Procalcitonin (PCT) level in the emergency department identifies a high-risk cohort for all patients treated for possible sepsis

Georgia Lucas*, Angela Bartolf*, Nicholas Kroll, Agampodi-Umanda De Thabrew, Zoya Murtaza, Siddarth Kumar, Abrar Gani, Andrea Annoni, Marie Parsons, Helen Pardoe

Princess Alexandra Hospital NHS Trust Harlow, United Kingdom
* Georgia Lucas and Angela Bartolf are both joint first authors

ARTICLE INFO

Corresponding author:
Helen Pardoe
Princess Alexandra Hospital NHS Trust
Harlow
United Kingdom
Phone: +44-1279-444455
E-mail: helen.pardoe1@nhs.net

Key words:
procalcitonin, high-risk, emergency department

ABSTRACT

What is already known?

1. The benefits of measuring PCT in the Emergency Department (ED) are not yet fully characterised.

2. PCT is widely used in the intensive care setting to guide antimicrobial prescribing.

What this adds?

Measurement of PCT as a routine in the emergency department for all patients treated for possible sepsis identifies a high-risk cohort.

Key improvement in patient care

1. A PCT measurement of >0.2ug/L in the Emergency Department identifies a patient at increased risk of deterioration and of in-hospital death.

❖❖❖❖❖

Background

Early recognition and management of sepsis in the Emergency Department (ED) is a clinical challenge. Our aim was to determine if measuring the biomarker PCT in patients with suspected sepsis enables the identification of patients at increased risk of deterioration or in-hospital death in the ED setting of a district general hospital in the United Kingdom.

Methods

A prospective observational study was conducted on all patients aged 18 and over presenting to ED fulfilling NICE criteria for moderate to high risk of sepsis admitted to hospital. Patients had a PCT test alongside the sepsis six protocol. PCT was measured using Brahms's chemiluminescent micro particle assay (CMIA) for the quantitative determination of PCT in human serum and plasma on the Abbott Alinity I analytical platform. The cost per test was approximately 13 GBP.

The analysis was performed on patients having a PCT in ED over a 7-month period, with in-depth scrutiny of an appropriate subgroup. A high level quality improvement (QI) approach was used in the study.

Results

A total of 1242 patients were included in the study. Mean/median age was 67.9/72, (range 18-102). 88.7% of deaths occurred in patients over 65 years of age. 42.4% (n=532) had a PCT level in ED of >0.2 ug/L. This identified a high risk group with a 2.4 fold increase in mortality rate (7.7%:18.2% p value <0.001). The median length of stay (LOS) was 5 (IQR 9) and 8 days (IQR 11) in patients with a first PCT of ≤0.2 ug/L versus >0.2 ug/L respectively.

Conclusion

An immediate PCT on patients presenting to ED with signs of sepsis in a non-specialised acute trust identifies those patients at an increased risk of deterioration and in hospital death.

❖❖❖❖❖

INTRODUCTION

Sepsis is responsible for approximately 37,000 deaths and 100,000 hospital admissions per year in the UK (1). Early recognition of sepsis in the ED is a clinical challenge due to the variability in presentation (2). ED staff need a quick, reliable test to diagnose sepsis and identify those patients at high risk of deterioration.

Procalcitonin (PCT) is a biochemical marker of bacterial sepsis which has excellent diagnostic and prognostic value to identify bacterial sepsis early and alert clinicians regarding disease severity (3). It can also be used to monitor response to antimicrobial treatment. Whilst PCT results can guide clinical decision making, they cannot replace standard sepsis management. Internationally, PCT is used widely in intensive care (ICU) (4) with serial PCT levels guiding continuation of antimicrobial treatment (Procalcitonin Guided Antimicrobial Therapy –PGAT) using the BRAHMs criteria (5). PGAT as described by Schuetz et al (5) is based on a cut off of 0.25ug/L. However, the cut off used in this study was 0.2ug/L reflecting the fact that the local laboratory LIMS system reports PCT measurements to only one decimal place.

