

MINIREVIEW

Use of Plasma Procalcitonin Levels as an Adjunct to Clinical Microbiology[∇]

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Procalcitonin (PCT) is synthesized by a large number of tissues and organs in response to invasion by pathogenic bacteria, fungi, and some parasites. Current PCT assays are rapid, specific, and of sufficient sensitivity to detect increases in PCT serum levels within 4 to 6 h of initiation of infection. Clinically, PCT levels may help in decisions regarding the need for empirical antibiotic therapy, “source control” of infection, and duration of antibiotic therapy. The addition of PCT levels to bacterial culture and viral detection results can assist with the separation of colonization and invasion by pathogenic bacteria.

Based on current data, the general concept is that an increase in the serum concentration of procalcitonin (PCT) signals activation of the innate immune system as a consequence of microbial invasion by bacteria, malaria, and some fungi (4, 7, 32). In patients with clinical evidence of infection and repeatedly normal PCT levels, it is highly unlikely that the infection is due to pathogenic bacteria. In contrast, available data indicate that patients with influenza, severe acute respiratory syndrome (SARS), and other pure viral infections have low serum PCT levels (9, 11, 35, 37, 41).

The clinical utility of serum PCT levels continues to evolve. At present, there are four common and reasonable bedside uses for PCT levels. In addition, PCT levels can assist with the interpretation of the clinical significance of the results of standard microbiologic methods used to detect bacteria and viruses.

What follows is an overview of PCT biology, the current clinical uses of PCT levels, and the potential use of PCT levels in clinical microbiology. To illustrate the use of PCT levels in clinical microbiology, data from patients with respiratory tract infections are discussed in detail.

PROCALCITONIN BIOLOGY

Although PCT is the prohormone for calcitonin, the biologic activities are distinctly different (3, 4, 7). In the C cells of the thyroid gland and K cells of the lung, elevated serum calcium concentrations or neoplastic change results in transcription of the procalcitonin gene. Subsequently, ribosomal synthesis of the 116-amino-acid procalcitonin molecule occurs, with the subsequent cleavage of amino acids 60 to 91 yielding calcitonin. Calcitonin's only recognized biologic activity is to lower

the serum calcium concentration by inhibition of bone resorption.

In contrast, in response to invasion by bacteria, *Plasmodium* spp., and some fungi, macrophages synthesize proinflammatory cytokines. *In vitro* and in animal models of infection, bacterial infection or endotoxin administration results in the synthesis of PCT and other calcitonin precursors by virtually all tissues and organs tested (3, 4, 7, 20, 22). Even adipose cells respond to endotoxin with the synthesis of procalcitonin (15).

PCT synthesis is detectable in serum within 4 h, and peak levels occur at 12 to 48 h (3). In distinction to synthesis of C-reactive protein and the other acute-phase reactants, the existing data suggest that PCT levels rarely increase in response to pure viral infection (9, 11, 35, 37, 41). The lack of response to viral disease is postulated to result from viral stimulation of macrophages to synthesize alpha interferon, which, in turn, inhibits tumor necrosis factor (TNF) synthesis (14, 15, 18). The presence of TNF is necessary for tissues to synthesize PCT.

There are likely other biologic roles for PCT, beyond signaling bacterial invasion. This subject needs more data. In an animal model of sepsis in guinea pigs, antibody to PCT increased survival (3, 7, 26). To my knowledge, there are no PCT studies of animals that have had some or all of the PCT genes knocked out. Similarly, I am unaware of data that focus on PCT levels in patients with genetic deficiencies of innate immunity. In theory, an inability to synthesize tumor necrosis factor would result in a deficiency in PCT production. Of interest, neutropenic bacteremic patients have no apparent deficiency in generating a PCT response (17, 28).

PLASMA/SERUM PCT ASSAYS

Based on a highly sensitive research assay, the normal level of PCT in the noninfected individual is 0.033 ± 0.003 ng/ml (4). The first commercial PCT assay (LUMI test) has a functional lower limit of sensitivity of 0.5 ng/ml. The second-generation FDA-approved PCT assay is technically a time-resolved cryptate emission (TRACE) immunoassay (4, 21). The

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assay quantifies both PCT and a portion of the N-terminal end of the PCT molecule. The functional lower limit of sensitivity is 0.05 ng/ml, and the assay has reliable linear quantitation to 1,000 ng/ml. Either serum or plasma is used, and results are available in 1 h or less.

Two additional assays are in development, and both measure only PCT (39). Within minutes after *in vivo* synthesis, a peptidase enzyme cleaves off the first two PCT amino acids. The assays in development can quantitate either the 1- to 116-amino-acid PCT or the 3- to 116-amino-acid PCT breakdown product.

