1] A hematologic scoring system (HSS) has been used in our neonatal unit for some years as a screening test for sepsis.[5, 6]

This prospective study examines the value of the HSS in the early diagnosis of sepsis in neutropenic newborns. The performance of an elevated I:T ratio which is more widely used as an indicator of neonatal sepsis is also presented. Other issues of practical importance are addressed including the frequency of neutropenia, the associated factors and outcome.

MATERIALS AND METHODS

Study population. This prospective study carried out between January 1, 1988, and April 16, 1989 was approved by the Ethics Committee of the Mater Misericordiae Hospital, Brisbane. Parental consent was not required. Eligibility criteria for inclusion were: (1) the performance of a complete blood count (CBC) and sepsis work-up in the first 24 hours of life; and (2) neutropenia as defined by the neutrophil reference ranges of Manroe et al.[7] In our unit infants undergo a sepsis work-up, which includes a CBC, peripheral blood culture, gastric aspirate microscopy and culture and cultures from superficial sites if there are clinical signs of infection or predisposing perinatal factors for infection.[8] Further tests are performed as indicated. The study population of 1000 infants included 455 preterm with a mean gestational age of 31.64 ± 3.13 (SD) weeks (range, 25 to 36 weeks) and 545 term infants with a mean gestational age of 39.65 ± 0.88 weeks. Infants in the study were examined by a neonatal registrar or consultant. Details regarding predisposing perinatal factors and clinical assessment of the neonate were recorded on a data acquisition sheet. Other clinical and therapeutic details (therapy was given at the discretion of the attending physician) and

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radiologic, microbiologic, hematologic and postmortem data where relevant on the mother-infant pairs were retrospectively collected from laboratory and patient records.

Hematologic investigations. The majority of blood samples were collected by heel stick puncture; the remainder were collected by umbilical artery catheter or peripheral venipuncture. The CBCs were performed by the staff of the clinical laboratory on a Coulter S plus IV counter (Coulter Electronics, Hialeah, FL); the white blood cell counts were subsequently corrected for the presence of nucleated red blood cells; and scores were generated by a computer program incorporated into the differential station and main frame pathology computer as described previously.[5, 6] The HSS allocates a score of 1 for each of seven abnormalities as shown in Table 1. Scores ≥3 are considered a positive test. The duration of neutropenia was defined as the time period between the initial test and the second of two successive normal tests.[1] Testing on neutropenic infants was performed twice on the first day of life and daily thereafter.

Designation infection and clinical status. Infants were classified in a hierarchal fashion such that they were assigned to the first applicable group or subgroup. Infants were first grouped as infected or noninfected. The infected group was subdivided into two subgroups: sepsis (clinical evidence of sepsis and positive blood or cerebrospinal fluid cultures or postmortem evidence of infection); and probable infection (clinical signs of sepsis, a radiograph consistent with infection, negative cultures, maternal chorioamnionitis treated with antibiotic therapy and in some cases positive urine latex test for Group B *Streptococcus* (GBS). The noninfected group was subdivided into four subgroups according to documented factors associated with neutropenia: possible infection (intrapartum antibiotic therapy, histologic and clinical chorioamnionitis and a healthy infant given antibiotic cover); severe maternal pregnancy-induced hypertension (PIH)[2, 7, 10] (diastolic pressure >110 mm Hg on two occasions >6 hours apart)[11]; birth asphyxia[5, 7] (Apgar score <6 at 5 minutes after birth and/or acidosis); or other, which included the remaining infants.

Statistical analysis. Data were analyzed by Student *t* test, chi square test or Fisher exact test. $P < 0.05$ was considered significant. Sensitivity, specificity and positive and negative predictive values were determined to examine the performance of hematologic findings as predictors of infection.

TABLE 1. Derivation of hematologic scores according to the hematologic scoring system*

	Abnormality	Score
I:T ratio†	↑	1
Total PMN count†‡	↓ or ↑	1
I:M ratio	≥0.3	1
Immature PMN count†	↑	1
Total WBC count	↓ or ↑ (≤5000/mm³ or ≥25 000, 30 000 and 21 000/mm³ at birth, 12–24 hours and Day 2 onward, respectively)	1
Degenerative changes in PMNs§	≥3+ for vacuolization, toxic granulation or Döhle bodies	1
Platelet count	≤150 000/mm³	1

* Taken from Reference 5 with permission from the publisher.
† Normal values as defined by reference ranges of Manroe et al.[7]
‡ If no mature PMNs are seen on blood film, score 2 rather than 1 for abnormal total PMN count.
§ Quantified on 0 to 4+ scale according to classification of Zipursky et al.[8]
PMN(s), polymorphonuclear leukocyte(s); WBC, white blood cell.

