Reactive Hyperemia and Interleukin 6, Interleukin 8, and Tumor Necrosis Factor-α in the Diagnosis of Early-Onset Neonatal Sepsis

Helena Martin, MD, PhD*; Bodil Olander, MD‡; and Mikael Norman, MD, PhD*

ABSTRACT. *Objective.* **To evaluate the diagnostic value of peripheral circulatory reactive hyperemia and serum levels of interleukin-6 (IL-6), IL-8, and tumor necrosis factor-α (TNF-α) in early-onset neonatal sepsis.**

Methods. **Reactive hyperemia in the dorsal hand and serum levels of IL-6, IL-8, and TNF-α were studied in newborn infants ($n = 32$; gestational age 39 ± 3 weeks) who had been admitted to the neonatal unit because of suspected sepsis <48 hours after birth. On admission, reactive hyperemia after a standardized arterial occlusion was measured with laser Doppler technique, and blood samples were taken for cytokine analyses. On the basis of predetermined criteria, the infants subsequently were classified as septic ($n = 12$) or not ($n = 20$).**

Results. **The degree of reactive hyperemia was higher in the group with sepsis (median + 170% perfusion increase) than in that without (+37%). On admission, serum levels of IL-6, IL-8, and TNF-α all were higher in septic (median values: 1620, 331, and 22 pg/mL, respectively) than in nonseptic neonates (median values: 42, 63, and 13 pg/mL, respectively). In the group with sepsis, the degree of reactive hyperemia correlated to log IL-6 ($r = 0.80$) and log IL-8 values ($r = 0.71$).**

Conclusion. **Newborn infants with septicemia have increased reactive hyperemia and elevated cytokine levels very early in their disease. Reactive hyperemia in skin can be analyzed at the bedside and noninvasively and therefore may serve as an additional diagnostic tool in neonatal sepsis.** *Pediatrics* **2001;108(4). URL: http://www.pediatrics.org/cgi/content/full/108/4/e61;** *neonatal sepsis, newborn infant, interleukin-6, interleukin-8, TNF-α, reactive hyperemia, diagnostic marker.*

ABBREVIATIONS. CRP, C-reactive protein; WBC, white blood cell count; IL-6, interleukin 6; TNF-α, tumor necrosis factor-α; IL-8, interleukin 8; LD, laser Doppler; PPV, positive predictive value; NPV, negative predictive value; ROC, receiver-operating characteristic curve; RDS, respiratory distress syndrome; GBS, group B streptococci.

Serious infections are still causing significant morbidity and mortality among newly born infants. Immediately after birth, the clinical picture of neonatal sepsis is difficult to distinguish from more benign conditions. Rapid and reliable diagnostic tools are not yet available at the bedside. Because a delay in instituting antibiotic therapy may have adverse consequences in cases of true neonatal sepsis, in many cases decisions to treat are based on risk factors and nonspecific signs and symptoms.

Experienced neonatologists and nurses recognize that in infants with sepsis, a poor peripheral circulation with a gray skin color often precedes more alarming symptoms, such as arterial hypotension and circulatory failure. Specific deviations in peripheral vascular reactivity have been found in late neonatal sepsis,[1] even before traditional markers, such as C-reactive protein (CRP) elevation and changes in white blood cell count (WBC) in peripheral blood, indicate serious infection. The advantages of peripheral circulatory measurements as diagnostic markers are that 1) they can be done rapidly and noninvasively, 2) the measurements are reproducible shortly after birth, and 3) the result of the test is available immediately.[2] However, before these observations can become useful in clinical work, they need to be confirmed and validated against other diagnostic markers of neonatal sepsis.

Cytokines, produced by monocytes, macrophages, and endothelial cells in response to infectious stimuli are important proinflammatory mediators in the early phases of the sepsis syndrome. Elevated serum levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and, in recent years, interleukin-8 (IL-8) have been found in both neonatal and adult sepsis.[3–6] Several studies have evaluated the role of cytokine determinations as early diagnostic markers in neonatal sepsis.[7–13] Although promising data have been published, problems with invasiveness, response time, and specificity remain to be solved.[7,8,14–17]

In sepsis, cytokines are involved in activating vascular and endothelial defense mechanisms that may cause changes in perfusion and vascular resistance in the microcirculation.[18,19] Accordingly, it is possible that cytokine activation is reflected in vascular reactivity. This study was conducted to evaluate the diagnostic use of a vascular reactivity test as compared with that of circulating cytokine levels in infants with suspected sepsis.

