Eur J Clin Microbiol Infect Dis (2011) 30:455–457
DOI 10.1007/s10096-010-0956-5

BRIEF REPORT

Concentrations of procalcitonin and C-reactive protein, white blood cell count, and the immature-to-total neutrophil ratio in the blood of neonates with nosocomial infections: Gram-negative bacilli vs coagulase-negative staphylococci

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Received: 26 December 2009 / Accepted: 30 April 2010 / Published online: 28 January 2011

Abstract This study was undertaken to determine whether concentrations of procalcitonin in the blood of neonates with nosocomial infections depend on the type of pathogen. Qualification for the study group was based on the clinical signs of infection. We found that infections with Gram-positive (chiefly coagulase-negative staphylococci) and Gram-negative bacteria are accompanied by elevated concentrations of procalcitonin. In the case of Gram-positive bacteria, other laboratory signs of infection studied by us (concentration of C-reactive protein, white blood cell count, immature-to-total neutrophil ratio) were not discriminatory, confirming the diagnostic usefulness of procalcitonin measurements in nosocomial infections of the neonate with Gram-negative or Gram-positive bacteria.

Nosocomial infections (late-onset infections) in neonates remain a serious problem at neonatal intensive care units [1], with an incidence rate of 17–25% [2] and mortality of 17–72% depending on the gestational age of the neonate and etiology of the infection [3]. It has been demonstrated that bacterial infections are accompanied by increased procalcitonin (PCT) concentrations [4, 5]. The present work was undertaken to determine whether PCT concentrations in neonates with nosocomial infections vary with pathogen type (Gram-negative bacilli vs coagulase-negative staphylococci [CoNS]). The study was conducted at the Department of Obstetrics and Perinatology, Pomeranian Medical University, the study protocol was approved by the local bioethics committee, and informed consent was obtained from the parents.

The study group (group A; gestational age 29.7± 3.7 weeks; body mass 1,264±574 g) included 52 neonates with nosocomial infection diagnosed by an experienced neonatologist on the basis of typical symptoms and laboratory findings.

Late onset neonatal infection was recognized based on the presence of three or more of the following five categories of clinical signs:

1. Skin color (pallor, jaundice, cyanosis)
2. Respiratory function (apnea, tachypnea >60/min, grunting, nasal flaring, intercostal or sternal retractions, need for high ventilator settings or oxygen)
3. Cardiovascular function (brady-/tachycardia, poor peripheral perfusion, hypotension)
4. Neurological findings (hypotonia, irritability, lethargy, seizures)
5. Gastrointestinal function (abdominal distension, green or bloody residuals, vomiting, temperature instability)

and positive peripheral blood culture. Nosocomial infection was diagnosed when symptoms appeared after 3 days of life.

Laboratory tests routinely performed in the management of infection included C-reactive protein levels (CRP values>5 mg/L in the neonate's venous blood were considered abnormal), white blood cell count with differential (WBC>15 or <5 G/L was considered abnormal), platelet count (Plt<100 G/L was considered abnormal), and the immature-to-total neutrophil ratio (I:T ratio> 0.2 was considered abnormal).

Venous blood in group A was obtained at the onset of clinical symptoms of infection (mean age of neonate 17± 12 days). We performed cultures to determine the type of

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pathogen and measured concentrations of PCT and CRP, WBC count, and the I:T neutrophil ratio. The control group (group B; gestational age 30.0±5.1 weeks; body mass 1,502±950 g) included 88 neonates without infection past the third day of life.

Groups were compared using the Mann–Whitney non-parametric *U* test. The Shapiro–Wilk W test revealed significant deviation from normal distribution in the case of PCT and CRP. Consequently, descriptive statistics for both parameters relied on median, minimal, and maximal values (mean and standard deviation values were also shown). The level of significance was taken as $p=0.05$.

Positive blood cultures were obtained in 34 infected neonates (65.4%). Gram-negative bacteria were cultured in 22 neonates—multi-resistant hospital strains of *Klebsiella* sp. extended-spectrum beta-lactamase (ESBL[+]; $n=12$), *Pseudomonas aeruginosa* metallo-b-lactamase (MBL; $n=1$), *Enterobacter* sp. AmpC, ESBL(+; $n=5$), *Serratia* sp. ($n=3$), and *Citrobacter freundii* ($n=1$). Gram-positive bacteria were revealed in 8 neonates—coagulase-negative, methicillin-resistant (MR) skin and hemolytic strains ($n=7$), *Staphylococcus aureus* MR ($n=1$)—and *Candida* in 4 neonates.

