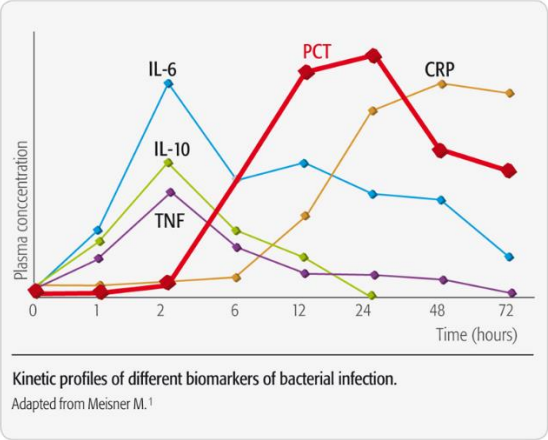
Duke University Health System (DUHS): Procalcitonin Guidance in Adults

Background

Serum procalcitonin (PCT) is a 116 amino acid precursor of calcitonin and normally produced by the thyroid C-cells. Under normal circumstances, serum concentrations of PCT are undetectable (< 0.05 mcg/mL). However, PCT may be produced in large quantities by extra-thyroid tissues (liver, pancreas, kidney, lung, intestine, *etc.*) and leukocytes in response to bacterial infection. Inflammatory conditions and sources of inflammation other than bacterial infection do not elicit a similar PCT elevation. Similarly, anti-inflammatory medications (*e.g.* steroids or NSAIDs) and immunosuppressive states (*e.g.* neutropenia) do not impair PCT production. PCT levels are dynamic over time (Figure 1). PCT rises quickly in response to bacterial infection, within 2 to 4 hours, peaks around 6 to 12 hours, and has a half-life around 24 hours.

Figure 1. Plasma Biomarker Concentrations



Kinetic profiles of different biomarkers of bacterial infection.
Adapted from Meisner M.[1]

Role for PCT in adults at DUHS

1. **Initiating or discontinuing antibiotics in suspected bacterial lower respiratory tract infections**
2. **Discontinuing antibiotics in patients with sepsis syndrome**

PCT use outside of these clinical scenarios is discouraged. PCT has key performance limitations and must be used and interpreted thoughtfully within a patient-specific context, considering infection syndrome, likelihood of bacterial infection, severity of illness, and other pertinent clinical data.

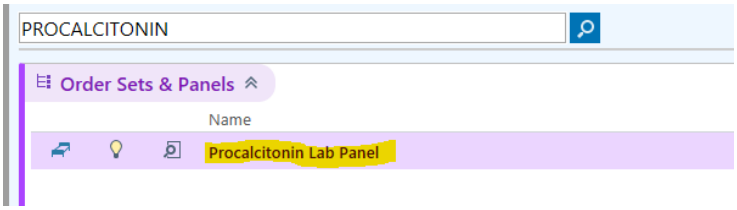
Key Principles of PCT Use and Interpretation

- Decisions regarding antimicrobial therapy should NOT be based solely on procalcitonin serum concentrations. PCT should NOT replace clinical judgement.
    - Antimicrobials should be continued in patients with a confirmed source of infection for an appropriate duration, regardless of PCT level.
    - Continuation of antimicrobial therapy beyond the standard duration of therapy in clinically stable patients is not recommended, regardless of PCT level.
- PCT levels should NOT be ordered if the resulting PCT value, regardless of the result, will not alter antibiotic therapy and/or duration decisions
- Identify and understand the limitations of PCT in select clinical scenarios (Table 1)
- PCT should NOT be used to decide to START antimicrobial therapy in patients with sepsis or septic shock syndromes

Table 1. Clinical scenarios where PCT use should be avoided or results should be interpreted with caution

