

PATHFAST™



The emerging role of
Presepsin for diagnosis
and monitoring of
neonatal sepsis

Neonatal sepsis

Neonatal sepsis, especially late-onset sepsis (LOS) continues to be a major source of morbidity and mortality in very- low-birth-weight infants (VLBW <1500 g) or pre-terms. The International Pediatric Sepsis Consensus Conference defined sepsis as “the systemic inflammatory response syndrome in the presence or as a result of a suspected or proven infection” (1). Major causes of infection include bacteria such as coagulase-negative Staphylococci and multiple other aggressive pathogens, such as the Klebsiella-Enterobacter-Serratia group, Pseudomonas, and Candida species. Survivors suffer from neuro-developmental impairment during at least the first 2 years of life (2).

Sepsis biomarkers in neonatal care

C-reactive protein (CRP) is generally considered an inflammation/infection marker for diagnosis of sepsis used in addition to bloodculture, but is not very specific. In newborns, procalcitonin (PCT) levels show a physiologic increase 24-48 hours after birth and decreases to normal levels after 3 days. PCT increases in hypoxia, respiratory distress syndrome (RDS) and hemodynamic instability, which lowers its specificity for sepsis. The proinflammatory cytokine IL-6 increases quickly after onset of the infection, but returns to undetectable levels during 24 h. D-Dimer is generated by thromboembolic situations that are not necessarily linked to sepsis. It is not a specific sepsis marker but

Therapy with antibiotics is the standard of care. Based on the timing of the infection newborn sepsis has been classified into early-onset sepsis (EOS) and late-onset sepsis (LOS). Early-onset sepsis (EOS) is discriminated from late-onset sepsis (LOS) depending on whether is present within or after the first 72 h of life, respectively (3,9).



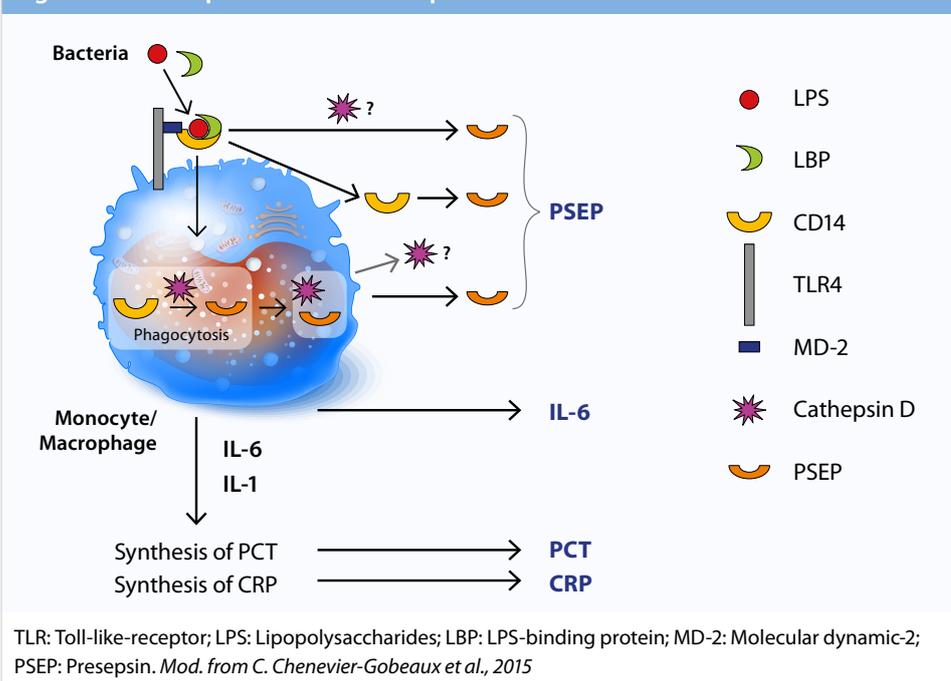
may be a useful indicator of the coagulation status of the infant and the requirement for anticoagulant therapy (4,5). Presepsin shows promising performance in diagnosing sepsis in neonates and prognosing severity of the disease.

