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REVIEW ARTICLE

Procalcitonin versus C-reactive protein: review of kinetics and performance for diagnosis of neonatal sepsis

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Abstract

Procalcitonin (PCT) and C-reactive protein (CRP) are commonly used biomarkers, but their diagnostic advantage for neonatal early-onset (EOS) or late-onset (LOS) sepsis is controversial. In a comprehensive literature review we found significant heterogeneity between studies in sample timing, cut-off values, consideration of blood culture results for sepsis classification, and definition of EOS versus LOS. We identified 39 studies directly comparing PCT with CRP, but only four in very low birth weight (VLBW) neonates. The mean sensitivity for EOS, LOS, and EOS + LOS was 73.6%, 88.9%, and 76.5% for PCT, compared to 65.6%, 77.4%, and 66.4% for CRP, respectively. Mean specificity of PCT and CRP was 82.8% versus 82.7% for EOS, 75.6% versus 81.7% for LOS, and 80.4% versus 91.3% for EOS + LOS. More studies directly comparing both biomarkers for EOS and LOS, especially in extremely and very-low-birth-weight infants, are needed to determine their clinical value for guidance of antibiotic therapy in neonatal sepsis.

Introduction

The burden of neonatal sepsis remains unchanged over the past decade at about 1–2/1000 live births for early onset sepsis (EOS) and 6/1000 live births for late-onset sepsis (LOS) [1, 2]. Very-low-birth-weight (VLBW) infants seem to be disproportionately affected with rates of 20/1000 for EOS and 200/1000 for LOS [3, 4]. Blood culture negative, clinically diagnosed sepsis accounts for the majority of these cases, which is problematic because the definition of clinical sepsis is variable and often includes subjective signs on physical exam [5–7]. A meta-analysis of neonatal sepsis prediction models from 2015 showed that physicians are unreliable at predicting neonatal sepsis. The range of sensitivity and specificity of the prediction models was 56–98% and 18–73%, respectively. Lethargy, pallor, and hypothermia, all vague clinical symptoms, had the highest sepsis associated odds ratios [8]. Blood cultures are considered the gold standard for diagnosis of neonatal sepsis, unfortunately the positivity rate is low and results may be affected by insufficient blood volumes, low-colony count bacteremia, prenatal antibiotic use, or pretreatment with antibiotics prior to culture being obtained [9]. In cases of low-colony count bacteremia, up to 60% of blood cultures can be falsely negative [10]. Because of these concerns, antibiotic use for rule out sepsis episodes and culture negative sepsis is 10–15 times higher than for culture proven sepsis [5, 11].

Biomarkers for diagnosis of neonatal sepsis have been proposed for decades, especially to help rule out infection and stop antibiotics [12]. While the use of biomarkers can lead to increased blood sampling, longer monitoring and increased length of hospital stay, biomarkers can be applied to decrease antibiotic exposure in patients with suspected sepsis [13, 14]. An ideal marker is one with almost perfect sensitivity to avoid missing even a single case of neonatal sepsis, but also high specificity to prevent false-positive tests resulting in unnecessary antibiotic exposure. The most common biomarker used for this purpose in the neonatal intensive care unit, is C-reactive protein (CRP). However, in childhood and adult populations, several studies advocate for procalcitonin (PCT) as a more sensitive and specific marker [15]. Meta-analyses

