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Role of Procalcitonin in Managing Adult Patients With Respiratory Tract Infections

Philipp Schuetz, MD, MPH; Devendra N. Amin, MD, FCCP; and Jeffrey L. Greenwald, MD

Respiratory infections remain the most common reason why patients seek medical care in ambulatory and hospital settings, and they are the most frequent precursor of sepsis. In light of the limitations of clinical signs and symptoms and traditional microbiologic diagnostics for respiratory infections, blood biomarkers that correlate with the presence and extent of bacterial infections may provide additional useful information to improve diagnostic and prognostic efforts and help with therapeutic decisions in individual patients. A growing body of evidence supports the use of procalcitonin (PCT) to differentiate bacterial from viral respiratory diagnoses, to help risk stratify patients, and to guide antibiotic therapy decisions about initial need for, and optimal duration of, therapy. Although still relatively new on the clinical frontier, a series of randomized controlled trials have evaluated PCT protocols for antibiotic-related decision making and have included patients from different clinical settings and with different severities of respiratory infection. In these trials, initial PCT levels were effective in guiding decisions about the initiation of antibiotic therapy in lower-acuity patients, and subsequent measurements were effective for guiding duration of therapy in higher-acuity patients, without apparent harmful effects. Recent European respiratory infection guidelines now also recognize this concept. As with any other laboratory test, PCT should not be used on a stand-alone basis. Rather, it must be integrated into clinical protocols, together with clinical, microbiologic data and with results from clinical risk scores. The aim of this review is to summarize recent evidence about the usefulness of PCT in patients with lower respiratory tract infections and to discuss the potential benefits and limitations of this marker when used for clinical decision making. ***CHEST 2012; 141(4):1063–1073***

Abbreviations: AUC = area under the receiver operating curve; CAP = community-acquired pneumonia; PCT = procalcitonin; VAP = ventilator-associated pneumonia

Respiratory infections remain the most common illness in humans, the most prevalent reason why patients seek acute medical care, and the most frequent and prevalent source of sepsis.[1,2] Despite advances in medical science, respiratory infections cause more disease and death than any other infection, with only little change in mortality rates over the past few decades.[3] Although mortality is attributable primarily to bacterial pneumonia and severe influenza infections, most patients with respiratory infections tend to have mild viral disease.[4] Importantly, around 75% of all antibiotic doses are prescribed for acute respiratory tract infections; of these, most are caused by viruses, not bacteria.[5] Early differentiation of severe cases from milder infections is essential and a major challenge when managing patients with respiratory infections. This fact is of particular importance

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Affiliations: From the Harvard School of Public Health (Dr Schuetz); Inpatient Clinician Educator Service (Dr Greenwald), the Department of Medicine, Massachusetts General Hospital, Boston, MA; and Medical/Surgical ICU (Dr Amin), Morton Plant Hospital, Clearwater, FL.
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Correspondence to: Philipp Schuetz, MD, MPH, Harvard School of Public Health, 667 Huntington Ave, Boston, MA 02115; e-mail: Schuetzph@gmail.com

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in light of studies demonstrating the benefit of early and appropriate antibiotic courses in cases of bacterial pneumonia,[6] and, at the same time, the need to reduce unnecessary antibiotic overuse to prevent bacterial resistance[7,8] and other complications of antibiotics, such as *Clostridium difficile* infection. In addition, accurate prognostication of patients improves initial triage and site-of-care decisions that have important health and financial implications.[9]

Reliable clinical signs and rapid microbiologic tests to diagnose bacterial infections confidently and to identify other, nonbacterial, causes not in need of antibiotic therapy are largely lacking.[10] Time-related delays inherent in culture methods, low sensitivity of blood cultures, and low specificity of sputum cultures due to quality of samples, colonization, or contamination are major limitations of these methods for everyday practice.[11] A novel approach to estimate the likelihood of bacterial infections and the severity of disease is the use of blood biomarkers mirroring the host response to infection, and indirectly, the severity of infection. Although an enormous number of different mediators and markers have been suggested as promising candidates, only a few of them have been tested rigorously in clinical outcome studies and have found their way into clinical practice.

One such blood marker, procalcitonin (PCT), has been evaluated in a number of clinical research studies and has been shown to be a more specific marker for bacterial infections compared with more traditional markers such as C-reactive protein and WBC.[10] PCT is released in multiple tissues in response to bacterial infections via a direct stimulation of cytokines, such as IL-1β, tumor necrosis factor-α, and IL-6. The upregulation of PCT correlates with the severity[10,12-14] and extent[11,15,16] of bacterial infections.

Conversely, interferon-γ, a cytokine released in response to viral infections, blocks the upregulation of PCT, resulting in a higher specificity of PCT toward bacterial infections.[17-20] Quantitatively, PCT may help distinguish severe bacterial infections from milder viral illnesses.[21]

In addition, PCT shows an interesting kinetic profile over time, with a prompt increase within 6 to 12 h upon stimulation and a daily decrease of around 50% in the event that the infection is controlled by the immune system supported by effective antibiotic therapy.[22] Another favorable characteristic of PCT is that it appears not to be influenced by corticosteroid treatments. Two studies found similar PCT levels in patients with and without corticosteroid treatment; one study included critically ill patients taking high doses of systemic corticosteroids (20-1,500 mg prednisone/d), whereas the other focused on biomarker levels of healthy volunteers after endotoxin injection treated with lower doses of prednisolone (30 mg/d).[23,24]

Based on these characteristics, many researchers have evaluated the usefulness of PCT in improving the clinical management of patients. The aim of this review, focusing on respiratory infections, is to give physicians an overview of the potential usefulness and limitations of PCT in diagnosing bacterial infections, differentiating bacterial from viral diseases, prognosticating regarding the severity of a patient's condition, and guiding clinical decisions about when to initiate antibiotic therapy and when it can be safely discontinued.

