ORIGINAL ARTICLES

The utility of point of care testing of Procalcitonin in pediatric acute assessment

Running title: Procalcitonin in pediatric acute assessment

Alasdair PS **Munro**[1,2], Charles **Hungwe**[3], Pratisksha **Patel**[4], Nick **Ward**[3], Simon **Struthers**[4], Kordo **Saeed**[2,5]

[1]NIHR Southampton Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom;

[2]University of Southampton, Southampton, United Kingdom;

[3]Department of Pediatrics, Basingstoke and North Hampshire Hospital, Basingstoke, United Kingdom;

[4]Department of Pediatrics, Royal Hampshire County Hospital, Winchester, United Kingdom;

[5]Department of Microbiology, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom.

Corresponding author:

Kordo Saeed

E-mail: kordosaeed@nhs.net

SUMMARY

Objective: Febrile illnesses are a common cause of presentation in acute pediatrics, with biomarkers frequently used to help differentiate mild infections from serious bacterial infections (SBI). We aimed to see if a point of care test for procalcitonin could help to reduce antibiotic use and avoid unnecessary admission.

Patients and Methods: A point of care procalcitonin machine which produces results within 20 minutes was introduced to two pediatric assessment units across both sites of a secondary-care hospital trust, alongside guidance for when tested would be appropriate. We performed a prospective, observational, pilot service evaluation, of all children tested during the study period of November 2018 to March 2019. We collected data at the time of testing, including the indication for testing and plan prior to testing, then retrospectively collected outcome data for children tested including diagnosis, treatment and whether the child was admitted to hospital.

Results: 68 tests were performed over 5 months. There are differing denominators due to missing data. Children were predominantly male (40/68, 58.8%) and pre-school age (median age 2.9y, Q1-Q3 1.3-6.7). Severity of illness was low, with 7/54 (11.5%) triggering sepsis tools. The primary indication for testing was febrile illness with no source of infection and some concerning features (31/59, 52.5%). Following testing, 35/67 (52.5%) of patients were admitted and 31/67 (47.1%) had IV antibiotics. A low procalcitonin (<0.5ng/L) was observed in 46/67 (69.1%) of patients, however 21/46 (45.7%) of these children were admitted and 16/46 (34.8%) were given IV antibiotics. Procalcitonin performed poorly at detecting SBIs in this cohort (result >0.5ng/L for 1/5 SBIs).

Conclusion: There was no clear impact of point of care procalcitonin on admission or antibiotic prescribing in this small pilot study. Clinicians often tested for reasons outside the recommended scenarios and often treated “low risk” patients, as determined by low procalcitonin, with antibiotics. These effects may be due to low familiarity with procalcitonin as a biomarker.

INTRODUCTION

Febrile illnesses make up a large burden of acute presentations in pediatric medicine [1]. Whilst the majority of these illnesses will be mild infections, differentiating these from children with serious bacterial infections (SBI) remains a challenge. There is a great tension in balancing appropriate antimicrobial stewardship against the drive to instigate treatment early for cases of suspected sepsis [2,3].

Biomarkers are a diagnostic tool often used to help differentiate mild from invasive infections. Procalcitonin is an acute phase reactant in infection, which rises earlier than C reactive protein (CRP), and responds faster to treatment [4]. It has shown similar performance in detecting infection in children to CRP, with perhaps greater ability to detect invasive infections in febrile infants [5-7]. A drawback of laboratory tests for children with suspected SBI is the time for results to become available for decision making.

Procalcitonin is used as a laboratory test across both sites of our large, secondary care NHS hospital trust. We sought to assess the utility of a rapid, point of care test for procalcitonin (POCT PCT) in the pediatric acute assessment units at these 2 hospital sites as a service evaluation pilot, in risk assessing children with suspected/confirmed infections to improve antimicrobial stewardship and help prevent unnecessary admissions.

PATIENTS AND METHODS

A non-interventional prospective evaluation of POCT PCT was conducted between November 2018 and March 2019, collecting data on all children who were tested during the evaluation period. A POCT PCT machine (B.R.A.H.M.S PCT Direct^{TM}, Thermo Scientific)

was introduced to acute pediatric assessment units on both sites at Hampshire Hospitals Foundation Trust (HHFT). The machine tests procalcitonin on 20 microlitres of blood with direct sampling, and will produce a result in 20 minutes from the sample being inserted into the machine. All pediatric clinicians working at both hospital sites participated, and were allowed to perform POCT PCT at their discretion. A local guideline was produced suggesting appropriate scenarios for performing POCT PCT (Figure 1), including guidance for interpreting results. A cut off <0.5ng/L was chosen for categorising children as being low risk of SBI, based on previous literature which has demonstrated this to be a reasonable and conservative method for determining lower risk children amongst generally higher risk cohorts [8,9]. As a non-interventional study, there were no exclusion or inclusion criteria. Testing was performed solely at the discretion of the clinician. Neither hospital had pediatric specific antimicrobial stewardship programs at the time the evaluation was conducted.

