Primary care guidelines for the use of C-Reactive Protein – Point of Care Testing (CRP-POCT) in Respiratory Tract Infections

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SUMMARY

- CRP-POCT can help primary care clinicians decide on whether antibacterials will benefit adult patients in the following clinical scenarios: ARTI, including LRTI* & infective exacerbations of COPD.
- CRP-POCT should ONLY be used where clinical assessment is unclear and NOT as a replacement for clinical decision making.
- There is currently a lack of evidence to support use of CRP-POCT in Children with RTI.
- Training and support should be sought before implementing CRP-POCT.

* when pneumonia is not suspected

WHAT IS CRP?

C-reactive protein (CRP) is released by the liver as part of an inflammatory response to tissue injury, which may be due to bacterial infection. Patients with possible bacterial infection may be identified by elevated levels of CRP, which can be detected using a finger-prick Point Of Care Test (POCT).

WHO IS THIS GUIDANCE FOR?

All GP practices in Wales, GP cluster leads, Out of Hours GP service, Local Medical Committees, Pharmacy Leads, Community Pharmacy Contractors, Directors of Primary Care, Point of Care Testing Leads, Laboratory Clinical Leads, Health Board Antimicrobial Stewardship Groups.

WHAT CRP-POCT CAN DO FOR YOU

- Support decisions regarding antibiotic prescribing for specific clinical presentations in primary care.
    - CRP can be used alongside clinical assessment to target antibiotic prescribing in patients with Acute Respiratory Tract Infections (ARTI), including Lower Respiratory Tract Infections (LRTI) (when pneumonia is not suspected) & infective exacerbations of Chronic Obstructive Pulmonary Disease (COPD).
- Reduce unnecessary antibiotic prescribing.[1,2]
- Help with patient communication and manage patient expectations for an antibiotic.[3,4]
- May produce cost savings through fewer follow-up appointments & unnecessary A&E attendance.
- There is good evidence for use of CRP-POCT in adults for Respiratory Tract Infection (RTI) to improve targeting of antibiotics to those who need them without having a detrimental impact upon clinical outcome. However there is currently lack of evidence for its efficacy in children.[5]

- It is important that when CRP-POCT is used, it DOES NOT replace clinical decision making.
- Regular quality testing should be performed on the CRP-POCT instrument to ensure clinically acceptable results are maintained.
- CRP-POCT is likely to be most effectively used and maintained when roll out is done with local POCT Department / Laboratory support.

RATIONALE FOR USING C-REACTIVE PROTEIN POINT-OF-CARE-TESTING (CRP-POCT)

Antimicrobial resistance is a major healthcare problem affecting increasing numbers of patients in Wales. One way to reduce resistance is through improved prescribing (NICE quality standard on infection prevention and control QS61)[5]. Antimicrobials prescribed for respiratory infections account for around 60% of all primary care prescriptions, which in turn comprise 80% of the total antibiotic burden. The use of diagnostic tools (CRP-POCT) has been shown to improve/reduce antibiotic prescribing in certain clinical scenarios such as ARTI, including LRTI (when pneumonia is not suspected) and infective exacerbations of COPD.
Optimising prescribing and improved antimicrobial stewardship will contribute to a reduction in antimicrobial resistance in Wales, and is likely to have an important impact on *Clostridioides difficile* infection rates across Wales.

CLINICAL USE OF CRP-POCT

CRP-POCT CRITERIA

If, after clinical assessment, it is unclear if antibiotics are needed for someone with ARTI, consider a CRP POCT test to support clinical decision making:

Acute Respiratory Tract Infection (ARTI), incl. LRTI
(Suspected acute respiratory infection in over 16s: assessment at first presentation and initial management NICE guideline [NG237][6]):

>100 mg/L	Offer immediate antibiotics. An assessment of severity plus the need for hospitalisation should be undertaken.
20-100 mg/L	Consider a back-up antibiotic prescription
< 20 mg/L	Do not routinely offer antibiotics

