The place of point of care testing for C-reactive protein in the community care of respiratory tract infections

The high rate of empirical antibiotic use for the treatment of suspected respiratory tract infections (RTIs) and COPD exacerbations remains a cause for concern in the face of increasing antibiotic resistance. Historically, clinical decision rules have been used to guide antibiotic prescribing for patients presenting with signs and symptoms that indicate possible RTIs or infectious exacerbations of chronic obstructive pulmonary disease (IE-COPD). Use of point of care testing (POCT) for C-reactive protein (CRP) addresses clinical uncertainty to support not prescribing antibiotics in appropriate low-risk patients. This approach has been shown to reduce unnecessary antibiotic use and is therefore an important tool in ensuring antibiotics are used appropriately. As further research is undertaken and local and national policy makers work towards integration of CRP-POCT into standards of care, PCRS has developed a pragmatic guide to support clinical decision making, especially when antibiotics are not indicated, and ensure antibiotics are deployed appropriately. This summary article provides an overview of the pragmatic guide and the evidence base to support it. You can read the full article online https://www.pcrs-uk.org/crp-point-care-testing

Introduction

Respiratory tract infections (RTIs) and infectious exacerbations of chronic obstructive pulmonary disease (IE-COPD) are frequent primary care presentations.[1] In 2017, there were 18.2 cases of clinically suspected pneumonia per 1000 person-years.[1] A study that followed 2138 patients with COPD found that they experienced at least two acute exacerbations during a year-long follow up.[2] Infections are estimated to cause about 70% of COPD exacerbations and while the majority are caused by bacterial infections, pathogenic viruses are detected in about half of IE-COPD cases, sometimes alongside a bacterial infection.[3,4] Less commonly, fungi can cause RTIs, particularly in immunocompromised patients.[5,6] Across Europe, primary care accounts for between 80% and 90% of antibiotic prescriptions, mostly for RTIs.[7,8] As a result, several pathogens that cause RTIs, including *Streptococcus pneumoniae, Haemophilus influenzae, Pseudomonas aeruginosa* and *Mycobacterium tuberculosis*, show reduced susceptibility to several classes of antibiotics.[9] Inappropriate antibiotic use in primary care, therefore, contributes to the growing problem posed by antimicrobial resistance. The Primary Care Respiratory Society (PCRS) takes the position that patients with diagnosed COPD who present with acutely worsening symptoms should receive antibiotics only when an exacerbation has been determined as the cause of the deterioration and then only when bacterial infection is considered to be the most likely trigger.

