Serial Serum C-Reactive Protein Levels in the Diagnosis of Neonatal Infection

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ABSTRACT. *Objective.* **To evaluate serial serum C-reactive protein (CRP) levels for diagnosis of neonatal infection.**

Setting. **A regional intensive care nursery and two community intensive care nurseries.**

Methods. **All neonates treated for suspected bacterial infection were prospectively evaluated using a standardized clinical pathway. Infants were categorized as having proven sepsis (bacteria isolated from blood, cerebrospinal fluid, or urine culture), probable sepsis (clinical and laboratory findings consistent with bacterial infection without a positive culture), or no sepsis (findings not consistent with sepsis), without consideration of CRP levels. Infants whose blood cultures yielded skin flora but who demonstrated no other signs of bacterial infection were not considered to have sepsis. CRP levels were determined at the initial evaluation and on each of the next two mornings. Sensitivity, specificity, predictive values, and likelihood ratios were calculated for the first (CRP #1), second (CRP #2), higher of the second and third (CRP #2 and #3), or highest of all three CRP levels (CRP × 3).**

Results. **Sepsis was suspected within the first 3 days after birth in 1002 infants (early-onset) and on 184 occasions in 134 older infants (late-onset). There were 20 early-onset and 53 late-onset episodes of proven sepsis, and 74 early-onset and 12 late-onset episodes of probable sepsis. CRP #1 had sensitivities of 39.4% and 64.6% for proven or probable sepsis and 35.0% and 61.5% for proven sepsis in early-onset and late-onset episodes, respectively. CRP levels on the morning after the initial evaluation (CRP #2) had higher sensitivities (92.9% and 85.0% for proven or probable sepsis and 78.9% and 84.4% for proven sepsis in early-onset and late-onset episodes, respectively), and normal results were associated with lower likelihoods of infection (likelihood ratios for normal results of 0.10 and 0.19 for proven or probable sepsis and 0.27 and 0.21 for proven sepsis, in early-onset and late-onset episodes, respectively). Three serial serum CRP levels had sensitivities of 97.8% and 98.1% for proven or probable sepsis and 88.9% and 97.5% for proven sepsis in early-onset and late-onset episodes, respectively. The negative predictive values for CRP × 3 were 99.7% and 98.7% for both proven or probable sepsis and for proven sepsis in early-onset and late-onset episodes, respectively. A CRP level obtained at the time of the initial evaluation can be omitted without significant loss of sensitivity or negative predictive value: the sensitivities of CRP #2 and #3 were 97.6% and 94.4% for proven or probable sepsis and 88.9% and 96.4% for proven sepsis in early-onset and late-onset episodes, respectively; negative predictive values were 99.7% both for proven and for proven or probable early-onset sepsis, 97.6% for proven or probable late-onset infection, and 98.8% for proven late-onset infection. Serial normal CRP levels were associated with a markedly reduced likelihood of infection as compared with that in the entire population before testing, with likelihood ratios ranging from 0.03 to 0.16 for the various subgroups. Maximum CRP levels >3 mg/dL had positive predictive values >20% for proven or probable early-onset infections and for proven or probable and proven late-onset infections, but only those >6 mg/dL had such a high positive predictive value for proven early-onset sepsis.**

Conclusions. **Serial CRP levels are useful in the diagnostic evaluation of neonates with suspected infection. Two CRP levels <1 mg/dL obtained 24 hours apart, 8 to 48 hours after presentation, indicate that bacterial infection is unlikely. The sensitivity of a normal CRP at the initial evaluation is not sufficient to justify withholding antibiotic therapy. The positive predictive value of elevated CRP levels is low, especially for culture-proven early-onset infections.** *Pediatrics* **1998;102(4). URL: http://www.pediatrics.org/cgi/content/full/102/4/e41;** ***bacterial infection, C-reactive protein, human, infant-newborn, sensitivity and specificity, acute-phase proteins, neonatal sepsis.***

ABBREVIATIONS. CSF, cerebrospinal fluid; CRP, C-reactive protein; ROC, receiver-operator characteristic; AUC, area under the curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

Bacterial sepsis is one of the most common diagnostic challenges in newborn medicine. A definitive diagnosis—based on culture of blood, cerebrospinal fluid (CSF), or urine—is usually reached only after a delay of a day or two, yet rapid progression of untreated infection may greatly increase morbidity or mortality. Initiation of antibiotic therapy before diagnostic results are available is recommended for neonates with clinical signs or epidemiologic factors associated with neonatal sepsis.[1] These findings are diverse, often subtle, and nonspecific,[2–5] so empiric therapy may result in treatment of as many as 30 uninfected infants for every 1 who is ultimately determined to have been infected.[6–8] There have been many attempts to develop screening tests or scoring systems that can identify infected infants at the time of initial assessment, sparing others from invasive diagnostic procedures, intravenous antibiotic therapy, mother-infant separation, and

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heightened parental anxiety. Various laboratory studies have been evaluated, but no single test or combination of findings is sufficiently sensitive to permit withholding treatment from at-risk infants on the basis of negative results, or sufficiently specific to avoid unnecessary treatment of uninfected infants with abnormal results. The sensitivity of laboratory methods is limited at the time of presentation, but may substantially improve within 12 to 24 hours. Recent reports indicate that serial C-reactive protein (CRP) levels during this interval may be useful for early identification of infants for whom antibiotic therapy can be safely discontinued.[9]

Prompted by reports of high negative predictive values (NPVs) of serial normal CRP levels, we adopted a standardized approach to evaluation of infants with suspected sepsis in June of 1993. CRP levels were obtained for all such infants, both with the initial diagnostic evaluation and on each of the next two mornings. To determine if the sensitivity of serial normal CRP levels is sufficient to justify discontinuation of therapy before final culture results are available, we reviewed our cumulative experience in >1000 infants. The sensitivity of CRP at the time of presentation was also reevaluated, and four different strategies for use of CRP measurements were compared. Measurement of CRP contemporaneously with initiation of empiric therapy is not sufficiently sensitive to permit withholding treatment, but levels determined on each of the next two mornings are sufficient to guide discontinuation of antibiotic treatment.

