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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Can procalcitonin guide decisions about antibiotic management?

A: Yes, but with caution. Multiple randomized controlled trials showed that procalcitonin testing can help guide antibiotic management in a variety of clinical scenarios including sepsis, respiratory tract infection, and exacerbation of chronic obstructive pulmonary disease (COPD), and that procalcitonin guidance led to less antibiotic use with either unchanged or better outcomes. Moreover, observational studies have shown high negative predictive values for procalcitonin testing in other clinical situations such as bacteremia and bacterial meningitis, allowing clinicians to rule out these diagnoses if the clinical probability is low or moderate.

Nonetheless, clinical judgment must be exercised to consider the possibility of false-positive and false-negative results, especially if clinical suspicion for bacterial infection is high.

A RESPONSE TO BACTERIAL TOXIN

Procalcitonin is a peptide precursor of calcitonin that is produced by C cells of the thyroid and by neuroendocrine cells of the lung and intestine in response to bacterial toxin. In contrast, procalcitonin levels are down-regulated in viral infection.

Levels of procalcitonin increase 6 to 12 hours after stimulation, and the half-life is roughly 24 hours.[1] This suggests levels should decrease by one-half daily if an infection is controlled and is responding to therapy (assuming normal clearance).

The test costs about $25, with a turnaround time of 20 to 60 minutes, or longer at institutions that send the test out or run the tests in batches.

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Point-of-care procalcitonin testing is emerging but not yet commercially available in the United States. Despite extensive observational studies and randomized controlled trials over the past 20 years, procalcitonin's physiologic role remains unclear. The large body of evidence of the clinical utility of procalcitonin measurement has been summarized in several meta-analyses in different diseases.

PROCALCITONIN TESTING IN SEPSIS

Trials of procalcitonin testing have had slightly different inclusion criteria that commonly overlap with similar diagnoses. Sepsis is the broadest cohort studied.

The Procalcitonin to Reduce Antibiotic Treatments in Acutely Ill Patients (PRORATA) trial[2] randomized 621 patients admitted to the intensive care unit (ICU) with suspected bacterial infections to antibiotic therapy guided by procalcitonin concentrations or to antibiotic therapy based on current guidelines. The source of infection varied, but 73% of patients had pulmonary infections. The procalcitonin algorithm was as follows:

- Starting antibiotics was discouraged if the procalcitonin concentration was less than 0.5 ng/mL, and strongly discouraged if less than 0.25 ng/mL
- Starting antibiotics was encouraged if the concentration was 0.5 ng/mL or higher, and strongly encouraged if 1 ng/mL or higher
- Stopping antibiotics was encouraged if the concentration dropped by at least 80% from the peak level or to a level greater than or equal to 0.25 ng/mL; stopping was strongly encouraged if the concentration fell below 0.25 ng/mL.

There was also guidance to change antibiotics if procalcitonin increased on therapy and

Procalcitonin can guide antibiotic management in sepsis, respiratory tract infection, and COPD exacerbation

was above 0.5 ng/mL.

Although the study physicians generally followed the algorithm, they were allowed to override it based on clinical judgment. The main results were that the number of days without antibiotics was higher in the procalcitonin group than in the controls (14.3 vs 11.6 days), with no other statistically significant difference between groups. These findings supported the idea that procalcitonin can guide clinicians to safely "deprescribe" antibiotics.

The Stop Antibiotics on Guidance of Procalcitonin Study (SAPS),[3] published in 2016, was a larger trial with similar design, in 1,575 patients admitted to the ICU with suspected infection. Antibiotic use was less and the 28-day mortality rate was lower with procalcitonin guidance: 20% vs 25% in the intention-to-treat analysis.

ACUTE RESPIRATORY TRACT INFECTION

The Procalcitonin Guided Antibiotic Therapy and Hospitalisation in Patients With Lower Respiratory Tract Infections (ProHOSP) trial[4] randomized 1,381 patients to antibiotic therapy guided by procalcitonin levels or standard guidelines. Most patients had community-acquired pneumonia, while the rest had exacerbations of COPD, acute bronchitis, or other lower respiratory tract infections.

