PRESEPSIN - New Marker of SEPSIS
Romanian Neonatal Intensive Care Unit Experience

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Difficulties in establishing the onset of neonatal sepsis has directed the medical research in recent years to the possibility of identifying early biological markers of diagnosis. Overdiagnosing neonatal sepsis leads to a higher rate and duration in the usage of antibiotics in the Neonatal Intensive Care Unit (NICU), which in term leads to a rise in bacterial resistance, antibiotherapy complications, duration of hospitalization and costs.Concomitant analysis of CRP (C Reactive Protein), procalcitonin, complete blood count, presepsin in newborn babies with suspicion of early or late neonatal sepsis. Presepsin sensibility and specificity in diagnosing neonatal sepsis. The study group consists of newborns admitted to Polizu Neonatology Clinic between 15th February- 15th July 2017, with suspected neonatal sepsis. We analyzed: clinical manifestations and biochemical markers values used for diagnosis of sepsis, namely the value of CRP, presepsin and procalcitonin on the onset day of the disease and later, according to evolution. CRP values may be influenced by clinical pathology. Procalcitonin values were mainly influenced by the presence of jaundice. Presepsin is the biochemical marker with the fastest predictive values of positive infection. Presepsin can be a useful tool for early diagnosis of neonatal sepsis and can guide the antibiotic treatment. Presepsin value is significantly higher in neonatal sepsis compared to healthy newborns (939 vs 368 ng/mL, $p < 0.0001$); area under receiver operating curve (AUC) for presepsine was 0.931 (95% confidence interval 0.86-1.0). PSP has a greater sensibility and specificity compared to classical sepsis markers, CRP and PCT respectively (AUC 0.931 vs 0.857 vs 0.819, $p < 0.001$). The cut off value for presepsin was established at 538 ng/mLwith a sensibility of 79.5% and a specificity of 87.2 %. The positive predictive value (PPV) is 83.8 % and negative predictive value (NPV) is 83.3%.

Keywords: presepsin, sepsis marker, NICU

Neonatal sepsis is a systemic inflammatory response, with clinical signs and symptoms, accompanied or not by bacteremia [1,2]. Despite the advances of the medical care in the NICU, 4 out of 10 infected newborn babies either die or end up with severe permanent neurological sequelae [3]. Early and correct diagnostic of neonatal sepsis allows treatment initialization and improved outcome.

On the other hand, prolonged or inadequate use of antibiotics is followed by adverse reactions and dysbiosis in the newborn.

Diagnosis of neonatal sepsis is based on clinical signs, laboratory and bacteriologic investigations. The risk of infection is greater in premature newborns [3-5], and often the clinical manifestations of sepsis overlap the manifestations associated with preterm newborn adaptation to extrauterine life.

The standard diagnosis is made the hemoculture, but the long duration (over 48 h) for pozitivation grants it a low utility in treatment initialization.

Laboratory investigation reveal early useful information about the presence and severity of the infection. Diagnosis is made using hematologic markers (leucocyte count, neutrophil count, immature per total neutrophil index) and biochemical markers (CRP or PCT) [2].

Systemic inflammatory response can have infectious or non-infectious causes. Procalcitonin (PCT), interleukins, pro-vasopressin, C-reactive protein (CRP) and myeloid cells expressing triggering receptor-1 (TREM-1) are biological markers used for diagnosing inflammatory response [3,6].

Among these, the usual sepsis biomarkers are CRP and PCT. Yet, their accuracy in neonatal sepsis diagnosis is still not established [3].

CRP presents a variable growth in neonatal period. The values can be physiologically higher after birth or in other non-infectious conditions [7], or lower in premature infants in relation with gestational age [8]. PCT rises under the influence of bacterial and fungi cytokines and endotoxins. PCT sensibility and specificity in neonatal sepsis diagnosis are low [9]. CRP and PCT have low positive predictive value and high negative predictive value in neonatal sepsis.

In neonate period sepsis can be early (0-3 days) or late onset (4- 90 days) [10]. Early symptoms are nonspecific and are not characteristic for a particular organism.

