How to use… Procalcitonin

Philip Robinson,¹ Surjo Kiran De²

ABSTRACT
Diagnosing bacterial infection in the unwell or febrile child is a common challenge faced by all paediatricians. Despite the advent of novel molecular techniques, there is ongoing need for diagnostic assays with adequate performance and turnaround time to facilitate safe clinical decision-making when bacterial sepsis is suspected, such as whether to commence empirical treatment with antibiotics. Procalcitonin is an established marker of infection that has a potential role in the diagnosis and exclusion of serious or invasive bacterial infection in neonates and children. Although enthusiastically adopted in many countries and institutions, national guidance in the UK does not yet support its routine use. This article reviews the relevant literature on the use of procalcitonin measurement in common paediatric clinical scenarios.

INTRODUCTION
Infection is a significant cause of mortality in paediatrics, accounting for an estimated 11% of neonatal deaths and 20% of deaths in infants and children.¹ Paediatricians and parents alike are duly concerned about the possibility of missing cases of potentially life-threatening infection. However, given the numbers of children presenting with signs and symptoms of possible bacterial infection, the risk of misdiagnosis is a daily challenge. While falling mortality rates due to infection suggest that we are improving our ability to identify and treat children with serious bacterial infection (SBI) and invasive bacterial infection (IBI),² we face a new challenge; to avoid overtreatment and maintain standards of antimicrobial stewardship in the face of increasing antimicrobial resistance.³ Moving forward, there is increasing focus on the potential of more accurate diagnostic tests to aid the identification and treatment of SBI or IBI in children; one such test is procalcitonin (PCT).

PCT was initially identified as a potential marker of bacterial infection over 20 years ago.⁴ Although subsequently hailed as a major advance for diagnosing bacterial infection, conflicting results have meant it has yet to become established as a mainstream investigation in the UK. ‘How To Use Procalcitonin’ was published in this journal in 2011.⁵ Since then, research into clinical applications of PCT has intensified, prompting a reappraisal of past and recent evidence.

PHYSIOLOGICAL BACKGROUND
PCT is a 116-amino-acid prohormone of calcitonin, which is physiologically released by the parafollicular (C cells) of the thyroid. Calcitonin was initially discovered in dogs over 50 years ago and has a key role in calcium metabolism. It reduces serum calcium levels by inhibiting osteoclastic bone resorption and increasing renal excretion of calcium and phosphate (figure 1). In response to raised levels of serum ionised calcium, PCT is cleaved to calcitonin, reducing levels of serum calcium and phosphate, inhibiting the action of parathyroid hormone and vitamin D. It is also released in response to certain infectious and inflammatory stimuli.

PCT is encoded by the CALC1 gene, which under physiological conditions is solely expressed by neuroendocrine tissues. In non-physiological states (such as bacterial infection), CALC1 is also expressed by non-neuroendocrine tissues, which leads to serum PCT levels that are hundreds or even thousands of times higher than normal.⁶ The role of PCT in infection is unclear; however, in vivo studies suggest that it may have a role as a driver of the inflammatory response to bacterial infection and is associated with worsened symptoms and increased mortality.⁷ Much of the interest in PCT relates to its potential to differentiate bacterial and viral infections, such as in the context of pneumonia and meningitis as will be expanded on later.

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**INTERPRETATIONS**

![Diagram of physiological effects of calcitonin on calcium homeostasis.]

**TECHNOLOGICAL BACKGROUND**

**How to sample?**

PCT is measured from a plasma sample collected in a lithium heparin sample bottle. It can be stored for up to 4 hours at room temperature. The minimum volume of blood required is between 20 and 200 µL depending on the assay. Semiquantitative and quantitative assays using smaller volumes of whole blood from finger prick samples are also available.

**When to sample?**

PCT levels start to rise 2 hours after the start of a septic insult and peak by 12 hours. It has a half-life of approximately 24 hours and levels decline to normal values between 48 and 72 hours.

