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Use of Procalcitonin as a biomarker for sepsis in moderate to major paediatric burns

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Running title: Procalcitonin as a biomarker for sepsis

ABSTRACT

Objective:

Accurate and early detection of sepsis poses a significant challenge in burn populations. Our objective was to assess whether Procalcitonin (PCT) is a marker of blood culture positive sepsis in moderate to severe paediatric burns.

Methods:

We analysed PCT in 27 children admitted with burns of 15-65% Total Body Surface Area. PCT was measured at admission (baseline), 24, and 48 hours post-admission and during periods of suspected sepsis (diagnosed against pre-defined criteria). Patients were categorised into controls with no episodes of suspected sepsis (n = 10) and those with episodes of suspected sepsis (SS, n = 17). The latter were split into two groups based on blood culture results: culture positive (bacteraemia) and culture negative patients.

Results:

Baseline PCT increased with burn size (OR [95%CI]: 1.15 [1.02-1.29]). SS patients had larger burns than controls (median 31% vs. 20%; p=0.003). Only 5/23 suspected sepsis episodes were blood culture-positive. PCT levels were similar in culture positive and culture negative patients (p = 0.43). Sensitivity for predicting positive blood culture was 100% (95%CI: 47.8-100.0%) but specificity was only 22.2% (95%CI: 6.4-47.6%). Area under the curve was poor at 0.62 (95%CI: 0.33-0.90). There was no significant change in PCT from baseline to septic episode in either group (positive: p=0.35; negative: p=0.95).

Conclusions:

We conclude that evidence for the use of PCT to diagnose bacteraemia in this population is poor with burn size playing a significant role implying a correlation with inflammation rather than sepsis.

Keywords: Procalcitonin; sepsis; burn injury; children; C-reactive protein

INTRODUCTION

Sepsis is an important cause of morbidity and mortality in burn patients and requires prompt treatment with appropriate antibiotics.[1-3] The prevalence of sepsis in burns patients varies from 8 – 43%.[4] However, the likely development of a Systemic Inflammatory Response Syndrome (SIRS) in patients with burns of more than 20% Total Body Surface Area (TBSA), means that criteria usually relied upon for the early identification of sepsis complicate decision-making about the diagnosis.[5] Definitive diagnosis of sepsis in burns patients still relies upon non-specific serum markers and the retrospective analysis of blood cultures which take at least 48 hours to obtain and are unavailable when decisions on antibiotic use must be made. A proportion of burned patients will therefore be considered to have sepsis and undergo broad-spectrum antibiotic treatment, when in fact their abnormal markers are a result of a systemic inflammatory process in the absence of sepsis. This results in overuse of antibiotics, increasing bacterial resistance within individuals (and in the wider community) and may compromise the response to treatment if true sepsis does subsequently develop.[6,7] A rapid and accurate method of identifying sepsis on which treatment decisions can be based is therefore required.

Procalcitonin (PCT), a precursor to the hormone calcitonin, has long been controversially discussed as a more specific marker of sepsis that might provide a way of identifying infection before blood culture results are available.[8-24] In general, PCT levels are very low in uninfected patients but can increase markedly within a few hours of sepsis onset.[25] The utility of PCT in diagnosis and decision-making regarding antibiotic therapy has already been well investigated in a variety of disease entities, including respiratory tract infections, and in the critically ill.[8-13] In respiratory tract infections, there is now evidence that use of PCT improves diagnosis and leads to

reduced antibiotic use with no evidence that this approach increases the risk of mortality.[10] A particular characteristic of PCT is that it has been shown to be helpful in distinguishing bacterial infections from viral infections and SIRS.[26] As most patients with severe burns will develop SIRS, it is this characteristic that has resulted in PCT being considered as a potential marker of sepsis in the adult burns population.[15-18,20-23,27] Very few studies have investigated its use in paediatric burns.[28,29]

