The Value of C-reactive Protein in Primary Health Care
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This booklet is intended to provide health care practitioners with an overview of QuikRead CRP, a rapid C-reactive protein assay, its diagnostic potential and value in routine primary care practice.

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Introduction

This booklet is intended to give primary care practitioners an overview of QuikRead® CRP, a rapid C-reactive protein (CRP) assay, its diagnostic potential and value in routine practice. The emphasis is on situations in which an immediately available, quantitative CRP result can help to make adequate and timely diagnostic and treatment decisions.

CRP is a protein normally present in very low concentrations in the blood of healthy people. In bacterial infections, CRP concentrations markedly increase, whereas viral infections usually only induce very modest CRP elevation or none at all.

In primary care, a large proportion of antibiotics is prescribed to treat conditions in which antibiotics are of little or no benefit. Excessive and inappropriate use of antibiotics, leading to the emergence of increasingly resistant bacteria, has become a severe problem worldwide. Against this background, the individual health care practitioner often faces the dilemma of how to identify patients who need – and particularly those who do not need – antibiotic therapy.

QuikRead CRP is an easy-to-use test for quantitative measurement of CRP. The test is designed to be performed on a finger-prick blood sample and the test result is available in a couple of minutes during the patient consultation. QuikRead CRP is a valuable tool helping the primary care practitioner to distinguish between bacterial and viral infections and to target antibiotic treatment to patients most likely to benefit from it.
Antibiotic use and resistance

Antibiotics are a cornerstone for the management of bacterial infections. Therefore, antibiotics should be used with caution and only when absolutely necessary.

Like all medicines, antibiotics can cause side effects. The most common side effects are generally considered to be mild, and include conditions such as headache, dizziness, gastrointestinal upset, nausea and vomiting.\(^1,2,3\)

However, antibiotics may alter the normal microbial flora of the patient and lead to acute or even chronic disease in some individuals.\(^4,5,6,7,8,9,10\) The effects of antibiotic treatment on the native gut microbial flora are well established and range from self-limiting mild diarrhea to life-threatening pseudomembranous colitis.\(^11,12,13,14\) Vaginal yeast infections are also common after taking antibiotics.\(^15,16,17,18\) Being a cause for concern and discomfort for many women, they may even be a reason for not wanting to take prescribed antibiotics.\(^15\) Even a short-term antibiotic course can cause long-term alterations in the commensal microbial flora of the individual patient\(^4,5,6,19\), and therefore unnecessary antibiotic courses should be avoided.

Antibiotics can also cause allergic reactions ranging from skin rash to severe life-threatening attacks that require immediate medical attention.\(^20\) Other serious adverse reactions that warrant for the judicious and cautious use of antibiotics include alterations in blood glucose levels, QTc interval prolongation, seizures, phototoxity and tendinopathy.\(^3,21\)

Recently, antibiotic use in early life has also been linked to childhood asthma.\(^22,23,24\)

Antibiotic resistance on the rise

Frequent use of antibiotics results in antibiotic resistance which is one of the most serious public health concerns today.\(^25–28\) A strong correlation between frequent use of antibiotics and a rising rate of antibiotic resistance has been established in many studies (Fig. 1).\(^27,29–31\)
Antibiotic-resistant bacteria have steadily increased and present a threat to disease management\textsuperscript{12} not only in hospitals but also in primary care.\textsuperscript{33} Many previously effective antibiotics are now ineffective, and the appearance of multidrug-resistant bacteria is contributing substantially to the problem.\textsuperscript{26,32–34}

About 80–90\% of antibiotics are prescribed within primary care\textsuperscript{27,35–37}, and as many as 50\% of these prescriptions are likely to be unnecessary.\textsuperscript{33,36} Moreover, broad-spectrum antibiotics are substantially overused, even for conditions where antibiotic therapy is not indicated at all, a practice additionally driving up resistance problems.\textsuperscript{38,39}