Neonatal sepsis diagnosis remains a challenge in the NICU due to nonspecific symptoms and insufficient research to set reference values of different sepsis biomarkers in newborn. The present study compares presepsin, a recent biomarker of sepsis, with the classic markers, in order to achieve a higher diagnostic accuracy.

Presepsin is a soluble fraction of CD14 (sCD14 st) [11]. CD14 is a glycoprotein expressed on the surface of the monocyte and macrophage membrane (mCD14) who plays the role of high affinity receptor of lipopolysaccharide-lipopoly-saccharide binding protein (LPS-LBP) complexes [12]. CD14 activates Toll 4 receptors (TLR4), the protein that activates the innate immune system. CD14 has two forms: membrane-bound CD14 (mCD14) and soluble CD14 (sCD14)[12,13].

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The soluble form of CD14 (sCD14) is secreted directly by the hepatocytes: during protease inflammation, plasma activates a cleavage of sCD14 in order to generate a form called sCD14-truncated subtype (sCD14-ST), well known as of presepsin [13].

Presepsin is normally present in very low serum concentrations of healthy individuals, finding that an increase in the concentration was recorded when bacterial infections occurred [14,15]. Still, presepsin can grow in other clinical conditions like cardiac or renal insufficiency, necrotizing enterocolitis or in lupus [16-18].

Experimental part

The study group consists of 86 newborn, admitted to the Polizu Neonatology Clinic between 15th February - 15th July 2017 for nonspecific symptomatology (sepsis like): 37 cases with neonatal sepsis (with or without positive blood culture) and 49 cases (control group) without sepsis. The infectious risk factors studied were: maternal history of corioamnionitis, premature labor, premature rupture of membranes, prolonged rupture of membranes (over 18 hours), infections during pregnancy, invasive treatment of premature birth (cerclage). Newborns with congenital malformations were excluded.

All the newborns included in the study had the following tests: complete blood count (CBC), CRP and presepsin taken at 24 hours of life and PCT at 48 h. In cases where late onset sepsis was suspected (onset after 72 h of life), all three blood tests were performed at the same time (in the first day of the symptoms). Peripheral cultures (gastric aspirate, skin) and central cultures (hemoculture) were taken in the first day of disease.

Diagnosis of sepsis was established based on Tollner sepsis score (≥10) [19,20], applied to all newborns in the study from the first day of the symptoms. Tollner score is the first system of neonatal sepsis diagnosis which includes clinical parameters (coloration, peripheral circulation, hypotonia, apnea, respiratory distress, hepatomegaly, abdominal distension) and laboratory parameteres (leucocyte count, thrombocyte count, immature per total neutrophil index, metabolic acidosis). The suspicion of neonatal sepsis was based on clinical examination, risk factors and laboratory investigations. Clinical examination includes at least one of the symptoms: dyspnea, apnea, cardiac arrhythmia (tachycardia, bradycardia), lethargy, hypotonia, poor feeding. Risk factors associated with neonatal sepsis are rupture of membranes over 18 h , chorioamnionitis, invasive procedures (endotracheal intubation, peripherally inserted central catheter). Laboratory investigations associated with sepsis are CRP over 1 mg/dL and procalcitonin over 0.5 ng/L.

Ethica considerations. The study was made with approval from INSMC Alessandrescu Rusescu local ethical comity and handwritten informed consent of the parents.

Blood was collected in a heparinized syringe, stored at room temperature and processed within 1 h after collection by physicians appropriately trained using a point-of-care assay system located in the NICU. To all the neonates enrolled in the study were given prophylactic antibiotics and were follow-up for a few days noticing changes in their clinical status.

Presepsin levels were measured with PATHFAST™ automated immunoassay analyzer, based on a non-competitive chemiluminescence enzyme immuno-assay1 [,2,15].