PCT for the Diagnosis of Respiratory Infections

Identifying a true "gold standard" for the diagnosis of respiratory infections is often problematic. The use of blood and sputum cultures have significant limitations[25,26] because of the duration of time required to obtain positive cultures and issues of colonization and contamination. Additionally, the inability to grow certain bacteria in standard cultures, as evidenced by the fact that causative microorganisms can be detected in only 10% to 20% of patients with respiratory infections, further confounds the diagnostic process.[9,11] Research on the diagnosis of respiratory infections is hampered by this lack of a gold standard and, therefore, may be difficult to interpret. Because of these limitations, previous studies and meta-analyses evaluating diagnostic markers that rely on observational studies have produced contradictory conclusions.[27,28]

In the clinical setting, one potential option for improving the diagnosis of bacterial infections is biomarkers that rise selectively in response to bacterial infection. To investigate this function of PCT, researchers have investigated a number of different clinical conditions to identify whether PCT has helped differentiate bacterial from other infections.

In one study, Müller et al[11] evaluated PCT in 925 patients with community-acquired pneumonia (CAP). In this cohort, 7.9% of subjects had bacteremic CAP with typical pathogens, mostly *Streptococcus pneumoniae*. PCT was increased significantly in bacteremic patients compared with patients without an identified bacterial pathogen with an area under the receiver operating curve (AUC) of 0.82. Less than 1% of patients had a positive blood culture when their initial PCT level was <0.25 μg/L, which increased to $>20\%$ in patients with PCT >2.5 μg/L. Similar results concerning bacteremia have been reported in other CAP cohorts (AUC, 0.85),[10] for patients with pyelonephritis[16] and patients in the ED with fever.[29]

Another study focused on the potential of PCT to differentiate patients with a viral respiratory infection

with or without bacterial superinfection. This was investigated in 103 patients with confirmed 2009 influenza A(H1N1) pneumonia in a critical care setting in France.[21] PCT had an AUC of 0.90 for differentiating the 48 patients with bacterial superinfection from patients with viral pneumonia only. At a PCT cutoff of 0.8 μg/L, the negative predictive value was 91% to exclude bacterial superinfection. Similar results were reported from other studies in Korea[30] and Spain.[31]

Other researchers have investigated whether PCT can predict the specific pathogens causing respiratory infections. Whereas patients with severe infections caused by *Legionella* species have shown high PCT levels,[32] other atypical pathogens such as mycoplasma do not appear to induce a strong PCT response in patients.[33] A large German CAP cohort found that PCT was highest in patients with typical bacterial causation, but did not allow prediction of specific cause in individual patients.[33]

For other respiratory infections, such as ventilator-associated pneumonia (VAP)[34] or TB,[35] clinical studies have produced mixed results and the clinical usefulness of PCT as a diagnostic test has not been established conclusively. For VAP, recent studies suggested that serial measurements may be the preferred approach, but at additional cost.[36,37]

These data show that PCT should not be used as a traditional diagnostic test because it does not clearly identify specific pathogens. Yet its impact may be more pronounced in identifying the higher likelihood of a relevant bacterial infection that increases with increasing PCT concentrations and, conversely, falls if the PCT level is low. Optimal "diagnostic cutoffs" are different according to the severity of presentation and clinical setting (eg, primary care or ICU), and may also depend on pathogen characteristics and antibiotic pretreatment (Fig 1).[38]

PCT for Prognostication in Respiratory Infections

Accurate assessment of disease severity and predictions regarding a patient's clinical course assist patients, families, and caregivers with setting appropriate expectations regarding the illness. These assessments and predictions are also prerequisites for the adequate allocation of health-care resources and therapeutic options in the management of respiratory infections.[9] This includes decisions regarding the need for regular hospital or ICU admission, diagnostic evaluation, and assessment for appropriate early discharge.

The role of prognostication is acknowledged by respiratory infection guidelines, which recommend stratifying patients with CAP based on predicted risk of mortality using validated risk scores (ie, the pneumonia severity index or the CURB-65 [confusion, urea, respiratory rate, BP] score).[39,40] Clinical risk scores are somewhat limited by practicality and risk of miscalibration due to different patient populations and, therefore, have only moderate operational characteristics.[41] Thus, there is interest in additional prognosticating mechanisms, using newly available biomarkers that are objectively and rapidly measurable and responsive to clinical recovery and that add relevant, reliable, and real-time information.

Different studies have evaluated the prognostic potential of PCT in patients with respiratory infections, mainly in patients with CAP (Table 1). Most studies have found that PCT levels were increased in patients not surviving their disease compared with survivors with moderate prognostic accuracy. In a large CAP cohort in the United States,[43] the greatest benefit of PCT was found in patients classified as high risk by the pneumonia severity index score. Having a PCT < 0.1 μg/L virtually excluded mortality in these high-risk patients. A Swiss study found that initial PCT levels did not improve clinical risk scores for mortality prediction[44]; subsequent repeated measurements of PCT in this population demonstrated improved clinical outcomes with falling PCT levels. In addition, the study found that PCT was more helpful in predicting serious adverse events other than mortality, such as ICU admission or CAP-related complications. For these outcomes, PCT significantly improved clinical risk scores. Another large CAP study from Germany, which included mostly low-risk patients, found that PCT was an accurate predictor of mortality and significantly improved clinical risk scores.[42]

Based on these studies, the prognostic usefulness of PCT in patients with respiratory infections who have had their clinical risk assessed (eg, using clinical risk scores) may be summarized as follows: (1) in low-risk patients with respiratory infections, PCT levels < 0.25 μg/L identify patients at lower risk of a bacterial cause and CAP and thus low mortality; (2) in low-risk patients with respiratory infections, PCT levels > 0.25 μg/L identify patients at higher risk of a bacterial cause and CAP and, perhaps, higher mortality; (3) in a high-risk population, PCT levels < 0.1 μg/L effectively decrease the likelihood of mortality from a bacterial cause, and other nonbacterial pathologies should be aggressively sought; (4) more helpful than initial values is the assessment of PCT kinetics over time in moderate and high-risk patients. Levels failing to decline during initial follow-up identify patients not responding to therapy. This last conclusion is also in accordance with ICU studies focusing on patients with sepsis[49,50] and patients with VAP[46] that demonstrated that a decreasing PCT

Table 1—*Prognostic Accuracy of PCT to Predict Adverse Outcome in Selected Studies*

