How to use C-reactive protein

Emma M Dyer, 1 Thomas Waterfield, 2 Hannah Baynes 3

ABSTRACT
A 3-month-old baby is brought to the paediatric emergency department by their parents because of a fever. You decide to check their inflammatory markers. Their C-reactive protein (CRP) level comes back as 20 mg/L. Does this affect whether or not you start antibiotic therapy? Does it influence your decision to admit or discharge the patient? CRP is a commonly used biochemical test and yet its use is constantly debated and challenged. We look at the current evidence and suggest the best way to use this test in clinical practice.

INTRODUCTION
The febrile child is a common paediatric presentation, accounting for 20% of attendances to the paediatric emergency department (ED). 1 Very few of these will have a serious bacterial infection (defined as septicaemia, meningitis, confirmed appendicitis, pneumonia, osteomyelitis, cellulitis, bacterial gastroenteritis or complicated urinary tract infection), and a large proportion of these will be viral in origin. However, the consequences of missing the serious bacterial infections can potentially be catastrophic. Infectious disease still accounts for 20% of paediatric deaths in the United Kingdom. 2 Distinguishing between a serious bacterial infection (SBI) requiring antibiotics and a viral infection is mostly a clinical decision and the National Institute for Health and Care Excellence (NICE) guidance is a useful tool in that scenario. 3

Historically, one of the markers clinicians have used to inform this and to guide both starting and stopping antibiotics is the measurement of the C-reactive protein (CRP). This will be a familiar tool to all paediatricians, but the usefulness of CRP continues to be debated. Nevertheless, it is the only biomarker that NICE currently recommend in the assessment of the febrile child. 3 Its use in the NHS is endemic and at over £1.00 per test ordered it is not without cost.

In this article, we discuss the diagnostic accuracy of CRP in a range of clinical scenarios.

PHYSIOLOGICAL BACKGROUND
CRP is one of the pentraxin proteins—these are pattern recognition proteins that make up an important part of the innate immune system. It is produced in the liver in response to cytokines, in particular interleukin (IL)1, IL-6 and tumour necrosis factor. CRP helps with complement binding and with the phagocytosis of pathogens by macrophages. 5 It may also help to clear necrotic or apoptotic cells (figure 1). 5 6

CRP starts increasing just 4–6 hours after the onset of inflammation, doubling every 8 hours and peaking at 36–50 hours. It has a short half-life, so rapidly decreases once the inflammation has resolved (figure 2). 4 7 Hence, when sampling CRP, it is important to think about when in the timeline of the inflammatory response you are taking the sample.

TECHNOLOGICAL BACKGROUND
Blood for CRP testing is collected in a lithium heparin bottle and a minimum volume of 0.3 mL of blood is typically required. As well as the traditional laboratory test for CRP which may take an hour or more for a result, there are now point-of-care tests. These use as little as 1.5 µL of blood which can be obtained from simple finger prick at the bedside and can give a result in 4 minutes or less. These assays often have a range of CRP that they will measure, and so over a certain value (commonly around 200 mg/L), the result will read as just >200 mg/L. 6

INDICATIONS/LIMITATIONS
In febrile children does a high CRP indicate the presence of a serious bacterial infection? An elevated CRP alone is not conclusive evidence of a serious bacterial infection. As with all biomarkers, the clinical context is vital, and no single biomarker has sufficient diagnostic accuracy to be used as a rule in test. The sensitivity and specificity of CRP for serious infection varies depending on the cut-off value applied. A very low cut-off value will be very sensitive but poorly specific and a very high cut-off will be specific but poorly sensitive.
Interpretations

In a recent study by Verbakel et al, the cut-off value of 75 mg/L has been suggested as highlighting those children at greater risk of SBI. Verbakel et al studied 4608 children with 5617 illness episodes across 12 paediatric units with point-of-care CRP performed at triage. Of the 5617 illness episodes, 378 (6.7%) had a CRP >75 mg/L. In this group, there were 100 SBIs (26.5%). The overall SBI rate for all patients was 4.9% meaning that an elevated CRP >75 mg/L conferred a 5.4× relative risk of SBI.9

While an elevated CRP alone cannot be used to rule in SBI an elevated CRP >75 mg/L does confer an increased risk. Other non-infectious causes of an elevated CRP are outlined in table 1.10 11

In a febrile child can a low CRP be used to exclude SBI?

In the same study by Verbakel et al, a cut-off CRP of 20 mg/L was suggested as being useful in identifying children at low risk of SBI. There were 3722 children with a low CRP <20 mg/L and of these 84 were diagnosed with SBI (2.3%). SBI was therefore around half as likely as in overall population and 11.5 times less likely than in the high CRP group. If the child appeared well the risk of SBI fell further to 0.4%. In summary a low CRP <20 mg/L confers a significantly reduced risk of SBI. It, however, cannot be used in isolation as a rule-out test. In the Verbakel’s study, six well-appearing children with low CRP levels were subsequently diagnosed as having SBI.9

Table 2 below outlines estimate pretest and post-test probabilities over a range of CRP values based on data from the Verbakel et al paper.9

Do the same principles apply to newborns and infants under 3 months of age?