Procalcitonin and C-reactive protein concentrations in group A and B differed significantly—PCT median (minimum–maximum): 4.3 (0.25–168.53) ng/mL vs 0.94 (0.20–35.05) ng/mL, $p=0.000001$; CRP median (minimum–maximum): 20.30 (0.1–199.7) mg/L vs 2.7 (0.10–57.0) mg/L, $p=0.000005$ respectively. No significant differences between groups were found for WBC and the I:T neutrophil ratio. Infection by Gram-negative bacteria led to highly significant increases in the concentrations of PCT and CRP, as well as in WBC and the I:T neutrophil ratio. PCT and CRP were also significantly higher for Gram-negative than Gram-positive bacteria. Infection by Gram-positive bacteria produced elevated PCT concentrations ($p=0.011$) and no significant change in CRP (Table 1). PCT concentrations in sepses caused by *Candida* sp. differed from those in the control group B ($p=0.029$), but no conclusions could be drawn because of the small number ($n=4$) of *Candida* infections.

Our observation that PCT concentrations are elevated in nosocomial infections (late-onset neonatal infections) regardless of the type of pathogen agrees with the report of Franz et al. [4]. What is important is that PCT was the only parameter measured by us that was elevated in sepses caused by Gram-positive bacteria. Therefore, CRP concentration, WBC count, and the I:T neutrophil ratio cannot serve to disclose Gram-positive infections. These findings are in agreement with the observations of Kawczyński and Polakowska [5]. Chiesa et al. [6] reported on the low sensitivity of CRP and lower PCT levels in sepses caused by CoNS compared with Gram-negative bacteria. Pourcyrous et al. [7] did not find elevated CRP concentrations in neonates with positive blood cultures for *Staphylococcus epidermidis*, confirming other reports on the relatively low pathogenicity of this species [8].

The usefulness of PCT for the early diagnosis of sepses caused by CoNS gains importance in view of the significant and rising contribution of these pathogens to the etiology of nosocomial infections in the neonate. Treatment at intensive care units often requires canulation of blood vessels and other invasive procedures. These facilitate infection by *Staphylococcus epidermidis*, which is known to adhere to silicon and form a protective coat composed of mucopolyssacharides, shielding this pathogen from the immune system of the organism and blocking the entry of drugs (antibiotics). Until recently, positive blood cultures for CoNS were regarded as contamination during collection of the sample. Contamination is more likely in term neonates and older infants. However, in neonates with very low birth weight, the detection of this pathogen in culture usually reflects true bacteremia. According to Freeman and Epstein [9], bacteremia caused by CoNS has a late onset (mean age at detection was 20 days). Even though this pathogen is not responsible for increased mortality, CoNS infection prolongs treatment with antibiotics and hospital stay by

Table 1 Procalcitonin (*PCT*), C-reactive protein (*CRP*), white blood cell (*WBC*) count, and immature-to-total (*I:T*) neutrophil ratio values in the blood of neonates with nosocomial infections (A) and in uninfected neonates (B)

Parameter	1 Group A Gram-negative bacteria, $n=22$	2 Group A Gram-positive bacteria, $n=8$	p 1 vs 2	3 Control group B, $n=88$	p 1 vs 3	p 2 vs 3
PCT (ng/mL)	9.15 (0.61–168.53) 41.22±57.25	4.20 (1.57–5.66) 3.81±2.07	0.019	0.94 (0.20–35.05) 1.82±3.87	0.00034	0.011
CRP (mg/L)	52.85 (4.10–199.70) 61.83±49.29	4.50 (2.30–25.0) 9.72±9.69	0.026	2.7 (0.10–57.0) 4.98±8.85	0.000003	0.283
WBC ($\times 10^9$/L)	15.40 (2.90–49.0) 22.96±15.26	11.55 (6.10–28.70) 12.28±8.15	0.097	10.0 (5.0–24.0) 10.92±3.82	0.007	0.975
I:T neutrophil ratio	0.46 (0.30–0.71)	0.40 (0.33–0.47)	0.423	0.12 (0.04–0.30)	0.005	0.059

approximately 12 days and 2.5 weeks respectively. It is also worth noting that CoNS are the cause of the greatest number of late sepses in neonates [3, 10].

In conclusion, elevated concentrations of PCT in venous blood may prove particularly helpful for the diagnosis of nosocomial infections of the neonate with Gram-positive bacteria (chiefly CoNS).

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