**How is the sample processed?**

There are several commercially available PCT assays, all of which use immunoassay technology. This involves detection of antibody complexes that bind PCT proteins in serum, using chemoluminescence, fluorescence or lateral-flow membrane technology. A number of methods can be used to automate the processing and measurement. Qualitative, semiquantitative and quantitative assays are available. Sample processing times range from 18 to 29 min. The functional sensitivity, which is the minimum PCT concentration that can be reliably detected, varies greatly (0.05–0.24 ng/mL). The maximum level of PCT also varies between assays (100–5000 ng/mL). Cut-off values for PCT in suspected sepsis are widely debated as will be described in greater detail below; however, they typically range from 0.3 to 1 ng/mL (µg/L).

Quantitative point-of-care-testing systems are also available which can provide results in 20 min from whole blood, opening the possibility of bedside testing. A single-use semiquantitative assay is also available and can be used with serum samples.

PCT assays from different manufacturers may have different product characteristics, such as limit of detection. Any diagnostic assay in clinical use should be internally and externally validated with appropriate quality control material and have a clear audit trail for reporting of results.

**METHODS**

Evidence for this article was collected by undertaking a structured review of electronic journal articles obtained from the National Institutes of Health PubMed database (online supplementary appendix 1).

**INDICATIONS AND LIMITATIONS**

**In a febrile child, does a low PCT rule out IBI?**

IBIs (infections associated with positive bacterial growth from blood or cerebrospinal fluid cultures; table 1) are rare but life-threatening events. A large prospective study of over 15 000 febrile children under 5 years of age presenting to the emergency department found that 0.04% of children had meningitis and 0.4% had bacteraemia. Other studies on febrile infants under 3 months of age suggested higher incidences between 1% and 2% for meningitis and bacteraemia combined. Can a low PCT exclude IBI (bacterial meningitis or bacteraemia) in the well-looking febrile child?

Several small prospective and retrospective studies have sought to identify the performance of PCT in identifying patients with bacterial meningitis and bacteraemia. Two small retrospective studies report different experiences with PCT in well-looking and unwell-looking infants less than 3 months of age. Olaciregui et al report that PCT alone was not sufficient to independently exclude a diagnosis of bacterial meningitis or bacteraemia. Gomez et al report that in infants less than 3 months of age with fever and a negative urine dip test, a PCT of <0.5 ng/mL has a negative likelihood ratio (NLR) of 0.25 for IBI. A negative

<table>
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<tr>
<th>Terminology</th>
<th>Definition</th>
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<tr>
<td>Serious bacterial infection (SBI)</td>
<td>Infections including urinary tract infection (UTI), pneumonia and bacterial gastroenteritis</td>
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<tr>
<td>Invasive bacterial infection (IBI)</td>
<td>Infection (microbiologically proven or suspected) in either blood or cerebrospinal fluid (CSF); that is, meningitis or bacteraemia</td>
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<tr>
<td>Early-onset neonatal sepsis (EONS)</td>
<td>Bacteraemia or bacterial CSF culture within the first 72 hours of life</td>
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<tr>
<td>Late-onset neonatal sepsis (LONS)</td>
<td>Bacteraemia or bacterial CSF culture after the first 72 hours of life</td>
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PCT (<0.5 ng/mL) therefore significantly reduces the probability of bacterial meningitis and bacteraemia but cannot be used to exclude these diagnoses.

More recently, in the largest trial of its kind, Milcent et al. recruited over 2000 febrile infants less than 3 months of age presenting to the emergency department. They report an NLR of 0.1 for bacteraemia and bacterial meningitis in infants with a PCT of <0.3 ng/mL, demonstrating that a negative PCT markedly reduced the post-test probability of an IBI in a well-looking febrile infant. Although the most compelling evidence to date for the use of PCT and far better than current markers, for example, C-reactive protein (CRP) and white cell count, the authors comment that an NLR of 0.1 remains too high to use PCT independently to exclude SBI/IBI in the febrile infant even at a lower serum PCT level of <0.3 ng/mL. On the basis of the available evidence, a serum PCT level with a cut-off value of 0.3 ng/mL significantly reduces the likelihood that a febrile child has an IBI. However, the studies unanimously conclude that PCT should not be used as the sole criterion to exclude potential IBIs. Rather, it should be interpreted in the context of both clinical evidence and other laboratory tests.