Study/Year	Patient Population	No. Patients	Outcome(s)	AUC	Optimal PCT Cutoff, μg/L	Main Finding
Krüger et al[42]/2010	CAP	1,671	30-d mortality	0.8	0.23	Initial PCT values were significant mortality predictors and improved clinical risk scores.
Haeuptle et al[32]/2009	*Legionella* CAP	29	Mortality, ICU admission	0.78	1.5	Initial PCT values were independent markers for adverse outcomes.
Huang et al[43]/2008	CAP	1,651	30-d mortality	NA	0.09	Overall, PCT showed a low performance for mortality prediction. The best performance was found in high-risk patients according to clinical scores.
Schuetz et al[44]/2011	CAP	925	30-d mortality and combined treatment failure (mortality, ICU, complications)	0.60 (mortality); 0.66 (treatment failure)	0.25	Initial PCT values provided only moderate prognostic information for mortality but were good markers for other adverse outcomes. Repeated measurements provided additional information.
Claessens et al[45]/2010	CAP	549	28-d mortality	0.65	NA	PCT values had a moderate prognostic performance in predicting mortality.
Luyt et al[46]/2005	VAP	63	Unfavorable outcome (death, VAP recurrence, or extrapulmonary infection) at 28 d	NA	1.0	PCT values on days 1, 3, and 7 were strong predictors of unfavorable outcome.
Seligman et al[47]/2006	VAP	75	28-d mortality	NA	NA	Initial values and a decrease in PCT from baseline to day 4 predicted survival.
Bloos et al[48]/2011	CAP, HAP, VAP	175	28-d mortality	0.74 (CAP), 0.70 (HAP), 0.69 (VAP)	1.1	PCT was associated with the severity of illness similar to APACHE II score.

APACHE = Acute Physiology and Chronic Health Evaluation; AUC = area under the receiver operating curve; CAP = community-acquired pneumonia; HAP = hospital-acquired pneumonia; NA = not available PCT = procalcitonin; VAP = ventilator-associated pneumonia.

level over time is a more sensitive outcome predictor than is the initial PCT level.

Importantly, prognostic outcome studies are largely lacking, and it remains unclear whether an improved initial prognostic assessment and later monitoring of patients with PCT translate into better triage decisions and/or outcomes in patients. Of note, a recent large sepsis trial with >50% of patients having respiratory infections found that PCT-guided escalation of diagnostic procedures and antimicrobial therapy in the ICU did not improve survival. Instead, the algorithm used led to increased risk of renal failure and prolonged ICU stays.[51] From the study it remains unclear, however, if it was primarily a failure of the PCT protocol to identify high-risk patients or if the therapeutic and diagnostic strategies were insufficient, similar to other interventions that have failed to improve outcomes in patients with severe sepsis.[52] Importantly, the study provided further convincing evidence that increased antibiotic exposure has potentially harmful effects in patients and should be avoided where possible. Similar outcome studies need to be done for patients with respiratory infections in and outside the ICU to investigate whether PCT adds useful prognostic information and thereby improves the daily clinical management and outcomes of patients.

PCT for Therapeutic Decision About Initiation and Duration of Antibiotics

Although timely use of antibiotics is the most effective measure of preventing mortality and morbidity from bacterial respiratory infections, overuse of antibiotics causes considerable harm by exposing individual patients to adverse events including *Clostridium difficile* infection, by increasing the development of bacterial resistance, and by generating high costs.[7,8] Because of the limitations of traditional signs and symptoms in differentiating viral from bacterial disease, overuse of antibiotics in respiratory infections is a major challenge. Overuse may result from both overprescribing in low-acuity patients[53] and unnecessarily prolonged duration of antibiotic therapy in higher-acuity patients in the hospital and ICU setting.[7] To limit antibiotic overuse, rapid and accurate differentiation of clinically relevant bacterial infection from other causes is essential, as is closely monitoring patients' clinical recovery to discontinue antibiotics at the earliest safe point in their