Our aim was to discover if measuring PCT in patients with suspected sepsis would allow us to identify those at increased risk of deterioration or death.

MATERIALS AND METHODS

Patients presenting to the ED at the Princess Alexandra Hospital Trust, a UK district general hospital, fulfilling the NICE 2016 (6) criteria for moderate to severe sepsis had a PCT blood test on triage alongside the sepsis six protocol between August 2019 and February 2020. A second PCT was recommended 24-36 hours later (Figure 1). PCT results were available within 60 minutes of receipt in the laboratory for ED samples and within four hours of receipt in the laboratory for samples received from inpatient wards. PCT was measured using Brahms's chemiluminescent micro particle assay (CMIA) for the quantitative determination of PCT in human serum and plasma on the Abbott Alinity I analytical platform. PCT levels were reported to one decimal place (ug/L). The result reproducibility was acceptable with within run imprecision of 2.9%, 3% and 2.5% determined using internal quality control (IQC) materials with concentrations 0.18, 1.79 and 64ug/L respectively. Between assay imprecision was tested at two levels 0.18 and 64ug/L and was shown to be 4% and 5% respectively. The cost per test (reagents only) was approximately 13GBP. The performance of the PCT assay was monitored using the Welsh External Quality Assurance Scheme (WEQAS) and has performed acceptably when compared to other laboratories performing PCT assays who are subscribed to the scheme. Overall lab SDI? score 0.05, with a median all laboratory SDI score of 0.30.
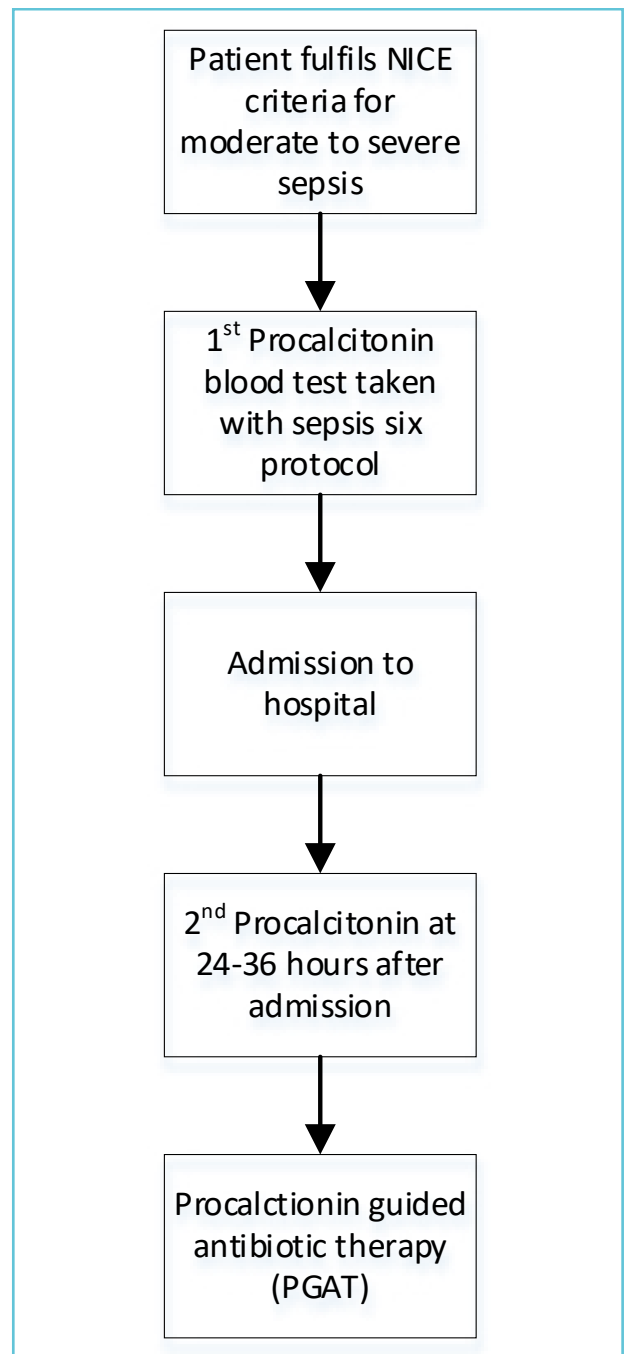
Outcome data was collected from local digital clinical systems. All patients 18 years old or above with at least one PCT test in ED were included in the sample.

