Point of care testing for C-reactive protein

A new path for Australian GPs?

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BACKGROUND
New approaches are needed to reduce antibiotic usage in respiratory tract infections in general practice without compromising patient safety. Point of care tests for C-reactive protein (CRP) are now being used for this purpose in some European countries.

OBJECTIVE
Current knowledge about the CRP response in respiratory tract infections is presented, as well as the usefulness of applying the test when sinusitis and pneumonia may be suspected.

DISCUSSION
A promising ability of the test in ruling in or out severe infection has been demonstrated in clinical studies. There are still controversies about the use of the CRP test in respiratory tract infections, however clinical research supports its use for some conditions, and therefore introduction into Australian general practice should be considered. Further evaluation of its utility is needed.

The use of 'point of care testing' is emerging as an important aspect of general practice care.[1] Assay for C-reactive protein (CRP) is used widely in Scandinavian countries and in Switzerland. In Norway, a CRP test is now performed in one out of 8 consultations, and in a Swedish survey from 2002, the CRP test was carried out in 41% of all patients consulting a general practitioner with an airway infection.[2] *Table 1* outlines the technical and economic aspects of point of care testing for CRP. In this review we focus on the use of the test in common respiratory tract infections.

CRP – what is it?

C-reactive protein is an acute phase protein produced in the liver.[3,4] Increased production of this protein is triggered by cytokines released by infection or tissue damage. The CRP molecules bind complement and enhance phagocytosis. The serum concentration of CRP is usually <3 mg/L, but can increase to 500 mg/L within a few days in cases of severe infection. Acute cardiovascular events may also induce raised levels and much interest has been attached to the proven association between slightly elevated CRP values and chronic cardiovascular diseases including metabolic syndrome.[3] A persistent CRP value >3 mg/L is now an established risk factor for such diseases. The CRP tests used in general practice are not yet suitable for assessing cardiovascular risk and can only detect CRP concentrations >8 mg/L.[5,6] It takes 6–12 hours to reach such a level after the start of the inflammatory response in infectious diseases. The CRP test is also used in diagnosing and monitoring chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease.[4,7]

Respiratory tract infections

There is increasing concern about the overuse of antibiotics and increased levels of bacterial resistance.[8] In Australia and in the United Kingdom, approximately three-quarters of lower respiratory tract infections are treated with antibiotics.[9,10] There is strong evidence that the majority of respiratory infections are caused by viruses.[11,12] Antibiotics probably shorten the illness in some patients with sinusitis, if the diagnosis has been correctly made,[13] but are probably of little help in patients with acute bronchitis.[14] More accurate diagnosis of respiratory tract infections is needed, both to avoid

inappropriate prescriptions and to identify those patients who really need antibiotics.[15]

Clinical diagnosis of acute bacterial sinusitis

A diagnosis of bacterial sinusitis should be considered when a patient presents with sinus or tooth pain, purulent nasal discharge, or persistent stuffy nose in connection with a flu, common cold, or fever. Physical findings that may contribute to a correct diagnosis are purulent secretions found in the nasal cavity or on the posterior wall of the pharynx.[16,17] Diagnoses of sinusitis made by GPs on the basis of symptoms and signs can be confirmed in one out of 2 patients when evaluated against a computerised tomography scan or sinus puncture.[16]

Clinical diagnosis of pneumonia

The diagnosis of pneumonia is even more difficult than that of sinusitis because the symptoms of this disease frequently resemble that of influenza, acute bronchitis, or exacerbation of chronic obstructive pulmonary disease (COPD).[12] Cough, dyspnoea, chest pain and fever are typical symptoms, but in the majority of cases in general practice only 1–2 of these symptoms are present.[18,19] Many patients thought to have pneumonia have normal chest X-rays and many of those with normal chest examination have pneumonia on chest X-ray.[18,19] Percussion can be valuable in the rare case of lobar pneumonia.[18] Crackles are heard in less than 40% of patients with pneumonia,[18–20] but are also heard in other pulmonary conditions. So although their presence can support a diagnosis, they are often misleading.

The clinical picture in pneumonia may sometimes be nonspecific, particularly in the elderly.[21] There is a risk of delay in diagnosis and treatment which may increase the probability of a fatal outcome, at least in severe cases.[22]

Viral respiratory tract infections

In viral respiratory tract infections the serum concentration of CRP usually increases and reaches a peak after 2–4 days.[23,24] The maximum value does not always exceed 8 mg/L, which is the limit for detection by the currently used CRP test, but peaks between 10–50 mg/L are frequently seen. Higher values are often found in influenza and adenoviral infections,[24,25] but they seldom exceed 100 mg/L. After the fourth day of illness, the serum concentration usually drops rapidly, and will, after 10 days, be lower than 10 mg/L if not complicated by a bacterial superinfection. The examples of CRP responses in uncomplicated viral infections in *Figure 1* show clearly that the interpretation of CRP values is time course dependent.

Table 1. Point of care testing for CRP – technical and economical aspects

- These are finger prick tests using small capillary tubes to collect 5 or 20 µL of blood (dependent on device)
- Test results are available within 4 minutes and can be used during the consultation
- The cost of each test (reagents and other articles of consumption) is $6–8 (a little less than is paid to medical laboratories for CRP analysis)
- The devices used for analyses (which are multipurpose devices) cost $1800–3000

CRP and bacterial sinusitis

C-reative protein values between 10–50 mg/L are frequently seen in acute bacterial sinusitis, but unlike rhinovirus infections, where moderate increases in CRP last for a few days, values >10 mg/L may persist after the first week of illness. By applying thresholds of 10 and 25 mg/L respectively, the test contributed to improved diagnostic certainty in two studies.[17,26] In bacterial sinusitis, higher values are seen when pneumococci or group A streptococci are the causative agents.[27] It is of particular importance to treat such infections with antibiotics due to increased tendency for complications.