Newborns and young infants are at higher risk of SBI and may not display the same clinical features of infection and sepsis as older children. This makes young infants and newborns particularly challenging to assess for SBI. In this situation, historically, CRPs have been

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Figure 1  Synthesis and action of C-reactive protein (CRP). Adapted from Smith et al.6

Figure 2  C-reactive protein (CRP) response to inflammation. Authors own, informed by Jaye et al.4

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used to help inform the decision to start and stop antibiotics and to treat for suspected bacterial infection.

Unfortunately, initial CRP measurements have been shown to be poorly accurate when assessing newborns. One American study of suspected sepsis in neonatal units found that the initial CRP result to be poorly sensitive for SBI indicating that a normal initial CRP in this group should not be used as justification to withhold antibiotics.

The same study was, however, able to demonstrate that serial CRP measurements were accurate in diagnosing SBI in newborns. They reported that an elevated CRP > 10 mg/L at 24–48 hours after presentation demonstrated a 97.6% and 94.4% sensitivity for proven (culture positive) or probable (clinical features but no positive cultures) bacterial infection. This would suggest that in newborns serial CRP measurements maybe useful in deciding when to stop antibiotics rather than when to initiate them.

It would appear that infants under 3 months of age behave similarly to newborns in terms of CRP kinetics. A large multicentred European study of over 2000 young infants under 3 months of age presenting with fever without source found that CRP was a poor predictor of serious bacterial infection. In this group, the most accurate predictor of SBI was appearing unwell.

**Does CRP have a role in stopping antibiotics in well, afebrile children?**

Historically, negative blood culture results have been used as an indicator to stop intravenous antibiotic therapy. Yet, blood cultures have a poor diagnostic accuracy for invasive bacterial infections with one study demonstrating that one blood culture alone identified only 73.2% of invasive bacterial infections. A more sensitive indicator for invasive bacterial infection would be useful in deciding the safety of stopping antibiotic therapy. As briefly discussed above, serial CRPs have been shown to be highly sensitive for diagnosing invasive bacterial infections and perform favourably when compared with blood cultures. For example, a study performed in newborns found that

<table>
<thead>
<tr>
<th>Condition</th>
<th>Effect on CRP</th>
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<tbody>
<tr>
<td>Liver failure</td>
<td>Suppressed levels</td>
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<tr>
<td>Immunocompromise</td>
<td>Suppressed levels</td>
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<tr>
<td>Pancreatitis</td>
<td>Elevated levels</td>
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<tr>
<td>Burns</td>
<td>Elevated levels</td>
</tr>
<tr>
<td>Inflammatory disorders, for example, juvenile idiopathic arthritis</td>
<td>Elevated levels</td>
</tr>
</tbody>
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**Table 1 Common conditions and their impact on C-reactive protein (CRP) levels**

<table>
<thead>
<tr>
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<th>Pretest (%)</th>
<th>Test result</th>
<th>Post-test (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unwell children attending emergency department</td>
<td>4.9%</td>
<td>CRP&lt;5 mg/L</td>
<td>1.5%</td>
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<td></td>
<td></td>
<td>CRP&lt;20 mg/L</td>
<td>2.0%</td>
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<tr>
<td></td>
<td></td>
<td>CRP&lt;80 mg/L</td>
<td>25.7%</td>
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<tr>
<td></td>
<td></td>
<td>CRP&gt;200 mg/L</td>
<td>65.7%</td>
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**Table 2 Diagnostic accuracy of C-reactive protein (CRP) in febrile children**

**Table 2**

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**Can CRP be used to rule in/out the presence of a bacterial infection?**

**Figure 3**

A single CRP measurement demonstrates a poor diagnostic accuracy for bacterial infection in newborns and infants under 3 months of age and should not be used to guide initial treatment. Serial CRP measurements can be useful in monitoring response to treatment.

**Figure 3** A summary of how to use C-reactive protein (CRP), authors own.
all those with positive blood cultures also had raised CRP levels, whereas a normalising CRP demonstrated a 100% negative predictive value for excluding invasive bacterial infection. Other studies in newborns have reached similar conclusions with negative predictive values of 99%.16

More studies are needed looking at this in an older population, although some evidence in adults suggests that CRP is useful as a guide for the duration of treatment with antibiotics.17

For a summary of the article, see figure 3.

Contributors EMD was responsible for all aspects of this work including the concept of the article and content of the manuscript. TW critically appraised the manuscript, contributed further ideas and designed the infographic. HB also critically appraised the manuscript. All authors edited the manuscript and agree to be accountable for all aspects of the work.

Competing interests None declared.

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REFERENCES