Presepsin biochemistry

Presepsin (sCD14-ST) is a specific and sensitive biomarker for sepsis. Presepsin levels rise after 2 h, earlier than IL-6 and PCT, with a peak 3 h after onset of the infection and a decline after 4-8 hours (6). Presepsin can be used for monitoring of treatment with antibiotics and can show effectiveness of antibiotics. It is a reliable tool for early diagnosis of sepsis caused by Gram-positive and Gram-negative bacteria or fungi (7) and is accurate in neonatal sepsis using special cut off values which are higher than in adults (8).

Presepsin secretion is linked to the Toll Like 4 Receptor (TLR) and its sensor function is well developed in newborns. Levy et al. (11) described in preterm and full-term neonates significantly higher expression levels of TLR4 on peripheral blood monocytes both at baseline and after LPS stimulation, compared to adults. In the same study, they also observed significantly higher CD14 expression at baseline and after LPS stimulation in full-term neonates compared to adults.

Fig. 1: Schematic production of Presepsin



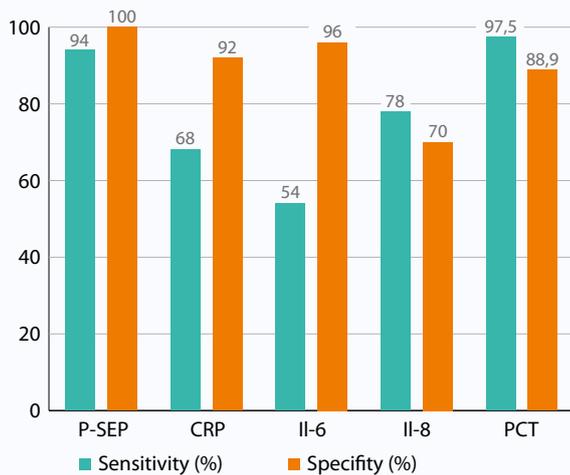
Presepsin is a 13 kDa fragment derived from cleavage of CD14, a glycoprotein of 55k Da anchored to the membrane of monocytes, macrophages and polymorphic neutrophils. CD14 acts as a receptor for lipopolysaccharide (LPS) complexes and the specific LPS binding protein (LBP). It can bind to peptidoglycans and other surface structures present in both Gram-Positive and in Gram-Negative bacteria. Once bound to the LPS-LBP complex, it activates the intracellular inflammatory response of the Toll-Like receptor 4 (TLR4), triggering the host's inflammatory cascade against the infectious pathogenic agent. The phagocytosis and the activity of the plasma proteases (lysosomal enzymes, cathepsin D) result in the formation of the fragment of the sCD14 subtype, in particular the 13 kDa fragment of sCD14-ST, known as Presepsin (Fig.1,6).

Presepsin in neonatal sepsis (LOS and EOS)

The diagnostic validity of Presepsin in neonatal sepsis has been evaluated in numerous clinical studies. Pugin et al. (12) enrolled 684 healthy neonates (484 born at term and 200 preterm) for evaluation of reference ranges for Presepsin. Presepsin median value in term infants was 604 pg/mL whereas in preterm infants the Presepsin median value was slightly higher (620 pg/mL). The normal reference ranges of Presepsin observed were higher than those seen in healthy adults. The Presepsin level was

not affected by gender, ethnicity, mode of delivery, small for gestational age (GA), twin, maternal fever/elevated CRP, and stained amniotic fluid. Reliable reference values are important for adequate diagnostic accuracy. Based on current clinical study results, most factors affecting C-reactive protein and procalcitonin levels do not affect Presepsin levels. Presepsin can discriminate between infections and non-infectious inflammatory conditions.