Clinical Scenario		PCT implications	Notes/Pearls
Scenarios with Elevations in PCT (False Positive for bacterial infection)			
Massive stress	Major surgery	↑ Post-operative PCT (peak POD 1-2)	Risk/extent of post-operative PCT elevation varies by surgery type & severity (*e.g.* major abdominal surgery >>> neurosurgery)
	Severe trauma and/or burns	↑ Post-traumatic PCT (peak 1-2 days after trauma)	Risk/extent of PCT elevation varies by location of trauma, burn size/type, etc. Significantly elevated PCT values have been seen with abdominal trauma
	Postpartum women	↑ Postpartum (peak 1-2 days after delivery)	PCT is elevated physiologically in the early postpartum period
	Non-septic shock leading to decreased organ perfusion (*e.g.* prolonged cardiac shock)	↑ PCT	PCT elevations may be frequently seen in patients with cardiogenic shock, especially in the setting of multiple organ failure
	Pancreatitis	↑ PCT	May be elevated in acute pancreatitis (AP); studied as a biomarker for AP severity & predicting the development of infected pancreatic necrosis
Abnormal host and/or comorbid conditions	Kidney disease (acute kidney injury and chronic kidney disease)	↑ Baseline PCT	Inconsistent increase in PCT reported. Higher PCT thresholds likely warranted. However, the extent of kidney disease and presence/type of renal replacement therapy provide difficulties in establishing PCT cutoffs (*e.g.,* HD and CRRT efficiently remove PCT)
	Acute graft-versus-host disease	–/↑ PCT	Neutral to slightly increased PCT
	Agents that stimulate cytokines (OKT3, anti-lymphocyte globulins, alemtuzumab, IL-2, granulocyte transfusion)	↑ PCT	Elevations seen with T cell-directed therapies or granulocyte infusions
	Paraneoplastic syndromes due to medullary thyroid and small cell lung cancer	↑ PCT	
Other	SARS-CoV-2 Infection	–/↑ PCT	SARS-CoV-2 infection may produce cytokines that induce PCT production. PCT elevations may be seen in patients with COVID-19 without bacterial pneumonia
Scenarios with Low PCT (False Negative for bacterial infection)			
Too early in bacterial infection onset (PCT levels rise within 2-4 hours)		–/↓ Normal PCT	A false negative or normal PCT may occur if obtained early in infection and before PCT rises. Consider repeating PCT in 6-12 hours if clinical suspicion remains high for bacterial infection
Infection due to *Chlamydophilia pneumoniae* and *Mycoplasma pneumoniae*		–/↓ Normal PCT	PCT elevations may be less pronounced in patients with atypical CAP compared to other bacterial pneumonias
Localized infections (*e.g.* tonsillitis, sinusitis, cystitis, intra-abdominal abscesses, and wound infections)		–/↓ Normal PCT	Localized infections may not always produce PCT elevations. A negative PCT should NOT replace clinical judgement
Scenarios with Limited Clinical Data			
Severe immunocompromise including hematologic malignancy and transplant. Baseline PCT values may be higher in this populatio n. Optimal PCT thresholds are not well defined.			

How to order PCT



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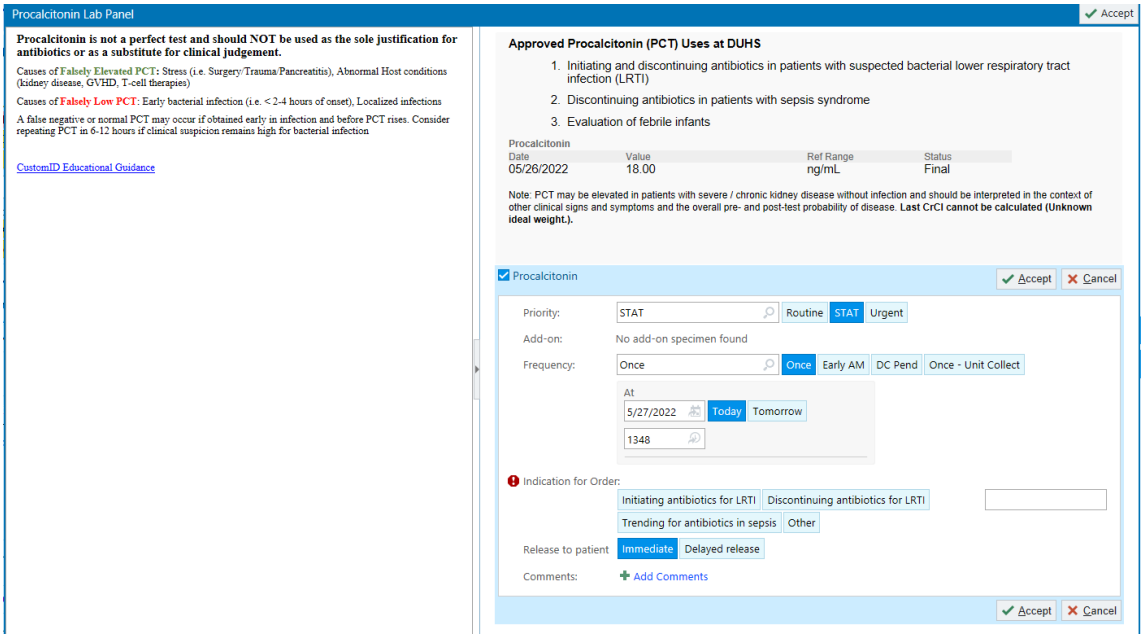