METHODS

Study Population

We studied 32 consecutive infants who were admitted to our neonatal unit because of suspected sepsis <48 hours after birth, all of whom had fulfilled previously used inclusion criteria[9,20]: 1) at least 1 risk factor for infection; 2) signs of respiratory or circulatory dysfunction (tachypnea >60 bpm, recurrent apnea >20 seconds, tachycardia >160 bpm, or bradycardia <100 bpm); and 3) at least

1 of the following symptoms: feeding intolerance, lethargy, irritability, temperature instability, or jaundice. The risk factors for early infection included rupture of membranes >24 hours, maternal body temperature of >38°C, chorioamnionitis, maternal colonization with group B streptococci, or preterm delivery. Infants who were >48 hours old at onset of suspected sepsis, unstable children with respiratory and/or circulatory failure, and infants with neonatal asphyxia (Apgar scores <7 at 5 minutes) or congenital malformations were excluded.

Parental informed consent was obtained for every patient before admission to the study. The protocol was approved by the Ethics Committee at Karolinska Hospital.

Protocol

On admission, skin perfusion was measured, followed by blood sampling for cytokine and CRP analyses, peripheral blood count, and blood glucose and blood gas values. Cultures from blood and upper airways were obtained from all infants, and spinal fluid cultures were done when clinically indicated. Intravenous antibiotic treatment was started immediately thereafter. Chest radiographs were taken for infants with signs of respiratory dysfunction. Additional data recorded for study infants included gender, birth weight, gestational and postnatal ages, mode of delivery, Apgar scores, heart and respiratory rates, blood pressure, rectal temperature, oxygen requirements, and O_2 saturation. A second blood sample for analyses of cytokines, CRP, and peripheral blood count was obtained 24 hours after the first sample.

Skin Perfusion Measurements

A laser Doppler (LD) instrument (Periflux PF 2B; Perimed AB, Järfälla, Sweden) was used to measure skin perfusion in the left dorsal hand skin. The LD signal is proportional to the number and velocity of moving blood cells in illuminated (wavelength 633 nm) superficial microvessels in a skin area of approximately 1 cm² (integrating probe PF 313, Perimed AB). The LD output is semiquantitative and expressed in perfusion units of output voltage (1 PU = 10 mV).[21,22] The mean skin perfusion was measured for at least 2 minutes, after which arterial occlusion for 1 minute was produced by inflating a pneumatic wrist cuff to a suprasystolic pressure. The postocclusive reactive hyperemia was evaluated in terms of peak perfusion, time-to-peak perfusion after cuff release, and relative perfusion change (peak/basal ratio, %). The complete recording sequence was performed twice, and data are presented as mean values. Only sequences that were free from movement artifacts were analyzed.

Cytokine Determinations

Blood samples for cytokine and CRP determinations were centrifuged within 30 minutes of collection, and sera were transferred to plastic tubes. Sera then were stored at −70°C pending simultaneous assay at the end of the study. The serum TNF-α, IL-6, IL-8, and CRP levels were measured with a chemiluminescence immunoassay (Immulite; Diagnostic Products Corporation, Los Angeles, CA). According to the manufacturer, the detection limits of the assays for IL-6 was 5.0 pg/mL, for IL-8 was 2.0 pg/mL, for TNF-α was 1.7 pg/mL, and for CRP was 0.1 mg/L.

Statistical Analysis

Values are given as means ± 1 SD, median (range), or as the number of subjects and proportions. The Student t test was used for group comparisons of normally distributed variables, and the Mann-Whitney U test and Wilcoxon signed-rank test were used for comparisons of variables with skewed distribution. The χ^2 test was used to compare proportions. Correlation coefficients were used to describe associations between variables, and multiple regression analysis was used to detect any relationships between the variables. $P < .05$ was considered significant.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated to analyze IL-6, IL-8, TNF-α, CRP, and reactive hyperemia as predictors of neonatal sepsis. The receiver operator characteristic (ROC) method was used to determine the best possible cutoff values; the curves were obtained by plotting sensitivity on the y axis against the false-positive rate (1 − specificity) on the x axis for all possible cutoff values of the tests.