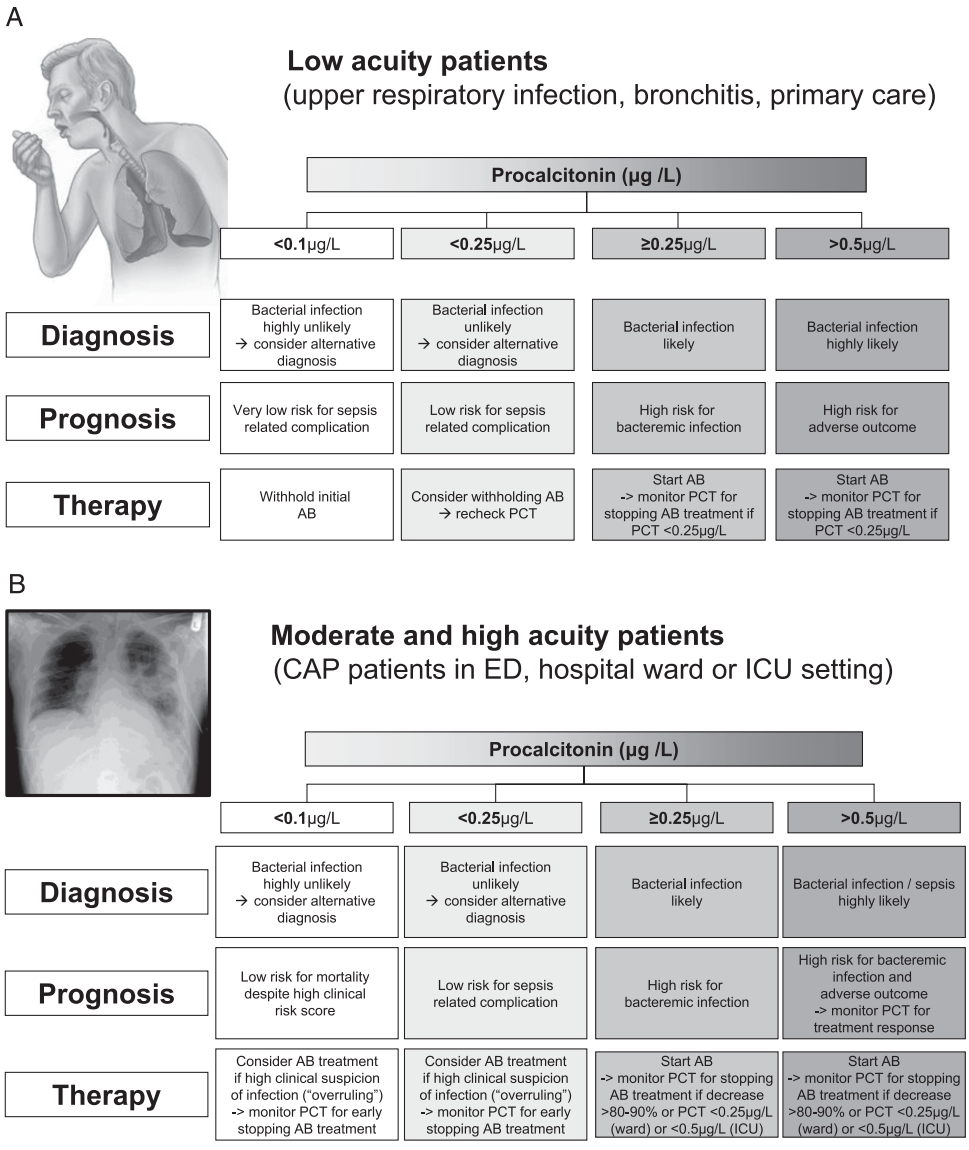

FIGURE 1. Use of PCT. A, In low-acuity patients. B, In moderate- and high-acuity patients. AB = antibiotics; CAP = community-acquired pneumonia; PCT = procalcitonin.

recovery. Because PCT becomes upregulated during bacterial infections and decreases upon recovery of patients, it may help determine the necessity and optimal duration of antibiotic therapy.[22,54]

Today, a total of 14 randomized controlled trials have evaluated the efficacy and safety of using PCT for antibiotic decisions (see an overview of the different trials in Table 2).[67] All studies used somewhat similar protocols, which recommended initiation or discontinuation of antibiotic therapy based on PCT levels.[67] Several PCT cutoff ranges were used, mirroring the increase in likelihood of bacterial disease with higher PCT levels. The protocols further adapted cutoffs to the clinical setting or the acuity of patients. In lower-acuity settings (primary care) or lower-acuity conditions (eg, bronchitis), PCT was used mainly to assist in the decision to prescribe or withhold antibiotic therapy. Conversely, in more severe respiratory infections (ie, pneumonia requiring hospitalization) or in the highest-acuity care settings (ie, sepsis or septic shock in the ICU), PCT was used not to determine whether antibiotics should be initiated, but rather when to discontinue them. All patients were reassessed in case antibiotics were withheld initially or if the clinical condition did not improve spontaneously over a day or two.

Within all trials, these strategies proved to be highly effective in terms of reductions of antibiotic exposure. In low-acuity patients, PCT guidance resulted in lower prescription rates by 40% to 75% in primary care patients with upper and lower respiratory infections,[57,64] by 60% to 75% in patients with acute

Table 2—*Overview of Current Randomized Controlled Trials Investigating Antibiotic Stewardship With PCT According to Schuetz et al*[67]

Study/Year	No. RI patients (Total No. Patients)	Diagnoses	Setting, Design	Research Question	Key Findings
Christ-Crain et al[55]/2004	243 (243)	CAP, ECOPD, bronchitis, asthma	ED only, single center	Reduction of AB for CAP in ED with single PCT measurement?	Reduction in AB prescriptions
Christ-Crain et al[13]/2006	302 (302)	CAP	ED and inpatients, single center	Reduction of AB for CAP with repeated PCT measurements?	Reduction in initiation and duration of AB without adverse outcomes
Stolz et al[56]2007	208 (226)	ECOPD	ED and inpatients, single center	Reduction of AB for ECOPD with repeated PCT measurements?	Reduced AB exposure without adverse outcome
Briel et al[57]/2008	458 (458)	Upper and lower RI	Multicenter, noninferiority	Safety and reduction of AB use with repeated PCT measurement?	Reduction in AB without additional days of restricted activity
Nobre et al[58]/2008	52 (79)	Sepsis	ICU, single center	Reduction of AB in ICU patients with sepsis?	Reduction in AB duration and ICU LOS without adverse events
Kristoffersen et al[59]/2009	210 (223)	CAP	ED and inpatients, single center	Reduction of AB for lower RI with single PCT measurement?	Reduction in duration of AB use
Schuetz et al[60]/2009	1,359 (1381)	CAP, ECOPD, bronchitis	ED and inpatients, multicenter	Safety, AB use, and feasibility in CAP, ECOPD, and bronchitis?	Noninferiority for clinical outcomes, and less AB use
Stolz et al[61]/2009	101 (101)	VAP	European and US ICU, multicenter	Reduction of AB in VAP in different ICUs?	Decreased AB use without increasing mortality
Hochreiter et al[62]2009	43 (110)	Post-op with infection	Surgical ICU, single center	Reduction of AB in post-op SICU patients with infection?	Reduction in AB duration and ICU LOS without adverse events
Long et al[63]/2009	127 (127)	CAP	ED at 2 centers	Reduction of AB for CAP in outpatients with repeated PCT measurements?	Reduction in AB use and shorter AB duration
Burkhardt et al[64]/2010	550 (571)	Upper and lower RI	Multicenter, noninferiority	Safety and reduction of AB use with single PCT measurement?	Reduction in AB without causing heath impairment
Bouadma et al[65]/2010	394 (630)	Sepsis	ICU, multicenter	Safety and reduction of AB in ICU patients with sepsis?	Reduction in AB use without increase in mortality
Long et al[66]/2011	156 (172)	CAP	ED at 2 centers	Reduction of AB for CAP in outpatients with repeated PCT measurements?	Reduction in AB use and shorter AB duration

AB = antibiotics; ECOPD = exacerbation of COPD; LOS = length of stay; Post-op = postoperative; RI = respiratory infection; SICU = surgical ICU. See Table 1 for expansion of other abbreviations.

bronchitis,[55,60] and by 30% to 45% in patients with exacerbation of COPD.[56,60] In higher-acuity patients, PCT guidance resulted in reduced duration of therapy by approximately 35% to 55% in CAP[13,60] and by around 35% in VAP.[61] Importantly, there was no increase in either mortality or any other adverse outcome tracked in any of the individual trials. Similarly, neither mortality nor other adverse events surfaced when pooling the data in different aggregate-data meta-analyses.[67,68-70] Still, particularly for ICU trials, lower adherence rates to the PCT protocol and the remaining uncertainty about safety relating to relatively large CIs calls for future trials in the ICU to validate these findings.

