Horizon Scan Report 0021 **13 February 2012**

Diagnostic Technology: Point-of-care test for procalcitonin to improve the early diagnosis of serious bacterial infections in patients presenting in primary care

Clinical Question:

1. What is the diagnostic value of point-of-care procalcitonin tests in the primary care setting?
2. In primary care patients presenting with symptoms of acute infection, does a point-of-care procalcitonin test compared with standard practice improve the early diagnosis of serious bacterial infection?
3. In primary care patients presenting with acute infections, does point-of-care procalcitonin testing improve the targeting of antibiotic prescription compared with standard practice?
4. What are the possible primary care clinical pathways in which the point-of-care procalcitonin tests may be used?

Advantages over Existing Technology:

In primary care patients presenting with an acute infection, it can be difficult to distinguish between a serious bacterial infection (SBI) and a self-limiting illness, particularly in children.[1] In situations of diagnostic uncertainty, and when tests are available, clinicians often measure the white blood cell count (WBC) despite it having poor diagnostic accuracy.[2] Other inflammatory markers have been proposed to aid the diagnosis of SBI, such as C-reactive protein (CRP) and procalcitonin (PCT).[3] PCT, the 13 kDa protein prohormone of calcitonin, is present in low levels in healthy individuals[4 5] and during viral infections, but rises rapidly during SBI.[6] In addition, improved targeting of antibiotic prescribing by having PCT levels guide treatment decisions has been evaluated for the management of respiratory tract infections as outpatients.[7] There is currently limited or no use of point-of-care tests for acute infections such as CRP or PCT in the UK, but PCT has many potential applications in primary care, out-of-hours and the emergency department (ED) by potentially excluding SBI and subsequently guiding judicious referral decisions and antibiotic usage.[3] In particular, point-of-care PCT tests may be especially useful in rural settings where extensive laboratory investigations are limited or not available. Point-of-care PCT tests may allow earlier diagnosis of sepsis as several studies have reported that PCT is a better diagnostic marker of sepsis than CRP.[8]

Details of Technology:

Only one point-of-care test procalcitonin test was identified:

1. **PCT-Q®** (Brahms, Germany) is a semi-quantitative rapid immunochromatographic test that uses lateral-flow immunochromatography to measure procalcitonin.[9] The test requires 200 µL of serum/plasma obtained from venepuncture and a 30-minute incubation period to complete.[9] At PCT concentrations of ≥0.5 ng/mL, a reddish band forms, the colour intensity directly proportional to the PCT concentration.[9] The test is read with a reference card, which allows the patient's PCT level to be classified into one of four semi-quantitative categories (<0.5 ng/ml, 0.5 to 2 ng/ml, 2 to 10 ng/ml and >10 ng/ml).[10] A centrifuge is required to separate the serum/plasma. In clinical practice, PCT values appear to be available within one hour of venepuncture.[11]

2. **In development:** Using a compact optical immunosensor, a feasibility assessment for the simultaneous multi-parameter detection of PCT, CRP and TNF-alpha has recently been demonstrated.[12]

Patient Group and Use:

- **Diagnosis of serious bacterial infections:** Acutely ill patients, particularly children, with clinical presentation suggestive of infection presenting to primary care, out-of-hours or the ED to rule out SBI.
- **Targeting of antibiotic prescription:** Patients with an acute infection presenting to primary care, out-of-hours or the ED to target antibiotic prescription, particularly adults.

Importance:
Lower respiratory tract infections (RTI) account for 17 million consultations in the European Union and 11 million in the United States each year.[2] The 2008 NICE guidelines on RTI reported that each year most people have an RTI and one-quarter visit their general practitioner as a result of the infection.[13] Childhood infections in UK general practice represented 60% of the annual consultation rates for children under 1 year – approximately 4 consultations per year – compared to 36% and 20% in the 1-4 and 5-15 age group respectively.[14 15]

Of all the antibiotic prescribing in general practice, 60% can be attributed to treatment for RTIs despite evidence demonstrating their limited effectiveness.[13] Excessive antibiotic use leads to antimicrobial resistance and increased health care costs managing complications.[1316] Indeed adherence to appropriate antibiotic prescribing guidelines could result in annual savings of greater than £3.5 million for the National Health Service according to NICE.[13] A Cochrane systematic review found multi-faceted interventions the most effective to improve antibiotic prescribing practices despite only decreasing prescriptions by 10 to 15%.[17]

