Horizon Scan Report 0017 **28 July 2011**

Diagnostic Technology: Point-of-care test (POCT) for C-reactive protein (CRP)

Clinical Question: In patients presenting to primary care with signs of lower respiratory tract infection (LRTI), what is the utility of POC CRP measurements in differentiating between viral and bacterial infection?

Advantages over Existing Technology:

The major advantage of a point-of-care test for CRP is that it provides results within a few minutes, and could feasibly be used during consultations in primary care to help determine the aetiology of LRTI. In addition, point of care tests for CRP involve only a droplet of blood, and may therefore be easier to use in children and other patients from whom it is difficult to obtain blood samples. Current clinical practice for diagnosing LRTI relies largely on clinical features from history and examination. Chest X-rays can be useful to confirm diagnosis (and exclude other diagnoses) but involve travel to a hospital and delay in obtaining results. Blood tests for inflammatory markers, white cell counts can be performed, but usually involve at least a day's wait for results. Blood cultures and serologic methods are rarely used in primary care. Quick and reliable measurements to characterize the possible aetiology of infection could help to avoid unnecessary prescription of antibiotics without compromising patient safety [1]. CRP is a non-specific marker secreted in response to a variety of infectious and inflammatory triggers, and levels are typically highest in patients with a bacterial infection (upwards of 350 mg/l compared to healthy levels of <10 mg/l) [2]. Point-of-care CRP measurements are generally available within 10 minutes of testing [2], with some devices providing results after only 2 minutes [3]. If CRP readings had a high enough specificity to effectively rule out bacterial infection, such a test could improve the efficacy of antibiotic prescription in primary care.

Details of Technology:

A small sample of blood is taken from the finger, and combined with a reagent containing anti-CRP antibodies. The antibodies form a complex with serum CRP and the resulting complexes can be measured using an automatic reader.

The following point-of-care (POC) devices have been identified to measure CRP levels:

1. QuikRead CRP (Orion Diagnostica, Espoo, Finland). CRP levels are measured using 0.2 mL of blood, and results are available after 2 minutes [3].
2. NycoCard II Reader (Axis-Shield, Olso, Norway) [4]. CRP levels are measured using 5 µl (1 drop) of blood, and results are available after 2 minutes
3. C-Reactive Protein on the Cholestech LDX® System (Inverness Medical, UK). Can measure a range of parameters from a fingerstick blood sample, including CRP (e.g. cholesterol, HDL, LDL etc.).
4. Modern health systems Ltd. C-reactive protein test. Semi-quantitative test measures CRP from 2 drops of whole blood within 5 min.
5. Eurolyser Smart (single method automated reading technology) point of care instrument. Can measure a variety of parameters, using different assay cassettes, from whole blood. CRP can be measured from 2 drops of whole blood within approximately 5 min.

Patient Group and Use:

- Patients presenting with signs of possible LRTI

- Differentiating between bacterial and viral infection to reduce antibiotic prescription for viral infection
- Monitoring response to treatment using serial CRP measurements

Importance:
A study published in 2009, using the UK General Practice Research Database (GPRD), found that of 151,088 patients in 346 primary care practices, 86.1% were prescribed antibiotics on the day they were diagnosed with LRTI [5]. This presents a problem, since LRTIs are a predominantly viral illness most commonly caused by rhinoviruses and influenza viruses [6]. Apart from the unnecessary use of antibiotics for such viral infections, over prescription contributes to the development of bacterial resistance, increases costs, can medicalise many self-limiting infection and adds risks of side effects and allergic reactions [7]. One of the reasons that GPs prescribe antibiotics for LRTI is the difficulty in distinguishing clinically the aetiology of LRTI, leading to concerns about failing to treat a bacterial infection. In order for CRP or any biological marker to be useful in diagnosis it must have a high enough specificity to confidently withhold treatment.

An additional contributor to antibiotic over prescription is pressure from patients with a misunderstanding of the nature of antibiotics and infection. A 2006 British Survey on antibiotic use found that 38% of people did not know that antibiotics do not work against most coughs and colds, and 43% did not know that antibiotics can kill the bacteria that normally live on the skin and in the gut [8].

