Serum procalcitonin as an early marker of neonatal sepsis

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Background. It has recently been suggested that procalcitonin (PCT) is of value in the diagnosis of neonatal sepsis, with varying results. This study was to evaluate the role of PCT as a single early marker of neonatal sepsis.

Setting. Neonatal Unit, Johannesburg Hospital, and Microbiology Laboratory, National Health Laboratory Service (NHLS), South Africa.

Subjects and methods. Neonates undergoing evaluation for sepsis between April and August 2002 were eligible for inclusion. Patients were categorised into 'no infection', 'possible infection' and 'definite infection' on the basis of C-reactive protein (CRP), white cell count (WCC), platelet count and blood culture results. PCT was correlated with infection categories.

Results. One hundred and eighty-three neonates were enrolled. One hundred and eighteen had no infection, 52 possible infection and 13 definite infection. PCT differed significantly among infection categories ($p < 0.0001$) and correlated significantly with CRP at presentation (correlation coefficient 0.404, $p < 0.001$) and CRP at 24 hours (correlation coefficient 0.343, $p < 0.001$). PCT predicted 89.5% of definite infection. Receiver operating characteristic (ROC) analysis for PCT to predict definite infection showed odds ratio (OR) 1.145 (95% confidence interval (CI): 1.05 - 1.25) with an area under the curve of 0.778. PCT had a negative predictive value of 0.95 (95% CI: 0.915 - 0.988) for definite infection.

Conclusions. Although PCT was significantly related to the category of infection, it is not sufficiently reliable to be the sole marker of neonatal sepsis. PCT would be useful as part of a full sepsis evaluation, but is relatively expensive. A negative PCT on presentation may rule out sepsis, but this needs to be evaluated further.

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Neonatal sepsis presents a diagnostic problem, as the signs are nonspecific and there is no single reliable laboratory marker available on presentation to rule out sepsis. Many babies are evaluated and treated for presumed sepsis with parenteral antibiotics while awaiting final culture results. Less than 10% of these babies actually have sepsis, resulting in unnecessary expense and hospitalisation — of relevance in developing countries with limited resources. Inflammatory markers including interleukin 6 (IL6) and interleukin 8 (IL8), C-reactive protein (CRP) and serum amyloid alpha have been evaluated as markers of neonatal sepsis with varying success. The best prediction is obtained using a combination of markers. Serum procalcitonin (PCT) is one of many inflammatory markers and is now available as a routine laboratory investigation.

PCT is the prohormone of calcitonin and occurs in very low concentrations in the serum of healthy people. PCT is preferentially induced in bacterial sepsis, especially in severe sepsis and septic shock.[1,2] PCT can therefore be used to discriminate systemic inflammation due to bacterial sepsis from other causes and can also be used to monitor the progress and prognosis of patients with sepsis.[1,3] PCT levels are higher in non-survivors and decline with a good response to antibiotic therapy.[4] PCT has been used as a marker of bacterial sepsis in both adult and paediatric patients, including neonates.

The aim of the present study was to evaluate the role of PCT as a single early marker of neonatal sepsis.

Subjects and methods

The study was conducted in the neonatal unit of Johannesburg Hospital between April and August 2002. All neonates undergoing sepsis evaluation were eligible for inclusion in the study. Evaluation for sepsis was done at the discretion of the attending physician for a variety of reasons including maternal risk factors for sepsis (e.g. prolonged rupture of membranes, chorio-amnionitis, maternal pyrexia, maternal urinary tract infection, foul-smelling liquor) and signs of neonatal sepsis, e.g. temperature instability, lethargy, feeding intolerance, seizures, ongoing respiratory distress, irritability, blood glucose abnormalities, hypotension, poor perfusion, acidosis. A baby was entered in the study after written informed consent was obtained from the parent or guardian. The routine sepsis evaluation included a full blood count (FBC) with total and differential white cell count (WCC), platelet count, CRP (CRP1)

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and blood cultures. PCT was done at the time of presentation with the initial sepsis evaluation. The CRP was repeated 24 hours after presentation as per the unit policy (CRP2). Cerebrospinal fluid and urine cultures were done as clinically indicated at the discretion of the attending physician. All babies were started on parenteral antibiotics pending repeat CRP and/or final blood culture results. If CRP2 remained negative and the baby was clinically well, antibiotic therapy was discontinued and the baby discharged if eligible, as per the unit policy.

Analysis

Categories of infection

Babies were grouped into different categories of infection before obtaining the PCT results, as follows:

No infection. Negative blood cultures with normal CRP1, CRP2, platelet count and WCC. As there is a high incidence of maternal problems including pregnancy-induced hypertension and HIV infection, a single low platelet count or abnormal WCC was not considered to be a reliable marker of infection and such babies would be classified as having no infection.

Possible infection. Negative blood cultures with abnormal CRP1 and CRP2 or a combination of at least two of the following: abnormal platelet count, WCC, CRP1 and CRP2.