Statistical analysis

All the collected data was included in IBM SPSS Statistics (Version software 21.0) and modeled to detect which variable can affect presepsin, PRC and procalcitonin levels. We made correlations to find out some statistical significances ($P > 0.05$). We used Independent sample T test, ROC curve and two-tailed test was considered significant when $p < 0.05$.

Results and discussions

We analyzed 86 newborns, of which 41 were under 32 weeks of gestation with clinical neonatal sepsis suspicion.

Two subgroups were defined: one with confirmed sepsis diagnosis (39 cases) and one with non-sepsis (47 cases). The two subgroups are similar regarding type of birth, birth weight, gestational age and sex (table 1).

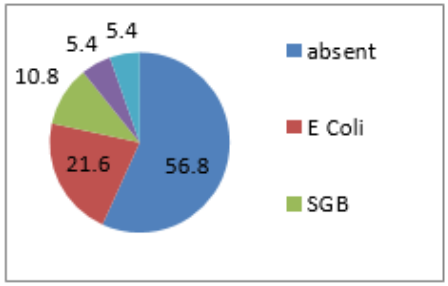
The characteristics of the two subgroups, sepsis and non-sepsis (control) were:

43.2% of patients with neonatal sepsis had positive peripheral cultures (coproculture, gastric aspirate,

Characteristics	Sepsis (39)	Non-sepsis (47)	Statistical semnification ($p \leq 0,05$)
Mode of delivery (vaginaly)	50 % (n=17)	46.2% (n=24)	n.s.
Cranial presentation	85.3% (29)	84.6% (44)	n.s.
Birth Weight	2106 ± 998,1 g	2182 ± 1006.1 g	n.s.
Gestation age (weeks)	33.5 ± 5 weeks	33.1 ± 1 weeks	n.s.
Sex (male)	64.7 % (22)	61.5 % (32)	n.s.
n.s. = non-semnificative statistic ($p > 0.05$)			

Table 1
CHARACTERISTICS OF SEPSIS AND NON-SEPSIS GROUPS

	Frequency	Percent %
Absent	21	56.8
E Coli	8	21.6
SGB	4	10.8
Enterobacter	2	5.4
Staphylococcus	2	5.4



Tabel 2
ETIOLOGY OF NEONATAL SEPSIS

pharyngeal exudate) and only 12.8 % (5 cases: 3 E-coli, 2 Group B Streptococcus) had positive hemocultures. The identified germs are presented in table 2. The most frequent germs were E-coli (21.6%; 8 cases) and GBS (10.8 %; 4 cases), which were also isolated in central cultures (hemocultures).

Presepsin value is significantly higher in neonatal sepsis compared to healthy newborns (939 vs 368 ng/mL, $p < 0.0001$) (table 3). Area under receiver operating curve (AUC) for presepsine was 0.931 (95% confidence interval 0.86-1.0). PSP has a greater sensibility and specificity compared to classical sepsis markers, CRP and PCT respectively (AUC 0.931 *vs* 0.857 vs 0.819, $p < 0.001$) (fig. 1 and table 4). The cut off value for presepsin was established at 538 ng/mL with a sensibility of 79.5% and a specificity of 87.2 %. The positive predictive value (PPV) is 83.8 % and negative predictive value is 83.3%.

In early onset sepsis the clinical signs were noted in the first 24 h of life and laboratory investigations were taken at 24 hours of life (complete blood count, CRP, PSP) and 48 h of life (PCT). The three biochemical markers studied had significantly high values, but PCT has the highest predictability (AUC 0.815; $p < 0.0001$) (fig. 2, table 5).

In late onset sepsis laboratory investigations we taken when clinical signs were noted, after 72 h of life. CRP and PSP are significantly higher compared to PCT (Table 6 and fig. 3).

PSP has a higher sensibility and specificity in predicting early onset sepsis, as well as late onset sepsis in premature newborns compared to PCT AND CRP (Table 7).

