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Is Procalcitonin Superior to CRP in Diagnosing Children with Suspected Acute Hematogenous Osteomyelitis?

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Abstract: ***This systematic review aims to measure the diagnostic accuracy of procalcitonin in detecting children with acute hematogenous osteomyelitis. A 6 - year - old boy presented with 4 days history of URTI, fever followed by left lower extremity pain and limping. His medical history is notable for eczema with a significant family history of Juvenile rheumatoid arthritis, and has been referred to rheumatology by his primary care physician for episodic bone pains over the last 6 months. On examination, he has a fever of 37.8, eczematous excoriation over his shins, is unable to bear weight due to pain, and his joints examination is normal. He is not miserable but not happy as well. You are wondering if this is a case of osteomyelitis that requires urgent managemet, or a case oftransient synovitis/reactive arthritis, or if you are the unlucky one who encountered his first episode of JRA. You remembered that Procalcitonin is used in adults to diagnose osteomyelitis and has been shown to outperform CRP in diagnosis and maximise patient outcomes. You are aware that PCT is very sensitive in detecting paediatric bacterial sepsis and meningitis and wondering whether it detects acute hematogenous osteomylitis.***

Keywords: diagnostic test accuracy, osteomyelitis, procalcitonin, sensitivity, septic arthritis, specificity

1. Introduction

Osteomyelitis, a severe bone infection, remains a substantial challenge in pediatric medicine due to its potentially debilitating consequences if not promptly and accurately diagnosed and treated. Timely and accurate diagnosis is critical for effective management, as it can prevent complications, reduce the length of hospital stays, and optimize patient outcomes. As a result, clinicians have long sought reliable diagnostic markers to aid in the early identification of this condition.

Among the multitude of diagnostic markers under consideration, two have emerged as prominent candidates for enhancing the diagnostic accuracy of osteomyelitis in children: Procalcitonin (PCT) and C - reactive protein (CRP). These biomarkers have gained increasing attention for their potential in differentiating between infectious and non - infectious causes of bone pain and inflammation. The ongoing debate centers on whether PCT holds a superior diagnostic advantage over CRP in the context of pediatric osteomyelitis, with clinicians and researchers alike eager to establish a clear hierarchy between these two markers.

Notably, in the realm of adult medicine, Procalcitonin (PCT) has proven to outperform C - reactive protein (CRP) as a diagnostic marker for osteomyelitis. The success of PCT in the adult population has ignited interest in its potential in pediatric osteomyelitis. This systematic review aims to explore and synthesize the existing body of evidence pertaining to the comparative diagnostic performance of PCT and CRP in children with osteomyelitis, building on the success observed in adults. By doing so, we aim to provide a comprehensive assessment of the utility of these biomarkers in enhancing the accuracy of osteomyelitis diagnosis and to identify potential areas of improvement in the diagnostic process.

2. Review Question

What is the diagnostic test accuracy of serum measurement of PCT compared with CRP in patients between one month and 18 years of age who are admitted to hospital with suspected osteoarticular infection?

PICO format:

- **Population:** Children with suspected acute hematogenous osteomyelitis
- **Intervention:** Procalcitonin as a diagnostic marker
- **Comparison:** C - reactive protein (CRP) as a diagnostic marker
- **Outcome:** Accuracy in diagnosing acute hematogenous osteomyelitis
- **Gold Standard:** Microbiology sample/tissue biopsy for definitive diagnosis

Search:
Search strategy attached in Appendex1.

Database searched:

1) Ovid MEDLINE (R) ALL 1946 to March 2023.
2) Embase (1996 - 2023 week 11).
3) Cochrane Database of Systematic Reviews (2005 - 2023).
4) Cochrane Central Registry of Controlled Trials (February 2023).
5) Manual articles reference search**.**

The search yielded 1636 articles (1485 from Medline, 104 from Embase, 3 from Cohrane, 41 from the Cohrane Registry of Controlled Trials, and 3 from a manual search of article references). The selection process with theinclusion and exclusion criteria explained in (figure1).