METHODS

Patient Population

Neonates who were treated for sepsis in the regional intensive care nursery at Lucile Packard Children's Hospital (Palo Alto, CA) and two affiliated community intensive care nurseries (El Camino Hospital, Mountain View, CA, and Washington Hospital, Fremont, CA) between June, 1993 and March, 1996 were assessed using a standard clinical pathway. Indications for initiation of antibiotic therapy included obstetrical factors (intrapartum fever, chorioamnionitis, prolonged rupture of membranes, premature preterm rupture of membranes, premature onset of labor, preterm labor refractory to tocolysis, fetal tachycardia, meconium staining of amniotic fluid) and neonatal clinical signs (meconium aspiration, lethargy, poor feeding, feeding intolerance, hypothermia, respiratory distress, increased or new apnea or bradycardia episodes, feeding intolerance, hematochezia, bilious emesis or other signs of necrotizing enterocolitis, impaired cardiac output, congestive heart failure, shock, abnormal glucose homeostasis or hyperlipidemia, metabolic acidosis, nonphysiologic jaundice, and signs of localized infection). Complete blood counts with differentials, platelet counts, and blood cultures were performed before antibiotic treatment. Other diagnostic studies, including cultures of CSF or urine obtained by suprapubic aspirate, and decisions regarding initiation or duration of therapy were at the discretion of the attending neonatologist. Radiographic findings consistent with sepsis included pulmonary infiltrates, pleural effusions, pneumatosis intestinalis, or intraperitoneal free air. Abnormal hematologic findings were defined as described by Manroe et al[10] and Rodwell et al.[11] Pleocytosis, an elevated protein concentration, or a decreased glucose level in the CSF were considered to indicate probable bacterial meningitis.[12] Serum CRP levels were obtained at the initial evaluation and on each of the next two mornings, with at least 8 hours between the first two measurements. Repeat CRP measurements were not required after an elevated CRP or positive culture was reported.

Birth weight, gestational age, postnatal age, discharge diagnoses, and final outcome were recorded for each infant. Infants >44-weeks' postconceptional age (estimated gestational age at birth plus postnatal age) were not included. For each episode of suspected infection, clinical and laboratory data, including white blood cell and platelet counts, CSF analyses, results of cultures, and CRP levels, were recorded. All laboratory studies were conducted in the clinical laboratory at each hospital. CRP levels were determined by rate immunonephelometry (Beckman Instruments, Fullerton, CA).

Patient Classification

The diagnosis at each evaluation was categorized without consideration of CRP levels. Infants were considered to have proven sepsis if a culture yielded pathogenic bacteria, probable sepsis if: clinical, radiographic, and laboratory findings were consistent with this diagnosis but cultures were negative; or no sepsis if there were no clinical, radiographic, or laboratory findings attributable to sepsis. Clinical signs were attributed to infection and the patient was considered to have probable sepsis unless these findings were fully explained by another diagnosis or resolved completely within 8 hours. Bacteria recovered in cultures were considered to be pathogenic unless they were normal skin or upper respiratory flora, all other laboratory studies were normal, and the infant either had no clinical signs of infection or such signs resolved without antimicrobial therapy.

Statistical Methods

Sensitivity, specificity, positive predictive value (PPV), and NPV were calculated as defined by Feinstein.[13] Differences in the prevalence of proven or probable sepsis between groups were analyzed using the G-test of independence.[14] Receiver-operator characteristic (ROC) curves were constructed to permit selection of threshold values for test results and comparison of different testing strategies.[15] Areas under ROC curves and their standard errors were determined using the method of Centor,[16] and compared using the normal distribution, with correction for correlation of observations derived from the same cases.[17] A larger area under a ROC curve (AUC) indicates superior test performance, with 1 representing 100% sensitivity and specificity and 0.5 representing no discriminatory utility. The cutoff limit for an abnormal test result that produces the point nearest the upper left corner on the ROC graph is optimal if false-positive and false-negative results are equally undesirable.[18] However, it is preferable to treat several infants with false-positive diagnoses rather than fail to adequately treat a single infant with sepsis because of a false-negative result, so we used ROC curves to identify threshold values with the maximum sensitivity consistent with specificity of at least 50%. Confidence intervals (CIs) for sensitivity, specificity, PPV, and NPV were calculated using the normal or binomial distributions.[19] Likelihood ratios and CIs were calculated as described by Armitage and Berry[20] and Fleiss,[21] respectively. All P values are two-tailed. Statistical significance was assumed at $P < .05$.

RESULTS

Patient Ascertainment and Classification

Evaluations for suspected infection were performed at age 3 days or less (early-onset) in 1002 infants and after that age (late-onset) on 184 occasions in 134 infants. The demographic characteristics of these populations are described in Table 1. There tk;2were 73 episodes of proven sepsis, 86 of probable sepsis, and 1027 of no sepsis. Organisms were isolated from 68 blood cultures, 5 urine cultures, and 7 CSF cultures (Table 2). Blood and CSF cultures were concordant in 5 of the 7 cases of meningitis, and blood and urine cultures were concordant in 2 infants with urinary tract infection. One infant had simultaneous urinary tract infection (*Candida parapsilosis*) and sepsis/meningitis (coagulase-negative Staphylococcus). In 1 case, *Staphylococcus aureus* was cultured from fluid obtained by direct aspiration of an osteomyelitis lesion. Blood cultures yielded coagulase-negative staphylococci in 256 episodes classified as proven sepsis; in these episodes, hematologic

TABLE 1. Demographic Characteristics of Study Population

	Early-onset Episodes	Late-onset Episodes
Total patients	1002	134
Total episodes	1002	184
Birth weight (g)*	2734 ± 1029 (550–6759)	1874 ± 1123 (385–4920)
Gestational age (weeks)*	36.2 ± 4.4 (23–43)	32.2 ± 5.8 (23–42)
Age at evaluation (days)*	0.2 ± 0.6 (0–3)	22.8 ± 20.2 (4–118)
Male:female	553:449	80:54
Proven sepsis	20	53
Probable sepsis	74	12
Sepsis excluded	908	119

* Mean ± standard deviation (range).