CRP and pneumonia

C-reative protein values >100 mg/L are frequently found in pneumonia. In patients hospitalised with community acquired pneumonia, mean CRP values on admission were 154 and 217 mg/L in two studies.[28,29] The CRP value has been found to be more valuable than information about temperature and crackles in differentiating pneumonia from other respiratory tract infections.[19,20,30] A CRP value >50 mg/L was found four times more frequently in patients with pneumonia than in patients without pneumonia who had been ill for less than a week, and 10 times as frequent when comparing patients who had been ill for more than a week.[30] The low frequency of elevated CRP values after 1 week in uncomplicated viral infections may explain the increased specificity of the test after one week of illness (*Figure 1*). The probability of pneumonia increases with increasing CRP value due to the increased specificity associated with higher thresholds. However, one should be aware that high values can also be found in myocardial infarction and pulmonary embolism.[4] The presence of pneumonia can usually be ruled out when the CRP value is <10 mg/L due to the high sensitivity of such a low threshold.[20] Caution should however, be shown on the first day of illness when a delayed rise in CRP may be falsely reassuring.

Scientific evidence for the usefulness of the CRP test in lower respiratory tract infections was examined by van der Meer et al in a recently published meta-analysis.[31] Although the test was found to be of significant diagnostic value in identifying patients with pneumonia, the authors did not find sufficient support for a wide introduction of the CRP test as a guide in the prescription of antibiotics. The test's ability to support or question a clinical diagnosis was not dealt with in this analysis, neither was it's usefulness in identifying patients with severe pneumonia who may need hospital treatment or close follow up by the GP.[32]

The test is also useful in detecting severe bacterial infections in patients with unclear clinical pictures.[33] On the other hand, when a normal CRP value is found in a patient suffering

severe cough and dyspnoea, exacerbations of asthma or COPD may become likely options.[12]

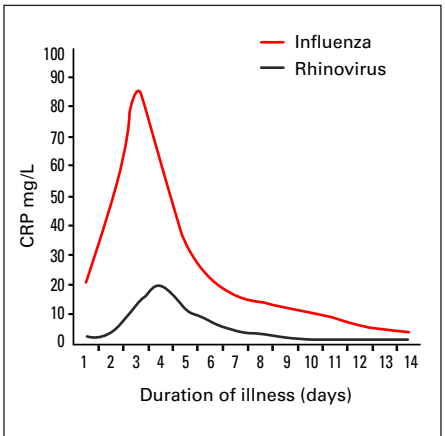

Figure 1. Examples of normal CRP values according to duration of illness in uncomplicated viral respiratory tract infections[24]

However, bacterial exacerbations of COPD are often associated with raised CRP levels.[34]

Evaluation of clinical usefulness

Although high CRP values may help distinguish patients with pneumonia and sinusitis from those with acute bronchitis and common cold, controlled trials have so far been unable to demonstrate improvement in clinical outcome or reduced antibiotic use.[7,35,36] In these trials, the participating GPs had limited prior experience with the test so the results should be interpreted cautiously. In contrast, two recent but less rigorous studies, have shown promising results. In a Norwegian study, GPs thought the test contributed to the diagnosis in 30% of patients with an infectious illness and a reduction in the use of antibiotics.[37] In a Danish study, GPs who used the CRP test were less likely to prescribe antibiotics for sinusitis than those who did not; 59% compared to 78%, respectively.[38] The prescribing behaviour was significantly associated with the CRP level. In a Swedish study, 14% of patients with a diagnosis of nonspecific respiratory infection were given antibiotics when the CRP value was <10 mg/L compared to 94% when the CRP value was >50 mg/L.[2]

Concerns about the CRP test

The widespread use of the test in general practice in Scandinavian countries has been questioned.[2,39] It has been stated that the CRP test is often used routinely with limited impact on diagnosis and treatment.[39] Moderately elevated CRP values in patients with respiratory tract infections may lead to prescriptions of antibiotics that would have been avoided if the test had not been carried out.[2] Research addressing these questions should be carried out in order to determine in which conditions the test might be beneficial.

Should the CRP test be introduced in Australian general practice?

The often difficult diagnostic and therapeutic decisions in respiratory tract infections in general practice call for new approaches to reduce antibiotic usage without compromising patient safety. We still await hard evidence for the usefulness of the CRP test in this respect. However, convincing predictive values for pneumonia have been demonstrated, and our understanding of the diagnostic value of the CRP test increases steadily with the results of new research. The increasing amount of evidence lends support to a cautious introduction of the test in Australian general practice. Updated guidelines for test usage, taking into account the clinical picture and the duration of illness, would ensure that the maximal benefit of the test was obtained.

Summary of important points

- Point of care tests for CRP are widely used in general practice in some European countries.
- The CRP test has been shown to be useful in differentiating pneumonia from other respiratory tract infections.
- A high CRP value (>100 mg/L) can indicate a severe bacterial infection.
- Antibiotic treatment can usually be avoided when the CRP value is low (<10 mg/L).
- The CRP test is only an adjunct to the clinical diagnosis. The duration of illness must be taken into account.

Conflict of interest: none declared.

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