At the time of testing, the clinician ordering the test had to complete a data collection form including demographic and baseline clinical information. We asked clinicians to choose what action they would have taken where the POCT PCT not available. Following prospective data collection, outcomes from each case were collected retrospectively. Descriptive statistics were performed using R studio (v1.1.456.).

The evaluation was approved by the Pediatrics Governance Group in Hampshire Hospitals, and as this project was performed as a service evaluation, no formal ethical approval was sought.

RESULTS

Demographics

POCT PCT was performed on 68 children (40 from site 1 and 28 from site 2) over a 5-month period from November 2018 to April 2019. Some patient data proformas were filled out incompletely at the time of testing, meaning data was unavailable, and therefore the denominators are different for some variables. Baseline characteristics of patients and indications for testing are presented in Table 1.

Decision making

Testing was performed on capillary blood for 31/67 (45.6%) patients, on venous bloods from phlebotomy in 12/67 (17.7%) and on venous bloods from a peripherally inserted cannula in 24/67 (35.8%).

At the time of testing, clinicians answered that without the point of care test being available, they would have discharged the patient in 7/68 (10.3%) cases, prescribed oral antibiotics for 10/68 (14.7%), prescribed intravenous (IV) antibiotics for 32/68 (26.5%), performed venous bloods for 36/68 (27.1%) and admitted 15/58 (22.1%) of patients. When outcomes were retrospectively assessed, 33/68 (48.5%) patients were discharged, 10/68 (19.1%) were given oral antibiotics, 32/68 (47.1%) were given IV antibiotics, 51/68 (74.1%) had venous bloods drawn and 35/68 (51.5%) of patients were admitted.

For patients with a procalcitonin of <0.5ng/L, 25/46 (54.4%) were discharged, 8/46 (17.4%) were given oral antibiotics, 16/46 (34.8%) were given IV antibiotics, 33/46 (71.7%) had venous bloods drawn and 21/46 (45.7%) were admitted to hospital (Table 2).

Antibiotics and other outcomes

The most frequently prescribed antibiotic overall was ceftriaxone (28/45, 62.2%), followed by co-amoxiclav (6/45, 13.4%) and amoxicillin (4/45, 8.9%). Of the 7 children who triggered the sepsis screening tool, the diagnoses were viral illness in 2 patients, and viral upper respiratory tract infection, GAS tonsillitis/pharyngitis, other bacterial lower respiratory tract infection, urinary tract infection and meningoencephalitis in one each. The most common diagnosis was of viral illness (14/68, 20.6%) followed by viral upper respiratory tract infection (11/68, 16.2%) and viral lower respiratory tract infection (7/68, 10.3%) (Table 3). The median duration of antibiotics was 6 days (Q1-Q3 5 -7 days). All hospital admissions were to the general medical ward. The median length of stay for admitted children was 1 day (both for those with PCT<0.5ng/L and equal to or above 0.5ng/L). There were 6/68 (8.8%) re-attendances, with 2/6 (33.3%) resulting in a further antibiotic prescription.

Investigation results

The PCT was <0.5ng/L in 69.1% of patients. A total of 5 patients had positive microbiology samples, with 4 positive urine cultures and one positive blood culture (*Staphylococcus aureus*). The procalcitonin was only >0.5ng/L for one of these patients, with a urinary tract infection (UTI) (procalcitonin 10ng/L, CRP 245mg/L). The child with a positive blood culture had a procalcitonin of 0.21ng/L, and a corresponding CRP mg/L of 58. The median CRP for patients with PCT <0.5ng/L was 12mg/L (Q1-Q3 3 – 58mg/L) and for patients with PCT equal to or above 0.5ng/L was 47mg/L (Q1-Q3 25 – 95mg/L).

DISCUSSION

Appropriateness of testing

Our results demonstrate the POCT PCT was often used inappropriately. There were 4 children diagnosed with UTIs who had a POCT PCT despite the availability of a point of care test for UTIs in dipstick urinalysis, which would render the POCT PCT redundant. A substantial number of children were tested for indications outside of the recommended pathways, with 20% having an indication of "Other".

Only 11.5% of children triggered the sepsis tool, indicating few required rapid decision-making regarding antibiotics, however over half of samples used for testing were from venous blood, indicating the child had venous phlebotomy or a peripheral cannula inserted. In these scenarios where the child was not being spared a blood test or cannula, waiting for a laboratory result would have been more appropriate.

Effect on clinician decision making.

