

Acute Phase Reactants in Infections: Evidence-Based Review and a Guide for Clinicians

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Acute-phase reactants such as erythrocyte sedimentation rate and C-reactive protein have traditionally been used as markers for inflammation and as a measure of “sickness index” in infectious and noninfectious conditions. In the last decade, more data have become available on the wider and more specific role for these markers in the management of complex infections. This includes the potential role in early diagnosis, in differentiating infectious from noninfectious causes, as a prognostic marker, and in antibiotic guidance strategies. A better defined role for biological markers as a supplement to clinical assessment may lead to more judicious antibiotic prescriptions, and it has the potential for a long-term favorable impact on antimicrobial stewardship and antibiotic resistance. Procalcitonin as a biological marker has been of particular interest in this regard. This review examines the current published evidence and summarizes the role of various acute-phase markers in infections. A MEDLINE search of English-language articles on acute-phase reactants and infections published between 1986 and March 2015 was conducted. Additional articles were also identified through a search of references from the retrieved articles, published guidelines, systematic reviews, and meta-analyses.

Keywords. acute phase reactants; antibiotic guidance; C-reactive protein; endocarditis; ESR; infections; meningitis; osteomyelitis; pneumonia; procalcitonin; prosthetic joint infections; sepsis.

Infections are a major cause of morbidity and mortality worldwide. There has been increasing focus on the use of acute-phase reactants (APRs) in the management of infections because the presence of these markers in the serum signifies inflammation and injury. Acute-phase reactants are a heterogeneous group of plasma proteins that increase or decrease in response to inflammatory stimuli such as infections, trauma, acute arthritis, systemic autoimmune disorders, and neoplasms [1]. The response is proportional to the severity of the inflammatory stimulus and is mediated by proinflammatory cytokines such as

interleukin (IL)-6, IL-1, tumor necrosis factor-alpha, and interferon gamma. These cytokines, which are produced by macrophages, monocytes, and other cells participating in the inflammatory response, then stimulate production of APRs by the liver. Most APRs are mainly produced by the liver, although other cell types such as macrophages, endothelial cells, fibroblasts, and adipocytes have been implicated in the synthesis [2]. C-reactive protein (CRP) was first discovered in 1930 in the serum of patients with acute pneumococcal pneumonia. The “C” in CRP stands for the C polysaccharide of *Streptococcus pneumoniae* [3].

Important APRs include erythrocyte sedimentation rate (ESR), CRP, procalcitonin (PCT), serum amyloid A (SAA) protein, fibrinogen, ferritin, alpha-1 antitrypsin, haptoglobin, alpha-1 acid glycoprotein, ceruloplasmin, and complement proteins C3 and C4. The level of response may vary among different APRs. C-reactive protein and SAA protein can increase a few thousand-fold in response. Ceruloplasmin and complement proteins rise by approximately 25% to 50%, and fibrinogen levels usually increase a few fold. Albumin, transferrin, transthyretin, and retinol binding proteins decrease in response to inflammation and are called negative

Received 13 April 2015; accepted 26 June 2015.

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Open Forum Infectious Diseases

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DOI: 10.1093/ofid/ofv098

APRs [2]. Erythrocyte sedimentation rate is a nonprotein APR that changes in response to plasma fibrinogen levels and plasma viscosity and hence is an “indirect” APR [4].

The ESR and CRP are currently the most commonly used acute-phase markers in clinical practice. Procalcitonin as a marker in bacterial infections has generated a lot of interest in the last decade, and there is increasing evidence to support its usefulness in specific infections. Other acute-phase markers are not used regularly in clinical practice for many reasons such as difficulty in measuring levels, lack of standardization and uniformity in reporting, and paucity of clinical data. Serum amyloid A proteins comprise a family of apolipoproteins synthesized in response to cytokines released by activated monocytes and macrophages. It is as sensitive a marker for the inflammation as CRP, and it may have a role in vascular injury, atherogenesis, and allograft rejection, but it is not used routinely [5].

