NICE advice

Alere Afinion CRP for C-reactive protein testing in primary care

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is the Alere Afinion C-reactive protein (CRP) point-of-care test. It is used to quantify CRP in blood, serum or plasma using the Afinion AS100 analyser.
- The **innovative aspects** are that the Alere Afinion CRP test has the potential to provide rapid results by point-of-care testing of a 1.5 microlitre blood sample, with a reading time of 4 minutes.
- The intended **place in therapy** would be in primary care, where it would be used by GPs or nurse practitioners to help guide appropriate prescribing of antibiotics to people with lower respiratory tract infection.

- The **key points from the evidence** summarised in this briefing are from 6 studies (n=1,615). One randomised controlled trial reported that Alere Afinion CRP testing resulted in a lower antibiotic prescribing rate and fewer referrals for chest X-ray compared with non-CRP-guided treatment. A diagnostic case-control study reported sensitivity as 55% and 20% for low (20 mg/litre) and high (100 mg/litre) thresholds respectively for the detection of radiographic pneumonia, and specificity as 73% and 99%. CRP testing improved simulated clinical management of pneumonia compared with a basic model without CRP testing. One study in a paediatric population, incorporating a randomised controlled trial component, reported an increase in antibiotic prescribing rate during 10-day follow-up.
- **Key uncertainties** around the evidence are that neither of the included randomised controlled trials provided diagnostic accuracy data on the system and clinical follow-up was limited. A diagnostic case-control study did provide diagnostic accuracy information, but had important methodological weaknesses in its design.
- The **cost** of the Afinion AS100 analyser is £1,200 and Alere Afinion CRP test cartridges are £3.50 per test (excluding VAT). These would represent an additional acquisition cost to standard care, along with costs associated with maintenance and quality assurance. Using this technology could contribute to fulfilling antibiotic stewardship programmes.
- NICE has also published a medtech innovation briefing on the QuikRead go for CRP testing in primary care.

The technology

CRP is a non-specific marker released into the blood in response to various infectious and inflammatory triggers. Measuring CRP in people presenting with suspected lower respiratory tract infection helps to differentiate viral and self-limiting infections from more serious bacterial infections that need antibiotics. Several clinical studies have evaluated point-of-care CRP testing in adults to guide antibiotic prescribing in respiratory tract infections when used along with clinical assessment (Aabenhus et al. 2014).

The Alere Afinion CRP test consists of the Afinion AS100 analyser and the Alere Afinion CRP assay. It is an in vitro diagnostic test intended to determine the amount of CRP in human whole blood, serum or plasma. It is a solid phase immunochemical assay which uses a membrane coated with anti-human CRP antibodies, which react with the CRP in the sample. The analyser measures the colour intensity of the membrane, and this is

proportional to the amount of CRP in the sample.

The CRP test cartridge comes with an integrated blood sampling device which is used with a suitable lancet to collect a finger-prick blood sample. The sampling device is then inserted back into a test cartridge and placed into the analyser. The test cartridge contains all the reagents needed to measure CRP in a blood sample.

The CRP concentration is displayed on the analyser screen within 4 minutes. The measurement range is 5 to 200 mg/litre for whole blood, and 5 to 160 mg/litre for serum and plasma samples. The Afinion data connectivity converter is an optional component to the Alere Afinion CRP test. It allows for results from the Afinion AS100 analyser to be transferred to laboratory and hospital information systems.

Full information of the Alere Afinion CRP test procedure, quality control and accuracy and precision data can be found in the manufacturer's instructions for use.

The manufacturer also supplies assays for glycated haemoglobin (HbA1c), lipid panel and albumin creatinine ratio (ACR) that can be run on the Afinion AS100 analyser. However, these are beyond the scope of this briefing.

The innovation

Point-of-care CRP tests have the potential to change current practice by informing the clinical decision to prescribe antibiotics for people with symptoms of respiratory tract infections during a primary care consultation. Tests that improve clinical decision-making in antibiotic prescribing may support antimicrobial stewardship.

