Diagnostic test accuracy of serum procalcitonin compared with C-reactive protein for bone and joint infection in children and adolescents

Recommendations*

- C-reactive protein (CRP) should be used as the preferred test for diagnosing children and adolescents with acute bone and joint infection. (Grade A)
- Procalcitonin (PCT) is currently not recommended as an add-on or replacement test for diagnosing acute bone and joint infection in children and adolescents. (Grade A)

* Please refer to: JBI’s Grades of Recommendation

Information source

This Best Practice Information Sheet is a summary of evidence derived from a systematic review published in 2021 in JBI Evidence Synthesis.[1]

Background

Osteoarticular infection is an infection of the bone and/or joint and is estimated to be prevalent in at least 2 per 10,000 children. It is more common in children under five years of age and is more likely to occur in boys than girls. Rapid diagnosis and early treatment of osteoarticular infection is essential to avoid severe and permanent sequela in children. The diagnosis of bone and joint infections can be difficult as the presentation and clinical features are similar to other non-infective conditions. While there is currently no single error-free and non-invasive diagnostic test to rule in and rule out osteoarticular infection in children, there is sufficient evidence to support the use of measuring serum C-reactive protein (CRP) as an acute inflammatory biomarker in suspected bone and/or joint infection. This biomarker is now performed routinely to help in the diagnosis of acute osteoarticular infections. A systematic review of acute pediatric hematogenous osteomyelitis in 2012 concluded that CRP was the most useful marker to distinguish osteomyelitis with or without septic arthritis, however no formal statistical analysis on the test characteristics of CRP was performed.

Procalcitonin (PCT) is another serum inflammatory biomarker that has recently emerged as being more specific for bacterial infections. This biomarker has diagnostic test accuracy characteristics that appear to favor serum measurement of PCT over CRP in suspected cases of acute osteoarticular infections. This evidence is based on one systematic review and meta-analysis performed in 2013 and a more recently conducted meta-analysis in 2017 using data extracted largely from the adult population. In both studies however, concerns regarding inconsistencies and limitations may have potentially biased the outcomes, raising some doubt over their findings and recommendations including the applicability for children and adolescents.

To date there has been no published meta-analysis specifically for children and adolescents that examines the test performance of either serum CRP or PCT for suspected osteoarticular infections. Estimates taken from individual trials alone may be underpowered with the potential for both false positive and false negative errors. Analyzing and summarizing all the available data using a statistical meta-analysis approach, may increase both the power and the precision of the diagnostic test effect estimates for both of these inflammatory markers.

Before any formal clinical recommendations can be made regarding the applicability of measuring serum PCT routinely in children and adolescents with suspected acute osteoarticular infections, further evidence from a systematic review and meta-analysis for this population, would be helpful to clinicians.

Objectives

The purpose of this Best Practice Information Sheet is to present the best available evidence presented in the systematic review examining the diagnostic accuracy of serum measurement of PCT compared with CRP in patients from one month to 18 years of age, admitted to hospital with suspected osteoarticular infection.

Diagnosis of Interest

The systematic review evaluated the diagnostic accuracy of PCT, alone or in combination with CRP, for identifying acute osteoarticular infection. The reference test (gold standard test) to which PCT and/or CRP was evaluated against included:

- A positive bacterial culture or polymerase chain reaction confirmation of an accepted pathogen from blood, biopsy, or aspirate, and/or
- Reported results for two or more of the following criteria:
  I. Purulent material from biopsy or aspirate specimen
  II. Positive radiological findings of osteoarticular infection
  III. Signs and symptoms consistent with osteomyelitis/ septic arthritis

[1] JBI EBP Database 23(9) 2021 [updated 2023] | 1
Quality of the research

Following the JBI approach to diagnostic systematic reviews, the review was conducted as per an a priori protocol. A comprehensive search was undertaken and studies selected against the inclusion and exclusion criteria. Assessment of methodological quality was undertaken by two independent reviewers with the studies assessed to be of moderate quality, with several sources of bias identified as judged using the Quality Assessment of Diagnostic Studies (QUADAS-2) tool.

Data was extracted using a standardized tool. In addition to sensitivity and specificity data, likelihood ratios, odds ratios, and predictive values with their respective 95% confidence intervals (CIs) were calculated and tabulated for all included studies.

Meta-analysis was conducted where possible.

Findings

A total of eight publications were included; six studies used a consecutive cohort-selected, cross-sectional design while the remaining two studies used a case-control design. Three studies included osteomyelitis while five studies examined septic arthritis. A total of 1,520 participants were included in the review with patient characteristics relatively uniform. The clinical setting was predominantly specialized hospital-based medical services with pediatric expertise. The index test thresholds reported for CRP included 20 mg/L and 10 mg/L, and the index test thresholds for PCT included 0.2 ng/mL, 0.5 ng/mL and 3.56 ng/mL.