According to the 2008/2009 annual report from the National Institute for Health and Clinical Excellence (NICE), each year one in four people visit their GP because of an acute respiratory tract infection [9]. Diagnosis of LRTI represents a considerable source of uncertainty for clinicians, since distinguishing between pneumonia and acute bronchitis is often impossible on clinical grounds, and this uncertainty often has led to the empirical over prescription of antibiotics [10]. 60% of all antibiotic prescribing in general practice comes from treatment for respiratory tract infections, and the NICE guideline on helping healthcare professionals decide when antibiotics are appropriate is estimated to save the NHS £3.5 million a year. [9, 18]

Previous Research:
Accuracy compared to existing technology
In a study comparing the QuikRead POC CRP test to a standard laboratory assay, the rapid test gave the same quantitative results as the laboratory technique. In a population of 231 children under the age of 14, the median CRP levels and ranges were compared for both techniques [11]. A similar comparison included the additional NycoCard CRP-Single Test and found that neither the QuikRead nor the NycoCard test had statistically significant systematic proportional bias when compared to a standard laboratory method, and were therefore useful in obtaining accurate CRP measurements [4]. In a study of 250 participants eligible for primary prevention of cardiocascular disease, blood lipids and CRP were measured simultaneously using a fingerstick sample and compared to laboratory analysis. Correlation for CRP was 0.81 ($p<0.01$) and both sensitivity and specificity were 75% [20].

A systematic review published in 2005 sought to evaluate the diagnostic accuracy of CRP (not point of care, but all CRP) in differentiating between viral and bacterial infection compared to radiologically proved pneumonia in adults and children. Sensitivities ranged from 8-99%, and specificities from 27-95%. For adults, the relation of CRP with a bacterial radiograph showed an area under the curve of 0.80 (95% confidence interval 0.75 to 0.85). The review concluded that rapid CRP testing lacks both the sensitivity and specificity needed to be applied in a clinical setting, and that current evidence does not support CRP testing as a guide to antibiotic prescription [14].

A meta-analysis conducted in 2008 investigated the utility of CRP as a predictor of bacterial pneumonia in acutely ill hospitalised children. 8 Studies were identified, representing a total of 1230 children, and cut-off values ranged from 35-60 mg/L. Positive bacterial infection was indicated by the presence of alveolar infiltrates on a chest radiograph, though it was noted that there is no universal standard for differentiating between viral and bacterial infection in LRTI. When all 8 studies were combined, children with bacterial pneumonia were significantly more likely to have a serum CRP concentration exceeding 35–60 mg/L than children with nonbacterial pneumonia (OR: 2.58; 95% CI: 1.20 –5.55). However, there were only two studies with specificity above 63%, both with cut-off values of 40 mg/L and sensitivities of 35% and 17%. It was suggested that CRP levels are only weakly predictive of bacterial infection and a lower CRP level is not in itself a reason to withhold antibiotics [13]. One subsequent small study, however, did report CRP to be a useful predictor of bacterial pneumonia in children. This prospective Israeli study of 50 children under the age of 17 compared CRP levels from the QuikRead POCT to diagnosis based on chest radiography. 36 patients (72%) were diagnosed as positive for bacterial infection based on lobar, lobular, or alveolar findings. An analysis of CRP in leftover blood found that raised CRP levels (>8 mg/L) had a positive predictive value (PPV) of 70% for bacterial pneumonia, and an odds ratio of 1.25 [95% confidence interval (CI): 1.07–1.45]. It was reported that within 96 hours from the onset of symptoms, CRP could be a useful predictor of bacterial pneumonia [3].

In 2009, a literature review compared 8 publications on the utility of CRP measurements in acute respiratory tract infections in assisting GPs in their prescription of antibiotics. The specificity and sensitivity ranged from 10% to 99%, depending on selected cut-off values. The review concluded that the literature was insufficient and too varied to reach any agreement on the utility of CRP in withholding or prescribing antibiotics to adults with LRTI. It was suggested that more thorough and careful studies should be done to investigate the value of CRP in assisting with the diagnosis of LRTI [15].

Impact compared to existing technology

The consensus across multiple studies is that POCT for CRP has limited utility in differentiating between bacterial and viral infection, mainly as a result of low specificity. Part of this problem arises from the kinetics of CRP – it is a non-specific marker that is released 4-6 hours after an inflammatory trigger, with levels peaking after 36 hours and a half-life of 4-7 hours [2,7]. Early readings may present low values that are not indicative of the severity of infection, and while rapid results are beneficial in the primary care setting, a single CRP reading is not sufficient to withhold antibiotic treatment.

A 2008 study from the Netherlands investigated the impact that POC CRP testing had on 20 GP's diagnosis and prescription decisions in LRTI [16]. 16 GPs reported that CRP results helped to avoid antibiotic prescription and also helped to confirm clinical findings and decrease diagnostic uncertainty. GPs believed that one of the main advantages of the POCT was that patients' satisfaction improved, since they felt that their complaints were being taken seriously. One GP reported, "If a patient clearly expects to get an antibiotic, it can support you in your explanation. And patients understand that. You explain to them that the test doesn't indicate anything serious—the CRP is normal—and then it's easier to get patients to accept a wait-and-see policy". However, half of GPs found intermediately elevated levels (20-100 mg/L) to be a limitation of the test [16].

