http://www.pjbs.org

PJBS

ISSN 1028-8880

Pakistan Journal of Biological Sciences

ANSInet
Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

Pakistan Journal of Biological Sciences 11 (14): 1785-1790, 2008
ISSN 1028-8880

The Role of the Procalcitonin in Diagnosis of Neonatal Sepsis and Correlation Between Procalcitonin and C-Reactive Protein in these Patients

[1]K. Sakha, [2]M.B. Husseini and [3]N. Seyyedsadri
[1]Department of Pediatrics, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Neonatal Service of Alzahra Hospital, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Tabriz Children's Hospital, Tabriz University of Medical Sciences, Sheshgelan St., Tabriz, Iran

Abstract: The goal of this study was to investigate the role of procalcitonin (PCT) in diagnosis of neonatal sepsis and its correlation with C-Reactive Protein (CRP). One hundred and seventeen neonates with the gestational age≥35 weeks with clinically suspected diagnosis of neonatal sepsis were studied during one year from 2007 in Tabriz Children's Hospital. Conventional sepsis workup was done in all cases and the diagnosis of neonatal sepsis was proved based on the results of blood culture. The serum procalcitonin was measured by quantitative Chemo-luminance methods and the results were compared with CRP levels between the neonates with and without proven sepsis. The results showed among in 117 neonates with suspected sepsis 27 (23.1%) cases have positive blood culture (proven sepsis). The mean levels of PCT in neonates with and without proven sepsis was 4.42±6.66 vs. 2.06±4.03 ng mL^{-1} and CRP 33.98±36.81 vs. 12.30±20.42 mg L^{-1} were significantly higher in neonates with proven sepsis ($p = 0.026$ and $p<0.001$). The sensitivity, specificity, positive predictive value and negative predictive value of PCT (more than 2 ng mL^{-1}) were 66.7, 50, 28.6, 83.3 and CRP (more than 3.5 mg L^{-1}) were 70.4, 72.2, 43.2 and 89%, respectively, in diagnosis of neonatal sepsis. There was a meaningful correlation between the level of PCT and CRP in the sepsis group ($r = 0.797$, $p<0.001$). The results of the current study showed that more relying on the level of PCT and CRP for planning the management of neonates with suspected sepsis is not logical, but a negative result may be helpful in ruling it out.

Key words: Neonate, sepsis, procalcitonin, C-reactive protein

INTRODUCTION

Neonatal sepsis is invasive bacterial infection occurring during the first month of life. The incidence of culture-proven sepsis is approximately 2 per 1000 live birth and from the 7-13 % of neonates who are evaluated for neonatal sepsis, only 3-8% have culture-proven sepsis. The early signs of sepsis in the newborn are non-specific and include diminished spontaneous activity, less vigorous sucking, apnea, bradycardia, temperature instability, respiratory distress, vomiting, diarrhea, abdominal distension, seizure and jaundice. Therefore many newborns undergo diagnostic studies and the initiation of treatment before the presence of sepsis has been proven, because the mortality rate of untreated sepsis can be as high as 50% (Angus and Wax, 2001). Rapid diagnosis of neonatal sepsis is problematic because the first signs of this disease may be minimal and are similar to those of various non infectious processes, furthermore bacterial culture are time-consuming and other laboratory tests are either not available for routine use or lack sensitivity or specificity. In this situation neonates with risk factors for infection or clinical suspicion of infection are empirically treated with antibiotics. To avoid the unnecessary treatment of non infected patients an early sensitive and specific laboratory test would be helpful to guide clinicians in neonatal units in deciding whether or not to start administering antibiotics. Several leukocyte indices and acute phase protein levels have been evaluated for the diagnosis of sepsis and more recently measurement of multiple plasma cytokines (Hodge *et al*., 2004b) and leukocyte activation markers (Hodge *et al*., 2004a) have showed promising results. However to date no single laboratory test has provided rapid and reliable identification of infected neonates. This inability has led to a search for new diagnostic markers (Polin, 2003; Lopez Saster *et al*., 2007). Procalcitonin is the precursor protein of calcitonin and has no hormonal activity. It is a 116 amino-acid protein with a molecular mass of 14. 5 kDa (Whicher *et al*., 2001). It was shown in healthy volunteers that PCT is detectable in the plasma two hours after the injection of a small amount of bacterial endotoxins, increasing rapidly in 6-8 h and reaching a plateau and then decreasing to normal levels after 24 h (Whicher *et al*., 2001; Dandona *et al*., 1994). PCT levels increase in sever sepsis