In ProHOSP, antibiotic use was less with procalcitonin guidance, as was the rate of adverse effects from antibiotics

In the study algorithm, starting or continuing antibiotics was discouraged if procalcitonin levels were 0.25 ng/mL or less, and strongly discouraged if less than 0.1 ng/mL. Starting or continuing antibiotics was encouraged if levels were greater than 0.25 ng/mL, and strongly encouraged if greater than 0.5 ng/mL.

The algorithm recommended stopping antibiotics if procalcitonin levels fell below 0.25 ng/mL or decreased by 80%, and strongly recommended stopping them if procalcitonin fell below 0.1 ng/mL or decreased by 90%.

The treating physician could override the algorithm if the patient was unstable, was in an ICU, or had *Legionella* infection.

Antibiotic use was less in the procalcitonin-guided arm (75.4% vs 87.7%; mean duration 5.7 days vs 8.7 days), as was the rate of adverse effects from antibiotics (19.8% vs 28.1%). Rates of recurrence or rehospitalization were also lower with procalcitonin guidance (3.7% vs 6.5%), presumably because of fewer antibiotic-related side effects or better diagnostic accuracy. Rates of death and ICU admission were similar in the 2 groups. These findings were similar to those of PRORATA and SAPS, demonstrating that guidance with procalcitonin levels decreased antibiotic utilization, with other outcomes either improved or unchanged.

Schuetz et al,[5] in a 2018 meta-analysis, collected data on 6,708 patients from 26 trials in 12 countries and found that procalcitonin guidance decreased antibiotic exposure by 2.4 days and reduced the rate of antibiotic-related side effects (16% vs 22%). Although there was skepticism about the mortality benefit reported in the SAPS trial, a similar mortality benefit was found in this meta-analysis (30-day mortality rates were 9% vs 10%), suggesting that measuring procalcitonin not only reduces unnecessary antibiotic exposure, but also saves lives.

Although decreasing antibiotic exposure may not confer a survival benefit, procalcitonin guidance likely clarifies the diagnosis and thus expedites proper treatment in patients with sepsis-like syndromes that are actually due to a non-infectious pathology (eg, pulmonary embolism, myocardial infarction, adrenal insufficiency).

Negative findings in ProACT

The Procalcitonin Antibiotic Consensus Trial (ProACT)[6] subsequently reported findings discordant with those above but was flawed in that adherence to the procalcitonin guideline by physicians was only 62% in the subgroup of patients with low procalcitonin results, which accounted for almost 90% of patients. Overall adherence by physicians to the procalcitonin guideline was 65%, much lower than in other trials (ProHOSP had over 90% adherence).[4] Further, ProACT was done in American centers unfamiliar with procalcitonin, and it seems they did not trust low procalcitonin values as a reason to stop or avoid antibiotics.

ACUTE EXACERBATIONS OF COPD

Multiple small randomized controlled trials and subgroups of larger studies like ProHOSP have studied the use of procalcitonin in acute exacerbations of COPD. Most studies used a design similar to the algorithm in ProHOSP.

procalcitonin levels (especially in metastatic disease), but a low concentration still has a fair negative predictive value (approximately 90%) for bloodstream infections.[13]

A retrospective study suggested that the ratio of procalcitonin to C-reactive protein could improve diagnostic accuracy in patients with malignancies, presumably because an elevation of procalcitonin out of proportion to elevation in C-reactive protein favored a bacterial infection rather than nonspecific inflammation related to malignancy.[14]

Cardiac syndromes

In cardiac syndromes, dyspnea and abnormal chest imaging may make it difficult to exclude respiratory infections. Schuetz et al[15] reviewed the potential value of procalcitonin testing in a variety of cardiac disorders, especially in acute cardiovascular conditions whose presentation resembles that of sepsis or acute respiratory tract infection. They concluded it may have a role in diagnosis and prognosis in these settings, as well as guiding drug therapy.