TABLE 2. Bacteriology of Positive Cultures

	Blood	CSF	Urine
Early-onset episodes			
Organism			
Acinetobacter lwolffi	1	1	0
Enterococcus faecalis	1	0	0
Escherichia coli	3	1	0
Listeria monocytogenes	1	0	0
Staphylococcus epidermidis	1	0	0
Streptococcus, group B	8	1	0
Total positive cultures	15	3	0
Total number of cultures performed	1002	633	48
Late-onset episodes			
Organism			
Candida albicans	3	0	2
Candida parapsilosis	3	0	1
Enterobacter cloacae	3	0	0
Enterococcus faecalis	5	0	0
Escherichia coli	2	0	0
Klebsiella pneumoniae	1	0	1
Pseudomonas aeruginosa	0	0	1
Serratia marcescens	2	0	0
Staphylococcus aureus	6	0	0
Staphylococcus epidermidis	16	2	0
Staphylococcus, other coagulase-negative	10	2	0
Streptococcus, group B	1	0	0
Streptococcus viridans	3	0	0
Streptococcus, other	2	0	0
Total positive cultures	53*	4	5
Total number of cultures performed	184	126	47

* Some cultures yielded more than one organism.

findings were abnormal in 15, the blood culture yielded an additional organism (*Enterococcus faecalis* or yeast) in 3, the CSF yielded the same organism in 2, signs of local infection (necrotizing enterocolitis, omphalitis, pneumonia) were noted in 3, and treatment was continued for 7 days or more at the discretion of the attending physician because of clinical instability along with the positive culture in 2 others. The most frequently isolated organisms were *Streptococcus agalactiae* in early-onset episodes and coagulase-negative staphylococci in late-onset episodes. Proven sepsis was less frequent in early-onset (attack rate 2%) than in late-onset episodes (attack rate 29%), but probable sepsis was diagnosed in ~7% of episodes in each group.

Thirteen blood cultures yielded only skin or upper respiratory normal flora, including 6 with multiple organisms. Two positive blood cultures were obtained from infants who never became ill and recovered without specific therapy. Fifteen episodes with positive CSF cultures were classified as no sepsis; those cultures yielded only normal skin flora or had scant bacterial growth in only 1 of 3 culture media, and all concomitant CSF cell counts, glucose, and protein levels were normal. These episodes were classified as having no sepsis.

Correlation of Diagnoses and Serum CRP Levels

CRP levels were obtained in 1002 episodes of suspected early-onset infection and 184 of suspected late-onset infection. The relationship between CRP levels and diagnoses is shown in Table 3. Four different uses of these measurements were considered: the initial level alone (CRP #1), the second level alone (CRP #2), the higher of the second and third levels (CRP #2 and #3), or the highest of all three levels (CRP × 3). For each test, the sensitivity was highest at a cutoff of 1 mg/dL; this value was used in all evaluations. Proven or probable sepsis was strongly correlated with elevated CRP levels (≥1.0 mg/dL) in all of these testing strategies, for both early- and late-onset episodes ($P < 10^{-5}$ by 2 × 3 G-tests, $<10^{-6}$ by 2 × 2 G-tests for no sepsis versus either proven or probable sepsis), supporting the diagnostic utility of CRP levels. The calculated sensitivities and specificities of each testing strategy are shown in Table 4.

TABLE 3. C-Reactive Protein Levels in Suspected Neonatal Infection

CRP #1	CRP #2	CRP #3	No Sepsis	Probable Sepsis	Proven Sepsis
Early-onset episodes					
<1	Not done	Not done	1*	0	1
	<1	Not done	0	0	1
		<1	692	0	2
		1	42	2	1
	1	Not done	20	12	5
		<1	38	7	1
		1	47	23	2
1	Not done	Not done	10	8	0
	<1	Not done	12	0	0
		<1	7	0	0
		1	0	0	0
	1	Not done	10	13	3
		<1	10	1	0
		1	19	8	4
		Total	908	74	20
Late-onset episodes					
<1	Not done	Not done	1†	0	9
	<1	Not done	1‡	0	4
		<1	78	0	1
		1	3	0	0
	1	Not done	3	0	2
		<1	1	0	1
		1	1	3	3
1	Not done	Not done	8	4	12
	<1	Not done	3	0	0
		<1	2	1	0
		1	0	0	0
	1	Not done	11	2	14
		<1	2	0	1
		1	5	2	6
		Total	109	12	53

* Blood culture positive for *Streptococcus salivarius.*
† Endotracheal aspirate culture positive for *Candida albicans* and *Staphylococcus aureus.*
‡ Blood culture positive for *Staphylococcus warneri.*

TABLE 4. Performance of C-Reactive Protein Measurements in Diagnosis of Neonatal Bacterial or Fungal Infection*