The aim of this study is to assess whether PCT is a specific marker for sepsis or whether it simply reflects the development of SIRS in moderate to severe paediatric burn patients. We specifically investigate: (1) the pattern of PCT levels during the first 2-3 days post admission (baseline) when wound infection and sepsis are likely to be absent, (2) whether PCT levels during a suspected sepsis episode differ in those patients whose blood cultures come back negative and those that come back positive (proven bacteraemia) from blood samples taken during a suspected sepsis episode, and (3) whether the change in PCT levels from baseline to that during a suspected sepsis episode could be a useful predictor of proven bacteraemia. We also look at the relationship between PCT and burn size. As C-reactive protein (CRP) is also a commonly used marker of acute inflammatory response and infection, we compared its performance to predict proven bacteraemia against PCT.

METHODS

This study was a prospective multicentre cohort study carried out in three UK hospitals: Bristol Children's Burns Centre, Alder Hey Children's Hospital, Liverpool and the Royal Manchester Children's Hospital. The inclusion criteria were children of less than 16 years of age admitted to the study hospitals with scalds of more than or equal

to 20% Total Body Surface Area (TBSA) or flame burns greater than or equal to 15% TBSA. The consent of all study participants and/or their parents was obtained before enrolment within the study. The study was designed such that participation would have no bearing on standard clinical management and to ensure there was no need for additional procedures. Ethical approval was obtained from the South West Research Ethics Committee. Patients were recruited between April 2009 and October 2013.

A Sampling

Blood samples were taken at three separate time points (0, 24, and 48 hrs) after admission as per routine clinical practice (baseline). Following this initial period, blood samples were only collected for patients showing clinical signs of possible sepsis (suspected sepsis). Suspected sepsis was defined using objective criteria which were comprised of both clinical and biochemical parameters that are routinely available to clinicians. The clinical aspect of the criteria was based on the American Burn Association definition of sepsis in burns.[30] The criteria applied are shown in Table 1. Suspected sepsis episodes separated by >24 hours were treated as independent episodes. At times of suspected sepsis, routine physiological observations and blood tests including White Blood Cell estimation, C-reactive protein and blood cultures were undertaken as per normal practice. A small volume of the blood samples was kept for PCT analysis. These were separated on receipt in the laboratory and frozen immediately at -80 degrees C (stored up to 13 months) until analysis. Samples were thawed at room temperature and mixed before analysis. The procalcitonin assay was performed using the Elecsys BRAHMS PCT assay (available from Roche, West Sussex, UK) on a Roche Cobas e602 immunoassay analyser (Roche, West Sussex, UK). We used two cut-offs for plasma PCT levels to assess diagnostic accuracy, ≥0.5 ng/mL and >2 ng/mL. Values below 0.5 ng/mL are considered normal and therefore

bacterial sepsis is unlikely. With PCT levels between 0.5 and 2 ng/mL, a systemic infection cannot be excluded and levels above 2 ng/mL represent an increased likelihood of bacterial sepsis being present.[25] Management of the suspected septic episode, including antibiotic administration, was in line with standard hospital care. 'Proven bacteraemia' was defined as an episode where the patient showed clinical signs of sepsis and had a confirmed positive blood culture. The PCT results were not available during the study period. CRP was measured using an immunoturbidimetric assay on the Roche Cobas analysers. CRP values ≤10mg/L were considered normal.[26]

Table 1. ABA (American Burns Association) criteria for the suspicion of sepsis. The presence of three or more components were required for any episode to be considered as suspected sepsis.

Criteria for the suspicion of sepsis
• **Temperature >38.9°C or <36.5°C for >2hrs**
• **Failure to absorb feed if previously absorbing**
• **WBC <4.0x109/L or >15x109/L**
• **Platelet count <100x109/L**
• **INR >1.5**
• **CRP > 10 mg/L**
• **Hyperglycaemia (>11mM/L) in the absence of pre-existing diabetes**
• **Progressive tachycardia or tachypnoea (>2 standard deviations above age-specific norms)**