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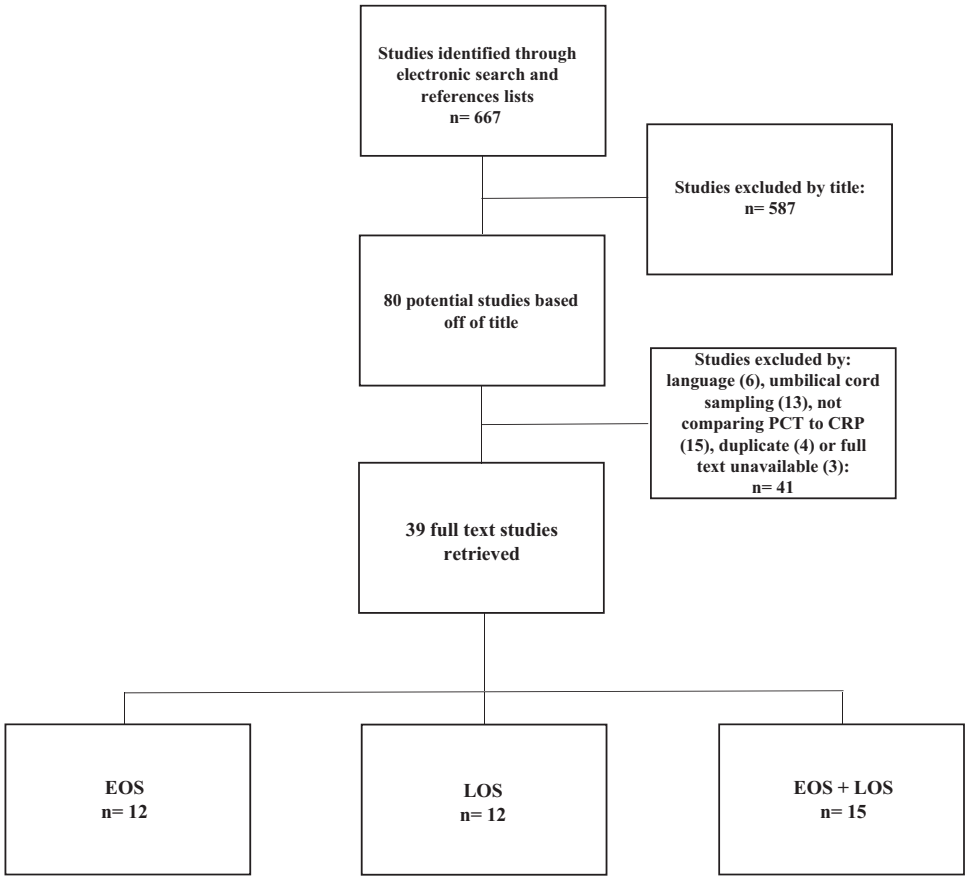

Fig. 1 Strategy for literature search and selection of studies directly comparing procalcitonin and C-reactive protein in the diagnosis of neonatal sepsis

on neonatal populations suggested PCT may be superior to CRP, with a sensitivity of 79% and specificity of 84%, compared to CRP with a sensitivity of 69% and a specificity of 77% [16, 17]. However, only 4 neonatal studies included in these meta-analyses compared PCT and CRP directly. Here, we summarize the available data for PCT and CRP in their performance as a biomarker for neonatal sepsis and point out gaps in knowledge needed to be closed before conclusions regarding their clinical use can be drawn.

We queried MEDLINE, PubMed, EMBASE, and the Cochrane Library databases searching for studies comparing accuracy of PCT and CRP for diagnosis of neonatal sepsis. No start date limit was used and the search strategy continued through October 2018. Search terms included "procalcitonin", "PCT", "c-reactive protein", "CRP", "biomarker", "diagnostic marker", "sepsis", "septicemia", "neonate", "neonatal", "newborn", "infant", and combinations of these terms. The reference lists of both primary and review articles were examined to identify cited articles not captured by electronic searches. Studies that evaluated and compared PCT and CRP concentrations as diagnostic markers for neonatal sepsis were considered. Studies were excluded if they were not accessible in English language, if the full text was unavailable, or if the samples originated from the infant's mother or from cord blood rather than the infant's postnatal blood. We also excluded studies that did not allow calculations of sensitivity or specificity (Fig. 1).

CRP kinetics

CRP is a cyclic homopentameric protein that acts as part of the acute-phase reaction in sepsis. It binds phosphorylcholine, a component of teichoic acids in gram-positive organisms, and lipopolysaccharides in gram-negative organisms. CRP can also bind lysophosphatidylcholine, ribonucleoproteins, chromatin, and histones that are exposed in apoptotic cells. It acts through interaction with complement component C1q and the crystallizable antibody fragment (Fc) receptors Fc-γRI and Fc-γRII to activate the classical complement pathway and induce phagocytosis [18–20]. CRP expression is primarily in the liver, though it has been reported in neurons, monocytes, lymphocytes, and in atherosclerotic plaques [21]. CRP production is induced by interleukin (IL)-6, IL-1β, and TNF-α [18–20]. Protein secretion begins 4–6 h after stimulation and peaks at about 36–48 h with a half-life of about 19 h [21, 22].

