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Chapter 4

The Role of C-Reactive Protein in the Diagnosis of Neonatal Sepsis

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1. Introduction

During the last decades advances in neonatal intensive care have led to an impressive decrease of neonatal mortality and morbidity. However, infectious episodes in the early postnatal period still remain serious and potentially life-threatening events with a mortality rate of up to 50% in very premature infants. [1, 2] The signs and symptoms of neonatal sepsis can be clinically indistinguishable from various noninfectious conditions such as respiratory distress syndrome or maladaptation. Therefore rapid diagnosis is crucial for preventing the child from an adverse outcome. The current practice of starting empirical antibiotic therapy in all neonates showing infection-like symptoms results in their exposure to adverse drug effects, nosocomial complications, and in the emergence of resistant strains. [3]

Sepsis results from the complex interaction between the invading microorganism and the host immune, inflammatory, and coagulation response. [4, 5] Inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8, IL-15, IL-18, MIF) and growth factors (IL-3, CSFs), and their secondary mediators, including nitric oxide, thromboxanes, leukotrienes, platelet-activating factor, prostaglandins, and complement, cause activation of the coagulation cascade, the complement cascade, and the production of prostaglandins, leukotrienes, proteases and oxidants. [6]

Laboratory sepsis markers represent a helpful tool in the evaluation of a child with clinical signs and complement the evaluation of a neonate with a potential infection. During the last decades efforts were done to improve laboratory sepsis diagnosis and a variety of the above mentioned markers and more were studied with different success. Despite the promising results for some of them current evidence suggests that none of them can consistently diagnose 100% of infected cases. C-reactive protein (CRP) is the most extensively acute phase reactant studied so far and despite the ongoing rise (and fall) of new infection markers it still remains the preferred index in many neonatal intensive care units.

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There is great interest in rapid diagnostic tests that are able to safely distinguish infected from uninfected newborns, especially in the early phase of the disease. [7] In fact, a delayed start of the antibiotic treatment may be no more able to stop the fulminant clinical course with development of septic shock and death within hours after the first clinical symptoms. [8] In the era of multi-resistant microorganisms, it is as well important to avoid the unnecessary use of antibiotics in sepsis-negative infants.

2. Structure and function of CRP

CRP was first described in 1930 by Tillet and Francis at Rockefeller University. [9] They observed a precipitation reaction between serum from patients suffering acute pneumococcal pneumonia and the extracted polysaccharide fraction C from the pneumococcal cell wall. This reaction could not be observed when using serum of neither healthy controls nor the same pneumonia patients after they had recovered. In view of the fact that the polysaccharide fraction was a protein the C-reactive component in the serum was named C-reactive protein. [9] By the 1950s CRP had been detected in more than 70 disorders including acute bacterial, viral, and other infections, as well as non-infectious diseases such as acute myocardial infarction, rheumatic disorders, and malignancies. [10] All of these disorders of disparate etiology had in common the theme of inflammation and/or tissue injury. [11]

CRP is composed by five identical subunits arranged in a cyclic pentameter shape. The whole protein has a diameter of 102 Å (1 Ångström = 10^{-10} m) and a molecular weight of 118 000 Daltons. [12] All subunits have the same orientation; therefore the whole protein has two faces, a 'recognition' face exhibiting five phosphocholin-binding sites and an 'effector' face containing complement and Fc-receptor-binding sites. [12] The principal ligand to CRP with the highest binding affinity is phosphocholin, which is found in lipopolysaccharid and cell walls of many bacteria and micro-organisms as well as in the outer leaflet of most biological membranes. [12]

After binding to a macromolecular ligand CRP is recognized by the component C1q of the complement system and activates it on the classical pathway. CRP-ligand complexes bind to the Fc-receptor on neutrophil granulocytes, macrophages, etc as well and thus promote phagocytosis of the pathogen. CRP further activates monocytes and macrophages and stimulates the production of pro-inflammatory cytokines such as Interleukin-1 and Tumor necrosis factor α. [12, 13]

3. CRP is part of the acute-phase-response

The acute-phase-response is a physiological and metabolic reaction to an acute tissue injury of different etiology (trauma, surgery, infection, acute inflammation, etc) which aims to neutralize the inflammatory agent and to promote the healing of the injured tissue. [11]

After a trauma or the invasion of microorganisms an acute localized inflammatory reaction is initiated by activation of local resident cells. The contact with bacterial endo-or exotoxins

initiates the release of prostaglandins, leucotriens, and histamine, which results in vasodilatation, elevated vascular permeability, sensibilization of nozizeptors, and attraction and activation of further inflammatory cells.