Testing for CRP is conventionally done by collecting a venous blood sample which is then sent for laboratory analysis, with the results being available 1 to 2 days later. Because of this delay, CRP testing is not typically used to assess acute infections in primary care, and is more commonly used when investigating chronic conditions.

Current NHS pathway

The decision to prescribe antibiotics for a suspected respiratory infection in primary care is generally made by a GP or nurse practitioner, and is based on medical history, clinical examination and assessment of risk.

Antibiotics can be prescribed at the time of the patient's first clinical examination (immediate), or prescribing could be postponed until a later time if symptoms have not resolved (delayed).

NICE's guideline on the diagnosis and management of pneumonia in adults recommends that point-of-care CRP testing should be considered for people with symptoms of lower respiratory tract infection in primary care if a diagnosis is unclear after clinical assessment, and that antibiotics should be prescribed based on the result. Immediate antibiotic treatment should be offered if the CRP level is more than 100 mg/litre and a delayed prescription should be considered at levels between 20 and 100 mg/litre. Antibiotics are not recommended for CRP levels less than 20 mg/litre.

NICE's quality standard on infection prevention and control states that in order to help prevent the development of antibiotic resistance in bacteria, it is important to prescribe antibiotics according to the principles of antimicrobial stewardship. These include prescribing antibiotics only when needed (and not for self-limiting mild infections such as colds and most coughs, sinusitis, earache and sore throats) and reviewing the continued need for them.

NICE is aware of the following CE-marked devices that appear to fulfil a similar function to the Alere Afinion system:

- AQT90 Flex (Radiometer Medical ApS)
- iChroma (Boditech Med)
- NycoCard Reader II (Alere)
- QuikRead go (Orion Diagnostica)
- Smart analyser (Eurolyser Diagnostica).

NICE has also published a medtech innovation briefing on the QuikRead go system for CRP testing in primary care.

Population, setting and intended user

The Alere Afinion CRP test would be done at the point of care in primary care for people with suspected bacterial lower respiratory tract infection. It would be done by primary care

clinicians during a consultation. The Alere Afinion CRP test would only be used in conjunction with a clinical examination and clinical judgement to help inform the decision to prescribe antibiotics.

The Medicines and Healthcare Products Regulatory Agency (MHRA) guideline on management and use of IVD point-of-care test devices provides advice and guidance for point-of-care testing services in primary and secondary care. This guidance addresses important issues including arrangements for training, management, quality assurance and quality control, assessment by an external accreditation body, and consideration of available evidence for the performance of the test.

Costs

Device costs

Table 1: Current costs of Alere Afinion CRP test components

Description	Cost (£, excluding VAT)	Additional information
Afinion AS100 analyser	1,200	Reusable
Afinion CRP test cartridges	3.50	Per test, available in packs of 15
Afinion CRP quality controls	36	Ready-to-use controls, includes 2x0.5 millilitre level 1 controls (20 mg/litre) and 2x0.5 millilitre level 2 controls (60 mg/litre)
Extended warranty	100	Per year (from year 2); covers technical support and machine replacement (if faulty)

The Afinion AS100 analyser requires no calibration and the only maintenance needed is cleaning of the cartridge chamber using a swab every month. A USB stick upgrade process provides the Afinion AS100 analyser with software updates.

The manufacturer provides both online learning videos and on-site training at no extra cost. On-site training is delivered by a member of a specialist support team and includes

both practical and competence-based training sessions.

Costs of standard care

Standard care for people presenting to primary care with symptoms of a lower respiratory tract infection would be a consultation with a primary care clinician without the use of a point-of-care test to aid the diagnosis and the clinical decision to prescribe antibiotics. The unit cost of a GP consultation, excluding antibiotic prescription, ranges from £33 to £65, depending on duration (Personal Social Services Research Unit 2015). The average cost of a course of amoxicillin is approximately £1.49; a course of erythromycin costs approximately £3.05.

The Alere Afinion CRP test would be an adjunctive test to a primary care consultation, and so represents additional acquisition, consumable and staff time costs.

Resource consequences

The Alere Afinion CRP test will incur both capital and consumable costs, and there will be costs associated with maintenance and quality assurance. However, it may reduce costs by avoiding unnecessary antibiotic prescribing. Antimicrobial stewardship is an important issue in healthcare and a number of guidelines have been published in relation to this (NICE 2015, Public Health England 2015, Royal College of General Practitioners and Beech, NHS England 2015).