Chronic Obstructive Pulmonary Disorder (COPD)
(*CRP levels as confirmed by the PACE*[7] study*):

>40 mg/L	Antibiotics are likely to be beneficial. Consider prescribing antibiotics unless the patient is assessed as being at lower risk of complications and unlikely to have a bacterial infection (no increased sputum purulence and no features suggesting severe exacerbation).
20-40 mg/L	Antibiotics may be beneficial, mainly if purulent sputum is present. You may decide to prescribe antibiotics after taking into account the patient's underlying health status and the features of the current exacerbation.
<20 mg/L	Antibiotics are unlikely to be beneficial and usually should not be prescribed.

** Point of care testing to target Antibiotics for Chronic obstructive pulmonary Exacerbations (PACE) study.*

CRP-POCT testing algorithms for clinicians for ARTI and COPD exacerbations are included in the appendix.

Advice on antimicrobial prescribing in patients with acute cough associated with an upper respiratory tract infection or acute bronchitis in adults, young people and children can be found in the in the Primary care antimicrobial guidelines – All Wales Medicines Strategy Group and the NICE document **Cough (acute):** antimicrobial prescribing NICE guideline [NG120][8]

Advice on antimicrobial prescribing for exacerbations in COPD patients can be found in the Primary care antimicrobial guidelines – All Wales Medicines Strategy Centre and the COPD (acute exacerbation) antimicrobial prescribing NICE guideline [NG114][9].

Guidelines on diagnosis and management of pneumonia in adults is available in NICE Clinical guideline [CG191] [10]

COMMUNICATING THE RESUTLS TO YOUR PATIENT

The majority of patients will have a low (< 20 mg/L) CRP level and can be reassured that the risk of serious infection, and the chance of having an infection that will benefit from antibiotic treatment, are minimal. Patients with high CRP values that are being managed in the community should be informed that their blood test indicates that their body is responding to something, and that this is likely to be a bacterial infection. They should be treated with antibiotics and given safety-netting information (Leaflets to discuss with patients: How to use these leaflets (rcgp.org.uk)), including what should prompt them to seek a further assessment. Patients with a CRP value in the intermediate range need to be assessed and a decision made about antibiotic treatment. It is important to inform the patient that although you have not identified any clear indicator of pneumonia, their blood test shows that their body is responding to something, and that this could be a bacterial infection. It is important to give them good safety-netting advice, and if you decide to give them a back-up prescription (see leaflets to discuss with patients weblink above) then it is important to give clear advice about what should prompt them to collect and use the prescription. This is not a replacement for safety-netting advice, as people with features of more severe illness should be re-

assessed rather than just starting to take antibiotics. It is important to ensure that the patient is supported in this and the use of leaflets such as the TARGET leaflets may help (see appendix).

Key public facing information (leaflets and posters) are available in Welsh and English from: (Leaflets to discuss with patients: How to use these leaflets (rcgp.org.uk)

CONTRAINDICATIONS

It is inadvisable to use CRP-POCT in patients with an active inflammatory condition that is likely to raise the CRP (such as rheumatoid arthritis).

CRP-POCT measurements may be unreliable in patients with a high risk of serious infection (e.g. immunosuppressed patients.

CLINICAL EFFECTIVENESS - EVIDENSE

Two Cochrane reviews (2014 & 2017)[11,12] of Randomised Controlled Trials (RCTs) investigating the efficacy of CRP-POCT in adult patients presenting with respiratory infections concluded that CRP-POCT in conjunction with clinical assessment can guide antibiotic treatment of ARTI, and in particular LRTI infections in primary care, and can reduce antibiotic use without affecting patient outcome. The degree of antibiotic reduction however, is uncertain.

Evidence from the Point of care testing to target Antibiotics for Chronic obstructive pulmonary Exacerbations (PACE) study concludes that CRP-POCT can lead to substantial reduction in antibiotic use for acute exacerbations in COPD patients in the trial setting, with no measurable detrimental effect to patients[7].

