Worcestershire Acute Hospitals NHS Trust

Procalcitonin (PCT) Measurement to Guide Antimicrobial Therapy on ICU

This guidance does not override the individual responsibility of health professionals to make appropriate decision according to the circumstances of the individual patient in consultation with the patient and /or carer. Health care professionals must be prepared to justify any deviation from this guidance.

THIS GUIDELINE IS FOR USE BY THE FOLLOWING STAFF GROUPS :

All Consultants in Anaesthesia/ Intensive Care Medicine employed by Worcestershire Acute Hospitals NHS Trust

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This is the most current document and should be used until a revised version is in place

Key amendments to this guideline

Date	Amendment	By:
April 2020	New guideline	Dr M McAlindon
January 2021	Document approved for 3 years	Directorate Governance and SCS Divisional Governance
January 2024	Updated guideline	Dr M McAlindon

INTRODUCTION

Procalcitonin (PCT) is a 116 amino acid prohormone with a molecular weight of approximately 12.7 kDa. PCT is expressed by neuroendocrine cells (C cells of the thyroid, pulmonary and pancreatic tissues) and successively enzymatically cleaved into (immature) calcitonin, katacalcin, and an N- terminal region.[1]

Procalcitonin is involved in maintaining calcium levels in the blood and is an indirect biomarker of infection. It is released into the circulation in response to pro-inflammatory

stimuli, especially those originating from bacteria. Procalcitonin levels are usually low in people with viral infections, chronic inflammatory disorders or autoimmune processes.

Procalcitonin is released into the bloodstream when there is a bacterial infection in the body and high levels can show that a person has a serious bacterial infection. Procalcitonin tests measure the amount of procalcitonin in the blood, and the results can help doctors to diagnose bacterial infection and decide about starting or stopping antibiotic treatment.[2]
The blood of healthy individuals contains only low levels of PCT. It was discovered that PCT increases during bacterial infection. It is probable that multiple tissues express PCT throughout the body in response to sepsis as was shown in an animal model.3 PCT circulating in septic patients consists of only 114 amino acids lacking the N‐terminal dipeptide Ala‐Pro.[1]

Increased PCT levels are often found in patients suffering from bacterial sepsis and septic shock. PCT is considered as a prognostic marker to support outcome prediction in sepsis patients.

In acute pancreatitis PCT was found to be a reliable indicator of severity and of major complications.

In patients suffering from community-acquired respiratory tract infections or ventilator‐induced pneumonia PCT has been proposed as a guide for the decision of antibiotic treatment necessity and to monitor treatment success.[1]

Procalcitonin levels may be normal on the day of deterioration of a patient on ICU; PCT can take 4-6 h to start to rise after the start of sepsis. Much like the clinical use Troponin in acute coronary syndrome, very early in the clinical course normal levels can be falsely reassuring.

Significantly raised PCT levels can be found in around 10% of non-infected patients on haemodialysis.

PCT levels can be increased in certain situations without infectious origin. These include, but are not limited to:

- Prolonged or severe cardiogenic shock
- Prolonged severe organ perfusion anomalies
- Small cell lung cancer or medullary C‐cell carcinoma of the thyroid
- Early after major trauma, major surgical intervention, severe burns
- Treatments which stimulate the release of pro‐inflammatory cytokines
- Neonates (< 48 h after birth)

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

Peak PCT levels (and CRP levels) correlate moderately with SOFA score and may help identify a group of patients at high risk of death.

PCT levels typically start to fall within 48h of the start of successful treatment. Failure of PCT (and CRP) levels to start to fall by day 3 should prompt further microbiological evaluation.

These levels may be predictive of poor outcomes in certain clinical situations such as ventilator associated pneumonia.

Thermo Fisher Scientific has a patent for using procalcitonin as a biomarker for sepsis. However, other companies have also licensed the use of procalcitonin and its antibodies. All commercial quantitative BRAHMS PCT assays use the same 'sandwich ELISA' principle to quantify procalcitonin by forming antibody–procalcitonin–antibody complexes. The main difference between these assays is the mechanism of detection of these complexes.