An individual patient data meta-analysis focusing on different patient-relevant outcomes and using standardized outcome definitions across trials, and predefined sensitivity and subgroup analyses is currently under way and should shed more light on these issues.[71,72] In addition to the randomized trials mentioned here, different studies evaluating PCT in "real life" and outside of study conditions found reductions in antibiotic usage without an apparent increase in adverse outcomes.[73,74]

Implementation of PCT In the Work-up of Patients With Respiratory Infections

Although further study of PCT in respiratory infections is warranted, it seems reasonable to begin using it clinically, based on the more robust areas of data summarized here. As previously reported, a number of protocols using PCT measurements can now be recommended that consider both clinical severity (based on patient characteristics or level of acuity of care site) and clinical entity (ie, which type of respiratory infection is being considered) to help physicians consider questions of initiation and duration of antibiotic therapy (Fig 1).[67]

(1) In patients with a low pretest probability for a bacterial infection (eg, a primary care or ED patient with suspected nonpneumonic respiratory infection), a single PCT measurement and a cutoff of <0.25 μg/L or certainly <0.1 μg/L appears to be safe to exclude a relevant bacterial infection and the need to initiate antibiotic therapy (Fig 1A). Clinical follow-up with remeasurement of PCT within 6 to 24 h should be considered in all patients in whom antibiotics are withheld but who show clinical deterioration. If PCT is >0.25 μg/L, and particularly >0.5 μg/L, a bacterial infection becomes more likely and physicians should consider expanding their diagnostic assessment, offering antibiotic therapy, and monitoring the patient more closely.

(2) For patients who are clinically stable and present to the ED or are hospitalized with pneumonia, a PCT level ≥ 0.25 μg/L strongly suggests that a bacterial infection is likely, and antibiotic therapy should be initiated expeditiously. In some settings, rapid results of PCT testing may be available ($<$ 1-2 h). In these settings, the decision to initiate antibiotics may be assisted by the initial level. In other settings, in which the PCT test may be delayed, initiation of antibiotics should be based on clinical suspicion, with the decision to discontinue antibiotics dependent on the PCT level. In patients in whom antibiotics are initiated, PCT should be reassessed every 2 days. Antibiotics may be discontinued if a patient shows clinical recovery and PCT decreases to <0.25 μg/L (or by at least 80% to 90% from the peak level). Highly elevated PCT levels in this situation make bacteremic disease more likely and suggest that the infection may be more severe than expected based on clinical signs and symptoms. In patients suspected of having a pneumonia based on the presence of infiltrates, a persistent ($>$ 24-48 h) PCT level of <0.1 μg/L or even 0.1 μg/L to <0.25 μg/L argues against a typical bacterial infection, and physicians should consider sooner rather than later including entities such as pulmonary embolism, acute heart failure, bronchiolitis obliterans organizing pneumonia, *Pneumocystis jiroveci* pneumonia, and viral pneumonia in their differential diagnoses. Particularly during flu season, influenza may be an important diagnosis to consider. If antibiotics are withheld initially, PCT should be rechecked after 6 to 24 h. If PCT levels are <0.25 μg/L but bacterial infection is still highly suspected based on the clinical presentation or microbiologic results, antibiotic therapy may still be considered, particularly in patients at higher risk of adverse outcome. If PCT remains low during follow-up, early discontinuation of antibiotics should be considered, as well as an aggressive diagnostic workup for other causes.

(3) For high-risk or patients in the ICU with severe respiratory infection (Fig 1B), empiric antibiotic therapy should not be delayed for PCT measurement. Still, an initial PCT level of <0.5 μg/L argues against a typical bacterial infection, and other diagnoses should be considered, including viral causes. Because the development of infection is a dynamic process and often progresses for the first 24 to 48 h despite starting appropriate antibiotics, repeating the PCT level at

6 to 24 h in high-risk patients may be important so as not to miss the evolution of the inflammatory cascade, similar to the strategy used for serial troponins in monitoring cardiac ischemia. Failure to catch the peak PCT level may result in underestimation of the severity of the infection. A careful clinical evaluation and periodic monitoring of PCT levels after antibiotic initiation appears to be an appropriate strategy in these patients. A drop of PCT to < 0.5 μg/L or by at least 80% to 90% from peak values is a reasonably conservative threshold for stopping antibiotic therapy in this fragile population, assuming patients also show a favorable clinical response. If PCT levels do not decrease by about 50% every 1 to 2 days, treatment failure should be considered and reassessment of patients is recommended.

(4) For patients with suspicion of respiratory infection after major surgery,[75] trauma, or cardiac shock,[76] PCT levels may reflect the cytokine response to the injury and may not necessarily point to a respiratory infection. Monitoring of PCT during follow-up may facilitate early discontinuation of antibiotics in this situation in patients showing a clear and favorable clinical response.[62] The same may be true for patients with VAP, in whom monitoring of PCT helps reduce length of antibiotic treatment.[61] A spike in PCT levels 3 to 4 days postoperatively or following trauma can indicate a secondary bacterial infection. It should be noted, however, that data in these clinical situations is less robust than in CAP, COPD, and bronchitis.

Importantly, these recommendations may be true only when highly sensitive PCT assays are used and may not be applied unconditionally to specific patient populations that have not been adequately studied, such as immune-compromised patients, neonates, and pregnant women.