The NICE guideline on pneumonia in adults: diagnosis and management included a cost-utility analysis of generic CRP point-of-care testing. The use of CRP point-of-care testing was associated with an incremental cost of £18.92 compared with standard care, and an incremental quality-adjusted life year gain of 0.0012. The use of a CRP point-of-care test was judged to be cost effective, at an incremental cost-effectiveness ratio of £15,763.

Regulatory information

The Alere Afinion CRP test was CE-marked as an in vitro diagnostic medical device in May 2005.

A search of the Medicines and Healthcare Products Regulatory Agency website revealed 1 manufacturer field safety notice (July 2016) for this technology. Two specific lots have

been identified that give an increased frequency of error codes when stored at room temperature. There are no indications that other lots are affected. The affected kits will be replaced by Alere and the replacement kits must be stored refrigerated between 2°C and 8°C only.

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to: promote race and disability equality and equality of opportunity between men and women, eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

No equality issues have been identified for the use of the Alere Afinion CRP test in primary care.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the published process and methods statement. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. The literature search strategy, evidence selection methods and detailed data extraction tables are available on request by contacting mibs@nice.org.uk.

Published evidence

Six studies are summarised in this briefing. These include a randomised controlled trial (Andreeva and Melbye 2014), a retrospective diagnostic nested case-control study (Minnaard et al. 2015) 2 analytical performance studies (Brouwer and van Pelt, 2015; Minnaard et al. 2013), a mixed-methods study (Van den Bruel et al. 2016) and a prospective observational study (Minnaard et al. 2016).

The randomised controlled trial by Andreeva and Melbye (2014) used an open-cluster

design to evaluate the effect of CRP testing on the prescribing of antibiotics, referral for radiography and recovery outcome of patients presenting to general practice with acute cough and respiratory tract infections.

The mixed-methods study by Van den Bruel et al. (2016) comprised an observational cohort of 297 children presenting with an acute illness. A nested randomised controlled trial was done (n=54) which compared CRP testing with no testing. This study included an embedded qualitative interview study to explore the acceptability of CRP testing.

The nested case-control study by Minnaard et al. (2015) aimed to determine the diagnostic accuracy of 5 point-of-care CRP tests, including the Alere Afinion CRP test, and whether they added diagnostic value in predicting radiographic-diagnosed pneumonia in adults presenting with acute cough in primary care.

The prospective observational study by Minnaard et al. (2016) included a total of 939 patients presenting to primary care with acute cough.

Two studies assessed the analytical performance of the Alere Afinion CRP test (Brouwer and van Pelt, 2015, Minnaard et al. 2013).

Table 2 summarises the clinical evidence as well as its strengths and limitations.

Table 2: Summary of the selected studies

Study size, design and location	Intervention and comparator(s)	Outcomes	Strengths and limitations

Andreeva and Melbye 2014 n=179. Cluster randomised controlled trial. Multicentre (18 general practices). Russia.	CRP-guided therapy using the Alere Afinion CRP test (n=101), compared with non-CRP guided therapy (n=78).	Antibiotic prescribing rate and referrals for chest X-ray were significantly lower in the intervention group than in the control group. A similar recovery rate was observed in both groups.	Cluster design reduces risk of contamination. There were some significant differences between groups at baseline, suggesting the presence of confounding factors (that was not controlled for). The study was adequately powered to detect a 20% reduction in antibiotic prescribing. The trial was not blinded, increasing the risk of performance bias.

Van den Bruel et al. 2016 n=297 children. Mixed methods study: observational cohort with a nested randomised controlled trial (n=54) and embedded qualitative study. Two out-of-hours general practices. UK.	Alere Afinion CRP test (not explicitly stated within the study, but confirmed by manufacturer; n=26) compared with no CRP test (n=28).	No statistically significant difference was reported in any outcome during the index consultation between those tested or not tested with the CRP test. In the 10-day follow-up period, significantly more children randomised to CRP testing had antibiotic prescriptions.	Open-label trial, but assessors were blinded to the group allocation. No power calculations were done to determine sample size. Relatively low number of children randomised. No information on diagnostic accuracy was reported. Nine patients were lost to follow-up at 10 days for both groups.