Laboratory turnaround time:

STAT: within 60 minutes from receipt of specimen in lab

ROUTINE: within 4 hours from receipt of specimen in lab

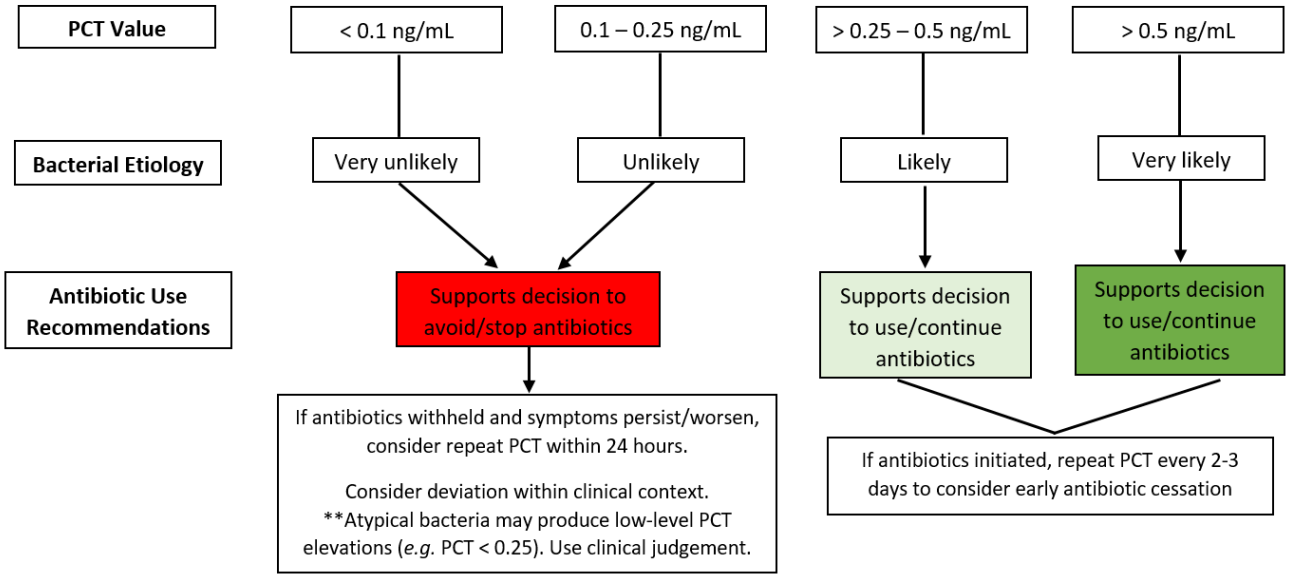
Syndrome-specific guidance

Lower respiratory tract infections (LRTIs)

PCT may help in evaluating patients with suspected bacterial LRTI to differentiate bacterial from viral disease. PCT should be obtained in the ED or onset of suspected LRTI (Figure 2) and every 2-3 days for further evaluation (Figure 3).

For ED treat and release patients, consider using initial PCT assessment (Figure 2) in conjunction with patient-specific symptoms, clinical assessment, and rapid diagnostic tests to help differentiate bacterial from viral disease and need for antibiotics.