Costs and Cost-Effectiveness

An important consideration when using a new diagnostic test is the cost associated with the test with respect to the potential for producing a cost saving (the current cost of a PCT test in the United States varies from about $25 to $30). A recent meta-analysis concluded that PCT in the critical care setting may be cost effective because of the high antibiotic costs in critically ill patients.[70] Although the same may not necessarily be true for general hospital inpatients with less expensive antibiotics, secondary costs due to side effects and the emergence of antibiotic resistance should also be considered. In addition, some studies have suggested that PCT measurement may help improve the use of other costly diagnostic tests, such as blood cultures, by focusing these tests on patients with higher PCT levels and, hence, a higher likelihood of positive results. A previous study calculated that if blood culture collection were limited to patients with CAP and an initial PCT level of > 0.25 μg/L, blood cultures could be reduced by almost 40%. The number needed to screen to have one positive culture would decrease from 13 to eight, whereas total patient costs (including PCT measurement costs) would decrease by almost 20%, with only 4% of positive cultures being missed.[11]

Conclusions and Future Directions

It is clear that the use of PCT is not a stand-alone test and will not replace clinical intuition or thorough clinical evaluations of patients.[77] PCT needs to be interpreted within the context of the clinical setting and the patient's situation because the correct understanding of PCT levels is predicated on the physician's pretest probability. In this way, it is similar to other markers such as the cardiac troponin or D-dimer. If PCT is embedded in clinical protocols adapted to the type of infection and clinical context, it clearly has the potential to improve clinical decision making in patients with respiratory infections.

Traditional culture methods, such as blood cultures, focus on identification and characterization of pathogens. Yet they have low sensitivity and thus, if negative, hardly influence clinical decision making in patients with respiratory infections. A blood marker, such as PCT, mirrors the patient's response to infection and thus, indirectly, the extent and severity of infection. The marker may not be able to identify the specific cause of infection, but the likelihood of a relevant bacterial pathogen increases with increasing marker levels. The marker may then help rule out infection and provide information about patient recovery. With new microbiologic methods becoming available that rapidly identify microorganisms with higher sensitivity, PCT may help increase specificity by providing information about the severity and "relevance" of culture results in individual patients.

Although the moderate prognostic value of initial PCT levels and further enhancement by considering its kinetics over time have been found in multiple observational studies, results from longer-term intervention studies evaluating the usefulness of clinical decision making concerning triage decisions based on PCT levels are largely lacking. The only intervention study available today, to our knowledge, that has evaluated the prognostic potential of PCT in patients

with sepsis in the ICU has been disappointing.[78] Similar types of studies should be conducted to see whether PCT measurement has the ability to improve triage decisions in patients, thereby safely reducing the costs of inpatient treatment.

Emerging bacterial resistance to antimicrobial agents and the huge increase in *Clostridium difficile* infections call for more effective efforts to reduce the unnecessary and prolonged use of antibiotics in self-limiting, nonbacterial, and resolving bacterial infections.[79] Randomized controlled studies have shown the efficacy of using PCT protocols to guide antibiotic decisions in patients with upper and lower respiratory infections. Even though previous meta-analyses consistently found no evidence for safety concerns with PCT-based algorithms for antibiotic therapy decisions, the remaining uncertainty associated with the relatively large CIs for mortality, particularly in patients in the ICU,[70] calls for further research in this high-risk patient population. In addition, most intervention studies today have been conducted in Europe and China; validation of PCT protocols and cutoffs in other countries is, therefore, warranted.

PCT-guided decision making is an innovative approach to managing patients with respiratory infections. It adds useful information about the patient's response to the infection and clinical recovery, thereby complementing a thorough clinical assessment and clinical intuition. Recent lower respiratory tract infection guidelines emphasize this concept and mention that "biomarkers can guide treatment duration by the application of predefined stopping rules for antibiotics. It has been shown that such rules work even in most severe cases, including pneumonia with septic shock…."[80] Instead of further observational studies reporting the accuracy of PCT in different clinical settings and situations, future intervention studies should propose PCT protocols with specific cutoffs and evaluate their impact on patient-relevant outcomes to tackle the existing vicious cycle of diagnostic uncertainty, overuse of antibiotics, and expanding use of hospital resources. The evidence suggests that using PCT for patients with respiratory infections can lead to more parsimonious antibiotic use and de-escalation, without safety concerns. Further studies are needed to illuminate whether PCT has a role in microbiologic diagnostic strategies and clinical prognostication.

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References

1. Fendrick AM, Monto AS, Nightengale B, Sarnes M. The economic burden of non-influenza-related viral respiratory tract infection in the United States. *Arch Intern Med*. 2003; 163(4):487-494.
2. Mizgerd JP. Acute lower respiratory tract infection. *N Engl J Med*. 2008;358(7):716-727.
3. Armstrong GL, Conn LA, Pinner RW. Trends in infectious disease mortality in the United States during the 20th century. *JAMA*. 1999;281(1):61-66.
4. Macfarlane JT, Colville A, Guion A, Macfarlane RM, Rose DH. Prospective study of aetiology and outcome of adult lower-respiratory-tract infections in the community. *Lancet*. 1993;341(8844):511-514.
5. Carlet J. Rapid diagnostic methods in the detection of sepsis. *Infect Dis Clin North Am*. 1999;13(2):483-494.
6. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34(6):1589-1596.
7. Lawrence KL, Kollef MH. Antimicrobial stewardship in the intensive care unit: advances and obstacles. *Am J Respir Crit Care Med*. 2009;179(6):434-438.
8. Ohl CA, Luther VP. Antimicrobial stewardship for inpatient facilities. *J Hosp Med*. 2011;6(suppl 1):S4-S15.
9. Mandell LA, Wunderink RG, Anzueto A, et al; Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(suppl 2):S27-S72.
10. Müller B, Harbarth S, Stolz D, et al. Diagnostic and prognostic accuracy of clinical and laboratory parameters in community-acquired pneumonia. *BMC Infect Dis*. 2007;7:10.
11. Müller F, Christ-Crain M, Bregenzer T, et al; ProHOSP Study Group. Procalcitonin levels predict bacteremia in patients with community-acquired pneumonia: a prospective cohort trial. *Chest*. 2010;138(1):121-129.
12. Schuetz P, Christ-Crain M, Albrich W, Zimmerli W, Mueller B; ProHOSP Study Group. Guidance of antibiotic therapy with procalcitonin in lower respiratory tract infections: insights into the ProHOSP study. *Virulence*; 2010;1(2):88-92.
13. Christ-Crain M, Stolz D, Bingisser R, et al. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med*. 2006; 174(1):84-93.
14. Gogos CA, Drosou E, Bassaris HP, Skoutelis A. Pro- versus anti-inflammatory cytokine profile in patients with severe sepsis: a marker for prognosis and future therapeutic options. *J Infect Dis*. 2000;181(1):176-180.
15. Schuetz P, Mueller B, Trampuz A. Serum procalcitonin for discrimination of blood contamination from bloodstream infection due to coagulase-negative staphylococci. *Infection*. 2007;35(5):352-355.
16. van Nieuwkoop C, Bonten TN, van't Wout JW, et al. Procalcitonin reflects bacteremia and bacterial load in urosepsis syndrome: a prospective observational study. *Crit Care*. 2010;14(6):R206.