A Statistical analyses

All statistical analyses were conducted in STATA v. 14.[31] All descriptive demographic analyses were performed using non-parametric tests (Mann-Whitney U-tests, Chi-square tests, Kendall's rank correlation). Differences in PCT (ng/mL) baseline levels at 0, 24, and 48 hours post-admission were analysed across time points using Friedman repeated measures tests. Logistic regressions with resulting odds ratios and 95% confidence intervals were used to assess associations between both baseline PCT levels and septic episode PCT levels and TBSA, age, gender and burn type. Diagnostic accuracy measures such as sensitivity, specificity, positive likelihood ratios (LR+), negative likelihood ratios (LR-), positive predictive values (PPV) and negative predictive values (NPV) were calculated for predicting positive blood culture results (i.e. proven bacteraemia) using two binary cut-offs of PCT levels (≥0.5 mg/mL [moderate/high risk] and >2 mg/mL [high risk]). Area under the curve (AUC) was established using Receiver Operating Curve (ROC) analysis using PCT as a continuous variable. All CRP analyses were conducted in the same way.

RESULTS

A Patient demographics

A total of 29 patients were recruited to the study across the three hospital sites. Two patients were excluded from the analyses; one patient was erroneously enrolled and the data for the second patient was incomplete due to a suspected error in PCT measurement with inadequate remaining sample for re-analysis. One of the sites recruited significantly more girls than boys compared to the other sites ($\chi^2 = 7.25$, $p = 0.03$) but there was no difference in age ($\chi^2 = 0.32$, $p = 0.85$), burn type ($\chi^2 = 2.56$, p

= 0.28) or % TBSA (χ^2 = 0.62, p = 0.73) seen at the different sites. All patients were pooled for analyses.

Of the 27 patients included, there was an equal distribution between male (n=13) and female (n=14) and between scalds (n=13) and flame burns (n=14). Median age of all patients was 39 months (Interquartile range [IQR]: 23-75). Median burn size was 27% TBSA (IQR 20-34). There was no difference in % TBSA between burn types (z=0.80, p=0.42).

A PCT levels during baseline

The timing of the blood samples taken varied around the three established time points (0, 24, and 48 hrs), but was never later than 60 hrs post admission (range 0 – 60hrs; mean [SD]: 29hrs [17]). Although for some individuals, PCT levels fluctuated over the first few days (Figure 1), repeated measures analysis showed no statistical difference across the three separate time points (p = 0.22). We therefore used the first baseline time point at which blood samples were taken (mean [SD] hrs after admission: 11 [8]) as a measure of baseline PCT levels. Using both the 0.5 ng/mL and 2 ng/mL cut-offs, logistic regressions showed that larger burns were more likely to exhibit PCT levels above the two cut-offs (≥0.5: OR [95% CI]: 1.15 [1.00 – 1.31]; >2: OR [95% CI]: 1.15 [1.02 – 1.29]). There was no association with either age (≥0.5: OR [95% CI]: 0.99 [0.97 – 1.01]; >2: OR [95% CI]: 0.98 [0.96 – 1.01]) or gender (≥0.5: OR [95% CI]: 4.27 [0.80 – 22.93]; >2: OR [95% CI]: 0.64 [0.14 – 3.04]).

[INSERT FIGURE 1]

A Using PCT to predict proven bacteraemia

Seventeen patients (63%) met the criteria for suspected sepsis at least once during their admission (range 1-4 episodes per patient). All multiple episodes were considered independent data points as there were >24 hrs in between them. In total 23 suspected sepsis episodes were recorded. The number of days post admission at which patients displayed first signs of suspected sepsis varied between 3 and 33 days (median [IQR] = 8 [4-13]). Only five out of the 23 (22%) episodes (five different patients) were classed as blood culture positive (proven bacteraemia) based on the sample taken during each episode. The remaining 18 episodes all had negative blood cultures. Although the 17 patients who developed signs of sepsis had larger burns than those remaining 10 who did not develop any signs during their hospital stay (median [IQR] % TBSA, suspected sepsis: 31 [27-40]; controls: 20 [19.5-22]; z = 2.94, p = 0.003), TBSA was not different between culture positive and culture negative patients (median [IQR] % TBSA, positive: 33.5 [32-47]; negative: 28 [25-47]; z = -1.10, p = 0.27).