RESULTS

Seventeen percent (170 of 1000) of the infants were neutropenic and the frequency was significantly ($P < 0.001$) higher in preterm than term infants (35% (158 of 455) *vs.* 2% (12 of 545)). The study population of 1000 infants was stratified according to the presence or absence of neutropenia to compare the mode of delivery and demographic data. There were no significant differences between the two groups for mode of delivery or sex of the infant. Neutropenia was significantly associated ($P < 0.001$) with prematurity, birth weight <2000 g and multiple gestation (Table 2).

Neutropenia was more commonly of noninfectious than infectious origin 83.5% (142) *vs.* 16.5% (28), $P < 0.001$. The frequency of thrombocytopenia (platelet count <150000/mm³) did not differ significantly between the noninfected and infected neutropenic infants 10% (14 of 142) *vs.* 14% (4 of 28), respectively. Median postnatal age at the time of testing for both the noninfected and infected groups was 1 hour. Table 3 shows the number of infants in each subgroup and the percentage that each comprises of the neutropenic population. Both obstetric (Table 3) and neonatal (Table 4) complications (often multiple) were common in the neutropenic infants. Premature rupture of the membranes and clinical chorioamnionitis were associated ($P < 0.001$) with infection in the neutropenic infants (Table 3). Neutropenia resolved within 24 to 48 hours of birth in 83% (118) of the 142 noninfected infants; in the remainder it persisted for 5 to 9 days. The latter infants with persistent neutropenia included 13 from the PIH subgroup, 4 from the birth asphyxia subgroup and 7 from the subgroup other.

Eighteen infants fulfilled the criteria for sepsis and

TABLE 2. Demographic factors associated with neutropenia in the newborn

	Neutropenic Infants ($N = 170$)		Nonneutropenic Infants ($N = 830$)		P
	n	%	*n*	%	
Prematurity	158	93	287	36	<0.001
Birthweight <2000 g	134	79	151	18	<0.001
Multiple gestation	44	26	50	6	<0.001

TABLE 3. Obstetric complications in 170 infants with neutropenia stratified according to infection and clinical status

Group or Subgroup	N	%	Obstetric Complications (N)				
			PROM	Clinical chorioamnionitis	APH	PIH*	Multiple pregnancies
Infected							
Sepsis	18	11	14	16	1	0	4
Probable infection	10	6	8	9	1	0	0
Noninfected							
Infection possible	15	9	15	15	0	0	0
PIH	37	22	4	1	1	37	2
Birth asphyxia†	11	6	3	1	1	0	4
Other	79	46	38	18	10	0	34
Combined groups	170	100	82	60	14	37	44

* Three with HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome, one with serum lupus erythematosus.
† Maternal respiratory problems ($n = 1$).
PROM, premature rupture of the membranes, APH, antepartum hemorrhage.

TABLE 4. Neonatal complications in 170 infants with neutropenia stratified according to infection and clinical status

Group or Subgroup	N	Neonatal Complications (N)				
		Prematurity	Birth asphyxia	RDS	Retained fetal lung fluid	IVH
Infected						
Sepsis	18	18	6	14	1	4
Probable infection	10	7	0	6	1	0
Noninfected						
Infection possible	15	14	2	12	2	1
PIH*	37	36	6	25	1	0
Birth asphyxia†	11	10	11	0	0	0
Other‡	79	75	0	53	13	4
Combined groups§	170	158	25	110	18	9

* One with RhD) hemolytic disease of the newborn, one with pulmonary hemorrhage, two with intrauterine growth retardation.
† Two with hydrops fetalis (one hemoglobin Bart's hydrops, one of unknown cause).
‡ Four with intrauterine growth retardation.
§ Eighty-nine of 170 (52%) were intubated at birth.
RDS, respiratory distress syndrome; IVH, intraventricular hemorrhage.

10 were classified as probable infection. Within the former subgroup 16 infants had septicemia and 1 developed meningitis; 2 infants had postmortem evidence of pneumonia and positive lung cultures; and 11 infants were transferred to our unit (10 *in utero*, one following delivery). Causative organisms were: GBS ($n = 8$), which included the infant with meningitis; Group A *Streptococcus* ($n = 1$); *Staphylococcus aureus* ($n = 3$); *Haemophilus influenzae* ($n = 1$); *Escherichia coli* ($n = 4$); and *Serratia marcescens* ($n = 1$).

