**An evaluation into procalcitonin levels in full term neonates managed for suspected early onset sepsis due to probable maternal intrapartum sepsis**

**Abstract**

Purpose: To investigate Procalcitonin (PCT) levels in full term neonates managed for suspected early onset sepsis (EOS) due to probable maternal intrapartum sepsis.

Methods: Prospective longitudinal observational study at University Hospitals of Bristol NHS Foundation trust. Included were a total of 117 neonates managed for suspected EOS from June-October 2020. In addition to routine full-blood-counts and c-reactive protein (CRP) tests, serum PCT levels were also measured as part of the septic screen and follow up blood tests. Placentas were sent for histopathology analysis.

Neonatal parameters were used to categorise cases into: ‘high-suspicion bacterial sepsis (BS),’ ‘equivocal BS’ and ‘low-suspicion BS.’ Statistical test Kruskal-Wallis compared categories with biomarker values and placental histopathology scores.

Results: A higher percentage of PCT levels showed elevation in comparison to CRP levels in the initial testing (55.3% versus 5.9%) and follow up testing (98.9% versus 35%). There was a significant difference between the ‘low-suspicion BS’ and ‘high-suspicion BS’ categories for both the initial and follow-up PCT results. 71.2% of placentas showed varying degrees of chorioamnionitis.

Conclusion: This study provides evidence to the physiological rise in PCT during the first few days of life. The significant difference in PCT levels according to clinical severity shows that PCT could be utilised in calculating odds for EOS, but as a standalone test will have limited use.

**Key Words:**

Procalcitonin, neonatal early onset sepsis, chorioamnionitis, biomarkers, intrapartum sepsis

**Introduction**

Neonatal early onset sepsis (EOS), occurring within 72 hours of birth, carries high morbidity and mortality, with a rate of approximately 1-1.5 per 1000 births.1,2 It requires prompt identification and treatment of affected neonates.2 However, early detection is difficult because the first signs of neonatal sepsis may be minimal and similar to those of other non-infectious processes. Furthermore, definitive blood culture results are not immediately available with poor yield.3,4 Consequently, the threshold is low to commence empirical broad‐spectrum antibiotics in neonates with risk factors.5

Organisms causing neonatal EOS are typically normal commensals of the maternal genitourinary tract, which ascend into the vagina, amniotic fluid and placenta either prior to onset of labour or once the amniotic membranes rupture, causing chorioamnionitis.6 Chorioamnionitis can be diagnosed by maternal fever, tachycardia, leucocytosis, uterine tenderness, foul odour of amniotic fluid, and fetal tachycardia at delivery.7 When membranes are ruptured ≥18 hours prior to delivery, the risk of EOS increases to 1% and the risk to neonates delivered to mothers with evidence of chorioamnionitis is estimated to be between 1-4%.7 As chorioamnionitis is a major risk factor for EOS, in this study we decided to look specifically at neonates born to women managed for suspected intrapartum sepsis.

While the identification and treatment of symptomatic neonates is essential, determining the management of asymptomatic neonates with risk factors alone is a challenge. Especially in the context of a considerable number of neonates in this group and the lack of good diagnostic tests to confirm or definitively rule out sepsis. This leads to a large number of healthy neonates receiving antibiotics. This impacts parental anxiety and separation, affecting bonding and breastfeeding. In addition, antibiotic exposure in the perinatal period can lead to alterations in infant intestinal microbiome over the first year of life.8,9 This can result in resistant organisms colonising the infant gut, potentially impacting early immune development and increasing risk of immune-mediated diseases such as atopy, allergy and asthma.8.9,10

In sepsis, biomarkers can play a role to provide a timely diagnosis, differentiate from other non-infectious inflammatory pathologies, predict clinical severity and guide antibiotic management.10 C-reactive-protein (CRP) which is known to be highly nonspecific for infection versus inflammation, is the most frequently employed biomarker used in the neonatal population.10,11,5 There are large numbers of asymptomatic neonates (with risk factors such as maternal intrapartum pyrexia) who undergo investigations and receive longer courses of antibiotics because of a raised CRP. There is need to urgently re-evaluate this and develop more specific investigations to confirm sepsis in order to prevent unaffected infants receiving unnecessary antibiotics.

