

evidence | *note*

In response to an enquiry from The Scottish Antimicrobial Prescribing Group (SAPG) and The Scottish Health Protection Network Public Health Microbiology Group

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What is the clinical and cost-effectiveness of C-reactive protein point-of-care testing to guide antibiotic prescribing in patients presenting to primary care with symptoms of lower respiratory tract infection?

Key points

- Evidence from randomised controlled trials indicates that, for adults with symptoms of lower respiratory tract infection (LRTI) presenting in primary care, C-reactive protein (CRP) point-of-care testing (POCT) can reduce antibiotic use where there is clinical uncertainty around the benefit of prescribing. In trials, this reduction is attained without negative impact on rates of recovery or re-consultation.
- There is uncertainty around the extent of the reduction in antibiotic use and the potential for increased rate of hospitalisation.
- CRP POCT has been shown to be cost-effective in four studies using different methodologies.
- The impact of introducing CRP POCT, on both NHS budgets and clinical practice in primary care, remains unclear.

What is an evidence note?

Evidence notes are rapid reviews of published secondary clinical and cost-effectiveness evidence on health technologies under consideration by decision makers within NHSScotland. They are intended to provide information quickly to support time-sensitive decisions. Information is available to the topic referrer within a 6-month period and the process of peer review and final publication of the associated advice is usually complete within 6–12 months. Evidence notes are not comprehensive systematic reviews. They are based on the best evidence that Healthcare Improvement Scotland could identify and retrieve within the time available. The evidence notes are subject to peer review. Evidence notes do not make recommendations for NHSScotland, however the Scottish Health Technologies Group (SHTG) produces an Advice Statement to accompany all evidence reviews.

Literature search

A systematic search of the secondary and primary literature was carried out between 20–24 October 2017 to identify systematic reviews, health technology assessments and other evidence based reports. The databases that were used were Medline, Medline in process, Embase, Cinahl and Web of Science. Results were limited to English language.

Key websites were also searched for guidelines, policy documents, clinical summaries, economic studies and ongoing trials.

Concepts used in all searches included: respiratory tract infections, pneumonia, point-of-care systems, C-reactive protein, primary Care, community. A full list of resources searched and terms used are available on request.

Introduction

A lower respiratory tract infection (LRTI) may be described as an acute illness (present for 21 days or less), usually with cough as the main symptom, and with at least one other lower respiratory tract symptom (fever, sputum production, breathlessness, wheeze or chest discomfort or pain) and no alternative explanation (such as sinusitis or asthma). Pneumonia, acute bronchitis and exacerbation of chronic obstructive airways disease are included within this definition¹.

Pneumonia is almost always of bacterial origin and antibiotics would be indicated. For most other acute respiratory conditions antibiotics should usually be avoided. Around 5–12% of patients attending their general practitioner (GP) with symptoms of a LRTI will have community-acquired pneumonia (CAP) diagnosed¹.

C-reactive protein (CRP) is released by the liver in response to tissue injury, including that due to bacterial infection. Measurement of elevation of this biomarker may have value in guiding prescription decisions where there is uncertainty around the presence of serious bacterial infection. There may be the potential to reduce inappropriate use of antibiotics².

Public Health England antibiotic guidance for primary care recommends that for LRTI³: *Consider CRP if antibiotic is being considered. No antibiotics if CRP<20mg/L and symptoms for >24 hours; delayed antibiotics if CRP 20–100mg/L; immediate antibiotics if CRP>100mg/L.*

Current NICE guidelines on pneumonia recommend that for people presenting with symptoms of LRTI in primary care, a CRP point-of-care test (POCT) should be considered if, after clinical assessment, a diagnosis of pneumonia has not been made and it is not clear whether antibiotics should be prescribed¹.