**Development of new antibiotics on the decline**

Development of new antibiotics is not keeping pace with the increase of antibiotic resistance. Despite the critical need for new antibiotics, the development of these drugs is declining.\textsuperscript{25,31,32,40} It is estimated that the development of a new antibiotic takes 10–15 years from discovery to approval.\textsuperscript{31,41}
Variation in antibiotic use and antibiotic resistance among countries

The use of antibiotics in primary care differs among countries (Fig. 2), which is unlikely to be caused by differences in frequencies of bacterial infections. Antibiotic-prescribing practices, attitudes towards antibiotic use and regulatory control of prescribing have been found to have an impact on the prevalence of antibiotic-resistant bacteria.

Most antibiotic prescriptions in primary health care are for acute respiratory tract infections. Antibiotic treatment of these conditions is, however, often inappropriate, since the vast majority have a viral cause (see Acute respiratory tract infection, page 15). A diagnostic test providing an objective and immediate result that confirms or rules out a viral infection could have an important role in ensuring more precise diagnoses and reducing inappropriate use of antibiotics.

Fig. 2. Outpatient antibiotic use in 21 European countries in 2006. DDD = defined daily doses.
C-reactive protein (CRP)

CRP is an acute-phase protein synthesised in the liver. CRP concentrations are normally low in the blood of healthy people; 99% have levels under 10 mg/l\textsuperscript{47} which is generally considered as the cut-off for inflammatory disease\textsuperscript{48-51} (see also QuikRead CRP in various clinical situations, page 14).

Production of CRP is rapidly induced by cytokines in response to infection, inflammation and tissue injury.\textsuperscript{47,52,53} Elevated CRP concentrations can be detected within 6–12 hours of the onset of an inflammatory stimulus\textsuperscript{54,55}, and the concentrations peak within 24–48 hours.\textsuperscript{47,51,56} The elevation can even be more than 1000-fold.\textsuperscript{47,57,58}

CRP has been found to reflect closely the extent, activity and severity of disease.\textsuperscript{47} With resolution of an infection or inflammatory process, CRP levels decline rapidly owing to the short half-life (19 hours) of CRP in the bloodstream.\textsuperscript{47,51}

Although elevated CRP concentration is not specific to any particular disease, quantitative measurement of CRP adds valuable information to the diagnosis, treatment and monitoring of an inflammatory process and the associated disease.

In a primary care setting, CRP can assist doctors in
• distinguishing between bacterial and viral infections
• monitoring the efficacy of antibiotic therapy.

CRP in distinguishing between bacterial and viral infections

Combined with careful clinical assessment, CRP can help to differentiate bacterial infection from viral infection.

CRP levels are increased markedly by invasive bacterial infection. 50–85% of patients with a CRP concentration exceeding 100 mg/l will have a bacterial infection.\textsuperscript{58-60} Acute Gram-positive and Gram-negative
bacterial infections are among the most potent stimuli for CRP production.\textsuperscript{47}

Bacterial infection without a clearly elevated CRP concentration is unlikely but may occasionally be encountered. Patients may have low or only moderately elevated CRP concentrations if the sample is taken during the first 6–12 hours after onset of the infection. Therefore, a normal CRP value on the first day of illness should be interpreted with caution.\textsuperscript{55} CRP results should also be interpreted with great care in the early neonatal period. The amount of CRP produced depends on the invasiveness and location of the infection in the body. Superficial or localised, minor bacterial infection may not stimulate CRP production significantly.\textsuperscript{47}

Uncomplicated viral infection usually has little effect on CRP concentration.\textsuperscript{47} A moderately elevated CRP concentration (10–60 mg/l) may, nevertheless, be found in some upper respiratory tract infections with a peak during days 2–4 of illness.\textsuperscript{55,61} The elevation may, however, in some cases reflect secondary bacterial infection.\textsuperscript{47} Higher CRP values can be found in infections caused by adenoviruses.\textsuperscript{62} In patients with signs and symptoms of common cold, a minor part of cases are, however, associated with adenoviruses.\textsuperscript{63-65}

