Procalcitonin Testing

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SYNOPSIS AND RELEVANCE

Procalcitonin (PCT) is a biomarker associated with serious bacterial infections that may be used in conjunction with other laboratory data and clinical assessment to predominantly guide the early discontinuation of antibiotic therapy in the appropriate setting. Due to limited sensitivity and specificity, treatment decisions should not be made on the basis of PCT alone. This module will:

1. Educate healthcare providers about the appropriate use of procalcitonin with respect to institution-specific guidelines.
2. Educate providers to assess compliance with institution-specific guidelines.
3. Describe the consequences of overutilization and underutilization of procalcitonin with respect to use of antibiotics.

OBJECTIVES

1. Recognize clinical scenarios for which procalcitonin is a useful biomarker.
2. Recognize that algorithms utilizing procalcitonin should be developed and approved individually by each institution.
3. Assess impact of procalcitonin use on antibiotic stewardship.

BACKGROUND

Procalcitonin is a 14.5 kilodalton (kDa) protein, derived normally from pre-procalcitonin produced in the C-cells of the thyroid, and ultimately converted to the calcium-regulating hormone calcitonin. Normally, levels of procalcitonin are very low, at <0.1 ng/mL. However, following bacterial infection and sepsis, levels rise rapidly, within 3-4 hours, generally in correlation with the degree of infection. Procalcitonin levels remain elevated until resolution of disease, with a half-life of approximately 24 hours.[1] In comparison with C-reactive protein (CRP), procalcitonin takes less time to rise and to peak, and is more specific for bacterial-based infections.

Procalcitonin was first recognized in 1993 as a marker of bacterial infection,[2] and has very high negative predictive values at very low levels. Since then, numerous studies have investigated the use of procalcitonin in various diseases, although most randomized controlled trials have focused on respiratory tract infections, sepsis, and post-operative infections, whereas other disease conditions have generally been relegated to observational studies only.[1,3-10] Early diagnosis and treatment of such conditions as sepsis and respiratory tract infections leads to decreased morbidity and mortality.[1] Proper use of antibiotics reduces the likelihood that new bacterial drug resistance will emerge and may avoid drug-related adverse events in patients.[11] However, early diagnosis of bacterial infection can be challenging due to current limitations of laboratory-based testing.

Although procalcitonin is a useful aid, numerous studies have shown that it, like many biomarkers, is not entirely sensitive or specific, and should never be used solely in the decision to start or stop antibiotics, but instead must be used carefully in the context of clinical history, physical exam, and other diagnostic studies.[1,9,12] As such, procalcitonin usage and subsequent decision making must be incorporated into established institution-specific clinical algorithms that differ based on patient population, disease context, and physical setting.[9,12] The current Food and Drug Administration (FDA) indications for use of procalcitonin include using it as an aid in the risk assessment of critically ill patients on their first day of intensive care unit (ICU) admission for progression to severe sepsis/septic

shock, as an aid in assessing the 28 day risk of mortality for patients with severe sepsis/shock in the ICU, as an aid in decision making for starting/stopping antibiotics in patients with lower respiratory tract infections, and as an aid in decision making for discontinuing antibiotics in patients with confirmed or suspected sepsis.[1]

There is a fair amount of evidence for procalcitonin's use in antibiotic stewardship for patients with suspected or confirmed respiratory tract infections,[4-6,13,14] as well as for discontinuation of antibiotics in the setting of bacterial infection and sepsis.[3,7,8,13,15,18] Most such approaches, as studied in randomized controlled trials, utilize four different cutoff ranges as shown in the appendix, with these cutoff ranges generally ranging from 0.1 to 0.5 ng/mL.[3-5,8] Such approaches have been shown, in general, to mildly reduce the use of antibiotics in these patient populations without worsening clinical outcome.[2,3,6,8] Additionally, these different algorithms suggest serial testing at various time intervals after the initial procalcitonin value, to further guide antibiotic management.[3,5,6,8,14] Time intervals vary, but based on the half-life of procalcitonin, repeat testing should generally be limited to a time interval not less than every 24-48 hours after antibiotic administration, with consideration of stopping antibiotics, in the appropriate clinical situation, at certain low levels of procalcitonin (such as <0.5 ng/mL) or at a defined decrease from the initial procalcitonin level (such as <80% of the initial level).[16,17]