RESULTS

Classification and Basic Characteristics

At discharge from the hospital, the 32 infants received a final diagnosis of septic or not. Twelve subsequently were classified as septic, whereas the remaining 20 infants were classified as nonseptic. Those assigned to the sepsis group had a positive blood and/or spinal fluid culture or all of the following predetermined criteria: 1) CRP >50 on admission and/or 24 hours (ie, above the level reported in healthy newborn infants immediately after birth),[23] 2) WBC less than 9×10^9 or more than 30×10^9 on admission and/or 24 hours, and 3) at least 1 of the following symptoms in the sepsis syndrome[20]: oliguria, metabolic acidosis, or hypoxemia.

The final diagnoses in nonseptic infants were transient tachypnea of the newborn ($n = 12$), minimal respiratory disease ($n = 4$), persistent pulmonary hypertension of the newborn ($n = 1$), pneumothorax ($n = 1$), neonatal hyperbilirubinemia ($n = 1$), and anemia of the newborn ($n = 1$). None of the infants included had respiratory distress syndrome (RDS).

The mean gestational age was 39 ± 2 weeks in the sepsis group and 39 ± 3 weeks in the no sepsis group ($P = .95$), and the mean postnatal age did not differ between the groups (11 ± 6 vs 12 ± 8 hours; $P = .70$). The distributions of preterm newborns (<37 weeks of gestational age) were similar in the 2 groups (3 of 12 in the sepsis group and 5 of 20 in the no sepsis group). There were no differences in gender, birth weight, Apgar score at 5 minutes, or mode of delivery between the groups. The frequency of antenatal maternal antibiotic treatment (4 of 12 in the sepsis group and 6 of 20 in the no sepsis group) and prolonged rupture of the membranes (>24 hours) were similar in both groups (7 of 12 in the sepsis group and 12 of 20 in the no sepsis group).

At study entry, we found no differences in body or hand skin temperatures, mean arterial blood pressure, respiratory and heart rates, or oxygen requirement between the 2 groups (Table 1). On admission, CRP values did not differ between the sepsis group (median: 19 mg/L) and the no sepsis group (median: 7.3 mg/L; $P = .67$), whereas 24 hours after inclusion, the CRP values were significantly higher in the sepsis group compared with the no sepsis group (median: 92 vs 17.5 mg/L; $P < .001$). Total WBC at inclusion was lower in the sepsis group (median: 5.9×10^9/L) than in the no sepsis group (17.4×10^9/L; $P <$

TABLE 1. Clinical Findings in Newborn Infants Admitted Because of Suspected Sepsis and 24 Hours Later

On Admission	Sepsis ($n = 12$)	No Sepsis ($n = 20$)	P Value
Body temperature (°C)	37.1 ± 0.5	37.0 ± 0.5	.63
Hand skin temperature (°C)	33.2 ± 1.1	33.1 ± 1.4	.88
MAP (mm Hg)	44 ± 4	48 ± 8	.17
Respiratory rate (min⁻¹)	79 ± 19	74 ± 20	.45
Heart rate (min⁻¹)	132 ± 17	130 ± 17	.73
FIO₂ (%)	21 (21–95)	21 (21–97)	.99

Data given as mean ± 1 SD or median (range). MAP indicates mean arterial blood pressure; FIO₂, fraction of inspired oxygen.

.01), and neutropenia (neutrophils $<3 \times 10^9$/L) was seen in 4 of 12 in the sepsis group but in 0 of 20 in the no sepsis group ($P < .01$). Leukocytosis (WBC $>30 \times 10^9$/L) was found in 1 infant in each group. After 24 hours, we found no differences in WBC or neutrophils between the groups. The red blood cell and platelet counts and blood glucose and blood gas values were similar in the 2 groups.

Two infants (17%) in the sepsis group had a culture-proven diagnosis (group B streptococci [GBS]), 1 of which had meningitis. An additional 60% among the septic infants had bacteria isolated from the upper airways (5 GBS and 1 *Escherichia coli*). Besides from blood, 80% of infants (16 of 20) in the no sepsis group showed negative cultures from nasopharynx or maternal cervix. In the remaining 4 nonseptic infants, a positive upper airway culture was found (3 GBS and 1 *Haemophilus influenzae*).