Looking at the continuous values of PCT during a suspected sepsis episode, median levels at the time of a septic episode were no different to those that were later confirmed positive on blood culture (median [IQR]: 4.05 [1.22 – 14.48]) compared to those confirmed as negative (1.28 [0.72 – 8.99]; z = 078, p = 0.43). Using the standard 0.5 ng/mL cut-off, only 4/23 (17%) patients with episodes of suspected sepsis had PCT levels considered normal. Using the 0.5 cut-off, sensitivity for predicting a positive blood culture result was 100% (95% CI: 47.8-100.0%) but specificity only 22.2% (95% CI: 6.4-47.6%; table 2). Using the higher cut-off of >2 ng/mL which is highly suggestive of a septic process, sensitivity was reduced to 60.0% (95% CI: 14.7-94.7%) but

specificity increased to 55.6% (95% CI: 30.8-78.5%; table 2). The ROC analysis suggests that a cut-off of 4 ng/mL would provide the optimum sensitivity and specificity without compromising one or the other, but values are still relatively low at 60% vs. 67%. AUC for predicting positive blood culture was poor at 0.62 (95% CI: 0.33 – 0.90).

Table 2. Contingency table of PCT levels during suspected sepsis episodes to predict positive blood culture (proven bacteraemia) using two different risk cut-offs: moderate/high risk ≥0.5 ng/mL (a), and high risk >2 ng/mL (b). LR+ = Positive Likelihood Ratio, LR- = Negative Likelihood Ratio, PPV = Positive Predictive Value, NPV = Negative Predictive Value, CI = Confidence Interval.

(a) PCT levels	**Blood-positive (N)**	**Blood-negative (N)**	**Total (N)**
Moderate/High (≥0.5)	5	14	19
Low (<0.5)	0	4	4
Total	5	18	23
Sensitivity (%, 95% CI)	100.0 (47.8 – 100.0)		
Specificity (%, 95% CI)	22.2 (6.4 – 47.6)		
LR+ (95% CI)	1.3 (1.0 – 1.7)		
LR- (95% CI)	Not quantifiable		
PPV (%, 95% CI)	26.3 (21.8 – 31.4)		
NPV (%, 95% CI)	100.0 (39.8 – 100.0)		
(b) PCT levels	**Blood-positive (N)**	**Blood-negative (N)**	**Total (N)**
High (>2)	3	8	11
Low/moderate (≤2)	2	10	12
Total	5	18	23
Sensitivity (%, 95% CI)	60.0 (14.7 – 94.7)		
Specificity (%, 95% CI)	55.6 (30.8 – 78.5)		
LR+ (95% CI)	1.4 (0. 6 – 3.3)		
LR- (95% CI)	0.7 (0.2 – 2.3)		
PPV (%, 95% CI)	27.3 (13.4 – 47.6)		
NPV (%, 95% CI)	83.3 (61.3 – 94.1)		

A Change from baseline to septic episode

When comparing the change in PCT levels from that shown at baseline to that shown during a suspected episode each patient was used as its own control using Wilcoxon matched pairs tests (first episode used for those with multiple episodes: n=17). Median PCT concentration at admission was 2.09 (IQR: 0.42-4.00) and 1.22 (IQR: 0.72-7.06) during septic episodes. There was no change in concentration from baseline to septic episode in either the culture negative group ($z = -0.06$, $p = 0.95$) or the culture positive group ($z = -0.94$, $p = 0.35$). Figure 2 shows the changes for all individuals with negative and/or positive episodes.

