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Relevance of Procalcitonin for the Diagnosis of Early and Late-Onset Sepsis in Newborns

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1. Introduction

In hospital neonatology, bacterial infections represent significant mortality and morbidity [1-2]. Early diagnosis of bacterial infection in neonatal resuscitation is difficult but essential. Any delay in the initiation of antibiotic therapy is deleterious for prognosis. The lack of specific clinical signs, the elevation of deferred C-reactive protein (CRP) and the time necessary to obtain bacteriological results often delay the establishment of diagnosis. It is usually confirmed by bacteriological analysis of central samples, in particular by exploring blood culture. Recently, new markers of infection status have been proposed for their sensitivity and specificity [3-5]. CRP is currently the most frequent marker used for diagnosis and monitoring of infections in neonates. This is the marker presenting low sensitivity and specificity for initial diagnosis of NS. It rises about 24 hours after the infectious stimulus. Procalcitonin (PCT) is the prohormonal peptide of calcitonin, consisting of 116 amino acids. To date, the site of synthesis and the action of this new biomarker are still unknown. It takes place into extrathyroïdal tissue and its secretion is induced by bacterial endotoxins, with an important role in liver parenchyma [6]. Its increase serum level when bacterial infections have been demonstrated in 1992. These data were confirmed by a prospective pediatric study in 1993 and applied to neonatal monitoring since 1998 [7-12]. In neonatology, studies on the usefulness of PCT are controversial.

For adults, it is shown that in emergencies and general medicine, the PCT may allow a reduction of ABT prescriptions [13-16]. The PCT also helps reduce the indications complementary examinations [17] and durations of ATB in the ICU [18].

2. Diagnosis and management of neonatal sepsis

Bacterial infections can be a devastating complication for newborns and continue to be a significant cause of mortality and long-term morbidity for hospitalized newborns and premature infants [2, 19]. In the United States, the estimated annual incidence of severe sepsis in newborns is 0.3 per 100 live births. The estimated mortality for neonates with severe sepsis is 10.3%, with most deaths occurring within the first 48 hours of infection. Mortality rates vary by causative organisms. Data from the National Institute of Child Health and Human Development Neonatal Research Network reported mortality rates with gram-negative infections at 36% and 32% with fungal infections. Infected infants had significantly longer hospital stays, ongoing neurodevelopmental impairment, and higher mortality rates than very low birth weight infants who did not have late-onset sepsis. The diagnosis of neonatal sepsis is difficult to establish and remains a challenge for neonatal health care providers. Early signs and symptoms of neonatal sepsis are often nonspecific and easily confused with conditions that are expected in this population. The fear of missing a case of neonatal infection with its serious outcomes has led to overuse of antibiotics in the neonatal intensive care environment and the emergence of resistant organisms. Neonatal care providers have evaluated numerous tests searching for one that would be helpful for the diagnosis of NS with a rapid confirmation. Despite extensive investigation over the past decades, there is still no single test to be ideal for the early diagnosis of sepsis in newborns. In usual practice and research, investigations include blood culture and bacteriologic samples, hematological examinations, acute phase reactants (proteins CRP and PCT) and polymerase chain reaction [1]. In this article, we mainly study acute phase proteins, with a special interest for PCT. A recent study demonstrates that level of umbilical cord blood PCT is considered as a risk factor for mortality in very premature infants [20].

3. Early-Onset Neonatal Sepsis (EONS)

Bacterial maternofetal infection is one of the most common cause of neonatal morbidity and mortality. Early diagnosis and treatment are vital to improve outcome. Bacteriological results are not relevant. In the absence of reliable infection markers during the first hours of life, pediatricians often start early antibiotic treatment in newborn infants with risk factors for infection, exposing a considerable number of patients to unnecessary treatment. PCT has been implicated as a sensitive and specific marker of bacterial infection. However, it is well established that PCT concentrations in the neonate show a physiological increase during the first two days of life, which complicates the interpretation of results during this period; CHIESA present the results of work on the kinetics postnatal of the PCT with distribution of PCT values obtained for uninfected and EONS patients between birth and 48 hours of age [9]. Turner [21] study PCT concentration of uninfected and EONS preterm infants between birth and 96

hours of age, with 2 groups to 24-30 and 31—36 weeks gestation; results of these two groups are different.

Serum PCT in cord blood seems to be a useful and early marker of antenatal infection and EONS. In a previous study [22], PCT and CRP concentrations in umbilical cord blood of 197 neonates were measured to evaluate their values as markers for infection. Sixteen of the neonates were infected. The sensitivity, specificity, and negative and positive predictive values were respectively 87.5%, 98.7%, 87.5%, and 98.7% for PCT and 50%, 97%, 67%, and 94% for CRP. Serum PCT in cord blood seems to be a useful and early marker of antenatal infection. PCT measurement in umbilical cord blood appears to be a sensitive and specific marker of antenatal infection, with high positive and negative predictive values. It also presents good positive and negative likelihood ratios, and appears to be more reliable than CRP. Focusing on PCT concentrations in umbilical cord blood before the physiological increase or eventual respiratory or hemodynamic failure makes interpretation for the diagnostic value of PCT concentration easier. On the other hand, the limitation of such an early PCT measurement is that it does not allow the detection of ''late'' maternofetal infection related to perpartum or postnatal contamination.

