Title: Role of C reactive protein and procalcitonin in the diagnosis of lower respiratory tract infection in children in the outpatient setting

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What you need to know?

Discriminating between viral and bacterial lower respiratory tract infection (LRTI) in children in ambulatory care using clinical features alone is challenging.

Biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) have a limited capacity to rule in bacterial pneumonia in ambulatory settings where the prevalence of bacterial pneumonia is low.

There is growing evidence supporting that antibiotic therapy can be safely withheld in well-appearing children with equivocal clinical presentation and low CRP and PCT levels.

Lower respiratory tract infections (LRTI) in childhood are commonly caused by viral infections. However, distinguishing viral from bacterial LRTI in children solely based on a medical history and physical examination can be challenging.[1] Therefore, an accurate marker for bacterial pneumonia will be useful when clinical discrimination between bacterial and viral infection is a challenge. The National Institute for Health and Care Excellence recommends point-of-care C-reactive protein (CRP) testing to guide antibiotic therapy for adults with symptoms of LRTI and diagnostic uncertainty after a clinical assessment (antibiotic treatment should be offered to patients with CRP levels >100 mg/L and avoided for CRP levels <20 mg/L).[2] Although CRP and procalcitonin (PCT) have not been deemed to have sufficient sensitivity and specificity to rule in bacterial pneumonia in children in ambulatory care,[3-4] data generated over the last years suggest that both biomarkers can help clinicians to reduce diagnostic uncertainty and unnecessary antibiotic prescriptions in a subset of children with LRTI and equivocal clinical features.

What are C-reactive protein and procalcitonin?

CRP and peripheral white blood cell (WBC) count are the most common biomarkers for infection in clinical practice worldwide. CRP, which is primarily produced by the liver in response to inflammation, plays a major role in inducing complement activation and facilitating phagocytosis by macrophages.[5-6] PCT is a precursor peptide of the hormone calcitonin, which is secreted by a wide range of parenchymal cells in response to systemic inflammation. Although both biomarkers have a good negative predictive value (NPV) to rule out serious bacterial infections, PCT is increasingly used to identify severe bacterial infections in children such as urinary tract infection and meningitis, and determine the risk of serious bacterial infection in infants with fever without source and oncology patients with neutropenic fever, since it shows a more specific increase in response to bacterial infection, becomes elevated faster, and decrease earlier in response to an appropriate antibiotic therapy than CRP (Table 1).[5, 7-8] Conversely, whereas PCT is mostly performed in emergency care settings in middle-high income settings due to its higher cost and longer turnaround time, CRP is widely used in primary care, including in some low-income countries, due to its affordability and fast turnaround time (Table 1).[5-8]

The optimal cut-off values for CRP and PCT to rule in or rule out bacterial LRTI in ambulatory care have not been established. Nevertheless, among febrile children assessed in acute care settings with intermediate (5.0-20.0%) to high (>20.0%) prevalence of serious bacterial infections, a CRP value <20 mg/L or a PCT value <0.5 μg/L makes a SBI improbable, whereas it should be suspected if CRP level is >80 mg/L or PCT value is >2 μg/L.[9]

Can CRP and PCT help doctors diagnose bacterial LRTI in children in ambulatory care?

LRTI commonly present in children with overlapping clinical and radiological features, leading to the overuse of antibiotics driven by the fear of leaving a patient with bacterial pneumonia untreated. Hence the need for reliable biomarkers that accurately identify children with bacterial infection.

Studies designed to evaluate the clinical performance of PCR and PCT to predict bacterial pneumonia caused by typical microorganisms in children assessed in the hospital emergency setting found variable sensitivities, ranging from 44.0 to 94.0% using optimal cut-off values exceeding 1.5 μg/L for PCT and 65 mg/L for CRP.[10-13] However, it should be considered that such high serum concentrations are often observed in patients who are sufficiently ill to require hospitalisation, and in whom bacterial pneumonia may be diagnosed efficiently by a thorough clinical assessment. Unfortunately, the assessment of the degree to which CRP and PCT could outperform clinical judgment in actual practice is hampered by the lack of studies comparing the performance of both biomarkers with clinical features. For example, Galetto-Lacour et al.[13] studied 75 children hospitalized with community-acquired pneumonia, including 37 patients with presumed pneumococcal aetiology based on combined serological and molecular testing. In this study, an optimal cut-off value of ≥ 1.5 μg/L for PCT for pneumococcal pneumonia yielded 94% sensitivity and 1.99 positive likelihood ratio, respectively. Also, based on a pre-test probability of 49%, PCT increased post-test probability to 65%. However, it is difficult to separate the proportion of patients that could have benefited from PCT testing without comparing this post-test probability with that generated by a medical history and physical exam. On the other hand, specificities and positive predictive values for both biomarkers in these studies rarely reached 80.0%,

indicating a substantial number of viral infections among patients with high serum CRP and PCT concentrations.[10-13]