PCT kinetics

PCT is a prohormone of calcitonin without hormonal activity. Its mRNA is synthesized by the *CALC-I* gene on chromosome 11 during sepsis and inflammation. In healthy individuals, it is only expressed in the thyroid and in small amounts in the lung. In cases of sepsis, the liver produces the largest amount of PCT and plasma concentrations can increase up to 1000-fold. PCT is also expressed in other body tissues and cell lines, such as the spleen, adrenal glands, and intestine, lymphocytes, and monocytes [23]. Synthesis is stimulated by similar cytokines as CRP, such as IL-6, IL-1β, and TNF-α, but can also be directly stimulated by lipopolysaccharides. PCT appears to be down regulated by interferon-γ which is commonly produced in response to viral infections [24–26]. The physiologic function of PCT during sepsis is largely unknown. In an in vitro study by Wiedermann et al. [27], PCT acted as a chemoattractant for monocytes and deactivated chemotaxis in the presence of additional inflammatory mediators. PCT also had a weak upregulatory influence on cytokine expression in vitro, but this has not been replicated in vivo [28]. PCT protein secretion starts within 2 h after stimulation, peaks at 12–24 h and has a half-life of about 24 h [22].

Factors affecting concentrations of PCT and CRP

Perinatal factors and mode of delivery

A 2003 study by Chiesa et al. [29] evaluated the effect of various perinatal circumstances on both CRP and PCT in the immediate postnatal period. Factors explored included gestational diabetes, gestational hypertension, mode of delivery, duration of active labor and rupture of membranes, use of intrapartum antimicrobial prophylaxis, antenatal steroid administration, fetal distress, and term versus preterm delivery. Concentration of CRP was increased by 0.4% per hour of ruptured membranes, 14.5% per hour of active labor, 40% for antenatal steroid administration, and 28% for intrapartum antimicrobial prophylaxis, all of which were statistically significant. PCT increased as well, however, only prolonged rupture of membranes approached statistical significance ($p = 0.05$). In an older study by Assumma et al., the same variables were evaluated for their effect on PCT with the addition of maternal colonization with Group B streptococci and use of anesthesia during delivery. They only found a statistically significant increase of PCT after rupture of membranes ≥18 h [30]. Mode of delivery did not affect PCT concentrations in contrast to CRP. Vaginal delivery caused an increase in CRP concentrations above the commonly used cut-off level of 10 mg/L in up to 28% of neonates within the first 48 h of life [31]. Operative vaginal delivery with vacuum or forceps increased the level of rise over the first 24 h of life, but did not correlate with severity of birth tissue trauma [32].

Type of pathogen

Both adult and neonatal studies found some correlation of CRP concentrations to the virulence of the infecting pathogen [30, 33, 34]. While data are scarce for neonates, PCT concentrations tended to be higher in adults with gram-negative compared to gram-positive infections [35]. In a meta-analysis of studies including adults, children, and neonates, PCT had a slightly higher sensitivity and specificity for differentiating bacterial versus viral infections at 92% and 73%, compared to CRP with 86% and 70%, respectively [15]. In a study of 1–15-year-old children, not included in the prior meta-analysis, sensitivity and specificity for differentiating bacterial versus viral infections were 83% and 93% for PCT > 1 ng/ml and 98% and 50% for CRP > 10 mg/L, respectively [36].

Illness severity

In both adults and neonates, PCT and CRP concentrations correlate with severity of illness as determined by the Score for Neonatal Acute Physiology (SNAP), SNAP perinatal extension, and sepsis-related organ failure assessment [29, 37]. PCT seems superior at differentiating bacterial sepsis from other causes of illness even in patients with higher baseline illness severity scores in both adults and neonates. PCT concentrations were 5–20-fold increased from baseline in the setting of sepsis compared to a 3–8-fold increase in CRP [29, 37]. In a neonatal study on illness severity in culture proven sepsis, PCT had a sensitivity of 82% and a specificity of 95%, compared to a sensitivity of 73% and a specificity of 83% for CRP [29]. A study in febrile neonates presenting to the emergency room between 7 and 90 days of age compared the potential of PCT and CRP to help differentiate between serious bacterial infection (SBI) such as urinary tract infections or pneumonia and invasive bacterial infection (IBI) such as bacteremia or meningitis [38]. In all infants, as well as in subgroup analysis of infants less than 30 days of age, PCT and CRP had similar sensitivity and specificity for diagnosis of SBI at 60% and 85% versus 77% and 75%, respectively, but showed improved diagnostic utility of PCT in diagnosing IBI at 85% and 85% compared to CRP at 75% and 75%, respectively.