Presepsin value in neonatal sepsis is inversely proportional with gestational age (GA) (1141 ± 467.87 pg/dL *vs.* 943 ± 467.29 pg/dL at GA < 28 weeks vs. GA ≥28 weeks; $p = 0.001$) and birth weight (1091 ± 483.2 pg/dL *vs.* 731 ± 324.3 pg/dL at BW < 1500 g vs. BW ≥1500 g; $p = 0.003$) (table 8). Cesarean section is associated with higher values of PSP compared to vaginal delivery. Preterm cesarean section is more frequently performed in cases with high risk of chorioamnionitis (rupture of membranes

Lots	No.	Presepsine ng/dl	Presepsine pozitive	p value
Sepsis	39	939.1 ± 512.0	71.8 %	0.000
Non-Sepsis	47	368.77 ± 171.49	12.8 %	

Table 3
PRESEPSINE VALUE OF NEWBORN WITH SEPSIS VERSUS WITHOUT SEPSIS

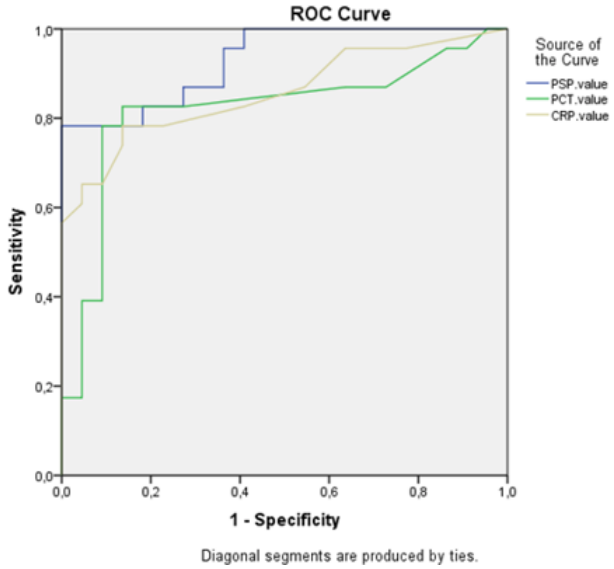


Fig. 1. ROC curve of neonatal sepsis markers

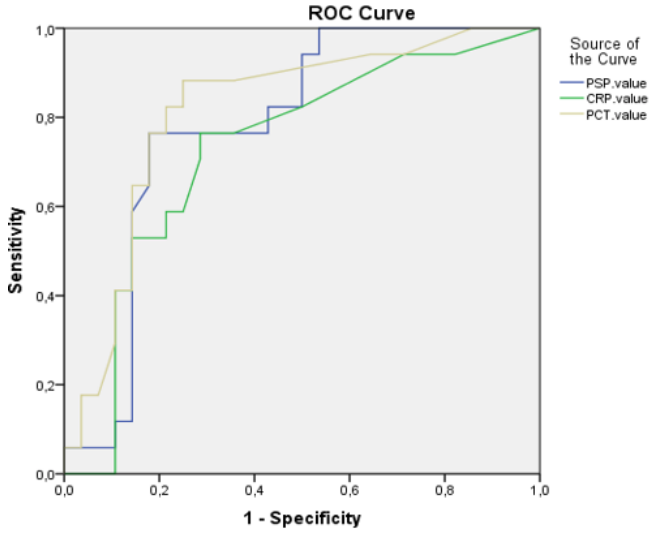


Fig. 2. CRP, PCT and PSP in the early neonatal sepsis

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
PSP.value	.931	.035	.000	.861	1.000
CRP.value	.857	.058	.000	.744	.970
PCT.value	.819	.069	.000	.683	.955

Table 4
AREA UNDER THE CURVE OF NEONATAL SEPSIS MARKERS

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
PSP.value	.780	.071	.002	.642	.919
CRP.value	.728	.079	.011	.573	.883
PCT.value	.815	.067	.000	.683	.947

Table 5
AREA UNDER THE CURVE OF NEONATAL SEPSIS MARKERS (EARLY NEONATAL SEPSIS)