Currently, CRP-POCT is widely used throughout Europe to support clinical decision making by clinicians for RTI patients. A recent Welsh small study saw antibiotic prescribing fall in relation to CRP-POCT use in patients with RTI.[13]

COST EFFECTIVENESS

A number of European & UK studies[7,14,15,16], two including studies in Wales[7,16], all conclude that CRP-POCT in RTI, and in particular LRTI, as well as COPD, may be cost effective in terms of QALYs gained and/or reduction in antibiotics prescribed/consumed. Four studies were evaluated for cost-effectiveness of CRP POCT as part of the recent NICE guideline [NG237] . The results suggested that CRP POCT is potentially cost-effective; although the studies were generally limited to capturing only short-term costs and consequences. One study demonstrated the impact of including the cost of antibiotic resistance in the analysis, indicating POCT CRP testing in Primary Care in Wales has potential to be both more effective and cost-saving[16].

SHOULD YOU INVEST IN CRP POCT TECHNOLOGY?

As the main role of CRP POCT is guiding antibiotic prescribing decisions, it is useful to have a clear picture of your antibiotic prescribing. Prescribing data from across Wales show considerable variation in the amount, class and duration of antibiotics prescribed. Primary Care prescribers based in general practice can access their prescribing data (CASPA) from the Shared Services Partnership Primary Care Services online application: Primary Care Services; together with their antimicrobial prescribing and resistance data, at a health board, cluster and/or practice level, from the Public Health Wales Antibiotic Data Library: Antibiotic Data Library for Wales (cymru.nhs.uk).

Practices with high levels of prescribing can benefit most from implementing CRP-POCT whilst a lower impact is seen in practices with low prescribing levels.[17]

> The decision to implement CRP-POCT in your practice/service must be based upon your overall antibiotic stewardship, the case mix of your population and the instances of uncertainty you face regarding treatment of bacterial infections within your daily practice.

COSTS ASSOCIATED WITH USING CRP POCT

Primary Care prescribers should seek advice and information on funding for CRP-POCT devices by contacting their local POCT department: Point of Care Testing webpages.

> A number of LumiraDx devices, QC and tests for CRP are available free of charge for a limited period (2024-2025). Please contact your local POCT Department for further information.

NICE Medtech innovation briefings, published in 2016, are available for the Afinion Alere and QuikRead go which provide a breakdown of costs for their intended use in primary care.

As well as initial device costs and consumables, time costs for staff should be estimated. Currently evidence suggests that time costs to clinical staff, following initial training, will be around 10 minutes per patient.

Costs including extraneous requirements have been published; however what is included is variable and is only correct at the time of publication.
In the North Wales cost evaluation study of CRP-POCT in ARTI/LRTI, total costs including the device, printer, scanner, connectivity, cartridges and consumable costs plus annual quality control, maintenance and laboratory support costs and healthcare assistant time [Band 4 for 5 minutes] costs arrive at **£9.58** per test (Holmes et al., 2018); (Price year 2016-17)[16]. Similarly in the evaluation of CRP-POCT in COPD patients (PACE study) the total cost per test was £11.31; includes clinician time, Quality Control, wipes, prick needle, cartridges, gloves and repeat testing but not External Quality Assurance (EQA) costs and laboratory POCT support costs.[7]

Overall the costs per test is estimated at between £10-£12 including necessary laboratory POCT support costs. Additional EQA costs (at £200 per year)

WHICH CRP POCT TECHNOLOGY TO USE?

Please contact your POCT department for advice on the suitability and performance of devices before purchase.

Newer CRP-POCT devices are now available which offer CRP alongside a viral marker. These devices offer an extended capability of distinguishing between bacterial and viral infection. NICE guidelines on the FebriDx machine can be found: NICE:mib224.

USING YOUR DEVICE

Devices should be used according to manufacturers' instructions.