Among the different molecules investigated as biomarkers of sepsis, procalcitonin (PCT) seems to be the most utilised and is now established in the adult population and showed to be promising in paediatrics.10,11,12 PCT is known to be of better diagnostic and prognostic value for bacterial infections.13,14 PCT produced by C cells of the thyroid gland, is involved in maintaining serum calcium levels and released into the circulation in response to pro-inflammatory stimuli and endotoxins, specifically originating from bacteria.10 PCT has a latent period of 2-4 hours and therefore increases significantly within the first few hours in severe bacterial infections. PCT also has a short half-life, helping guide antibiotic therapy and monitor response. 10,14,15

The use of PCT levels for neonatal sepsis is controversial and reference values in neonates are yet to be established.15 PCT levels can increase physiologically during the first few days of life, which interfere with the interpretation of PCT levels.6,16 A meta-analysis by Pontrelli et al, looking at the accuracy of PCT as an early biomarker of sepsis in neonates concluded; serum PCT values in healthy neonates increase gradually after birth,17 reach peak values after 24 hours and then decrease to normal values by 48-72 hours of age.9,17 This seems to be due to the reaction of birth with nonspecific activation of the immune system.16

**Study Objective**

To investigate PCT levels in full-term neonates managed for suspected EOS due to probable maternal intrapartum sepsis and to determine if PCT could be utilised to optimise diagnosis and management.10

**Methods**

A prospective longitudinal observational study was carried out at University Hospitals of Bristol and Weston (UHBW) NHS Foundation trust. The hospital averages 5000 deliveries a year. UHBW ethics committee approved the research and the department provided the funding.10

All neonates born to women treated for suspected intrapartum sepsis over a 4-month period (June–October 2020) were included in the study. At UHBW all neonates born to women treated for suspected intrapartum sepsis routinely have blood collected within an hour of birth for full blood count, CRP and blood cultures and intravenous antibiotics are commenced,10 according to local and national guidelines.18 These are stopped at 36 hours, according to blood culture results, repeat CRP levels taken 24 hours later and clinical state. For this study, septic screen CRP blood samples (‘Time 0’ bloods) alongside the 24-hour CRP samples (‘Day 1’ bloods), were also tested for PCT levels. To avoid influencing management, PCT results were concealed from clinicians.10

Elecsys BRAHMS PCT assay was used to measure PCT, with a level <0.25ng/ml considered normal for non-intensive care unit (ICU) patients and a level <0.5ng/ml considered normal for ICU patients.10,19,,20

The placentas were sent for histopathological examination by a consultant perinatal pathologist,10 who scored any inflammation present using published criteria.21 The staging and grading of chorioamnionitis was scored out of a maximum of 24, using the following criteria; membranes inflammation stage (maximum 3), membranes inflammation grade (maximum 2), chorionic plate inflammation stage (maximum 3), chorionic plate inflammation grade (maximum 3), chorionic vasculitis stage (maximum 3), chorionic vasculitis grade (maximum 3), villitis (maximum 1), intervillositis score (maximum 1), umbilical cord inflammation stage (maximum 3) and umbilical cord inflammation grade (maximum 2).10,22,23

Neonatal infection clinical markers were identified by reviewing neonatal records. Neonatal variables reviewed included gender, birth weight, neonatal antibiotic course and length of hospital stay.10 Risk factors for intrapartum pyrexia reviewed were, fetal blood samples, induction or augmentation of labour, epidurals, mean time from membrane rupture to delivery and mode of delivery.10 A dedicated database was use to record and store all information.

The neonates were divided into three categories of ‘high-suspicion BS,’ ‘equivocal BS’ and ‘low-suspicion BS,’ using a composite of clinical features (fetal temperature, tachycardia, respiratory distress, poor feeding), Kaiser neonatal early-onset sepsis calculator (takes into account highest maternal antepartum temperature, intrapartum antibiotics, maternal GBS status, length of rupture of membranes)23,24 and results of investigations (biomarkers, microbiology). Categorisation was carried out by three clinicians blinded to each other and PCT results. No disagreement in categorisation was found. The perinatal pathologist who performed the histopathological assessment of the placentas was also blinded to clinical findings.10

Statistical analysis was performed using the Kruskal-Wallis test to correlate each biomarker and placental histopathological score with the three clinical categories. P-value <0.05 was considered significant. We used the STARD checklist when writing our report.10,25

**Results**

Table 1 shows the total of 117 neonates included in the study. A previous departmental audit demonstrated the number of neonates investigated for suspected EOS on our postnatal wards is 13.5%,10 and therefore, we estimated that we included approximately 53% of the cases. Exclusion criteria included incomplete data, gestation <37 weeks, mothers with immunocompromising conditions or known chronic infection, neonates treated for suspected EOS whose mothers were not treated for suspected intrapartum sepsis and neonates treated for suspected EOS beyond day 0.