17. Christ-Crain M, Müller B. Procalcitonin in bacterial infections—hype, hope, more or less? *Swiss Med Wkly*. 2005;135(31-32):451-460.
18. Christ-Crain M, Müller B. Biomarkers in respiratory tract infections: diagnostic guides to antibiotic prescription, prognostic markers and mediators. *Eur Respir J*. 2007;30(3):556-573.
19. Linscheid P, Seboek D, Zulewski H, Keller U, Müller B. Autocrine/paracrine role of inflammation-mediated calcitonin gene-related peptide and adrenomedullin expression in human adipose tissue. *Endocrinology*. 2005;146(6):2699-2708.
20. Schuetz P, Christ-Crain M, Müller B. Procalcitonin and other biomarkers to improve assessment and antibiotic stewardship in infections—hope for hype? *Swiss Med Wkly*. 2009; 139(23-24):318-326.
21. Cuquemelle E, Soulis F, Villers D, et al; A/H1N1 REVA-SRLF Study Group. Can procalcitonin help identify associated bacterial infection in patients with severe influenza pneumonia? A multicentre study. *Intensive Care Med*. 2011; 37(5):796-800.
22. Becker KL, Nylén ES, White JC, Müller B, Snider RH Jr. Clinical review 167: Procalcitonin and the calcitonin gene family of peptides in inflammation, infection, and sepsis: a journey from calcitonin back to its precursors. *J Clin Endocrinol Metab*. 2004;89(4):1512-1525.
23. Müller B, Peri G, Doni A, et al. High circulating levels of the IL-1 type II decoy receptor in critically ill patients with sepsis: association of high decoy receptor levels with glucocorticoid administration. *J Leukoc Biol*. 2002;72(4):643-649.
24. de Kruif MD, Lemaire LC, Giebelen IA, et al. The influence of corticosteroids on the release of novel biomarkers in human endotoxemia. *Intensive Care Med*. 2008;34(3):518-522.
25. Bossuyt PM, Reitsma JB, Bruns DE, et al; Standards for Reporting of Diagnostic Accuracy. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. *Ann Intern Med*. 2003;138(1):W1-12.
26. Bachmann LM, Jüni P, Reichenbach S, Ziswiler HR, Kessels AG, Vögelin E. Consequences of different diagnostic "gold standards" in test accuracy research: carpal tunnel syndrome as an example. *Int J Epidemiol*. 2005;34(4):953-955.
27. Uzzan B, Cohen R, Nicolas P, Cucherat M, Perret GY. Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: a systematic review and meta-analysis. *Crit Care Med*. 2006;34(7):1996-2003.
28. Tang BM, Eslick GD, Craig JC, McLean AS. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. *Lancet Infect Dis*. 2007; 7(3):210-217.
29. Albrich WC, Mueller B. Predicting bacteremia by procalcitonin levels in patients evaluated for sepsis in the emergency department. *Expert Rev Anti Infect Ther*. 2011;9(6): 653-656.
30. Song JY, Cheong HJ, Heo JY, et al. Clinical, laboratory and radiologic characteristics of 2009 pandemic influenza A/H1N1 pneumonia: primary influenza pneumonia versus concomitant/secondary bacterial pneumonia. *Influenza Other Respi Viruses*; 2011;5(6):e535-543.
31. Piacentini E, Sánchez B, Arauzo V, Calbo E, Cuchi E, Nava JM. Procalcitonin levels are lower in intensive care unit patients with H1N1 influenza A virus pneumonia than in those with community-acquired bacterial pneumonia. A pilot study. *J Crit Care*. 2011;26(2):201-205.
32. Haeuptle J, Zaborsky R, Fiumefreddo R, et al. Prognostic value of procalcitonin in *Legionella* pneumonia. *Eur J Clin Microbiol Infect Dis*. 2009;28(1):55-60.
33. Krüger S, Ewig S, Papassotiriou J, et al; CAPNETZ Study Group. Inflammatory parameters predict etiologic patterns but do not allow for individual prediction of etiology in patients with CAP: results from the German competence network CAPNETZ. *Respir Res*. 2009;10:65.
34. Luyt CE, Combes A, Reynaud C, et al. Usefulness of procalcitonin for the diagnosis of ventilator-associated pneumonia. *Intensive Care Med*. 2008;34(8):1434-1440.
35. Prat C, Domínguez J, Andreo F, et al. Procalcitonin and neopterin correlation with aetiology and severity of pneumonia. *J Infect*. 2006;52(3):169-177.
36. Charles PE, Kus E, Aho S, et al. Serum procalcitonin for the early recognition of nosocomial infection in the critically ill patients: a preliminary report. *BMC Infect Dis*. 2009;9:49.
37. Tsangaris I, Plachouras D, Kavatha D, et al. Diagnostic and prognostic value of procalcitonin among febrile critically ill patients with prolonged ICU stay. *BMC Infect Dis*. 2009; 9:213.
38. Krüger S, Ewig S, Kunde J, et al; CAPNETZ Study Group. C-terminal provasopressin (copeptin) in patients with community-acquired pneumonia—influence of antibiotic pre-treatment: results from the German competence network CAPNETZ. *J Antimicrob Chemother*. 2009;64(1):159-162.
39. Niederman MS, Mandell LA, Anzueto A, et al; American Thoracic Society. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am J Respir Crit Care Med*. 2001;163(7):1730-1754.
40. Woodhead M, Blasi F, Ewig S, et al; European Respiratory Society; European Society of Clinical Microbiology and Infectious Diseases. Guidelines for the management of adult lower respiratory tract infections [published correction appears in *Eur Respir J*. 2006;27(2):439]. *Eur Respir J*. 2005; 26(6):1138-1180.
41. Schuetz P, Koller M, Christ-Crain M, et al. Predicting mortality with pneumonia severity scores: importance of model recalibration to local settings. *Epidemiol Infect*. 2008;136(12): 1628-1637.
42. Krüger S, Ewig S, Kunde J, et al. Assessment of inflammatory markers in patients with community-acquired pneumonia–influence of antimicrobial pre-treatment: results from the German competence network CAPNETZ. *Clin Chim Acta.* 2010; 411(23-24):1929-1934.
43. Huang DT, Weissfeld LA, Kellum JA, et al. Risk prediction with procalcitonin and clinical rules in community-acquired pneumonia. *Ann Emerg Med* 2008; 52(1):48-58.e2.
44. Schuetz P, Suter-Widmer I, Chaudri A, et al. Prognostic value of procalcitonin in community-acquired pneumonia. *Eur Respir J.* 2011;37(2):384-392.
45. Claessens YE, Mathevon T, Kierzek G, et al. Accuracy of C-reactive protein, procalcitonin, and mid-regional pro-atrial natriuretic peptide to guide site of care of community-acquired pneumonia. *Intensive Care Med*. 2010;36(5):799-809.
46. Luyt CE, Guérin V, Combes A, et al. Procalcitonin kinetics as a prognostic marker of ventilator-associated pneumonia. *Am J Respir Crit Care Med*. 2005;171(1):48-53.
47. Seligman R, Meisner M, Lisboa TC, et al. Decreases in procalcitonin and C-reactive protein are strong predictors of survival in ventilator-associated pneumonia. *Crit Care*. 2006;10(5):R125.
48. Bloos F, Marshall JC, Dellinger RP, et al. Multinational, observational study of procalcitonin in ICU patients with pneumonia requiring mechanical ventilation: a multicenter observational study. *Crit Care*. 2011;15(2):R88.
49. Jensen JU, Lundgren J. Procalcitonin monitoring in trauma intensive care patients: how helpful is it? *Crit Care Med*. 2009;37(6):2093-2094.
50. Karlsson S, Heikkinen M, Pettilä V, et al; Finnsepsis Study Group. Predictive value of procalcitonin decrease in patients