TWO CONCERNS

There are two major challenges in the interpretation of the reported PCT levels in patients with respiratory infections. Until recently, attempts to evaluate serum PCT levels in patients with respiratory tract infections used the relatively insensitive first-generation PCT assay (LUMI test). With a functional lower limit of sensitivity of 0.5 ng/ml, the use of PCT levels to discriminate viral from bacterial infection is problematic. For example, an emergency department patient has a serum PCT level reported to be <0.5 ng/ml with the LUMI test. With the current more sensitive assay (functional lower limit, 0.05 ng/ml), the emergency department patient's PCT level may be <0.05 ng/ml due to a viral infection or 0.25 ng/ml, consistent with an early bacterial pneumonia. Hence, it is hard to interpret earlier studies that evaluated PCT levels as measured by the LUMI test as a surrogate marker and/or discriminator of viral versus bacterial infection.

The other concern is the basis of calculating the sensitivity and specificity of PCT levels as a surrogate marker for a viral or bacterial infection. Since present-day standard microbiology techniques to detect potential viral and/or bacterial respiratory tract pathogens are limited in their sensitivity, determination of the analytic sensitivity and specificity of PCT levels is problematic. Hopefully, multiplex molecular diagnostic platforms in development will increase the ability to detect the presence of viral and bacterial pathogens (12, 23, 25). The better that the pathogen detection is, the better that the critical evaluation of the value of PCT levels as a surrogate marker will be. Perhaps some viral infections do result in elevated PCT levels; perhaps PCT levels do not increase in all bacterial infections. Despite definitive laboratory data, PCT levels have proved useful clinically in several ways.

CLINICAL USES OF PLASMA PCT LEVELS

The initial 1993 clinical study of serum procalcitonin levels were in children in France (1). Seventy-nine children ranging from newborns to age 12 years were prospectively evaluated. Very high PCT levels (6 to 53 ng/ml) were found in 19 patients with severe bacterial infection. In contrast, very low levels (<0.1 ng/ml) were found in 21 children with no evidence of infection. The authors noted low PCT levels in patients with viral infections. A recent 2009 retrospective study analyzed, in detail, 327 children, ages 1 month to 17 years, seen in an emergency room in Germany for acute respiratory tract infections (35). Despite the use of modern viral diagnostics and a sensitive specific PCT assay, the results are similar to those of

the 1993 study. Patients with bacteremic pneumonia had very high PCT levels; patients with evidence of only viral respiratory infection had low PCT levels. The clinical evaluation of PCT levels continues. At present, there are four common uses of PCT levels.

First, the current immunoassay was approved by the FDA for establishing the likelihood of mortality in critically ill septic patients (4, 32). A maximum PCT level of from 1 to 5 ng/ml correlated with a 90-day mortality of 11%; a maximum PCT level of 51 to 100 ng/ml correlated with a 90-day mortality of 42%.

Second, colleagues in Europe, especially Switzerland, have used PCT levels to guide empirical antibacterial therapy in patients with acute exacerbations of chronic bronchitis, community-acquired pneumonia, and sepsis (7, 8, 32–34, 38). Two low PCT levels, over the first 4 to 6 h of hospital admission, resulted in fewer patients started on empirical antibacterials. The low PCT levels over the first 4 h of inpatient care have an excellent negative predictive value for bacterial infection.

PCT levels, along with standard clinical parameters, can assist with judging whether the patient's empirical antibacterial therapy is effective (5). For example, if the surgery and empirical antibacterial therapy are effective in a patient with delayed recognition of peritonitis from a ruptured appendix, the elevated baseline PCT should fall by roughly 50% per day in patients with normal renal function. One could term the fall in the PCT level "control of the source" of the problem.

The fourth, and perhaps most useful, application is the use of sequential PCT levels to determine when there is no longer a need for antibacterial therapy. A variety of cutoffs are reported (8, 13, 34, 38). In the intensive care unit at my institution, we have used a fall of the PCT level to ≤ 0.1 ng/ml as a signal that bacterial invasion has ceased and that it is safe to discontinue antibiotic therapy. Several studies have successfully adopted this approach rather than an arbitrary one-size-fits-all duration of therapy (8, 13, 24, 34, 38). Virtually every study to date in sepsis or pneumonia patients demonstrates substantive decreases in the duration of antibacterial therapy when it is guided by sequential PCT levels.

COMMUNITY-ACQUIRED PNEUMONIA: INTEGRATION OF PROCALCITONIN LEVELS WITH CLINICAL MICROBIOLOGY

Consider patients with community-acquired pneumonia. For discussion purposes, assume that such patients require intensive care. Blood and sputum samples are obtained for culture. Antigens of *Streptococcus pneumoniae* and *Legionella pneumophila* are sought in the urine. A nasopharyngeal swab is submitted for multiple reverse transcription-PCR (RT-PCR) tests for respiratory viruses and perhaps atypical respiratory pathogens. A serum PCT level is performed upon admission and 4 h later.