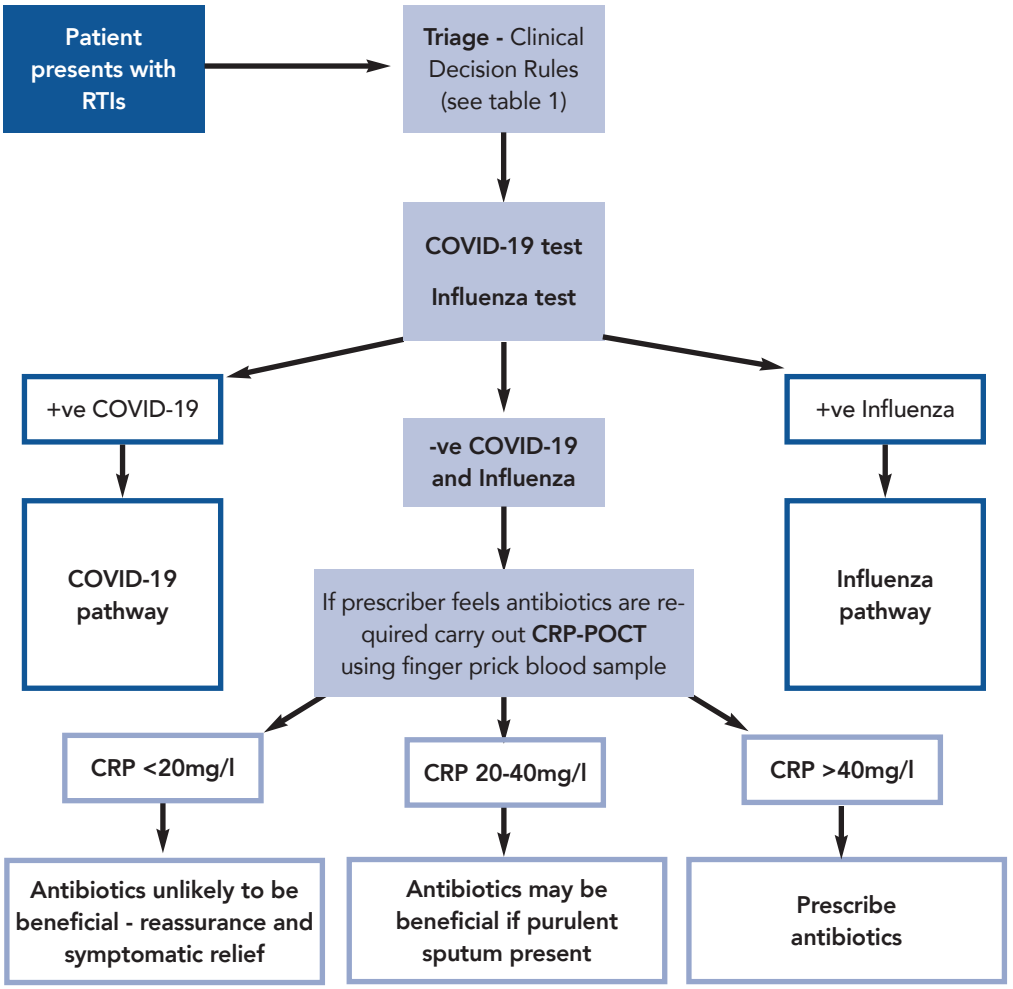
Pragmatic guide to the use of CRP-POCT in primary care

A multidisciplinary panel of PCRS members developed this 'pragmatic guide', based around two algorithms, one for IE-COPD (Figure 1) and one for RTIs that are not associated with COPD (Figure 2), to help reduce inappropriate antibiotic prescribing and implement point of care testing (POCT) for C-reactive protein (CRP). Fundamentally, the panel agreed that CRP POCT addresses clinical uncertainty to support not prescribing antibiotics in appropriate low-risk patients as well as being used educate and reassure patients when antibiotics are not needed.

Why CRP?

In 1930, Tillet and Francis reported that serum from people infected with *S. pneumoniae* contained a protein that could precipitate the C polysaccharide in bacterial cell walls. Levels of CRP, an acute phase reactant, rose in the early stages of *S. pneumoniae* infection.[10,11] Levels of CRP increase within hours of tissue injury or bacterial infection and can rise more than 1000-fold during acute inflammation.[11] CRP POCT in primary care may help reduce unnecessary prescribing of antibiotics by enabling a more considered diagnostic approach to people with suspected IE-COPD (Figure 1) and RTIs (Figure 2). Not only will a more considered diagnostic approach slow the spread of antibacterial resistance, but fewer people will experience avoidable adverse events such as hypersensitivity reactions, overgrowth of pathogenic bacteria, gastrointestinal

Figure 1. Algorithm for IE-COPD[28-30]



disturbances and nephrotoxicity.[12] A number of studies have demonstrated the usefulness CRP-guided decisions in reducing antibiotic prescribing and use, without any evidence of harm.[13–15]