A Plan-Do-Study-Act (PDSA) approach using the Institute of Healthcare Improvement quality improvement (QI) model was used to optimise staff understanding and engagement with the protocol (Figure 1). PCT was introduced as a routine diagnostic test for the investigation of sepsis following local governance approval.

Adherence to the protocol for the second PCT blood test was poor. This can be attributed to a number of system factors including high medical staff turnover, patient ward changes, phlebotomy

Figure 1	Recommended protocols

Patient fulfils NICE criteria for moderate to severe sepsis

↓

1st Procalcitonin blood test taken with sepsis six protocol

↓

Admission to hospital

↓

2nd Procalcitonin at 24-36 hours after admission

↓

Procalctionin guided antibiotic therapy (PGAT)

arrangements and PCT measurement not yet being embedded within the hospital culture. A decision was made to run an additional PDSA cycle to try to increase adherence to the Procalcitonin protocol. There was a period of intensive teaching and training for ward staff highlighting the importance of the second PCT test and intervention from the laboratory to ensure the phlebotomy team bled requests for the second PCT.

Subgroup analysis data was collected on the patients presenting between 1st September 2019 and 31st October 2019 as this was the period following increased education and the direct laboratory intervention. Analysis was performed on the following outcome measures (OM): compliance with protocol, confirmed diagnosis, antibiotic usage, length of stay (LOS), ITU admission, and readmission.

Results were analysed in Microsoft Excel 2016, retrospective Chi Squared was used to calculate p-value. Binomial confidence intervals (CI) were used for mortality and Z and T scores used for all other CI.

RESULTS

A total of 1242 patients were included in the study (male:female 610:632) following the exclusion of 16 patients due to the lack of a valid PCT measurement in ED.

The mortality rate was 12.2% (95% CI 10.3%-14.0%). Mortality rate in patients with PCT >0.2 ug/L was 18.2% (95% CI 14.9% to 21.5%) compared to 7.7% (95% CI 5.7% to 9.7%) when PCT ≤0.2 ug/L (p value: <0.001 retrospective Chi Squared) (Table 1). 62% of patients within the study population were >65 years old, with 88.7% of deaths occurring in this age group.

Subgroup analysis (264 patients) identified the following: Patients with a final diagnosis of sepsis had a mean PCT of 5.6 ug/L (95% CI 0.7 to 10.5). 28.8% (76 patients) completed the

protocol (Figure 2); of those who completed the protocol, 47(61.8%) had at least one PCT of >0.2 ug/L and were prescribed a full course of antibiotics as per local antimicrobial prescribing guidelines (Figure 2). 38.2% (29 patients) had both PCT levels of ≤0.2 ug/L. For prescribers following the B.R.A.H.M.S criteria for Procalcitonin guided antibiotic therapy (PGAT), two PCT levels of ≤0.2ug/L >24 hours apart indicates that the source of symptoms is highly unlikely to be bacterial sepsis. Only 6 of our patients had their antibiotics de-escalated within 48 hours of admission. The remaining 23 of these 29 patients (79.3%) were prescribed antibiotics with a mean antibiotic duration of 8.9 days (95% CI 7.2 to 10.6). For these 23 patients antimicrobial therapy is likely to yield little or no benefit.