The detection of infected neonates and its good negative predictive value should result in the reduction number of patients unnecessarily treated. In particular, PCT measurement should allow the clinician to distinguish infections from simple colonizations.

Interestingly, PCT seems to be present in full term and preterm neonates. This reduction in antibiotic prescriptions would represent a direct advantage for neonates, because of the potential toxicity for antibiotics, and an indirect ecological advantage by reducing antibiotic selection pressure. Although the specificity and negative predictive value for PCT in this study were precisely evaluated with a confidence interval of 1%, the number of infected patients was too small to provide definitive sensitivity and positive predictive value. Although these rapid tests look promising for PCT as a useful tool for diagnosing sepsis in newborn infants, our results on a relatively small number of neonates should be confirmed by a properly designed trial.

Two others important studies demonstrate interest for PCT in the diagnosis of NS at 24 hours of age, and in the decision of antibiotic therapy duration [23-24]. Stocker [24], with multicenter study and with large number of subjects and correct methodology, show that Procalcitonin determinations allowed to shorten the duration of antibiotic therapy in newborns with suspected EONS.

4. Late-Onset Neonatal Sepsis (LONS)

Our study [25] has evaluated the contribution of PCT assay to Central catheter during a prolonged hospitalization. Using the quantitative KRYPTOR1-PCT method, we determined

the sensitivity (Se) and the specificity (Sp) for PCT and C-reactive protein (CRP). Newborns with a suspicion of BNI were included. They were divided into two groups: not infected (group 0), infected (group 1). Comparing the two groups, we established a threshold value for PCT and CRP using the ROC curves. We also highlighted Se, Sp, positive (VPP) and negative predictive values (VPN) for PCT and CRP.

Forty premature newborns of 28.3 weeks gestational age average were included during a 17 months period. The distribution was as follows: 26 patients in group 0 and 14 patients in the group 1. The threshold value was 0.8 ng/ml for PCT, 6 mg/l for CRP. The Se, Sp, VPP and VPN values were 79, 96, 92 and 89% for PCT, 50, 88, 70 and 77% for CRP. From the ROC curves, the surface under curve was 0.94 for PCT, 0.68 for CRP ($p < 0.05$). In conclusion, this study confirms the interest of PCT assay in the diagnosis of BNI in premature newborns.

There are several biases in our study: the difficulties of sampling in children premature unstable represent a major obstacle to get adequate blood volume in our study. Some infants with nosocomial infection could therefore not be included in this study period, but their number is small (<5) and our sample is probably representative Moreover, Group 0 uninfected children is not a group of healthy children, since they had a clinical suspicion of infection. As a result, the reference values calculated for the PCT from the population in group 0 are not those of children "completely healthy" but children free from infection. Finally, unlike other case-control studies, we have not studied as controls. This mode of recruitment does not allow us to establish normal values really, but seems close to daily practice. Indeed, the difficulty of establishing a diagnosis of infection in neonatal intensive care and neonatology in a population largely consisting of premature is the lack of specificity of clinical signs of appeal that may also be revealing a multitude of other diseases that would be particularly associated with preterm children. Another possible bias in selection: non-homogeneous population, with two children with a digestive surgery. We kept them in the study, this corresponds to the actual recruitment service during the study period.

through grading, defined by the difficulty of defining the bni, is probably one of the main problems of our study. in the absence of gold standard defined, we chose the bacteriological results for reference, but we know that the blood culture may result in false negatives by insufficient sampling or contamination by false positives, this being related to the number blood cultures, the amount of blood and the realization of the sample. we included children with clinical features suggestive of initial infection. we have not included other bni definitions, based on other predictors or proposed for the older child. we have not studied the value of pct and crp markers for confirmation of diagnosis and decision for the continuation or discontinuation of the antibiotic.

The sensitivity of the PCT (nearly 80%) clarifies that the PCT is an interesting marker for the diagnosis of BNI in this study. These results are limited, this corresponds to