ANTIMICROBIAL STEWARDSHIP

Infections, such as pneumonia, may be caused by bacteria or viruses. Bacterial infections can be treated with antibiotics, but antibiotic treatment is inappropriate for viral infections. Many people, especially children, are often treated with antibiotics without the causative agent being known. Common side effects of antibiotics include mild stomach upset and diarrhoea. Less commonly, people may have an allergic reaction to an antibiotic. Furthermore, overuse of broad‐spectrum antibiotics contributes to the development and spread of antimicrobial resistance. Therefore, rapid and accurate determination of the presence or absence of bacterial infection is important to reduce unnecessary exposure to antibiotics.

Sepsis is one of the most common reasons for admission to an intensive care unit. In its most severe form, septic shock, it has a mortality rate of 40% to 60%, which is thought to increase substantially (6-8%) for every hour of delay in starting appropriate antibiotic treatment. Therefore, broad‐spectrum, high‐potency antibiotics are widely used in intensive care units. It is important for clinicians to be able to monitor the progression of sepsis and the response to antibiotic treatment so that broad‐spectrum antibiotic treatment can be narrowed or reduced (de‐escalated) as soon as possible.[3]

Bacteria are the most common cause of sepsis, but systemic viral and fungal infections can also occur. Symptoms of sepsis include fever or a very low body temperature, rapid breathing and altered mental status, such as reduced alertness or confusion. These symptoms also occur with systemic inflammatory response syndrome, a life‐threatening condition that can be caused by the body's overreaction to an infection or a non‐infectious event such as trauma or burns. Clinicians must be able to rapidly distinguish between infectious and non‐infectious causes of systemic inflammatory response syndrome, as well as between different agents of infection, to guide appropriate therapy.

The Department of Health has set out actions to slow the development and spread of antimicrobial resistance in the UK Five Year Antimicrobial Resistance Strategy 2013 to 2018. One aim of the strategy is to conserve and steward the effectiveness of existing antimicrobials by ensuring antibiotics are used responsibly and less often. Rapid and accurate determination of the presence or absence of bacterial infection is important to guide appropriate antibiotic therapy and to reduce unnecessary exposure to antibiotics.

NICE RECOMMENDATIONS

NICE diagnostics guidance [DG18] suggests that PCT measurement shows promise but there is currently insufficient evidence to recommend routine adoption in the NHS however addition of PCT testing to standard clinical care was unlikely to result in worse clinical outcomes. Further research on procalcitonin tests is recommended for guiding decisions to:

- Stop antibiotic treatment in people with confirmed or highly suspected sepsis in the intensive care unit or
- Start and stop antibiotic treatment in people with suspected bacterial infection presenting to the emergency department.

Centres currently using procalcitonin tests to guide these decisions are encouraged to participate in research and data collection.

PCT ASSAY IN SARS-CoV-2 INFECTION (COVID-19)

Although bacterial infections are usually regarded as a leading cause of sepsis, viral infection can also cause sepsis syndrome. Previously, we determined that sepsis occurred in nearly 40% of adults with community-acquired pneumonia due to viral infection.

During the initial phase of the COVID-19 pandemic; a cohort of patients presented with acute respiratory failure, signs of systemic inflammatory response syndrome and raised inflammatory markers. Although the cause was presumed viral in origin many patients often receive antibiotic therapy for community or hospital acquired pneumonia on admission to ICU in case of superadded bacterial infection.

In a recent study, it was found that more than half of patients developed sepsis. Additionally, more than 70% of patients had white blood cell count below 10·0 × 109 per L or procalcitonin below 0·25 ng/mL, and no bacterial pathogens were detected in these patients on admission. Sepsis was a common complication, which might be directly caused by SARS-CoV-2 infection, but further research is needed to investigate the pathogenesis of sepsis in COVID-19 illness.[4]

Results of a concise meta-analysis of the literature would suggest that serial procalcitonin measurement may play a role for predicting evolution towards a more severe form of COVID-19 disease.