The most frequent first line antibiotics prescribed were Co-Amoxiclav and Piptazobactam. Gentamicin was the most frequent second line prescription. Potential antibiotic cost reduction was estimated. Our first step was to assume our prescribers had followed the BRAHMS algorithm in the antimicrobial prescribing for these 23 patients. Theoretical application of the BRAHMs criteria to de-escalate antibiotic prescription after 2 PCT tests of ≤0.2ug/l demonstrated a potential cost saving of approximately 44GBP per patient. The calculation was based on the average cost for 1 day's usage, multiplied by the number of days antibiotics were prescribed. This reflects the cost of the drug only; in reality, the costs will be much higher when factors such as staff time (medical/nursing/pharmacy) and overheads are taken into account.

The median LOS was 5(IQR 9) and 8 days (IQR 11) in patients with a first PCT of ≤0.2 ug/L versus>0.2 ug/L respectively. Data samples were too small to identify any significant correlation between ED levels of PCT and ITU admission or hospital readmission.

Table 1	The association of PCT in ED and patient mortality		
Patient group	**Deaths**	**Discharges**	**Mortality**
Patient group = 1242 patients, 610:632 Male:Female			
All	151	1091	12.2% 95% CI (10.3%-14.0%)
PCT in ED ≤0.2 ug/L	55	660	7.7% 95% CI (5.7%-9.7%)
PCT in ED >0.2 ug/L	96	431	18.2% 95% CI (14.9%-21.5%)

Figure 2	Observational study profile*
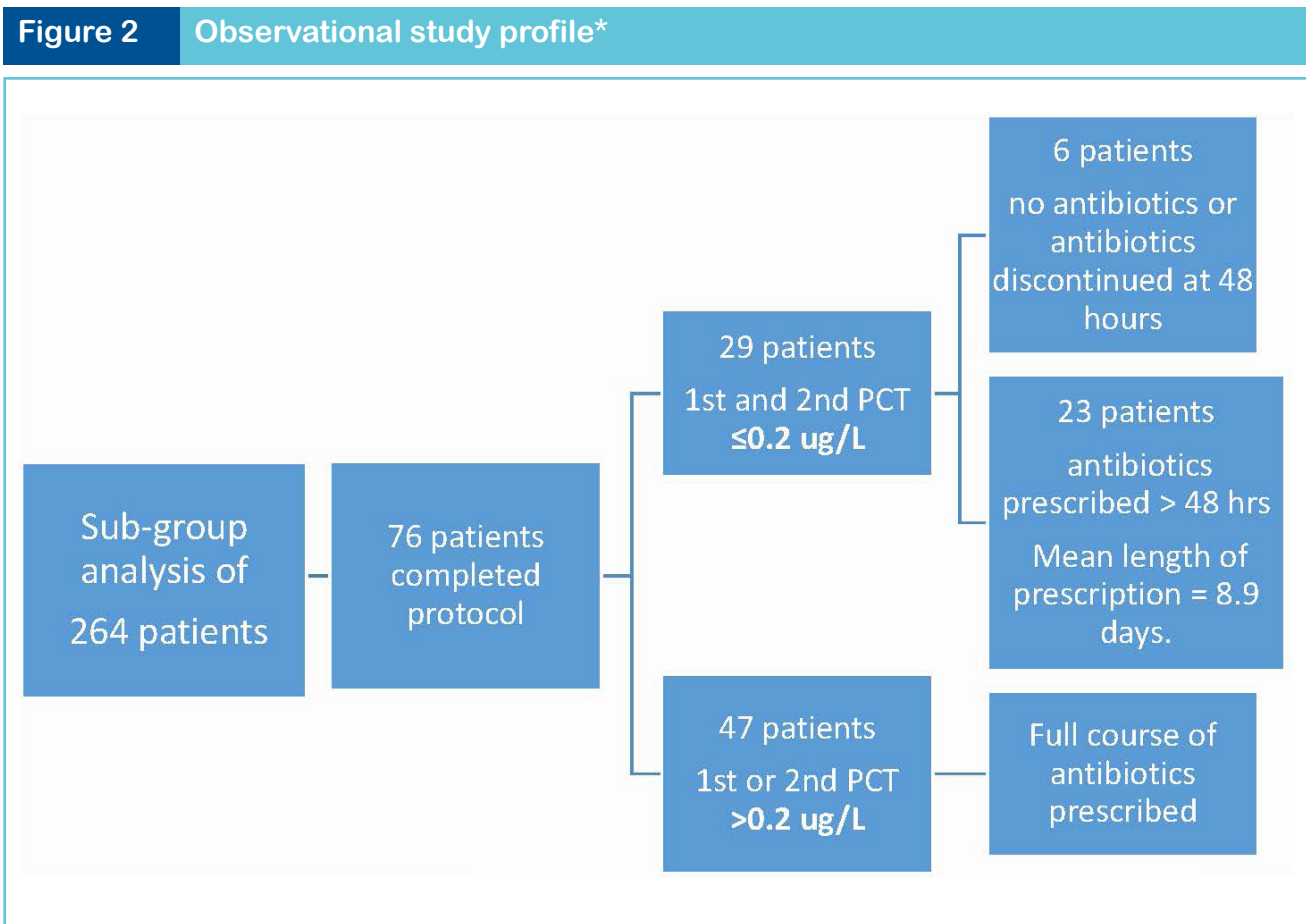
* Subgroup analysis was performed over the collection period 01/09/2019-31/10/2019, as compliance with the second PCT measurement was highest during this period. This was following the additional PDSA cycle to highlight the importance of the second PCT measurement to clinical staff.