	CRP #1	CRP #2	CRP #2 and #3	CRP × 3
Early-onset episodes				
n	1002	982	987	999
Proven sepsis				
Sensitivity	35.0% (30.2–40.6)	78.9% (72.0–86.4)	88.9% (80.8–94.3)	88.9% (80.8–94.3)
Specificity	90.0% (88.1–91.9)	78.4% (75.8–81.0)	73.8% (71.1–76.6)	70.5% (67.7–73.4)
Positive predictive value	6.7% (1.9–11.4)	6.7% (3.4–10.0)	6.0% (3.1–8.8)	5.2% (2.2–7.7)
Negative predictive value	98.6% (97.8–99.3)	99.5% (99.3–99.6)	99.7% (99.5–99.9)	99.7% (99.5–99.8)
Posterior:previous likelihood ratio for normal result	0.72 (0.36–1.44)	0.27 (0.10–0.76)	0.15 (0.04–0.59)	0.16 (0.04–0.61)
Posterior:previous likelihood ratio for abnormal result	3.51 (1.48–8.31)	3.66 (1.85–7.23)	3.40 (1.73–6.68)	3.02 (1.53–5.92)
Either proven or probable sepsis				
Sensitivity	39.4% (29.5–49.2)	92.9% (87.5–98.4)	97.6% (95.8–98.8)	97.8% (96.2–98.9)
Specificity	92.5% (90.8–94.2)	83.9% (81.5–86.3)	79.3% (76.6–81.9)	76.3% (73.5–79.1)
Positive predictive value	35.2% (26.1–49.4)	35.4% (29.1–41.7)	30.6% (25.1–36.1)	29.5% (24.4–34.6)
Negative predictive value	93.6% (92.0–95.2)	99.2% (98.6–99.8)	99.7% (99.5–99.9)	99.7% (99.5–99.8)
Posterior:previous likelihood ratio for normal result	0.66 (0.47–0.92)	0.10 (0.05–0.21)	0.03 (0.008–0.11)	0.03 (0.008–0.11)
Posterior:previous likelihood ratio for abnormal result	5.26 (3.35–8.25)	5.72 (4.03–8.13)	4.71 (3.34–6.63)	4.13 (2.98–5.72)
Late-onset sepsis episodes				
n	184	150	145	169
Proven sepsis				
Sensitivity	61.5% (48.3–74.8)	84.4% (80.5–87.3)	96.4% (90.9–99.1)	97.5% (93.6–99.4)
Specificity	68.9% (61.0–76.8)	74.6% (66.7–82.4)	71.8% (63.6–79.9)	60.5% (52.0–68.9)
Positive predictive value	43.8% (32.5–55.2)	47.4% (34.4–60.5)	45.0% (32.4–57.6)	43.3% (33.1–53.6)
Negative predictive value	82.0% (74.8–89.1)	94.6% (93.3–95.5)	98.8% (97.0–99.7)	98.7% (96.7–99.7)
Posterior:previous likelihood ratio for normal result	0.56 (0.31–0.97)	0.21 (0.08–0.54)	0.05 (0.008–0.30)	0.04 (0.008–0.24)
Posterior:previous likelihood ratio for abnormal result	1.98 (1.13–3.47)	3.32 (1.74–6.34)	3.42 (1.78–6.56)	2.47 (1.43–4.25)
Either proven or probable sepsis				
Sensitivity	64.6% (53.0–76.2)	85.0% (73.9–96.1)	94.4% (90.3–97.1)	98.1% (95.0–99.5)
Specificity	73.9% (66.1–81.8)	79.1% (71.5–86.7)	76.1% (68.1–84.1)	66.7% (58.1–75.2)
Positive predictive value	57.5% (46.2–68.9)	59.6% (46.9–72.6)	56.7% (44.1–69.2)	56.7% (46.4–66.9)
Negative predictive value	79.3% (71.7–86.8)	93.5% (88.6–98.5)	97.6% (95.8–98.8)	98.7% (96.7–99.7)
Posterior:previous likelihood ratio for normal result	0.48 (0.28–0.97)	0.19 (0.08–0.54)	0.07 (0.02–0.28)	0.03 (0.005–0.24)
Posterior:previous likelihood ratio for abnormal result	2.48 (1.43–4.30)	4.07 (2.15–7.69)	3.96 (2.11–7.44)	2.94 (1.74–4.99)

* Parentheses indicate 95% confidence limits.

The sensitivity of a single measurement with the initial evaluation (CRP #1) for early-onset infection was low, both for proven sepsis (35.0%) and for proven or probable sepsis (39.4%). Although the sensitivity of CRP #1 was higher for late-onset infections, initial CRP levels were normal in more than one-third of all sepsis episodes. The sensitivity of a delayed (8–24 hours after presentation) CRP level (CRP #2) was substantially higher, but maximum sensitivities were achieved only by combination of the second and third (CRP #2 and #3) or all three (CRP × 3) CRP levels. The discriminatory power (AUC, Fig 1) of CRP #2 and #3 or CRP × 3 was significantly greater than that of either CRP #1 or CRP #2 for both proven sepsis and proven or probable sepsis in both early- and late-onset episodes ($P < .005$). The AUC for CRP #1 differed from that for CRP #2 only for proven or probable sepsis in early-onset episodes ($P < .001$). The AUC for CRP #2 and #3 and CRP × 3 ROC curves were not significantly different.

Predictive Values and Bayesian Analysis

To assess the ability of abnormal and normal CRP levels to identify the presence or absence of infection, respectively, the positive and NPV for each testing