C-reactive protein

A meta-analysis of studies that evaluated the diagnostic accuracy of CRP at a threshold of 20 mg/L reported a sensitivity with 95% confidence interval as 0.86 (0.76-0.92) and a specificity of 0.90 (0.83-0.94). This meta-analysis included four studies where the target condition included septic arthritis only.

A second meta-analysis was undertaken by combining six studies that evaluated suspected osteomyelitis and septic arthritis cases at different CRP thresholds (20 mg/L and 10 mg/L) using a hierarchical summary receiver operating characteristics model, or HSROC as it is commonly referred to. The HSROC curve describes how sensitivity and specificity trade off at different threshold values. The overall test accuracy of CRP was reported as a diagnostic odds ratio (DOR) of 39.48 (14.85-104.96). The wide confidence interval was attributed to differences of subjects with and without disease and exacerbated due to the smaller studies that were included in the analysis.

Serum procalcitonin

Only three studies were included in the review that evaluated the diagnostic accuracy of PCT for osteoarticular infection in children and adolescents; a meta-analysis was therefore unable to be undertaken.

Of the three studies, only one study examined osteoarticular infection and compared PCT (at threshold of 0.2 ng/L) to CRP (at a threshold of 10 mg/L). The findings reported PCT to be less sensitive than CRP (91.7% [61.5-99.8] versus 100 [73.5-100]) but more specific (81% [58.1-94.6] versus 26.3% [9.2-51.2]).

The global measure for diagnostic accuracy reported PCT outperforming CRP with a DOR of 46.8 [5.51-475] to 9.5 [0.5-189], respectively. The two studies examining PCT only however both reported a much lower global measure for the diagnostic accuracy of PCT. The second study included both septic arthritis and osteomyelitis cases with PCT at a threshold of 0.5 ng/L. Sensitivity was reported as 25% (3.19-65.1) and specificity of the test at 96.9% (94.2-98.6), with a DOR reported as 10.5 (0.0-53.1). The remaining third study examined children with osteomyelitis only with a PCT threshold of 3.56 ng/L. Sensitivity was reported as 77.2% (67.2-85.3) and specificity of the test at 69.7% (62.3-76.4); the DOR was reported as 7.8 (4.3-13.9).

Conclusions

The purpose of the systematic review was to formally examine the diagnostic accuracy of CRP and PCT in children and adolescents presenting to hospital with suspected bone and/or joint infection. The findings from this systematic review and meta-analysis are only applicable to comparable populations and setting.

The findings of the review demonstrate the sensitivity and specificity of using serum CRP as a diagnostic test for suspected osteomyelitis and septic arthritis in children. However, due to the limited number of studies included in the review, a meta-analysis evaluating the test accuracy of PCT was not possible and a direct comparison of the diagnostic accuracy of CRP with PCT could not be undertaken.

Implications for practice

The findings from this systematic review and meta-analysis provide clinicians and researchers with the best available evidence related to the test accuracy of CRP in children and adolescents with suspected osteoarticular infection.

The results highlight and provide increased support for the use of CRP as a diagnostic test for children with suspected acute bone and joint infection. The authors recommended that CRP remains the preferred adjunctive investigation to assist with the diagnosing of bone and joint infection.

Based on the current evidence presented in the review, the use of PCT as an add-on or replacement test is not recommended. Clinicians are advised to be cautious when recommending or requesting PCT in isolation until further evidence is available.
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**POPULATION**
Children between 1 month - 18 years

**DIAGNOSIS OF INTEREST**
Suspected osteoarticular infection

**INDEX TEST**
CRP and PCT for acute osteoarticular infection

**REFERENCE TEST**
Positive microbiology result (from biopsy, aspirate or blood) and/or radiological findings or signs and symptoms consistent with condition.

**C-REACTIVE PROTEIN (CRP)**
At a threshold of 20mg/L, the estimated pooled sensitivity of CRP was 0.86 (0.76-0.92) and the pooled specificity was 0.9 (0.83-0.94) for septic arthritis (moderate level of certainty)
When combining both osteomyelitis and septic arthritis cases, the overall test accuracy of using CRP (at thresholds of 10mg/L and 20mg/L) was reported as a diagnostic odds ratio of 39.48 (14.85-104.96) with positive likelihood ratio of 5.3 (2.3-11.9) and negative likelihood of 1.3 (1.1-1.6).

**PROCALCITONIN (PCT)**
Only 3 studies evaluated serum PCT for osteoarticular infection, therefore meta-analysis was not possible. The findings from individual PCT studies were inconclusive as to the overall diagnostic accuracy of this test.

**CRP VS PCT**
For osteoarticular infection in children and adolescents, there is currently insufficient published data to perform a comparative analysis of test performance.

**RECOMMENDATIONS FOR PRACTICE**

**C-reactive protein (CRP)**
- C-reactive protein (CRP) should be used as the preferred test for diagnosing children and adolescents with acute bone and joint infection. *(Grade A)*

**Procalcitonin (PCT)**
- Procalcitonin (PCT) is currently not recommended as an add-on or replacement test for diagnosing acute bone and joint infection in children and adolescents. *(Grade A)*
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References

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