Activated fibroblasts, leukocytes, and endothelial cells produce pro-inflammatory cytokines including IL-1, TNF- α, and IL-6. They are responsible for the development of fever, lethargy, arthralgia, and headache, they activate the vascular endothelial cells, regulate proliferation of T-and B-lymphocytes, activate macrophages, have pro-coagulatory effects on endothelial cells, and they induce the production of acute-phase-proteins in the hepatocytes of the liver.

Acute-phase-proteins form a heterogeneous group and include components of the complement system, coagulation factors, protease inhibitors, metal binding proteins, CRP, and other proteins that increase or decrease by more than 25% during an inflammatory reaction. [11-13]

The production of CRP in the hepatocytes is mainly induced by IL-6 but can be further increased by synergy with IL-1. [14]] Some authors have aimed to determine the normal serum CRP concentration in healthy adults: In 1981 Shine et al. [15] evaluated serum concentration of CRP determined by radioimmunoassay in 468 sera from normal adult volunteer blood donors and reported on a median concentration of 0.8 mg/l with a 90th percentile of less than 3.0 mg/l. More recently, Rifai and Ridker [16] used three different high-sensitivity techniques to determine CRP distributions in their cohort consisting of 22 thousand healthy adults from the Unites States. The median CRP values for men and women were 1.5 and 1.52 mg/l, the 90th percentiles were 6.05 and 6.61 mg/l, respectively. Similarly, Imhof et al [17] examined CRP values from 13 thousand apparently healthy men and women from different populations in Europe. The reported median concentration in the single cohorts ranged from 0.6 to 1.7 mg/l, the 90th percentiles from 3.2 to 8.0 mg/l.

During the acute-phase-response the hepatic synthesis rate increases within hours and can reach levels 1000 fold. [10, 12] CRP levels remain high as long as the inflammation or tissue damage persists and then decrease rapidly. The half life time of CRP is 19 hours under all conditions, which shows the synthesis rate alone is responsible for the actual serum concentration. [18]

4. Serial CRP determinations are of high sensitivity in diagnosis of neonatal sepsis

CRP passes the placenta only in very low quantities, therefore, any elevation in the neonate always represents endogenous synthesis. [19] De novo hepatic synthesis starts very rapidly after a single stimulus with serum concentrations rising above 5 mg/l by about 6 hours and peaking around 48 hours. [20]

In diagnosis of early onset sepsis previous studies reported on widely differing sensitivities and specificities of CRP ranging from 29% to 100% and from 6% to 100%, respectively. [11,

21, 22] These extreme variations are a result of different reference-values, test methodologies, patient characteristics and inclusion criteria, number of samples taken, and sampling time. Furthermore, definitions of sepsis widely differ between studies making serious comparisons hardly possible.

The sensitivity of CRP is known to be the lowest during the early stages of infection. [23-25] For a single CRP determination at the time of first sepsis evaluation the sensitivity and specificity range from 22% to 69% and from 90% to 96%, respectively. [23, 24, 26-29] Similar results were reported for cord blood CRP. Even with low cut-off values being used [1 to 5 mg/l) sensitivities and specificities ranged from 22 to 74% and from 78 to 97%, respectively. [30-33] Thus, a single normal value at the initial sepsis work-up is not sufficient to rule out an infection [11].

