Role of Procalcitonin in the Management of Infected Patients in the Intensive Care Unit

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KEYWORDS

• Procalcitonin • Multiplex PCR • Respiratory panel • Antimicrobial stewardship
• Sepsis • Septic shock • Community-acquired pneumonia

KEY POINTS

- With available diagnostic "bundles," an etiologic agent or agents can be quickly identified in 70% or more of patients with severe community-acquired pneumonia (CAP).
- In patients with CAP and a serum procalcitonin (PCT) level <0.25 ng/mL, the likelihood of an invasive bacterial etiology is 5% or less.
- In patients with CAP, serum PCT levels can help determine if detected potential bacterial pathogens are colonizing or invading.
- Elevated serum PCT levels do not discriminate between the major categories of shock. However, a normal serum PCT eliminates a bacterial etiology of the shock in more than 95% of patients.
- For both severe CAP and bacteremic septic shock, sequential PCT levels assist in both assessing source control and determining the duration of antimicrobial therapy.

INTRODUCTION

Approximately 70% of patients admitted to critical care units are started on some type of antimicrobial therapy.[1–4] The most common indications are empiric therapy for suspected community-acquired pneumonia (CAP) or sepsis/septic shock. Of concern, the empiric therapy was continued beyond 3 days in one study and for more than 4 days in another.[3,5]

In critically ill patients, with ultimately documented severe bacterial pneumonia or septic shock, the aggressive early use of antibacterials can decrease attributable mortality.[6] When no microbial etiology is identified, clinical uncertainty drives the

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continuation of empiric antimicrobial therapy. The goal is to quickly define etiologic pathogens, or pathogens, so as to apply individualized focused therapy.

In patients with CAP, molecular diagnostics can rapidly detect potential viral and bacterial pathogens. The biomarker procalcitonin (PCT) can help clarify if a detected bacterial pathogen is colonizing or invading. As a consequence, empiric therapy can become specific therapy in an increasing number of patients.

In patients with shock, earlier detection and rapid speciation of blood culture isolates is increasingly available. Normal serum PCT levels strongly suggest the patient's hypotension is not due to invasive bacterial infection. Sequential PCT levels assist in documenting "source" control and allow individualization of the duration of antibiotic therapy.

SEVERE COMMUNITY-ACQUIRED PNEUMONIA

Standard Diagnostic Methods

Detection of the etiology, or etiologies of CAP results in a change from empiric to specific antimicrobial therapy. The higher the diagnostic yield, the better. The traditional diagnostic bundle for patients admitted to the intensive care unit (ICU) with CAP and hypoxemic respiratory failure consists of the following:

- Sputum, or if intubated, endotracheal tube aspirate, for culture and sensitivity
- Urine to test for presence of *Streptococcus pneumoniae* antigen, and *Legionella pneumophila*, serogroup 1 antigen
- Usually 2 blood cultures

If not intubated, it is not possible to collect a valid sputum in up to half or more of the patients.[7–10] Blood cultures are easily obtainable, but blood cultures are positive in fewer than 10% of the patients.[11] *S pneumoniae* antigen is found in urine in roughly 11% of the patients.[12] Using the urine antigen for detection, *L pneumophila* is found in 1% or less of the patients with CAP.[11,13] In short, the overall diagnostic yield with the standard bundle is less than 50%.[14,15]

Further, the turnaround time is slow. Urine antigen results return in 2 to 12 hours, sputum cultures in a minimum of 2 to 3 days, and blood cultures can take many days.[15]

Addition of Molecular Diagnostics

The diagnostic yield can be increased, with fast turnaround times, by adding molecular polymerase chain reaction (PCR) probes to the diagnostic bundle.