The potential to use CRP POCT as an intervention to support antimicrobial stewardship in Scotland has been evaluated in a small pilot study undertaken during Winter 2015/16⁴. Ten GP practices participated and 246 adult patients received the test. The majority of patients were aged 16–64 and in most cases (72%) the test recorded CRP<20mg/L supporting a 'no antibiotic' management strategy. In 6% of cases no result was recorded due to problems with error messages displayed by the instrument. Prescribers indicated that access to a CRP POCT was beneficial to clinical decision-making in consultations with adult patients presenting with symptoms of LRTI. The main practical issue highlighted was the additional time required in the consultation to conduct and explain the test. This point was also raised in a qualitative study which examined the barriers to adoption of CRP point-of care testing in primary care in the NHS⁵. A small implementation study conducted in one GP practice in NHS Wales was also identified⁶.

Health technology description

POCTs for CRP may be conducted on small volume whole blood samples, typically obtained through finger pricks. Samples are combined with appropriate reagents using a test kit. A desktop instrument is then used to measure the results of the assay, providing a CRP reading.

NICE has developed Medtech Innovation Briefings (MIBs) on two specific CRP POCT technologies^{7, 8}, and identified a number of other devices which fulfil a similar function. Characteristics of the two technologies are outlined in Table 1:

Table 1: NICE Medtech Innovation Briefings^{7, 8}

Device (manufacturer)	Sample volume/read time	Cost of desktop instrument/cost of CRP test kit	CRP measurement range
QuikRead go (Orion Diagnostica)	20 microlitre blood sample 2 minutes	£1,050 £4.30 per test (excluding VAT)	5–200mg/L
Afinion AS 100 analyser (Alere)	1.5 microlitre blood sample 4 minutes	£1,200 £3.50 per test (excluding VAT)	5–200 mg/L
CE marked devices with similar function: AQT90 Flex (Radiometer Medical ApS), iChroma (Boditech Med), Nycocard Reader II (Alere), Smart analyser/Eurolyser CRP (Eurolyser Diagnostica).			

Another point-of-care technology, spinit[®] CRP (biosurfit) was used in a UK case control study⁹.

A study evaluating use of a disposable CRP test (FebriDx, RPS Diagnostics) - not requiring a desktop analyser - has been identified by another NICE Medtech Innovation Briefing¹⁰. The setting was secondary rather than primary care.

Epidemiology

Experiencing symptoms of LRTI is a common reason for consulting with a GP and antibiotics are frequently prescribed. In a 2010 audit of prescribing practice in UK and Europe, 55.3% of 6,771 patients with respiratory tract infection (approximately 80% of whom had LRTI) were prescribed antibiotics¹¹.

The Scottish Antimicrobial Prescribing Group (SAPG) has focused on reducing unnecessary antibiotic prescribing in primary care particularly for self-limiting respiratory infections. There has been steady progress with three successive reductions - amounting to a 9.5% fall in overall primary care (excluding dental) antibiotic prescribing rates - between 2012 and 2015, from 2.21 to 2.00 items per 1,000 population per day¹².

A prospective observational study conducted in primary care in 1997/98 in England reported that the incidence of community acquired LRTI leading to GP attendance was 44 per 1,000 adult population per year. There was a seasonal pattern with 82% of cases being recorded between October and March¹³. Extrapolation of these figures suggests that in Scotland there are likely to be in the region of 200,000

consultations for LRTI in adults each year. A UK longitudinal study focused on older adults, aged ≥ 65 year between 1997–2011. It provided evidence that the incidence of LRTI (analysed separately from community acquired pneumonia) increases with age and deprivation¹⁴.

Clinical effectiveness

Several relevant systematic reviews were identified.^{2, 15-18} A Cochrane review with a literature search up to January 2014 was selected for this Evidence Note as it had the most up to date meta-analysis of randomised controlled trials (RCTs) focusing specifically on the primary care context². The review sought studies on point-of-care biomarkers of acute respiratory infections including CRP, procalcitonin and white blood cell count. The only biomarker for which eligible studies were identified was CRP. No studies compared different biomarkers.

The meta-analysis incorporated six trials, parameters of which are outlined in table 2. Owing to the nature of the intervention, none of the studies were blinded. Three studies were cluster randomised trials. These have a higher risk of selection bias than trials with randomisation of individuals but may be indicated where aspects of intervention (for example enhanced communication skills) cannot be randomised at individual consultation level. The cluster design may well reflect implementation in practice in that the test is either available or not in a given setting. Within the meta-analysis, events and samples sizes from the cluster trials were adjusted to account for study design effects.