Corresponding Author: K. Sakha, Department of Pediatrics, Tabriz University of Medical Sciences, Tabriz, Iran

and its plasma concentration is related to the patients clinical condition and capacity of immune reaction. Serum PCT levels appeared to correlate with the severity of microbial invasion and decreased rapidly after appropriate antibiotic therapy. (Whicher *et al*., 2001; Ghillani *et al*., 1989). It has been recently reported that PCT increases markedly in septic condition (Gendrel *et al*., 2000) and it appears to be a good predictor of infection severity (Muller *et al*., 2001). The results of recent studies suggest the usefulness of PCT for early diagnosis of neonatal sepsis (Blommendahl *et al*., 2002; Franz *et al*., 1999), although other investigators have observed lack of accuracy for this marker (Koskenvuo *et al*., 2003; Lapillonne *et al*., 1998). CRP is one of the acute phase proteins, although it is a classical and sensitive marker of inflammation, it cannot be used to differentiate between bacterial and other infections (Jaye and Wistes, 1997). It is a disadvantage that CRP increases after PCT for the follow-up of the progression of the infection (Whicher *et al*., 2001). Hatherill reported in critically ill children the admission procalcitonin is better diagnostic marker of infection than CRP or leukocyte count. A procalcitonin concentration of 2 ng mL^{-1} might be useful in differentiating severe bacterial disease in infant and children (Hatherill *et al*., 1999). Monneret study showed elevated PCT levels correlate with sepsis and that appropriate antibiotic therapy lowers it rapidly, they also found that CRP did not show a similar correlation (Monneret *et al*., 1997). The aim of our study was to determine the role of the procalcitonin in diagnosis of neonatal sepsis and correlation between procalcitonin and C-reactive protein in these patients.

MATERIALS AND METHODS

This is a retrospective cross-sectional study on 117 suspected sepsis neonates at the age of 0-28 days who were admitted in neonatal service of children hospital of Tabriz University Medical Sciences during April 2007 to April 2008. In this study we excluded all newborn with congenital anomaly, gestational age under 34 weeks, suspected haemorrhage and neonates delivered with asphyxia.

Before antibiotic therapy conventional sepsis workup was carried out in all cases including: CBC counts, ABG, Chest x-ray, Urine culture and analyzes, Lumbar puncture for CSF culture and biochemical analyzes and 0.5 mL blood sample with sterile method for blood culture. CRP was determined using an immunonephelometric methods (using BN II device, Germany).

Three milliliter blood sample was drawn from all neonates, and blood samples were centrifuged within 30 min of collection. Serum was stored at -20°C before analysis. PCT was measured by quantitative Chemo-Luminance method (Diasorin, Germany). The neonates were divided in two groups regarding their laboratory results and general appearances, proven sepsis who had positive blood culture and suspected sepsis who had negative blood culture but had positive CRP and either nutropenia or thrombocytopenia and positive chest x-ray. The increase in PCT more than 2 ng mL^{-1} and CRP more than 3.5 mg L^{-1} were investigated in two groups and then correlation between serum PCT level and CRP was evaluated in these patients. Statistical analysis with the SPSS version 15 software, correlation between the variable and the statistical differences were analyzed using Pearsons, Chi-squared test, Mann-Whitney U test and Student t-test. The reliability of serum PCT and CRP concentration for the diagnosis of neonatal sepsis was calculated by Receiver Operating Characteristic (ROC) curves. Sensitivity, specificity and the likelihood ratio of a positive and negative result with the 95% Confidence Interval (CI) were calculated Statistical significant was set at ($p<0.05$).

The research review board and ethic committee of Tabriz University of Medical Sciences approved the study (Code No. 8528).

RESULTS AND DISCUSSION

From 117 term neonates 27 patients (group 1) had proven sepsis (blood culture positive) and 90 of them (group 2) had suspected sepsis (blood culture negative).

Mean variable comparison between two group is shown in Table 1.

As shown in Table 1, except PCT and CRP there are not statistically meaningful differences between two group. The mean level of PCT and CRP were significantly higher in neonates with proven sepsis as shown in Fig. 1 and 2.