Minnaard et al. 2015 n=200. Retrospective diagnostic case-control study. Multinational (16 primary care research networks across 12 European countries). Belgium, Finland, Germany, Hungary, Italy, Netherlands, Norway, Poland, Spain, Slovakia, Sweden, UK.	5 point-of-care devices including the Alere Afinion CRP test, and a laboratory analyser (Vitros 5.1 FS, Ortho Diagnostics; Dimension Vista Systems, Siemens). Diagnostic accuracy outcomes were determined from 200 patient blood samples (100 with pneumonia, 100 without pneumonia). A clinical algorithm was used to determine the incremental predictive power of each CRP test to predict pneumonia.	The sensitivity and specificity of Alere Afinion CRP in predicting pneumonia was consistent with other point-of-care tests and a laboratory reference test. In all cases the discriminatory power of the tests to predict pneumonia were reduced when a higher threshold of CRP (>100 mg/litre) was used. Sensitivity was 55% and 20% for low (20 mg/litre) and high (100 mg/litre) thresholds respectively for the detection of radiographic pneumonia, and specificity as 73% and 99%.	Retrospective case-control design subject to inherent bias (likely to overestimate effect). Radiographs were used as the reference standard. Samples were analysed retrospectively at a central laboratory. A diagnostic model was used to evaluate the incremental predictive power of CRP when added to symptoms and signs. This may not completely represent clinical judgement in real life.

Minnaard et al. 2016 n=939. Prospective observational study. Multicentre, 9 general practices. Netherlands.	Comparison of GPs' 'pre-test decision' to prescribe antibiotics (following routine history-taking and physical examination) with their 'post-test decision' after reviewing the CRP test result using Alere Afinion CRP.	In 41% of tested patients, the indication for testing was in accordance with Dutch guidelines. Point-of-care CRP test results prompted changes in antibiotic prescribing decisions in 27% of all CRP-tested patients. There was no significant reduction in net antibiotic prescribing decisions before and after CRP testing.	No comparator group was included and no diagnostic information was reported. Decision to perform CRP test was according to Dutch guidelines, which may not be generalisable to current UK practice. Baseline antibiotic prescribing rate was low in comparison to international data from other studies and may not be representative for the UK population. Case registration forms were not completed for patients who did not have a CRP test.

Brouwer and van Pelt, 2015 Analytical performance study. Netherlands.	8 point-of-care devices including Alere Afinion CRP, compared with a comparative laboratory method (Synchron CRP). All blood samples were from GPs' patients, aged over 18 years, with CRP concentrations ranging from 5 to 200 mg/litre, determined with the Synchron analyser.	The linear regression equation of the Alere Afinion CRP test revealed an underestimation of CRP values compared with the laboratory method. However, the correlation and coefficient of variance of the Alere Afinion CRP test met the set acceptability criteria. The correlation of the CRP tests to the reference standard varied considerably. The Alere Afinion CRP test was considered to be one of the preferred analysers for point of care.	Patient blood samples were used with CRP values determined from an appropriate reference standard. Patient characteristics and diagnosis were not reported.

Minnaard et al. 2013 Analytical performance study. The Netherlands.	5 point-of-care devices including Alere Afinion CRP compared with a laboratory method (Olympus AU2700). Residual stored material from routinely done laboratory blood tests was pooled to obtain lithium heparin plasma pools with CRP concentrations of approximately 10, 15, 20, 25, 50, 90, 100 and 110 mg/litre.	The analytical performance and agreement of the CRP tests to the laboratory method varied considerably, but was considered adequate. For high CRP values (>100mg/litre), agreement with the laboratory standard systematically decreased for all 5 point-of-care tests.	Lithium heparin plasma samples were used instead of blood obtained by finger-prick.
Abbreviation: CRP, C-reactive protein.			