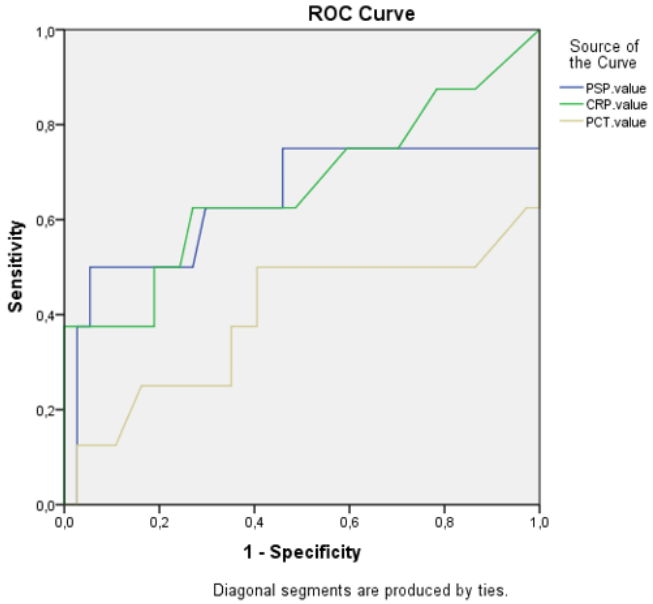


Fig. 3

Test Result Variable(s)	AUC	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
PSP.value	.640	.143	.218	.359	.921
CRP.value	.667	.126	.142	.421	.913
PCT.value	.395	.142	.357	.118	.673

Table 6
AUC CURVE OF PSP, CRP AND PCT IN LATE NEONATAL SEPSIS

over 18 h, maternal clinical signs), which has a higher probability of markedly increased inflammatory response. There were no observed differences in presepsin values in relation with gender among newborns with sepsis.

Neonatal sepsis is a medical emergency with high mortality especially in the premature population. The clinical signs are non-specific and are associated with other frequent pathologies of premature newborns (ex. RDS, NEC, cardiac malformations) [21]. This leads to treat a higher number of healty newborn for an newborn with sepsis respective NNT= 37 (Number Needed to Treat), for a real benefit from the antibiotic therapy for the newborn [22]. Early and targeted treatment is essential for lowering morbidity and mortality associated to neonatal infection. For this, a rapid and precise diagnosis of sepsis is necessary. Hemoculture is the standard criteria in diagnosing neonatal sepsis, but its sensibility is reduced and false negative results are frequent. A higher sensitivity marker with greater negative predictive value (NPV) is necessary for neonatal sepsis (especially early onset) in order to avoid unnecessary antibiotic treatment in symptomatic patients with lower risk of sepsis [23].

The purpose of presepsin determination in early diagnosis and treatment of neonatal sepsis is to prevent

Neonatal sepsis		Cut Off value	Sensibility	Specificity	PPV	NPV
All patients	PSP (ng/ml)	538	79.5	87.2	83.8	83.7
	CRP (mg/dl)	0.45	73.5	68.4	69.4	74.3
	PCT (ng/ml)	0.51	56.4	42.6	88	83.3
Early	PSP (ng/ml)	538	77.4	86.7	80	84.8
	CRP (mg/dl)	0.45	70.4	66.7	63.3	75
	PCT (ng/ml)	0.51	54.8	40.9	85	90
Late	PSP (ng/ml)	554	77.8	89.1	58.3	95.3
	CRP (mg/dl)	0.65	75	88.9	60	94
	PCT (ng/ml)	0.76	71.5	95.7	85.7	91.7
GA ≤ 32 weeks	PSP (ng/ml)	554	90.5	90	90.5	90
	CRP (mg/dl)	0.45	58.8	81.3	83.3	65
	PCT (ng/ml)	0.46	61.9	45	92.9	90
GA > 32 weeks	PSP (ng/ml)	538	66.7	88.9	80	80
	CRP (mg/dl)	0.65	60.6	89.2	83.3	71.7
	PCT (ng/ml)	0.71	80.8	95.7	96.5	81.5
PSP – prespsine; CRP – C proteine reactive; PCT – procalcitonin; PPV - Pozitive predictive value; NPV- Negative predictive values						