Table 5 shows the performance of the HSS as a predictor of infection in the neutropenic infants. Two of 28 infected infants were not identified by the HSS. Both infants received early antibiotic therapy; one infant died 4 hours after birth before repeat testing was performed; the second had a score of 3 on repeat testing 19 hours after birth. Table 6 details the findings associated with false positive results with the HSS. If infants with possible infection are excluded (i.e. those in whom maternal antibiotic therapy may have influenced clinical and microbiologic findings) the positive predictive value of scores ≥3 was 68%. Repeat testing within 24 hours of birth was performed on 165 neutropenic infants giving a sensitivity and positive predictive value of 100 and 59%, respectively. An elevated I:T ratio, i.e. >0.165 at birth to >0.155 at 24 hours of age, according to the reference ranges of

TABLE 5. Performance of hematologic scores as predictors of infection in 28 infants with sepsis or probable infection from 170 evaluations performed at a median postnatal age of 1 hour (range, birth to 17.5 hours) in 170 neutropenic newborns*

Hematologic Criteria	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative Predictive Value (%)
Scores ≥2	100	59	31	100
Scores ≥3	93	82	50	98
Scores ≥4	50	93	58	90
Scores ≥5	11	99	60	85

* According to the reference ranges of Manroe et al.[7]

TABLE 6. Details of the neutropenic newborns with false positive results (scores ≥3) with the hematologic scoring system

Subgroup	N	Clinical Findings
Infection possible	14	Clinically well
Pregnancy-induced hypertension	3	Maternal HELLP syndrome ($N = 1$)
		Severe IUGR ($N = 2$)
		Leukopenia and thrombocytopenia ($N = 3$)
Birth asphyxia	3	Hydrops fetalis ($N = 2$)
Other	6	Intraventricular hemorrhage and pneumothorax ($N = 1$)
		Retained fetal lung fluid ($N = 3$)
		IUGR with leukopenia and thrombocytopenia ($N = 1$)
		Mild respiratory distress syndrome ($N = 1$)

HELLP, hemolysis, elevated liver enzymes and low platelets; IUGR, intrauterine growth retardation.

Manroe et al.,[7] identified all infected infants but was less predictive (43%) of infection than scores ≥3. The I:T ratios in infected infants ranged from 0.24 to 1.0 (median, 0.4) and in noninfected infants from 0 to 0.87 (median, 0.07).

Antibiotic therapy was given to 59% (100 of 170) of the neutropenic infants. This included all infants with sepsis and with probable and possible infection. Only one infant (who died) received a granulocyte transfusion (and fresh frozen plasma); two (who died) received exchange transfusions (one also had fresh frozen plasma); and a further six (three of whom died) received fresh frozen plasma.

The overall mortality with neutropenia was 15% (26 of 170) with 81% (21) dying within 48 hours of birth and 19% (5) between 5 and 73 days after birth. Mortality was higher in the infected than in the noninfected group (39%, 11 of 28 *vs.* 11%, 15 of 142 ($P < 0.001$). Mortality was highest in the sepsis subgroup (61%, 11 of 18); 9 infants died within 24 hours of birth and 5 within 7 hours of birth. Causative organisms included GBS ($n = 6$), *E. coli* ($n = 4$), and *H. influenzae* ($n = 1$). Mortality was significantly ($P < 0.001$) associated with neutrophil counts ≤500/mm³. The combination of a neutrophil count ≤500/mm³ with a score ≥3 or an elevated I:T ratio identified a poor prognostic group: 67% (8 of 12) and 70% (7 of 10), respectively, with these combinations died, 6 in the infected group.

DISCUSSION

Our findings substantiate a previous report that neutropenia is common in preterm newborns, particularly those with obstetric and neonatal complications.[1] In the present study the majority of infants had neutropenia of noninfectious origin which resolved within 24 to 48 hours, although in 17% of noninfected infants it persisted for 5 to 9 days. A link with PIH, a well-documented association, was found in 22% of all neutropenic newborns.[2, 7, 10] In infants with sepsis GBS was the predominant causative organism, accounting for 44% of all cases. The HSS in conjunction with clinical findings allowed early discrimination between infected and noninfected neutropenic newborns, although two infants were not identified on the initial test. The combination of a neutrophil count ≤500/mm³ and scores ≥3 signified a poor prognostic group. In infected infants mortality was high despite early administration of antibiotics, and adjunctive therapy in some cases.