In 2 separate studies of patients admitted with CAP, the following tests were added to the previously discussed bundle:

- Anterior nasal swab for nucleic acid amplification test (NAAT) for *Staphylococcus aureus* (results within 24 hours)
- Nasopharyngeal swab for FilmArray Multiplex PCR panel for 17 viral strains and 3 bacteria (results within 2 hours)
- Nasopharyngeal swab for NAAT for *S pneumoniae* (results within 24–48 hours)

With the enlarged bundle, a potential pathogen was detected in 70% to 80% in 2 cohorts of patients enrolled over 2 respiratory winter seasons.[14,15]

Similar results with a slightly smaller diagnostic package were reported for patients with acute exacerbations of chronic bronchitis and other lower respiratory tract infections.[16]

Gadsby and colleagues[17] retrospectively performed quantitative PCR of purulent sputum for 26 pathogens: that is, 8 bacteria, 5 atypical bacteria, and 13 respiratory viruses. Potential pathogens were detected in 87% of 323 specimens. A potential bacterial pathogen was found in 71.5% and a respiratory virus in 30%.

In sum, these results demonstrate the ability to detect the presence of potential pathogens. The next question is whether the bacteria detected is colonizing or invading.[18]

Colonization or infection: procalcitonin

Reported nasal colonization with *S pneumoniae* in adults varies from 0.3% to 18.0%.[19] The tracheobronchial tree of 35% of smokers with chronic bronchitis is frequently colonized with *Haemophilus* species.[20] *S aureus* colonizes the nose of 30% of the general population.[21] Traditionally, clinicians have relied on signs, symptoms, and white blood cells (WBCs) to decide if detected bacteria are colonizing or invading.

PCT serum levels may help. PCT is a biomarker of activation of the innate immune system by bacteria and serum PCT levels rise within 4 to 6 hours in response to invasive bacterial infection.[22] Serum PCT levels remain low in the presence of colonization by potential pathogens.

Further, the PCT assay is user friendly. The lower limit of sensitivity is 0.06 ng/mL, and the turnaround time is less than 2 hours. In our CAP clinical trials, if a pneumococcus was detected by PCR but the PCT serum level was low, we interpreted the pneumococcus as colonizing and not invading.[14,15]

Procalcitonin levels distinguish viral and bacterial infection

Procalcitonin levels can distinguish bacterial from viral infection. In an animal model of *Escherichia coli* peritonitis, transcription of the PCT gene, as evidenced by elevated PCT messenger RNA, was found in virtually all body cells, tissues, and organs.[22,23] As elevation of PCT levels does not depend solely on activation of phagocytic cells, tumor necrosis factor (TNF), or other proinflammatory cytokines, it is not surprising that PCT increases occur in profoundly neutropenic patients with focal or bloodstream infections.[24]

Further, the PCT response is rapid. Human volunteers given low doses of lipopolysaccharide (LPS) developed detectable elevations of serum PCT over 4 to 6 hours.[25] With 1 LPS injection, the PCT level peaked at 24 hours. The increase in PCT serum levels occurred several hours earlier than the increase in C-reactive protein concentration.

In contrast, pure invasive viral infection rarely increases the PCT level above 0.25 ng/mL.[26] The biologic basis of the blunted PCT response is believed to result from inhibition of PCT transcription by gamma interferon. Gamma interferon levels rise in response to most respiratory viral infections. When adipose cells were cultured in vitro in the presence of interleukin (IL)-1, PCT levels increased. If interferon gamma was added to the IL-1, virtually no PCT was synthesized.[27]

In pediatric emergency department patients with documented viral infections, the PCT levels did not increase.[26] In several European PCT trials, patients with clinical viral respiratory tract infection had PCT serum levels of $\leq$0.25 ng/mL.[28,29] In the latter trials, there was no systematic attempt to correlate PCT levels with the microbial etiology of the infection.

In US studies of both acute exacerbations of chronic bronchitis and CAP, low PCT levels were found in patients with detection of only a respiratory virus. Of interest, in an average of 26% of the patients, there was evidence of a mixed infection due to a respiratory virus and a bacterial pathogen.[7,9,15,17] Note, PCT levels increased in patients

with viral and bacterial coinfection. It appears invasion by a bacterium nullifies the inhibitory effect of viral-induced gamma interferon on PCT increases.