There is a plausible explanation for this evidence. The production and release into the circulation of procalcitonin from extra-thyroidal sources is enormously amplified during bacterial infections, actively sustained by enhanced concentrations of interleukin (IL)-1β, tumour necrosis factor (TNF)-α and IL-6. Nevertheless, the synthesis of this biomarker is inhibited by interferon (INF)-γ, whose concentration increases during viral infections. It is hence not surprising that the procalcitonin value would remain within the reference range in several patients with non-complicated SARS-CoV-2 infection, whereby its substantial increase would reflect bacterial coinfection in those developing severe form of disease, thus contributing to complicate the clinical picture, as recently shown in children with viral lower respiratory tract infections.[5]

LOCAL ASPCECT OF CARE

Procalcitonin (PCT) measurement has been authorised for use to identify bacterial infection and guide antimicrobial therapy on ICU at WAHT using **The Elecsys BRAHMS PCT assay (Roche Diagnostics).**

The Elecsys BRAHMS PCT assay is an automated electrochemiluminescent immunoassay for the determination of procalcitonin in human serum and plasma. The assay principle combines a sandwich immunoassay with the detection of light emission by a photomultiplier. The assay is for use on the Elecsys, Modular and Cobas e analysers. It has a measuring range of 0.02 to 100 nanograms per millilitre, a functional sensitivity of 0.06 nanograms per millilitre and an analytical sensitivity of less than 0.02 nanograms per millilitre. The time to result is 18 minutes.

DIAGNOSIS OF INFECTION ON ICU

(See also Guidelines for Management of Sepsis and Septic Shock in Adults WAHT-KD-022).

- Inflammatory variables:
  - low or high white blood cell count or more than 10% immature forms
  - Raised plasma C‐ reactive protein
  - Raised plasma PCT

- Relevant microbiological samples for culture (including blood cultures) should be taken before antibiotics are started.
  - This sampling should not significantly delay antibiotic treatment (more than 45 minutes).

- In patients with sepsis broad-spectrum intravenous antibiotics to cover likely pathogens should be administered within one hour of diagnosis.
  - In stable patients (moderate risk group), in whom the diagnosis of infection is uncertain, it may be appropriate to wait for the results of microbiological testing.

- Obtain two or more blood cultures (during the first hour for sepsis) provided this does not significantly delay antimicrobial administration.
  - One or more blood cultures should be collected by percutaneous venepuncture and undertaken according to WAHT guidelines

- Take one blood culture from each vascular access device in place for more than 48 hrs.

- Take samples for culture from other sites as clinically indicated (e.g. urine, wounds, faeces, CSF).
  - Including atypical pneumonia screen (urinary legionella and pneumococcal antigen testing).

- Perform imaging studies promptly to confirm source of infection.

ANTIBIOTIC THERAPY

- Close liaison with the Consultant Microbiologist and Infectious Disease Consultants represents the gold standard.
- http://nww.worcsacute.nhs.uk/antibiotic-treatment-guidelines-adults/ provides the detail of the Worcestershire Secondary Care Adult Prescribing Policy.
    - See also https://viewer.microguide.global/guide/1000000243
- Review results of previous microbiological investigations as this may inform the choice of empirical antimicrobial therapy (e.g. previous infection/colonisation with MRSA or other resistant organisms).
- Begin intravenous antibiotics as early as possible and always within the first hour of recognising sepsis and septic shock.
- Broad-spectrum: one or more agents active against likely bacterial/fungal pathogens and with good penetration into presumed source.
- Reassess antimicrobial regimen daily to optimize efficacy, prevent resistance, avoid toxicity, and minimise costs.
- Consider combination therapy in *Pseudomonas* infections.
- Consider combination empiric therapy in neutropaenic patients (see also Guideline for the management of suspected Neutropenic Sepsis Induced by Cytotoxic Therapy WAHT-HAE-003)
- Review microbiology culture and other results daily and amend antibiotic therapy as dictated by antibiotic sensitivities and/or clinical progress.
- Duration of therapy: review after 72h along with clinical progress and microbiology results. A longer course may be indicated if response is slow or there are inaccessible foci of infection or immunologic deficiencies.
- Stop antimicrobial therapy if cause is found to be non-infectious.