Given the role of PCT as a systemic marker of inflammation and infection, it has greater sensitivity identifying invasive (bacteraemia and meningitis) infections than those that are localised, for example, urinary tract infections (UTI) and pneumonia (also known as SBI). In patients with SBIs, several studies have shown PCT to be insufficiently specific and potentially worse than CRP.

In a subset of paediatric oncology patients with febrile neutropenia, meta-analysis of CRP, PCT and interleukin-8 reported that study protocols were too heterogeneous to make any reliable conclusions about the effectiveness of these biomarkers either in the diagnosis of bacterial infection or in monitoring response to antibiotics. There is insufficient evidence at present to guide the use of PCT in children with febrile neutropenia.

In a febrile infant, does a raised PCT predict IBI?

Elevated levels of PCT in the febrile child have been consistently reported to be associated with an increased risk of bacterial infections. When compared with conventional markers of bacterial infection (CRP and neutrophils) in infants, PCT has better sensitivity and specificity for invasive infection (ie, bacteraemia and meningitis) than less invasive infections such as UTI and pneumonia.

Milcent et al. report that febrile infants with a raised PCT (>0.3 ng/mL) have a positive likelihood ratio of 4, suggesting that the likelihood of an IBI in such an infant is moderately raised. Furthermore, they report a sensitivity of a raised PCT level (>0.3 ng/mL) of 90%; for every 10 febrile infants with confirmed IBI, PCT alone would have correctly identified 9. By comparison, CRP (≥20 mg/L) had a sensitivity of 75%. Of the 21 patients with confirmed IBI, 20 had an elevated PCT level (≥0.3 ng/mL) whereas 5 had CRP levels of <20 mg/L. These results are consistent with previously reported findings in smaller cohorts and subsequent meta-analysis. A raised serum PCT level (>0.3 ng/mL) may therefore be useful to support a diagnosis of suspected IBI with a good level of sensitivity. However, as noted elsewhere, a negative PCT does not reliably exclude a diagnosis of bacterial infection whether less (SBI) or more invasive (IBI).

In a child with suspected lower respiratory tract infection or pneumonia, does a raised serum PCT level predict bacterial aetiology? Does it have a role in guiding the duration of antibiotic therapy?

Clinical assessment, conventional blood tests and radiographs cannot reliably differentiate between viral and bacterial causes of lower respiratory tract infection (LRTI) and pneumonia. Evidence for the use of serum biomarkers in guiding a decision to start and complete a course of antibiotics is limited. Although there is limited evidence that stratifying the duration of antibiotics based on conventional clinical markers can shorten the duration of oral antibiotics in non-severe pneumonia in low-resource countries, there is very limited evidence for guiding the use of parenteral antibiotic duration in patients with severe pneumonia (associated with desaturations or abnormal work of breathing). Use of a serum biomarker could guide both the decision to start antibiotics and the duration of treatment.

ProPAED was a randomised trial designed to assess the use of PCT in the antibiotic management of LRTI and pneumonia, involving 337 children with a mean age of 3.8 years. It asked three key questions; first, can PCT reduce antibiotic prescribing rates? Second, can PCT monitoring reduce the duration of antibiotic therapy and, third, can PCT reliably predict response to antibiotic therapy? Using decision algorithms for commencing antibiotics and review of course duration at day 5 of treatment, the study found that in patients with undifferentiated LRTI/Community-acquired pneumonia (CAP), use of PCT did not reduce the rate of antibiotic prescribing, incidence of antibiotic side effects or rate of hospital admission. However, it was associated with a significant reduction in the duration of antibiotic therapy in children with LRTI (6.3 vs 4.5 days) and pneumonia (9.1 vs 5.7 days).