Erythrocyte Sedimentation Rate

The ESR measures the distance that a vertical column of anticoagulated blood has fallen in one hour. Although there have been abundant publications on the clinical use of ESR in the last several decades, its value and specificity in diagnosis of infections remains unclear. Any condition that affects red blood cells or fibrinogen levels alters the value of the ESR. Noninflammatory conditions such as age, anemia, pregnancy, drugs, and obesity can cause elevation in ESR. It may be elevated up to 60 mm/hour in patients with chronic renal insufficiency and nephrotic syndrome [6]. Causes for decreased ESR level include polycythemia, disorders of erythrocytes such as sickle cell disease or hereditary spherocytosis, low fibrinogen levels, and severe liver disease. Normal ESR value is generally calculated in men as age divided by 2 and in women as age +10 divided by 2. The ESR rises within 24–48 hours of the onset of inflammation and falls back slowly with resolution of inflammation [6]. Erythrocyte sedimentation rate levels of more than 100 mm/hour should prompt a search for underlying etiology. In a large retrospective study of 1006 patients, an ESR of 100 mm/hour or more had low sensitivity of 0.36 among patients with infection, 0.25 among those with malignant neoplasms, and 0.21 among patients with noninfectious inflammatory disorders. However, specificity was high: 0.96 for malignant neoplasms, 0.97 for infections, and 0.99 as a “sickness” index. The positive predictive value (PPV) for an identifiable cause of marked ESR elevation was 90% [7].

C-Reactive Protein

C-reactive protein has some advantages over ESR because it seems to be a better measure of an acute-phase response and is also more sensitive than ESR to subtle changes in the acute-phase response [1]. It is primarily produced by the liver in response to cytokines, mainly IL-6. The sole determinant

of circulating CRP concentration is the synthesis rate, which increases proportionally with the intensity of the inflammatory process stimulating CRP production, and vice-versa [8]. In healthy individuals, the CRP level is generally below 2 mg/L but can be up to 10 mg/L. There may be slight variation with age, sex, and race [8]. It has a half-life of approximately 19 hours, begins to rise after 12–24 hours, and peaks within 2–3 days. With mild to moderate stimulus, such as uncomplicated skin infection, cystitis, or bronchitis, it can rise to 50–100 mg/L within 6 hours [8]. Low levels of elevated CRP, with values between 2 mg/L and 10 mg/L, may be seen with “metabolic inflammatory” states such as smoking, uremia, cardiac ischemia, and other low level noninfectious inflammatory conditions. The only difference between high-sensitivity CRP (hsCRP) and standard CRP is that hsCRP assay is designed to measure very low levels of CRP [9]. Extremely high CRP elevation of more than 500 mg/L, in 1 study, was associated with more than 80% likelihood of bacterial infections [10].

Procalcitonin

Procalcitonin is the peptide prehormone of calcitonin that, under normal conditions, is secreted by the C-cells of the thyroid gland in response to hypercalcemia or as a result of medullary carcinoma of thyroid. In systemic inflammatory conditions and, in particular, bacterial infections, PCT secretion is stimulated by various cytokines such as IL-1, IL-6, and tumor necrosis factor-alpha. In viral infections, the PCT production is downgraded, likely from increased interferon gamma production [11]. Procalcitonin has several advantages over CRP and ESR as a biological marker. Serum concentrations of PCT are normally <0.05 ng/mL. Procalcitonin levels become detectable within 3–4 hours and peak within 6–24 hours, which is earlier than both CRP and ESR. Elevated PCT levels are not seen in other noninfectious inflammatory conditions such as polymyalgia, inflammatory bowel disease, polyarteritis nodosa, systemic lupus erythematosus, gout, and temporal arteritis. However, levels of PCT can transiently rise in massive trauma such as severe burns or major surgery. Any therapy that stimulates cytokines such as T-cell antibody therapy, granulocyte transfusion, or graft-versus-host disease can raise PCT levels. It has also been reported to be high in Addisonian crisis, malaria and severe fungal infections, and medullary carcinoma of thyroid. Many assays (BRAHMS) have been developed to measure PCT, including a rapid, semiquantitative point-of-care test that provides result in 30 minutes or less [11, 12].

In a systematic review comparing PCT and CRP as markers for bacterial infections, the authors reported that PCT level was more sensitive, 0.88 (95% confidence interval [CI], 0.80–0.93) vs 0.75 (95% CI, 0.62–0.84), and more specific, 0.81 (95% CI, 0.67–0.90) vs 0.67 (95% CI, 0.56–0.77), than CRP for differentiating bacterial from noninfectious causes of inflammation. The Q value for PCT markers was higher

(0.82 vs 0.73) compared with CRP. A Q value is an adjusted *P* value that provides quantitative information about the probability of clinical significance. The sensitivity for differentiating bacterial from viral infections was also higher for PCT with a higher Q value (0.89 vs 0.83). This review concluded that the diagnostic accuracy of PCT markers was higher than that of CRP markers among patients hospitalized for suspected bacterial infections [12]. Another study reported that initial high levels of PCT were indicative of a more severe disease, and persistently increased levels of PCT were indicative of an unfavorable outcome in patients with legionella pneumonia [13] (Table 1).

