Editorials

C-reactive protein:

guiding antibiotic prescribing decisions at the point of care

C-reactive protein (CRP) is an acute-phase protein, which was originally named for its capacity to precipitate the C-polysaccharide of *Streptococcus pneumoniae*. The acute-phase response comprises the non-specific physiological and biochemical response to most forms of tissue damage, infection and inflammation. It is now a widely used and acknowledged marker to diagnose and monitor infections, especially in secondary care. But it is now also being used increasingly by primary care physicians to identify patients who are unlikely to benefit from an antibiotic. Thus, CRP is potentially a useful tool to enhance antibiotic stewardship.

In the current (March) issue of the *BJGP*, Lemiengre and colleagues performed a cluster-randomised trial in 2227 children with a non-severe acute infection.[1] They were randomised to a brief intervention that elicited and attempted to address parent concerns, GP use of a CRP test, both, or usual care. The brief intervention paradoxically increased antibiotic prescribing, while GP use of CRP alone or GP use of CRP plus the brief intervention had no significant effect on prescribing. Hence, this large study performed in general practice indicates that GP use of CRP in children with non-severe acute infections cannot be supported. This is in line with another interesting paper from this group, which suggests that there may be a role for CRP to guide referral in children with infections, but only in those children at risk of serious infections based on a clinical decision rule.[2]

In this editorial we look at the role of CRP in guiding antibiotic prescribing decisions. Specifically, we identify the patient populations where we currently have evidence that CRP use by GPs improves prescribing decisions, and will discuss whether adding CRP to decision rules can further improve these antibiotic prescribing decisions in general practice.

THE IMPACT OF CRP ON ANTIBIOTIC PRESCRIBING DECISIONS

The largest trial to date recruited over 4000 patients from over 200 practices in countries with differing rates of antibiotic prescribing (Spain, Belgium, The Netherlands, Poland, and the UK). This trial confirmed the results of the smaller trials, namely that GP use of CRP can safely reduce antibiotic prescribing in adult patients presenting with acute cough.[3–5] These findings are further confirmed by the 2014 Cochrane review evaluating biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care, with a pooled risk ratio derived from the six included randomised controlled trials (RCTs) of 0.78 for antibiotic prescribing (95% CI = 0.66 to 0.92).[6] A recent Cochrane umbrella review of clinician-targeted interventions to influence antibiotic prescribing concluded that CRP is one of three effective strategies, along with shared decision making and procalcitonin-guided management.[7] However, the latter was only studied in two trials, and in the largest general practice diagnostic study aiming to develop a clinical rule for pneumonia in 3106 patients with cough, procalcitonin did not add any diagnostic information. However, in the same study CRP at the optimal cut-off of 30 mg/L improved the accuracy of a clinical rule based on signs and symptoms.[8] This was recently confirmed by a meta-analysis of individual patient data of eight studies including 5308 patients with lower respiratory tract infections (LRTIs), showing that adding CRP measurement to the diagnostic work-up for patients with possible pneumonia improved the discrimination and risk classification of patients. However, like many other clinical decision rules, it still left a group of patients classified at intermediate risk, in which clinical decision-making remains challenging.[9] This is very much in line with qualitative evidence showing that GPs sometimes struggle with intermediate results.[10] The current NICE guideline for pneumonia now advises physicians to consider a delayed prescription for patients with intermediate CRP values between 20 mg/L and 100 mg/L.[11] It is important to note, though, that only 20% of tested patients with LRTI have intermediate results. The majority (70%) had a CRP <20 mg/L and only 5% had a CRP >100 mg/L, which warrants antibiotic treatment.[3,4]

> *"... GP use of CRP seems very useful in the clinical management of adults with acute cough and is effective as an antimicrobial stewardship intervention ..."*