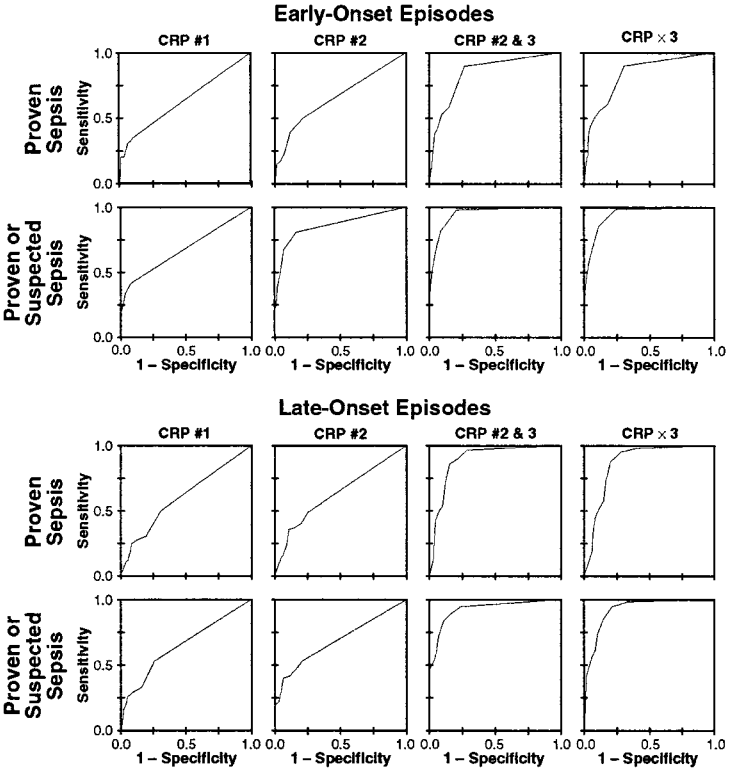

Fig 1. Receiver-operator characteristic curves for serum C-reactive protein (CRP) levels and neonatal infection. Sensitivity is plotted against (1 – specificity) for serum CRP level thresholds between 0 and 10 mg/dL, for early- and late-onset episodes of suspected infection for infants with proven sepsis and those with proven or probable sepsis. Data are shown for single CRP measurements at the time of presentation (CRP #1), single levels 8 to 24 hours after the initial evaluation (CRP #2), the highest of three levels obtained within 48 hours after the initial assessment (CRP × 3), or the higher of the second and third levels (CRP #2 and #3).

strategy were calculated (Table 4). The PPV were low: among episodes in which a CRP level was elevated, proven sepsis was diagnosed in fewer than 10% of early-onset and fewer than 50% of late-onset evaluations, and proven or probable sepsis was identified in only 30% to 35% of early-onset and 55% to 60% of late-onset evaluations. The NPV were >90% for all groups except those evaluated with a single CRP level at the time of presentation (CRP #1) with suspected late-onset disease, reflecting the low prevalence of sepsis in these populations. To quantify the extent to which CRP measurements added diagnostic information, the Bayesian ratios of the likelihoods of infection before and after obtaining each test result were also calculated (Table 4). Normal initial CRP levels (CRP #1) were associated with modest (28%–52%) reductions in the likelihood of infection ($P <$ .05 except for proven sepsis in early-onset episodes). Normal CRP levels 8 to 24 hours later (CRP #2) were associated with more substantial (75%–90%) reductions in the likelihood of both proven and probable infection ($P <$ .05). If the last 2 (CRP #2 and #3) or all 3 (CRP × 3) levels were normal, the likelihood of infection was only 3% to 15% of that in the entire population. Abnormal CRP results were associated with increases in the likelihood of infection of ~3- to 6-fold for early-onset episodes and 1.5- to 2.5-fold for late-onset episodes.

To determine whether greater elevations in CRP levels were associated with a higher probability of infection, the PPV were calculated for maximum CRP levels obtained 8 to 48 hours after presentation (CRP #2 and #3) for each successive interval of 1 mg/dL up to 10 mg/dL, for both early- and late-onset and proven or probable infection (Fig 2). In the first 3 days of life, the PPV for mildly elevated CRP levels (1–2 mg/dL) were only 5% and 12% for proven and either proven or probable sepsis, respectively. All infected infants with such mildly elevated CRP levels were symptomatic. CRP levels >2 mg/dL were associated with a probability of either proven or probable infection >25%, but the probability of proven infection was >10% only of episodes in which CRP levels exceeded 5 mg/dL (Fig 2A). In contrast, episodes with CRP levels >2 mg/dL after the first 3 days of life had at least a 12% risk of proven infection and a 20% chance of proven or probable infection (Fig 2B).

Potential False-negative Results

Elevated CRP levels were not observed in 18 episodes in which blood cultures yielded pathogenic organisms. In 11 of these episodes, CRP levels were obtained only with the initial evaluation, and CRP levels were obtained only in the first 16 hours after presentation in 4 additional episodes. Subsequent levels were not measured because positive culture results had already been reported. An infant delivered by cesarean section at 32-weeks' gestation for maternal indications was evaluated because of mild respiratory distress; she had neither a left-shifted differential blood count nor other clinical findings suggestive of Gram-negative sepsis, but *Acinetobacter lwolffi* was recovered from her blood culture and three CRP levels were <1 mg/dL. One infant had $>10^5$ colonies of *Klebsiella pneumoniae* per mL in a urine sample obtained by suprapubic aspiration; he had an increased proportion of immature granulocytes but CRP levels were persistently normal. One premature infant born after prolonged rupture of

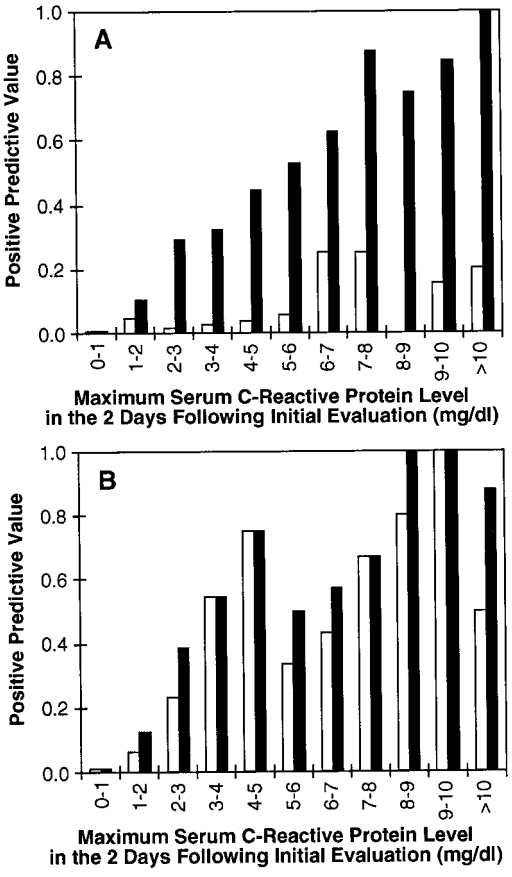

Fig 2. Positive predictive values for the highest of two serum C-reactive protein levels obtained during the 8 to 48 hours after presentation of infants with possible infection. Predictive values for proven (open bars) and proven or probable (solid bars) sepsis are shown separately for infants evaluated for early-onset (panel A) and late-onset (panel B) infection.

membranes for >10 days died with *Streptococcus viridans* sepsis and progressive granulocytopenia, but serial CRP levels were not elevated.