Two children in the sepsis group needed mechanical ventilation during the course of their infection, no infant in the no sepsis group did. No infant died, and there were no cases of intracerebral hemorrhages.

Skin Perfusion

On admission, the relative perfusion increase during reactive hyperemia was greater in the sepsis group (median: 170%) than in the no sepsis group (37%; $P < .001$; Table 2, Fig 1). This finding was attributed to lower basal perfusion values in the sepsis group, whereas postocclusive peak perfusion values were similar in the 2 groups. Postocclusive time-to-peak perfusion was longer in the sepsis group (median: 6.2 seconds) than in the no sepsis group (4.2 seconds; $P < 001$; Table 2).

Cytokine Serum Levels

Newborns in the sepsis group had higher serum levels of all 3 cytokines. At study entry, the median value of IL-6 was 1617 pg/mL in the sepsis group compared with 42 pg/mL in the no sepsis group ($P < .001$). The median serum level of IL-8 was 331 pg/mL in the sepsis group and 63 pg/mL in the no sepsis group ($P < .01$). TNF-α levels also were higher in the sepsis group (21.7 pg/mL) than in the no sepsis group (13.3 pg/mL; $P < .05$; Fig 1).

At 24 hours of follow-up, IL-6 values still were higher in septic than in nonseptic infants (median: 40 vs 9.8 pg/mL; $P < .01$). There were no significant differences in serum levels of IL-8 (median: 70 vs 43 pg/mL) and TNF-α (median: 12.6 vs 10.6 pg/mL) between the groups 24 hours after inclusion.

TABLE 2. Reactive Hyperemia in Newborn Infants With Suspected Early-Onset Sepsis

	Sepsis ($n = 12$)	No Sepsis ($n = 20$)	P Value
Reactive hyperemia (%)	170 (78–396)	37 (0–122)	<.001
Basal perfusion (PU)	6.0 (2.0–12)	12 (3.2–23)	<.01
Peak perfusion (PU)	16 (9.0–24)	16 (4.3–26)	.55
Time-to-peak perfusion(s)	6.2 (5.0–11)	4.2 (2.5–7.0)	<.001

Data given as median (range). PU indicates perfusion units.

In the sepsis group, a correlation was found between log IL-6 and log IL-8 levels ($r = 0.89$, $P < .001$). No other correlations were found between the cytokines studied.

Relation Between Skin Perfusion and Cytokine Serum Levels

In the sepsis group, the degree of reactive hyperemia correlated to log IL-6 ($r = 0.80$, $P < .001$) and log IL-8 values ($r = 0.71$, $P < .001$). Variations in basal skin perfusion correlated weakly to log IL-6 ($r = 0.65$, $P < .001$) and log IL-8 values ($r = 0.39$, $P < .05$). No other correlations were found between circulatory measurements and cytokines.

Relation Among Cytokine Serum Levels, WBC, and CRP

In the group with sepsis, a negative correlation was found between WBC and log IL-6 levels on admission ($r = -0.57$, $P < .05$). The values of CRP at 24 hours after admission correlated to log IL-6 ($r = 0.65$, $P < .05$) and log IL-8 values ($r = 0.77$, $P < .01$) obtained at study entry in the sepsis group. No other correlations were found among cytokine levels, WBC, and CRP in the sepsis group. In the no sepsis group, no correlations were found among cytokine levels, WBC, and CRP.

Evaluation of IL-6, IL-8, TNF-α, and Reactive Hyperemia as Diagnostic Tests

The ideal cutoff point for IL-6, IL-8, and TNF-α serum concentrations is the point that allows detection of as many true-positive findings as possible (high sensitivity) and with few false-positive results (high specificity). In our study, the optimal cutoff point obtained with the ROC method was 160 pg/mL for IL-6, 70 pg/mL for IL-8, and 20 pg/mL for TNF-α (Table 3). The optimal cutoff point for peripheral circulatory measurements was a reactive hyperemia of 75% or more (Table 3). At these cutoff points, the PPV for early-onset neonatal sepsis for IL-6 was 67%, for IL-8 was 65%, for TNF-α was 73%, and for reactive hyperemia was 86%. The NPV for IL-6 was 100%, for IL-8 was 93%, for TNF-α was 81%, and for reactive hyperemia was 100%. Combining reactive hyperemia with 1 or more cytokines studied did not improve sensitivity, specificity, or the predictive values for neonatal sepsis.