Serum PCT level was higher in 18 cases of group 1 and 45 patients of group 2 ($p = 0.128$), and also CRP level was higher in 19 cases of group I and 25 neonates of group 2 ($p<0.001$).

Simultaneous increase in serum CRP and PCR was seen in 17 cases of group 1 and 19 patients of group 2 and this relationship was statistically meaningful in group I than other group ($p<0.001$). The diagnostic value of PCT and CRP in neonatal sepsis is shown in Table 2.

ROC curves in PCT value for diagnosis of neonatal sepsis are depicted in Fig. 3. The area under the curve were 0.614 (95 CI, 47 to 75%). Cut off level with the optimum diagnostic efficiency derived from the ROC curve were 1. 36 ng mL^{-1} and the sensitivity and specificity of PCT in diagnosis of neonatal sepsis were

Table 1: Mean variable comparison between two group

Variables	Group 1 (No. 27)	Group 2 (No. 90)	p-value
Age	11.12±8.94	7.99±8.01	0.086
Gender			
Male	17	58	
Female	10	32	0.888
Weight (g)	2715.93±412.31	2871.89±640.64	0.236
Height (cm)	48.22±4.23	47.61±3.56	0.456
Head circumferences	34.5±2.50	34.15±2.25	0.468
Positive CSF culture	2	0	0.999
Positive urine culture	1	2	0.548
WBC			
Total	10096.30±5384.27	11578.89±5874.44	0.244
Immature/Total	2.11±4.22	1.36±2.23	0.222
Platelet	181962.96±103213.18	222188.89±119856.55	0.118
Bilirubin			
Total	22.43±9.56	14.77±7.92	0.070
Direct	0.63±0.32	0.74±0.93	0.070
Positive CXR	10	33	0. 972
Procalcitonin (ng mL^{-1})	4.42±6.66	2.06±4.03	0.026
CRP (mg L^{-1})	33.98±36.81	12.30±20.22	0.001

Table 2: The diagnostic value of PCT and CRP in neonatal sepsis

Variables	Sensitivity	Specificity	Positive predictive value	Negative predictive value
	(%)			
Higher PCT	66.7	50.0	28.6	83.3
Higher CRP	70.4	72.2	43.2	89.0
Higher PCT and CRP	63.0	78.9	47.2	87.7
Normal PCT and CRP	43.3	74.1	84.8	28.2

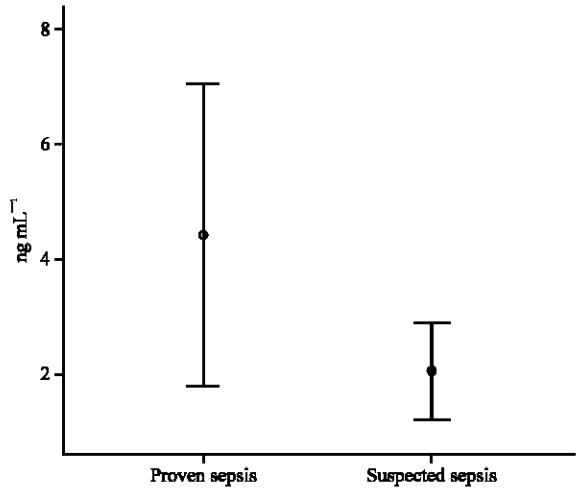

Fig. 1: Serum PCT level in neonates with and without proven sepsis

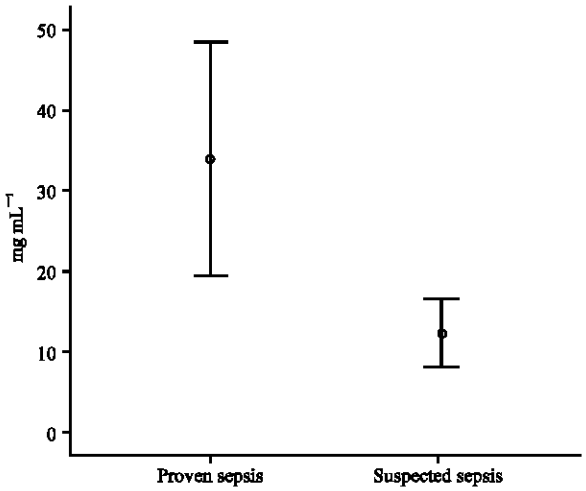

Fig. 2: The level of serum CRP in neonates with and without proven sepsis

55/6, 63.3%, respectively. In Fig. 3 the CRP value for diagnosis of neonatal sepsis with regard to area under the ROC curve were 0. 734 (95 CI, 62-85%). The cutoff level with the optimum diagnostic efficiency derived from the ROC curve for CRP were 4. 86 mg L^{-1} and the sensitivity and specificity of CRP in diagnosis of neonatal sepsis were 70.4 and 74.4%, respectively.