DISCUSSION

PCT is not routinely measured on patients with signs of sepsis in ED in the UK. Our study conducted in the emergency department stands out from the published literature on PCT where the target population is in the critical care setting (8). We have shown that for patients in ED with signs of sepsis, a PCT >0.2 ug/L at presentation is a prognostic indicator for a significantly increased risk of in hospital death. ED is a high volume, high risk area in the treatment of patients with sepsis. A PCT level of 0.2 ug/L was chosen as the cut-off to align with BRAHMS criteria (<0.25ug/L) to ensure clear guidance to clinicians. Raised mortality was observed in PDSA cycle 1 in those patients with an ED PCT level greater than 0.2ug/L and there was clinical concern that a higher cut off would potentially be clinically unsafe in an ED setting. Early identification of a high risk cohort of patients can help alert the clinical teams to an increased need for monitoring and early review by a senior clinician in a patient who may at first appear clinically stable. Early identification of high-risk patients could mean that intensive monitoring and treatment is initiated at an earlier point in the development of sepsis, potentially reducing secondary organ damage and reducing the number of deaths from sepsis.

The study was performed when COVID-19 was present in the population, but the subgroup analysis was completed before the COVID-19 pandemic, indicating that the results are applicable to routine ED practice (9).

PCT as a routine diagnostic test for investigation of sepsis in ED was successfully introduced using a QI program. Use of PCT in the non-ICU setting to guide antibiotic prescribing was more challenging. Completion of the 2nd PCT test did not exceed 29%. High medical staff turnover, patient ward changes and phlebotomy arrangements and the fact the PCT use was not embedded in current practice were responsible system factors identified for low compliance with performing the 2nd PCT test. Automation of the 2nd PCT at ordercomms level was considered the single most effective way to improve compliance, but was not achieved.