SOURCE IDENTIFICATION AND CONTROL

- A specific anatomic site of infection should be established as rapidly as possible and within first 6 hrs of presentation.

- Formally evaluate patient for a focus of infection amenable to source control measures (e.g. abscess drainage, tissue debridement).

- Implement source control measures as soon as possible following successful initial resuscitation (exception: infected pancreatic necrosis, where surgical intervention is best delayed).

- Choose source control measure with maximum efficacy and minimal physiologic upset.

- Remove intravascular access devices if potentially infected. Pay attention to the "Matching Michigan" campaign in this regard.

MEASUREMENT OF PROCALCITONIN (PCT)

Elecsys BRAHMS PCT assay.

- Immunoassay for the in vitro quantitative determination of PCT (procalcitonin) in human serum and plasma.
- PCT assay can be used to aid in the early detection of clinically relevant bacterial infections.
- The electrochemiluminescence immunoassay "ECLIA" is intended for use on cobas e immunoassay analyzers.

Specimen collection:

- Serum collected using standard sampling procedure
    - **Serum separating tube (Gold top).**
    - After drawing the blood, measure samples within 24 hours or freeze at -20 °C (± 5 °C). Frozen samples can lead to a lower recovery of up to 8 %.

Measuring range: **0.02-100 ng/mL**

All results should be interpreted in the context of the clinical situation.

< 0.05 ng/mL:	Normal range
< 0.5 ng/mL:	Low risk of sepsis and/or septic shock.* Local bacterial infection possible. Antibiotic use discouraged unless clinically indicated.
0.5-2 ng/mL:	Moderate risk of sepsis and/or septic shock.* Antibiotics use should be considered.
2.0-10 ng/mL:	High risk of sepsis and/or septic shock** Antibiotics use strongly encouraged.
> 10 ng/mL:	Septic shock.

For patients on antibiotics a decline in value of >80% of the peak value suggests stopping antibiotics should be considered.

If PCT increasing consider a change in antibiotic due to failure of therapy.

* cut-off at 0.5 ng/mL: sensitivity 65 %, specificity 66 %, positive predictive value 59 % and negative predictive value 72 %.
** cut-off at 2 ng/mL: sensitivity 23 %, specificity 93 %, positive predictive value 70 % and negative predictive value 62 %.[5]
SIRS/sepsis categories based on the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM)

REFERENCES

1. Elecsys BRAHMS PCT pack insert

2. Procalcitonin testing for diagnosing and monitoring sepsis, Diagnostics guidance [DG18], Published date: 07 October 2015, https://www.nice.org.uk/guidance/dg18

3. Sepsis: recognition, diagnosis and early management. NICE guidelines [NG51]. Published date: July, 2016. https://www.nice.org.uk/guidance/ng51

4. Zhou, F. Yu, T. Du, R. Fan, G. Liu, Y. Liu, Z. et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. Articles, Volume 395, ISSUE 10229, P1054-1062, March 28, 2020. DOI:https://doi.org/10.1016/S0140-6736(20)30566-3

5. Lippia, G. Plebani M: Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. Clin Chim Acta. 2020 Jun; 505: 190–191. Published online 2020 Mar 4. doi: 10.1016/j.cca.2020.03.004. PMCID: PMC7094472. PMID: 32145275

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Appendix 1: Protocol for Procalcitonin (PCT) measurement and interpretation on ICU