Surgery

Surgery has a significant effect on all inflammatory mediators due to the underlying pathology and the tissue

injury that occurs during the actual procedure. In 2002, Bolke et al. described that neonates with gastroschisis had higher baseline CRP concentrations preoperatively and a higher peak response after surgery compared to other pathologies such as congenital diaphragmatic hernia, omphalocele, esophageal, or intestinal atresia. In addition, the older the child was at time of surgery, the more profound the CRP response was postoperatively [39]. Children aged 4 months to 3 years, studied by Arkader et al., PCT concentrations increased slightly postoperatively but never exceeded the 2 ng/ml cut-off. In contrast, CRP increased above the 10 mg/L cut-off point on postoperative day (POD) 0 and did not start to normalize until POD 2–3 [40]. Other studies of PCT and CRP in the postoperative setting had conflicting results. While some described persistently elevated CRP concentrations up to POD 6, others showed either an equivalent or poorer performance of PCT when compared to CRP in differentiating postoperative infectious complications from postsurgical systemic inflammatory response [41–43].

Birth weight, gestational age, and physiologic increase in the first 48 h after birth

In healthy newborn neonates, both CRP and PCT increase physiologically over the first 24–48 h postpartum, typically with maximum concentrations reached at 24 h. Baseline concentrations are not affected by sex, but birth weight and gestational age both influence the concentrations of CRP and PCT. However, the relationship between these factors and levels of the inflammatory markers is inversely related [44–47]. For each 100 g increase in birth weight, the PCT concentrations decreased by 2.2%, while CRP concentrations increased by 2.4%. PCT concentrations decreased by 11.4% with each week of increasing gestational age, while CRP concentrations increased 6% per week [44].

Determination of appropriate cut-off values

Because both CRP and PCT have a physiologic increase after birth affected by birth weight and gestational age, defining normal reference concentrations for term and preterm infants is critical for determining optimal cut-off values for both markers, in particular for EOS. The data from three separate studies determining the 95th percentile of normal, which is typically used as a cut-off point, are listed in Table 1. The 95th percentile for PCT concentrations for both term and preterm infants was 1 ng/ml at 0 h of life (HOL) in all three studies. In contrast, the cut-off points at 24–36 HOL differed by a factor of 4–5 between studies. Chiesa et al. considered the impact of gestational age and birth weight on baseline concentrations of both PCT and CRP. Cut-off levels for PCT at 12, 24, and 36 HOL in preterm infants were about 3 times higher than in term infants. Although data varied between studies, the physiological PCT peak at 24 HOL was more commonly 10–20 ng/ml for term infants and 50–60 ng/ml for preterm infants.

Comparing C-reactive protein and PCT as a biomarker for the diagnosis of neonatal sepsis

When comparing PCT to CRP in all patient populations—adult, child, and neonate—a meta-analysis found a significant difference between the two markers. PCT had a sensitivity of 88% and specificity of 81%, while CRP had a sensitivity of 75% and specificity of 67% [15]. While the number of studies directly comparing PCT and CRP are limited (Fig. 1), a large body of literature lists performance measures for individual markers. For CRP alone, one meta-analysis found an overall sensitivity of 69% and specificity of 77% in accuracy of neonatal sepsis diagnosis. In a subgroup analysis focused on evaluation at time-point 0 h and

Table 1 Studies determining the 95th percentile of normal for PCT

	Term			Preterm		
95th percentile (PCT, ng/ml)	Chiesa [44]	Fukuzumi [45]	Turner [46]	Chiesa [44]	Fukuzumi [45]	Turner [46]
0 HOL	1	1	1	1	1	1
12 HOL	10	8	7	30	5	8
24 HOL	20	60	10	60	50	12
36 HOL	10	50	10	30	30	12
48 HOL	9	20	8	10	20	10
60 HOL	5	10	5	8	10	7
72 HOL	3	8	3	6	5	5
84 HOL	3	5	2	5	2	4
96 HOL	5	1	2	2	1	1

cut-off of 10 mg/L, sensitivity was 54% and specificity 92%, suggesting that CRP at a single-time point does not seem to be a very effective biomarker for neonatal sepsis [16]. In a study of serial CRP measurements in neonates by Benitz et al., both sensitivity and specificity were poor at single-time points and improved significantly with multiple measurements. When evaluating the efficacy of CRP over 3 serial measurements, the positive predictive value of CRP for diagnosis of neonatal sepsis was only 5% for EOS and 43% for LOS. However, the negative predictive value was 99.7% for EOS and 98.7% for LOS, making CRP a clinically useful marker for ruling out infection when serial measurements are obtained [48]. A recent retrospective cohort study aiming to determine the clinical necessity of serial CRP measurements for LOS concluded that a high-negative predictive value of 93% is reachable with only two tests: a complete blood count at time of blood culture (T0) and a CRP concentration 24 h later (T24) [49]. This would allow antibiotics to be stopped already at 36 h of negative blood culture rather than waiting for serial CRP measurements to return at 48 h.