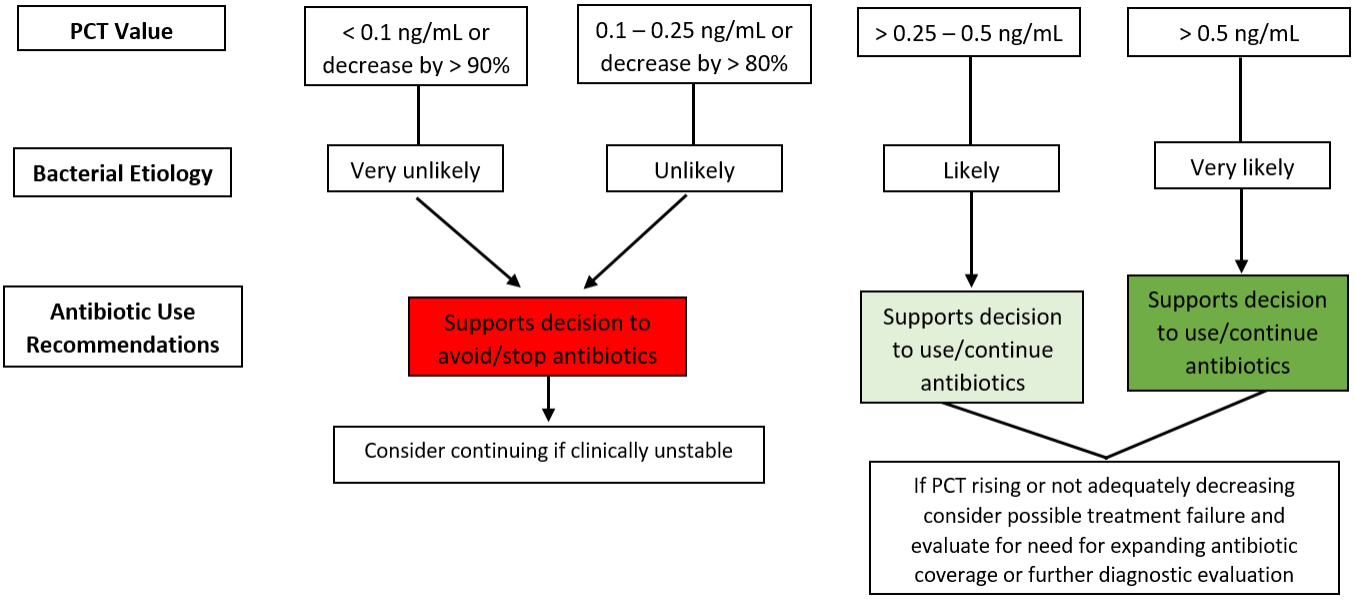
Figure 2. LRTI Initial Antibiotic Use & PCT Assessment



Supporting Data Summary: LRTI

A patient-level meta-analysis of 26 randomized controlled trials including data from 6,708 individual patients assessed the safety of procalcitonin to guide antibiotic decisions in patients with respiratory tract infections (*e.g.* pneumonia, COPD, bronchitis) from various clinical settings. PCT use resulted in a decrease in total antibiotic exposure (5.7 days vs 8.1 days, $p < 0.0001$), reduction in antibiotic-related side-effects (16% vs 22%, $p < 0.0001$), and reduced mortality (9% PCT vs 10% control, $p = 0.037$). In contrast, a recent 2018 randomized study conducted in 14 hospitals with 1,656 patients found that procalcitonin guidance was not associated with a difference in antibiotic days (4.2 vs 4.3 days, $p = 0.87$) or proportion of patients with adverse outcomes (11.7% vs 13.1%, $p < 0.001$ for noninferiority) within 30 days. Procalcitonin guideline adherence was not mandatory (overall guideline adherence = 64%). These data demonstrate the consistent safety of procalcitonin guidance with overall variable efficacy in LRTIs depending on patient population, PCT guideline adherence, and local antibiotic use and stewardship practices.