Last, in patients with documented meningitis, the serum PCT concentrations were low in patients with viral meningitis and elevated in patients with bacterial meningitis.[30–32]

Value of viral detection and procalcitonin levels in patients with community-acquired pneumonia

European studies document the safety of using PCT serum levels to guide antibiotic use decisions in patients with CAP.[28,29] However, there was no systematic attempt to associate the microbial etiology of the airway infection with the PCT concentrations.[27,28] In the United States, studies have used various diagnostic bundles and then correlated the results with PCT serum levels.[7,9,15,17] The inclusion of multiplex PCR platforms for respiratory viruses plus NAATs for *S pneumoniae* and *S aureus* have identified an etiology in up to 70% of the patients, with turnaround times of only a few hours.[15] The combination of enhanced etiologic diagnosis and serum PCT levels offer significant guidance in the management of severe CAP. Suggested interpretations are summarized in **Table 1**.

Some general points:

- All the interpretations in **Table 1** assume a compatible clinical illness.
- In adults or children, detection of influenza, respiratory syncytial virus, and human metapneumovirus likely indicates an etiologic role. Other respiratory

Table 1
Suggested interpretation of microbial diagnostics and procalcitonin (PCT) levels in patients with community-acquired pneumonia

Potential Bacterial Pathogen Detected[a]	Potential Viral Pathogen Detected with Multiplex Polymerase Chain Reaction	PCT, ng/mL	Hemodynamic Shock Present	Interpretation
No	No	≤0.10	No	No infection
No	Yes	≤0.10	No	Consistent with pure viral infection
No	Yes	0.25–1000	No	Likely dual infection: virus + nondetected bacteria
Yes	No	0.25–1000	No	Consistent with pure bacterial infection
Yes	Yes	0.25–1000	No	Dural viral and bacterial infection
Yes	No	≤0.10	No	No respiratory virus; bacterial colonization
Yes	Yes	≤0.10	No	Viral infection and bacterial colonization
No	No	0.25–1000	Yes	Gastrointestinal translocation (see shock discussion) or noncultured airway bacterial pathogen

[a] Detection by some combination of nucleic acid amplification test (eg, *Streptococcus pneumoniae, Staphylococcus aureus*), detection of antigen of *S pneumoniae* or *Legionella pneumophila* serotype 1 in urine, or traditional sputum culture and sensitivity.

viruses, especially in children, may be infection or asymptomatic carriage.[33,34] For this reason, Raoult[35] has emphasized the need for negative controls in future studies assessing the role of detected viral pathogens.

- Caution is suggested in a patient with clinical features of an acute bacterial pneumonia and a PCT level of ≤0.25 ng/mL. As the increase in PCT levels can take 4 to 6 hours from the initiation of bacterial invasion, it is advisable to repeat the PCT level in 4 to 6 hours before concluding the infection is nonbacterial.[22]
- The magnitude of the PCT rise correlates with the acuity and severity of the infection. A mild bronchitis or a chronic walled-off infection (eg, chronic empyema) may not stimulate an increase in the serum PCT concentration.[36]
- With pure viral infection, the magnitude of the gamma interferon response varies with the strain of virus (eg, influenza A vs influenza B) and from one respiratory virus to another. The result is reflected in low but variable levels of serum procalcitonin.[37–39]
- Gamma interferon plays a role in the complex host inflammatory response to bacterial, as well as viral, pneumonia. Somewhat surprisingly, neutrophils express gamma interferon in animal models of pneumonia.[40,41] Gamma interferon was expressed in mouse pneumococcal or staphylococcal pneumonia and not *E coli* or *Pseudomonas aeruginosa* pneumonia. As evidence supports lower PCT levels in the presence of interferon gamma, there is biologic plausibility of the anecdotal reports of lower PCT levels in patients with invasive gram-positive bacteria as compared with gram-negative bacteria.[42,43]
- Even with an adequate sputum specimen, a bacterial pathogen may not be detected. An example are patients with aspiration of large volumes of saliva and/or gastric content. In such patients, we, and others, have accepted an elevated PCT level, in the absence of clinical shock, as a surrogate for likely bacterial invasive infection and justification for antibiotic therapy.[9,15]

With these caveats, the suggested interpretation of serum PCT levels is summarized in **Table 1**. PCT levels remain low with a pure viral infection and increase with either a pure bacterial or a mixed viral-bacterial infection. If a respiratory virus is detected and the PCT level increases and even if no potential bacterial pathogen is detected, and the patient has a clear CAP clinical syndrome, it is reasonable to postulate the presence of undetected invading bacteria.