**CRP in monitoring the efficacy of antibiotic therapy**

CRP concentrations drop rapidly, at roughly 50% a day\textsuperscript{51}, in response to effective treatment. Serial measurement of CRP is therefore of great value in monitoring the effect of antibiotic therapy, and antibiotics can usually be stopped upon normalisation of the CRP value.\textsuperscript{47,51,66,67} In contrast, inadequate treatment is reflected in persistently high CRP levels which may even rise further if the infection takes a turn for the worse.\textsuperscript{47,59} Monitoring of CRP concentration can alert to complications and predict the outcome earlier than clinical signs.\textsuperscript{68}
CRP versus erythrocyte sedimentation rate ESR

ESR is a nonspecific inflammation marker and a commonly performed laboratory analysis. CRP has many advantages over ESR. ESR is greatly influenced by the size, shape and number of erythrocytes, gender and age of the patient, as well as serum proteins such as fibrinogen and immunoglobulins. Therefore, ESR results can vary and sometimes mislead. As a patient’s condition worsens or improves, ESR changes rather slowly, whereas plasma CRP concentration reacts rapidly. ESR is also greatly affected by technical factors, such as assay temperature, sample dilution and tilting of the ESR tube.

CRP versus white blood cell count WBC

CRP has been found to be more sensitive and specific than WBC for differentiation between bacterial and viral infection. In young febrile children, CRP is superior to WBC in predicting which febrile children have occult severe bacterial infection requiring antibiotic therapy. WBC values are also not consistent enough to be used in monitoring the effect of antibiotic treatment in bacterial infections.

CRP versus procalcitonin PCT

Similarly to CRP, PCT is a general marker of bacterial infection. However, PCT measured at central laboratory is not ideal for routine primary care where timely results often are needed to support therapy decisions.

CRP is a good servant

CRP must not be used as the only measure of a patient’s condition. Yet, interpreted in the context of the patient’s symptoms and history, a timely CRP result is a substantial aid helping the health care practitioner reach the right diagnosis and correct treatment decision.
QuikRead® CRP guides the use of antibiotics

Diagnostic dilemma

The primary care practitioner has to make judgement on the cause of patients’ infections more or less every day. A key question is whether the presenting symptoms are related to a serious bacterial infection requiring antibiotic treatment or a benign, self-limiting viral illness.87,88

The clinical signs and symptoms of patients with bacterial and viral infections frequently overlap and may not clearly differentiate between these groups of patients.54,87-93 This, together with pressure from patients, time constraints and the lack of diagnostic tools, may lead to prescription of unnecessary antibiotics.44,94-96

Although a sample or the patient may be sent to a laboratory for testing, a test result that is received hours or days later seldom has any effect on the treatment decision or the course of treatment. Today’s technology allows the health care practitioner to rapidly perform a diagnostic test and obtain the result during patient consultation without unnecessary delay.97

QuikRead CRP

QuikRead CRP is an easy-to-use test for quantitative measurement of CRP on a finger-prick blood sample. The system – consisting of a small portable instrument and a ready-to-use kit – is especially designed for use in the primary care setting. When the test is performed near the patient, the result will be available in a couple of minutes during the patient consultation to support diagnosis and therapeutic decision-making.
In combination with patient history, physical examination and careful clinical judgement, QuikRead CRP is a valuable tool assisting the health care practitioner in differentiating between viral and bacterial infections.

A clearly elevated QuikRead CRP result indicates bacterial infection warranting antibiotic treatment. Conversely, QuikRead CRP can also provide reassurance to both the health care practitioner and the patient in cases where prescription of antibiotics does not appear justified. By confirming a likely viral infection, QuikRead CRP can help to reduce unjustified use of antibiotics\textsuperscript{98} particularly in connection with respiratory tract infections.\textsuperscript{99-101} Avoidance of unnecessary antibiotic use will substantially reduce the number of patients who experience antibiotic-associated adverse events.\textsuperscript{20} Appropriate use of antibiotics may also contribute to slowing down or even reversing the development of antibiotic resistance.\textsuperscript{102,103}