Cellulitis

In skin and soft tissue infections, ESR and CRP levels on admission may predict the severity of the infection and the duration of hospitalization. In a retrospective study at a tertiary hospital, patients who required longer hospitalization had significantly higher levels of ESR and CRP on admission but similar white blood cell (WBC) counts. The mean CRP and ESR values for the group with more severe disease requiring longer hospitalization was 100 mg/L and 70 mm/hour compared with a mean CRP and ESR of 40 mg/L and 50 mm/hour for the group with less severe disease requiring shorter hospitalization [14]. Another retrospective study reported a statistically significant association between longer hospitalization and a high ESR on admission. The cutoff for ESR in this study was 50 mm/hour, and the mean CRP level was 78 mg/L [15].

Table 1. Acute Phase Reactants

ESR	Extremely elevated ESR (>100 mm/hour)-high specificity for infection, malignancy, or arteritis. Rises within 24–48 hours of the onset of inflammation and falls back slowly with resolution.
CRP	Begins to rise after 12–24 hours and peaks within 2–3 days. Low levels of CRP elevation with values between 2 and 10 mg/L measured by a “high sensitivity CRP” assay seen in noninfectious “metabolic inflammatory” states such as cardiac ischemia, uremia, or smoking.
PCT	Detectable within 3–4 hours and peaks within 6–24 hours. Elevated levels not seen in other noninfectious inflammatory conditions such as polymyalgia, inflammatory bowel disease, polyarteritis nodosa, systemic lupus erythematosus, gout, and temporal arteritis. More sensitive and specific than CRP for distinguishing bacterial from noninfectious causes of inflammation
Others	Apolipoproteins: SAA proteins Coagulation Pathway: Fibrinogen, Protein S, Plasminogen Complement System: C3, C4, C9, Factor B, C1 inhibitor Antiproteases: Alpha-1 antitrypsin, Alpha-1 acid glycoprotein Proteins: Haptoglobin, Hemopexin, Hcpidin, Ferritin, Ceruloplasmin Cytokines: IL-1, IL-6, tumor necrosis factor-alpha

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL, interleukin; PCT, procalcitonin; SAA, serum amyloid A.

Necrotizing Skin and Soft Tissue Infections

It is often clinically challenging to differentiate between early necrotizing fasciitis versus more superficial skin and soft tissue involvement. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) is a laboratory-based scoring method that, in its original validation study, reported a PPV of 92% and a negative predictive of 96% for necrotizing skin and soft tissue infection for a LRINEC score of equal to or more than 6 [16]. A CRP level of more than 150 mg/L was assigned a score of 4 in this scoring system. Some subsequent reports on attempts at validating LRINEC score have failed to show reliable sensitivity [17]. Another study reported that a PCT ratio of 1.14 or more between the postoperative day 1 and day 2 after surgery for necrotizing fasciitis indicated successful surgical treatment with a sensitivity of 0.83 and a specificity of 0.71. The PPV was 75.8%, and the negative predictive value (NPV) was 80.0% [18].

Osteoarticular Infections

The likelihood of diabetic foot osteomyelitis increases with ESR value of more than 70 mm/h [19]. In another prospective study, the sensitivity and specificity of CRP for the diagnosis of osteomyelitis at a level of more than 14 mg/L was 0.85 and 0.83; the sensitivity and specificity of ESR at a level more than 67 mm/hour was 0.84 and 0.75; and the sensitivity and specificity of PCT at a level more than 0.30 ng/mL was 0.81 and 0.71. All values declined after initiation of treatment with antibiotics. The CRP and PCT values returned to near-normal levels by day 7, whereas the values of ESR remained high for up to 3 months only in patients with osteomyelitis. The authors recommended that ESR be used for the follow-up of patients with osteomyelitis [20]. A meta-analysis on the diagnostic value of PCT in osteoarticular infections indicated that PCT may be more suitable as a marker for rule-in diagnosis rather than for exclusion of septic arthritis or osteomyelitis, and that use of a lower cutoff value at 0.2–0.3 ng/mL may improve its diagnostic performance [21].