Table 2: Characteristics of studies included in Aabenhus (2014)²

	Setting and patients	Unit of randomisation Number of patients	Primary outcome	CRP test algorithm cut offs
Andreeva 2014	Russia Adults >18 years LRTI/acute cough	Cluster (8) n=179	Antibiotic use within 2 weeks of index consultation	<20mg/L >50mg/L
Little 2013	Multinational (included England and Wales) Adults >18 LRTI and upper respiratory tract infection (URTI) reported separately	Cluster (228) n= 4,264	Antibiotic prescribing at index consultation	≤20mg/L 21-50mg/L 51-99mg/L ≥100mg/L
Cals 2010	Netherlands Adults >18 Two patient groups: LRTI /rhinosinusitis	Individual n=258 (107 LRTI/151 rhinosinusitis)	Antibiotic use (delayed + immediate) at index consultation	<20mg/L >100mg/L
Cals 2009	Netherlands Adults >18 years Suspected LRTI	Cluster (20) n=431	Antibiotic prescribing at index consultation	<20mg/L >100mg/L

Diederichsen 2000	Denmark All ages with respiratory tract infection	Individual n=812 adults n=673 children n=139	Antibiotic use at index consultation	Guidance: CRP<50mg/L seldom the result of bacterial infection
Melbye 1995	Norway Adults>18 years Symptoms of LRTI	Individual n=239	Antibiotic use at index consultation	Varied according to duration of illness
Trial identified as ongoing in review (now published) ¹⁹				
Do 2016	Vietnam 1–65 years Symptoms of non-severe RTI	Individual n=1,008 (15–65 years) n=1,028 (<15 years)	Antibiotic use within 2 weeks of index consultation	(1–5yr) ≤10mg/L ≥50mg/L (6–65yr) ≤20mg/L ≥100mg/L

In the random effects meta-analysis of all the included trials, the rate of antibiotic prescribing at the index consultation was lower in the arm where CRP testing was available for use (in situations of uncertainty around antibiotic prescribing), relative risk (RR) 0.78 (95% confidence interval (CI) 0.66 to 0.92), $p=0.003$. The number needed to test (NNT) to save one antibiotic prescription was nine (see table 3). There was a high level of heterogeneity $I^2=68\%$. This heterogeneity was not present when trials were analysed by study design and the review authors suggest this may indicate that it is not valid to pool the results.

Table 3: Effect of CRP test on antibiotic prescribing rates at index consultation²

Table heading	Full data set	Individually RCTs (N=3)	Cluster RCTs (N=3)
Antibiotic prescribed at index consultation	RR= 0.78 (95% CI 0.66 to 0.92) $p=0.003$ $I^2=68\%$ NNT=9	RR=0.90 (95% CI 0.80 to 1.02) $p= 0.09$ $I^2=5\%$ NNT=20	RR=0.68 (95% CI 0.61 to 0.75) $P<0.00001$ $I^2=0.0\%$ NNT=6

There was no evidence of a difference between groups in rates of clinical recovery at day seven (three trials) RR= 1.03 (95%CI 0.93 to 1.14) $p=0.53$, or in the number of patients with re-consultations at 28 days of follow up (four trials) RR=1.08 (95%CI 0.93 to 1.27) $p=0.31$.

No deaths or complications were reported in any of the studies.

The systematic review authors highlighted that two of the included trials (Cals *et al*, 2009 and Little *et al*, 2013) compared communication skills training to CRP POCT and found the interventions to have similar potential to reduce antibiotic use, with an additive effect when combined.

An important safety concern was raised in the review. Although five of the six included studies reported no hospitalisation in the follow-up period, the largest trial identified a potential adverse effect. This four arm, cluster RCT compared usual care with CRP training, advanced communication skills training and with a combination of CRP training and advanced communication skills training¹¹. CRP testing and advanced communication skills training had similar effects on reducing antibiotic use. There was a higher rate of hospitalisation across the two CRP intervention groups when compared with the groups which did not include CRP (odds ratio (OR) 2.61, 95% CI 1.07 to 6.35, $p=0.034$). The number of events was low (22/2224

(1%) versus 8/2040 (0.40%) and the difference between groups was not statistically significant following adjusting for confounders. Full interpretation of this finding was limited due to lack of information on the number of hospital admissions in the CRP group related to patients not initially prescribed an antibiotic.

