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Development of Material for use in a Proficiency Testing Programme for Procalcitonin

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Introduction

Procalcitonin (PCT) has developed into a promising biomarker for both early diagnosis of sepsis and antibiotic stewardship. A recent meta-analysis on the diagnostic accuracy of procalcitonin and presepsin in detecting infection was found to be similar and both useful for early diagnosis of sepsis and subsequent reduction of mortality in critically ill adult patients. [1].

Current evidence suggests that PCT to guide antibiotic treatment in patients with acute respiratory infections (ARI) reduces antibiotic exposure and side-effects, and improves survival. PCT protocols in ARI have the potential to improve antibiotic management with positive effects on clinical outcomes and on the current threat of increasing antibiotic multiresistance. [2] In the UK there has been a steady increase over the last year of laboratories now providing this service.

Aim

To develop a Proficiency Programme for PCT to meet current need;

- to determine suitability of material such as stability and commutability and to develop samples at the appropriate clinical range.
- to determine appropriate performance specification based on clinical utility.

Method

During the study period, PCT was assayed on both Radiometer AQT90 and the Roche Cobas e601. Both methods were verified prior to use for within and between batch reproducibility using manufacturers' IQC material. The AQT90 was compared with the Roche Cobas assay using a series of samples ranging from 0 – 50 ng/mL.

For the stability study, serum was spiked with recombinant PCT to target concentrations of 1 ng/mL and 10 ng/mL to produce 2 master pools. For each master pool, three different protease inhibitors were added to produce 4 further pools, a baseline pool (no inhibitors) and 3 further pools with the different protease inhibitors. All 8 pools were assessed over a 21 day period at storage temperature of 20°C and 4°C.

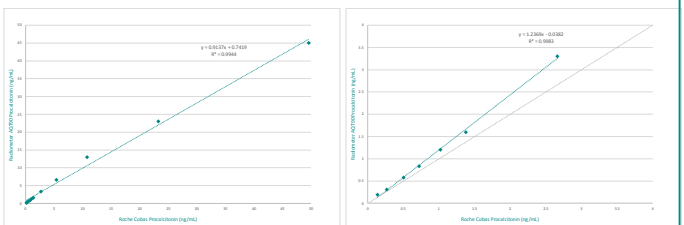
Sixteen laboratories were recruited for the study and three samples were distributed to each participating laboratory each month for the study period. A wide range of methods and platforms were used by the participants including Roche Cobas, Abbott Architect, Siemens Centaur, Radiometer AQT90 and Vidas methods.

The validated material was distributed over 5 rounds over a 5 month period of the pilot study. Samples were targeted at low concentrations around the clinically important cut-offs and also at higher concentrations to test the full range of the assay.

Results - Method verification

The Radiometer AQT90 showed good correlation across the analytical range compared with the Roche Cobas e601 assay, $R^2 = 0.9944$, linear regression of 0.914x + 0.74 ng/mL (Figure 1). However at clinically important concentrations (<3 ng/mL) a positive proportional bias of 24%, $R^2 = 0.9983$, y= 1.24x - 0.04 ng/mL was observed between the methods.

Figure 1a,b. Comparison of PCT Results from the Radiometer AQT90 and Roche Cobas



Within batch CV's of 2.8% and 5.0% were observed at concentrations of 1 and 10 ng/mL respectively for AQT90 and CV < 2% for the Roche e601. Between batch CV's of 8.0% and 6.9% were observed at 0.5 and 9.1 ng/mL respectively for the AQT90 and 3.2% and 1.1% at 0.5 and 9.9 ng/mL respectively for the Roche method.

Results - Material Development

Pools 1 and 2 (no protease inhibitor) showed a decay in PCT concentration of 13% at 1 ng/mL (Pool 1) and 16% at 10 ng/mL (Pool 2) within 24 hours at ambient temperature. Good results were achieved with protease inhibitor 2 (Pools 5 and 6) with no significant decrease in PCT for 2 days at ambient temperature and 7 days at 4°C

Figure 2. Procalcitonin stability of 8 pools stored at ambient temperature for 96 hours (4 days)

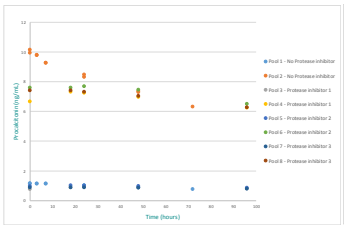
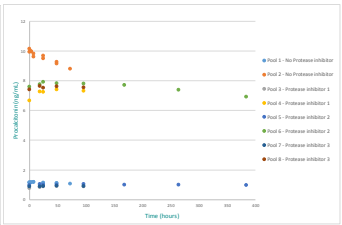


Figure 3. Procalcitonin stability of 8 pools stored at 4°C for over 396 hours (16.5 days)

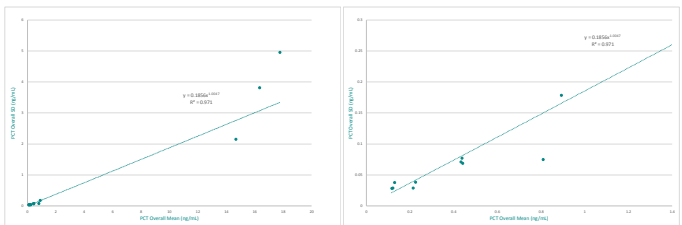


Protein inhibitor 2 was therefore used for all other sample production. The first preparation of samples using this material for the PT programme showed excellent between vial homogeneity, with a CV <2% for all pools analysed on the Roche Cobas.

Results – PT Programme

The precision profile calculated from the overall SD of all participants' results at each concentration is shown in figure 4a. The clinically important low concentration range is highlighted in figure 4b. The precision profiles include components of both interlaboratory variation and method bias.

Figure 4a,b. Procalcitonin PT participant results - Overall Mean and SD data for 5 distributions of pilot programme



Conclusions

The material developed was found to be suitable for use as PT material showing good stability when protease inhibitor 2 was used and excellent vial to vial reproducibility. Although, provisional performance criteria can be established from the pilot study, additional samples will be distributed over the coming months to provide further evidence as to the "state of the art" of the PCT methods used in the UK.

1. Kondo Y *et al.* Diagnostic value of procalcitonin and presepsin for sepsis in critically ill adult patients: a systematic review and meta-analysis. *J Intensive Care* 2019 Apr 15;7:22

2. Schuetz P *et al.* Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis. Lancet Infect Dis 2018 Jan; 18(1):95-107