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ADULT PROCALCITONIN USAGE GUIDELINES

Background

Procalcitonin (PCT) is a 116 amino acid precursor of calcitonin that has both hormonal and cytokine-like activities. Normally it is produced locally in the thyroid gland by C-cells. Thus, serum concentrations of PCT are usually undetectable. It can also be produced in response to bacterial infection and it is produced in large quantities by many body tissues, especially the lung. Sources of inflammation other than bacterial infection, such as autoimmune disorders and viral infections, do not raise PCT levels. Furthermore, anti-inflammatory medications such as steroids and NSAIDs do not lower PCT levels. PCT levels rise quickly in response to bacterial infection, within 2-4 hours, but may take as long as 6-12 hours to reach its peak. It also has a half-life of about 24 hours. PCT can be contrasted with C-reactive protein (CRP) which takes longer to rise (12-24 hours), takes longer to peak (48 hours), is not specific to bacterial infection, and is influenced by anti-inflammatory medications. **This combination of characteristics makes PCT potentially a very useful, specific biomarker for the diagnosis and monitoring of acute bacterial infections.**

The FDA has approved procalcitonin assays for initiating or discontinuing antibiotics in lower respiratory tract infections (LRTIs) and for discontinuing antibiotics in patients with sepsis. Numerous studies have evaluated procalcitonin-based treatment algorithms in these settings and found them to be safe compared to standard care. In particular, the use of PCT allows cessation of antibiotic therapy without increased morbidity and mortality. This makes PCT a potentially useful tool for the prevention of the emergence of antibiotic resistant organisms while still ensuring appropriate treatment for serious bacterial infections.

PCT has not been extensively studied in pediatrics, pregnant women, and in significantly immunocompromised patients. Use PCT with caution and consider an infectious diseases consultation if there are doubts or questions about interpretation of the results.

When do false positives occur with PCT?

- Neonates
  - PCT is often elevated physiologically in the first few days of life (<72 hours)
- Postpartum women
  - PCT is often elevated physiologically in the immediate post-partum period
- Severe trauma or burns (massive cell death / necrosis)
- Major surgery
- Therapeutic cooling after cardiac arrest
- Treatment with agents which stimulate cytokines (OKT3, anti-lymphocyte globulins, alemtuzumab, IL-2, granulocyte transfusion)
- Kidney disease
  - Patients with CKD and AKI have falsely elevated PCT levels, with increasing disease associated with progressively increased levels. HD and CRRT efficiently remove PCT. As such, some literature recommends measuring pre-dialysis levels and using a higher threshold for interpretation, but such thresholds have not been validated.
- Acute graft vs. host disease
- Non-septic shock causing decreased organ perfusion and/or infarction

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When do <u>false negatives</u> occur with PCT?

- Early in infections
    - If low and bacterial infection is suspected, repeating a PCT in 6-12 hours is recommended
- Chronic infections (endocarditis, osteomyelitis, prosthetic device / graft infections)
- Some localized infections (cellulitis, wound infections, intra-abdominal abscess)
- Infection due to *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*.

Information on specific uses:

The FDA has approved procalcitonin assays for **initiating or discontinuing antibiotics in lower respiratory tract infections (LRTIs)** and for **discontinuing antibiotics in patients with sepsis. Use outside these scenarios is discouraged.**

<u>Respiratory tract infections (RTIs) with/without sepsis:</u>

There is a good body of evidence to support the use of procalcitonin in clinical decision-making algorithms for the use of antibiotic therapy for RTIs, including pneumonia, to avoid inappropriate antibiotic use safely, without adversely affecting morbidity or mortality. A patient-level meta-analysis of 26 randomized, controlled trials with 6,708 patients found the use of PCT in RTI resulted in a 30% decrease in duration of antibiotics, a reduction in antibiotic-related adverse effects, and a decrease in mortality (9% in procalcitonin-guided patients versus 10% in controls, p= 0.37) (Schuetz Lancet ID 2018). Another meta-analysis found procalcitonin use in RTIs to result in a significant decrease in rates of antibiotic initiation (Schuetz JAMA 2018). A recent large randomized trial in 14 hospitals in the United States of 1,656 patients with LRTI found that procalcitonin guidance (but not mandatory adherence) was not associated with a reduction in antibiotic-days (4.2 days in procalcitonin group vs. 4.3 days in control group) (Huang NEJM 2018). These findings illustrate the consistent safety of procalcitonin guidance but variable efficacy depending on adherence, patient population, and local antibiotic prescribing and stewardship practices.