There are not many studies evaluating the performance of CRP and PCT to predict bacterial pneumonia in children in primary care. A Finnish group measured CRP and PCT in 193 and 190 serum samples of children with radiologically confirmed pneumonia managed in primary care. There were no significant differences in mean CRP and median PCT concentrations among children with serological evidence of pneumococcal infection compared with those with atypical and viral pneumonia. In fact, it was found that mean CRP and median PCT concentrations were <30 mg/L and <0.5 μg/L regardless of the aetiology.[14-15] These studies suggest that CRP and PCT are not accurate markers of bacterial aetiology in children in ambulatory settings with low prevalence of serious bacterial LRTI.

Can CRP and PCT assist clinicians to improve antimicrobial prescribing in children with LRTI in the outpatient setting?

There is compelling evidence supporting that low PCT concentrations can accurately identify ambulatory adults and children who have a low risk of pneumonia caused by typical bacteria, particularly *Streptococcus pneumoniae*, suggesting that antibiotic therapy can be safely withheld in well-appearing children with low PCT levels and equivocal clinical presentation.[7, 13, 16-18] For instance, a multicentre study that analysed PCT levels in 532 hospitalized children with radiologically confirmed pneumonia found a 96.0% NPV for typical bacteria among 242 children (45.0% of the cohort) with PCT values <0.25 μg/L. In fact, none of the 120 children with PCT values <0.1 μg/L had typical bacteria detected.[16]

Likewise, low CRP concentrations have similar diagnostic accuracy to rule out bacterial LRTI. Currently, point-of-care (POC) CRP is routinely used in the diagnostic work-up of adults with LRTI in primary care in several high-income countries. In this particular setting, low CRP concentrations combined with clinical assessment have improved clinical decision-making by reducing antibiotic prescription.[6, 19] Interestingly, this benefit has not always been observed in children, which may have been related to a reduction of the clinical value of the test due to poor adherence to CRP-guided prescribing guidelines.[20-22] For example, in the Netherlands where national guidelines on the management of LRTI are similar to NICE guidelines,[23] a trial that randomized 309 children aged 3 months-12 years with fever and cough from 28 primary practices to receive either clinical assessment plus POC CRP or clinical assessment only, did not find a significant difference in antibiotic prescription rates between both groups. However, among 170 children who had CRP measured, 14.0% with CRP <10 mg/L and 44.0% with CRP between 10-100 mg/L had antibiotics prescribed,

suggesting an inappropriate use of antibiotics in a fraction of patients with low and intermediate CRP values.[22]

By contrast, a study performed in 9 primary practices in Tanzania enrolled 1726 non-seriously ill febrile children aged 2-59 months with cough, who were randomly allocated to two groups: The intervention group received antibiotic treatment based on sequential use of the World Health Organization clinical criteria to define childhood pneumonia (tachypnea and chest indrawing) and POC CRP. Patients meeting clinical criteria plus a CRP > 80 mg/L were deemed to have a bacterial LRTI and had oral antibiotics prescribed (20/865 patients; 2.3%). The control group was treated with antibiotics based on clinical criteria only (345/854 patients; 40.4%). Notably, antibiotic prescription was not only almost 20-fold lower in the intervention group (risk ratio [RR], 0.06; 95% confidence interval [95% CI], 0.04-0.09) but also secondary hospital admissions and deaths were significantly lower compared with the control group (RR, 0.30; 95% CI, 0.10-0.93).[24]

CASE

George is a previously healthy and fully vaccinated (including 13-valent pneumococcal conjugate vaccine) 22-month-old boy brought to the Emergency Department (ED) because of a 12-hour history of high fever (up to 40° C). He had been suffering from low-grade fever, runny nose, cough, and decreased oral intake for the last 2 days. On examination, he did not look particularly ill but was febrile (38.3° C). His respiratory rate was 45 breaths/minute (normal range 18-24 months: 25-40 breaths/minute), heart rate was 140 beats/minute (normal range 18-24 months: 98-135 beats/minute), and blood oxygen level was 95%. Although breath sounds were not decreased, some bibasal crackles were noted on chest auscultation. A chest X-ray was interpreted as having bilateral peribronchial infiltrates and haziness in the right lower lobe. Although a lower respiratory tract infection was diagnosed and he was considered to be clinically stable at that stage, the dilemma of differentiating between bacterial and viral infection, and the need to initiate antimicrobial therapy prompted clinicians to request some blood tests.