Blood cultures were performed in 117 neonates as part of the initial ‘Time 0’ septic screen and none of them grew clinically significant organisms. Lumber punctures were performed in 26 (22.2%) neonates and none of them grew clinically significant organisms.

Table 2 shows the biomarker and microbiology results. Six neonates had a raised WCC >30x109/L (5.6%, range 8.36-36.7x109/L) at the ‘Time 0’ blood samples. Forty-seven neonates had a raised PCT ≥0.25ug/L (55.3%, range 0.3-4.6) at the ‘Time 0’ blood samples and 95 neonates (98.9%, range 0.3-58.5ug/L) at the ‘Day 1’ blood samples. Seven neonates had a raised CRP of ≥10mg/L (5.98%, range 10-58mg/L) at the ‘Time 0’ blood samples and 41 neonates (35.04%, range 10-88mg/L) at the ‘Day 1’ blood samples.

Correlations were carried out comparing values of neonatal biomarkers between the different blood samples. Where PCT and CRP was raised for the neonate on initial sampling it was likely to be raised on the follow-up samples. There was a positive correlation between both ‘Time 0’ and ‘Day 1’ PCTs with the CRP results for the neonate, +0.509 and +409 respectively.10

The 3 determined categories the neonates were divided into are shown in table 1. Figure 1 illustrates the spread of biomarker results for the initial and follow up bloods according to the three categories.

Figure 2 illustrates the mean PCT results for the three categories of blood tests taken during the initial and follow-up bloods. There was a significant difference between ‘low-suspicion BS’ and ‘high-suspicion BS’ categories for both the ‘Time 0’ (p=0.0349) and the ‘Day 1’ PCT results (p=0.008).10

There was no significant difference between the WCC results in the 3 neonatal categories of likelihood of infection. There was a significant difference in CRP results between ‘equivocal BS’ and ‘high-suspicion BS’ for the neonatal ‘Time 0’ (p=0.022) and the ‘Day 1’ (p=0.0002) CRP results.

Eighty neonates (68.3%) had placental histopathology completed. They were given a score out of 24 for their staging and grading of chorioamnionitis. A total of 57 out of 80 (71.2%), showed varying degrees of chorioamnionitis (mean score 10.6, range 5-18,). Figure 3 shows the scores for the three clinical categories. There was a correlation between scores for placental inflammation and clinical condition, with mean scores of 12.66 for ‘high-suspicion BS,’ 6.82 for ‘equivocal BS’ and 3.89 for ‘low-suspicion BS.’ There was a significant difference between the categories of ‘high-suspicion BS’ and ‘low-suspicion BS’ (p=0.002).10

**Discussion**

We present a cohort of full-term neonates managed for suspected EOS due to probable maternal intrapartum sepsis. The objective was to determine if PCT levels would help in the differentiation of neonates who would demonstrate clinical features highly suggestive of clinically significant EOS.

CRP and PCT are two of the most commonly studied acute-phase reactants in neonatal sepsis. In general, in children and adults PCT is more sensitive than CRP for earlier detection of sepsis, is more likely to be elevated during bacterial infections and declines more rapidly with correct therapy.7 Therefore, PCT is becoming a superior biomarker to CRP in the management of sepsis in children and adults. However, in neonates during the first 72 hours of life it remains controversial.