Definite infection. Positive blood cultures with any abnormal CRP1, CRP2, platelet count or WCC.

Contamination. Positive blood cultures with normal CRP1, CRP2, platelet count and WCC.

PCT levels were then compared between the different categories of infection.

Statistical analysis

Descriptive statistics included mean and standard deviation (SD) for continuous variables and proportions for categorical variables. The distribution of the data was skewed so non-parametric statistics were used. Kruskal-Wallis one-way analysis of variance was done to determine whether any variables differed significantly among infection categories. Spearman's rank correlation and logistical regression were also done to determine the best predictors of infection. Receiver operating characteristics (ROC) analysis was done to evaluate the application of PCT as a diagnostic test for neonatal infection.

Ethical considerations

The Committee for Research on Human Subjects of the University of the Witwatersrand approved the study. Written informed consent was obtained from the parent or guardian of the infant before entering the study.

Results

Two hundred and sixteen patients were entered into the study — 28 were excluded because of incomplete data (e.g. missing blood culture results, no PCT levels obtained). A further 5 babies classified as having contaminated blood cultures were also excluded. There were therefore 183 babies in the final analysis. The mean birth weight was 1 996 g (SD 893 g) and gestational age 34.6 weeks (SD 4.3 weeks). The majority of babies (167/183) were evaluated for sepsis within the first 72 hours of life. There were 13 babies with definite infection, 52 with possible infection and 118 with no infection (as defined above). There were 13 positive microbial isolates including 3 *Klebsiella pneumoniae* (1 with extended beta lactamase activity), 3 coagulase-negative staphylococci, 1 *Escherichia coli*, 2 *Acinetobacter lwoffi*, 1 Viridans streptococcus, 1 *Streptococcus agalactiae*, 1 *Acremonium* spp. and 1 *Candida albicans*. The PCT levels for the various categories of infection are shown in Table I.

Table I. Procalcitonin levels among the different infection categories

Category	Number of subjects	PCT level (median) (ng/ml)	Range	IQR
None	118	0.4	33.6	0.65
Possible	52	2.55	187.6	10.05
Definite	13	7.0	34.8	12.55

IQR = interquartile range (non-parametric equivalent of standard deviation).

One-way analysis of variance (Kruskal-Wallis) showed that birth weight ($p = 0.001$), gestational age ($p = 0.0005$) and PCT ($p < 0.0001$) differed significantly among the categories of infection. (Note CRP1, CRP2 and platelet count were used to define the different categories of infection and so are not included in the above analysis.) Spearman's rank correlation showed that PCT correlated significantly with CRP1 ($p < 0.001$ correlation coefficient 0.404) and with CRP2 ($p < 0.001$ correlation coefficient 0.343).

Because of the likelihood that some babies in the 'possible infection' group were in fact infected, logistical regression and ROC analysis was done using 'no infection' versus 'any infection' (possible/definite) and 'no infection' v. 'definite infection'. PCT alone correctly predicted 72.5% of any infection and 89.2% of definite infection. If birth weight, gestational age and platelets were added into the equation, the prediction improved to 79.1% and 90.4% respectively. The predictive values for PCT using a cut off of 0.5 ng/ml are shown in Table II. ROC analysis using PCT to predict 'no infection' v. 'any infection' gave an odds ratio (OR) of 1.148 (95% CIs 1.06 - 1.23) with an area under the ROC curve of 0.75 (Fig. 1). The OR for the prediction of PCT for 'no infection' v. 'definite infection' was 1.145 (95% CI: 1.05 - 1.25). The area under this ROC curve was 0.778 (Fig. 2).
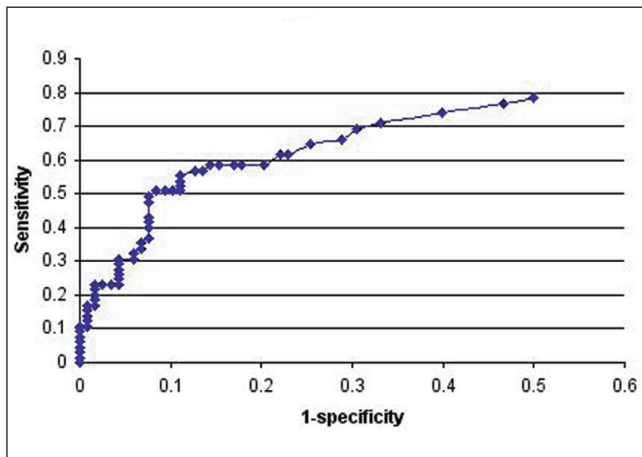
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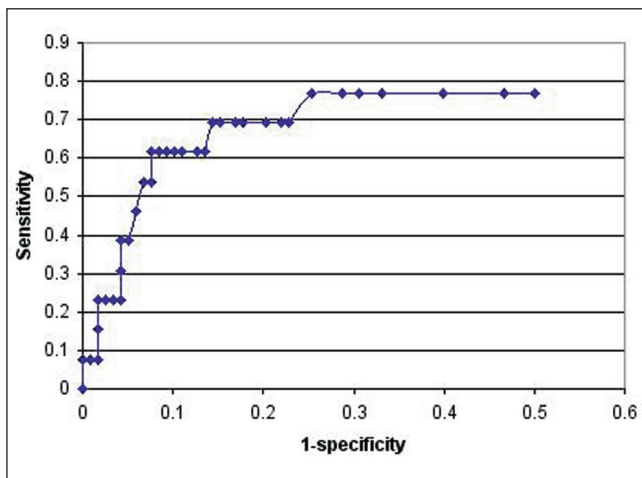*Fig. 1. ROC analysis for 'no infection' v. 'any infection'.*