In this study there was meaningful correlation between the level of serum PCT and CRP in the sepsis group ($r = 0.797$, $p<0.001$) (Fig. 4).

In the present study we investigated serum level of PCT and CRP in neonates with or without proven sepsis. The results of this study shows that mean level of these factors are higher in neonates with proven sepsis than those without sepsis, and these difference is statistically meaningful. Kocabas *et al.* (2007) study in 29 neonates with proven sepsis and 29 normal neonates showed that mean level of serum PCT and CRP is significantly higher in neonates with proven sepsis.

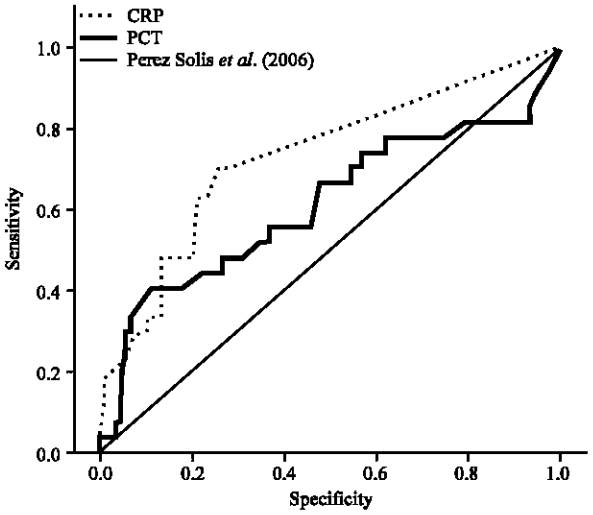

Fig. 3: ROC curve in PCT and CRP for diagnosis of neonatal sepsis

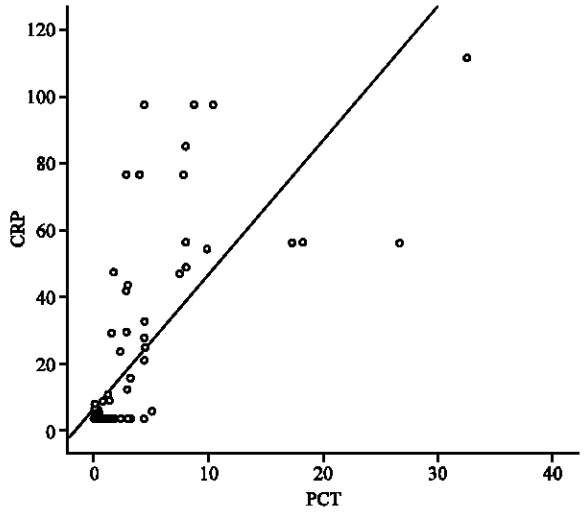

Fig. 4: Correlation between level of serum PCT and CRP in evaluated neonates

Perez Solis *et al.* (2006) compared serum level of PCT and CRP in 20 neonates with nosocomial sepsis and 20 normal neonates, the results of this study showed the serum level of PCT and CRP is statistically meaningful in sepsis group. This result of our study is similar to above findings. In present study the sensitivity and specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of PCT with cutoff level more than 2 ng mL^{-1} were 66.7, 50, 28.6 and 83.3%, respectively and for CRP with cutoff level more than 3.5 mg L^{-1} were 70.4, 72.2, 43.2 and 89%, respectively, in diagnosis of neonatal sepsis. Boo *et al.* (2008) showed in 18 neonates from 87 infants with confirmed sepsis based on positive blood culture results at a PCT cutoff level of greater than or equal to 2 ng mL^{-1} the sensitivity and specificity, PPV and NPV were 88.9, 65.2, 40 and 95.7% and for CRP 55.6, 89.9, 58.8 and 88.6%, respectively. Ballot *et al.* (2004) studied 52 neonates with possible infection and only 13 neonates had definite infection, in these neonates sensitivity and negative predictive value of serum PCT was 89.5 and 95%, respectively, but they stated that 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 full sepsis evaluation, but is relatively expensive. A negative PCT on presentation may rule out sepsis. Joram *et al.* (2006) investigated umbilical cord blood PCT and CRP concentration for early diagnosis of very early onset neonatal infection, they measured PCT and CRP concentration in umbilical cord blood of 197 neonates for evaluating their value as markers of infection. Sixteen of the neonates were infected, the sensitivity and specificity, PPV and NPV were respectively, 887.5 98.7, 98.7 and 87.5 for PCT and 50, 94 and 67% for CRP. They believe that serum PCT in cord blood is useful as early marker of antenatal infection. Recently Vazzalwar *et al.* (2005) assessed PCT for the diagnosis of late-onset sepsis in 67 neonates. At a PCT cutoff value of 1.0 ng mL^{-1} sensitivity was 97% and specificity 80% while with CRP sensitivity 72% and specificity 93%.