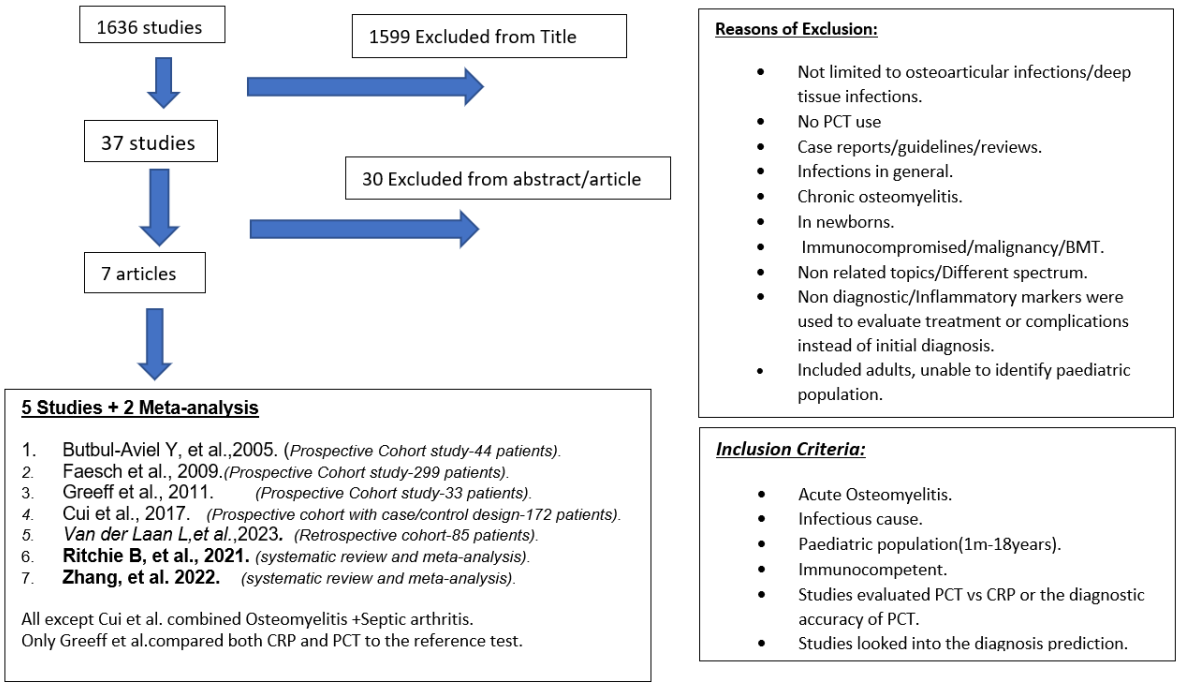

Figure 1: Search flow with inclusion and exclusion criteria.

The search yielded seven results. Five research studies (Butbul - AvielY, et al.2005, Faesch et al., 2009, Greeff et al., 2011, Cui et al., 2017 and Van der Laan L, et al., 2023). as well as two large - scale reviews (Ritchie B, et al., 2021 and Zhang, et al.2022). The first four investigations were previously included in the systematic reviews; so, in this review, we will analyse the findings of the most recent study Van der Laan L, et al., 2023 as well as the systematic reviews Ritchie B, et al., 2021 and Zhang, et al.2022. (**Table 1).**

Citation	Study group	Study type	Outcome	Key Result	Comments
Zhang, et al.2022 [1] **(Search until 10August 2021)** *"looked into diagnostic accuracy of PCT"*	Meta - analysis of 4 studies: - Butbul, et al., 2005 [2] - Faesch et al, 2009 [3] - Greeff., 2011 [4] - Cui et al., 2017[5] 654 children. Goldstandard: bacterial culture.	Level I Meta - analysis	PCT may serve as a biomarker for diagnosis of osteomyelitis, the specific optimal cut off value of PCT and specific population still needed to be verified by large sample studies. No evidence to support PCTuse in septic arthritis	PCT>0.1 had a sensitivity of 0.72, 95%CI (0.65−0.79), specificity of 0.90, 95% CI (0.87−0.93) positive LR of 3.87, 95% CI (2.53−5.90), negative LR of 0.39, 95%CI (0.22−0.70), diagnostic OR was13.13, 95% CI (6.46−26.66), AUC of PCT was 0.88.	**Significant statistical heterogeneity**. I square >80% Mixed population osteomyelitis & septic arthritis. **Sub group analysis** for OM group revealed sensitivity and specificity of 0.77, 0.70 respectively.
Ritchie B, et al.2021 [6] (Search until January 2021) *"Looked into PCT vs CRP"*	8 studies included: 3 - included in the Systematic review of PCT. Other 5 were specific for septic arthritis. PCT studies: - Faesch et al, 2009 - Greeff., 2011 - Cui et al., 2017 Gold standard: bacterial culture.	Level I Meta - analysis for CRP, systematic review for PCT	Insufficient evidence to statistically evaluate the diagnostic accuracy of procalcitonin.	Only CRP diagnostic accuracy results were reported. **Unable to perform meta - analysis on PCT**	Only studies in English. Mixed Osteomylitis ans septic arthritis. Tight inclusion criteria led to smallernumber and size. Butbul - Aviel et al. study was not included as age in septic arthritis group didn't fulfil the criteria although was valid for Osteomyelitis group. Statistical heterogenity not reported. ++Extensive list ofexcluded studies with the reason was provided.
Van der Laan L, et al.2023. [7] (Study from July 2020 to	85 children were categorized into cohorts of: Deep infection (n = 21) (17 had OM+ 4 had SA);	Level III – Retrospective cohort comparison	**Combination** of parameters: PCT<0.1, ESR<18, CRP<3.3, Temp<37.8 provide	PCT > 0.1 ng/mL independently predicted deep infection in 84.7% of cases, outperforming	Newest, after the 2 meta - analyses. Combined deep infections,