QUALITY ASSURANCE

It is important that the quality of the CRP-POCT process is monitored regularly. The clinical governance, management and quality assurance requirements are covered in detail in the Welsh Government Policy on the Management of Point of Care Testing (POCT). What, When and How? [18]

As a minimum, Quality Assurance should include undertaking QC and EQA.

TRAINING

Please contact your local POCT department who will be able to advise as to the most appropriate training sources. Initial device training may be available free of charge for specific CRP-POCT devices from the manufacturers.

Further information on relevant training, including E-Learning modules for clinicians and information for patients is freely available via the RCGP TARGET program at: http://www.rcgp.org.uk/TARGETantibiotics.

MORE INFORMATION AND SUPPORT

- Further education and training modules are available via the HEIW training website.
- The Y Ty Dysgu AntiMicrobial Stewardship module can be viewed here.
- CRP testing in primary care; evidence summary document for a synopsis of the current evidence for clinical efficacy and cost effectiveness of CRP-POCT (Appendix B)

- An observational study from Sweden provides insight on the physician's view of CRP testing.[19]

FURTHER RESEARCH

The current guidance focuses on respiratory tract infections in largely adults. There is a need therefore for further RCTs investigating the clinical effectiveness and cost-effectiveness of the CRP point of care test in children.

This document will be reviewed at regular intervals (3 years) to include relevant evidence. Any changes to NICE guidelines in the use of CRP to better diagnose and treat other infections will be incorporated in future reviews.

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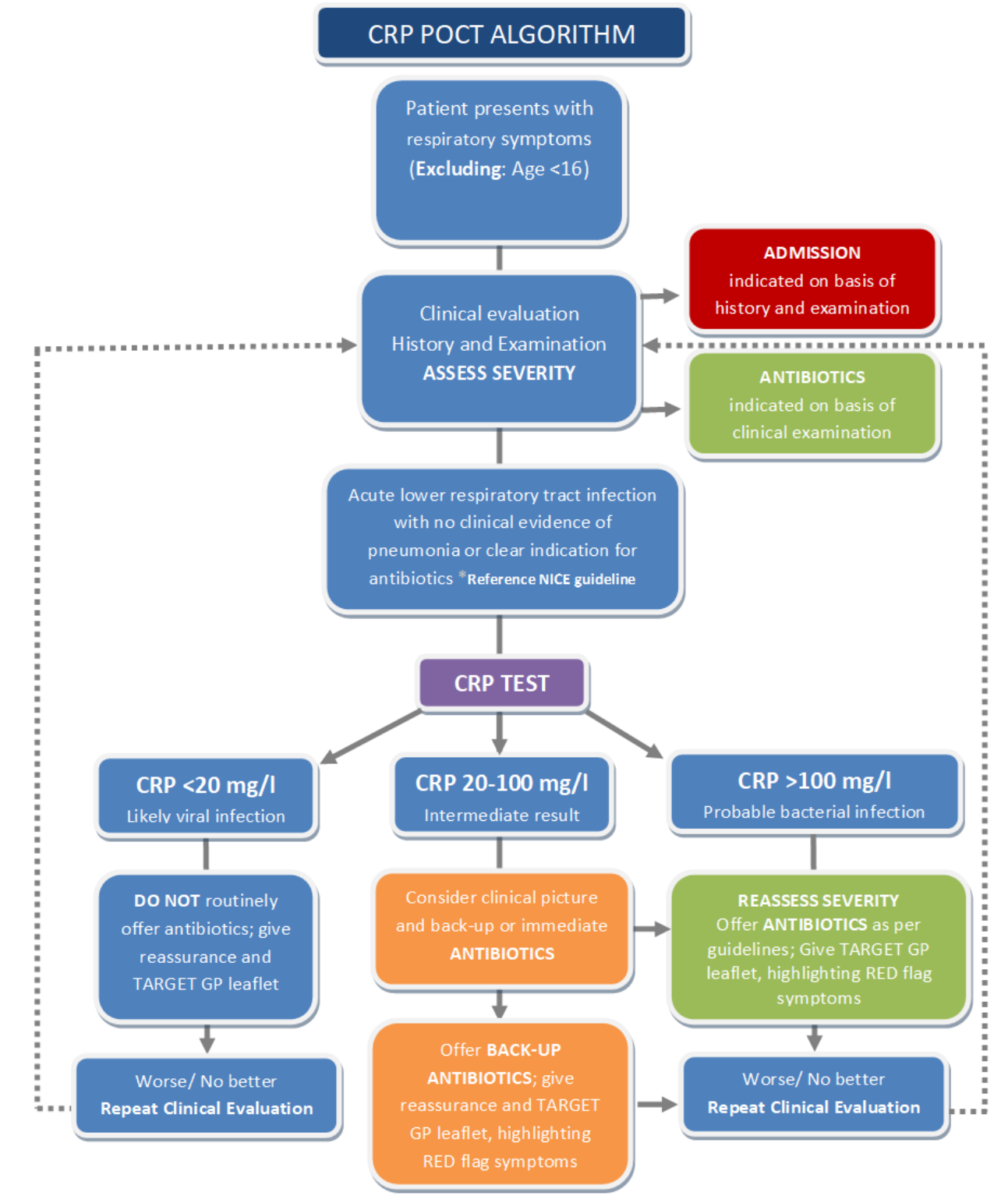
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APPENDIX A: CRP POCT ALGORITHM FOR ACUTE RESPIRATORY INFECTION