Fig. 2: Comparison of Presepsin specificity and sensitivity data with other Biomarkers (8)

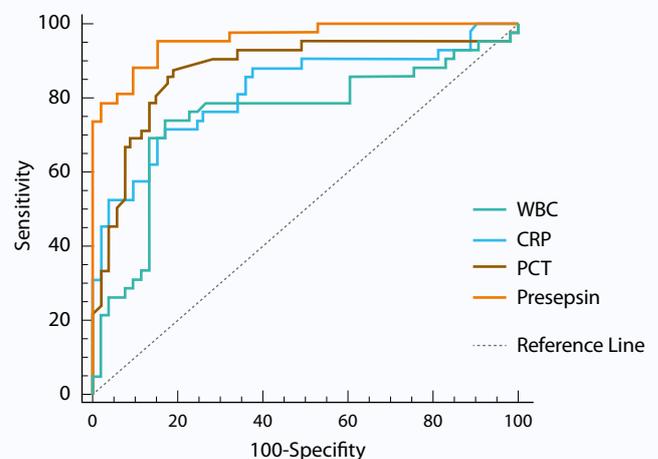


Based on data from Poggi et al.

Xiao et al. (7) evaluated 42 neonates with hematosepsis, 54 newborns with nonhematosepsis, 44 noninfectious SIRS neonates (n=140) and 53 healthy controls. Before treatment Presepsin, CRP, white blood cells (WBC) and PCT was determined. Furthermore, APACHE-II score was assigned for all samples before and after treatment. Presepsin levels were significantly higher in neonatal hematosepsis than in noninfectious SIRS or control group. Interestingly, Presepsin levels were positively correlated with APACHE-II score. During treatment with antibiotics, Presepsin levels decreased together with APACHE-II score, PCT, CRP and WBC. Presepsin showed an Area under the curve (AUC) value of 0,942 with a corresponding sensitivity of 95,2% and specificity of 84,9%, respectively. The calculated cut off value was 786 pg/ml (7, Fig. 3).

Poggi et al. (8) prospectively studied newborns ≤ 32 weeks gestational age with LOS (n=19) and noninfected controls (n=21) at 4 to 60 days postnatal age. At enrollment and at day 1, 3 and 5 the biomarkers CRP, PCT and Presepsin were measured in the LOS group with single measurements of Presepsin in the control group. Presepsin was higher in the LOS than in the control group at enrollment (1295 vs. 562 ng/L) and was elevated throughout the evaluation period. The Receiver-Operating-Characteristic curve (ROC) for Presepsin at enrollment showed specificity of 94% and sensitivity of 54% for IL-6, 78% sensitivity and 70% specificity for IL-8, sensitivity of 97,5% and specificity of 88,9% for PCT. Presepsin showed 100% sensitivity and 94% specificity (Fig. 2). Other studies showed lower sensitivity and specificity for CRP, PCT and IL-6. These data support the potential role for Presepsin as a marker for monitoring the response to antibiotic treatment in preterm infants.

Fig. 3: ROC curves of Presepsin, WBC, CRP and PCT results in 42 neonates with hematosepsis (7)



Mod. from Ting Xiao et al.

Tab. 1: Comparison of Presepsin between Gram-positive and Gram-negative bacteria group in 42 neonates with hematosepsis (7)

Group	Cases	Presepsin (pg/ml)
Gram-positive group	25	802.92 (669.55–936.28)
Gram-negative group	17	761.24 (550.54–971.92)
Healthy control group	53	124.20 (113.73–134.68)

Presepsin is a biomarker for early identification and disease valuation in newborns hematosepsis infection with Gram-positive and Gram-negative bacteria with a high diagnostic value compared to other laboratory indexes like CRP, PCT and WBC (7, Tab.1).