Procalcitonin continues to be studied, and further work will undoubtedly help define and refine further indications for the use of procalcitonin. To date, procalcitonin has been studied in only a limited manner in children and pregnant women, although some clinical uses appear valid.[1,18]Additionally, procalcitonin values can be elevated naturally in the setting of other conditions, such as trauma, burns, chronic kidney disease, carcinomas, shock, and cirrhosis, and therefore procalcitonin values must be interpreted carefully in the setting of patient history.[16,19]

Current assays for procalcitonin are based on immunoassay methodologies, and procalcitonin can now be measured on numerous different analyzers, with a lower limit of quantification that can range to well below 0.05 ng/mL.[1] Additionally, procalcitonin assays have a fast analytical turnaround time, such that in-house results can be available to providers within an hour of collection, depending on the laboratory's workflow.

INSIGHTS

1. Procalcitonin may be used in conjunction with other laboratory data and clinical assessments to manage patients with a suspected infection given its general availability in hospital labs, relatively fast turnaround time, and high negative predictive value.
2. Procalcitonin may be used as an aid in the risk assessment and antibiotic decision making of certain adult patient populations, including those with sepsis, but should not be used alone.
3. Procalcitonin usage and interpretation must be incorporated into institution-specific clinical algorithms.

INTERVENTIONS

Disease-specific algorithms utilizing procalcitonin should be established within each institution, as overutilization of procalcitonin provides no value in the management of patients and can increase healthcare costs, whereas underutilization may be associated with overuse of antibiotics. However, as discussed above, the most evidence-based uses of procalcitonin involve antibiotic initiation and discontinuation in the setting of respiratory tract infections, and the discontinuation of antibiotics in the ICU in the setting of sepsis or septic shock. Some approaches for appropriate testing are described here, but are generally institution specific.

1. Discuss current procalcitonin-based algorithms with clinical stakeholders and verify that they are published within the institution and supported by the literature and/or institution specific data.
2. If not already established, work with clinical stakeholders to develop institution-specific procalcitonin-based algorithms, such as presented in the appendix, for patients with respiratory tract infections, especially in the emergency department (ED), and for patients in the ICU/ED with suspected sepsis or septic shock.
3. For those areas with a known potential overutilization of procalcitonin (especially emergency departments), consider collaborating with ED stakeholders to develop more institution-specific protocols for their specific patient disease conditions associated with high ordering frequencies.

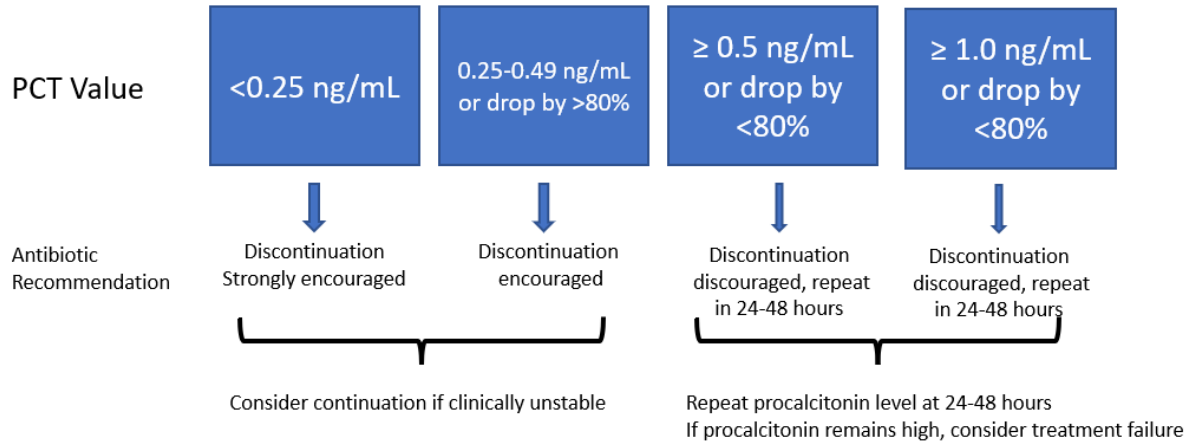
INTERVENTION IMPACT

Given the role of procalcitonin in potentially complex clinical algorithms, it can be difficult to assess the impact, from a laboratory perspective, of the implementation of such algorithms.

