Procalcitonin: the new kid on the block

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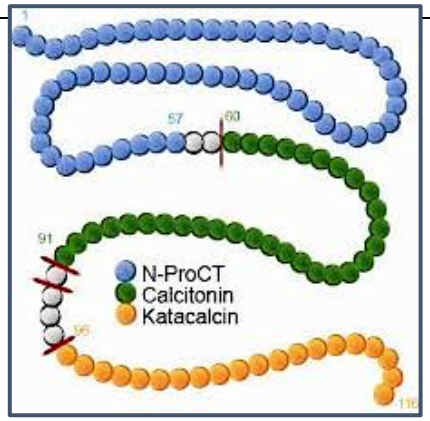
Growing effort to reduce unnecessary antibiotic use has stimulated interest in the use of various biomarkers to differentiate bacterial from viral and noninfectious causes of inflammation and to monitor response to therapy. Acute phase reactants such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are commonly used biomarkers that may indicate presence of infection or response to treatment. Procalcitonin (PCT) offers several distinct advantages over CRP and ESR for this indication, namely the quicker response time and increased sensitivity and specificity for inflammation due to bacterial infection. Although use in pediatrics has been somewhat limited by the lack of studies in this population and conflicting findings, newer data have shown PCT can be used as reliably in children as it can in adults.

What is Procalcitonin?



- PCT is a 116-amino acid precursor of calcitonin, normally undetectable in the serum and produced by C-cells of the thyroid gland
- Produced in large quantities by several body tissues as part of a systemic inflammatory response, particularly in cases of bacterial infection
- Compared to other commonly used acute phase reactants, PCT is produced rapidly in response to an insult, clears quickly once the

How is Procalcitonin interpreted?

Biomarker	Detectable within...	Advantages	Disadvantages
PCT	2-4 hours	▪ Highly sensitive and specific; unaffected by noninfectious inflammation or NSAIDs ▪ Declines rapidly with control of infection, so persistently elevated levels can be a sign of inadequate control of the infection	▪ May be **falsely elevated** with ECMO, surgery, trauma/burns, lung cancers, ESRD, and any condition affecting the immune response and cytokine production (T-cell therapy, GVHD) ▪ Less pediatric data
CRP	12-24 hours	▪ More sensitive for infection than ESR	▪ Affected by metabolic inflammatory conditions (uremia, cardiac ischemia)
ESR	24-48 hours	▪ High specificity for infection ▪ Useful for long-term monitoring of response to treatment with certain infections (i.e., osteomyelitis)	▪ Altered by conditions affecting RBC or fibrinogen (i.e., anemia, pregnancy, drugs, obesity, renal disease, etc.) ▪ Low sensitivity for infection

PCT measurements are most helpful when ordered sequentially – although most studies don't recommend ordering levels daily, at least two levels are necessary for most interpretations. Initial levels can be drawn to guide clinical decision-making for various indications; some algorithms recommend rechecking levels 6-12 hours after admission if they are initially low and clinical suspicion for infection is high. Once antibiotics are initiated, levels should be rechecked every 2-3 days during therapy to monitor response to therapy; levels that remain high warrant further clinical investigation. Note that the majority of data regarding appropriate use of PCT and its role in antimicrobial stewardship protocols have been collected in adults.

When and How should Procalcitonin be used in Pediatrics?

Indication	Study Findings & Clinical Application
Urinary Tract Infections	Increased PCT levels have been correlated with renal parenchymal damage and therefore may be used to differentiate lower UTIs from acute pyelonephritis[3] ▪ PCT ≥ 1.0ng/mL showed high sensitivity (84%) and specificity (91%) for renal involvement ▪ PCT ≥ 0.5ng/mL showed similar sensitivity and specificity, but the pooled analysis had significantly more heterogeneity and a lower diagnostic odds ratio than 1ng/mL
Respiratory Tract Infections	Low/normal PCT levels can be used to rule out bacterial involvement and identify children at low risk for community-acquired pneumonia due to "typical" bacterial pathogens, but are not useful in differentiating bacterial and viral etiologies[4] ▪ PCT < 0.1ng/mL effectively rules out presence of typical bacterial pneumonia (antibiotics strongly discouraged); PCT < 0.25ng/mL is associated with very low risk of CAP due to typical bacteria (antibiotics discouraged) ▪ PCT was not shown to be useful for differentiating etiologies of CAP or for ruling out etiologies other than typical pathogens
Sepsis	In neonates, the physiological boost of inflammatory markers (including PCT) causes increased levels through the third day of life; PCT levels that remain high after this time should be investigated for possible neonatal sepsis[5] ▪ Using a PCT cutoff of 1.2ng/mL yields a 93% negative predictive value for invasive bacterial infections in neonates > 72 hours old Among PICU patients, PCT was superior to CRP for detecting sepsis[5] ▪ Using a PCT cutoff of 1.16ng/mL yields 92% sensitivity and 76% specificity for sepsis
Febrile Neutropenia	Because PCT is not affected by immunosuppressive conditions, high PCT levels are associated with increased risk for bacterial infections ▪ Most studies used typical cutoff values for PCT; levels ≥ 0.5ng/mL have 60% sensitivity and 85% specificity for bacterial etiologies
Fever of Unknown Origin	In detecting bacterial infections in ED patients, PCT levels < 0.5ng/mL indicate lower risk and levels > 2 ng/mL indicate high risk[1]; use of intermediate levels is more controversial ▪ A recent study[6] found that a cutoff value of 1.28ng/mL showed similar sensitivity and increased specificity for serious bacterial infections (negative predictive value of

	88.9%) in PICU patients compared with traditionally used cutoff values of 0.5, 1, and 1.5ng/mL
Bone & Joint Infections	PCT levels may be useful in diagnosing osteomyelitis but are not recommended for evaluation of possible septic arthritis due to low sensitivity and specificity[2,5] ▪ One study[5] found a cutoff of 0.5ng/mL yielded 43.5% sensitivity, 100% specificity, and a 100% positive predictive value for detecting osteomyelitis
Meningitis	In differentiating bacterial and viral causes of meningitis, higher PCT levels have been associated with bacterial etiology[1] ▪ PCT < 0.5ng/mL can be used to rule out bacterial meningitis
Antimicrobial Stewardship	Unlike data found in adult studies, introduction of PCT assays has not been associated with a reduction in antimicrobial use, either due to the lack of an algorithm to guide use and interpretation of PCT[8] or to prescriber nonadherence to the suggested PCT algorithm[7] ▪ One study[9] showed that low CRP and PCT at onset of illness was associated with safe discontinuation of antibiotics after 48 hours

What's the Bottom Line for use of Procalcitonin?

Because of the increased sensitivity and specificity and the rapid response to infection and treatment, PCT has unique advantages over CRP and ESR as a biomarker of bacterial infection, but appropriate use is critical to correct interpretation. PCT is highly dynamic, so individual levels are much less useful than trends.

- Levels should be drawn with initial labs, prior to antibiotic administration, and interpreted in the context of relevant published data and the overall clinical picture
- If antibiotics are initiated, recheck PCT every 2-3 days to monitor response to therapy; if PCT was initially low/normal, consider discontinuing antibiotics after 48-72 hours based on clinical status of the patient

Most data support theoretical use of PCT as a component of antimicrobial stewardship protocols but highlight the importance of having an algorithm in place to guide clinicians to interpret the data appropriately and maintain physician adherence. PCT assays are more expensive than other commonly used biomarkers, so any reduction in healthcare costs would be the result of overall reduction in unnecessary antibiotic exposure and the risk associated with exposure.

→ Bottom Line: if you order the test, be sure to use the results!

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