[INSERT FIGURE 2]

A CRP levels

There was no difference in CRP measured for those patients with positive blood culture (median [IQR]: 84.6 [39.9 – 246]) to those who had negative cultures at the time of the septic episodes (median [IQR]: 100 [28.2 – 184]; $p = 0.51$). Only 1 patient had CRP levels below the normal cut-off of 10 mg/L. Therefore, sensitivity reached 100% but specificity was very low at 5.6% (table 3). AUC for proven bacteraemia was 0.60 (95% CI: 0.29 – 0.91), not significantly different ($p = 0.95$) from that using PCT. There was also no correlation between CRP levels and PCT levels during episodes of suspected sepsis (Kendall's tau-a: 0.08, $p = 0.63$).

Table 3. Contingency table of CRP levels during suspected sepsis episodes to predict positive blood culture (proven bacteraemia) using a cut-off of 10 mg/L. LR+ = Positive Likelihood Ratio, LR- = Negative Likelihood Ratio, PPV = Positive Predictive Value, NPV = Negative Predictive Value, CI = Confidence Interval.

CRP levels	**Blood-positive (N)**	**Blood-negative (N)**	**Total (N)**
High (≥10)	5	17	22
Low (<10)	0	1	1
Total	5	18	23
Sensitivity (%, 95% CI)	100.0 (47.8 – 100.0)		
Specificity (%, 95% CI)	5.6 (0.1 – 27.3)		
LR+ (95% CI)	1.1 (0.9 – 1.2)		
LR- (95% CI)	Not quantifiable		
PPV (%, 95% CI)	22.7 (7.8 – 45.4)		
NPV (%, 95% CI)	100.0 (2.5 – 100.0)		

DISCUSSION

We found that baseline PCT levels were related to burn size with larger area burns displaying higher levels of PCT within 24 hours of admission. Patients who developed signs of suspected sepsis during their hospital stay also had larger area burns compared to those who did not have any suspected sepsis episodes, suggesting that burn size may contribute to the development of systemic inflammatory episodes and raised PCT. We found that PCT levels measured during the suspected sepsis episodes were of limited use to predict proven bacteraemia. As all patients with positive cultures showed PCT levels indicating either moderate or high risk of infection, sensitivity was high. However, specificity for ruling infection out was very low as levels were elevated in most patients. We also saw no difference between culture negative and culture positive patients in terms of the change in PCT levels from baseline to that

during septic episodes. CRP levels also showed poor predictive value in our population, as all but one episode had values above normal.

There are some limitations with our study. As this was a small scale preliminary study, the main limitation is the low statistical power due to small sample size and low prevalence of blood positive patients. The small sample size spread across three different centres may have introduced variability in the data as different interpretations of clinical signs may be present. However, there is no reason why this variability should be different between blood positive and blood negative patients. It is possible that freezing and storing the PCT samples for varying lengths of time before analysis could affect our results. However, Meisner et al. have shown that PCT shows a great stability under different conditions of storage; no differences in concentrations were found between samples stored at different temperatures and the percentage decay was similar for high and low PCT concentrations. Also, repeated freezing and thawing had no effect on PCT concentrations.[32]

Several studies have been carried out in burns populations investigating the utility of PCT as a predictor of sepsis. However, results are conflicting and inconsistent. A systematic review by Mann et al. in 2011 considered the available evidence in adult critically ill patients (both burned and non-burned) and concluded that PCT may be a promising adjunct to clinical management but varying definitions of sepsis amongst the included studies, most of them observational, rendered conclusive findings difficult.[19] Similarly, a recent meta-analysis and a subsequent retrospective study from the same authors examining the use of PCT as a marker for sepsis showed positive results with a strong diagnostic ability to discriminate between septic and non-septic burn patients.[22,23] Again however, studies included in the meta-analyses showed large heterogeneity as they varied in how PCT was measured in the lab, in cut-offs used

and sample size was generally low giving rise to doubt about its utility as a reliable biomarker.