Below is an FDA-approved procalcitonin-based algorithm that can be used to make decisions about the diagnosis and treatment of LRTI with antibiotics:

Procalcitonin Level (ng/mL)	Bacterial Etiology	Recommendation
<0.1	Very unlikely	Antibiotics strongly discouraged
0.1 – 0.25	Unlikely	Antibiotics discouraged
>0.25- 0.5	Likely	Antibiotics encouraged
>0.5	Very likely	Antibiotics strongly encouraged

- Procalcitonin should be evaluated in context with all findings and the total clinical status; clinical judgment always necessary. Procalcitonin should not be used in isolation to decide whether to initiate antibiotics in patients with suspected bacterial pneumonia.
- If the PCT is low and no antibiotics are started, a repeat PCT measurement may be considered *if clinical suspicion for infection persists* 6-24 hours after the first measurement.
- Procalcitonin levels may be utilized to support decision-making regarding duration of antibiotics in LRTIs in patients who have not achieved clinical stability; PCT levels ≤0.25 ng/mL or a >80% decrease in PCT level (from the highest PCT level) support antibiotic discontinuation IF a minimal standard duration has been completed. However, these thresholds are not necessary to stop antibiotic therapy. For example, some patients with very

high initial levels may not achieve this target by the end of a standard course of therapy, but therapy should not be extended solely on the basis of a PCT level.
    - In other words, procalcitonin should NOT be routinely used to *extend* treatment duration, and continuation of antibiotics beyond standard durations, in the setting of clinical stability, is NOT recommended, regardless of PCT level
- Increasing levels *may* signify treatment failure; Infectious Diseases can be contacted to help determine whether antibiotic therapy should be extended and/or changed.

Sepsis (SIRS, sepsis, severe sepsis, septic shock):

Note: For patients in whom pneumonia is thought to be the cause of sepsis, please refer to the LRTI algorithm above.

DO NOT use PCT to decide to START treatment for sepsis or septic shock. Early initiation of antibiotics is critical in such patients, and a low PCT should NOT delay treatment. PCT often takes 6-12 hours to rise after an acute bacterial infection and can be falsely low at the beginning. Institutional guidelines should be followed in such patients, including prompt administration of antimicrobial therapy. Procalcitonin can be useful to determine if antibiotics can be *discontinued*, not *initiated*.

There have been a number of randomized trials evaluating the use of PCT in guiding antibiotic therapy for **critically ill adult patients with sepsis**. Two recent systematic reviews/meta-analyses showed a decrease in antimicrobial duration of 1-3 days without adverse impacts on mortality, length of stay, or recurrent infection.

For patients admitted to the ICU with sepsis (see definition below), obtain a PCT level. In patients with an initial PCT <0.5 ng/mL, a repeat level should be drawn in 6-12 hours. Follow-up samples should be sent every 1-2 days. Antibiotic therapy may be discontinued if the PCT is ≤0.50 ng/mL or if the PCT value decreases by >80% compared to the highest observed previous concentration.

- Antibiotics should be continued in patients with a confirmed source of infection, regardless of PCT level. In other words, PCT levels should NOT supersede proven infection findings. The above algorithm should only be utilized in patients with sepsis *without a confirmed source of infection*.
- Consider continuing antibiotics in unstable patients or patients with disease progression.
- If procalcitonin remains high or is increasing, consider treatment failure or other causes.
- Continuation of antibiotic therapy beyond the standard duration of therapy, in the setting of clinical stability, is not recommended, regardless of PCT level.

Sepsis is defined as concern for infection + ≥2 SIRS criteria. SIRS criteria include the following:

- Temperature >38°C or <36°C
- Heart rate >90 bpm
- Respiratory rate >20 or $PaCO_2$ <32 mmHg
- White blood cell count >12,000/uL, <4,000/uL or >10% bands

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References / Further Reading

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The recommendations in this guide are meant to serve as treatment guidelines for use at Michigan Medicine facilities. If you are an individual experiencing a medical emergency, call 911 immediately. These guidelines should not replace a provider’s professional medical advice based on clinical judgment, or be used in lieu of an Infectious Diseases consultation when necessary. As a result of ongoing research, practice guidelines may from time to time change. The authors of these guidelines have made all attempts to ensure the accuracy based on current information, however, due to ongoing research, users of these guidelines are strongly encouraged to confirm the information contained within them through an independent source.

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