Localized infections

Though localized infections such as cystitis, cellulitis, and osteomyelitis often do not affect procalcitonin levels, the test may help assess illness severity and rule out associated bacteremia.

One study found that a low procalcitonin level was insufficient to rule out urinary tract infection, but procalcitonin levels predicted bacteremia better than any other variable or combination of variables; moreover, procalcitonin had a negative predictive value as high as 97% for ruling out bacteremia associated with urinary tract infection.[16]

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ROLE IN PROGNOSIS

In addition to being a useful marker for diagnosis of bacterial infections, the procalcitonin level has significant prognostic implications, as a high or persistently elevated level correlates with a higher rate of all-cause mortality.[17] The prognostic capability may enhance triage decisions.

Because the procalcitonin level lacks specificity, clinicians need to be aware of noninfectious causes of elevations such as malignancy, surgery, impaired renal function,[8] and myocardial infarction.[18] In these scenarios, it is important to think critically about the procalcitonin result and consider an adjusted cutoff.

A study of procalcitonin to predict a positive blood culture in patients with renal disease suggested an optimal cutoff value of 1.06 ng/mL for patients with an estimated glomerular filtration rate of 30 to 60 mL/min/1.73m^2, and a value of 2.50 ng/mL for a rate less than 30 mL/min/1.73m^2.[8]

In a chronic process like malignancy, the procalcitonin level is usually not markedly elevated. But it can also remain persistently elevated, with no improvement associated with effective antibiotic treatment and no clinical deterioration associated with treatment failure.

Use of procalcitonin and troponin

For some patients, there may be diagnostic uncertainty about interpreting procalcitonin and troponin results, as both plaque-rupture myocardial infarction and demand ischemia from sepsis can cause elevation in both values. In a study of patients with acute myocardial infarction, the procalcitonin level peaked at 3.57 ng/mL and troponin peaked at 60 ng/mL at about 24 hours after admission.[18] This suggests that a troponin-to-procalcitonin ratio may help distinguish acute myocardial infarction from demand ischemia, though the optimal cutoff is unknown.

Both troponin and procalcitonin levels can help rule out acute severe illness (eg, bloodstream infection, acute myocardial infarction). But both can be falsely negative in early presentation or in less severe disease (eg, localized infection, unstable angina), as well as in noninfectious inflammation and nonobstructive myocardial injury.

Both are important prognostic markers. Furthermore, both can be chronically elevated in patients with renal disease, but both still have a characteristic rise and fall in acute disease states. But neither should be used in isolation without information from electrocardiography, other tests, and the clinical context.

CAVEATS AND CHALLENGES

Based on clinical experience and reported studies, procalcitonin testing has proven valuable in the diagnosis, prognosis, and management of a range of diseases, particularly certain infections.

However, procalcitonin testing must be ap-

Mathioudakis et al,[7] in a meta-analysis of 8 trials with a total of 1,062 patients with acute exacerbation of COPD, found that with procalcitonin guidance, prescription of antibiotics on admission decreased by almost one-half, and courses of antibiotics were approximately 4 days shorter without any statistically significant difference in rates of treatment failure, length of hospital stay, recurrence, rehospitalization, or overall mortality.

However, the quality of the studies included in the meta-analysis was deemed only low to moderate, and thus the authors concluded, "Procalcitonin-based protocols appear to be clinically effective; however, confirmatory trials with rigorous methodology are required."[7] Nonetheless, given the lack of data supporting current practices for patient selection for antibiotics in COPD exacerbations, a strategy involving procalcitonin seems to be reasonable.

BACTEREMIA

Observational studies from as far as back as 1999 have examined the association of procalcitonin levels with bacteremia. The study designs were generally similar, with procalcitonin levels checked at time of blood culture, mostly in emergency rooms, and the procalcitonin value correlated with blood culture results. The general conclusion has been that procalcitonin has diagnostic value in ruling out bacteremia but should be used in the context of pretest probability rather than in isolation.