Strengths and limitations of the evidence

Two of the studies were randomised controlled trials that provided direct comparative data on the use of point-of-care CRP testing with the Alere Afinion CRP test compared with standard practice (Andreeva and Melbye, 2014 and Van den Bruel et al. 2016). However, neither of these provided diagnostic accuracy data on the system and clinical follow-up was limited. Furthermore, the study by Van den Bruel et al. (2016) only included children with acute illness. There are currently no UK guidelines that recommend CRP testing in this population.

A diagnostic case-control study did provide diagnostic accuracy information, but had important methodological weaknesses in its design (Minnaard et al. 2015), as outlined in table 2. The observational study by Minnaard et al. (2016) reported the potential effect of the Alere Afinion CRP test on prescribing practice, but lacked a comparator group.

The diagnostic case-control study (Minnaard et al. 2015) and analytical performance study (Brouwer and van Pelt, 2015) also did measurements in a laboratory setting, and may not be representative of the primary care setting for which the test is intended.

Recent and ongoing studies

There are 2 large clinical trials currently investigating the Alere Afinion CRP test:

- ERNIE2 – Investigating point-of-care CRP in children in primary care and the emergency department (study protocols published by Verbakel et al. 2014 and Lemiengre et al. 2014).
- PACE – Investigating use of a CRP point-of-care test in patients with chronic obstructive pulmonary disease in primary care to help target antibiotic prescribing to patients who are most likely to benefit.

The manufacturer also highlighted 2 recent pilot studies which are due for publication:

- Cross et al. (2016) – Responsible antibiotic prescribing in primary care: implementing point-of-care CRP testing in the management of acute lower respiratory tract infection.
- Evaluation of C-reactive protein in primary care settings to support reduction in antibiotic prescribing for self-limiting respiratory infections by the Scottish Antimicrobial Prescribing Group – This has evaluated the feasibility of using CRP testing in primary care and unscheduled care settings (such as out-of-hours service).

Specialist commentator comments

The specialist commentators reflected that the Alere Afinion CRP test may produce cost savings through fewer follow-up appointments in primary care, less unnecessary A&E attendance, and by improving sensitivity in diagnosing pneumonia (thus preventing costly inpatient admissions). By using point-of-care CRP testing, clinicians are better equipped to prescribe antibiotics only when needed.

Several commentators noted that there are a range of point-of-care CRP tests currently available. Two commentators noted that there was a body of evidence on point-of-care CRP testing independent of the device used. One commentator noted that there is very

little published data on the accuracy or precision of the Alere Afinion CRP test. They noted that the outcomes from the available studies did not give clear conclusions on these issues.

One commentator described a range of factors that may influence results and should be accounted for in any point-of-care test. For example, it is unclear whether testing whole blood, serum and plasma could give different results. The commentator also mentioned the hook effect, where beyond a critical concentration of CRP (the hook point), the signal level decreases as the CRP concentration increases. The commentator felt that there should be more technical awareness around these tests in users.

Commentators pointed out that the Afinion AS100 analyser can also be used for point-of-care testing of glycated haemoglobin, lipid profile and ACR for other national programmes. This could potentially reduce the costs associated with the Afinion AS100.

Specialist commentators

Comments on this technology were invited from clinical experts working in the field. The comments received are individual opinions and do not represent NICE's view.

The following clinicians contributed to this briefing:

- Ann Marie Carroll, Pathology POCT Manager, Nottingham University Hospitals Trust.
- Professor Jonathan Cooke, Visiting Professor in the Infectious Diseases and Immunity Section, University of Manchester and Imperial College London (has received consultancy, educational and research grants from Alere).
- Liz Cross, Advanced Nurse Practitioner, Attenborough Surgery (Alere paid for her project at a workshop in Parliament in May 2016).
- Dr Tha Han, Consultant in Public Health Medicine, Enfield Council (previously worked for an organisation that purchased the Alere Afinion for NHS Healthcheck).
- Michael Moore, Professor of Primary Care Research, University of Southampton (co-author on several publications using CRP for management of lower respiratory tract infection in primary care and was on the NICE guidelines development group for the pneumonia guideline).

Development of this briefing

This briefing was developed for NICE by Newcastle and York external assessment centre. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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