Turner *et al.* (2006) with using high cutoff levels for both PCT (2.3 ng mL^{-1}) and CRP (30 mg L^{-1}) in work up assess in 100 neonate with suspected sepsis. They found the specificity and positive predictive value for PCT and CRP was 97, 91 and 96, 87%, respectively, but had low sensitivity (48 and for CRP 41%) to detect neonatal sepsis, in this study area under the ROC curve was 0.74 and 0.73 for PCT and CRP, respectively. Chiesa *et al.* (1998) studied the reliability of PCT concentration in 28 infants who had severe early onset of neonatal sepsis. They found sensitivity, specificity, PPV and NPV were 92.6, 97.5, 94.3 and 96.8%, respectively, they also found that 24 infants had PCT levels higher than normal at the time of diagnosis. However at that time only 13 of them had high CRP levels. Hatherill *et al.* (1999) study showed the sensitivity and specificity of serum PCT level were 92.6 and 97.5%, respectively, in diagnosis of early onset neonatal sepsis and 100% in neonates with late onset sepsis. We did not consider the type of neonatal sepsis in present study. In this study the sensitivity and specificity of CRP was more than PCT, this was due to delayed increase in CRP level in comparison to PCT, in other words, in early onset neonatal sepsis PCT releases earlier than CRP.

The results of the reports are various, the causes of these differences are age of newborns, methods of PCT and CRP measurement and determination of cutoff levels of them, sepsis workup technic, amount of blood sample taken for blood culture, previous use of antibiotic and organism involved in sepsis that all may interfere in results.

CONCLUSION

The results of the current study showed more relying on the level of PCT and CRP for planning the management of neonates with suspected sepsis is not logical, but a negative results may be helpful in ruling it out.

ACKNOWLEDGMENT

We acknowledge from research vice chancellor of Tabriz University of Medical Sciences for this research.

REFERENCES

Angus, D. C. and R. S. Wax, 2001. Epidemiology of sepsis: An up date. Crit. Care. Med., 29: 109-116.

Ballot, D. E., O. Perovic, J. Galpin and P. A. Cooper, 2004. Erum procalcitonin as an early marker of neonatal sepsis. S. Afr. Med. J., 94: 851-854.

Blommendahl, J., M. Janas, S. Laine, A. Miettinen and P. Ashorn, 2002. Comparison of procalcitonin with CRP and differential white blood cell count for diagnosis of culture-proven neonatal sepsis. Scand. J. Infect. Dis., 34: 620-622.

Boo, N. Y., A. A. Nor Azlina and J. Rohana, 2008. Usefulness of a semi-quantitative procalcitonin test kit for early diagnosis of neonatal sepsis. Singapore. Med. J., 49: 204-208.

Chiesa, C., A. Panero, N. Rossi, M. Stegagno, M. De Giusti, J. F. Osborn and L. Pacifico, 1998. Reliability of procalcitonin concentration for diagnosis of sepsis in critically ill neonates. Clin. Ifect. Dis., 26: 664-672.

Dandona, P., D. Nix and M. F. Wilson, 1994. Procalcitonin increase after endotoxin injection in normal subject. J. Clin. Endocrinol. Metab., 79: 1605-1608.

Franz, A. R., M. Kron, F. Pohlandt and G. Steinbach, 1999. Comparison of procalcitonin with interleukin8, C-reactive protein and differential white blood cell count for the early diagnosis of bacterial infections in newborn infants. Pediatr. Infect. Dis. J., 18: 666-671.