In this study, a higher percentage of PCT levels showed elevation in comparison to CRP levels in the initial testing (55.3% versus 5.9%) and follow up testing (98.9% versus 35%). There was a significant increase in the neonatal ‘Day 1’ PCT compared to their ‘Time 0’ PCT. This may reflect the known physiological peak in PCT levels in the first 24 hours from birth, and not necessarily be related to a sepsis-induced inflammatory response.11

However, when comparing PCT levels in the 3 categories of likelihood of infection there was a significant difference between the ‘low-suspicion BS’ and ‘high-suspicion BS’ categories for both the ‘Time 0’ (p=0.0349) and the ‘Day 1’ PCT results (p=0.008).10 This shows a potential role in the level of elevation of PCT reflecting clinical severity, which could be utilised in the management of EOS once a normal range of PCT has been determined.3,16

After an initial inflammatory trigger, CRP starts to rise within 5-6 hours and peaks at 36-50 hours, with levels falling as inflammation resolves (half-life 19-hours).26 Therefore, an increasing CRP level is a better predictor than individual values.7  Two normal CRP levels (<10mg/dL), obtained 24 hours apart, indicate that bacterial infection is unlikely, and for proven neonatal sepsis have been shown to have a negative likelihood ratio of 0.15 and a negative predictive value of 99.7%.27 This is the evidence behind the current NICE guidelines followed in our unit to take two CRP levels 24 hours apart after birth from neonates managed for suspected maternal intrapartum pyrexia in order to determine antibiotic treatment.18 This study appears to support that two normal CRP levels, obtained 24 hours apart is superior to influence treatment compared to two normal PCT levels.

Studies have shown that PCT could be useful in guiding antibiotic therapy duration in neonates with suspected EOS on established treatment 72 hours after birth. A multicentre, randomised controlled trial by Stocker et al, concluded procalcitonin-guided decision making was superior to standard care in reducing antibiotic therapy in neonates with suspected EOS.28 PCT has also shown to return to the normal range more quickly than CRP, suggesting PCT may be an early marker of favourable outcome.29,30

In this study, all 117 neonates had blood cultures performed at ‘Time 0’ and none of them grew clinically significant organisms, supporting a poor yield in neonatal blood cultures.2,3 This could be due to the known effect of cultures remaining negative as a result of maternal antimicrobial treatment prior to delivery.6 But this may reflect that this cohort of neonates is largely well, with a low yield of bacteraemia resulting in overuse of antibiotics. However, you cannot reliably ignore a negative blood culture as many studies have underlined the concern about clinical sepsis in culture-negative neonates, particularly in the setting of increasing maternal antibiotic use.3

This study demonstrated that the majority (71.2%) of placental histopathological analysis showed varying degrees of chorioamnionitis.10 Placental histopathology has long been the investigation of choice for definitive diagnosis of chorioamnionitis. Many studies now demonstrate higher rates of histological chorioamnionitis compared to clinical chorioamnionitis which challenges its correlation.10,31,32,33 A study by Smulian et al,30 looked at clinical versus histological chorioamnionitis in 139 pregnancies and concluded that clinical chorioamnionitis and possible neonatal infection were not supported by histological evidence of infection in 38.1% and 26.8% of cases respectively, suggesting other noninflammatory causes of signs and symptoms.10 A study by Roberts et al,34 demonstrated 96% cases of histological chorioamnionitis occurred without infection, suggesting there may be alternative causes amongst low-risk women at term.10 In this study the presence of inflammation in a large proportion of the ‘low-suspicion BS’ group could be supportive of these studies assertion that not all placental inflammation is the result of infection.10

**Conclusion**

This study provides evidence to the physiological rise in PCT during the first 72 hours of life.35 When dividing cases into categories of clinical severity we found a significant difference in the PCT levels. Owing to its short half-life, PCT may have utility as a reliable early biomarker when interpreted in combination with clinical sepsis risk calculators, once normative data is available in neonates through well designed trials.

**Previous Published Work**

*Walker S, Harding I, Soomra K, Bamber AR, Carrick S, Waheed AH, Liebling RE. “An evaluation into the use of Procalcitonin levels as a biomarker of bacterial sepsis to aid the management of Intrapartum Pyrexia and Chorioamnionitis,” American Journal of Obstetrics and Gynaecology (AJOG) Global Reports, 2022.*

We have previously published on the above article which evaluates whether Procalcitonin levels could be used in the diagnosis and management of intrapartum sepsis in women. It specifically looks at the results in women, whereas this article focuses on the results in the neonates.