Our findings substantiate other reports (including unpublished data from our previous study), which indicate that preterm infants have lower neutrophil counts than term infants.[1, 5, 12-14] The lower neutrophil counts found in venous and arterial specimens than in capillary specimens has not been taken into account in the present study.[15] The neutrophil reference ranges of Manroe et al.[7] are now generally acknowledged as the most reliable for interpretation of neutrophil values in the neonate. Previous reports verify their sensitivity in screening for infection.[5, 16] However, the reference ranges were derived from infants of >29 weeks of gestation.[7] Our data suggest that different reference ranges may be required for infants <2000 g.

Previous studies attest to the difficulty of management of sepsis in neutropenic neonates.[3, 4, 17] Christensen et al.[3] found that depletion of the NBMSP was associated with a mortality of almost 90% and showed that survival could be greatly improved by granulocyte transfusions. An I:T ratio >0.8 correlated with NBMSP depletion.[18] Subsequent studies reveal there is great variability in the frequency of NBMSP depletion (range, 3 to 62%)[3, 4, 17, 19-23] and show that mild to moderate degrees of NBMSP depletion are also associated with increased mortality.[20, 23] Quantitation of the NBMSP is recommended to prognosticate the severity of sepsis and the necessity for granulocyte transfusions.[23] However, in a study by Engle et al.,[17] five infants died (median age, 7 hours) before infection was confirmed and bone marrow aspiration was performed. They recommended that bone marrow aspiration should be performed at the time overwhelming sepsis is clinically suspected. Baley et al.[1, 20] found that an elevated I:T ratio was of no value in the prediction of infection and an I:T ratio of >0.8 was not predictive of either NBMSP depletion or outcome. Their study population comprised infants in the first month of life, in contrast to the present study, which focused on the newborn.

In the present study, although it was not statistically significant, the HSS (scores ≥3) was less sensitive, but more predictive of infection, than an elevated I:T ratio. Therapy was given at the discretion of the attending physician and the NBMSP, the major prognostic criterion, was not assessed. Only 1 of 11 infants with sepsis who died had an I:T >0.8. The data indicate that this finding has limited practical value as a prognostic indicator. We observed intracellular organisms in the direct blood film of one infant who died, a finding shown in previous studies to indicate fulminant infections.[24, 25]

The CBC is readily available in most institutions and scoring adds only 5 seconds to the performance of the CBC.[5] In contrast other screening tests for neonatal sepsis comprise a battery of four or five tests including the CBC, C-reactive protein, haptoglobin, micro-erythrocyte sedimentation rate, nitroblue tetrazolium test, fibronectin and acridine orange leukocyte cytospin test, which are not usually available on a 24-hour basis.[26-28] Recent studies suggest that elevated elastase alpha-1-proteinase inhibitor levels may also be useful in this setting.[29, 30] In a previous study, on the initial test the HSS identified 98% of infants with sepsis or probable infection from 298 evaluations in the first month of life.[5] A recent report found a

sensitivity of only 67% on the initial test in infants with early onset GBS sepsis but 100% on the repeat test performed within 12 to 24 hours of birth.[31] A single time frame was used for interpretation of lower and upper limits for neutrophil counts. This may have contributed to the lower sensitivity, inasmuch as the infants were tested between 1 and 7 hours after birth when rapid changes in neutrophil values occur.[7] Alternatively the findings reflect a delay in hematologic response, which may be as long as 4 hours in infants with GBS.[18, 32]

We conclude that the HSS or I:T ratio in conjunction with clinical findings is valuable in the early identification of sepsis in neutropenic newborns and could be applied to the development of strategies for early management of these infants. Repeat testing is recommended to identify infants who have a delayed hematologic response.[32] In the neutropenic newborn with clinical suspicion of overwhelming sepsis, scores ≥3 or an elevated I:T ratio indicate a high likelihood of infection. These findings in combination with a neutrophil count ≤500/mm^3 provide useful prognostic information for newborns at high risk of mortality for whom novel interventional therapy may be appropriate. We have reviewed previously described prognostic indicators and demonstrated the utility of combining them to enhance the overall identification of a poor prognostic group. These findings could be applied to the early identification of candidates for granulocyte transfusions or other experimental treatments including immunomodulation such as intravenous immunoglobulin or cytokine therapy.

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