In spondylodiscitis, ESR is elevated in over 90% of cases, with mean values ranging from 43 mm/hour to 87 mm/hour [22]. In the same review, no correlation in the value of ESR was found to the severity of infection or patient’s age. The authors also noted that a fall in ESR to more than 25% of its presenting value was a good prognostic marker, but an unchanged or rising ESR was more difficult to interpret. C-reactive protein has a good sensitivity and was noted to be elevated in patients with acute spondylodiscitis in a number of studies. In these patients, CRP returned to normal within 3 months after the successful treatment of infection [22, 23].

In septic arthritis, both CRP and ESR have a high sensitivity at a cutoff value of 20 mg/L and 15 mm/hour, respectively [24]. Measurement of CRP in the synovial fluid does not offer a better diagnostic advantage [25]. Procalcitonin can be useful in the diagnosis of bacterial joint infections in patients with inflammatory rheumatic diseases [26].

Prosthetic Joint Infections

In a meta-analysis involving more than 30 studies and 300 patients, the authors concluded that the diagnostic accuracy for prosthetic joint infection was best for serum IL-6 level, followed by serum CRP level and ESR [27]. The pooled sensitivity and specificity were noted to be 0.97 and 0.91 for IL-6, 0.88 and 0.74 for CRP, and 0.75 and 0.70 for ESR, respectively. C-reactive protein may remain elevated for up to 6 weeks and ESR may remain elevated up to 26 weeks after prosthetic joint surgery. Another study on the diagnosis of early prosthetic joint infection reported a high sensitivity of CRP, with optimal cutoff value of 93 mg/L, and high specificity of synovial WBC count, with optimal cutoff value of 12 800 cells/mL. The combination of a normal ESR and CRP level is reliable for predicting the absence of prosthetic joint infection [28].

Sepsis and Septic Shock

In a meta-analysis involving 30 studies and 3244 critically ill patients, the authors concluded that PCT is a helpful biomarker for early diagnosis of sepsis in critically ill patients. The cutoff for PCT concentrations differed between 0.5 ng/mL and 2.0 ng/mL, with a median of 1.1 ng/mL. The pooled sensitivity and specificity of serum PCT levels in the early diagnosis of sepsis was noted to be 0.77 (95% CI, 0.72–0.81) and 0.79 (95% CI, 0.74–0.84), respectively [29]. In another systematic review, the authors concluded that PCT levels in early stages of sepsis are significantly lower among the survivors compared with nonsurvivors of sepsis. A maximum PCT level of 1–5 ng/mL correlated with a 90-day mortality of 11%; a maximum PCT level of 51–100 ng/mL correlated with a 90-day mortality of 42% [29, 30]. In a meta-analysis comparing PCT with CRP as a diagnostic test for sepsis after surgery or trauma, the authors concluded that PCT was superior to CRP [31]. Another meta-analysis examining patients with bacteremia concluded that low PCT levels can be used to rule out the presence of bacteremia [32]. Procalcitonin level elevations of 0.5 ng/mL occur very early during sepsis with levels increasing from systemic inflammatory response syndrome (0.6–2.0 ng/mL) to severe sepsis (2–10 ng/mL) and septic shock (10 ng/mL). Most importantly, viral infections, recent surgery, and chronic inflammatory states are not associated with an increment in PCT levels [33].

A meta-analysis of 16 studies examining serum PCT as a diagnostic marker in neonatal sepsis reported a pooled sensitivity and specificity of 0.81 and 0.91, respectively [34]. The diagnostic accuracy of PCT seemed higher for neonates with late-onset sepsis (>72 hours of life) than for those with early onset sepsis. A persistently negative CRP or a CRP that decreases to < 10 mg/L in 24 hours has a good NPV in neonatal bacterial sepsis [35].