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| Neonatal Demographics: | Number (Percentage) Mean (Standard Deviation) |
| Number  | 117 |
| Female  | 62 (52.9) |
| Male  | 55 (47.1) |
| Mean birth weight  |  3458 grams (460.7) |
| Risk factors for Intrapartum Pyrexia:  |  |
| Epidurals | 95 (81.2) |
| Fetal blood samples  | 11 (9.4) |
| Induction of labour  | 76 (64.9) |
| Time from ruptured membranes & delivery  |  23.8 hours (59.3) |
| Labour augmentation  | 20/41 (48.8) |
| Intrapartum antibiotics mother received prior to neonates’ birth |
| Broad spectrum >4 hours prior to birth | 22 (18.8) |
| Broad spectrum 2-3.9 hours prior to birth | 19 (16.2) |
| GBS specific >2 hours prior to birth | 6 (5.1) |
| None or any <2 hours prior to birth | 70 (59.9) |
| Birth location:  |  |
| Obstetric theatre  | 58 (49.6) |
| Obstetric led delivery suite  | 56 (47.8) |
| Midwifery led unit  | 3 (2.6) |
| Mode of delivery: |  |
| Normal Vaginal delivery  | 26 (22.2) |
| Ventouse assisted delivery  | 10 (8.5) |
| Forcep assisted delivery | 41 (35.1) |
| Emergency Caesarean section  | 40 (34.2) |
| Other: |  |
| Meconium  | 29 (24.8) |
| Fetal Tachycardia prior to delivery  | 47 (40.2) |
| Admission to neonatal ICU  | 15 (12.8) |
| Neonates requiring assisted ventilation  | 11 (9.4) |
| Day of discharge  |  6.6 days (2.2) |
| Neonatal Intravenous Antibiotic length of course: |
| 36 hours  | 46 (39.3) |
| 48 hours | 29 (24.8) |
| 72 hours  | 10 (8.5) |
| 5 days  | 29 (24.8) |
| 7 days  | 3 (2.6) |
| Categorisation: |
|  | **Low-suspicion BS** |  **Equivocal BS** | **High-suspicion BS**: |
| Number (percentage) | 20 (17) |  55 (47) | 42 (36) |

**Table 1**: Neonatal Demographics of results. Data are presented as number (percentage). The bottom row shows the number of neonates in the 3 determined categories of bacterial sepsis. \* ICU = intensive care unit, BS = Bacterial sepsis, GBS = Group B Streptococcus.

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| **Neonatal Time 0 Bloods:** |
| **Biomarker** | **Number (%)**  | **Number Raised** |
| WCC | 108 (92.3) | 6 (5.6) |
| CRP | 117 (100) | 7 (5.98) |
| PCT | 85 (72.7) | 47 (55.4) |
| **Neonatal Day 1 Bloods:** |
| **Biomarker** | **Number (%)** | **Number Raised** |
| CRP | 117 (100) | 41 (35.04) |
| PCT | 96 (82.1) | 95 (98.9) |
| **Neonatal Microbiology Results:** |
| **Microbiology Sample** | **Number (%)** | **Positive Culture Growth** |
| Blood Cultures | 117 (100) | 0 |
| Lumbar Puncture CSF | 26 (22.2) | 0 |

**Table 2**: Total number of neonatal biomarker and microbiology samples completed with results. Data are presented as number (percentage). \*Raised PCT = ≥0.25ug/L, Raised CRP = ≥10mg/L, Raised WCC = >30x109/L

**Figure Legends:**

**Figure 1**: Box Plot graphs showing the spread of biomarker (WCC, CRP and PCT) results with quartiles represented by the lines across the 3 determined categories of ‘high-suspicion bacterial sepsis,’ ‘equivocal bacterial sepsis’ and ‘low-suspicion bacterial sepsis.’ The top three graphs represent the ‘Time 0’ blood results and the bottom two graphs represent the ‘Day 1’ blood results.

\*BS = Bacterial sepsis.

**Figure 2:** Neonatal Mean PCT results for the 3 determined categories of ‘high-suspicion bacterial sepsis,’ ‘equivocal bacterial sepsis’ and ‘low-suspicion bacterial sepsis,’ for their ‘Time 0’ and ‘Day 1’ blood samples. \*BS = Bacterial sepsis. PCT units = ug/L

**Figure 3:** Box Plot graphs showing the spread of placental histopathology scores with the quartiles for the 3 determined categories for ‘high-suspicion bacterial sepsis,’ ‘equivocal bacterial sepsis’ and ‘low-suspicion bacterial sepsis.’