DISCUSSION

In neonatal sepsis, the need for an early diagnosis and speedy, appropriate antibiotic treatment must be weighed against the aim to avoid unnecessary antibiotics and hospitalization of newborn infants. At early onset in particular, the clinical symptoms are nonspecific and difficult to differentiate from transient problems with extrauterine adaptation. This study showed that the degree of reactive hyperemia in skin may be helpful as a diagnostic marker in newborn infants with early-onset neonatal sepsis.

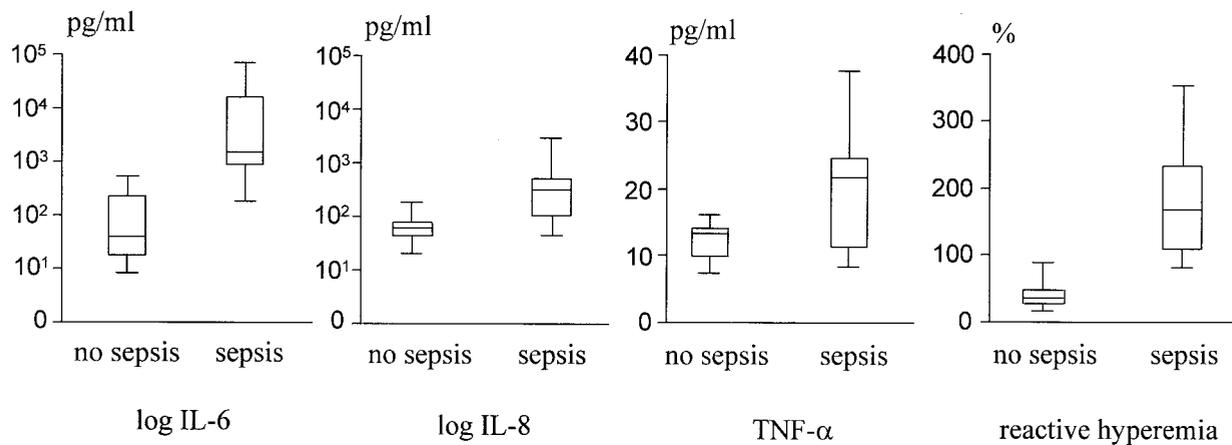Although cytokine analyses are far from being diagnostic for bacterial sepsis, serum levels of IL-6,

Fig 1. Serum levels of IL-6, IL-8, and TNF-α and the degree of postocclusive reactive hyperemia in newborn infants admitted to the neonatal unit because of suspected sepsis. On the basis of predetermined criteria, the infants subsequently were classified as septic ($n = 12$) or not ($n = 20$).

TABLE 3. Sensitivity, Specificity, and Predictive Values of IL-6, IL-8, TNF-α, and Reactive Hyperemia in Early-Onset Neonatal Sepsis

	IL-6 (>160 pg/mL)	IL-8 (>70 pg/mL)	TNF-α (>20 pg/mL)	Reactive Hyperemia (>75%)
Sensitivity (%)	100	92	67	100
Specificity (%)	70	70	85	90
PPV (%)	67	65	73	86
NPV (%)	100	93	81	100

Cutoff values are given in parentheses.

IL-8, and TNF-α were suggested previously as early markers of neonatal sepsis. In our study, the sensitivity and specificity of reactive hyperemia were equal to or even higher than those of IL-6, IL-8, and TNF-α found by us and others.[6–8]

Similar to our findings, reactive hyperemia has been reported to discriminate late-onset neonatal sepsis as well, before other laboratory tests could.[1] In the study of Pöschl et al[1], LD skin perfusion measurements were performed at the back, thigh, and heel. Irrespective of skin region, a deviating reactive hyperemia was found in neonates with sepsis. Taken together, these studies suggest that systemic vascular changes are induced rapidly in sepsis and that early systemic alteration can be detected at different local, skin microvascular beds.