PCT levels are very helpful when they remain low despite culture of potential respiratory bacterial pathogens: for example, *S pneumoniae, Haemophilus influenza,* and *Moraxella catarrhalis*. This is the classic pattern for colonization without invasion by potential bacterial pathogens.

In patients with CAP plus another site of infection (eg, urinary tract infection (UTI), peritonitis, or bacteremia), it is difficult to ascertain which process is stimulating an increase in the PCT concentration. In patients with shock, possible gastrointestinal translocation is possible as discussed later in this article under the role of PCT levels in patients with clinical shock syndromes.

For emphasis, whether a patient has CAP and/or possible septic shock, a normal PCT serum concentration strongly suggests the etiology is not a bacterial infection. The negative predictive values are 92% or greater.[44]

Influence of renal function on interpretation of serum procalcitonin levels

The serum concentration of PCT increases in patients with stage 5 end-stage renal disease (ESRD) or as defined by a creatinine clearance of less than 15 mL/min. In the absence of renal replacement therapy in uninfected patients, the reported PCT levels range from 0.12 to 1.8 ng/mL (**Table 2**).[45,46] After hemodialysis is initiated,

Table 2
Procalcitonin (PCT) serum concentrations in uninfected and infected patients with end-stage renal disease[a]

Renal Function or Renal Replacement Therapy	PCT, ng/mL Uninfected Patients	PCT, ng/mL Infected Patients
Creatinine clearance:		
15 to >90 mL/min	0.05 to <0.25	≥0.25
<15 mL/min	0.12–1.8	≥0.5
Hemodialysis patients	<0.5	≥0.5
Peritoneal dialysis patients	0.32–1.2	≥0.05
After renal transplantation[a]	≤0.25	≥0.25

[a] As OKT-3 and/or antithymocyte globulin can increase PCT levels greater than 10-fold in the absence of infection, PCT levels are not interpretable in patients on such therapy.[47,48]

Data from Grace E, Turner RM. Use of procalcitonin in patients with various degrees of chronic kidney disease including renal replacement therapy. Clin Infect Dis 2014;59:1761–7; and Dahaba AA, Rehak PH, List WF. Procalcitonin and C-reactive protein plasma concentrations in nonseptic uremic patients undergoing hemodialysis. Intensive Care Med 2003;29:579–83.

and in the absence of infection, serum PCT levels decrease to less than 0.5 ng/mL in most patients. In infected patients with ESRD, the PCT levels increase to ≥0.5 ng/mL. In patients undergoing peritoneal dialysis, with sparse available data, the PCT levels range from 0.32 to 1.2 in the absence of active infection.[45] For all patients undergoing dialysis, a reasonable "cutoff" suggesting active bacterial infection is ≥0.5 ng/mL.

PCT levels are not a valid biomarker in renal transplant patients receiving therapy with OKT-3 and/or antithymocyte globulin. The latter can, via cytokine effects, increase the PCT level greater than 10-fold.[47,48]

Two benefits of sequential procalcitonin levels

"Source" control. With the right drug in the right dose and, in the absence of confounding nonpulmonary infections, the PCT level, like the WBC, quickly trends toward normal values if the source of the infection(s) has/have been identified and controlled.

Duration of antimicrobial therapy for CAP. Management reviews and guidelines provide general suggestions for the duration of CAP antibiotic therapy. The 2007 CAP Infectious Diseases Society of America Guidelines, "UpToDate," and more recent reviews suggest a minimum of 5 days of therapy with resolution of fever for 48 to 72 hours.[49] There are many caveats. Duration can vary with the etiologic bacteria (longer for *S aureus*, aerobic gram-negative bacilli), presence of extrapulmonary infection, host comorbidities that impede recovery (eg, congestive heart failure, continued aspiration, immunodeficiency), and other factors.