Using CRP POCT in primary care

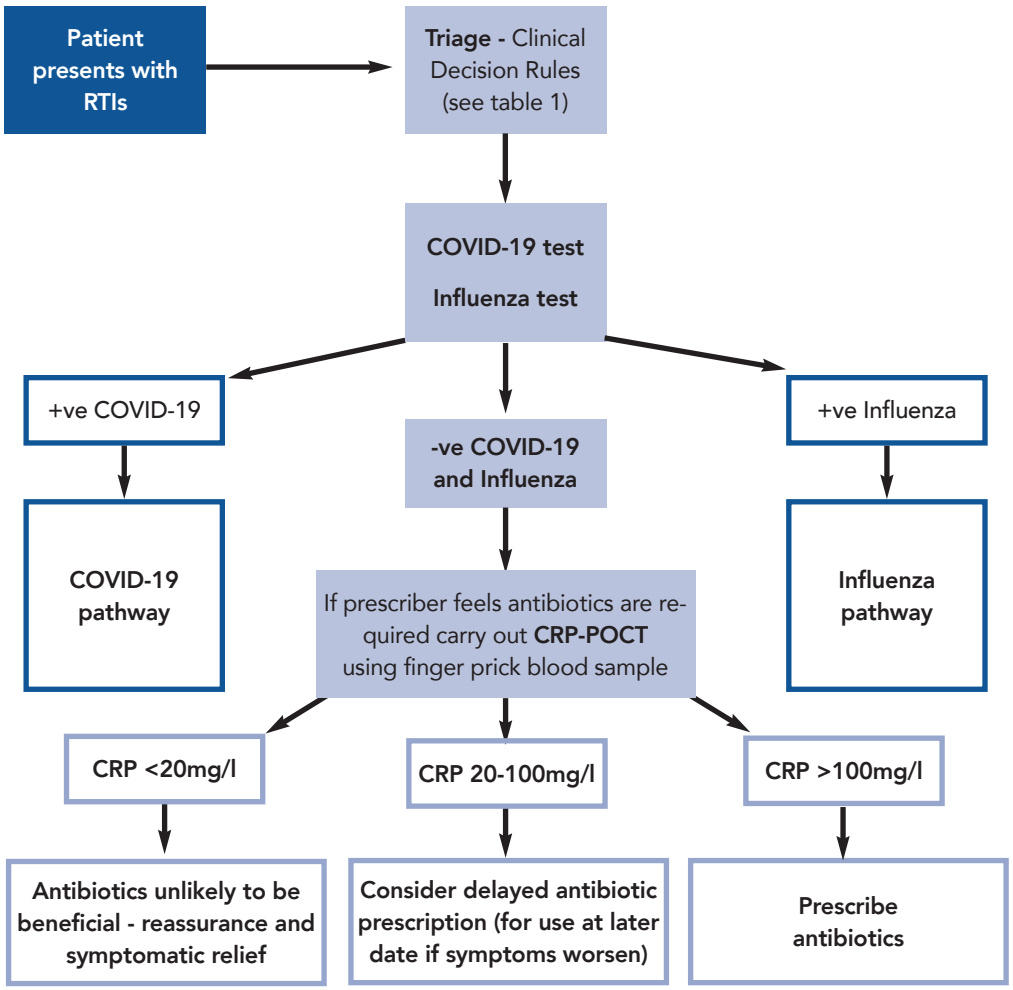
Clinical decision rules

Until the advent of CRP POCT, patients who presented with signs and symptoms (Table 1) consistent with possible RTI or IE-COPD were diagnosed and treated empirically, based on, for example, sputum colour.[4] An example of such a chart can be viewed at https://rdcu.be/cJJrK.[16] Sputum culture testing early in the course of management to guide antibiotic choice and limit the spread of antimicrobial resistance driven by overuse of broad-spectrum antibiotics. Other signs and symptoms can support an empirical diagnosis of IE-COPD and RTIs including respiratory rate ≥20 per minute, temperature ≥38°C, pulse rate >100 per minute and crackles on auscultation.[5] Clinical decision rules can also be used to determine whether people with RTI require hospitalisation (Figure 3).[16–18] Nevertheless, clinical decision rules still rely on non-specific clinical observations and laboratory tests including procalcitonin and CRP better predictors of an infectious causation for pneumonia among adults in primary care than clinical signs and symptoms alone.[5]