For PCT, a meta-analysis of neonatal studies listed sensitivity and specificity at different time-points, but did not evaluate serial measurements. While the average sensitivity for EOS and LOS at T0 was 79% and specificity was 84%, highest sensitivity and specificity of PCT was reached between T24 and T48 at 79.5% and 89%, respectively [17]. These findings correlate well with the known physiologic peak of PCT around 24 h after stimulation and suggests optimal timing of testing would be around 24 h after suspicion of infection or at T0 and T24 if trending serially like CRP.

Studies directly comparing PCT and CRP as a marker for neonatal sepsis for EOS, LOS and the combination of EOS and LOS are listed in Tables 2–4. Overall, the-mean and median sensitivity of PCT were higher when compared to CRP for EOS, LOS, and EOS + LOS (Table 5). This is likely due to the kinetics of PCT and its earlier release into the plasma after a stimulus. When comparing the specificity of PCT and CRP, they appear equivalent for EOS, but CRP specificity was higher in both LOS and EOS + LOS studies. There was a high variability in cut-off concentrations used, but less for CRP studies, most of which used a cut-off of ≥10 mg/L. When we compared mean and median sensitivities and specificities between biomarkers only considering studies with a CRP cut-off of ≥10 mg/L, results were not appreciably different (Table S1). Interpretation of this data is limited by the variable times used to discriminate between EOS and LOS, different sampling time points (most commonly T0 and T48), and different definitions of sepsis (culture positive, clinical, or a combination) (Tables S2–S5).

Conclusion

Both CRP and PCT are nonspecific acute-phase response molecules produced primarily in the liver in response to infection and tissue damage, but may remain falsely low in patients with immature liver or multisystem organ dysfunction. While PCT was found to be slightly more sensitive and specific in adult, pediatric, and some neonatal populations, it remains unclear which marker is clinically superior for evaluation of neonatal sepsis. Both may require different cut-off levels based on gestational and postpartum age, specifically affecting their use as an EOS marker. PCT appears to be less affected by mode of delivery or surgical procedures. It may also be a better differentiator between viral and bacterial infection although this will need to be confirmed for neonates as the current data were generated from older children and adults. Most studies were conducted outside of the United States with a paucity of studies directly comparing CRP and PCT in VLBW infants. Investigators applied varying cut-off levels and definitions of sepsis, which significant limits meaningful, accurate assessment of the performance of biomarkers for neonatal sepsis. In addition, more research is needed for both markers in specific patient populations, including preterm and term neonates undergoing surgery and VLBW infants.

More data are needed to determine optimal cut-off levels for PCT in neonates in order to standardize its use for clinical trials. Future studies should also consider biomarker kinetics for sample timing. Works by Yu et al. [17] and Beltempo et al. [49] suggested that optimal timing for both PCT and CRP measurement in VLBW infants with suspected LOS is between T0 and T24 in order to balance accuracy for sepsis diagnosis with minimizing antibiotic exposure. To rule-out EOS with suspected perinatal infection, first measurements at T12 rather than T0 seem to be more clinically reasonable. However, the recent stewardship effort of stopping antibiotics already after 36 h of negative-cultures limits the number of serial values one can obtain every 12–24 h and have results returned prior to stoppage. Biomarker performance data with direct comparison for specific clinical scenarios (e.g., suspected pneumonia, urinary tract infection, meningitis, meconium aspiration, vaccinations) will be needed. Few studies directly compare the various measurement platforms for CRP and PCT, overall showing good correlation between technologies except for required processing time [51]. However, interpretation of test results has to be individualized considering methodology, population, and clinical circumstances [52].

While the clinical value of using neonatal sepsis biomarkers continues to be debated, both PCT and CRP perform better when trended serially and need to be used in combination with other clinical and laboratory data when making clinical decisions regarding initiation or