QuikRead CRP provides a reproducible and quantitative result that is as accurate as that obtained using clinical chemistry analyzers.\textsuperscript{98,104-107}

**QuikRead CRP features**

- assists in differentiating between viral and bacterial infections
- immediate test result allows the treatment decision to be made during patient consultation
- small finger-prick blood sample convenient for the patient
- aids in targeting antibiotic therapy to patients most likely to benefit from it
- contributes to reducing unjustified antibiotic prescribing in respiratory tract infections
- allows monitoring of the efficacy of antibiotic therapy
- simple to operate, easy to read, no special laboratory skills required
- consistent day-to-day results
- quantitative CRP result within the range 5–200 mg/l for QuikRead go and within the range 8–160 mg/l for QuikRead 101
- comparable to clinical chemistry analysers in accuracy
- in-built calibration
- instrument requires minimum servicing
Interpreting the QuikRead® CRP test result

Optimally, a diagnostic test should have high sensitivity (= the ability of the test to correctly identify diseased individuals) and high specificity (= the ability of the test to correctly identify non-diseased individuals).

A cut-off point – a clinical decision threshold – is usually set to discriminate between diseased and non-diseased individuals. As diagnostic tests, however, rarely demonstrate 100% sensitivity and specificity, using any single value as a cut-off will usually cause some overlap, yielding following categories of test results:

- True positive (TP) = a positive/abnormal test result on a diseased individual
- True negative (TN) = a negative/normal test result on a non-diseased individual
- False negative (FN) = a negative/normal test result on a diseased individual
- False positive (FP) = a positive/abnormal test result on a non-diseased individual

<table>
<thead>
<tr>
<th>Test with low cut-off</th>
<th>Test with high cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>high sensitivity, low specificity</td>
<td>high specificity, low sensitivity</td>
</tr>
<tr>
<td>likely to identify all diseased individuals</td>
<td>likely to identify all non-diseased individuals</td>
</tr>
<tr>
<td>negative/normal result indicates non-diseased individual:</td>
<td>positive/abnormal result indicates a diseased</td>
</tr>
<tr>
<td>the disease can be excluded</td>
<td>individual: the disease is confirmed</td>
</tr>
<tr>
<td>will give some false positive results</td>
<td>will give some false negative results</td>
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The positioning of the cut-off affects both the sensitivity and specificity of the test (Fig. 3). When the result of a quantitative test such as QuikRead CRP is interpreted, various cut-off levels may be set depending on what is considered optimal for each condition – as evidenced by the clinical examples cited in the following chapter.
A low CRP cut-off is generally used to exclude infections of bacterial aetiology. On the other hand, a high CRP cut-off is needed to confirm bacterial aetiology of an infection. Low and high cut-offs also can be used simultaneously. Results falling between the cut-offs ("grey area") require special consideration.

![Diagram of diagnostic test results](image)

Fig. 3. Effects of changing the cut-off point of a diagnostic test.108 By permission of Cambridge University Press.

As with any diagnostic test, the QuikRead CRP test result should always be evaluated in the light of all clinical findings before making the final diagnosis and therapeutic decision.

**QuikRead® CRP in various clinical situations**

The following sections discuss the value of QuikRead CRP in various clinical situations with emphasis on infections commonly encountered in primary care.
Serious bacterial infections

Septicaemia, endocarditis, osteomyelitis, septic arthritis, bacterial pneumonia and meningitis as well as pyelonephritis are usually associated with markedly elevated CRP concentrations.70,71,73,92,109-119 Measurement of CRP is also useful in the management of feverish conditions without localising signs. Fever is a common symptom in self-limiting, benign viral illness. However, some febrile patients without apparent source of infection may have an occult severe bacterial infection that a CRP test can help confirm.74-76,115