Table 7
PREDICTION ACCURACY OF NEONATAL SEPSIS

Caractersistics of newborn with sepsis		N	Presepsine value (Mean, pg/dl)	Std. Deviation	T-test	p- value
Gestational Age	sub 28 weeks	7	1141.00	467.879	6.452	.001
	28-32 weeks	13	943.08	467.299	7.277	.000
	> 32 weeks	19	862.00	559.239	6.719	.000
Birth Weight	< 1500 g	15	1091.33	483.267	8.746	.000
	1500-2000 g	6	731.50	324.338	5.524	.003
	>2000 g	18	881.44	568.805	6.575	.000
PRM	< 18 ore	37	959.86	513.749	11.365	.125
	> 18 ore	2	555.00	386.080	2.033	
Sepsis	prematurely	31	901.58	501.592	90.089	.210
	tardive	8	1084.50	560,768	198,261	
Sex	Male	27	948.44	505.776		0.43
	Female	12	918.08	547.983	0.163	
Mode of delivery	Vaginaly	19	762.37	406.639		0.033
	C-section	20	1107.00	553.847	2.2	

Table 8

deterioration of the patient and multi-organ disease, along with the short and long term complications. Presepsin has a short response time, of 2 h from the onset of sepsis, compared to the classic markers - 12-24h for CRP and 6-12 h for PCT (but PCT can be false positive in the first 48h of life) [24]. PSP is a valuable biomarker for early neonatal sepsis diagnosis, both early onset and late onset, allowing a good management of the disease.

This study show a significantly higher presespsin value for patients with neonatal sepsis compared to the non-sepsis ones (939 *vs* 368 ng/mL, $p < 0.0001$). There are no significant differences regarding PSP values in early onset sepsis compared to late onset sepsis. Presepsin has a higher sensibility and specificity in neonatal sepsis, compared to CRP and PCT. c similar to the value stated in other recent studies regarding early onset sepsis in term/ preterm newborns [25,26]. Higher PSP cutoff values, found in other studies, are in relation with the chronological age when the sample was taken. Thus, in early onset sepsis, presepsin is significantly higher at 24 h of life versus 12 h of life [27].

CRP and PCT, frequently used in neonatal sepsis management, have a lower diagnostic value, with AUC of 0.85 (95% CI 0.74-0.97) and 0.81 (95% CI 0.68-0.95) respectively. These two markers are useful in monitoring the treatment and its cessation, with the highest NPV of 94% for CRP in LOS and 90% for PCT in EOS [28].

Our limit is the small population with sepsis and with positive blood cultures, which limits the presepsin study with a multi-factor stratification of the risk. However, presepsin response in sepsis in statistically significant related to smaller gestational ages inversely proportional. Birth mode impact on presepsin for neonatal sepsis (C section *vs* vaginaly - 1107 *vs* 762, $p = 0.033$) can help for a better antenatal infectious risk assessment, which contributed to the obstetrical decision.

Conclusions

PSP is significantly higher in sepsis compared to non-sepsis. Presepsin value is significantly higher in neonatal sepsis compared to healthy newborns (939 *vs* 368 ng/mL, $p < 0.0001$); area under receiver operating curve (AUC) for presepsine was 0.931 (95% confidence interval 0.86-1.0). PSP has a greater sensibility and specificity compared to classical sepsis markers, CRP and PCT respectively (AUC 0.931 *vs* 0.857 *vs* 0.819, $p < 0.001$). The cut off value for Presepsin was established at 538 ng/mL with a sensibility of 79.5% and a specificity of 87.2 %. Presepsin is the best negative predictive factor for sepsis in all newborns at risk for sepsis, late neonatal sepsis and sepsis in preterm infants under 32 weeks of gestation age. Procalcitonin is the best positive predictive factor for neonatal sepsis. The combined use of the three markers is optimal for neonatal sepsis management.

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