Fig. 2. ROC analysis for 'no infection' v. 'definite infection'.

Discussion

The value of PCT in the diagnosis of neonatal sepsis is still under evaluation. PCT has been shown to be useful in the diagnosis, prognosis and response to treatment of patients with neonatal sepsis.[3,5] PCT may be a more reliable marker for early onset neonatal sepsis within the first 12 hours of life than either CRP or IL6.[6,7] Also, umbilical cord blood PCT may be a useful indicator in the diagnosis of early onset neonatal sepsis.[8] However, specific cut-off values of PCT may be required in the

first 48 hours of life, as various maternal and perinatal factors affect the PCT level.[9] However, Blommendahl *et al.*[10] report that PCT does not offer any advantage over more conventional markers of sepsis in neonates, especially CRP and the immature-to-total neutrophil ratio. PCT has also been shown to have no value in predicting infection in paediatric patients.[11]

Our results show that although PCT is reasonably predictive of neonatal sepsis, it is not sufficiently reliable to be used as the sole marker of infection. PCT would be useful as part of a complete laboratory work-up for sepsis, rather than as a single marker, as suggested by Giamarellos-Bourboulis *et al.*[3]

The negative predictive value for definite infection in our study was 95%. This is in agreement with Guibourdenche *et al.*[12] who have suggested that a negative PCT on presentation may be useful to rule out sepsis in neonates. This approach is similar to our current unit policy where we discontinue antibiotic therapy if the CRP2 (done at 24 hours) is negative.[13]

The high negative predictive value of PCT may allow a negative PCT on presentation to rule out sepsis and limit hospital stay and antibiotic use in neonates treated for suspected sepsis. The PCT assay costs approximately R130 compared with approximately R30 for CRP. Potential savings in antibiotic use and hospital admissions, however, could balance the relatively high cost of PCT. This approach and possible cost benefits need to be evaluated further before being recommended as standard management.

Comments and criticisms

These data once again confirm the low incidence of actual infection in neonates evaluated for sepsis and highlight the large numbers of babies unnecessarily treated for this condition. A single reliable marker of infection at presentation would solve this problem. Unfortunately, our results do not confirm that PCT is such a marker.

Two of the isolates from the blood cultures in this study were fungal and not bacterial. We did not exclude these results from the analysis, as these babies were clinically septic and PCT has been reported to correlate with the severity and outcome of fungal infection.[14]

Babies were categorised into 3 groups of infection, rather than just present and absent infection as it is acknowledged that some babies with sepsis will have negative blood cultures. Therefore some of the babies with 'possible' sepsis will have

Table II. Predictive values for PCT < 0.5 ng/ml (95% CI)				
Infection category	Sensitivity	Specificity	Positive predictive value	Negative predictive value
None v. any	0.78	0.5	0.46	0.8
	(0.725 - 0.844)	(0.427 - 0.572)	(0.391 - 0.535)	(0.751 - 0.865)
None v. definite	0.769	0.5	0.14	0.95
	(0.697 - 0.841)	(0.414 - 0.586)	(0.085 - 0.205)	(0.915 - 0.988)

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actual sepsis. The analysis using 'no infection' v. 'any infection' (possible and definite sepsis) and 'no infection' v. 'definite infection' was done to cover this possibility. Excluding the patients with possible infection would result in the potential exclusion of some patients with actual infection.

Six of the organisms isolated in our study are of low virulence (*Acinetobacter lwoffi*, streptococci viridans and coagulase-negative staphylococci (CoNS)). These organisms may contaminate blood cultures. These isolates were regarded as significant in the present study because there were other abnormal markers of infection. Of interest is that the PCT level was low in 3 of these patients. This may indicate that these were indeed contaminants, although the PCT response is less marked in low-virulence organisms.[5]

Conclusions

Our results confirm the low incidence of culture-proven neonatal sepsis. Although PCT is reasonably predictive of neonatal sepsis, it is not sufficiently reliable to be used as the sole marker. PCT would be more useful as part of a full sepsis evaluation. A negative PCT on presentation may be useful to rule out sepsis, but this should be evaluated further.

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