In addition to a potential benefit on antibiotic prescribing, PCT testing may also improve the recognition of serious infections, especially in children.[3] In the UK infections account for 20% of childhood deaths, with the greatest number in children aged 1 to 4 years.[1 18] Childhood febrile illness accounts for one-fifth of all visits to the emergency department,[19] frequently leads to health advice out of hours[20] and results in the most number of paediatric admissions.[14] Recent studies have identified a number of important red flags in the diagnosis of SBI in children[1] but also made it clear that clinical features alone result in diagnostic uncertainty, especially in low prevalence settings such as general practice. Laboratory tests identified as most useful in reducing this diagnostic uncertainty are CRP and PCT.[3]

Previous Research:
Accuracy compared to existing technology

The standard laboratory method of measuring PCT is quantitatively, using Lumitest® (Brahms, Germany), a luminometric immunoassay or Kryptor® (Brahms, Germany), an ultra-sensitive immunoassay using TRACE (Time Resolved Amplified Cryptate Emission) technology.[21] Conversely, PCT-Q® (Brahms, Germany) semi-quantitatively measures PCT values in the serum of patients. Previous studies have validated the correlation between PCT-Q® and quantitative assays, but few have validated the assay clinically in the primary care setting.[11 22-24] The accuracy of the PCT-Q® test varies based on the number of technicians involved: the rate of disagreement (discordance) is low in studies with a limited number of technicians (1-2) but higher when several technicians are involved.[11]

Table 1 – Reproducibility of PCT-Q® compared to quantitative assay in various studies

Study	N	Comparator	Population	Setting	Correlation (Kappa)	Discordance	Inter-observer variability
Manzano[11]	359	Kryptor®	1-36 mo	ED	0.44	29% (103/359)	p=0.018
Gervaix[25]	54	Lumitest®	0.2 mo-16 yr	ED	'Good'	11% (6/54)	None
Thayyil[24]	72	Lumitest®	1-36 mo	ED	0.72	-	-

ED, emergency department

In a Canadian prospective cohort study, part of a randomised controlled trial (RCT) evaluating the effect of PCT measurement on the management of children presenting to ED with fever without a focus, the agreement between PCT-Q® and Kryptor® was "moderate" (linear weighted kappa, 0.44; 95% CI 0.36, 0.51) with 103 (29%) discordant results.[11 26] Before the study, all 61 laboratory technicians received training for PCT measurement using PCT-Q®. However, the distribution of results varied depending on the technician (p=0.02). In detecting SBI (as defined in the study independent of PCT values), the sensitivity of PCT-Q® was higher (77%, 95% CI, 66-86) compared to the quantitative assay Kryptor® (56%, 95% CI, 45-66). However, specificity of PCT-Q® was lower (64%, 95% CI, 59-69) compared to Kryptor® (86%, 95% CI, 84-88).[11] *Thayyil et al.* completed a prospective study of children presenting with fever without a focus to paediatric units and showed that PCT measurement with PCT-Q® compared to Lumitest® showed good correlation (r=0.72).[24] However, the study only presented the findings of the quantitative assay Lumitest® and not the

findings of the semi-quantitative PCT-Q®.[24] Another study comparing PCT measurements with PCT-Q® and Lumitest® in 54 children with a urinary tract infection found results discordant in 11% (6/54) of tests.[25]

Impact compared to existing technology

We identified five studies that evaluated the impact of point-of-care (PCT-Q®) compared to quantitative (Lumitest® or Kryptor®) PCT testing on the diagnosis of SBI in the emergency department (pyelonephritis,[25] meningitis,[23] serious bacterial infections as a composite outcome,[10 26] and occult bacteraemia[27]), of which two evaluated the impact on both diagnosis and antibiotic use.[23 26] A summary of identified studies is included in Table 2.

Table 2 – Summary of included studies

Study name	Study type	N	Age	Prev.	Diagnosis	PCT Cutoff (ng/mL)	Sensitivity, % (95 CI)	Specificity, % (95 CI)
Gervaix[25]	Prsp, Cx-sect	54	0.2 mo-16 yr	63%	Pyelonephritis	0.5	74 (55.6-87.1)	85 (62.1-96.8)
Budgen[23]	Prsp, Cx-sect	183	14-40 yr	4.9%	Meningitis	0.5	100 (66.4-100)	89 (83.1-93.1)
Manzano[26]	RCT	384	3-36 mo	16%	SBI	0.5	77 (66-86)	64 (59-69)
Galetto-Lacour[10]	Prsp, Cx-sect	99	0.2-36 mo	29%	SBI	0.5	93 (77-99)	74 (62-84)
Guen[27]	Prsp	215	3-36 mo	3.3%	OB	2.0	57 (20-94)	87 (81-91)