The aim of the present study was to distinguish between infants with and without sepsis, all having nonspecific symptoms on admission. We previously studied healthy control subjects, and the degree of reactive hyperemia among subjects without sepsis did not differ from that found in age-matched, healthy newborn infants.[2]

Our findings point to the possibility that a decreased basal skin blood flow and a longer time to peak hyperemia explain the elevated reactive hyperemia in septic infants. Because of the semiquantitative nature of LD perfusion measurements, basal skin blood flow data are not completely reliable in interindividual comparisons. The predictive values for sepsis using time to peak was lower (PPV: 77%; NPV: 89%) than for reactive hyperemia, which limits the use of the former variable as a diagnostic marker.

Hemodynamic changes during sepsis involve regional differences in blood flow mediated by early vasoconstriction and, in later stages of the disease, general vasodilation and shock.[24–26] The microcirculation is particularly important in the vascular response to sepsis because microvascular disturbances affect blood pressure and tissue perfusion. Our findings suggest early peripheral vasoconstriction in sepsis. Besides vasoconstriction, the accumulation and adherence of leukocytes to the vascular wall seen in sepsis may add to the impaired microcirculation.[27–29] Possible mediators of these early microvascular changes include cytokines, which have been reported to increase vascular tone,[18] and endothelial expression of adhesion molecules in early stages of sepsis.[30] In later stages of the disease, the microvascular tone and reactivity, as well as their correlation to cytokine levels, may well differ from the findings in our study. Absent reactive hyperemia has been found in adult patients in septic shock.[31,32]

Other clinical methods of studying skin blood flow or skin vascular reactivity in neonates include transcutaneous P_{O_2} measurements and capillary refill time. Neither of the methods has been evaluated in neonatal sepsis. In comparison with the LD method, an advantage of the transcutaneous P_{O_2} method is that many neonatal units have this instrument and are familiar with its use. It has been evaluated for postocclusive reactive hyperemia at 37°C of electrode temperature and shown to have some correlation with LD measurements of skin perfusion in healthy children and adults.[33–35] Capillary refill time can be used clinically, but marked interobserver vari-

ability has been reported even with experienced observers.[36–38] It was assessed recently in pediatric intensive care patients but showed only a weak correlation to indicators of hemodynamic status.[39] Additional studies are needed to pursue its usefulness and relation to measurements of reactive hyperemia in suspected sepsis.

Because of frequent use of intrapartal antibiotics to the mother and only 1 blood culture obtained from the infant, we found few infants with positive blood/spinal fluid cultures (17% in the sepsis group). A similarly small proportion of culture-proven infection also was found in other recent and larger studies of neonatal sepsis,[6,13] and this problem may limit the conclusions that can be drawn from the present data. However, the strict diagnostic criteria for clinical sepsis used in this study ensured that the infants assigned to this group were diagnosed correctly. The reactive hyperemia and cytokine levels in the 2 infants with culture-proven sepsis did not differ from the data found in infants with clinical sepsis.

Three nonseptic neonates had CRP values above 50 at study entry ($n = 2$) or 24 hours later ($n = 1$). They were deemed not to have sepsis because they did not fulfill the other diagnostic criteria for clinical sepsis. In addition, upper airway cultures were negative, and these infants were discharged from the neonatal unit within 3 days. All had a final diagnosis of transient tachypnea, complicated in 1 case by a small pneumothorax.

Although not an exclusion criteria, our sample did not include any infant with RDS. This is another group of neonates who should be studied in the future, as distinguishing clinically between RDS and GBS sepsis may be very difficult.[14]

CONCLUSION

Newborn infants with early-onset neonatal sepsis showed increased postocclusive reactive hyperemia and elevated cytokine levels even on admission to the neonatal unit. We suggest that reactive hyperemia, a fast, noninvasive skin test, could be used as an additional diagnostic marker in neonatal sepsis.