* **NICE guideline [NG237]** 1.3 In-person contact with NHS services at first presentation These recommendations cover people with symptoms and signs of an ARI who present in-person at sites that provide NHS services, including general practice and community pharmacies. 1.3.1 For people with symptoms and signs of an ARI, use clinical assessment to make a diagnosis and decide whether to prescribe antimicrobials, either immediately or with a back-up prescription, and offer them self-care advice (see recommendation 1.1.2). If pneumonia is suspected, see also the section on clinical diagnosis of pneumonia. 1.3.2 Consider the person's ARI symptoms and signs in the context of their overall health and social circumstances. The threshold for treatment or referral for further assessment may be lower for people who are more likely to have a poor outcome, for example, people with comorbidities or multimorbidity and people who are frail.

CRP-POCT ALGORITHM FOR COPD

All-Wales-Primary-Care-Management-of-Acute-COPD-Exacerbation-Guideline-.pdf

RESOURCES FOR HEATHCARE PROFESSIONALS

Course: TARGET antibiotics toolkit hub | RCGP Learning

Leaflets to discuss with patients: How to use these leaflets | RCGP Learning

Discussing antibiotics with patients: Overview | RCGP Learning

Resources and materials - Public Health Wales (nhs.wales)

APPENDIX B: CRP TESTING IN PRIMARY CARE – EVIDENSE SUMMARY

NICE GUIDANCE

NICE clinical guideline [CG191, December 2014] *Pneumonia in adults: diagnosis and management* recommends that for people presenting with symptoms of lower respiratory tract infection in primary care, consider a CRP-POCT if after clinical assessment a diagnosis of pneumonia has not been made and it is not clear whether antibiotics should be prescribed, and to use the results to guide antibiotic prescribing in these patients.

Two published (September 2016) medical technology innovation briefings relevant to CRP testing in primary care; MIB 78 and MIB 81 address the QuickRead go and AlereAfinion CRP point of care tests. The guidance addresses the use of CRP with people with lower respiratory tract infection. The medical briefings suggest for both technologies that using the technology could contribute to fulfilling antibiotic stewardship programs.