November 2021) USA *"Looked into PCT and CRP"*	Superficial infection (n = 10), and non - infection (n = 54).		high NPV and might support predictive judgment.	WBC, CRP, and absolute neutrophil count. PCT of > 0.1 ng/mL had sensitivity of 90.4%, specificity of 84.4%, PPV 64.3, NPV 94.7, AUC of 0.852, Accuracy 84% for deep infection. CRP>2: SN 85%, SP71%, PPV 50%, NPV 93% Accuracy 75%.	unable to determine isolated Ostemylitis. High risk of selection bias, PCT acquisition trends varied throughout the study. Small sample, during COVID pandemic may affect disease prevalence.

3. Discussion

Certainly, here's the revised text with the percentages and numbers included:

In the reviewed literature, Procalcitonin (PCT) as a diagnostic marker for pediatric osteomyelitis is discussed. The primary focus of the literature search was the diagnostic accuracy of PCT compared to C - reactive protein (CRP). However, due to limited evidence, studies investigating the diagnostic accuracy of PCT alone were also included.

One notable observation is that, except for Cui et al., all cohorts considered in these studies examined a combined population of children with osteomyelitis and septic arthritis, potentially introducing bias into the results. Additionally, significant clinical and statistical heterogeneity, along with inconsistencies in PCT and CRP cutoff values, were observed across these studies.

Two systematic reviews, namely Zhang et al. and Ritchie B et al., examined these studies. Zhang et al. aimed to assess the diagnostic value of PCT in osteomyelitis and septic arthritis, combining relevant studies[2, 3, 4, 5]. The analysis revealed significant statistical heterogeneity, possibly due to clinical heterogeneity, small study size, or methodological limitations. Subgroup analysis for isolated osteomyelitis suggested a sensitivity of 0.77 (95% CI: 0.67−0.85) and specificity of 0.70 (95% CI: 0.59−0.80). The result of the Area Under the Curve (AUC) showed that the overall diagnostic accuracy of PCT was higher when the cutoff value of PCT was greater than 0.4 and 0.5.

Ritchie B et al. attempted a meta - analysis of the diagnostic accuracy of serum PCT compared with serum CRP for suspected osteomyelitis and septic arthritis. However, due to limited results and clinical heterogeneity in PCT studies, they conducted a meta - analysis for CRP and a systematic review of PCT. The studies addressing osteomyelitis were appraised with detailed questions for their validity and bias potential and marked as high risk due to their methodological limitations.

They reported that Greff et al. had less sensitivity (91.7% [61.5–99.8]) than CRP but more specificity (81% [58.1–94.6]) than CRP. Faesch et al. at PCT cutoff 0.5 had sensitivity of 25% (3.19–65.1) and a specificity of 96.9% (94.2–98.6). Cui et al. at PCT 0.35 ng/ml showed sensitivity of 77.2 (67.2–85.3) and specificity of 69.7% (62.3–76.4).

An additional study by Van der Laan L et al., not included in the above systematic reviews, examined the utility of PCT during initial infection evaluations. It identified limitations such as selection bias, varied PCT request rates throughout the study timeframe (67% to 82%), and concerns about the generalizability of findings.

Clinical bottom line:
The collective evidence suggests that PCT, when used in combination with other clinical and laboratory markers, has a high negative predictive value and can aid clinical judgment. However, the standard practice of directly comparing alternative index tests with a reference standard is not consistently followed, and further research comparing these index tests head - to - head or directly against a single reference standard is warranted.

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