Diagnostic accuracy of Presepsin, cut off values and blood sampling in neonates

Tab. 2: Study compilation Presepsin in neonates and cut off values

Cut off/ mean reference values (pg/ml)	Cases	AUC	Reference
604; preterms: 620	684 healthy neonates, 200 preterms	n.a.	Pugni et al., 2015 (12)
885	19 LOS neonates, 21 healthy neonates	0,972	Poggi et al., 2015 (8)
600	65 critically ill, 25 non-infective neonates	0,995	Mussap et al., 2015 (13)
788	32 EOS, 38 non-infective neonates	0,97	Montaldo et al., 2016 (9)
786	140 septic, 53 healthy neonates	0,942	Xiao et al., 2016 (7)
812	50 septic, 20 healthy neonates	0,99	Tabl et al., 2016 (14)
539	29 EOS, 40 healthy neonates	0,772	Ozdemir et al., 2016 (15)
801	42 EOS, 40 healthy neonates	0,864	Topcuoglu et al., 2016 (16)
722	80 septic, 40 healthy neonates	0,99	Sabry et al., 2016 (17)
875	40 septic, 15 healthy neonates	0,95	Osman et al., 2015 (18)
672	28 EOS, 34 healthy neonates	0,95	Motalib et al., 2015 (19)
795	48 septic, 18 healthy neonates	0,868	Miyosawa et al., 2018 (20)
406	40 preterm LOS, 40 healthy neonates	0,896	Astrawinata et al., 2017 (21)
686	49 septic, 29 healthy neonates	0,784	Mostafa et al., 2015 (22)



Tab. 3: Diagnostic accuracy of Presepsin and resulting cut off values (13)

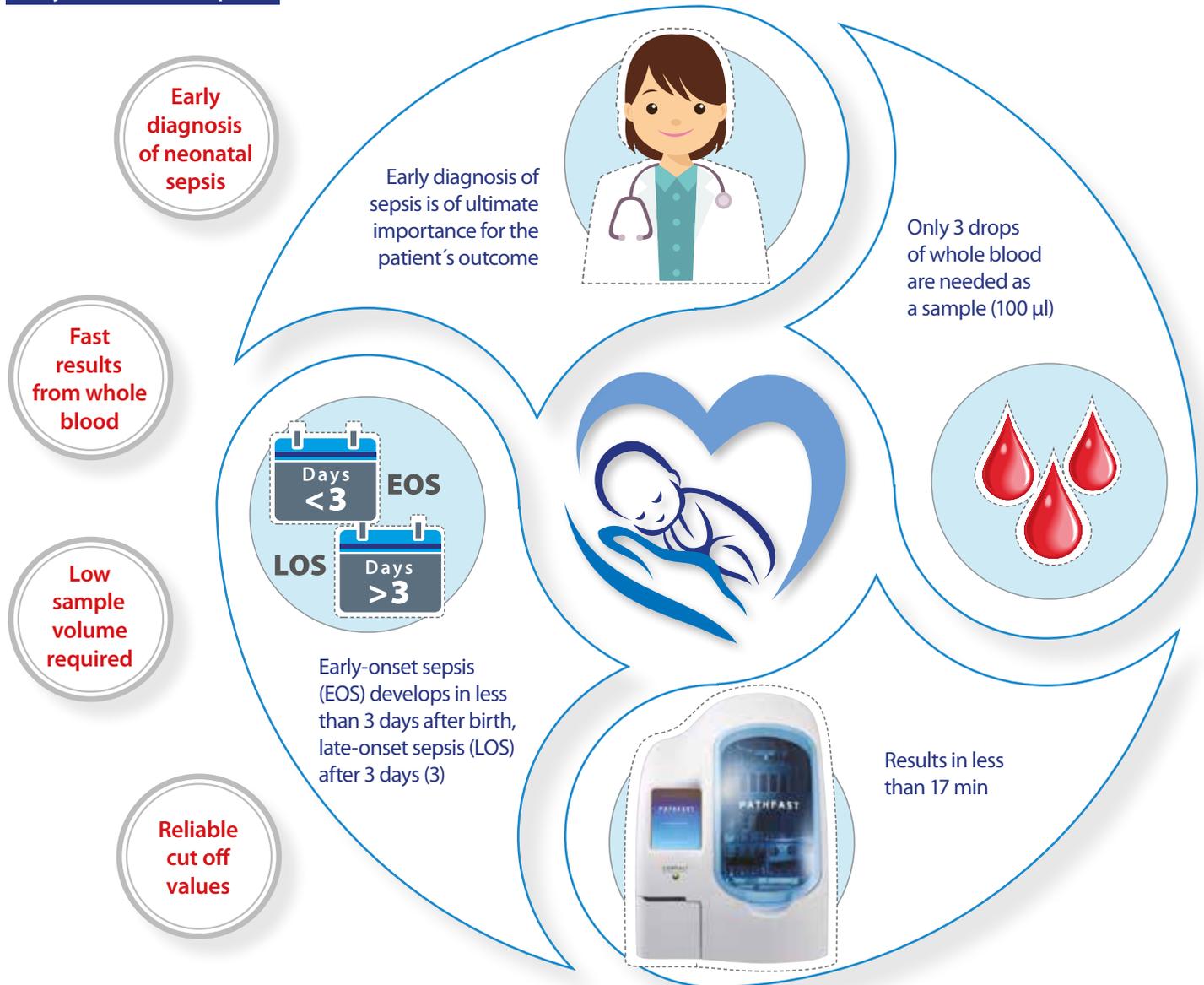
Cut off (pg/ml)	Sensitivity (95% CI)	Specifity (95% CI)	DOR (95% CI)	AUC (SE)
≤ 650	0.91 (0.83-0.96)	0.85 (0.77-0.91)	71.78 (7.46-690.56)	0.9634 (0.0439)
650-850	0.91 (0.86-0.95)	0.97 (0.94-0.99)	542.72 (156.62-1880.60)	0.9915 (0.0046)
≥ 850	0.90 (0.82-0.95)	0.86 (0.77-0.93)	75.60 (8.32-686.53)	0.9681 (0.0316)



