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# The role of elevated central-peripheral temperature difference in early detection of late-onset sepsis in preterm infants

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ABSTRACT

*Aims:* The study investigated the association between clinical symptoms and late-onset sepsis (LOS) in preterm infants with the aim of identifying a non-invasive tool for the early detection of LOS.
*Methods:* This was a prospective study of 83 episodes of suspected LOS in 67 preterm infants. At the time LOS was suspected, we recorded a standardized set of clinical symptoms. A diagnosis of "clinical LOS" (Clin-LOS), "culture-proven LOS" (Prov-LOS) or "LOS not present" (No-LOS) was made on the basis of C-reactive protein (CrP) and blood culture results where Clin-LOS was defined as CrP > 10 mg/l, Prov-LOS was defined as CrP > 10 mg/l AND positive blood cultures, or it was established that there was no sepsis present (No-LOS). We examined univariable associations between clinical signs and LOS using odds ratio (OR) analysis and then adjusted the odds ratio (adOR) through binary regression analysis.
*Results:* Clin-LOS was diagnosed in 20/83 episodes, 19 cases were found to have Prov-LOS. Clinical signs which had a significant association with Clin-LOS were capillary refill time >2 s (OR 2.9) and decreased responsiveness (OR 5.2), whereas there was a negative association between gastric residuals and LOS (OR 0.35). However, the most marked association was found for a greater central-peripheral temperature difference (cpTD) >2 °C (OR 9). In Prov-LOS an increased heart rate (OR 3.1), prolonged capillary refill time (OR 3.3) and again an increased cpTD (OR 16) had a significant association with LOS, whereas gastric residuals were negatively associated (OR 0.29). Regression analysis showed that cpTD was the most striking clinical sign associated with both Clin- (adOR 6.3) and Prov-LOS (adOR 10.5).
*Conclusions:* Prolonged capillary refill time and – more impressive – elevated cpTD were the most useful clinical symptoms for detection of LOS in preterm infants. We especially suggest using cpTD as a predictor of LOS. It is a cheap, non-invasive and readily available tool for daily routines.


## 1. Introduction

Despite all the improvements in neonatal intensive care, late onset sepsis (LOS) remains a major cause of morbidity and mortality in neonatal intensive care units (NICUs) [1,2]. Up to 15–20% of very low birth weight infants suffer from bacterial infection [3,4]. Early detection is still a formidable task. Blood cultures continue to be the gold standard in detecting LOS, but results are not immediate. Nor are the results of tests for other well-established laboratory indicators of infection such as C-reactive protein (CrP), IL-6 and IL-8, white blood cell count and I/T ratio available immediately, and especially in the important first hours these are not sensitive enough to confirm diagnosis in the absence of other clinical signs. For this reason, clinicians often administer empirical antibiotic therapy as first-line treatment of a potential infection. On order to close this diagnostic gap, we decided to focus on the traditional wisdom of observing clinical symptoms. Compared to the enormous number of studies establishing the usefulness of laboratory tests for early detection of LOS, only a few studies have investigated clinical signs as early markers of LOS [5–8]. In these papers different parameters were measured and a list of different symptoms was found for detecting sepsis early. In 2012 the role of peripheral-central temperature measurements for the detection of LOS was investigated in a small patient group [9]. Our prospective study observed and collected different clinical signs that can be easily detected at the bedside, and analysed the association between these clinical findings and LOS.

*Abbreviations:* adOR, adjusted odds ratio; CI, confidence interval; Clin-LOS, clinical late-onset sepsis; CNS, coagulase-negative staphylococci; cpTD, central-peripheral temperature difference; CrP, C-reactive protein; CRT, capillary refill time; cT, central temperature; IL-6 & IL-8, interleukin 6 and 8; I/T ratio, immature neutrophil to total neutrophil ratio; LOS, late-onset sepsis; NICU, neonatal intensive care unit; No-LOS, late-onset sepsis was established to be absent; OR, odds ratio; P, *p*-value; PDA, patent ductus arteriosus; Prov-LOS, proven late-onset sepsis; pT, peripheral limb temperature.

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## 2. Methods

### 2.1. Study population and setting

We performed a prospective cohort study at the level III NICU of the University of Leipzig, Germany, over a period of two years. All neonates born < 34 weeks' gestation and with an episode of suspected infection after 72 h postnatal age were included.

Suspicion of an episode of infection was based on the infant's clinical status and deteriorating vital signs. If the attending neonatologist suspected LOS, the infant was included in the study. On first suspecting LOS but before blood samples were drawn, a panel of both subjective and objective clinical symptoms and signs were recorded (see below). As a rule in our NICU the LOS-workout had to be started if two clinical symptoms from two different major sign-groups (see below) were manifest. On the other hand it is in the responsibility of the neonatologist on duty to start the diagnostic process if only one sign-group is severely affected. To reduce the risk of a hasty conclusion being reached, intravascular volume depletion, a major cause of circulatory symptoms (e.g., tachycardia) in preterm infants [10], was ruled out by administration of 10 ml/kg isotonic electrolytes intravenously. If symptoms persisted after volume therapy, blood samples were drawn to determine blood cultures and CrP, and antibiotic treatment was initiated. CrP was analysed at the time LOS was initially suspected (day 1), as well as 24 h and 48 h later (on days 2 and 3).