Prev, prevalence; PCT, procalcitonin; Prsp, prospective; Cx-sect, cross-sectional; RCT, randomised controlled trial; SBI, serious bacterial infection; OB, occult bacteremia;

A Swiss prospective study of 99 children aged 7 days to 36 months assessed for fever without a focus (>38°C) at a paediatric ED reported a sensitivity of 93% (95% CI, 77-99) and a specificity of 74% (95% CI, 62-84) of point-of-care PCT to diagnose SBI.[25] In 54 children, PCT <0.5 ng/mL nearly ruled out SBI (likelihood ratio [LR]: 0.09).[25] However, the incidence of SBI in this study was high (29%) and the number of patients low (n=99), therefore the applicability to other settings with lower pre-test probabilities is unknown.

Guen et al. completed a 215 patient prospective study in children aged 3 to 36 months assessed with fever without a focus (≥39ºC) to detect occult bacteraemia.[27] Using a cut-off value of ≥2.0 ng/mL, the sensitivity was only 57% (95% CI, 20-94) compared to a specificity of 86% (95% CI, 81-91). In 54 children with febrile illness and confirmed urinary tract infections, of which 63% had renal involvement, point-of-care PCT had a sensitivity of 74% (95% CI, 55.6-87.1) and a specificity of 85% (95% CI, 62.1-96.8) to predict renal involvement.[25] The calculated LRs of PCT were 3.8 using a cut-off value of ≥0.5 ng/mL and 7 using a cut-off value of ≥2 ng/mL; 87-92% of kidney involvement would be identified using any positive PCT value.[25] However, the sample size was small (n=54) and prevalence of pyelonephritis was high (63%) in the study.

A prospective cross-sectional New Zealand study evaluated the diagnostic characteristics of point-of-care PCT to identify meningococcal disease in young adults (14 to 40 years) with fever presenting to ED during an epidemic.[23] In 183 patients that presented with fever without a focus (≥38°C) or with meningococcal disease symptoms, PCT had a sensitivity of 100% (95% CI, 66.4-100) and a specificity of 89% (95% CI, 83.1-93.1) with a meningitis prevalence of 4.9% (9/183).[23] Further, if a positive PCT result had been used to justify treatment, the number needed to treat would have reduced from 20 to 3.[23] However, the study has several limitations that need to be highlighted: 1) the study took place during a prolonged meningococcal epidemic in New Zealand; 2) small number of patients; 3) wide confidence intervals; 4) the study excluded patients with a diagnosis of pneumonia, UTI, purulent tonsillitis and soft tissue infections yet included patients with upper RTIs and gastroenteritis as they have similar presentations to meningitis; and 5) the authors caution

against over-interpreting the findings without further validation. Therefore, the spectrum of patients is not generalisable to a general ED population.
Finally, one of the 5 studies that were identified was a high quality RCT (i.e. computer-generated block randomisation, allocation concealment, intention-to-treat and no loss to follow-up) evaluating point-of-care PCT tests in children between the ages of 1 and 36 months.[26] The RCT investigated the impact of PCT-Q® on antibiotic use in febrile children without a source in an urban paediatric ED (Canada).[26] Children with fever without a source were randomised into two groups, each containing 192 patients: one group had the PCT result revealed to the physician assessing the child (PCT+) while the other group did not (PCT-).[26] To diagnose SBIs in 384 children with 16% prevalence, the semi-quantitative PCT-Q® assay had a reported sensitivity and specificity of 77% (95% CI, 66-86) and 64% (95% CI, 59-69) respectively.[26] The corresponding negative LR was 0.35 (95% CI, 0.22-0.56) and positive LR was 2.2 (95% CI, 1.76-2.62) for PCT.[26] However, the PCT result had no impact on antibiotic use when it was revealed to the clinician.[26] Using PCT to guide prophylactic antibiotic use would have increased the prescribing rate by 13% (95% CI, 4-22%) using a ≥0.5 ng/mL cut-off value.[26] There would have been a further increase of 24% (95% CI, 15-33) in antibiotic prescribing had patients treated for an infection after investigations or for neutropenia been excluded.[26]

