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Presepsin: a biomarker of early-onset neonatal sepsis

Valentina Botondi[1,*], Ebe D'Adamo[1], Oriana Trubiani[2], Diego Gazzolo[1]

[1] *Neonatal Intensive Care Unit, G. d'Annunzio University, Chieti, Italy*
[2] *Department of Innovative Technologies in Medicine & Dentistry, University "G. D'Annunzio", Chieti, Italy*
*Corresponding author. E-mail: valentina.botondi.91@gmail.com

Abstract. Neonatal early-onset sepsis represents one of the most common diseases leading to morbidity and mortality in preterm infants. A prompt diagnosis is still a challenge in the clinical practice due to several biases affecting the current standard of care performance. In this regard, the soluble cluster of differentiation CD14 subtype, namely Presepsin, has been shown to be a promising diagnostic biomarker of sepsis in newborns. Although Presepsin provides high accuracy and short results output, its reliability in daily clinical practice is still an issue that needs further investigation. Therefore, in the present review we offer an overview of Presepsin role as diagnostic tool of early-neonatal onset sepsis.

Keywords: presepsin, newborns, early onset sepsis.

1. INTRODUCTION

Neonatal sepsis is still a major cause of morbidity and mortality in NICUs (Shah BA and Padbury JF) with an incidence of 12–17% in very low birth weight infants (Shane AL et al).

The definition of early-onset sepsis (EOS) is still debated since symptoms are non-specific. However, among several EOS classification the one commonly accepted is *"a bacterial infection occurring in the first 3 days of life"* (Ahmed AM et al).

At present, EOS diagnosis is mainly based on blood culture, C-reactive protein (CRP) and Procalcitonin (PCT) blood assessment although their poor performance in terms of accuracy and diagnostic value (Poggi C et al). Nonetheless, several bias such as gestational age and hypoxia have been shown to affect CRP and PCT reliability suggesting the need of new diagnostic tools (Van Maldeghem I et al). Recently, presepsin (P-SEP), the soluble cluster of differentiation CD14 subtype (sCD14-ST), has been shown to be an early diagnostic tool of sepsis in adults, children and newborns (Montaldo P et al; Botondi V et al).

In the present review we offer an update of recent advances in the use of P-SEP as a biomarker of EOS in newborns.

2. RESEARCH STRATEGY

We searched in the PubMed database for the period 2011 to 2022 all records matching the terms "Newborns", "Presepsin" and "Early onset sepsis". We found 6 records in whom P-SEP was assessed specifically as an early onset sepsis diagnosis biomarker.

3. CONTENT

3.1 P-SEP molecule

P-SEP can be defined as a truncated form of CD14 that is a cell surface glycoprotein expressed by various innate immunity cells, like monocytic and neutrophils. CD14 receptor has a high-affinity for bacterial lipopolysaccharides and activates the toll-like receptor 4-specific proinflammatory signaling cascade. At the end of the process, P-SEP is released in the blood stream (Mussap M et al).

3.2 P-SEP accuracy

The P-SEP sensitivity and specificity as predictor of EOS are shown in Table 1. In detail, a wide heterogeneity among the studies has been found. In particular P-SEP: i) sensitivity ranged from 66 to 97% and specificity from 75 to 100%, ii) cut-off references values ranged from 304.5 ng/L to 1442 ng/L. Nonetheless, a series of limitations have been also reported affecting its accuracy such as: i) the different monitoring time points (from birth to 72h); ii) different studied populations (preterm and term), and iii) different measurement techniques. In particular, 4 out of 6 studies used CLEIA assay that is to date the main assessment technique providing results output within 15' (Seliem W and Sultan AM). Moreover, 2 out of 6 series performed P-SEP measurement by ELISA assay, that can provide results output about 1-h (Alhajj M and Farhana A). Another issue deserving further consideration resides in the possibility that, similarly to CRP and PCT, perinatal asphyxia (PA) and gestational age could somewhat affect P-SEP reliability as early biomarker of EOS (Botondi V et al). Recently, P-SEP blood and urine levels of PA newborns have been found not to be affected by PA and/or multiorgan failure.

4. DISCUSSION

Despite recent advances in EOS management the early mortality rate is still high (about 50%) particularly in preterm infants (Maddaloni C et al). The main weakness points regard EOS non-specific symptoms, the low predictive value of diagnostic parameters to date standard of care suggesting a pivotal role for new diagnostic markers (Poggi C et al; Van Maldeghem I et al). On this scenario, the need of new tools able to early provide useful information to frontline physicians on the occurrence of EOS is of utmost relevance. In this respect, P-SEP *pros* and *cons* need to be considered (Poggi C et al). From one hand pros regard its: i) measurability in non-invasive biological fluids (i.e. saliva and urine) (Biria M et al; Koh J et al), ii) speed activation and early peak of concentration after 3h from EOS occurrence (Maddaloni C et al) iii) results output in 15 minutes (Maddaloni C et al). On the other hand, *cons* regard the: i) small number of patients enrolled in the studies, ii) lack of consensus on a valuable P-SEP cut-off value, iii) studies heterogeneity in inclusion and exclusion cri-

Table 1. Available studies of Presepsin as predictor of early onset sepsis.

Population	Fluid	Assay	Time-points	P-SEP cut-off (ng/L)	SE (%)	SP (%)	Ref.
T	PB	C	birth	539.0	80.0	75.0	16
T	PB	C	48-72h	672.0	97.0	98.0	9
PT	CB	E	birth	1442.0	NA	NA	12
PT	PB	C	birth	453.0	66.0	84.0	6
PT	PB	C	12h	653.0	88.0	94.0	6
PT	PB	C	24h	788.0	93.0	100.0	6
PT	PB	C	48h	744.0	79.0	92.0	6
T	PB	C	T*	304.5	95.8	84.9	17
T	PB	E	24h	480.0	96.77	95.0	18

Abbreviations: T, term; PT, preterm; PB, peripheral blood; CB, cord blood; C, CLEIA; E, ELISA; d, days; NA, not available; SE, sensitivity; SP, specificity; Ref, references; T*, before and after therapy.

teria, monitoring time-points and assay used for P-SEP measurement (CLEIA vs ELISA), and iv) potential biases due to associated adverse perinatal conditions (maternal diseases, acute/chronic hypoxia, prematurity) (Botondi V et al; Poggi C et al). Altogether, despite today P-SEP constitutes a promising early biomarker of EOS its inclusion in clinical guidelines requires the fulfilment of the aforementioned critical points.

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