Diagnostic work up

Nasal antigen test or polymerase chain reaction should be used to exclude COVID-19 and influenza (Figures 1 and 2) before considering other pathogens and all potential triggers including tobacco exposure, air quality, psychosocial factors, viruses and bacterial infection should be considered. CRP POCT should be performed if the presentation suggests bacterial infection as cause of a COPD exacerbation (Figure 1) or antibiotics are needed for another RTI (Figure 2). In some circumstances (e.g. based on sputum purulence, auscultation), antibiotics may be clinically indicated without CRP testing (Table 1). CRP POCT

Figure 2. Algorithm for RTIs that are not associated with COPD[28-30]



will still be valuable in equivocal cases. Management depends on the CRP threshold and whether patients have RTI or COPD (Figures 1 and 2).

Follow up

CRP POCT can inform follow up. For example, if CRP levels do not change or increase further after 72 hours, the prescriber should consider whether the antibiotic is appropriate.

Overcoming barriers

Numerous barriers potentially hinder implementation of CRP POCT in the management of RTIs and IE-COPD.

Barriers related to healthcare setting

CRP POCT for IE-COPD and RTIs needs to be implemented in the right setting, delivered to the right patients and used in the right way to support clinical decision making to not prescribe antibiotics in appropriate low-risk patients. For instance, to realise economies of scale and an adequate caseload to ensure quality, the CRP POCT needs to be used routinely and regularly in GP practices, pharmacies,[19] diagnostic hubs and nursing homes. The place of testing needs to offer good accessibility for patients, particularly given the functional limitations of some people with COPD, such as those who experienced deconditioning during the COVID-19 pandemic. A system needs to be in place to ensure the results are fed-back to responsible healthcare professionals and recorded in the medical records.

Barriers related to staffing

Patients with possible IE-COPD or RTIs face a potential barrier accessing GPs in a timely fashion, especially given the pressures on the NHS arising from the COVID-19 pandemic. Limited work-force capacity, even aside from the pandemic, presents a barrier in terms of training (e.g. in using POCT equipment and clinical examination skills), reimbursement and having the staff to perform testing. CRP POCT could be

encompassed by the increasing number of Clinical Support Services, supported by an expansion of the range of health-care professionals eligible to prescribe antibiotics.

Barriers related to finance

Introducing CRP POCT is associated with upfront costs in terms of equipment, training and External Quality Assessment system. A negative or subthreshold CRP valve may also increase costs due to the greater need for inhaled therapies and step-up to triple therapy (inhaled corticosteroid, long-acting muscarinic antagonist and long-acting β2-agonist) in people with COPD. Reduced prescribing of antibiotics, costs associated side effects of antibiotics and contribution to antimicrobial resistance may offset some of the additional expenditure. CRP POCT is unlikely to impact hospitalisation rates, at least during a 6 month follow-up.[14] CRP POCT is, however, likely to reduce unscheduled reattendance, which can help build the business case supporting implementation. Considering COPD-related health-care costs only, CRP POCT was associated with similar costs as usual care in the PACE study: savings in healthcare resource use slightly offset the cost of £11.31 per CRP POCT. The cost per quality-adjusted life-year (QALY) gained at 6 months was £15,251,20 suggesting that CRP POCT is cost effective. NICE uses a cost-effectiveness threshold of £20,000 to £30,000 per QALY for reimbursing new drugs.[21] Primary care should work with diagnostic companies to introduce CRP POCT as cost-effectively as possible, which may depend on the setting. Integrated Care Systems should introduce incentives to adopt CRP POCT and other innovative diagnostic processes as soon as practicable in routine primary care.