EFFICACY AND EFFECTIVENESS

Review level evidence is provided by the key Cochrane Reviews (2014 & 2017) *Biomarkers as point of care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care* (2014) included studies up to January 2014. The authors concluded that CRP-POCT can guide antibiotic treatment of acute respiratory infections in primary care and can reduce antibiotic use, although the degree of reduction remains uncertain. Used as an adjunct to a doctor's clinical examination this reduction in antibiotic use did not affect patient-reported outcomes, including recovery from and duration of illness. However, a possible increase in hospitalisations was of concern. A more precise effect estimate is needed to assess the costs of the intervention and compare the use of a point-of-care biomarker to other antibiotic-saving strategies.

In the second Cochrane overview of systematic reviews, *Clinician-targeted interventions to influence antibiotic prescribing behavior for acute respiratory infections in primary care: an overview of systematic reviews* (2 reviews,9 trials up to May 2017) the authors found evidence that CRP testing, shared decision making, and procalcitonin-guided management reduce antibiotic prescribing for patients with Acute Respiratory Infection (ARI) in primary care. These interventions may therefore reduce overall antibiotic consumption and consequently antibiotic resistance. There do not appear to be negative effects of these interventions on the outcomes of patient satisfaction and re-consultation, although there was limited measurement of these outcomes in the trials.

The largest study analysed within the Cochrane review 2014 was a multi-Country, cluster randomise control trial (RCT) (Little *et. al* 2013) looking at effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections. The trial was carried out across wide range of settings (6 EU countries). Practices were randomised to CRP-POCT with training, internet based interactive training in enhanced communication skills targeted at prescribers, usual care, and a combination of CRP training and communication training. The antibiotic prescribing rate was lower with CRP training than without (33% vs 48%, adjusted risk ratio 0·54, 95% CI 0·42-0·69) and with enhanced-communication training than without (36% vs 45%, 0·69, 0·54-0·87). The combined

intervention was associated with the greatest reduction in prescribing rate (CRP risk ratio 0·53, 95% CI 0·36-0·74, p<0·0001; enhanced communication 0·68, 0·50-0·89, p=0·003; combined 0·38, 0·25-0·55, p<0·0001A meaningful effect size impact on antibiotic prescribing was seen for all interventions with the greatest effect in the combined intervention (CRP-POCT alone 33% vs 48% ARR 0.54 95%CI 0.42-0.69, Communications training 36% vs 45% ARR 0.69 95%CI 0.54-0.87). No intervention affected symptom severity however slightly lengthened symptom duration was seen with communication training.

The role of communication with the patient alongside CRP-POCT was highlighted in the second Cochrane overview (2017) and a previous Cochrane Review (2015): *Interventions that facilitate shared decisions between primary care clinicians and patients about antibiotic use for acute respiratory infections*. Authors found moderate quality evidence to support CRP-POCT in general practice to reduce antibiotic prescribing with no differences in symptom duration, patient satisfaction, or re-consultation. The authors also concluded that there was moderate quality evidence to support shared decision making in the management of ARI in general practice to reduce antibiotic prescribing whilst maintaining patient satisfaction and without increasing likelihood of re-consultation. However, there was not enough information to decide whether shared decision making affects other clinically adverse secondary outcomes.

Non-Cochrane reviews such as Huang et al. 2013 carried out a systematic review and meta-analysis on papers published up to June 2013 (prior to the Cochrane review) and concluded that POCT-CRP testing significantly reduced antibiotic prescribing for respiratory tract infections (RTIs) (this was not limited to lower RTIs).

A further review of RCTs with interventions that aimed to facilitate shared decision making concluded that antibiotic prescribing was reduced in primary care in the short term. Effects on longer-term rates of prescribing are uncertain and more evidence needed to determine how any sustained reduction in antibiotic prescribing affects hospital admission, pneumonia and death. [12]

OTHER RELEVENT STUDIES

USE OF CRP POCT IN CHILDREN

A trial limited to children presenting with fever and/or respiratory symptoms reported no effect seen, however the study limited power to detect an effect (Rebnord et al. 2016). A further trial focussing on CRP-POCT in acutely ill children found that antibiotic prescriptions increased in the CRP-POCT group. One of the limitations of this study was low participant numbers.[13] Overall the evidence for using CRP-POCT in children is not adequately high enough for inclusion within the CRP-POCT guidelines.