Table 2 Studies of procalcitonin in early onset sepsis

Study	Design	Age	Country	*n*	Prevalence of sepsis	PCT lab assay	Timing of test*	PCT cut off (ng/ml)	CRP cut off (mg/L)	Inclusion criteria	Sepsis diagnosis	PCT sensitivity (%)	PCT specificity (%)	CRP sensitivity (%)	CRP specificity (%)
Al-Zarhani et al. [53]	Prospective	0–7 days	Saudi Arabia	100	32%	PCT ELISA Abrams	0–24 h	1.7	2.5	Suspected sepsis	MC, PCR, or CC	30	80.5	91.1	72.4
Naher et al. [54]	Cross Sectional	0 days	Bangladesh	50	20%	PCTQ	0 h	0.5	6	Suspected Sepsis	CC	65	90	55	100
Guibourdenche et al. [55]	Prospective	0 days	France	120	17.5%	PCT-LIA Lumitest	0–24 h	2.5	7.5	Suspected sepsis	MC, CC	87	90	68	80
Canpolat et al. [56]	Prospective	0–72 h	Turkey	74	43%, 20% MC	PCT-LIA Lumitest	0 h 72 h	0 h:1.74 72 h: 1.8	0 h: 7.2 72 h:7.8	PPROM	MC, CC	0 h: 76 72 h: 89	0 h: 85 72 h: 86	0 h: 56 72 h: 60	0 h: 58 72 h: 63
Resch et al. [57]	Prospective	0 days	Austria	76	54%, 21% MC	PCT-LIA Lumitest	0–12 h 24–36 h	6 2 14	2.5 8	Suspected sepsis	MC, CC	77 83 63	91 61 100	69 49	96 100
Chiesa et al. [29]	Prospective	0–2 days	Italy	134	14%, 8% MC	PCT-LIA Lumitest	0 h 24 h 48 h	0 h: 1 24 h: 100 48 h: 50	0 h: 4 24 h: 10 48 h: 10	Suspected sepsis	MC, CC	0 h: MC 82 MC + CC 79 24 h: MC 100 MC + CC 95 48 h: MC 91 MC + CC 84	0 h: 95 24 h:96 48 h:100	0 h: MC 73 MC + CC 74 24 h: MC 91 MC + CC 89 48 h: MC 91 MC + CC 89	0 h: 83 24 h: 87 48 h: 84
Koksal et al. [58]	Prospective	0–72 h	Turkey	67	43%, 8.9% MC	PCT-LIA Lumitest	0 h 24–48 h	2	10	Suspected sepsis	MC, CC	48	100	48	87
Franz et al. [33]	Prospective	0–10 days	Germany	162	28.3%, 5.5% MC	PCT-LIA Lumitest	0 h	0.27 0.5 3.5	10	Suspected sepsis	MC, CC	80 57 30	53 66 91	28	97
Altunhan et al. [59]	Prospective	0 days	Turkey	171	39%	PCT-LIA Lumitest	0 h 24 h	0 h: 0.56 24 h:5.38	0 h:5 24 h: 12	Suspected sepsis	MC, CC	0 h:48.7 24 h:83.3	0 h:68.8 24 h:88.6	0 h:44.5 24 h:76.4	0 h:59.4 24 h:78.9
Mohsen and Kamel [60]	Cross Sectional	0–72 h	Egypt	35	100%	PCT ELISA	0 h	1.1	12	EOS	MC	80	85.7	72.9	100
Schlapbach et al. [61]	Prospective	0–3 days	Switzerland	137	24%	PCT-LIA	0 h	2	20	Suspected sepsis	MC, CC	88	51	36	89
Abd Elmouttaleb et al. [62]	Prospective	1–6 days	Egypt	50	100%	PCT-ELFA	0–24 h	2	60	Suspected sepsis	MC	76.3	78.2	51.6	70.7

PCT procalcitonin, *CRP* C-reactive protein, *EOS* early onset sepsis, *LOS* late-onset sepsis, *h* hour, *d* day, *MC* microbiologically confirmed, *CC* clinical criteria, *ELISA* enzyme-linked immunosorbent assay, *LIA* immunoluminescence assay, *ELFA* enzyme-linked fluorescent assay, *PCTQ* rapid semiquantitative immunocromatographic test, *CLIA* chemoluminescence assay