On the other hand a raised CRP is not necessarily diagnostic for sepsis, as elevations may as well occur due to the physiologic rise after birth or non infection associated conditions (see below). Therefore, concerns were raised about the reliability of CRP during the early stage of the disease being neither able to diagnose nor to rule out an infection with certainty. [23]

Benitz et al. [23] found that the sensitivity in the diagnosis of culture proven early onset sepsis increased from 35% at the initial sepsis work-up to 79% and 89% when CRP determination was performed on the two following days. In a large series of 689 neonates (187 with sepsis) Pourcyrous et al. [24] reported a higher sensitivity for CRP levels determined at least 12 hours after the initial evaluation compared to the first value (54% vs. 74%). In general the sensitivity substantially increases with serial determinations 24 to 48 hours after the onset of symptoms, and several studies reported on sensitivities and specificities ranging from 78% to 98% and from 81% to 97%, respectively. [11, 21, 23-27, 34]

Some authors have suggested that serial determinations may be useful for identification of infants who do not have a bacterial infection as well: Two consecutive CRP values <10 mg/l carry a 99% negative predictive value in accurately identifying infants not infected. [6, 21, 23, 35-37] At 48 h after onset of symptoms with at least two normal CRP values and negative blood cultures infection can be ruled out and antibiotics can be stopped. [38]

Similarly, serial CRP measurements can be helpful in monitoring the response to treatment in infected neonates, to determine the duration of antibiotic therapy, and to recognize possible complications. [24, 25, 39] In a cohort of 60 neonates with early onset sepsis Ehl et al. [40] demonstrated that after initiation of a successful antibiotic therapy CRP values further increased, peaking and consecutively decreasing after 16 hours. A CRP level that returned again to the normal range may indicate that the duration of antibiotic treatment has been sufficient allowing discontinuation of antibiotics. [35]

5. CRP values can be elevated in non-infectious conditions

In adults, elevated CRP concentration was described in a large variety of disorders apart from bacterial, viral, and fungal infections including burns, surgery, rheumatic disorders, malignancies, and vasculitis. [20]

In neonates, non infection associated elevation of CRP was described in conditions of maternal and perinatal distress, neonatal hypoxia, and tissue damage. Several authors have described links of CRP to maternal fever, stressful delivery, prolonged rupture of membranes and/or prolonged labor, asphyxia, meconium aspiration syndrome, intraventricular hemorrhage, pneumothorax, and tissue injury. [19, 24, 34, 41-49] (see table 1)

-Perinatal asphyxia/ shock [34, 41, 43, 45]
-Maternal fever during labor [41, 42]
-Prolonged rupture of membranes [41-45]
-Stressful delivery or fetal distress [19, 41, 43]
-Prolonged labor [42, 44, 46]
-Clinically silent meconium aspiration[42]
-Surfactant application [48, 64]
-Intra-ventricular hemorrhage[34, 43]
-Pneumo-thorax.[34]
-Tissue injury[24]

Table 1. Non-infectious conditions associated with increased CRP values during the first days of life.

However, the issue on non-infectious CRP elevations in the neonate is not undisputed. Different studies gave to some extent inconsistent results and conditions that some authors described being associated with CRP elevation were not found in other analyses. The earliest descriptions on non infectious conditions influencing CRP derive from simple observations that elevated values in not infected infants might be connected to coincidental non-infectious conditions, though no statistical confirmation is given.

Few investigations were performed on the association of CRP with non infectious conditions in healthy neonates. Chiesa et al. evaluated conditions influencing what constitutes normal CRP values in healthy neonates. In their analysis on 148 healthy term or near term neonates they identified low 5-minute Apgar score and premature rupture of membranes being significantly associated with CRP response at birth and pregnancy induced hypertension with CRP response at 24 hours of life. [45] In a similarly selected cohort of 421 healthy neonates including 200 premature infants they confirmed an association with the time of ruptured membranes and added duration of active labor, prenatal steroids, and intrapartum antimicrobial prophylaxis as variables that had a significant effect on CRP concentrations when adjusted for gestational age, gender, and sampling time. [44]

The current literature suggests that CRP may be elevated in some non-infectious conditions, of which some may per se clinically mimic a bacterial infection as well. Thus, the up to date available information lacks in robust evidence to support a claim that withholding antibiotics may be justified in infants with raised CRP in the above mentioned conditions.