- PCT will primarily be used to aid the **decision to de-escalate** antibiotic therapy.
- Using **PCT to start or change antibacterial** therapy on ICU:
    - PCT level **>0.5 ng/mL** – moderate risk of sepsis; **consider antibiotics**
    - PCT level **>2.0 ng/mL** – high risk of sepsis; **start antibiotics**

1. Send PCT with initial bloods on admission to ICU.
    a. Annotate request as admission sample (Day 0)
    b. Can be 'added on' to sample within 24h.
2. Send PCT with ICU daily bloods (06:00) for duration of ICU admission.
3. Review PCT result (and trend) in clinical context and association with other inflammatory markers:
    a. CRP.
    b. WCC (and panel breakdown).
4. Review antibiotic therapy on daily Microbiology WR in association with above markers and relevant microbiological test results.
    a. Use algorithm to inform decision regarding antibiotic therapy on a daily basis.
    b. Antibiotic review mandated at day 3, 5 and 7 as a minimum.
5. Document antibiotic therapy review and decision in medical notes on a daily basis.

PCT algorithm for stopping antibiotics in patient with sepsis on ICU

PCT (ng/mL)	Ongoing infection?	Recommendation	Considerations
< 0.5	Unlikely	STOP antibiotics	Clinical correlation
0.5-2	Possible	Review antibiotics	Stop antibiotics if a decline in value of >80% of the peak value or when 0.5ng/mL reached. Clinical correlation required.
>2	Very likely	Continue daily review of antibiotics	If serial PCT remains high:

			consider treatment failure/ change in antibiotic therapy

Notes:

- Results of **>10ng/mL will be telephoned** through to ICU for action due to high risk of sepsis/septic shock.
- PCT levels typically start to fall within 48h of the start of successful treatment.
- Failure of PCT (and CRP) levels to start to fall by day 3 should prompt further microbiological evaluation.

Appendix 2: Systemic markers of infection and organ dysfunction

General variables

- Fever (>38°C)
- Hypothermia (core temperature <36°C)
- Heart rate >90 min-1
- Tachypnoea >20 breaths min-1
- Acutely altered mental status (AVPU score V or less)
- Significant oedema or positive fluid balance (>20 mL/kg over 24 hrs)
- Hyperglycaemia (plasma glucose >7.7 mmol/L) in the absence of diabetes

Inflammatory variables

- Leucocytosis >12 x 109/l
- Leucopaenia <4 x 109/l
- Normal WBC count with >10% immature forms
- Significantly elevated plasma C-reactive protein (CRP)
- Significantly elevated plasma pro-calcitonin

Haemodynamic variables

- Arterial hypotension (SBP <90 mmHg; MAP <65 mmHg; or an SBP decrease >40 mmHg)
- Heart rate >130 min-1

Organ dysfunction variables

- ALI with paO2/fiO2 <250 in the absence of pneumonia as infection source
- ALI with paO2/fiO2 <200 in the presence of pneumonia as infection source
- New need for oxygen to keep SpO2 over 90%
- Raised respiratory rate greater than 25 breaths min-1
- Acute oliguria (urine output <0.5 mL/Kg hr for at least 2 hrs, despite adequate fluid resuscitation)
- Creatinine increase > 44.2 µmol/L or Creatinine >176.8 µmol/L
- Coagulation abnormalities (INR >1.5 or PTT >60 secs
- Ileus (absent bowel sounds)
- Thrombocytopenia (Platelet count<100x109)
- Hyperbilirubinaemia (Bilirubin >34.2 µmol/L)

Tissue perfusion variables

- Elevated plasma lactate > 2mmol/l
- Decreased capillary refill or skin mottling
- Non-blanching rash

Appendix 3: History or signs suggestive of a new infection

- Fever
- Dysuria/ loin pain
- Cough / sputum / chest pain
- Headache with neck stiffness
- Abdo pain / distension / diarrhoea
- Cellulitis / wound infection / septic arthritis
- Line infection/ device –related infection
- Immunosuppression/ chemotherapy within last 6 weeks
- Endocarditis
- Site unclear