Our results demonstrate that the results of the POCT PCT did not significantly influence decision making. There was little change in outcomes compared to clinicians reports of what they would have done where the POC PCT not available. We set a conservative cut off point for ruling out SBI (PCT <0.5ng/L), and provided guidance that a result below this level suggested a bacterial source was unlikely, and antibiotics were not advised. Despite this, over half of patients who had a result of <0.5ng/L received antibiotics, and 35% of them received IV antibiotics. Indeed, 45% of these patients were admitted to hospital overnight. This is despite the top 3 most common diagnoses, accounting for nearly half of all patients, being of viral origin. We hypothesise the reasons for this may include a lack of trust in procalcitonin due to limited experience with the test. Junior doctors who are often the initial decision

makers for children rotate around different hospitals every 6 months, and most hospitals in the region do not have procalcitonin available. Studies of POCT other than PCT have demonstrated they are frequently used inappropriately and that clinicians often do not trust, or act appropriately on results [10]. Adding to this uncertainty may have been the time taken for results to be available. 20 minutes may have felt too long to wait for clinicians debating the presence of a SBI.

Whilst our study was not designed for commenting on the performance of procalcitonin as a biomarker for bacterial infection, we note that it performed poorly, being >0.5ng/L for only 1 out of the 5 SBIs detected, and not being raised for the only invasive bacterial infection (*Staphylococcus aureus* bacteraemia associated with an osteomyelitis).

Strengths and limitations

Strengths of the study include that patients were identified prospectively, and as clinicians could test at their discretion (although guidelines were provided), the results reflect a "real world" experience with using POCT PCT. Our study has several limitations. It is an observational study and there is no comparator group, therefore we can draw limited conclusions regarding the effects of the POCT against usual care. It is not possible to discern any causal effects on changes of behaviour based on POCT PCT results. Our sample size was small; however, this is not uncommon for pilot programmes such as this. We asked clinicians what they would have done if the test was not available, however asking questions in this manner is inherently subject to bias (Hawthorne effect) and clinicians cannot truly know what they would have done under other circumstances [11]. As such the results should be interpreted with caution.

Despite limitations, the utility of point of care testing of procalcitonin for reducing blood tests, antibiotic use or admissions in an undifferentiated acute pediatric setting appears to be limited. We saw high rates of phlebotomy, intravenous cannulation, antibiotic use and admission in children tested, even following reassuring procalcitonin results.

Conclusion

In our small, pilot project assessing the clinical utility of POCT PCT, there did not appear to be an appreciable impact on decision making, venous blood testing, antibiotic prescription or admission to hospital. This is likely due to inappropriate use of the test, and clinicians making decisions which are inconsistent with recommendations based on the results of the test. Lack of familiarity with PCT may have been a significant contributing factor. Future research should focus on the utility of POCT PCT on targeted populations to determine if any subgroups of children may benefit from rapid risk stratification using this test.

FINANCIAL DISCLOSURE

All authors have no financial relationships related to this article to disclose

CONFLICT OF INTEREST

All authors have no potential conflicts of interest to disclose

DATA SHARING STATEMENT

De-identified data is available on reasonable request

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CONTRIBUTORS STATEMENTS

Alasdair Munro conceived and designed the project, collected the data, conducted the data analysis, drafted the initial manuscript and edited and gave approval of the final manuscript. Charles Hungwe and Pratisksha Patel were involved in designing the project, data collection and analysis and editing and giving approval to the final manuscript. Nick Ward, Simon Struthers and Kordo Saeed were involved in conceiving and designing the project, data analysis and editing and giving approval to the final manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Baseline Characteristics	
Number of patients	68
Age(yrs) (Med, Q1-Q3)	2.9 (1.3 - 6.7)
Male	40/67 (58.8%)
Duration of symptoms (hrs)	48 (24 - 132)
Sepsis tool triggered	7/54 (11.5%)
Indication for testing	
No focus of infection, unsure if bacterial source and some concerning features	31/59 (52.5%)
Focus of infection known, unsure if bacterial source and some concerning features	12/59 (20.3%)
Current inpatient for monitoring response to treatment	1/59 (1.7%)
Nurse initiated (any reason)	3/59 (5.1%)
Other	12/59 (20.3%)