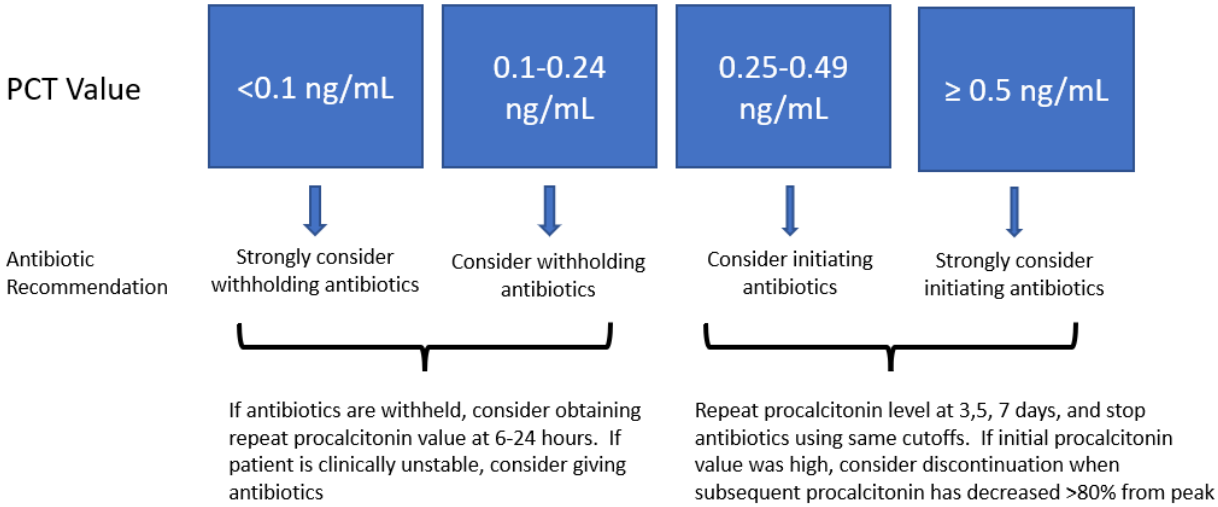
- A relatively simple initial analysis is to analyze the temporal use of procalcitonin before (if possible) and after the development of algorithms; ideally, procalcitonin should be repeated only once every 24-48 hours in a particular patient.
- If frequency is not following established algorithmic recommendations, discussion with the appropriate clinical teams may be warranted, to address potential under or overutilization.
- More globally, as discussed in the Background section, one of procalcitonin's most useful features is that it may decrease overall average antibiotic use, as this could reduce the development of antibiotic resistance and drug-related harm. Although the reduction in antibiotic usage in a hospital, or even within a certain ward of a hospital, may be difficult to gather, this may be possible with the appropriate clinical and informatics partners. For instance, one may be able to gather average days of antibiotic use in patients with symptoms of sepsis in the ICU, both before and after use of the algorithmic use of procalcitonin.

APPENDIX: SAMPLE ALGORITHMS FOR ANTIBIOTIC USE BASED ON PROCALCITONIN (PCT) VALUES

Sample algorithm for discontinuation of antibiotics in patients with symptoms of sepsis in the ICU.



Sample algorithm for utilization of antibiotics in patients with lower respiratory tract infections.



QUESTIONS AND ANSWERS

QUESTION 1 OBJECTIVE

Recognize clinical scenarios for which procalcitonin is a useful biomarker.

QUESTION 1

A 65-year-old female patient is admitted to the ICU with mental status changes, a blood pressure of 80/55, a respiratory rate of 35/minute, and an initial procalcitonin value of 1.6 ng/mL. After 3 days of antibiotics, the patient is clinically better and has a procalcitonin value of 1.1 ng/mL. Which of the following courses of action is most appropriate?