Trending PCT levels is one way to individualize duration of therapy.[50] The usual suggestion is to repeat the PCT level every 2 to 4 days and discontinue antimicrobial therapy when the PCT concentration is ≤0.25 ng/mL. An alternative, used in Europe, is to stop when the PCT levels have decreased by ≥80% from the peak value.[51] We have not endorsed this approach, as the peak value may not be known. Numerous studies have found that this trending approach shortens treatment duration, and is safe.[51]

Community-acquired pneumonia summary

In short, the combination of expanded diagnostics, to include multiplex PCR panels plus PCT levels, rapidly provides physicians with information that

- Can decrease overuse of antibacterials for viral infections; a "normal" PCT level virtually excludes an invasive bacterial infection
- Detects coinfection due to bacteria and viruses
- Discriminates colonization from invasion by potential bacterial pathogens
- A downward trend in sequential PCT levels supports "source control" of the infection that is stimulating the innate immune system
- Trending PCT levels allows individualization of the duration of antibacterial therapy

Community-acquired pneumonia: the future of diagnostics

There is no doubt that the evolution in molecular diagnostics and understanding host genomic responses to infection will continue. We can anticipate the following:

- Discrimination of viral versus bacterial invasion based on the pattern of activated host genes[52–55]
- Discovery of biomarkers other than PCT that distinguish viral from bacterial infection
- Next-generation PCR multiplex platforms designed to detect more pathogens in sputum or sputum equivalent (endotracheal aspirate, bronchoalveolar lavage)
- Evolution of methods that quickly ascertain the presence and expression of antibiotic resistance genes
- Additional prospective trials that combine enhanced diagnostics with markers of activation of pertinent genes or gene products
- Point-of-care application of affordable multiplex PCR platforms and PCT levels in a variety of settings: primary care clinics, emergency departments, and others

SEPTIC SHOCK AND PROCALCITONIN

Case Presentations

Case 1

A 19-year-old female college coed is admitted with purpura fulminans. Within hours, blood cultures confirm the diagnosis of meningococcemia. PCT and other biomarkers are not needed to facilitate the diagnosis of bacteremic shock. The higher the peak PCT concentration, the higher the risk of patient mortality.

Case 2

A 55-year-old man with advanced alcoholic cirrhosis is admitted to the ICU with hypotension, fever, hematemesis, oliguria, and confusion. Ascites and other stigmata of cirrhosis are present. There is endoscopy evidence of bleeding varices. Echocardiogram documents an ejection fraction of 25%. His serum creatinine is 2.5 mg/dL. The serum lactate concentration is elevated. Blood pressure is 70/40 mm Hg. The ascitic fluid absolute neutrophil count is 600 cells/μL. The serum PCT is 2.0 ng/mL. The serum soluble CD14 (sCD14) level (generic name is presepsin) is 1000 pg/mL (N 48–171). What is/are the etiology/etiologies of the patient's shocklike state?

Procalcitonin and Etiology of Shock

As the example patient with cirrhosis illustrates, patients often have more than 1 process contributing to the pathogenesis of their clinical shock. The example patient with cirrhosis has findings compatible with hemorrhagic shock from bleeding esophageal varices, cardiogenic shock from alcohol-induced cardiomyopathy, and septic shock due to likely spontaneous bacterial peritonitis with or without bacteremia.

Well documented increases of serum PCT occur in all categories of shock: that is, hypovolemic, anaphylactic, cardiogenic, obstructive (tamponade, pulmonary embolus),

toxic shock syndrome, and bacteremic shock.[56–62] In some patients, the elevated PCT may result from a bacterial infection complicating a noninfectious shock etiology.

Translocation of gut bacteria is an oft-suggested explanation for the PCT increase in all types of nonbacteremic shock and the associated impaired perfusion of the bowel wall.

Translocation of Gut Bacteria

The literature on translocation of gut bacteria is voluminous and increasingly sophisticated. In early studies in humans and animals, translocation was detected by finding bacteria in mesenteric lymph nodes or in portal venous blood.[63] Serum was tested for the presence of bacterial lipopolysaccharide using the Limulus amebocyte lysate assay, which is fraught with risk of contamination by environmental LPS.