Table 1. Baseline characteristics and indications for POCT PCT testing

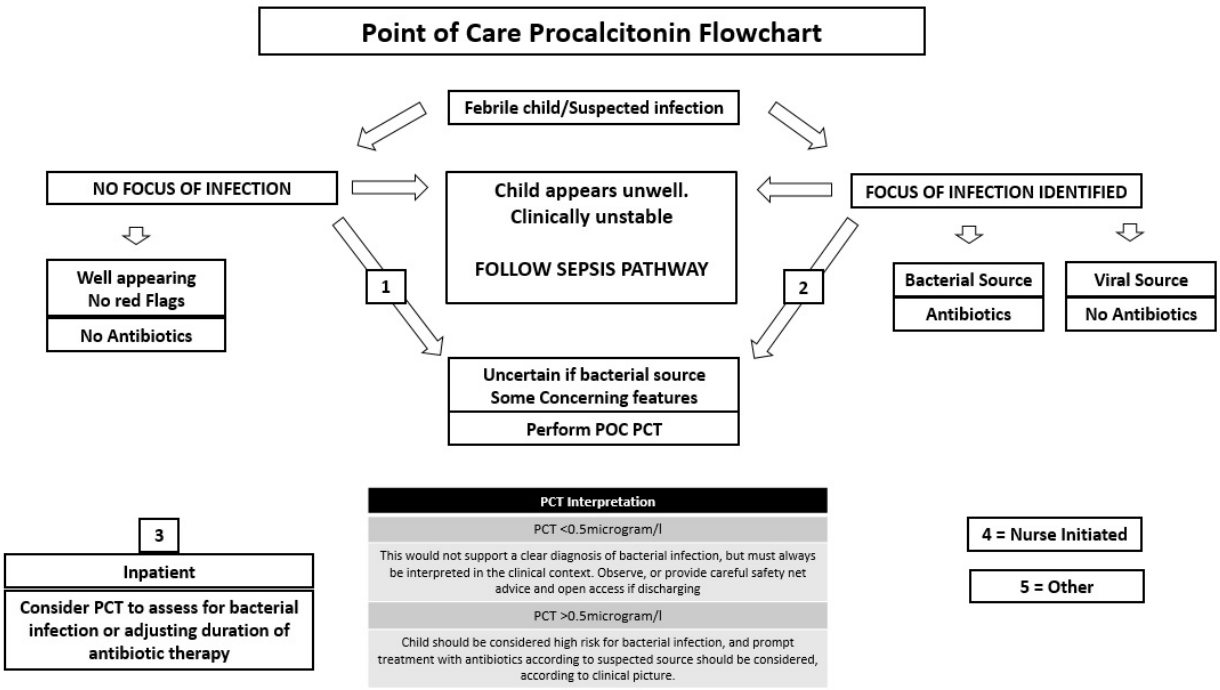

Figure 1 - Local guideline/ scenarios for performing POCT PCT

Without POCPCT, you would:	**Answer prior to result**		**Outcome following result**	
	PCT <0.5	**PCT =>0.5**	**PCT <0.5**	**PCT =>0.5**
Discharge	3/46 (6.5%)	4/21 (19.1%)	25/46 (54.4%)	7/21 (33.3%)
Oral antibiotics	8/46 (17.4%)	2/21 (9.5%)	8/46 (17.4%)	5/21 (23.8%)
Venous bloods	26/46 (56.5%)	9/21 (42.9%)	33/46 (71.7%)	17/21 (81%)
Intravenous cannulation	23/46 (50%)	13/21 (38.1%)	*NA*	*NA*
Intravenous antibiotics	12/46 (26.1%)	5/21 (23.8%)	16/46 (34.8%)	15/21 (71.4%)
Observation	19/46 (41.3%)	10/21 (47.6%)	*NA*	*NA*
Admit	12/46 (26.1%)	3/21 (14.3%)	21/46 (45.7%)	14/21 (66.7%)
Further tests	10/46 (21.7%)	6/21 (28.6%)	*NA*	*NA*

Note: the POCT POC result for one patient was not documented and irretrievable, so their results are not presented in this table.

Table 2 -. Clinicians reported alternative actions in absence of POCPCT compared to patient outcome stratified by POCPCT result.

Diagnosis	N (%)	PCT <0.5
Viral illness	14/68 (20.6%)	10/14 (71.4%)
Viral URTI	11/68 (16.2%)	7/11 (63.6%)
Viral LRTI	7/68 (10.3%)	6/7 (85.7%)
Tonsillitis	6/68 (8.8%)	1/6 (16.7%)
Community acquired pneumonia	6/68 (8.8%)	5/6 (83.3%)
Non-infective/other	6/68 (8.8%)	5/6 (83.3%)
Other bacterial LRTI	5/68 (7.4%)	3/5 (60%)
Urinary tract infection	3/68 (4.4%)	2/3* (66.7%)
Pyelonephritis	2/68 (2.9%)	1/2 (50%)
Gastroenteritis	2/68 (2.9%)	1/2 (50%)
Osteomyelitis	2/68 (2.9%)	2/2 (100%)
Other bacterial infection	2/68 (2.9%)	1/2 (50%)

Note: *One patient had POCPCT result missing

Table 3 - Discharge diagnoses of children who had a POC PCT performed