A. Discontinuation of the patient's antibiotics
B. Changing the patient's antibiotics or dosing
C. Continuation of the patient's antibiotics as prescribed
D. Continuation of the patient's antibiotics as prescribed and repeating the procalcitonin level within 12 hours

The correct answer is C. The patient's procalcitonin value is lower than the initial value, but has only dropped by 31% and is not less than 0.5 ng/mL. Therefore, algorithms that use procalcitonin to help determine whether antibiotics can be discontinued in the setting of sepsis, would essentially all support continued use of antibiotics in this setting.
A is incorrect. Discontinuation of antibiotics in the setting of sepsis would generally require a value of procalcitonin at <0.5 ng/mL, or a decrease of 80% from the initial value.
B is incorrect. The patient is improving on the current antibiotic and dose. There is no imminent need based on the data given above to adjust the patient's antibiotic course.
D is incorrect. Repeat procalcitonin values are generally performed every 24-48 hours when monitoring for discontinuation of antibiotics. A repeat value at 12 hours would likely not be useful in this clinical scenario.

QUESTION 1 REFERENCE

1. Schuetz P. How to best use procalcitonin to diagnose infections and manage antibiotic treatment. *Clinical Chemistry and Laboratory Medicine.* 2022; 61(5): 922-828.

QUESTION 2 OBJECTIVE

Recognize that algorithms utilizing procalcitonin should be developed and approved individually by each institution.

QUESTION 2

A local ED doctor orders procalcitonin on all patients who present with fever, and uses a cutoff of 0.1 ng/mL to initiate antibiotics in the vast majority of such patients. Which of the following is a subsequent direct potential consequence of this action?

A. Decreased total cost of the visit to the patient
B. Increased opportunistic infections, such as *C difficile*, in this patient population due to inappropriate antibiotic usage
C. Improved morbidity/mortality rates in this patient population
D. Decreased usage of other laboratory testing in this patient population

The correct answer is B. Procalcitonin is best used algorithmically, based on institution developed protocols, for specific clinical scenarios. Overuse of procalcitonin with a low threshold for antibiotic initiation can lead to increased costs and increased patient exposure to antibiotics, which can lead to antibiotic-associated infections such as C. difficile.
A is incorrect. There is no evidence to suggest that increased procalcitonin usage would decrease total costs for patients when used across a large, nonspecific population of patients.
C is incorrect. Although morbidity/mortality may be improved in specific patient populations utilizing procalcitonin-based algorithms, there is no evidence to suggest that widespread non-algorithmic use of this testing would improve morbidity/mortality.
D is incorrect. There is no evidence that procalcitonin usage decreases other laboratory-based testing utilization.

QUESTION 2 REFERENCES

1. Chambliss, A, Patel K, Colon-Franco J, et al. AACC guidance document on the clinical use of procalcitonin. *J Appl Lab Med*. 2023;8(3):598-634. doi:10.1093/jalm/jfad007

2. Deege M, Paterson D. Reducing the development of antibiotic resistance in critical care units. *Curr Pharm Biotechnol*. 2011; 12(12): 2062-2069 . doi: 10.2174/138920111798808301062-9
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QUESTION 3 OBJECTIVE

Assess impact of procalcitonin use on antibiotic stewardship.

QUESTION 3

A hospital initiates a procalcitonin-based algorithm for discontinuation of antibiotics in septic patients. A direct outcome of this algorithm may be:

A. Decreased total cost of stay per patient
B. Decreased antibiotic usage
C. Worsening patient mortality rates
D. Increased usage of other laboratory testing in this patient population

The correct answer is B. Procalcitonin-based algorithms can shorten antibiotic usage, which may lead to reduced drug-related harm.

A is incorrect. There is no evidence to suggest that increased procalcitonin usage would decrease total costs for patients.

C is incorrect. There is no evidence to suggest that procalcitonin-based antibiotic decisions worsen patient mortality rates.

D is incorrect. There is no evidence that procalcitonin usage increases other laboratory-based testing utilization.

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