Before potential results are analyzed, some assumptions are necessary. Bacteria identified by culture or molecular diagnostic methods may represent invasive pathogens or may simply be colonizing the airway. In contrast, when a respiratory virus (excluding herpesviruses) is identified by culture or molecular diagnostic methods, the virus is considered the etiology of the infection, as, in general, known respiratory viruses do not col-

TABLE 1. Role of PCT levels in the interpretation of clinical microbiology data in patients with lower respiratory tract infections

Bacterial pathogen detected	Viral pathogen detected	Procalcitonin level (ng/ml)	Interpretation
No	No	≤0.05	No evidence of bacterial or viral infection
No	No	0.5–1,000	Innate immunity activated; suspect noncultured bacteria, e.g., oral anaerobic organisms
No	Yes	≤0.05	Viral infection
No	Yes	0.25–1,000	Dual viral and bacterial infection; failure to identify etiologic bacteria
Yes	Yes	0.25–1,000	Dual infection with virus and bacteria
Yes	No	≤0.05	Bacterial colonization
Yes	Yes	≤0.05	Bacterial colonization and viral infection

onize the airway. However, some patients, especially adults, can asymptotically shed virus for weeks to months. Shedders generally have small quantities of virus present compared to the quantities present in actively infected patients.

It takes at least 4 h from the onset of illness for the current PCT assay to detect an increase in serum levels, hence the suggestion to obtain two baseline PCT levels roughly 4 h apart.

For the purposes of the following examples, the focus is only on viral and bacterial respiratory pathogens. In reality, patients in critical care units may have concomitant infections due to nonrespiratory bacterial pathogens causing infection in the abdomen, urinary tract, skin, intravenous lines, or elsewhere.

In patients with only lower respiratory tract infections, there are at least seven possible combinations of microbiologic and PCT results, Table 1. The first is the failure to detect any viral or bacterial pathogen in the presence of a normal PCT level. The powerful negative predictive value of a normal PCT level strongly supports the absence of bacterial infection. Failure to detect a virus depends on the specifics of the viral culture or molecular diagnostic method used. Just because influenza virus and adenovirus are not detected does not exclude infection by one of the many other recognized respiratory viruses.

A second possibility is no detection of virus or bacteria but the serum PCT level is definitely elevated. The innate immune system is activated but by what? Perhaps there was a failure to detect the pneumococcus or other pathogenic bacteria. For example, the patient may have aspirated large numbers of normal oral aerobic and/or anaerobic bacteria.

A third possibility is detection of a respiratory virus but no detection of a bacterial pathogen. As expected, the serum PCT level is very low. The fourth example could occur if both a viral pathogen and an undetected bacterial pathogen are present. The evidence for the undetected bacterial infection is the elevated PCT level. The fifth example is another dual infection, but in this example, the bacterial pathogen was detected.

The sixth possibility illustrates the power of the negative predictive value of a low serum PCT value. Even though a potential respiratory bacterial pathogen is found, the low PCT level means that the innate immune system is not activated, and hence, the bacteria detected are colonizing and not invading. The last possibility again displays how the serum PCT level allows distinction between colonization and invasion by a bacterial respiratory pathogen. The low PCT level indicates, in this case, colonization of the potential bacterial pathogen.

The seven examples in Table 1 are not meant to imply that PCT levels are the only tool available to assess the host inflammatory response. The PCT levels should be viewed as part

of a comprehensive clinical assessment that includes the patient's temperature, physical examination, white blood cell (WBC) count and differential, chest X ray, and more.

FURTHER STUDY

There is a lot more to learn about PCT. What is the biologic role/purpose of PCT? Specifically, which viruses activate PCT transcription and to what degree (31)? Why do PCT levels increase in dual viral-bacterial infections? Are there examples of coinfection with a specific virus blunting the PCT response to invasive bacteria?

OTHER POTENTIAL USES OF PCT LEVELS

PCT levels may help sort out the etiology of the fever in patients with the fever of unknown origin (FUO) syndrome, in that PCT levels do not increase in some of the disease entities that cause the FUO syndrome, e.g., Still's disease, systemic lupus erythematosus, and inflammatory bowel disease (6, 10, 36, 40).

Initial data indicate that PCT levels are not affected by the patient's use of nonsteroidal anti-inflammatory agents or glucocorticoids (27, 29). If so, PCT levels remain a valuable marker of the host inflammatory response even when nonsteroidal anti-inflammatory drugs and pharmacologic doses of corticosteroids have altered the patient's temperature curve, WBC count, and WBC differential.

UNEXPLAINED PCT ELEVATIONS

There are reports of elevated PCT levels in the absence of sepsis, respiratory tract infections, and other traditional infectious diseases. Elevated PCT levels are reported in patients with cirrhosis, pancreatitis, mesenteric infarction (ischemic bowel), cardiogenic shock, and hypotension during surgery and as a consequence of posttraumatic hemorrhagic shock (4). There is some evidence, albeit incomplete, that in the latter circumstances, PCT level elevation signals a breakdown of intestinal barriers and translocation of bacteria to the pancreas, bowel wall, or regional lymph nodes (2, 19, 30). Similarly, PCT level elevation in patients with burns, pulmonary edema, and pulmonary aspiration may indicate the early stages of bacterial invasion (16, 30, 42).

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