More recently, blood specimens were tested with primers and a probe that targeted the conserved region of the 16s ribosomal DNA.[64] Testing takes days and there is risk of bacterial DNA contamination of the specimen or the PCR reagents.

Current literature criteria for translocation of gut bacteria is some combination of the following:[65]

- An increase in serum concentration of LPS-LPS–binding protein complex[66]
- In the absence of overt pneumonia, UTI, or other bacterial infection, an increase in the serum concentration of sCD14 (generic name, presepsin)[67]
- In the absence of invasive bacterial infection, elevated concentration of serum PCT[68]

Serum Soluble CD14 (Presepsin)

The CD14 gene encodes a cluster-of-differentiation glycoprotein found on the surface of monocytes, macrophages, and dendritic cells.[67,68] CD14-encoded protein is a high-affinity receptor for the complex of LPS with LPS-binding protein. Binding of the complex to the CD14 receptor activates Toll-like receptor (pattern recognition receptor) 4. The result is twofold: signal transduction to initiate nuclear transcription of proinflammatory cytokines and concomitantly, the release of a soluble form of CD14 (sCD14) into the circulation.

In volunteers given endotoxin, sCD14 levels rose within 2 hours.[69] It is possible to quantitate the sCD14 level with a chemiluminescence enzyme immunoassay (PATHFAST [Mitsubishi Chemical Corporation, Tokyo, Japan]). Results are available in 17 minutes using an automated instrument.[70]

In addition, the proinflammatory cytokines (TNF, IL-1, IL-2, IL-6), stimulated by membrane activation in turn stimulate transcription of the PCT gene.

Example: the following are clinical syndromes with documented translocation of gut bacteria in animals and patients:

- All categories of clinical shock[65]
- Neutropenia[71]
- Low-level translocation documented in
  - Hepatic cirrhosis[72,73]
  - Incompletely controlled human immunodeficiency virus infection[74,75]

Translocation of gut bacteria may not be the sole explanation for an increase in PCT serum levels in the absence of overt invasive bacterial infection. The host response to mitochondrial DNA may help explain PCT increases in patients with massive organ necrosis: for example, trauma-associated rhabdomyolysis, severe burns, large myocardial infarction, and liver necrosis due to mushroom poisoning. Shock may or may not be present.

Mitochondria were originally saprophytic bacteria that eukaryotic cells captured with eventual evolution to a critical intracellular eukaryotic organelle.[76] The circular DNA of mitochondria retains some characteristics of bacterial DNA. In a series of experiments, Zhang and colleagues[77] demonstrated the rapid appearance of mitochondrial DNA in the plasma of 15 patients who suffered major trauma. The data are consistent with the release of DNA that initiated an innate immune-type inflammatory response as would occur in bacterial invasive infection. It is postulated that tissues either directly respond to the bacterialike DNA with a rise in PCT levels or the proinflammatory cytokines indirectly increase PCT levels.[78,79]

Negative Predictive Value in Patients with Shock

One of the benefits of serum PCT levels in patients with shock is the power of the negative predictive value. With a few caveats, a normal PCT concentration in a hypotensive patient virtually excludes bacteremia as an etiology (**Table 3**).[24,80–84]

Two cautions are in order. It takes 4 to 5 hours for the serum level of PCT to increase after an initial microbial stimulus.[22] With an acute illness, we suggest a second PCT serum level after 4 to 6 hours. Acute appendicitis is a good example. With early, less than transmural inflammation, the PCT concentration may not increase, as clearly happens with transmural inflammation or perforation of the appendix.[85]

Procalcitonin, Source Control, and Mortality

Source control is a major objective in the management of clinical sepsis. Sequential PCT serum levels, in concert with clinical assessment and normalization of the WBCs, are an objective measurement of the degree of source control.

In a study from France, the magnitude of the decrease in serum PCT between days 2 and 3 of therapy correlated with survival.[86] Similar results were reported from Australia[87] and the Netherlands.[88]

There is no known toxic effect of elevated PCT levels. To the contrary, there is in vitro evidence of an anti-inflammatory function.[89] Our current view is that PCT serum levels are best considered as a marker of activation of the host innate immune response.