small numbers, with very wide confidence intervals. The number of studies in the literature on the subject is important enough, but the methodologies are different (Type of study, measurement method, study population, definition of infection. . .) and the results are variable [26-36]. Kuhn et al. [28] found a sensitivity and specificity less important that in our study (Se: 76.5 versus 78.6%; Sp: 82.7 versus 96.2%) in case of nosocomial infection. In contrast, Chiesa et al. [32] with excellent results since the sensitivity and specificity of 100% are obtained. It is Similarly Enguix et al. [33], but it is case- witnesses. Van Rossum et al. [31] indicate that studies give results of sensitivity and specificity vary because of different methodologies or children's associations with early infections (maternofetal) and late (nosocomial). The study Vazzalwar et al. [27] is a cohort study a population of premature infants, finding results satisfactory and in line of great interest to the PCT. The measurement method is the Lumitest1-PCT, in addition, two blood cultures are performed before the initiation antibiotic treatment (one in our study). Other authors found different results: Lopez Sastre et al. [34] and Perez Solis et al. [35] conclude moderate interest in the PCT, but do not compare to the CRP, the result of the Youden index in the study Lopez Sastre et al. is lower than in our study (0.62 versus 0.75). Turner et al. [21] found a similar interest of PCT and CRP, but this study with a methodology and a population different from ours. Isidor et al. [36], with a semi-quantitative method, found values close to our study (likelihood ratio 14.9 and 0.09 versus 20.7 and 0.2). It is important to note that the dosages quantitative PCT in other studies were performed by quantitative technique to immunoluminometric using the PCT-Lumitest1 of Brahms.

A priori, the results obtained with the Kryptor1-PCT and PCT-Lumitest1 well correlated. In our study, from the ROC curve, we determine a threshold value of PCT to 0.8 ng / ml for the diagnosis of BNI. It is relatively comparable to that obtained during the study by Kuhn et al. [3] which includes 38 patients aged three to 61 days of life (16 infected and 22 non-infected) and evaluates the threshold of the PCT to 0.6 ng/ml. Vazzalwar et al. [27] found a threshold value 0.5 ng / ml. This is not what the study authors found following, but it is case-control studies. Chiesa et al. carry out a study [32] in a population composed of 23 infected newborns matched to 92 neonates not infected, aged three to 30 days of life. All newborns PCT infected have a greater than 2 ng / ml and all control children have a PCT less than 1 ng / ml. Enguix et al. [33] also obtained excellent results during a prospective study of 20 newborns infected and 26 infants free of any infection, aged three to 30 days of life, with a threshold value of 6.1 ng / ml. Comparison with other parameters biological, CRP is the marker most commonly used. The sensitivity of the CRP, 50% in our study was 72% in the study Vazzalwar et al. [27] studies similar to ours in terms of methodology and the target population. Cytokines can also assayed in a timely manner to clinical use, but are not yet used in routine. Kuhn et al. [3, 28] compared the value of the assay the PCT, interleukin 6 and interleukin 8 in the early diagnosis of nosocomial infection. The interleukin 6 appears to be the most interesting of the three. In addition, the diagnostic performance of these three markers are greatly increased when combined with dosing

CRP. Using meta-analysis [29, 30], PCT is a valuable additional tool for the diagnosis of NS, but methodologies of studies, and age of patients are different. This sensitive analysis shows that differences in PCT assay producer, gestational age and severity of sepsis in the population studied may partially explain the between-studies heterogeneity.

In conclusion in our study of very premature bearing a central line, with a new quantitative method, the PCT has better sensitivity and specificity than CRP for early diagnosis of nosocomial infection. The dosage of the PCT is useful and applicable in neonatology current in the detection of BNI.

The PCT is an early marker of bacterial infection in NICU. Bacteriological results are also not relevant. In our study using a new quantitative method, the PCT has better sensitivity and specificity than CRP for early diagnosis of nosocomial infection for very premature infants bearing a central line.

However, it is necessary to confirm these results by including more patients.

Larger multicenter trials, in respect with CONSORT statement, are required to validate the routine use of PCT as a marker of LONS in NICU [37].

This could improve the outcome of neonatal infection by initiating early treatment but above all by limiting duration of unnecessary antibiotic treatments.

5. Conclusion

Accurate diagnosis of NS is difficult on account of the imperfect diagnostic sensitivity of laboratory tests. All predisposing factors to infection such as prenatal history, clinical presentation of the newborn, and laboratory results must be considered to treat all those who have infections, and yet minimize the use of antibiotics in those without infection.

A better understanding of the neonatal inflammatory response to infection has led to the identification of multiple diagnostic markers of sepsis. At present, The PCT is an early marker of NS, but none of the current diagnostic markers are sensitive or specific enough to influence with certainty the decision to start antibiotic therapy. These diagnostic markers are promising for the early diagnosis for EONS and LONS, and for discontinuation of antibiotic treatment with suspected sepsis. Further evidence from large multicenter trials is needed to evaluate the newer diagnostic markers prospectively for their incremental diagnostic value before they can be considered reliable for diagnosing early infections and be included as part of a routine sepsis evaluation for neonates. Therefore, the neonatal care provider remains dependent on a thorough history and physical assessment in combination with available laboratory tests to guide treatment for presumptive sepsis while awaiting culture results.

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Appendix

Abbreviations : CRP, C reactive protein; PCT, Procalcitonin; EONS, Early-onset neonatal sepsis; LONS, Late-onset neonatal sepsis; NS, Neonatal sepsis; BNI, Bacterial nosocomial infection; NICU, Neonatal Intensive Care Unit; ICU, Intensive care unit; ABT, Antibiotherapy.

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