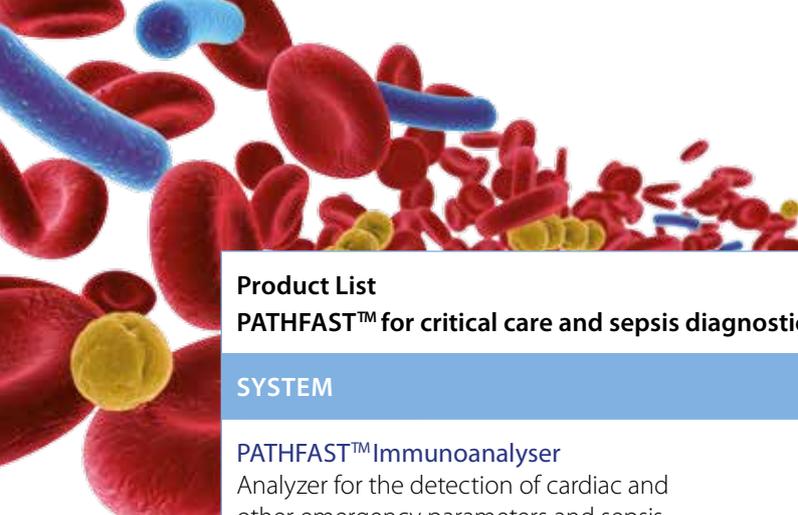
Bellos et al. (10) and Ruan et al. (23) recently published two meta-analysis' summarizing cut off values of Presepsin for exclusion of sepsis in neonates. Furthermore, Ruan et al. showed superior diagnostic accuracy of Presepsin for neonatal sepsis diagnosis when compared with simultaneous use of CRP and PCT (AUC = 0,99 vs AUC = 0,96) whereas Bellos et al. recommended the use of three different threshold values which are in good alignment with 14 clinical study publications shown in **Tab. 2**. Recommended cut off values were 650, 650-850, 850 pg/ml with corresponding AUC of 0,9634, 0,9915, and 0,9681, respectively. These findings are comparable with the summary listed in **Tab. 3**. A preliminary cut off value of ≤650 pg/ml for exclusion of sepsis seems to be appropriate for neonates. Presepsin values ≥850 pg/ml indicate a bacterial infection. A grey zone from 650-850 pg/ml still remains to be validated by further studies. Blood sampling for Presepsin measurements can be taken on the first day of sepsis prior to the initiation of empirical antibiotic therapy, 12, 24 and 48 hours of age (9).



Why to use Presepsin



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