*From time of delivery

Table 3 Studies of procalcitonin in late-onset sepsis

Study	Design	Age	Country	*n*	Prevalence of sepsis	PCT lab assay	Timing of test*	PCT cut off (ng/ml)	CRP cut off (mg/L)	Inclusion criteria	Sepsis diagnosis	PCT sensitivity (%)	PCT specificity (%)	CRP sensitivity (%)	CRP specificity (%)
Park et al. [63]	Retrospective	5–29 days	Korea	269	27.5% 7% MC	PCT-ELFA	0 h	0.5	1	Suspected sepsis	MC, CC	88.3	58.2	100	85.7
Fendler and Piotrowski [64]	Prospective	8–23 days	Poland	73	80%	PCT-LIA	0 h	0.99	2.2	Suspected sepsis	MC, CC	97.5	88.9	85	88.9
Vazzalwar et al. [65]	Prospective	10–42 days	USA	51	71% 35% MC	PCT-LIA Lumitest	0 h 48 h 5d	0.5	8	Suspected sepsis, VLBW	MC, CC	MC 94 MC + CC 97	MC 36 MC + CC 80	MC 78 MC + CC 72	MC 61 MC + CC 93
Ucar et al. [66]	Prospective	6–8 days	Turkey	36	72%	PCT-LIA	0 d 4 d 8 d	0.8	8	Suspected sepsis	MC, CC	0d:86.1 4d:83.3 8d:69.4	0d:97.2 4d:86.1 8d:97.2	0d:97.2 4d:100 8d:100	0 d:100 4 d:100 8 d:100
Ertugrul et al. [67]	Case–Control	7–28 days	Turkey	24	100%	PCT-LIA Kryptor	0 h	0.5	10	LOS	MC	91.7	75	58.3	80
Jacquot et al. [68]	Prospective	8–18 days	France	73	41%	PCT-LIA	0 h	0.6	10	Suspected sepsis	MC	100	65	58	86
Bohnhorst et al. [69]	Prospective	4–112 days	Germany	170	34%	PCT-LIA	0 h	0.7	10	Suspected sepsis	MC	79.3	75.9	68.9	83.9
Distefano et al. [70]	Case–control	3–10 days	Italy, Switzerland	35	77%	PCT-LIA	3 d 7 d 10d	0.7	10	Suspected sepsis, VLBW	MC, CC	All infection: 96 Bacterial:99 Fungal: 77	All infection: 84	All infection: 88 Bacterial:88 Fungal: 58	All infection: 70
Verboon-Macioleket et al. [71]	Prospective	3–24 days	Netherlands	92	71%, 40% MC	PCT-LIA Lumitest	0 h 48–72 h	0.5	14	Suspected sepsis	MC, CC	69	82	65	52
Enguix et al. [72]	Prospective	3–30 days	Spain	46	43%	PCT-LIA	0 h	6.1	23	Suspected sepsis	MC, CC	98.6	88.9	95.8	83.6
Turner et al. [73]	Prospective	4–66 days	Israel	36	40%	PCT-LIA Lumitest	0 h 24 h 48 h 72 h	2.3	30	Suspected sepsis	MC, CC	97	48	91	41
Bustos and Araneda [74]	Prospective	3–40 days	Chile	53	100% 53% MC	PCT-LIA Lumitest	0 h	0.9	111	Suspected sepsis, VLBW	MC, CC	88	72	12	100

PCT procalcitonin, *CRP* C-reactive protein, *EOS* early onset sepsis, *LOS* late-onset sepsis, *h* hour, *d* day, *MC* microbiologically confirmed, *CC* clinical criteria, *ELISA* enzyme-linked immunosorbent assay, *LIA* immunoluminescence assay, *ELFA* enzyme-linked fluorescent assay, *PCTQ* rapid semiquantitative immunocromatographic test, *CLIA* chemoluminescence assay