6. CRP performance in diagnosis of neonatal sepsis and baseline CRP concentrations differ between term and preterm neonates

Even though advances in neonatal intensive care have led to increasing preterm birth rates and survival rates, the influences of prematurity on laboratory test results are poorly understood and have not been assessed systematically. This is also true for CRP, which is one of the most extensively studied infection markers in the neonatal period. Reports on the influence of gestational age on kinetics of CRP in infected and uninfected infants are limited:

Turner et al. [50] demonstrated an association of gestational age with the magnitude of clinically relevant CRP responses during the first seven days after birth. In case of a clinically relevant CRP rise >10 mg/l the proportion of a pronounced response >60 mg/l increased with gestational age from 8% in newborns from 24 to 27 weeks to 25% in newborns from 40 to 41 weeks.

Several other authors have contributed to the growing body of evidence further supporting the difference in CRP response to infection between term and preterm infants. In a cohort of 348 infants Kawamura et al. [25] reported a lower sensitivity of CRP in the diagnosis of neonatal sepsis in preterm compared to term newborns (61.5% vs. 75%).

Doellner et al. [51] described a significantly lower CRP increase induced by infection in preterm compared to term infants. In their cohort of 42 newborns with either culture proven or probable sepsis infants with a gestational age less than 35 weeks had lower CRP values and lower CRP peak values compared to infants with a gestational age greater than 35 weeks (CRP values 0 vs 18 mg/l, CRP peak values 15 vs 52 mg/l).

We have recently reported on a lower CRP response to infection in preterm compared to term newborns with a lower sensitivity (53% vs. 86%), lower median values (9 vs. 18.5 mg/l), and a lower area under the receiver operating characteristics curve (0.799 vs. 0.890). [48]

What might explain the observed differences of CRP values between term and preterm newborns? One fact might be the differences in pre- and postnatal care regarding more frequent prophylactic antibiotic treatment in preterm infants and their mothers during birth. Timing of blood sampling might be another critical point being possibly earlier in preterm newborns. CRP is thought to play an important role in innate immunity, as an early defence system against infections. As far as the endogenous immune response depends on gestational age CRP responses might be lower due to a less mature immunological system of the preterm newborn.

Table 2 gives an overview on current literature on the association of CRP kinetics with gestational age and/or birth weight.

For neonates, assessment of laboratory tests occurs within a complex context of prenatal growth and neonatal development. [52] Though the current literature reveals some minor disagreement on the effect of gestational age on CRP there is a body of growing evidence suggesting that the so far reported characteristics of CRP may not be as suitable for the use in preterm as in term newborns. Their baseline CRP values may be lower and their response

to infection less distinct. Prematurity of the organ systems and maturational changes in the immune system might result in a more distinct CRP response to delivery in uninfected newborns and to bacterial invasion in infected newborns. The few studies so far addressing this issue suggest that the diagnostic accuracy of CRP in preterm infants may benefit from a re-evaluation of the reference intervals in this age group. [25, 44, 48, 51]

Author	Cohort			
Diagnostic accuracy		Sensitivity (%)		
Kawamura et al. [25]	348 neonates with suspicion of infection	61.5 vs. 75		(preterm vs. term neonates)
Hofer et al. [48]	532 uninfected and infected neonates	53 vs. 86		(preterm vs. term neonates at 8 mg/l cut-off value)
		Highest sensitivity in preterm infants at the cut-off 5.5 mg/l (74%) and at 10.5 mg/l in term infants (86%)		
CRP concentration		median (mg/l)	peak (mg/l)	
Doellner et al. [51]	42 neonates with probable or proven sepsis	0 vs. 18	15 vs. 52	(<35 weeks vs. ≥35 weeks)
Hofer et al. [48]	499 uninfected neonates	0.2 vs. 2.0	9.0 vs. 26.2	(preterm vs. term neonates)
	33 neonates with proven sepsis	9.0 vs. 18.5	40.4 vs. 98.6	(preterm vs. term neonates)
Ishibashi et al. [46]	110 uninfected symptomatic neonates	Gestational age and birth weight significantly influence hsCRP concentration within 48 hours after birth. Infants with low gestational age and low birth weight had lower hsCRP concentration (p=.013 and .024, respectively).		
Chiesa et al. [44]	421 healthy neonates	By regression analysis mean CRP increased by 6% per week gestational age at delivery (p<.01) and per 2.4% per 100 g increase in birth weight (p<.01)		
Turner et al. [50]	3574 neonates	In case of a clinically relevant CRP rise >10 mg/l, the proportion of a pronounced response >60 mg/l increased with gestational age from 8% in newborns from 24 to 27 weeks to 25% in newborns from 40 to 41 weeks.		