Acute respiratory tract infections

Acute respiratory tract infection (ARTI) is the most frequent reason for seeking medical attention in primary care121, 122, also accounting for most antibiotic prescriptions.27,36,37,100,121-126 ARTIs are caused by viruses, bacteria or a combination of both, and cases of different aetiology often present with similar symptoms. Identifying patients with a viral infection and patients suffering from a bacterial infection requiring antibiotics is therefore a daily challenge in primary health care.
Upper respiratory tract infections

**Common cold.** The common cold is a viral illness in which symptoms like runny nose, sneezing, sore throat and cough are present but not prominent. The common cold usually resolves spontaneously, although a small proportion may be complicated by bacterial co-infection.\(^{127,128}\) Despite the viral origin, antibiotics are widely prescribed for patients with the common cold.\(^{100,127-129}\)

A normal CRP concentration can help to identify patients with the common cold for which antibiotics are not indicated.

**Acute sinusitis.** Most cases of sinusitis are viral and uncomplicated but patients are frequently prescribed antibiotics.\(^ {90,130-132}\) Up to 90% of patients with a cold exhibit symptoms of sinusitis in the early stages of their illness but only a minor part develop bacterial sinusitis.\(^ {130,133}\)

Bacterial and viral sinusitises are difficult to differentiate based on clinical symptoms and signs only.\(^ {54,80,91}\) Measurement of CRP assists in diagnosing bacterial sinusitis and in deciding whether to prescribe antibiotics to a patient with symptoms of sinusitis.\(^ {54,100,134}\)

Implementing the CRP test in primary care may lead to reduction in antibiotic prescribing to patients with sinusitis.\(^ {54}\)

**Acute pharyngitis.** Most cases of acute pharyngitis are caused by viruses. The most common bacterial cause of acute pharyngitis is *Streptococcus pyogenes*, also known as group A β-haemolytic streptococcus (Strep A). Strep A infection is the only commonly occurring form of sore throat warranting antibiotic treatment.\(^ {136-139}\)

Only a minority of sore throats in adults are caused by Strep A, while children have a higher incidence.\(^ {136-141}\) Antibiotics are nonetheless prescribed to most patients\(^ {140-142}\), often to avoid such potentially severe, but nowadays rare, complications as rheumatic fever and acute glomerulonephritis.\(^ {139,143}\)
As the signs and symptoms of Strep A infection and those of pharyngitis caused by other micro-organisms (most commonly viral) often overlap, it is difficult to make an accurate diagnosis on clinical grounds only. To avoid inappropriate antibiotic treatment of large numbers of patients with pharyngitis, it is important to verify or exclude Strep A infection using a diagnostic test, such as the QuikRead Strep A test.

An immediately available CRP result may also increase the proportion of sore-throat patients diagnosed correctly and treated adequately. Elevated CRP concentrations have been found in patients with Strep A pharyngitis.

Acute otitis media. The incidence of acute otitis media (AOM) is highest between the ages of 6–12 months, and more than 70% of children have AOM before their second birthday. AOM is generally considered to be a bacterial infection, although also viruses seem to have a role in the development of AOM. Bacterial and viral AOM cannot be differentiated on clinical signs and symptoms alone.

An elevated CRP concentration has been found to suggest bacterial AOM.

Lower respiratory tract infections

Acute bronchitis. In acute bronchitis cough is the most frequently observed symptom, and the illness usually lasts one to three weeks. About 70–95% of cases of acute bronchitis are caused by viruses. Bacterial aetioloogy has been established in only about 5–10% of patients with acute bronchitis.

Despite its overwhelmingly viral nature, an estimated 50–90% of doctor’s office visits for acute bronchitis result in an antibiotic prescription. There is little evidence to support the effectiveness of such an approach in
acute bronchitis, and routine antibiotic treatment of this illness is therefore not recommended.

The evaluation of patients should focus on ruling out community-acquired pneumonia (CAP) caused by bacteria. Quantitative measurement of CRP can help to distinguish acute bronchitis from bacterial CAP. Low CRP concentration along with a history and clinical findings suggesting a viral infection indicates that antibiotics are not needed.