Respiratory Infections

There is increasing evidence on the usefulness of PCT as a biomarker in lower respiratory tract infections. Procalcitonin levels

can be useful in early identification of bacterial pneumonia, guide antibiotic management, and help stratify patients with a higher risk of developing complications. In a randomized trial involving 302 consecutive patients, PCT guidance substantially reduced antibiotic use in lower respiratory tract infections without compromising outcomes from withholding antibiotics. In the PCT group, antibiotic treatment was based on serum PCT concentrations as follows: strongly discouraged, <0.1 µg/L; discouraged, <0.25 µg/L; encouraged, >0.25 µg/L; strongly encouraged, >0.5 µg/L [36]. A Cochrane database review of more than 14 trials also concluded that the use of PCT to guide initiation and duration of antibiotic treatment in patients with pneumonia was not associated with higher mortality rates or treatment failure [37]. Two other studies reported on the usefulness of a higher PCT level as a measure of severity in patients with bacteremia or a higher Pneumonia Severity Index score [38, 39]. The serum PCT levels do not correlate well with culture-proven empyema with a sensitivity and specificity of 0.76 and 0.81 at a cutoff value of 0.19 µg/L [11]. Two systematic reviews on the usefulness of CRP in the diagnosis and management of lower respiratory tract infections did not report any significant benefit in its role as a diagnostic or management modality [40]. Another study reported extremely high CRP levels (mean levels >166 mg/L) in patients with pneumococcal and legionella pneumonia [41]. There is good quality evidence to suggest that PCT guidance to discontinue antibiotic therapy in pneumonia reduces antibiotic usage in intensive care units (ICUs) and reduces duration of antibiotic use and prescription rates with a reduction in total antibiotic exposure in ambulatory care or inpatient setting in patients with pneumonia. There is also at least moderate evidence that PCT guidance to discontinue antibiotic therapy does not increase morbidity, as indicated by ICU length of stay, and that PCT guidance does not increase mortality, hospital length of stay, or ICU admission rates in patients diagnosed with pneumonia in an inpatient or ambulatory care setting [42] (Table 2).

Neurological Infections

Serum and cerebrospinal fluid (CSF) levels of both CRP and PCT have been evaluated in the diagnosis of bacterial meningitis. A meta-analysis involving both adult and pediatric studies reported that the serum concentrations of CRP had a sensitivity that ranged from 0.69 to 0.99 and a specificity that ranged from 0.28 to 0.99. The authors concluded that CRP may have a good NPV, but the overall usefulness in diagnosing meningitis remained uncertain [43]. Serum and CSF PCT level can be more useful in the diagnosis of bacterial meningitis and in distinguishing bacterial from viral meningitis. A prospective study of 105 adults and children with suspected meningitis reported that a serum PCT level of more than 0.2 ng/mL had a sensitivity and specificity of up to 100% in the diagnosis of bacterial meningitis [44]. Another recent prospective study of 105 patients

Table 2. Procalcitonin Guidance in Respiratory Infections and Sepsis

Acute respiratory tract infections including community acquired pneumonia [36–40, 42] (PCT-ng/mL)	<p>PCT <0.10: Strongly discourage antibiotic PCT <0.25: Discourage antibiotic PCT >0.25: Encourage antibiotic PCT >0.50: Strongly encourage antibiotic Good quality evidence suggests that PCT guidance reduces antibiotic duration of use and prescription rates. Moderate to good quality evidence suggests that PCT guidance did not increase mortality, hospital length of stay, or ICU admission rates. This guidance will need further validation in large multicenter trials.</p>
Sepsis and fever in a critically ill patients [29–34, 42]	<p>PCT >0.5 within 2–3 hours of onset of sepsis PCT levels (0.6–2.0): Systemic inflammatory response syndrome PCT levels (2–10): Sepsis PCT >10: Septic shock There is moderate quality evidence to suggest that PCT guidance in ICUs decreases overall antibiotic use and has no significant effect on morbidity (based on the length of stay). More research is needed to study the effect on PCT antibiotic guidance on the mortality in ICU patients.</p>

Abbreviations: ICU, intensive care unit; PCT, procalcitonin.

reported that with a cutoff of ≥ 0.74 ng/mL, PCT achieved 94.7% sensitivity, 100% specificity, an NPV of 93.9%, and a PPV of 100% to predict meningitis in emergency room patients [45]. In a prospective study of patients after neurosurgery, the authors reported that in contrast to conventional markers of inflammation, PCT levels did not increase during the postoperative period after major neurosurgery and remained <0.2 ng/mL. Thus, elevated serum PCT levels of >0.2 ng/mL could serve as a useful tool for the evaluation of fever of unknown origin after neurosurgery [46]. Another prospective study in neurosurgical patients reported a combined sensitivity and specificity of 0.85

and 0.92 respective for serum PCT level of more than 0.15 ng/mL, CRP level of more than 25 mg/mL, and a WBC count of more than 9500 per cubic mm [47].