Discontinuation of Antibiotics

Three normal CRP levels were obtained in 694 of the 1002 infants evaluated for early-onset infection. Of the 499 such infants for whom antibiotics were discontinued within 3 days, 13 required reevaluation for suspected infection within 14 days of the initial evaluation. Five of these infants were infected: 2 with *Staphylococcus epidermidis* sepsis, 1 with *S aureus* sepsis, 1 with combined *S aureus* and *E faecalis* sepsis, and 1 with *K pneumoniae* urinary tract infection. Antibiotics were administered for >3 days in 195 infants, but only 85 infants were treated for 7 days or more. Indications for prolongation of antibiotic therapy included positive blood cultures in 2 patients (*Acinetobacter lwolffi* and *S viridans*, see above), abnormal hematologic findings alone in 40, a history of chorioamnionitis in 1, radiographic findings consistent with pneumonia in 3, and persistent clinical instability without other explanation in the remainder.

Three normal CRP levels were obtained in 79 of the 184 episodes of suspected late-onset infection. Of the 43 such episodes in which antibiotics were discontinued within 3 days, reevaluation for suspected infection within 14 days of the initial evaluation was required in 9, and 2 (5%) were associated with bacteremia (*S epidermidis*, *E faecalis*). In retrospect, among the 36 episodes in which multiple CRP levels were normal but treatment was given for >3 days, only 1 had evidence of bacterial infection (*K pneumoniae* urinary tract infection). Twenty of these episodes were treated for 7 days or more. Treatment was continued for 3 to 7 days in 5 episodes in which blood cultures were positive for coagulase-negative staphylococci and three CRP levels were normal; only 1 was evaluated for suspected sepsis within 14 days and was not infected.

DISCUSSION

Serum concentrations of CRP increase several hundredfold in response to bacterial infection, making it an attractive diagnostic test for neonatal sepsis. Because many of the more than 70 publications on this subject that have appeared during the past 30 years were flawed by imprecise diagnostic criteria, absent or inappropriate controls (eg, healthy neonates), incomplete description of results, or inadequate sample sizes, the role of this test in evaluation of neonates remains controversial. Early reports described a high prevalence of elevated CRP levels in infected infants, but levels are elevated in only 35% to 65% of neonates with bacterial infection at the onset of illness. Recognition that a delay of at least several hours is intrinsic to the cascade of events leading to elevation of serum CRP levels (including activation of neutrophils, elaboration of interleukin-6, and induction of hepatic synthesis of CRP) led to appropriate criticism of this test as having insufficient sensitivity to guide therapy either by reliably diagnosing or excluding bacterial infection. Noting that CRP levels are consistently elevated 24 to 48 hours after the onset of infection, Philip[22] and later others[23–26] suggested that serial normal levels may be useful for identification of infants who do not have bacterial infection. In a series of 218 infants (13 with sepsis), Gerdes and Polin[8] reported high sensitivity (93%) and NPV (99%) for CRP levels determined by a latex agglutination method at the time of evaluation and 12 to 24 hours later. Pourcyrous et al[9] found that two levels measured over the first 3 days in 140 neonates (36 with infection) had a high NPV, and suggested that the utility of CRP levels might be optimized by obtaining serial levels at 12-hour intervals in the first 24 to 36 hours of illness. In 292 evaluations, Krediet et al[27] found that two levels in the first 24 hours had only modest sensitivity (53% to 88%) and NPV (80% to 97%), depending on the criteria for diagnosis (proven or probable sepsis) and the time of onset of the infection (early or late). In the largest series published to date, including 689 evaluations in 491 infants and 187 episodes of culture-proven or clinically definite sepsis, Pourcyrous et al[9] described similar results when CRP levels were obtained at the initial evaluation and twice at 12 hour intervals, emphasizing the importance of serial levels for achievement of optimum sensitivity. Philip and Hewitt[7] reported no recurrence of infection within 7 days of discontinu-

ation of antibiotics based on three normal CRP determinations within 48 hours and negative cultures in 147 low birth infants at risk for early-onset infection. Based on these data, determination of serial CRP levels was incorporated into our diagnostic approach to suspected neonatal sepsis. Levels were obtained at the initial evaluation and with routine morning laboratory studies on each of the next 2 days. This analysis was undertaken to determine whether our experience was similar to previous reports.

Evaluation of the performance of a diagnostic test requires an objective and reliable reference method for identifying patients with and without the disease of interest, but there are no simple criteria for diagnosis of sepsis in the neonate. The most objective evidence of invasive infection is usually considered to be recovery of an organism from body fluids obtained using sterile technique: blood, CSF, or urine obtained by suprapubic aspirate, in particular. These studies may yield false-positive results, particularly for organisms that may represent either skin flora or potential pathogens in low birth weight or debilitated neonates, such as coagulase-negative staphylococci. To minimize false-positive diagnoses, patients whose cultures were positive for skin flora only and who had no other clinical findings consistent with infection were not considered to have infection. The remaining patients with positive culture results constituted the group with proven sepsis. This category is most useful for assessment of the sensitivity of CRP levels—that is, the probability of an abnormal CRP level in those patients who are unequivocally septic. False-negative results may result from submission of small aliquots of blood for culture, intermittent or low-density bacteremia, or suppression of bacterial growth by earlier (eg, intrapartum) antibiotic administration. To minimize errors resulting from false-negative culture results, infants with negative cultures but whose clinical and laboratory findings were suggestive of infection were assigned to a group with probable sepsis. Patients who lacked findings suggestive of infection were assigned to a group with no sepsis, in which infection could be excluded with confidence. This group is most useful for evaluation of the specificity and NPV of one or more normal CRP levels. The possibility that infants may have been assigned an incorrect diagnosis remains, however, and is intrinsic to all studies of this nature.