This study supported the findings of an earlier trial by Esposito et al. which found that PCT-guided antibiotic therapy could shorten the overall duration of antibiotics and reduce the incidence of antibiotic-related side effects, and also highlighted the issue of setting appropriate PCT cut-offs. The level of <0.1 ng/mL for ‘definitely not’ requiring antibiotics at the outset was thought to be inappropriately low for children.
Interpretations

These studies provide reasonable evidence that PCT monitoring may help reduce the duration of antibiotic use, particularly in children with more severe CAP. Further studies are required to define the most appropriate cut-off values and to further interrogate whether PCT has a role in children with less severe and hospital-acquired LRTI/pneumonia, and those on oral antibiotics.

In neonates, can a low serum PCT be used to exclude a diagnosis of sepsis?

Early-onset neonatal sepsis (EONS) usually associated with bacterial infection is reported to affect 1 term infant per 1000 live births. CRP is currently used to help support a diagnosis of EONS and guide subsequent investigation and management. One of the key advantages of CRP is that it does not cross the placenta; however, it can be elevated in response to a number of non-infective events and can take up to 48 hours to rise following an infective insult. PCT, like CRP, does not cross the placenta (hence is not affected by maternal fever in labour). However, it has been shown to display greater and more rapid response to infection.

PCT levels need to be interpreted with caution as they vary according to gestational age at birth and the time of sampling particularly over the first 48 hours (when there is a physiological increase in serum PCT levels). Peak physiological PCT levels may not be reached until 48 hours of life. Although attempts have been made to produce a nomogram for neonatal PCT measurements over the first 48 hours of life, the numbers have been too low to validate the test’s performance.

PCT has been evaluated in both EONS (<72 hours old) and late-onset neonatal sepsis (>72 hours old). Studies suggest that PCT may be a better marker for early-onset sepsis than late sepsis.

Several small studies have sought to define optimal cut-off values for diagnosing early-onset sepsis in the newborn. Altunhan et al conducted a trial of 171 newborns with risk factors for suspected sepsis. They found similar levels of PCT in the at-risk and control groups immediately after birth. However, at 24 hours there was a marked and significant difference in PCT levels. They propose a cut-off of 0.59 ng/mL at birth and 5.4 ng/mL at 24 hours with a sensitivity of 83.3% and specificity of 88.6%, results that are far more favourable than CRP at a cut-off of 12 mg/L. Although impressive, these values correspond to an NLR of 0.19 which drastically reduces but does not exclude the possibility of EONS in a newborn with a negative test.

In preterm and very low birthweight infants (<1500g), who are at higher risk of contracting EONS and in whom morbidity and mortality are higher, the role of PCT is even less clear, with studies showing varying normal values for PCT depending on gestational age.

Based on current evidence, PCT alone should not be used to exclude bacterial infection in the newborn.

However there is a potential role for PCT to guide duration of antibiotic usage in early-onset suspected sepsis. In a trial of 121 term newborns with EONS, serial PCT monitoring resulted in a 27% absolute reduction in the number of newborns receiving antibiotics ≥72 hours and reduced the mean duration of antibiotic exposure by 22 hours with comparable clinical outcomes and number of adverse effects. All babies underwent risk stratification prior to treatment based on history and clinical

Clinical applications of procalcitonin under evaluation in children

► Diagnosis of sepsis (due to bacterial infection) in neonates, infants and children.
► Identifying bacterial aetiology in lower respiratory tract infection or pneumonia.
► Diagnosis of sepsis (due to bacterial infection) in HDU and ITU environments.
► Identification of pyelonephritis in febrile children with UTI.
► Risk of vesicoureteric reflex (VUR) and reflux nephropathy in children with UTI.
► Differentiation of bacterial and viral meningitis.
► Guiding duration of antibiotic therapy in suspected sepsis, LRTI/pneumonia and meningitis.
► Monitoring neonates and children at risk of postoperative infections.