PGAT supports good antimicrobial stewardship; however, in our study compliance with PGAT was only 20.7% for de-escalation of treatment. Our study suggests that there may be a potential to reduce antimicrobial costs by using the BRAHMS criteria to guide antibiotic de-escalation in the non-ICU setting. Larger studies with higher levels of compliance with PGAT for de-escalation of treatment are required to confirm the findings of our study. Resistance of prescribers at all levels to apply evidence based PGAT to prescribing practice was identified as the prime factor causing low compliance with PGAT (10). In our hospital the staff continued to rely on a more familiar, less specific biomarker, namely C-reactive protein (CRP). Education and digital clinical decision support are two key strategies that hospitals could utilise to improve compliance with PGAT. Engaging education programmes delivered by PCT ambassadors such as training meetings, short videos and tea trolley training can encourage adoption of change (11). Digital clinical decision support could also encourage behaviour change by automated ordering of the second PCT, preventing the daily ordering of CRP analysis and prompts and alerts associated with antibiotic prescribing. If the hospital culture transitioned to the use of PCT evidence based prescribing practice in non-ICU patients, the benefits of PCT measurement in ED would be further enhanced (12).

CONCLUSION

A Procalcitonin level >0.2 ug/L in patients presenting to the Emergency Department with signs of sepsis identifies a patient cohort at increased

risk of in hospital death. Early senior review and enhanced monitoring for signs of deterioration of these patients has the potential to reduce the numbers of deaths from sepsis.

❖ ❖ ❖ ❖ ❖

❖ ❖ ❖ ❖ ❖

REFERENCES

1. Angus DC, Linde-Zwirble WT, Lidicker J, et al. MR: Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001, 29: 1303-1310. 10.1097/00003246-200107000-00002

2. Lever A, Mackenzie I: Sepsis: definition, epidemiology, and diagnosis. BMJ 2007, 335: 879-883. 10.1136/bmj.39346.495880.AE

3. Delevaux, I., Andre, M., Colombier, M., et al. 2003. Can procalcitonin measurement help in differentiating between bacterial infection and other kinds of inflammatory processes? Annals of the rheumatic diseases, 62(4), pp.337-340.

4. L. Bouadma, C.E. Luyt, F. Tubach, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial Lancet, 375 (2010), pp. 463-474

5. Schuetz P, Chiappa V, Briel M, Greenwald JL. Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms. Archives of internal medicine. 2011 Aug 8;171(15):1322-31.

6. National Institute for Health and Care Excellence. Sepsis: recognition, diagnosis and early management; 2016. https://www.nice.org.uk/guidance/ng51. Accessed 20th August 2020.

7. Procalcitonin(PCT) test (immunoassay), https://www.who.int/medical_devices/diagnostics/selection_in-vitro/selection_in-vitro-meetings/sub-id-81-23/en/. Accessed on 29th August 2020

8. Huang HB, Peng JM, Weng L, et al. Procalcitonin-guided antibiotic therapy in intensive care unit patients: a systematic review and meta-analysis. Ann Intensive Care. 2017 Nov 22;7(1):114. doi: 10.1186/s13613-017-0338-6. PMID: 29168046; PMCID: PMC5700008.

9. COVID-19 Pneumonia: Procalcitonin (PCT) for Risk Assessment and Rule-out of Bacterial Coinfection https://www.procalcitonin.com/media-downloads/news/covid-19-pneumonia-procalcitonin-for-risk-assessment-and-rule-out-of-bacterial-coinfection Accessed on 27th August 2020.

10. Singer, M., Inada-Kim, M. and Shankar-Hari, M., 2019. Sepsis hysteria: excess hype and unrealistic expectations. The Lancet, 394(10208), pp.1513-1514.

11. https://blogs.bmj.com/bmj/2018/07/23/combining-the-day-job-with-time-for-training-and-tea

12. Procalcitonin-guided antibiotic therapy: an expert consensus. Clin Chem Lab Med 2018 56(8): 1223-1229.

13. Strain C and Ravalico TH. Laboratory medicine and healthcare excellence; Till death do us part. eJIFCC 2021; 32:1:007-019.

ADD-131812-GBL-EN