Gendrel, D. and C. Bohuon, 2000. Procalcitonin as a marker of bacterial infection. Pediatr. Infect. Dis., 19: 679-687.

Ghillani, P. P., P. Motte and F. Troalen, 1989. Identification and measurement of calcitonin precursors in serum of patients with malignant diseases. Cancer Res., 49: 6845-6851.

Hatherill, M., S.M. Tibby, K. Sykes, C. Turner and I.A. Murdoch, 1999. Diagnostic markers of infection, comparison of procalcitonin with C-reactive protein and leucocyte count. Arch. Dis. Child., 81: 417-421.

Hodge, G., S. Hodge, P. Han and R. Haslam, 2004a. Multiple leucocyte activation markers to detect neonatal infection. Clin. Exp. Immunol., 135: 125-129.

Hodge, G., S. Hodge, R. Haslam, A. McPhee, H. Sepulveda, E. Morgan, I. Nicholson and H. Zola, 2004b. Rapid simultaneous measurement of multiple cytokines using 100 micro sample volumes association with neonatal sepsis. Clin. Exp. Immunol., 137: 402-407.

Jaye, D.L. and K.B. Wsites, 1997. Clinical applications of C-reactive protein in pediatrics. Pediatr. Infect. Dis. J., 16: 735-747.

Joram, N., C. Boscher, S. Denizot, V. Loubersac, N. Winer, J. C. Roze and G. C. Gras-Le, 2006. Umbilical cord blood procalcitonin and C-reactive protein concentrations as markers for early diagnosis of very early onset neonatal infection. Arch. Dis. Child. Fetal. Neonatal. Ed., 91: F65-F66.

Kocabas, E., A. Sarikcioglu, N. Aksaray, G. Seydaoglu, Y. Seyhun and A. Yaman, 2007. Role procalcitonin, C-reactive protein, interleukin-6, interleukin-8 and tumor necrosis factor-alpha in the diagnosis of neonatal sepsis. Turk. J. Pediatr., 49: 7-20.

Koskenvuo, M.M., K. Irjala, A. Kinnala, O. Ruuskanen and P. Kero, 2003. Value of monitoring serum procalcitonin in neonates at risk of infection. Eur. J. Clin. Micribiol. Infect. Dis., 22: 377-378.

Lapillonne, A., E. Basson, G. Monneret, J. Bienvenu and B. L. Salle, 1998. Lack of specificity of procalcitonin for sepsis diagnosis in premature infants. Lancet, 351: 1211-1212.

Lopez Sastre, J.B., D. Perez Solis, V.R. Serradilla, B.F. Colomer and G.D. Coto Ccotallo, 2007. Evaluation of procalcitonin for diagnosis of neonatal sepsis of vertical transmission. BMC. Pediat., 7: 9-9.

Monneret, G., J.M. Labaune, C. Isaac, F. Bienvenu, G. Putet and J. Bienvenu, 1997. Procalcitonin and C-reactive protein levels in neonatal infection. Acta. Pediatr., 86: 209-212.

Muller, B., J.C. White, E.S. Nylen, R.H. Snider, K.L. Becker and J.F. Habener, 2001. Ubiquitous expression of the calcitonin-i gene in multiple tissues in response to sepsis. J. Clin. Endocrinol. Metab., 86: 396-404.

Perez Solis, D., J.B. Lopez Sastre, G.D. Coto Cotallo, M.A. Dieguez Junquera, E. M. Deschamps Mosquera and M. Crespo Hernandez, 2006. Procalcitonin for diagnosis of nosocomial neonatal sepsis. An. Pediat (Barc), 64: 349-353.

Polin, R.A., 2006. The ins and outs of neonatal sepsis. J. Pediatr., 143: 3-4.

Turner, D., C. Hammerman, B. Rudensky, Y. Schlesinger and M.C. Schimmel, 2006. The role of procalcitonin as a predictor of nosocomial sepsis in preterm infants. Acta Paediat., 95: 1571-1576.

Vazzalwar, R., E. Pina-Rodrigues, B.L. Puppala, D.B. Angst and L. Schweig, 2005. Procalcitonin as a screening test for late-onset sepsis in preterm very low birth weight infants. J. Perinatol., 25: 397-402.

Whicher, J., J. Bienvenu and G. Monneret, 2001. Procalcitonin as an acute phase marker. Ann. Clin. Biochem., 38: 483-493.