This analysis of the relationship between serum CRP levels and neonatal infection, which includes 1186 diagnostic evaluations in 1066 neonates, is the largest such study yet published. In these populations, proven infection was much less likely in early-onset (2%) than in late-onset (40%) episodes, reflecting early evaluation of many infants without clinical signs of infection because of obstetrical factors (eg, prolonged rupture of membranes) alone. The prevalence of probable sepsis was similar in the early- and late-onset groups. The higher rate of confirmed infection in the late-onset patients is similar to that previously reported in other comparisons of the performance of CRP in early- and late-onset disease,[27–29] and probably results from selection of infants for late-onset evaluations only if they had clinical signs of possible infection. As in previous series, elevated CRP levels strongly correlated with infection for both early- and late-onset episodes, whether single or serial levels were considered, and independent of whether probable cases were grouped with proven cases, with noninfected infants, or considered separately. There were few differences in test performance between early- and late-onset groups. Other than the higher PPV of elevated CRP levels in late-onset episodes, which reflects the much higher prevalence of sepsis in this group, only the higher sensitivity of the initial CRP in the late-onset group (for both proven and proven or probable sepsis) was statistically significant. The higher prevalence of elevated CRP levels in these patients is not unexpected, because their infections had necessarily been present for sufficient time to produce persistent clinical signs that led to diagnostic assessment. ROC curve analysis (Fig 1) established a serum level of 1 mg/dL, an appropriate threshold above which results should be considered abnormal, provided the first statistical confirmation that serial levels are diagnostically superior to single measurements, and confirmed previous observations that a single CRP level at the beginning of an evaluation lacks sensitivity and negative predictive power. The sensitivity and NPV are improved by delaying testing for 8 to 24 hours, as previously reported,[18,30] but the highest levels of these performance parameters were achieved only with multiple serial levels. These observations, as well as more recent reports,[31–33] support the previously reported clinical superiority of serial CRP determinations.[8,27,34]

Traditional descriptors—sensitivity, specificity, PPV, and NPV—may not accurately represent test performance, because they are heavily influenced by the prevalence of disease in the sample population. For example, the NPV of a nondiscriminant test will be high in a population in which the disease of interest is rare. Diagnostic test performance is better reflected in Bayesian ratios of the likelihood of infection in each of the subgroups defined by the test results (posterior probability) to that in the entire population (previous probability).[35] Such posterior: previous probability ratios are an effective indication of the information added by the test result. In earlier studies in which CRP measurements were performed only during the first 24 hours after presentation, the Bayesian ratios associated with normal serial CRP levels were 0.09 (95% CI, 0.02–0.55; n = 218),[8] 0.41 (95% CI, 0.27–0.63; n = 292),[27] and 0.30 (95% CI, 0.22–0.42; n = 689).[9] More consistent reductions in the risk of neonatal infection have been associated with serial normal CRP levels for >2 to 3 days, for which Bayesian ratios of 0.07 (95% CI, 0.02–0.28; n = 140),[34] 0.08 (95% CI, 0.01–0.52; n = 40),[36] 0.12 (95% CI, 0.05–0.30; n = 309),[31] and 0.04 (95% CI, 0.01–0.22; n = 139)[32] have been reported. In our population, the risks of both proven sepsis and either proven or probable sepsis were similarly reduced for infants in whom CRP levels remained normal during the first 32 to 48 hours after presentation, for whom

the Bayesian ratio for infection was 0.16 or less for early-onset cases and 0.08 or less for late-onset cases (Table 4). These data, based on nearly twice the number of episodes included in all previous reports, indicate that serial normal CRP levels during the first 2 to 3 days of suspected infection are associated with a substantial reduction in the probability that such a neonate is infected.

Our data confirm previous reports of poor sensitivity of single CRP levels on presentation of an infant with possible infection. In isolation, a normal initial CRP is associated with a risk reduction of only ~50% or less (Table 4), which will rarely affect treatment. If combined with two subsequent normal levels, the initial CRP had little impact on the NPV and Bayesian likelihood ratios, as the differences between these values for CRP #2 and #3 and those for CRP × 3 were small and neither clinically nor statistically significant. Exclusion of episodes in which an elevated initial CRP level precluded performance of subsequent levels could artifactually skew these results, but the data in Table 3 indicates that this does not lead to diagnostic errors. Of the 37 infants in the early-onset group in whom only the initial level was elevated, none had proven infection, and none of the 8 with probable sepsis had a second CRP level. Of the 30 late-onset episodes in which only the initial level was elevated, 12 had proven infection (a positive culture), and only 1 of the 5 with probable sepsis had more than one CRP. In that patient, the initial level was 1.0 mg/dL and two subsequent levels were ≤0.5 mg/dL; infection was probable because the proportion of immature granulocytes was increased. The second or third CRP level was elevated in all of the 66 infants with early-onset probable sepsis and in 7 of the 8 episodes of late-onset probable sepsis in which more than one CRP was obtained, making it unlikely that subsequent levels would have been normal had they been done. Exclusion of these patients from the CRP #2 and #3 group did not compromise the NPV of that test. Omission of subsequent levels in episodes with positive cultures reduced the prevalence of proven infection in the sample populations and may have reduced the calculated specificity and PPV of CRP #2, CRP #2 and #3, and CRP × 3. CRP levels at the initial evaluation can be omitted without compromising the diagnostic utility of serial levels obtained during the next 48 hours. These data do not address the possibility that early levels may have utility as a component of a multifactorial screening panel.