Infective Endocarditis

In a prospective study involving 123 consecutive patients, the authors reported that high CRP level after 1 week of treatment and a slow percentage decline in CRP level during the first week of treatment are indicators of poor clinical outcome. The normalization of CRP is a good predictor of a favorable late outcome (surgery, death) of infective endocarditis (IE) [48].

Table 3. Acute Phase Reactants in Specific Infections

Clinical Infection	Acute-phase reactant (ESR-mm/hour, CRP-mg/L, PCT-ng/mL)
Cellulitis and Erysipelas Necrotizing Skin and Soft Tissue Infections (NSSTIs)	<p>CRP >70 and ESR >50 have a higher predictive value for the duration of hospital stay, which is an indirect index of severity [14, 15]. CRP >150 may suggest a higher likelihood of NSSTI [16]. PCT ratio of more than 1.14 between postoperative day 1 and day 2 after surgical debridement associated with favorable clinical recovery [18].</p>
Osteomyelitis Spondylodiscitis Prosthetic Joint Infection	<p>CRP >32 and ESR >70 helpful in distinguishing osteomyelitis from cellulitis in diabetic foot infections [19, 50]. CRP, PCT decrease rapidly with treatment. Fall in previously elevated ESR is a marker for response to treatment [20, 50]. Both ESR (median value 60) and CRP have high sensitivity for diagnosis of pyogenic spondylodiscitis. Decreasing values (25–50%) in the first 4 weeks of treatment suggest favorable prognosis [22, 23]. CRP may remain elevated for up to 6 weeks and ESR for up to 26 weeks after prosthetic joint surgery. Serum IL-6, CRP, and ESR have the best diagnostic value. Likelihood of infection very low if both ESR and CRP are normal. Procalcitonin has a low sensitivity [26, 27].</p>
Meningitis Neurosurgical infections	<p>Serum and cerebrospinal PCT levels likely have a high diagnostic accuracy in bacterial meningitis [44, 45]. CSF lactate at a cutoff of 35 mg/dL has a high negative likelihood ratio for distinguishing bacterial from viral meningitis [51]. Serum PCT levels of >0.15 have a high diagnostic value for bacterial infections after neurosurgical procedures [46, 47].</p>
Infective Endocarditis	<p>An initial value of PCT > 0.5 is predictor for poor outcome. High levels of CRP (>122) after first week of treatment and slow decline are indicators of poor outcome [48, 49].</p>
Pyelonephritis in children	<p>PCT level >0.5 is associated with high likelihood of pyelonephritis and renal scars in pediatric patients with urinary tract infection [52].</p>

Abbreviations: CRP, C-reactive protein; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; IL, interleukin; PCT, procalcitonin.

Another study reported PCT to be better marker for IE than CRP with sensitivity of 0.81, specificity of 0.85, and NPV of 92% and a PPV of 72% at a cutoff value of 2.3 ng/mL. An initial value of PCT of more than 0.5 ng/mL is a useful predictor of poor outcome, ie, death or serious infectious complications [49].

Conclusions

There is increasing evidence to support the use of various APRs in different patient populations and clinical settings. Procalcitonin has an advantage over CRP and ESR due to its better specificity. However, the future role of APRs will likely continue as an important adjunct to comprehensive clinical assessment. This would be especially important in patients with multiple comorbidities and in the ICUs where the timely and complex clinical decision making in a heterogeneous patient population will require more than 1 parameter alone. In this population, a higher NPV with repeatedly with low serum PCT levels may have a better clinical utility (Table 3).

There is good quality evidence to suggest that using PCT guidance strategies decrease antibiotic usage in ICUs and outpatient settings, but more research involving heterogeneous patient groups in multicenter trials is needed to assess its effect on patient morbidity, mortality, antimicrobial stewardship, and drug resistance. Clinical reassessment is important in patients when the antibiotics have been withheld due to low serum PCT levels.

Other areas for research include the role of biological markers in diagnosing infections in immunosuppressed and transplant populations and the effect of antibiotic guidance strategies in the pediatric population.

Acknowledgments

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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