REFERENCES

1. Pöschl JM, Weiss T, Fallahi F, Linderkamp O. Reactive hyperemia of skin microcirculation in septic neonates. *Acta Paediatr*. 1994;83:808–811
2. Martin H, Norman M. Skin microcirculation before and after local warming in infants delivered vaginally or by caesarean section. *Acta Paediatr*. 1997;86:261–267
3. Hack CE, De Groot ER, Felt-Bersma RJ, et al. Increased plasma levels of interleukin-6 in sepsis. *Blood*. 1989;74:1704–1710
4. Hack CE, Hart M, van Schijndel RJ, et al. Interleukin-8 in sepsis: relation to shock and inflammatory mediators. *Infect Immun*. 1992;60:2835–2842
5. de Bont ES, Martens A, van Raan J, et al. Tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-6 plasma levels in neonatal sepsis. *Pediatr Res*. 1993;33:380–383
6. Franz AR, Kron M, Pohlandt F, Steinbach G. Comparison of procalcitonin with interleukin 8, C-reactive protein and differential white blood cell count for the early diagnosis of bacterial infections in newborn infants. *Pediatr Infect Dis J*. 1999;18:666–671
7. de Bont ES, Martens A, van Raan J, et al. Diagnostic value of plasma levels of tumor necrosis factor alpha (TNF alpha) and interleukin-6 (IL-6) in newborns with sepsis. *Acta Paediatr*. 1994;83:696–699
8. Buck C, Bundschu J, Gallati H, Bartmann P, Pohlandt F. Interleukin-6: a sensitive parameter for the early diagnosis of neonatal bacterial infection. *Pediatrics*. 1994;93:54–58
9. Harris MC, Costarino AT Jr, Sullivan JS, et al. Cytokine elevations in critically ill infants with sepsis and necrotizing enterocolitis. *J Pediatr*. 1994;124:105–111
10. Doellner H, Arntzen KJ, Haereid PE, Aag S, Austgulen R. Interleukin-6 concentrations in neonates evaluated for sepsis. *J Pediatr*. 1998;132:295–299
11. Kuster H, Weiss M, Willeitner AE, et al. Interleukin-1 receptor antagonist and interleukin-6 for early diagnosis of neonatal sepsis 2 days before clinical manifestation. *Lancet*. 1998;352:1271–1277
12. Franz AR, Steinbach G, Kron M, Pohlandt F. Reduction of unnecessary antibiotic therapy in newborn infants using interleukin-8 and C-reactive protein as markers of bacterial infections. *Pediatrics*. 1999;104:447–453
13. Berner R, Niemeyer CM, Leititis JU, et al. Plasma levels and gene expression of granulocyte colony-stimulating factor, tumor necrosis factor-alpha, interleukin (IL)-1beta, IL-6, IL-8, and soluble intercellular adhesion molecule-1 in neonatal early onset sepsis. *Pediatr Res*. 1998;44:469–477
14. Kallman J, Ekholm L, Eriksson M, Malmström B, Schollin J. Contribution of interleukin-6 in distinguishing between mild respiratory disease and neonatal sepsis in the newborn infant. *Acta Paediatr*. 1999;88:880–884
15. Panero A, Pacifico L, Rossi N, Mancuso G, Stegagno M, Chiesa C. Interleukin 6 in neonates with early and late onset infection. *Pediatr Infect Dis J*. 1997;16:370–375
16. Atici A, Satar M, Cetiner S, Yaman A. Serum tumor necrosis factor-alpha in neonatal sepsis. *Am J Perinatol*. 1997;14:401–404
17. Silveira RC, Procianoy RS. Evaluation of interleukin-6, tumour necrosis factor-alpha and interleukin-1beta for early diagnosis of neonatal sepsis. *Acta Paediatr*. 1999;88:647–650
18. Baudry N, Rasetti C, Vicaut E. Differences between cytokine effects in the microcirculation of the rat. *Am J Physiol*. 1996;271:H1186–H1192
19. Minghini A, Britt LD, Hill MA. Interleukin-1 and interleukin-6 mediated skeletal muscle arteriolar vasodilation: in vitro versus in vivo studies. *Shock*. 1998;9:210–215
20. Saez-Llorens X, McCracken GH Jr. Sepsis syndrome and septic shock in pediatrics: current concepts of terminology, pathophysiology, and management. *J Pediatr*. 1993;123:497–508
21. Nilsson G, Tenland T, Öberg P. Evaluation of a laser Doppler flowmeter for measurement of tissue blood flow. *IEEE Trans Biomed Eng BME 27*. 1980;10:597–604
22. Smits G, Roman R, Lombard J. Evaluation of laser Doppler flowmetry as a measure of tissue blood flow. *J Appl Physiol*. 1986;61:666–672
23. Marchini G, Berggren V, Djilali-Merzoug R, Hansson L-O. The birth process initiates an acute phase reaction in the fetus-newborn infant. *Acta Paediatr*. 2000;89:1082–1086
24. Thijs L, Schneider A, Groeneveld A. The haemodynamics in septic shock. *Intensive Care Med*. 1990;16:S182–S186
25. Baker CH, Sutton ET. Arteriolar endothelium-dependent vasodilation occurs during endotoxin shock. *Am J Physiol*. 1993;264:H1118–H1123
26. Tucker JJ, Wilson MA, Wead WB, Garrison RN. Microvascular endothelial cell control of peripheral vascular resistance during sepsis. *Arch Surg*. 1998;133:1335–1342
27. Harris NR, Russell JM, Granger DN. Mediators of endotoxin-induced leukocyte adhesion in mesenteric postcapillary venules. *Circ Shock*. 1994;43:155–160
28. Piper RD, Pitt-Hyde M, Li F, Sibbald WJ, Potter RF. Microcirculatory changes in rat skeletal muscle in sepsis. *Am J Respir Crit Care Med*. 1996;154:931–937
29. Lam C, Tyml K, Martin C, Sibbald W. Microvascular perfusion is impaired in a rat model of normotensive sepsis. *J Clin Invest*. 1994;94:2077–2083
30. Meager A. Cytokine regulation of cellular adhesion molecule expression in inflammation. *Cytokine Growth Factor Rev*. 1999;10:27–39
31. Hartl WH, Gunther B, Inthorn D, Heberer G. Reactive hyperemia in patients with septic conditions. *Surgery*. 1988;103:440–444
32. Astiz ME, DeGent GE, Lin RY, Rackow EC. Microvascular function and rheologic changes in hyperdynamic sepsis. *Crit Care Med*. 1995;23:265–271
33. Ewald U, Huch A, Huch R, Rooth G. Skin reactive hyperemia recorded by a combined TcPO2 and laser Doppler sensor. *Adv Exp Med Biol*. 1987;220:231–234