Table 3
Representative negative predictive values (NPV) of serum procalcitonin levels in patients with possible severe sepsis

Ref No.	Clinical Setting	Clinical Endpoint	Procalcitonin "Cutoff" Concentration, ng/mL	NPV, %
Reitman et al,[24] 2012	Febrile neutropenia in children	Bacteremia	<0.5	93
Riedel et al,[80] 2011	Sepsis in emergency department	Bacteremia	<0.1	98
Garcia-Granero et al,[81] 2013	Gastrointestinal surgery	Anastomotic leak	<0.35	100
Markogiannakis et al,[82] 2011	Bowel obstruction	Ischemic bowel	<0.25	95
Menacci et al,[83] 2012	Hospitalized with sepsis syndrome	Bacteremia	<0.25	99
Menendez et al,[84] 2012	Community-acquired pneumonia	Bacteremia	<0.36	98

A recent Cochrane Review concluded that PCT-guided antimicrobial therapy did not lower the risk of death.[90] Mortality risk and source control is multifactorial. In the septic patient, source control often requires some combination of surgery, prompt and appropriate antibacterial therapy, reversal of organ failure, successful treatment of a concomitant malignancy, and a long list of other potential confounders. In short, PCT levels alone do not influence mortality; rising or persistently high PCT levels indicate a failure to control the process triggering the PCT genes, which in turn reflects poor source control and is associated with an increased risk of mortality.[89,90]

Procalcitonin Levels and Individualization of Treatment

Guidelines on how long to treat bacteremia vary with the following:

- The source of the bacteremia: for example, uncomplicated versus complicated UTI
- The etiologic organism
- The immune status of the host and other factors[91]

In theory, sequential serum PCT levels create the potential to individualize the duration of therapy. The goal is to treat until the innate immune system is no longer activated.

In prospective clinical trials, duration of therapy was guided by sequential PCT serum levels or by physician choice without knowledge of the PCT values. In the PCT-guided patients, treatment was continued until the PCT level fell by 80% from its peak or reached a concentration in the range of $\leq$5.0 or $\leq$2.5 ng/mL.

The results consistently showed that patients in the PCT guidance group discontinued antibacterial therapy roughly 2 days sooner than patients with no PCT levels available to guide duration.[88,91–94] Of import, the PCT guidance was safe with no infection relapses reported. The results have been consistent, as reflected in systematic reviews and meta-analyses.[94,95]

Subsummary: What Does, and What Does Not, Increase the Serum Concentration of Procalcitonin?

Knowledge as to what increases, or does not increase, the PCT serum concentration is constantly changing. The current status is summarized in **Table 4** with the caveat that some of the conclusions need validation. The summary is organized by microorganisms, clinical syndromes, neoplasms, and drugs. In **Table 4**, we selected a PCT concentration of $\geq$ 0.25 ng/mL as the usual or mean "cutoff" for a meaningful PCT elevation. Some literature may use cutoff levels as high as 0.50, or rarely 1.0, as definition of a low PCT category. Such levels are hard to interpret, as often important details like patients' renal function and possible concomitant viral and bacterial infection are not provided.

Perhaps most useful is the list of microorganisms, inflammatory clinical syndromes, neoplasms and drugs that DO NOT substantively activate the PCT gene: for example, pure viral infection,[25–32] *Chlamydia* species,[26] and *Mycoplasma* species[26] do not stimulate PCT increases. Yet, other intracellular bacterial pathogens, like Scrub typhus, do increase PCT serum levels.[96] Mycobacteria may or may not stimulate PCT.[97,98]

Note the list of inflammatory conditions that do not substantively increase PCT:

- Chronic walled-off infections: for example, chronic empyema[36]
- Edematous/necrotizing pancreatitis unless secondary bacterial infection is present[99,100]
- Uncomplicated regional enteritis or ulcerative colitis[101–103]

Table 4
Summary of microorganisms, clinical syndromes, neoplasms, and drugs that DO or DO NOT increase serum levels of procalcitonin (PCT)