Overall, it appears that PCT-Q® point-of-care PCT tests in the emergency department, where the pre-test probability is high and serious infections are relatively common (typically 1 in 5 children had serious infection[3]), have similar sensitivities and specificities to other inflammatory markers, mainly CRP. A recent systematic review showed that PCT provides superior clinical information for decision making than the WBC in diagnosing SBI in the hospital emergency department setting.[3] In primary care, where the prevalence of SBI decreases 1 in 150 children,[3 28] we did not identify any studies that directly assessed the diagnostic value of PCT in diagnosing SBI in primary care. In this setting, point-of-care PCT tests will unlikely change the probability of SBI enough to modify clinical decision-making and risk thresholds and taking an invasive serum sample in children needs to be considered.[3]

The question of whether point-of-care PCT tests impact antibiotic usage in primary care remains unresolved. One study reported that if used as an indication for antibiotic treatment there would have been a theoretical reduction in prescriptions to treat meningitis.[23] In spite of the findings, the numerous limitations of the study minimise any potential extrapolation into clinical practice. However, the only RCT included in the report demonstrated that point-of-care PCT tests had no impact on antibiotic usage in the emergency department.[26] In fact, it appeared that using information derived from point-of-care PCT assays increases antibiotic prescribing in children with suspected SBI.[26] However, the SBI prevalence was relatively high (16%) and 35% of the study population received antibiotics.[26] Whether these results are generalizable to primary care where less than 1% of acutely ill children have a serious infection is unclear.[28]

Guidelines and Recommendations
There have been no guidelines or recommendations published on the use of PCT-Q® or other point-of-care PCT tests for the diagnosis of SBI. The 2007 NICE Guideline on Feverish illness in children and 2010 Guideline on Bacterial meningitis and meningococcal septicaemia in children do not recommend the use of PCT tests (either point-of-care or serum tests) to diagnose SBI in children due to CRP being less costly and providing a more correct diagnosis than PCT while acknowledging the evidence base is limited.[14 29]

Cost-effectiveness and economic impact:
Currently no evidence exists on the cost-effectiveness and economic impact of point-of-care PCT testing for patients presenting in primary care. The tests are relatively costly (£30 to £65) and an economic evaluation is required to ascertain the cost-effectiveness of implementing a point-of-care test compared with standard PCT testing. The increased cost of the additional diagnostic PCT test may be balanced by savings from reduction in laboratory time and equipment used and from savings from the likely reduced antibiotic use. In addition savings may come in the form of reduced adverse events related to antibiotics and reduced costs associated with antibiotic resistance.

A simple cost-effectiveness analysis was produced by the Centre for Evidence-based Purchasing.[30] They explored the use of PCT to guide the prescription of antibiotics to LRTI patients in a secondary care setting.[30] The incremental cost-effectiveness ratio (ICER) was estimated to be between £45 and £120 per additional correctly treated case.[30] Moreover,

two important cost factors were not included in the analysis, namely savings resulting from the reduction in patient side-effects and antibiotic resistance.[30]

Research Questions:

1. What is the accuracy and precision of point-of-care PCT tests in the primary care setting?
2. What is the usefulness of point-of-care PCT tests in targeting antibiotic prescriptions in patients presenting with acute infections to primary care?
3. In primary care patients presenting with acute infection is a point-of-care PCT test able to exclude serious bacterial infections?
4. Does a point-of-care PCT test combined with a clinical prediction rule aid diagnoses of acute infections?
5. What is the ideal healthcare setting where point-of-care PCT tests would have the greatest impact on confirming or excluding serious bacterial infections?
6. What is the cost effectiveness of PCT testing in primary care?

Suggested next step:

Studies of the accuracy and utility of point-of-care PCT tests in the general practice and primary care setting (outside of ED), including the appropriate timing of the blood tests in the patients course of illness and the comparative diagnostic value of PCT compared to CRP and WBC either alone or combined at different (and multiple) points along the time course.

Comparisons of point-of-care PCT tests with point-of-care devices for other inflammatory markers for patients presenting with acute infections – to include effects on prescribing, patient satisfaction, re-consultation rates, referrals, complications (e.g. hospital admission, delayed diagnosis), cost effectiveness.

Expected outcomes:

Point-of-care PCT tests may better identify patients that are at risk for serious bacterial infections earlier than currently available investigations.

Point-of-care PCT tests alone, or in combination with other inflammatory markers (e.g. CRP) or WBC count may improve the earlier diagnosis of serious bacterial infections.

Point-of-care PCT tests may be better for use in rural or remote settings (e.g. rural hospital) where standard laboratory assays are not available.

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