In this experience, false-negative results (positive cultures with normal CRP levels) were most common in infants who had serum samples obtained only early in the evaluation. In these instances, positive culture results were available before CRP levels became elevated, and additional levels were not obtained. As noted by Buck and Pohlandt,[37] the timing of CRP levels is critical to achievement of optimal sensitivity, and it is possible that abnormal levels did develop, but were not measured, within 48 hours of diagnosis. Others have described inconsistent responses to infections caused by mildly pathogenic organisms (particularly coagulase-negative staphylococci),[38,39] which may also produce false-negative results. In the 2 cases in which pathogenic organisms (*Acinetobacter lwoffi* and *E faecalis*) were isolated from blood but no other clinical or laboratory findings consistent with sepsis were apparent, the positive culture results may have been factitious. Lack of a demonstrable acute phase response in the patient with urinary tract infection is consistent with previous reports that CRP levels are often not elevated in infants and children whose infection is limited to the lower urinary tract.[40,41] In addition, infants with overwhelming bacterial sepsis may exhibit little or no increment in serum CRP levels when the infection is associated with severe granulocytopenia.[42] Thus, whereas serial measurements increase sensitivity substantially, perfect sensitivity is not achievable.

The outcome of at-risk infants in whom antibiotic therapy is discontinued on the basis of serial normal CRP levels may be the best indicator of their utility for exclusion of infection. Because discontinuation of antibiotic therapy was left to the judgment of the attending neonatologist, the data reported here are not conclusive. In episodes in which antibiotics were discontinued after three normal CRP levels, the nosocomial infection rate (1 per 1000 patient days) was much less than the prevalent rate in our nurseries during that period (6–9 per 1000 patient days). The organisms associated with subsequent infectious episodes after early discontinuation of therapy for suspected early-onset sepsis were typical of late-onset nosocomial infections, and these episodes occurred 7 to 11 days after the initial evaluation. Of those episodes in which serial CRP levels were normal and treatment was given for >3 days, antibiotic therapy was discontinued before completion of a 7 day course in more than half, reflecting the belief of the attending neonatologists that these infants were not infected. Among the 105 episodes in which a full course (≥7 days) of antibiotic therapy was provided, only 2 infants would have been at serious risk had antibiotics been discontinued prematurely. Because these infants had Klebsiella urinary tract infection and *S viridans* sepsis with severe granulocytopenia, the diagnosis was not obscure, and a basis for discounting the normal CRP levels was readily evident. These data suggest that the risk of recurrence of an inadequately treated infection is extremely small when normal serial CRP levels are the basis for discontinuation of antibiotics. However, the latter 2 cases emphasize the need for continued application of this test within the context of other clinical data, and additional experience is needed to demonstrate that discontinuation of antibiotics based on serial normal CRP levels is safe in infants whose blood cultures are positive for coagulase-negative staphylococci.

In this population, a positive test result was associated with an increase in the probability of bacterial or fungal infection (posterior:previous likelihood ratio) of 2- to 6-fold, compared with 3- to 25-fold increases reported by others. This variability in PPV and likelihood ratios for positive results may be attributable to different prevalences of CRP elevation from noninfectious causes (false-positives) in the

study populations. Elevated CRP levels occur in association with many other conditions in addition to bacterial or fungal infection. Interleukin-6 of maternal origin[43] in cord blood may produce elevated CRP levels in uninfected infants born to women with chorioamnionitis. CRP levels may be elevated in neonates with thermal burns,[44,45] pneumothoraces,[46] intraventricular hemorrhage,[46] meconium aspiration syndrome with negative cultures,[23,34] necrotizing enterocolitis,[47–49] and after surgical procedures,[50,51] cardiopulmonary bypass,[52–54] or immunizations[55] but not in those with uncomplicated respiratory distress syndrome,[46,56,57] perinatal asphyxia,[56] prolonged rupture of membranes,[56] or jaundice.[56] Most acute viral infections are not associated with abnormal CRP levels.[58,59] Severe viral infections, such as herpes simplex,[60] may be associated with elevated CRP levels, which may be an indication of bacterial superinfection.[58] We identified 4 patients with positive viral cultures and others with acute tissue injuries, hematologic disorders, or during extracorporeal life support, who did not have apparent bacterial infection but did have increased CRP levels (data not shown). In >80% of the cases in which CRP levels were abnormal in the absence of bacterial or fungal infection, the levels did not exceed 5 mg/dL, suggesting that markedly elevated levels might have a higher PPV. The additional analysis summarized in Figure 2 demonstrated that CRP levels >2 mg/dL were associated with a risk of either proven or probable sepsis of >25%, and levels >3 mg/dL in infants evaluated for late-onset infection were associated with proven bacterial or fungal infection in ~50%. Infants with modest elevations (up to 2 mg/dL) may not require antimicrobial therapy, but those with greater elevations probably should be treated until infection can be excluded using other data.

Measurements of serial CRP concentrations in serum may be useful in treatment of suspected neonatal sepsis. The greatest utility is in the ability of serial levels within the first 48 hours of suspected illness to distinguish infants with bacterial infection and negative nonpermissive cultures (false-negative cultures), who may require continuation of antibiotic treatment, from those whose clinical findings are not related to bacterial or fungal infection (true-negative cultures), for whom antibiotic therapy can be safely discontinued. Persistent normal CRP levels may also identify infants with false-positive cultures, especially if other data (clinical course and blood counts) are also inconsistent with infection. An elevated CRP level may help guide initiation or adjustment of antimicrobial therapy, as in routine postoperative screening for intercurrent infection[36] or monitoring for acquisition of resistance to antibiotic treatment. In most cases, however, information from CRP levels obtained at that juncture will not alter a decision to start antibiotic therapy. The role of CRP levels taken at the time of admission as part of a multicomponent sepsis screen was not addressed by this study, and the utility of such a sepsis screen may be demonstrated by future prospective studies.

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