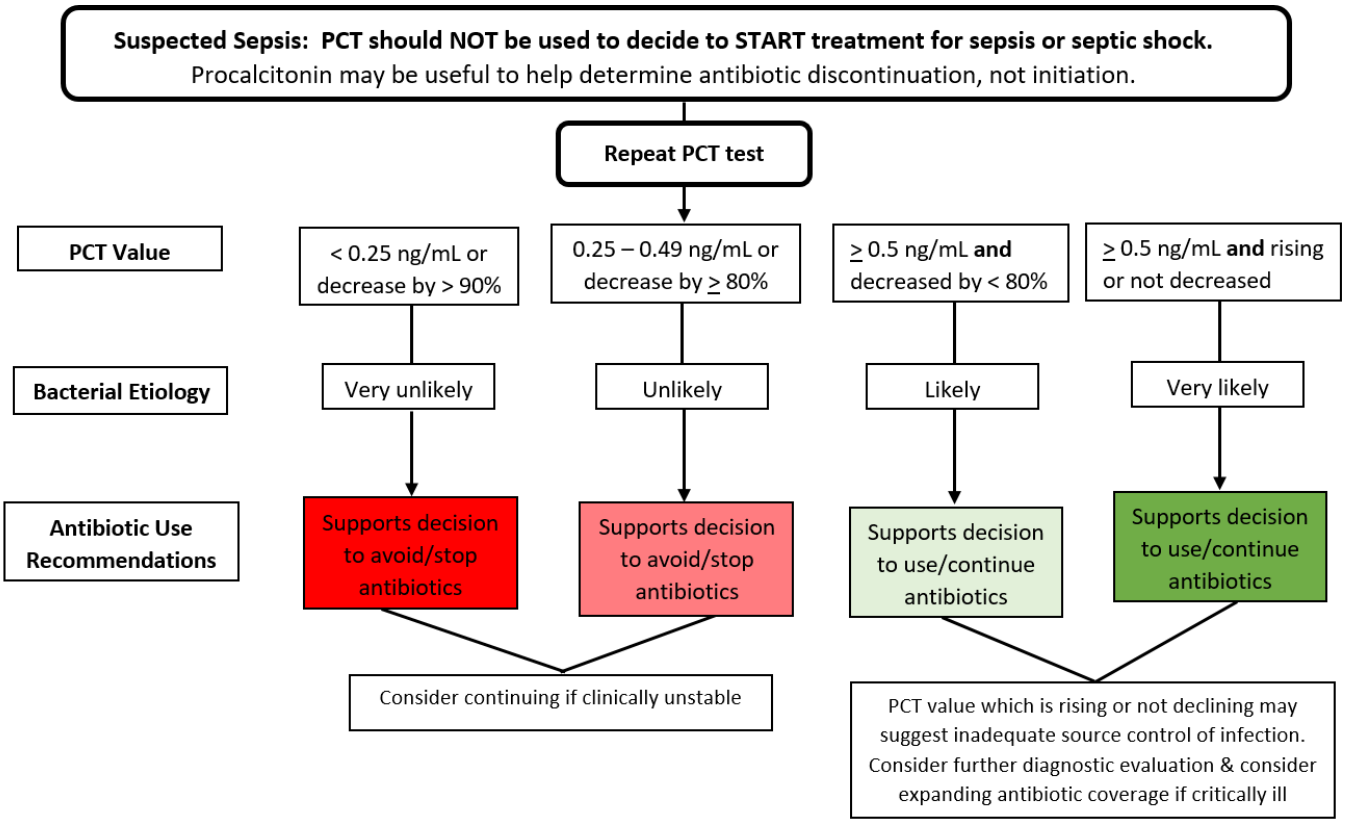
Figure 3. LRTI PCT Follow-up & Assessment



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

PCT should aid in assessing antibiotic discontinuation, **NOT** antibiotic initiation, in patients with suspected sepsis or septic shock. Patients with confirmed bacterial infection (*e.g.* bloodstream infection) should be treated according to site of infection and recommended duration of therapy. Early initiation of antibiotics is critical in such patients; a low PCT should not delay antibiotic initiation. PCT should be obtained on admission or onset of suspected sepsis and every 1-2 days for further evaluation (Figure 4).

Figure 4. Sepsis PCT Assessment & Evaluation



Supporting Data Summary: Sepsis (SIRS, sepsis, severe sepsis, septic shock)

Surviving Sepsis Campaign 2021 guidelines **suggest against** using procalcitonin to decide to start antimicrobials in suspected sepsis or septic shock. Limited data exists to use procalcitonin for initiating antibiotics in suspected sepsis or septic shock with no reported difference in short-term mortality, length of ICU stays, or length of hospitalization in a meta-analysis of 3 RCTs. Early antibiotic initiation in suspected sepsis or septic shock is critical. However, procalcitonin may be used in conjunction with clinical evaluation to facilitate appropriate antibiotic discontinuation. A recent systematic review and meta-analysis of 10 RCTs demonstrated a significant reduction in antibiotic duration with PCT guidance and no observed adverse effects on ICU length of stay and mortality. A second meta-analysis confirmed these findings with an antibiotic reduction of 1-3 days and no impact on short-term mortality, ICU length of stay, hospital length of stay, or recurrent infections.

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