So where does this leave us? Good evidence is accumulating that GP use of CRP safely reduces antibiotic prescribing in adults with acute cough. A UK-based trial which has just finished recruiting patients will evaluate if GP use of CRP in patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) leads to a reduction in antibiotic use with no worse COPD health status.[12] For other respiratory infections, firm evidence is lacking. A systematic review in the *BJGP* showed that though CRP can help to rule in sinusitis when positive, there is no randomised evidence showing effects on prescribing, so its use in sinusitis cannot be advocated as an individual test.[13] Based on the study by Lemiengre and colleagues, use of CRP to guide antibiotic prescribing decisions for children cannot be recommended either.[1] The only study that showed an effect of physician use of CRP in children was a large multicentre RCT in 10 primary healthcare centres in Vietnam. It recruited over 1000 children, and reduced antibiotic prescribing from 77% to 68% in children with acute infections.[14] However, given possible variations in case-mix we cannot extrapolate this to high resource economies like that in the UK.

INCORPORATING CRP INTO CLINICAL DECISION RULES

The incorporation of CRP into clinical decision rules (CDRs) is a potentially useful strategy. These CDRs combine several signs and symptoms with CRP, and typically generate a risk score that classifies patients as low, moderate or high risk for bacterial infection. Using data from a multinational European study of patients with acute cough, a group of researchers developed a CDR to determine the risk of radiographic pneumonia in patients presenting with acute cough. It incorporates six signs and symptoms with CRP, and classifies patients as low (0.7%), moderate (3.8%), and high (18.2%) risk for community acquired pneumonia.[8] A second CDR

uses six signs and symptoms plus CRP to identify patients who are at low (16%), moderate (49%), or high (73%) risk for acute bacterial rhinosinusitis.[15] However, both rules still require prospective validation in different populations, and an assessment of their impact on prescribing. Held and colleagues developed a simple CDR to rule out pneumonia in Swiss outpatients with acute cough, which was then validated in a separate Swiss population. The rule states that pneumonia can be ruled out in patients with a CRP <10 mcg/mL, or in those with a CRP between 11 mcg/mL and 50 mcg/mL but who deny both dyspnoea and daily fever since the onset of illness.[16]

This approach has the advantage of using the best independent predictors to make the diagnosis, rather than just relying on a single test result. It also corresponds well to the threshold model for decision-making: if low-risk patients have a risk of disease that falls below the test threshold, and high-risk patients have a risk of disease above the treatment threshold, then only moderate risk patients requiring further testing.[17] Another strategy would be to use CRP selectively for those at intermediate risk, where GPs have diagnostic uncertainty, or for high-risk patients to improve specificity.[2]

FUTURE DIRECTIONS

How do we reconcile these data with the results of the Lemiengre study? Physicians had a lower than average rate of prescribing in the study population, possibly creating a 'basement effect' that made it harder to go even lower. It is also possible that the deliberate attempt to elicit parental concerns with the brief intervention may have led physicians to address those concerns with an antibiotic; adding a negative CRP test might therefore have provided reassurance and helped the physician avoid an antibiotic prescription. The physicians were also not given any guidance regarding an appropriate cut-off to define an elevated or abnormal CRP, and this could easily lead to uncertainty about how to use the results of the test to guide prescribing. Guidance on the use and interpretation of cut-offs is very much desired by GPs.[10,18] Moreover, there are concerns about overuse of point-of-care tests (POCT).[18] For example, in Denmark, which was an early adopter of POCT, their use increased by 45% in 10 years. Further, nearly half of antibiotic prescriptions were preceded by some kind of POCT in 2013, and there was a 5-fold interpractice variability in testing.[19]

In conclusion, GP use of CRP seems very useful in the clinical management of adults with acute cough and is effective as an antimicrobial stewardship intervention. While several CDRs that integrate signs and symptoms with CRP are promising, they require prospective validation in different populations. Until then, let's remember that GP use of C-reactive protein can guide decisions about antibiotics, but only when used in the right population.

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Provenance
Commissioned; not externally peer reviewed.

Competing interests
The authors have declared no competing interests.

DOI: https://doi.org/10.3399/bjgp18X694901

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