

Procalcitonin (serum, plasma)

1 Name and description of analyte

1.1 Name of analyte
Procalcitonin (PCT)

1.2 Alternative names
None

1.3 NLMC code
To follow

1.4 Description of analyte
Procalcitonin (PCT) is a 116 amino acid precursor to calcitonin. In normal metabolic conditions, calcitonin is produced solely by the C-cells of the thyroid medulla and neuroendocrine cells in the lungs.

1.5 Functions of analyte
Following proinflammatory stimulation (particularly systemic bacterial infection), PCT is produced by numerous cell types. PCT affects the immune response by modulating the induction of proinflammatory cytokines. It also acts as a chemokine, influencing the migration of monocytes and parenchymal cells to the site of inflammation. PCT plays a role in vascular contraction through inhibiting or activating the induction of inducible NO-synthase (iNOS).

2 Sample requirements and precautions

2.1 Medium in which measured
Serum, heparinised plasma and K⁺-EDTA plasma

2.2 Precautions re sampling, handling etc.
Where possible, samples for PCT analysis should be separated and analysed within four hours of the blood draw. Samples can be stored at 2-8 °C for up to 24 h; and samples should be frozen at -20 °C within 48 h. A single freeze-thaw cycle may lead to a reduction in recovery of up to 8%. All samples should be centrifuged prior to analysis to ensure they are free of fibrin or other particulate matter.

3 Summary of clinical uses and limitations of measurements

3.1 Uses

1. Diagnosis of bacterial lower respiratory tract infections (LRTIs) and sepsis
2. Monitoring the progression of sepsis and its response to treatment
3. Informing the initiation, a change in or the cessation of antimicrobial treatment for bacterial sepsis

3.2 Limitations

Whilst PCT exhibits a degree of specificity for bacterial infection, sepsis, severe sepsis and septic shock as the [PCT] seen in such conditions can be extremely high (>10 ng/mL), [PCT] can be raised as a result of other pro-inflammatory stimuli such as surgery, trauma, severe viral infections and fungal infections. It is therefore essential to use all available clinical information when interpreting the results of a PCT measurement.

4 Analytical considerations

4.1 Analytical methods

All methods for the quantification of PCT are based on immunoassay. The time taken from assay start to the generation of a result varies from 18 minutes to 2.5 h according to the assay used.

The original PCT assay was developed as a luminometric immunoassay (LIA) using a coated tube system with two monoclonal antibodies and a luminometric tracer. Based on this, a number of automated assays have been developed using TRACE (time resolved amplified cryptate emission), ELFA (enzyme-linked fluorescent assay), CLIA (chemiluminescent immunoassay) and ECLIA (electrochemiluminescent immunoassay) technologies for use on the automated platforms BRAHMS Kryptor®, BioMérieux VIDAS®, Siemens Advia Centaur® and Roche Elecsys® respectively.

A semi-quantitative point of care test, PCT-Q, incorporating an immunochromatographic assay using immunogold labelling is also available. Quantitation is based on comparing the intensity of colour development after 30 minutes to a chart provided by the manufacturer. The strength of colour development can be interpreted as >2 ng/mL or >10 ng/mL.

4.2 Reference method

There is currently no agreed reference method for procalcitonin. However, all automated and PoCT assays have been developed to, the results compared with, and the published reference ranges have been determined by, the LIA method.

4.3 Reference materials

No reference material is currently available.

4.4 Interfering substances

Haemolysis, icterus and lipaemia do not interfere with the measurement of PCT unless gross.

4.5 Sources of error

The presence of fibrin or other particulate matter in the sample can lead to falsely low results. The high dose hook effect is a possibility at very high [PCT].

5 Reference intervals and variance

5.1.1 Reference interval (adults)

Healthy individuals: ≤ 0.05 ng/mL

Diagnosis of lower respiratory tract infections:

Absence of infection:	PCT < 0.1 ng/mL
Bacterial infection unlikely:	PCT ≥ 0.1–< 0.25 ng/mL
Bacterial infection possible:	PCT ≥ 0.25–< 0.5 ng/mL
Suggestive of bacterial infection:	PCT ≥ 0.5 ng/mL

Diagnosis of systemic bacterial infection or generalised sepsis:

Systemic infection unlikely:	PCT < 0.5 ng/mL
Systemic infection possible:	PCT ≥ 0.5– < 2 ng/mL
Systemic infection likely:	PCT ≥ 2 ng/mL
Severe sepsis or septic shock likely:	PCT ≥ 10 ng/mL

5.1.2 Reference intervals (others)

The cut-off values described in section 5.1.1 are generally also applicable to a paediatric population. However, variations in cut-off concentrations have been published, particularly for ruling in/out bacterial meningitis.

5.1.3 Extent of variation (Barassi A, Pallotti F, Melzi d'Eril GV. Clin Chem 2005; 50:1878)

5.1.3.1 Interindividual CV: 22% in healthy individuals

5.1.3.2 Intraindividual CV: 16% in healthy individuals

5.1.3.3 Index of individuality: 0.7

5.1.3.4 CV of method

Typically < 10%

5.1.3.5 Critical difference

60.6% (if assay CV 15%)

5.1.4 Sources of variation

Plasma [PCT] is affected by the presence of inflammation, most significantly in response to bacterial infection. However, plasma [PCT] may be raised in patients with medullary thyroid carcinoma.

6 Clinical uses of measurement and interpretation of results

6.1 Uses and interpretation

1. PCT can be indicated in the diagnosis of bacterial infection (in particular lower respiratory tract infections) and sepsis, to assist in determining whether antimicrobial treatment should be commenced. This is most frequently done in the emergency department, but PCT can also be used to diagnose nosocomial infections such as hospital-acquired pneumonia.