Despite a multitude of studies conducted, very few have been conducted in paediatric burn populations. One study addressing use of PCT in paediatric burns assessed PCT levels in 20 children with the aim of determining whether a rise in PCT could identify times at which the treating surgeon clinically diagnosed sepsis. The authors found that PCT was less sensitive than CRP and/or platelet count.[28] The study was limited by small sample size and using subjective surgeon decisions of sepsis as their gold standard. A study published in 2015 assessed both CRP and PCT as biomarkers for septic episodes in 48 paediatric burn patients.[29] This study, in line with ours, found that both PCT and CRP levels were high in majority of patients, regardless of infection status. Although this patient group had larger area burns than ours, possibly explaining their much higher rate of confirmed infection (67% vs. 22%), their results were similar. PCT had a 90% sensitivity but only 19% specificity in predicting proven infection, making its clinical utility questionable. Although failure to diagnose infection, and potentially serious outcomes as a result, is unlikely, an inability to rule out infection can lead to over-prescription of antibiotics with the associated problems this brings. It is entirely possible that PCT in paediatric populations is predicting no more than a SIRS response, especially as we found that TBSA seems to influence not only baseline PCT levels but also those patients who developed suspected sepsis had larger % TBSA burns and it is expected they would be more likely to develop SIRS. Several studies have shown that severe trauma such as burns can cause elevation of PCT and CRP levels in the absence of sepsis.[18,25,29] CRP concentration was also part of the diagnosis of suspected sepsis in our study so would be naturally high in these

patients. However, at the time of bloods being taken during an episode, the absence or presence of infection was unknown to us, so a comparison of CRP levels between culture positive and negative episodes is still valid.

Although we used the standard PCT level cut-off of <0.5 ng/mL which in SIRS patients means a systemic bacterial infection can be excluded,[25] studies have shown that other cut-offs may be more useful in predicting infection.[33] We did also use a cut-off of > 2.0 ng/mL, suggesting a systemic infectious process is highly likely,[25] but despite the specificity increasing using this cut-off, predictive accuracy was still relatively poor and AUC using the two different cut-offs were no different. The ROC analysis suggested that a cut-off of 4 ng/mL would provide the optimal sensitivity and specificity without the expense of one or the other, but confidence intervals are too wide to accurately confirm this.

The use of PCT in the diagnosis and monitoring of sepsis has recently been the subject of a National Institute for Health and Care Excellence (NICE) Diagnostics Assessment Programme published in October 2015 (https://www.nice.org.uk/guidance/dg18). This programme evaluated whether PCT testing in children and in adults presenting with suspected bacterial infection either to the emergency department or in an intensive care setting represents clinically- and cost-effective use of NHS resources. The decision from NICE currently, is that there is insufficient evidence to support the routine adoption of procalcitonin tests in the NHS.

CONCLUSION

Given the low incidence of blood culture positive individuals in our study, it is difficult to draw any firm conclusions regarding the use of PCT as a biomarker for sepsis in this type of paediatric populations. We agree with Cabral et al.'s recent proposal,[22] that to better evaluate the utility of PCT as a biomarker for sepsis in burns, PCT levels should be determined frequently, particularly in burn patients with a high risk of infection (for example those with larger TBSA), and a large sample size should be used. A larger study using more frequent timepoints would also have more power to usefully examine whether the combination of baseline PCT and measurement during any episode of suspected sepsis would be more useful than a single time-point measurement. It would also be crucial to review the importance of different cut-off values, methods used to quantify PCT levels and whether combining PCT with several other biomarkers is a more useful way to predict a septic process in these patients. The effect of burn size and perhaps also response to antibiotics is something that needs further exploration. Considering the NICE guidance suggesting there is insufficient evidence to support regular testing in the NHS, the time is therefore ripe for a multi-centre trial of the utility of PCT testing in children with burns, taking all the above factors into account.

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CONFLICT OF INTEREST

Authors declare no conflict of interest

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FIGURE TEXTS

Figure 1. PCT values over the first two days post-admission for all 27 individuals included in the study. Time point 1 = 0 hrs, time point 2 = 24 hrs, time point 3 = 48hrs.

Figure 2. The change in PCT levels from baseline to septic episodes (blood culture negative and positive) for the 17 individuals who developed signs of sepsis. Some individuals had multiple episodes.