A diagnosis of clinical LOS (Clin-LOS) was made if CrP increased above 10 mg/l at least once during the first three days (at the measure points on days 1–3), whether or not blood cultures were positive. A culture-proven LOS (Prov-LOS) was defined as a positive blood culture combined with an increase of CrP above 10 mg/l. Possible contamination was defined as a combination of a positive blood culture with coagulase-negative staphylococcus (CNS) and CrP < 10 mg/l at all three measure points [11–13]. If CrP remained negative during 72 h of observation and no positive blood cultures were obtained, LOS was deemed to be absent (No-LOS).

### 2.2. Symptoms and clinical signs

As a source for objective clinical data (heart rate, RR, temperature) the MP70 Intelli Vue Neonatal Monitor (Philips, The Netherlands) was used. These data are stored for 48 h, so for calculation of "baseline data" the monitor data were analysed between 12–24 h before inclusion into the study. Besides standard monitoring (heart rate, pulsoximetry, blood pressure) every infant had skin temperature probes ('Mona-Therm', Covidien, Mansfield, MA) placed to record both core body (central temperature, cT) and peripheral limb temperature (peripheral temperature, pT). The probe for recording cT was placed at the chest/back-bed interface, depending on whether the infant was prone or supine. The pT probe was placed on the sole of the foot. Temperature inside the incubator was modified to maintain a core body temperature of 36.5–37.5 °C. pT was not regulated but used for diagnostic purposes. We named the difference between cT and pT the central-peripheral temperature difference (cpTD). We assumed a difference of ≤ 2 °C to be normal as described in recent papers [9,14].

Clinical signs were recorded using a standardized form designed for this study. Based on the literature [7,8,15], we selected four major sign-groups: 1. Circulatory — cpTD > 2 °C, CRT > 2 s [16,17], increased heart rate > 10% above individual base-line, bradycardia with pulse < 100 bpm (for at least 20 s), change of skin colour (pallor, "grey" skin) and blood pressure; 2. Neurological — apnoea (blood saturation below 80% by pulse oximetry, measured by Philips FAST algorithm) and decreased responsiveness; 3. Respiratory — increase of $FiO_2$ requirement >0.05 and deterioration in breathing mechanics (chest retractions, nasal flaring); 4. Gastrointestinal — distended abdomen and gastric residuals. All symptoms and signs were determined to present or not and annotated as such. Objective data were additionally recorded as absolute values.

Other information collected was: gender, gestational age and weight, APGAR, NA-pH, type of respiratory support (none, continuous positive airway pressure [CPAP], artificial ventilation), type of IV line (none, peripheral, central), and patency of the ductus arteriosus (PDA) at the time LOS was first suspected.

### 2.3. Statistical analysis

An independent clinical assistant who was not involved (M.U.) analysed the data. Because the LOS definitions had been determined a priori, diagnosis was independent of the analyser. Some infants had more than one episode of suspected infection. We included the basic data at birth only once per infant (n = 67). In all further analyses we refer to the full number of 83 episodes of suspected infection. Univariate associations between individual outcomes (sepsis, no sepsis) and study variables were tested using contingency table analysis to produce first estimates of odds ratios (OR) and 95% confidence intervals (95% CI). Binomial logistic regression analysis was performed to test clinical signs for their ability to predict an accurate diagnosis of LOS. Results were described using adjusted odds ratios (adOR) and 95% CI. The use of ROC curve areas specified the models discrimination. All statistical analyses were executed with SPSS Version 22 or earlier.

## 3. Results

### 3.1. Study population

Over the study period of two years, a total of 938 infants were admitted to the NICU. 609 infants were initially excluded from the study (born after 33 6/7 weeks' gestation). In the remaining 329 preterm infants, 254 had no sepsis suspected and 8 were subsequently excluded because they suffered from volume depletion only. This study ultimately analysed 67 infants with 83 episodes of suspected infection.

### 3.2. Groups: diagnosis of LOS and blood culture outcomes

Clin-LOS was diagnosed in 20 of 83 (24%) episodes. Positive blood cultures were obtained in 19 infants, making up the Prov-LOS group (23%). None of these positive cultures were considered contaminated according to our definition. CNS were the most common pathogens (13/19). The non-CNS agents included two instances each of Pseudomonas aeruginosa and Klebsiella pneumoniae, and one each of Citrobacter freundii and Staphylococcus aureus. In 44 episodes the diagnosis of sepsis was not confirmed (No-LOS group).

### 3.3. Basic data

The main demographic characteristics were similar across the three groups (Table 1). There was equal distribution of male infants, gestational age at birth and for birth weight. Postnatal adaptation (APGAR values, NA-pH) was not significantly different. Time of inclusion into the study was similar as well. Nor did we find any significant differences between the three groups when analysing the type of catheter or the type of ventilation at time of inclusion. Overall, five preterm infants had a PDA at the point of inclusion with no significant differences between the groups.

### 3.4. Objective clinical data at time of inclusion

The infants in all three groups had equal baseline values for heart rates, RR, cT, pT and cpTD (Table 2). Heart rates increased in all three groups with higher values in infants with Prov-LOS. We found no differences in blood pressure parameters when comparing infants with an infection to those without. Analysis of body temperature revealed a