A randomized controlled trial from 2007-2008 in the Netherlands compared the treatment of LRTI in 258 patients among 32 family physicians who had been divided into CRP assistance (test group) and routine care (control group). In the test group, CRP was measured by the nurse practitioner and test results were used in the clinical assessment. Physicians in the test group were advised to withhold antibiotics when CRP<20 mg/L, give immediate antibiotics when CRP>100 mg/L, and consider delaying prescription when levels were between 20

and 99 mg/L. However, they were allowed to deviate at any time if they felt it was necessary. If antibiotics were withheld, the physician explained the decision based on the CRP reading and the patient was given an information sheet with additional details about the technology. Compared to the control group who prescribed 56.6% of patients with antibiotics, the test group had only 43.4% antibiotic usage (relative risk [RR]=0.77; 95% CI, 0.56-0.98), and that difference remained after a 28-day follow-up period (52.7% vs 65.1%). The report concluded that POC CRP testing may be a useful tool to assist with clinical decisions that could decrease antibiotic usage without compromising patient safety, as long as patients with delayed prescription are monitored after initial consultation [17]. In addition, Cals et al compared POC CRP testing with GP education strategies and found that GPs in the CRP test group prescribed antibiotics to31% of patients compared with 53% in the no test group (P=0.02), and GPs trained in enhanced communication skills prescribed antibiotics to 27% of patients compared with 54% in the no training group (P<0.01) [19]. The study concluded that both use of POC CRP testing and training in enhanced communication skills significantly reduced antibiotic prescribing for lower respiratory tract infection without compromising patients' recovery and satisfaction with care.

Guidelines and Recommendations

The NICE guideline on *Feverish Illness in Children* (CG47, May 2007) recommends the use of CRP in conjunction with full blood count, blood cultures and urine testing. They report that CRP is useful, but no specific cut-off level could be recommended. High CRP does suggest the presence of bacterial infection, but it must be used together with other information to inform clinical decision-making on a case-by-case basis.

Cost-effectiveness and economic impact:

Current evidence on the cost impact of POC CRP testing in a primary care setting comes from a Danish randomized crossover study conducted using NyoCard CRP [21]. The implementation of CRP POC testing was found to be cost-saving, although there was no difference in antibiotic prescriptions between the intervention and control periods, the use of ESR's, mailed blood samples to the laboratories and follow-up telephone consultation were reduced. The main cost driver was the savings for the laboratories yielding savings of $111,160US (£70,000) per annum for a Danish county with a population of 340,000.

Cost-effectiveness evidence is available from a Dutch based randomised trial that investigated the effect of POC CRP testing in a primary care setting combined with training in communication skills on antibiotic use in lower respiratory tract infections [17;19]. Cost –effectiveness is reported as a cost per % decrease in antibiotic prescribing compared with usual care. The total mean cost per patient of GP use of CRP testing was estimated to be Euro 37.58 compared with Euro 35.96 for usual care, when combined with the 0.28 decrease in antibiotic use, the ICER of POC CRP testing amounts to Euro 5.75 [22].

Research Questions:

- What are the effects on antibiotic prescription when physicians use the POC CRP test as a supplement to clinical diagnosis of LRTI?
- What are the consequences of the false negatives on POC CRP testing, i.e. re-consultation, hospital admission, complications etc?
- How does POC CRP compare with other strategies for reducing or targeting antibiotic prescriptions in patients with suspected LRTI, e.g. GP education, patient/parental interventions, delayed antibiotics?
- Are there subgroups of patients in whom POC CRP would be more helpful than others, for example those with frequent attendances for suspected LRTI and frequent antibiotic use; patients with high risk of infections e.g. patients with COPD or compromised airways; children, who often attend?
- What is the utility of combining biological markers such as CRP with other diagnostic technologies to differentiate between bacterial and viral LRTI?

Suggested next step:

Systematic reviews, meta-analyses, and prospective studies have shown the limited utility of the POC CRP in differentiating between bacterial and viral infection in LRTI. However, positive results from combining these tests with GP and patient education suggest that there may be some utility in decreasing the number of unnecessary antibiotic prescriptions. Further studies comparing rates of antibiotic prescription when using a POC CRP test are needed to evaluate the applications of the technology.

Expected outcomes:

While prospective studies have indicated the limited utility of POC CRP testing in differentiating aetiology due to low sensitivity and specificity, further investigation of the effects of CRP testing in the clinical setting may provide support for the implementation of such a test. Antibiotic prescription is guided by diagnostic evidence as well as patient and physician sentiment, and CRP testing may prove to be influential in removing some diagnostic uncertainty.

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