**Community-acquired pneumonia.** A wide variety of viruses, bacteria and atypical agents can cause community-acquired pneumonia (CAP).

While antibiotics are seldom required for acute lower respiratory tract infections, which are to a great extent of viral origin, antibiotics are nearly always indicated for bacterial CAP. A delay in treatment of bacterial CAP increases the risk of a fatal outcome.

The prevalence of bacterial CAP is about 5% among patients suspected of having the infection.

In primary care, CAP is often diagnosed on the basis of symptoms and physical examination alone, which may be insufficient to identify patients with bacterial CAP requiring antibiotic treatment. This is particularly true in primary care because of the lower incidence and lower severity of CAP found there.

Quantitative measurement of CRP in combination with patient history and clinical findings can contribute to the diagnosis of CAP. Patients with confirmed bacterial CAP have considerably higher CRP levels than patients with other acute lower respiratory tract infection. High CRP values may also correlate with disease severity, which may be of value in deciding about the necessity of inpatient care. CRP is also useful in monitoring the response to antibiotic therapy.
Urinary tract infections

Acute uncomplicated cystitis (lower urinary tract infection) is one of the most common bacterial infections.\textsuperscript{172-174} As almost 80–90\% of uncomplicated urinary tract infections in primary care are caused by \textit{Escherichia coli}\textsuperscript{172,175}, typical clinical cases are usually managed with minimal evaluation and routine prescription of an antibiotic.\textsuperscript{176,177}

The most severe form of urinary tract infection is acute pyelonephritis (upper urinary tract infection), which is associated with significant short-term morbidity and can cause permanent renal damage.\textsuperscript{174} If pyelonephritis is suspected, further investigation is required.

While increased CRP concentration is seldom encountered in patients with acute uncomplicated cystitis, it is commonly found in patients with acute pyelonephritis.\textsuperscript{119,178} Quantitative measurement of CRP therefore provides diagnostic support for differentiating between cystitis and pyelonephritis. A high CRP concentration in a patient with urinary tract infection indicates the possibility of pyelonephritis.\textsuperscript{119,178-180}
QuikRead® CRP in the routine diagnosis of acute respiratory tract infection

The decision tree on the following page illustrates potential courses of action when QuikRead CRP is used to support clinical decision-making in acute respiratory tract infection.

In this scheme, a CRP concentration of 10 mg/l is used as the clinical cut-off for excluding bacterial infection, although it may lead to overdiagnosis and unnecessary treatment in some patients without bacterial infection. The health care practitioner is therefore advised to set an optimal cut-off value for each condition to achieve the best possible treatment outcome.

An increase in CRP concentration between successive measurements is usually a sign of the patient’s infection having taken a turn for the worse. A reduction in CRP concentration, on the other hand, is a sign of patient recovery.

This decision tree should be considered only a guide for clinical decision-making and should never be relied upon as a substitute for professional medical judgement.
The decision tree

Asthma, allergy, COPD etc ruled out

Clinical signs, duration of symptoms

ACUTE RESPIRATORY TRACT INFECTION

Measure CRP

CRP < 10 mg/l

Probable viral cause

Symptomatic treatment

Patient recovers

Patient returns: symptoms persist / turn to worse

Measure CRP

CRP < 10 mg/l

Additional investigations / treatment based on clinical picture

Patient recovers

CRP > 10 mg/l

Most likely bacterial cause

Antibiotic prescription (if clinical picture requires)

Patient recovers

CRP > 50 mg/l

Probable bacterial cause

CRP > 10 mg/l

Patient returns: symptoms persist / turn to worse

Measure CRP

CRP < 10 mg/l

Additional investigations / possible change of antibiotics

*) CRP increased compared to previous measurement / not considerably decreased

Patient recovers
The QuikRead® CRP System

Please also visit www.quikread.com
### References


Teie DW et al. Epidemiology of Otitis Media During the First Seven Years of Life in Children in Greater Boston: A Prospective, Cohort Study. J Infect Dis 1989;160(1):80-84.