Table 2. Overview on current literature on the difference in CRP kinetics between term and preterm neonates.

7. Performance of CRP in diagnosis of neonatal sepsis can further be enhanced by combining it with early sensitive markers

An important limitation of CRP is the low sensitivity during the early phases of sepsis. By then values are often still normal, though the consequences of the bacterial invasion are

already apparent and a delay of the initiation of antibiotic therapy may be associated with an adverse outcome. CRP takes ten to twelve hours to significantly change after the onset of infection. [6] Earlier in the inflammatory cascade activated macrophages release pro-inflammatory cytokines (IL-1, IL-6, TNF-α) and growth factors (IL-3, CSFs) inducing the hepatic synthesis of acute-phase-reactants and the activation of neutrophils. The increase of cytokines therefore precedes the changes of CRP. Of the many mediators studied, much attention has been focused on IL6, IL8, and TNF-α.

IL-6 increases rapidly after the bacterial invasion and was demonstrated to have a high sensitivity during the early stages of sepsis (80%-100%) even when determined from umbilical cord blood (87%-100%). [29, 53) However, a short half life caused by plasma protein binding, hepatic clearance, and inactivation results in a rapid normalization of serum levels and a decrease of sensitivity during the later course of the disease, even though the infection persists. IL-8 and TNF-α have very similar characteristics and kinetic properties to IL-6. Both are pro-inflammatory cytokines predominantly produced by activated phagocytes in response to systemic infection and inflammation. [53] While studies report on a reliable diagnostic accuracy of IL-8 with a sensitivity of 69%-100%, the usefulness of TNF-α as a diagnostic marker has not been found to be as good as either IL-6 or IL-8. [53, 54]

Similar to CRP procalcitonin is another important acute-phase reactant produced by monocytes and hepatocytes. It has the advantage of increasing more rapidly after contact to bacterial endotoxin with levels rising after four hours and peaking at six to eight hours [55] In a recent meta-analysis the sensitivity and specificity in the diagnosis of early onset sepsis were 76% (range 68–82%) and 76% (60–87%). [56] Though the sensitivity during the early stages of sepsis may be superior to CRP, the significant rapid variations of basal levels after birth, the increase after non-infectious conditions such as asphyxia, maternal pre-eclampsia, and intracranial hemorrhage,[57] and the need for several different cut-off values with changing neonatal age, have limited its diffusion as an early marker in comparison to CRP.

Specific leukocyte cell surface antigens are known to be expressed in substantial quantities after inflammatory cells are activated by bacteria or their cellular products. [62] From the amount of surface markers studied neutrophil CD11b and CD64 appear most promising for diagnosis of neonatal sepsis. CD11b expression increases considerably within a few minutes after the inflammatory cells come into contact with bacteria and endotoxins. [58, 59] The sensitivity and specificity of CD11b for diagnosing early onset neonatal sepsis are 86–100% and 100% respectively. [7, 53] CD64 has a sensitivity ranging between 81% and 96% and a NPV between 89% and 97%. [60] Though promising, estimation of cell surface markers is limited by the need for sophisticated equipment and the need to process blood samples rapidly before neutrophils die from apoptosis or the surface antigens are down regulated. [61]

Despite the favorable claims by many studies, many of these diagnostic markers fail to meet the stringent demands required for clinical practice. High costs, limited availability of specimens at the appropriate time, and complexity of the assay methods all limit the clinical applicability. More importantly, the relatively small sample size in most studies, the lack of clear reference values for many diagnostic markers still prohibit the use of most of these parameters in clinical practice.