Hattori et al[8] performed one of the largest studies, in 1,331 patients, using a procalcitonin level cutoff of 0.9 ng/mL. The sensitivity was 72% and specificity was 69%, which are not impressive; however, the negative predictive value was 95%, and even higher at lower cutoff values. Further, procalcitonin was significantly better at predicting bacteremia than either the white blood cell count or C-reactive protein level, with the latter two being hardly better than random chance.

Hoeboer et al[9] performed a meta-analysis of various studies with a total of 16,514 patients. Using a cutoff of 0.5 ng/mL, they reported a sensitivity of 76% and a specificity of 69% with a negative predictive value of 97% in emergency rooms, 95% on regular wards, and 98% in ICUs. The high negative predictive value of procalcitonin can allow clinicians to stratify bacteremia risk to determine which patients need blood cultures, which in turn may help clinicians order blood cultures more appropriately and avoid unnecessary costs, delays, and harms associated with false-positive results, such as additional visits, additional testing, and unnecessary use of antibiotics.

MENINGITIS

As with bacteremia, observational studies have reported fairly high negative predictive values for procalcitonin in bacterial meningitis. The correlation is not surprising, given that most cases of bacterial meningitis occur due to hematogenous dissemination.

A 2015 meta-analysis of 9 studies and 725 patients reported a pooled sensitivity of 90%, specificity 98%, positive likelihood ratio 27.3, and negative likelihood ratio 0.13.[10] Cutoffs for procalcitonin levels varied, but the most common value was 0.5 ng/mL. The authors also noted that the diagnostic utility of procalcitonin was far superior to C-reactive protein in this scenario, concluding that serum procalcitonin is a highly accurate test to distinguish between bacterial and viral causes in suspected meningitis.[10]

OTHER CLINICAL APPLICATIONS

Postoperative infection

Small studies have assessed procalcitonin as a marker to rule out postoperative infections,[11,12] but the heterogeneity of study designs and populations makes it difficult to combine the studies for meta-analysis. Nevertheless, the general trend is that there may be a role for procalcitonin, and that procalcitonin has better diagnostic yield than the white blood cell count or C-reactive protein level. The optimal cutoff depends on the surgery, since a small elevation in procalcitonin can be expected with the stress of surgery; and since the degree of elevation varies with type of surgery, the result must be interpreted with caution.

Malignancy

In malignancy-associated conditions such as neutropenic fever and tumor fever, the clinical utility of procalcitonin is somewhat diminished, as malignancy can cause elevated

Observational studies have shown that procalcitonin testing has value in ruling out bacteremia if used in the context of pretest probability

plied cautiously and judiciously. There is a potential for early false-negative results, and false-positive results can occur in conditions such as kidney disease, myocardial infarction, postoperative stress response, and malignancy, though there may be ways to factor these conditions into interpretation of procalcitonin results.

Widespread procalcitonin testing may lead to excessive costs, though the cost for each test is reasonable and probably offset by benefits of diagnostic clarification and decreased use of antibiotics, if appropriately applied.

The primary roles for procalcitonin testing are to rule out infection in patients with low probability of infection and to allow safe early cessation of antibiotic therapy in patients with presumed bacterial infection. Procalcitonin testing can enable providers to stop antibiotics safely, with the general trend showing decreased antibiotic utilization without patient harm. This can result in healthcare cost savings and improved patient outcomes such as decreased length of hospital stay, decreased readmission rates, fewer adverse effects from antibiotics, and possibly improved mortality rates.

Despite the potential benefits from procalcitonin testing, results must be interpreted within the clinical context because a host of factors can affect the values. Extreme values are more useful than intermediate values, which are difficult to interpret and have poor predictive value.

Although all current biomarkers for infection are imperfect, procalcitonin appears to have better diagnostic accuracy than other markers such as the white blood cell count and C-reactive protein in multiple clinical scenarios, and its appropriate use appears to improve important outcomes such as survival.

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