With regards to patient satisfaction, the systematic review pooled the results from two studies (Cal *et al* 2009 and Cal *et al* 2010). The authors reported that there was no statistically significant difference in patient satisfaction between groups who received CRP and those who received usual care (RR 0.79, 95% CI 0.57 to 1.08).

In subgroup analysis of two trials, the results were similar for URTI and LRTI for the outcome 'antibiotics prescribed at index consultation'.

Only one trial in the review included children (Diederichsen *et al* 2000; n=139). For children, there was no difference between the study groups in rates of antibiotic prescribing. The results of the overall meta-analysis should be considered to apply only to adults. Additionally, studies in the review excluded a range of patient groups including, variously, immunocompromised patients, those with recent hospitalisation(s) and patients with chronic inflammatory diseases.

A trial identified as ongoing by the Cochrane review was published in 2016 and examined the effect of CRP point-of-care testing in adults and children presenting with symptoms of non-severe respiratory tract infection (not specifically LRTI) in primary care in general practice in Vietnam¹⁹. This study reported an overall reduction in antibiotic use at 14 days in the CRP arm compared with usual care; OR 0.49 (95% CI 0.40 to 0.61), $p < 0.0001$. Time to resolution of symptoms was similar between study groups. Findings were similar for adults and children. The relevance of this study, from a resource-constrained setting, to Scottish primary care practice is questionable.

Safety

See clinical effectiveness section for information on identification of potential safety issue around rate of hospitalisation in one study.

The NICE MIB on the Alere Afinion CRP test⁷ identified information on a problem with particular lots of the CRP kits which resulted in increased frequency of error codes. This led to a revision to the storage instructions for the kits.

Cost effectiveness

Four cost-effectiveness studies were identified^{1, 21-23}. All were published within the last seven years and were applicable to European countries. The most recent two studies were UK-based^{1, 22}. The older two studies from the Netherlands²¹ and Norway and Sweden²³ respectively, involved prospective data collection of resource use and outcomes, whereas the UK-based studies both applied secondary analysis to existing data (including parameters from at least one of the earlier two prospective studies). The patient population in all cases was specifically those with LRTI except for the most recent study where the study population included patients with all respiratory tract infections (RTIs).

All four studies considered a 28-day time frame for either data collection purposes or as the length of one cycle²² of the model base case. All four studies had also compared at least one strategy whereby CRP point-of-care testing was performed by a primary care clinician; three of which considered a current practice standard of care comparator which did not involve CRP point-of-care testing. In the study by Oppong *et al* the study design was observational and compared results for patients who received CRP

testing with those who did not, on the basis of the primary care clinician's discretion. This was because point-of-care testing is already part of routine current practice in Norway and Sweden²³.

Oppong *et al* used regression techniques to estimate changes in outcomes depending on whether or not the patient had received a CRP point-of-care test²³. After adjusting for patient characteristics, CRP was shown to lead to significantly more medical investigations ($p < 0.001$) but fewer hospital admissions ($p = 0.03$). There was no significant increase in either costs or QALYs and the strategy was deemed to be cost-effective at a willingness-to-pay threshold of €30,000 (Incremental Cost-Effectiveness Ratio (ICER) €9,391 at 2007 prices). The 10% reduction in antibiotic use associated with CRP point-of-care testing was not considered statistically significant but may be of clinical relevance.

The Cals *et al* study was a within-trial economic evaluation for a cluster RCT whereby point-of-care CRP testing performed by a GP was compared with: CRP testing plus GP communication skills training, GP communication skills training alone, and usual care (in the Netherlands) which did not involve CRP testing²¹. ICERs were calculated as the cost per percentage point reduction in antibiotic prescribing, as no utility data were collected. Results showed communication skills training was the most cost-effective strategy, as it was both cheaper than usual care and it also reduced antibiotic prescribing, whereas providing CRP incurred higher costs than usual care. The ICER for adding a CRP point-of-care test to communications training was found to be €121.70 (price year not stated) per 1% reduction in antibiotic prescribing, which the study authors noted to be cost-effective.