Sensitivity is low during the early phase of infection. The performance of serial determinations 24 to 48 hours after the onset of symptoms is recommended, as it clearly improves diagnostic accuracy.
CRP is particularly useful for ruling out an infection and for monitoring the response to treatment and guiding the duration of the antibiotic therapy. Two consecutive values <10 mg/l determined more than 24 hours apart identify infants unlikely to be infected or in whom infection has resolved.
CRP values undergo a physiological 3-day-rise after birth and non-infectious confounders such as meconium aspiration syndrome and perinatal maternal risk conditions may elevate CRP values in otherwise healthy newborns.
Preterm neonates have lower baseline CRP values and a lower CRP response to infection in compared to term newborns.
Data on non infectious CRP elevations in otherwise healthy newborns are inconsistent and does currently not allow drawing recommendations on the continuation or withdrawal of antibiotics in these infants.
Up to date the most used cut-off value is 10 mg/l irrespective of the gestational and postnatal age of the neonate. Cut-off values adapted to the gestational and postnatal age may better reflect neonatal physiology.
In order to compensate for the diagnostic weakness during the early phases of infection initial CRP determination should be combined with determination of early and sensitive markers. Suitable markers include but are not limited to PCT, IL6, and IL8. Many further parameters may provide similar good results but are not yet sufficiently examined to be applied to clinical practice.

Table 3. CRP facts.

At the moment none of the described current diagnostic markers are sensitive and specific enough to influence the judgment to withhold antimicrobial treatment independent of the clinical findings. Efforts were done to improve diagnostic accuracy by combining multiple markers in order to further enhance the diagnostic accuracy of these mediators in identifying infected cases.

CRP has been investigated in combination with a variety of "new" infection markers including cytokines, surface markers, and other acute-phase-reactants with promising results. Especially the combination with an early sensitive marker such as PCT, IL6, IL8, CD11b, and CD64 increases the sensitivity to values between 90% and 100% in most studies.

8. Do special subpopulations need special CRP reference values?

Especially in the early neonatal period, many physiological and metabolic processes are in change and differ from every later moment in life. These changes affect several laboratory parameters as well and many reference values and serum kinetics substantially differ to later periods. [62]

Reliable reference values are crucial for obtaining an adequate diagnostic accuracy. Upper limits for CRP during the first days of life have mainly been established from uninfected but symptomatic neonates. The cut-off values reported in the literature range from 1,5mg/l to 20 mg/l with thus wide ranging sensitivities and specificities. [11, 63] The up to date most used upper limit for CRP during the first days of life of 10 mg/l has been established in 1987 by Mathers and Pohlandt. [28] One decade later, Benitz et al. evaluated CRP levels in 1002 episodes of suspected early onset sepsis and confirmed the value being an appropriate threshold level. [23]

Use of CRP in the first few days after birth is complicated by a nonspecific rise primarily related to the stress of delivery. [11, 45] This rise of CRP starts shortly after birth and peaks with 13 mg/l in term and 11 mg/l in preterm newborns during the second and third day of life, respectively. [44] These observations raise concern about the static cut-off value not reflecting the physiologic kinetics of CRP after birth. In view of the physiologic dynamics of CRP during the first days after birth and the influence of gestational age on its response to infection, it appears reasonable to reconsider this static cut-off value and evaluate the possible advantages of the introduction of dynamic reference values. However, the current literature lacks sufficient evidence to make recommendations for the use in clinical practice.

9. Conclusion

CRP is one of the most widely available, most studied, and most used laboratory tests for neonatal bacterial infection and despite the continuing emergence of new infection markers it still plays a central role in the diagnosis of early onset sepsis of the neonate. CRP has the advantage of being well characterized in numerous studies and the extensive knowledge on its properties and limitations makes it safer compared to other, newer markers. Still, further research is needed on the topics of the influence of gestational age on CRP kinetics in infection, non-infectious confounders, and the evaluation of dynamic and gestational age dependent reference values.

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