34. Franzeck U, Huch A, Zimmermann A, et al. A triple electrode for simultaneous investigations of transcutaneous oxygen tension, laser Doppler flowmetry and dynamic fluorescence video microscopy. *Int J Microcirc Clin Exp*. 1994;14:269–273

35. Beinder E, Trojan A, Bucher HU, Huch A, Huch R. Control of skin blood flow in pre- and full-term infants. *Biol Neonate*. 1994;65:7–15

36. Schriger D, Baraff L. Defining normal capillary refill: variation with age, sex and temperature. *Ann Emerg Med*. 1988;17:932–935

37. Gorelick M, Shaw K, Baker M. Effect of ambient temperature on capillary refill in healthy children. *Pediatrics*. 1993;92:699–702

38. Raju N, Maisels M, Kring E, Schwarz-Warner L. Capillary refill time in the hands and feet of normal newborn infants. *Clin Pediatr*. 1999;38:139–144

39. Tibby SM, Hatherill M, Murdoch IA. Capillary refill and core-peripheral temperature gap as indicators of haemodynamic status in paediatric intensive care patients. *Arch Dis Child*. 1999;80:163–166

Reactive Hyperemia and Interleukin 6, Interleukin 8, and Tumor Necrosis Factor- α in the Diagnosis of Early-Onset Neonatal Sepsis

Helena Martin, Bodil Olander and Mikael Norman

Updated Information & Services	including high resolution figures, can be found at: http://pediatrics.aappublications.org/content/108/4/e61
References	This article cites 39 articles, 6 of which you can access for free at: http://pediatrics.aappublications.org/content/108/4/e61#BIBL
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): **Infectious Disease** http://www.aappublications.org/cgi/collection/infectious_diseases_sub
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.aappublications.org/site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: http://www.aappublications.org/site/misc/reprints.xhtml

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

PEDIATRICS

Reactive Hyperemia and Interleukin 6, Interleukin 8, and Tumor Necrosis Factor- α in the Diagnosis of Early-Onset Neonatal Sepsis

Helena Martin, Bodil Olander and Mikael Norman

The online version of this article, along with updated information and services, is located on the World Wide Web at:

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®