2. PCT can be used to guide antimicrobial treatment with particular relation to continuing, changing or ceasing antimicrobial agents, most frequently in the critical care environment.

3. PCT can be used in the diagnosis of neonatal sepsis, although care should be taken when interpreting results as [PCT] may be > 10ng/mL in neonates in the absence of infection.

6.2 Confounding factors

Plasma [PCT] can be raised from non-bacterial causes such as surgery (particularly abdominal surgery), trauma, severe pancreatitis, severe liver damage, severe multi-organ dysfunction syndrome, severe burns and severe fungal infections.

7 Causes of abnormal results

7.1 High values

7.1.1 Causes

- Bacterial infection
- Sepsis
- Trauma
- Surgery (in particular abdominal surgery)
- Severe multi-organ dysfunction syndrome
- Severe pancreatitis
- Severe liver damage
- Severe burns
- Severe fungal infections
- First days of life in neonates.

7.1.2 Investigation

Procalcitonin is generally used to support the diagnosis of bacterial infection or sepsis in the emergency department, or to monitor the treatment of sepsis with regards to reviewing antimicrobial treatment (generally in a critical care environment). When measured for any of these reasons, no additional investigation is required apart from the determination of the causative organism and its antibiotic sensitivity. Unexpectedly high values should not therefore occur.

7.2 Low values

Not applicable

7.3 Notes

Procalcitonin is not recommended as a routine screening test for infection, e.g. as part of an emergency department admission profile. In patients in whom a diagnosis of systemic inflammatory response syndrome (SIRS) is made, where the cause of the SIRS is uncertain, PCT may be used as a rule in/out test for prescribing antimicrobial treatment. PCT results should be used to assist and guide clinicians towards a diagnosis or treatment strategy, but they should not be used to replace clinical judgement; treatment should not be withheld on the basis of PCT test results.

8 Performance

8.1 Sensitivity, specificity etc. for individual conditions

A recent review of a number of studies investigating the use of PCT stated a sensitivity of 88% with a specificity of 81% for PCT as a marker of bacterial infection compared with non-infective causes of inflammation (see review by Simon *et al.*, 9.1).

PCT concentrations >2 ng/mL have a 94% sensitivity and 93% specificity for diagnosing meningococcal disease in children (Carrol ED, Newland P, Riordan FAI *et al.* Arch Dis Child 2002; 86:282-285).

PCT has a sensitivity of 91% and specificity of 96% for the detection of active medullary thyroid carcinoma (Algeciras-Schimmich A, Preissner CM, Theobald JP *et al.* J Clin Endocrinol Metab 2009; 94:861-868).

PCT concentrations > 0.4 ng/mL have a sensitivity of 75% and a specificity of 75% in predicting severe attacks of acute pancreatitis (Ammori BJ, Becker KL, Kite P *et al.* Br J Surg 2003; 90:197-204).

9 Systematic reviews and guidelines

9.1 Systematic reviews

Numerous reviews on the biochemistry and use of PCT have been published. The following examples cover a lot of background and how PCT can be used to diagnose bacterial infections/sepsis and to guide treatment.

1. Meisner M. Procalcitonin – Biochemistry and Clinical Diagnosis. Bremen: UNI-MED Verlag AG. 2010, 3-125
2. Simon L, Gauvin F, Amre DK *et al.* Serum Procalcitonin and C-Reactive Protein Levels as Markers of Bacterial Infection: A Systematic Review and Meta-Analysis. *Clin Infect Dis* 2004; 39:206-217.
3. Kopterides P, Siempos II, Tsangaris I *et al.* Procalcitonin-guided algorithms of antibiotic therapy in the intensive care unit: A systematic review and meta-analysis of randomized controlled trials. *Crit Care Med* 2010; 38:2229-2241.
4. Schuetz P, Müller B, Christ-Crain M *et al.* Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. *Cochrane Database of Systematic Reviews* 2012;(9):CD007498. DOI: 10.1002/14651858.CD007498.pub2
5. Wacker C, Prkno A, Brunkhorst FM *et al.* Procalcitonin as a diagnostic marker for sepsis: a systematic review and metaanalysis. *Lancet Infect Dis* 2013;13:426-435.

9.2 Guidelines

There are currently no UK Guidelines regarding the use of PCT. However German sepsis guidelines have been published that advocate the use of PCT.

Reinhart K, Brunkhorst FM, Bone H-G *et al.* Prevention, Diagnosis, Therapy and Follow-up Care of Sepsis: 1st revision of the S-2k guidelines of the German Sepsis Society (Deutsche Sepsis-Gesellschaft e.V. (DSG)) and the German Interdisciplinary Association of Intensive Care and Emergency Medicine (Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin (DIVI)). *GMS German Medical Science* 2010; 8:Doc 14. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2899863/>
These guidelines recommend early determination of serum procalcitonin concentrations to rule out severe sepsis and/or confirm the diagnosis, and state that serial procalcitonin measurements may be considered in order to shorten the duration of antimicrobial therapy.

9.3 Recommendations

None identified.

10 Links

10.1 Related analytes

Calcitonin

10.2 Related tests

Other cytokines such as IL-6, IL-8, IL-10 and TNF- α have previously been identified as possible makers of sepsis; however, their short half life inhibits their development as useful biomarkers.

CRP is a routinely available non-specific marker of inflammation, whose usefulness is not superseded by PCT. However, the use of PCT and CRP in parallel may improve the specificity and sensitivity of the diagnosis of bacterial infection/sepsis.

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