A Scandinavian study ERNIE-2 (of the impact of CRP-POCT in acutely ill children suggested that normal CRP levels discouraged immediate antibiotic prescribing, even when evidence based medicine practice guidelines advise differently. Most likely, a normal CRP convinces GPs to withhold antibiotics when guidelines go against their own gut feeling. Future research should focus on

whether POC CRP can effectively identify children that benefit from antibiotics more accurately, without increasing the risks of under-prescribing.[11]

LOCAL STUDIES

A small North Wales pilot of CRP-POCT testing for patients presenting at a practice with acute RTI demonstrated a reduction in prescribing of antibiotics during the study period compared to the same period in the previous year (Hughes et al. 2016). This reduction was significantly greater than that observed in other GP practices within the health board (21.4% vs. 10.6%). Whilst this is consistent with a real beneficial effect there are clearly potential uncontrolled confounders that may influence these findings. A follow up study by the same authors focussing on economic evaluation of implementing CRP-POCT will be discussed in the costs section. [16]

A NIHR HTA funded study called PACE: General Practitioner (GP) use of CRP-POCT to help target antibiotic prescribing to patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD) was performed in Wales. Antibiotic prescribing in COPD patients accounts for around 5% of all antibiotics prescribed. Only around 60% of exacerbations in these patients are caused by infectious agents (bacteria, viruses etc.), making some antibiotic prescribing redundant. The CRP criteria used in COPD patients was: <20 antibiotics should not be prescribed, 20-40 antibiotics may be beneficial if other clinical factors are taken into consideration & >40 antibiotics will be beneficial. Antibiotic consumption was lower in patients using CRP-POCT (57%) compared with control patients (77.4%); a similar health status was seen in both groups.

COST EFFECTIVENESS STUDIES

A review of studies by Hunter, 2015 looked at the cost effectiveness of CRP-POCT testing in England, comparing standard practice; CRP-POCT by GP, CRP-POCT by practice nurse, and by GP with communication training for the GPs. Compared with current standard practice, the GP plus CRP and practice nurse plus CRP test strategies result in increased Quality Adjusted Life Years (QALYs) and reduced costs, while the GP plus CRP testing and communication training strategy is associated with increased costs and reduced QALYs. Additionally, all three CRP arms led to fewer antibiotic prescriptions and infections over 3 years.

A cost effectiveness study performed in North Wales looked at CRP-POCT in adults with Acute Respiratory Infection (ARTI) and a sub-category of patients with Lower Respiratory Infection (LRTI). Their analysis was based on the incremental cost-effectiveness ratio (ICER), using the NICE criteria of £20,000 as being cost effective. For ARTI the ICER was just cost effective at £19,705 per QALY gained whilst for LRTI the ICER showed cost effectiveness at £4390 per QALY gained.[14]

Two cost effectiveness studies were carried out in contexts outside of the UK (Netherlands, Norway and Sweden), it is thus difficult to determine from these the likely situation in a scale up of CRP across Wales.

EVIDENSE FOR OPTIMISING IMPLEMENTATION OF CRP TESTING

A qualitative study (Huddy et al. 2016) addressed barriers and facilitators for the adoption of CRP testing in primary care. The primary barrier was an absence of a UK funding and reimbursement model. Concerns were raised around the maintenance, stocking arrangements and quality assurance of test device and cartridges. Laboratories could take an active role in supporting CRP testing in test administration, quality control and training. The North Wales pilot (Hughes et al 2016) demonstrated the importance of considerable close support of the biochemistry laboratory service within the health board. This was required to ensure quality, comply with governance and to sort out problems with the testing process. An observational study from Sweden (Lindström et al. 2015) provides insight on the physician's view of CRP testing.

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