DO Increase Serum PCT to ≥0.25 ng/mL	DO NOT Increase Serum PCT to ≥0.25 ng/mL
Microorganisms	
Bacteria: • Alone or with viral coinfection[9,15,16] • Gram-positive and gram-negative pathogens • *Legionella* species[118,119] • *Mycobacteria* species[a,97,98] • Scrub typhus[96] Bacterial toxin-mediated inflammation: • *Clostridium difficile* toxin[120] • Toxic shock syndrome toxins[62] Fungi: *Candida* species[122] Parasites: *Plasmodium* species (malaria)[121] Viruses: None, so far	Bacteria: • *Chlamydia* species[26] • *Mycoplasma pneumoniae*[26] • *Mycobacteria* species[a,97,98] • Lyme borreliosis[131] Fungi[122–124]: • Aspergillosis • Coccidioidomycosis[123] • Mucormycosis[124] Viruses: Virtually all, so far
Clinical Syndromes	
Bacterial: • Aspiration pneumonia[125–127] • Bacterial meningitis[30–32] • Bacterial pancreatitis[99,100] • Bacterial peritonitis[132] • Bacterial pneumonia[7,9,15,17] • Bacterial septic shock[135] • Febrile neutropenia[24,128] • Mushroom poisoning[130] • Pyelonephritis[129] • Renal insufficiency[45,46] • Septic arthritis[108,109] • Shock[54–62,117,133]: anaphylactic, bacteremic, cardiogenic, toxic shock syndrome, adrenal insufficiency, hemorrhagic, obstructive • Thermal injury, burns[133] • Trauma: crush injury (case reports)[134]	Viral: respiratory tract infections[9,15,17] • Meningitis[30–32] Abscess, chronic: for example, empyema[36] Gout, pseudogout[108] Inflammatory bowel disease[101–103] Rheumatic diseases[104–108]: • Behcet syndrome • Polyarteritis nodosa • Rheumatoid arthritis • Systemic lupus erythematosus • Still disease • Temporal arteritis • Wegener granulomatosis
Neoplasms	
Medullary thyroid cancer[23,110,111]	[110,111] Lymphomas Pancreas Renal cell Sarcomas
Drugs[47,48,114–116]	
Alemtuzumab (CD52 antibody) Granulocyte transfusions Interleukin-2 Rituximab (anti-CD20 antibody) T-cell antibodies	Most have no effect unless influence innate immune inflammatory response NOTE: glucocorticoids do not impede a PCT response[111]

[a] Reports of Mycobacterial infections either increasing or decreasing serum levels of PCT.

- Viral meningitis or pericarditis[30–32]
- Rheumatologic syndromes: for example, gout/pseudogout, temporal arteritis, systemic lupus erythematosus, polyarteritis nodosa, rheumatoid arthritis, reactive arthritis, Behcet syndrome, adult Still disease[104–109]
- Neoplasms associated with a fever of unknown origin syndrome (lymphoma, renal cell carcinoma, sarcomas, pancreatic carcinoma) do not cause a substantive increase in the PCT serum level[110,111]
- Of interest, glucocorticoids do not block an increase in PCT concentrations.[112,113] In one report, nonsteroidal anti-inflammatory drugs increased the peak PCT level in human volunteers given endotoxin.[114] In contrast, a variety of immune-modulating drugs are reported to increase PCT levels.[47,48,115,116]

Much of the data in **Table 4** derive from uncontrolled observational studies of small numbers of patients. Hence, conclusions are guarded and confirmatory studies needed.

SUMMARY

More than half of the patients admitted to a critical care unit are administered empiric antimicrobial therapy. The most common empiric indications are CAP or "sepsis." The combination of multiplex PCR platforms and biomarkers like PCT are powerful tools that allow quick and precise identification of etiologic pathogens. The result is transition to specific or directed therapy. The anticipated result is fewer days of antimicrobial therapy, fewer drug-related adverse effects, and, hopefully, greater therapeutic efficacy with slower emergence of resistance pathogens. Better panels, better understanding of host genomic responses to infection, and controlled prospective studies are needed to better understand the strengths and weaknesses of our new tool box. As to PCT, there is need for further basic study to clarify its role in the host inflammatory response.

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