NICE reviewed the studies by Oppong *et al* and Cals *et al* and excluded both studies from their Pneumonia Guideline due to a combination of limited applicability, methodological limitations and the availability of more applicable evidence¹. Instead, they estimated an ICER for the use of a CRP point-of-care test in primary care by applying routinely collected English and/or UK cost data to key items of resource use. They then used the QALY data from one of the two studies they excluded²³ generating an ICER of approximately £15,763 per QALY gained (price year 2011-12) – said to be below the commonly accepted threshold for cost-effectiveness.

The study by Hunter developed a decision tree model with additional Markov states for a hypothetical cohort of patients receiving either CRP testing (performed by either the GP or the practice nurse), GP-performed CRP testing with additional GP communications training, or current practice²². Over a 3-year time horizon, at the end of every 28-day cycle each patient could be either healthy or have an RTI. Results showed that both the practice nurse and GP point-of-care CRP testing strategies were less costly and more effective than current practice. The difference between practice nurse and GP-performed point-of-care CRP was minimal. Providing both CRP and GP communication skills training incurred further additional resources, but all CRP testing strategies reduced antibiotic prescribing. The study concluded that CRP point-of-care testing (without communication training for GPs) would be cost-effective.

Overall, the results indicate that a CRP point-of-care strategy is cost-effective. This conclusion was robust to the sensitivity analyses performed. The differences in methodologies used is either confirmation of the cost-effectiveness of the intervention regardless of the method of economic evaluation used, or symptomatic of the fact that there are so few relevant studies on this subject that they all rely on the same data from very few primary studies (particularly for utility data) and that the conclusions are robust to variations in the analytical techniques used. Although there was consistency in the resource use items being costed, the studies had not considered the potential budget impact of introducing CRP point-of-care testing into primary care. For this reason, and because studies could not show whether acute care resource use was appropriate (for example, attendance due to complications rather than anxiety), NICE recommended 'consideration' of these tests rather than a stronger recommendation to 'offer' them¹.

Conclusion

There is moderate quality evidence that addition of a CRP point-of-care test to clinical examination to guide antibiotic prescribing for adults in primary care who have symptoms of LRTI can reduce prescribing rates without adversely affecting recovery. There is uncertainty around the extent of the reduction and the likelihood of increased rates hospitalisation as a potential adverse consequence. The impact of the test will depend on the clinical and cultural context and the effectiveness of other antibiotic stewardship measures which are in place²⁴. The intervention has been shown to be cost effective in four studies which used a range of methodologies. No evidence was identified on the potential budget impact for NHSScotland.

Ongoing trials

One ongoing RCT was identified²⁰. This UK trial examines primary care use of a CRP POCT to help target antibiotic prescribing to patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD) who are most likely to benefit. Findings are likely to be published in 2018.

Identified research gaps

There is a need for RCTs investigating the effectiveness and cost-effectiveness of the test in children and older people.

A review outlined research gaps in detail including the need to develop methods to measure both appropriateness of antibiotic prescribing (including minimally important differences) and the effects of interventions on microbial resistance¹⁸.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

The process for producing evidence notes has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on www.healthcareimprovementscotland.org

About evidence notes

Evidence Notes are produced to inform a decision at a particular point in time and are therefore not routinely updated. They will however be considered for review if requested by stakeholders, based upon the availability of new published evidence which is likely to materially change the advice given. For further information about the evidence note process see:

www.healthcareimprovementscotland.org/our_work/clinical_cost_effectiveness/shtg/standard_operating_procedures.aspx

To propose a topic for an evidence note, email shtg.hcis@nhs.net

References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network www.knowledge.scot.nhs.uk, or by contacting your local library and information service.

A glossary of commonly used terms in Health Technology Assessment is available from htaglossary.net.

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