HDU, high dependency unit; ITU, intensive therapy unit; LRTI, lower respiratory tract infection; UTI, urinary tract infection.

Clinical bottom line

► PCT should not be used as a ‘rule-out’ test for sepsis or suspected SBI or IBI in febrile infants and children.
► Serial PCT measurements can help guide the duration of parenteral antibiotics given to children with LRTI/pneumonia.
► Evidence for the use of PCT in preterm and term neonates suggests a potential role as a marker of infection for term newborns with EONS. However, PCT levels should not be used to diagnose sepsis at the initial presentation.

Quick summary

► Procalcitonin is a serum marker of inflammation and infection.
► Serum procalcitonin levels are higher in bacterial infections involving the bloodstream, lower respiratory tract, cerebrospinal fluid and urine than viral infections.
► Procalcitonin-guided therapy has been shown to reduce the duration of antibiotic therapy for children with lower respiratory tract infection, pneumonia and febrile illness.
► Although it can aid in decision-making, a low serum procalcitonin does not exclude the possibility of bacterial meningitis or bacteraemia.
Test your knowledge

**Procalcitonin**
1. Can be relied upon to diagnose suspected bacteraemia in the febrile child.
2. Peak serum procalcitonin levels are seen 48 hours after a septic insult.
3. Serial PCT monitoring can reduce the duration of antibiotic therapy in LRTI and pneumonia.
4. Procalcitonin levels may remain elevated for 4–5 days after the resolution of a bacterial infection.
5. Higher serum procalcitonin levels are usually observed in bacterial infection, compared with viral infection.
6. A low procalcitonin level strongly suggests that there is no bacterial infection in a child with febrile neutropenia.

**Regarding neonates**
1. Procalcitonin levels are affected by gestational and corrected gestational age.
2. Procalcitonin can cross from maternal to fetal circulation.
3. Neonatal procalcitonin levels are highest at birth and decline by 24 hours of age.
4. Neonatal procalcitonin levels may be increased by maternal fever.
5. Procalcitonin is a reliable biomarker for sepsis in the very low birthweight neonate.

*The answers are after the references.*

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assessments, perhaps unsurprisingly, the benefit of PCT was greatest in neonates stratified into the lower risk groups. A subsequent international multi-centre trial (Neonatal Procalcitonin Intervention Study (NeoPInS), NCT 00854932) reported reductions in antibiotic duration of up to 12 hours using a procalcitonin-guided protocol with no difference in morbidity or mortality.

**Topics for further research**
- PCT is a potentially useful adjunct for diagnosing invasive infections. It is not however sufficiently sensitive for use as a standalone diagnostic marker.
- Combining PCT levels with clinical parameters may improve test performance sufficiently to rule out invasive sepsis in the febrile infant, further research is warranted.
- Further prospective evidence is required to support the use of PCT for monitoring infections in the infant and newborn, for example, CAP and EONS.
- More evidence is required for the use of PCT in the diagnosis EONS. Results from the NeoPInS trial support the use procalcitonin to guide the duration of antibiotics particularly in low-risk groups. Further data regarding normal reference values for PCT in the term and preterm newborn are required.
- PCT may have a role in monitoring response to antibiotic treatment in patients with meningitis, further prospective evidence is required to evaluate its potential role in guiding the duration of antibiotic therapy.
- Several trials are also ongoing to refine and broaden the potential clinical applications of PCT in pediatrics (box).

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**REFERENCES**
Interpretations


Answers to the questions:

Procalcitonin: 1F, 2F, 3T, 4F, 5T, 6F

Regarding neonates: 1T, 2F, 3F, 4F, 5F
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