*Time from onset of illness

Table 4 Studies of procalcitonin in early + late-onset sepsis

Study	Design	Age	Country	*n*	Prevalence of sepsis	PCT lab assay	Timing of test*	PCT cut off (ng/ml)	CRP cut off (mg/L)	Inclusion criteria	Sepsis diagnosis	PCT sensitivity (%)	PCT specificity (%)	CRP sensitivity (%)	CRP specificity (%)
Celik et al. [75]	Prospective	1–47 days	Turkey	227	51% 17.6% MC	PCT-LIA	0 h	0.004	1.6	Suspected sepsis	MC, CC	MC 75, MC + CC 69.2	MC 86, MC + CC 83.9	MC 75, MC + CC 71.8	MC 76.3, MC + CC 76.3
Pravin Charles et al. [76]	Prospective	0–28 days	India	75	75% 12% MC	PCT-ELISA	0 h	1.32	3	Suspected sepsis	MC, CC	88.9	80.3	88.9	89.4
Sakha et al. [77]	Retrospective	0–28 days	Iran	117	23.1%	PCT-CLIA	0 h	2	3.5	Suspected sepsis	MC	66.7	50	70.4	72.2
Cetinkaya et al. [78]	Prospective	–	Turkey	163	75% 54%	PCT-LIA Lumitest	0 h, 48 h, 7d, 10d	0.5	5	Suspected sepsis	MC, CC	0 h: 74.8 48 h: 57.7 7d: 28.4	0 h: 100 48 h: 100 7d: 100	0 h: 72.3 48 h: 71.5 7d: 50	0 h: 100 48 h: 100 7d: 100
Rashwan et al. [79]	Prospective	0–28 days	Egypt	168	60% MC	PCT-ELISA	0 h	0.389	6	Suspected sepsis	MC, CC	97	100	79.4	93.3
Cekmez et al. [80]	Prospective	–	Turkey	105	59%	PCT-LIA Lumitest	0 h	2.1	8.2	Suspected sepsis	MC	86	81	82	79
Boo et al. [81]	Prospective	0–54 days	Malaysia	87	20.7%	PCTQ	0 h	2	10	Suspected sepsis	MC	88.9	65.2	55.6	89.9
Kocabas et al. [82]	Case–control	1–30 days	Turkey	41	63%	PCT-LIA Lumitest	0, 3, 7 days	0.34	10	Suspected sepsis	MC, CC	100	96.5	80.8	100
Chiesa et al. [83]	Prospective (EOS), Case–Control (LOS)	0–24 days	Italy	EOS: 120 LOS: 23	EOS: 23%, 12% MC LOS: 100%	PCT-LIA Lumitest	0–48 h, 3–30 days	0.7	10	EOS: Suspected sepsis LOS: MC sepsis	MC, CC	EOS: 92.6 LOS:100	EOS: 97.5 LOS:100	EOS: 46.4 LOS:69.5	–
Groselj-Grenc et al. [84]	Prospective	0–18 days	Slovenia	46	37%	PCT-LIA	0 h, 24 h	2.28	11	Suspected sepsis	MC	82	48	59	100
Adib et al. [85]	Cross-sectional	–	Iran	87	79%, 23% MC	PCT-LIA	0 h	1.1	12	Suspected sepsis	MC, CC	70	80	45	95
Bonac et al. [86]	Prospective	0–20 days	Slovenia	58	43%, 15.5% MC	PCT-LIA Lumitest	0 h 24 h 48 h	0 h: 9.98 24 h: 13 48 h: 3.07	0 h: 14 24 h: 29 48 h: 12	Suspected sepsis	MC, CC	0 h: 59 24 h: 50 48 h: 52	0 h: 82 24 h: 100 48 h: 91	0 h: 36 24 h: 44 48 h: 68	0 h: 92 24 h: 100 48 h: 83
Blommendahl et al. [87]	Prospective	<32 weeks GA	Finland	169	8%	PCT-LIA Lumitest	0 h	1	30	Suspected sepsis	MC	77	62	58	84
Kumar et al. [88]	Case–Control	–	India	82	50% 23% MC	PCT-ELISA	0 h	0.2	32	Suspected sepsis	MC, CC	80.5	80.5	80.5	97.5
Pavanik-Arnol et al. [50]	Prospective	0–26 days	Slovenia	47	44.6%	PCT-LIA	0 h, 48 h	EOS: 1.39 LOS:2.52	EOS: 21 LOS:45	Suspected sepsis	MC, CC	EOS: 100 LOS: 92	EOS: 35 LOS: 50	EOS: 88 LOS: 69	EOS: 100 LOS: 100

PCT procalcitonin, *CRP* C-reactive protein, *EOS* early onset sepsis, *GA* gestational age, *LOS* late-onset sepsis, *h* hour, *d* day, *MC* microbiologically confirmed, *CC* clinical criteria, *ELISA* enzyme-linked immunosorbent assay, *LIA* immunoluminescence assay, *ELFA* enzyme-linked fluorescent assay, *PCTQ* rapid semiquantitative immunocromatographic test, *CLIA* chemoluminescence assay

*Time from hour of delivery or onset of illness

Table 5 Sensitivity and Specificity for EOS, LOS, and EOS + LOS

Number of studies			Sensitivity			Specificity		
			Mean	Median	Range	Mean	Median	Range
12	EOS	PCT	73.6%	80%	30–100%	82.8%	87.3%	51–100%
		CRP	65.6%	68.5%	28–91.1%	82.7%	85.5%	58–100%
12	LOS	PCT	88.9%	91.7%	69–100%	75.6%	80%	36–97.2%
		CRP	77.4%	85%	12–100%	81.7%	85.7%	41–100%
15	EOS + LOS	PCT	76.5%	77%	28.4–100%	80.4%	83.9%	35–100%
		CRP	66.4%	70%	36–88.9%	91.3%	94%	72.2–100%

discontinuation of antibiotic therapy in patients with concern for sepsis. Further evaluation of biomarkers for antibiotic guidance should include patient outcomes such as number of antibiotic days, length of stay, morbidity, and mortality.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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