A pilot study could aid implementation

A pilot study would be useful to demonstrate the benefits of CRP POCT in terms of antibiotic prescribing, patient-reported outcomes and other measures. The pilot study could also explore how to overcome the barriers and offer a benchmark for future development. As part of this, the Medicine Management Team should work with diagnostic companies to identify the best model and CRP POCT system for a particular location. The panel suggested that identifying a local champion can help build a case for CRP POCT in primary care. The OpenPrescribing website allows comparisons of antibiotic prescribing between practices in England. The pilot study should be based in a practice with at least one of the following to maximise patient enrolment: high users of antibiotics despite efforts to improve stewardship by the practice and local Medicine Management Team; a large cohort of COPD patients, which could be in areas of high socioeconomic deprivation; a large proportion of COPD patients attending accident and emergency departments; or a large proportion of COPD patients who frequently exacerbate.

Future perspectives

Political and managerial perspectives

The algorithms in Figures 1 and 2 should help improve the integration of diagnostics into primary care, which aligns with government recommendations in the report *Rapid Diagnostics: Stopping Unnecessary Use of Antibiotics*.[22] PCRS suggests that NICE should re-open the review of the current COPD management guideline and come to a position regarding the use of CRP POCT. The discussions should consider the growing body of high-quality data showing that testing can reduce inappropriate prescribing of antibiotics without compromising patient safety.[3,7,13–15,17,23–25] Without national guidance, the NHS could face 'postcode diagnostics' and, possibly, differences in antimicrobial resistance patterns. The use of CRP POCT also aligns with the current pan-national environmental agenda by reducing

Table 1: Clinical signs and symptoms that indicate possible bacterial causes of RTI or IE-COPD

Chest crackles: In people with raised temperature, chest crackles could indicate the need for antibiotics irrespective of CRP levels
Cough: prescribers should exclude post-infective cough
History of recent antibiotic use
Increased breathlessness
Oxygen saturation <95%
Possible fever (≥38ºC); viral infections are more likely than bacterial pathogens to cause a fever
Raised heart rate >100 beats per minute
Raised respiratory rate ≥20 breathes per minute
Sputum colour (especially green or yellow)

Based on a consensus of the PCRS panel and Htun and colleagues[5]

Figure 3. Matrix showing clinical decision rules used in RTIs

	Confusion	Urea >7mmol/l	Resp Rate >30/min	Low systolic BP <90mmHg Diastolic <60mmHg	Age >65 years	
CURB 65	+	+	+	+	+	
CRB 65	+		+	+	+	Temp
	Inter-subcostal recession	Illness duration <4 days	Vomiting in last 24 hours	Wheeze present	Age <2 years	>37.8 in last 24 hours
STARWAVe (children)	+	+	+	+	+	+
	Pulse rate >100/min	Crackles	Resp Rate >20/min	Pro-Calcitonin	C-Reactive Protein	>38
HTun	+	+	+	+	+	+

the carbon footprint associated with antibiotic production and minimising environmental contamination with antibiotics and environmental levels of multidrug resistant bacteria.[26,27]

Further research

There are numerous areas for further research, including characterising cost-effectiveness encompassing the costs of antibiotics, changes in drug costs and the cost of antimicrobial resistance. Studies should, for example, characterise the proportion of patients with IE-COPD who subsequently develop exacerbations with 'resistant' bacteria in those managed based on CRP POCT compared with usual care. Economic analyses could also estimate the indirect costs associated with IE-COPD, RTI and antimicrobial resistance, such as absenteeism, presentism and environmental footprint. Future studies also need to characterise the place of CRP POCT in the management of paediatric RTIs and the least distressing way to obtain a sample from children and adults with needle phobia. Capturing real-world epidemiologic data on the proportion of patients with a COPD exacerbation who have microbiologically confirmed bacterial infection at the various CRP levels could facilitate implementation and decision making. Finally, there is a pressing need to assess long-term outcomes associated with timely appropriate management and early referral to palliative care, the long-term implications for service utilisation and distinguishing true and frequent exacerbators from patients who need a different management approach.

Summary

The PCRS CRP POCT pragmatic guide has been developed to encourage the use of CRP POCT to support not prescribing antibiotics in appropriate low-risk patients with the aim of ensuring appropriate antibiotic prescribing and slowing the spread of antimicrobial resistance.

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