Blood tests revealed a WBC count of 22.5 X 10^9/L (60.0% neutrophils), a CRP of 30 mg/L (normal <5 mg/L) and a PCT of 0.25 μg /L (normal <0.5 μg/L).

So, what is the role of CRP and PCT in children with LRTI in the outpatient setting?

Neither CRP nor PCT are sufficiently reliable to rule in bacterial LRTI in the outpatient setting. For ill-appearing children who meet traditional clinical criteria for bacterial pneumonia in the hospital emergency setting, CRP and PCT at the thresholds that best predict bacterial pneumonia do not seem to provide additional information beyond a comprehensive clinical evaluation. Furthermore, there is still a substantial overlap between bacterial and viral infection amongst patients with high serum concentrations. PCT and CRP lack diagnostic accuracy to rule in bacterial LRTI in well-appearing children in primary care, since the pre-test probability for serious bacterial infections is low in this scenario, at least in high-income countries.

Although most ambulatory children with LRTI do not need antibiotic treatment, we acknowledge the adjunctive value of low CRP and PCT levels to rule out bacterial pneumonia and reduce antibiotic exposure in well-appearing children in whom the distinction between bacterial and viral LRTI infection is not possible after a thorough clinical assessment. While this approach is formalized in adult guidelines, emerging evidence is also supporting that the approach is effective and safe in children.

OUTCOME

Since the patient was clinically stable and PCT was low, mum was reassured that George likely had a viral infection that would not benefit from antibiotic treatment. Consequently, the child was discharged home without antibiotics. A follow-up visit 3 days later with his General Practitioner showed that he had been completely apyrexial for the last 24 hours and feeding better. No further follow-up was advised.

PATIENT INVOLVEMENT

PCT and CRP are available 24 hours a day in the authors' hospital of this review. We sought feedback from parents of a group of children with fever and respiratory symptoms assessed in our EDs in whom PCT and CRP were used in combination with clinical judgment to withhold antibiotics. The case discussed here is fictitious and the clinical scenario presented was elaborated based on their experiences in ED and precious comments. Interestingly, all of them believed that antibiotics are often overprescribed in acute respiratory infections in children, which led us to emphasize the value of low CRP and PCT concentrations to improve clinical decision-making in children with LRTI and diagnostic uncertainty in ambulatory care.

Rational testing into practice

Think about how many children with LRTI are prescribed antibiotics due to diagnostic uncertainty in real clinical practice. Do you think that POC CRP or PCT could help optimize antibiotic prescribing in LRTI in children in your practice?

High serum concentrations of CRP and PCT are often found in seriously ill children with pneumococcal pneumonia assessed as emergency department outpatients. However, what proportion of these patients would be missed by a meticulous clinical assessment?

How this article was made?

We reviewed British national guidelines on the assessment and management of children and adults with lower respiratory tract infections. Relevant articles were searched using PubMed and the following keywords: C-reactive protein (CRP), procalcitonin (PCT), biomarkers, lower respiratory tract infections, pneumonia, and children. Furthermore, the manuscript was reviewed by four internationally renowned specialists in the fields of Paediatric Infectious Diseases and Emergency Medicine whose valuable comments and views contributed to produce this review.

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Table 1. Comparison between C-reactive protein and procalcitonin as biomarkers for bacterial infection.

	C-reactive protein	**Procalcitonin**
Detectable rise	12 hours	3 hours
Peak	2-3 days	6 hours
Response after antibiotic treatment	Remains elevated for several days	Decreases 24 hours after infectious insult ends
Cost	Inexpensive and cost-effective in low-income countries	Significantly higher, which represents an obstacle for its implementation in low-income countries
Serum measurement in hospitals	Widely and commonly available around-the-clock	Not available in many laboratories and during out-of-hours in some hospitals
POCT availability	Widely available in primary care (turnaround time ≤ 5 minutes)	Mostly available in Emergency Departments (turnaround time 15-30 minutes)

POCT: Point-of-care testing.