with severe sepsis: a prospective observational study. *Crit Care*. 2010;14(6):R205.
51. Jensen JU, Hein L, Lundgren B, et al; Procalcitonin And Survival Study (PASS) Group. Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: a randomized trial. *Crit Care Med*. 2011;39(9):2048-2058.
52. Schuetz P, Mueller B. To escalate or to de-escalate—that is the question. *Crit Care Med*. 2011;39(11):2590.
53. Evans AT, Husain S, Durairaj L, Sadowski LS, Charles-Damte M, Wang Y. Azithromycin for acute bronchitis: a randomised, double-blind, controlled trial. *Lancet*. 2002;359(9318):1648-1654.
54. Müller F, Christ-Crain M, Bregenzer T, et al. Procalcitonin levels predict bacteremia in patients with community-acquired pneumonia: a prospective cohort trial. *Chest*. 2010; 138(1):121-129.
55. Christ-Crain M, Jaccard-Stolz D, Bingisser R, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet*. 2004;363(9409): 600-607.
56. Stolz D, Christ-Crain M, Bingisser R, et al. Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. *Chest*. 2007;131(1):9-19.
57. Briel M, Schuetz P, Mueller B, et al. Procalcitonin-guided antibiotic use vs a standard approach for acute respiratory tract infections in primary care. *Arch Intern Med*. 2008; 168(18):2000-2007.
58. Nobre V, Harbarth S, Graf JD, Rohner P, Pugin J. Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. *Am J Respir Crit Care Med*. 2008;177(5):498-505.
59. Kristoffersen KB, Søgaard OS, Wejse C, et al. Antibiotic treatment interruption of suspected lower respiratory tract infections based on a single procalcitonin measurement at hospital admission—a randomized trial. *Clin Microbiol Infect*. 2009;15(5):481-487.
60. Schuetz P, Christ-Crain M, Thomann R, et al; ProHOSP Study Group. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. *JAMA*. 2009;302(10):1059-1066.
61. Stolz D, Smyrnios N, Eggimann P, et al. Procalcitonin for reduced antibiotic exposure in ventilator-associated pneumonia: a randomised study. *Eur Respir J*. 2009;34(6):1364-1375.
62. Hochreiter M, Köhler T, Schweiger AM, et al. Procalcitonin to guide duration of antibiotic therapy in intensive care patients: a randomized prospective controlled trial. *Crit Care*. 2009;13(3):R83.
63. Long W, Deng XQ, Tang JG, et al. The value of serum procalcitonin in treatment of community acquired pneumonia in outpatient [in Chinese]. *Zhonghua Nei Ke Za Zhi*. 2009; 48(3):216-219.
64. Burkhardt O, Ewig S, Haagen U, et al. Procalcitonin guidance and reduction of antibiotic use in acute respiratory tract infection. *Eur Respir J*. 2010;36(3):601-607.
65. Bouadma L, Luyt CE, Tubach F, et al; PRORATA trial group. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet*. 2010;375(9713):463-474.
66. Long W, Deng X, Zhang Y, Lu G, Xie J, Tang J. Procalcitonin guidance for reduction of antibiotic use in low-risk outpatients with community acquired pneumonia. *Respirology*. 2011;16(5):819-824.
67. Schuetz P, Chiappa V, Briel M, Greenwald JL. Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms. *Arch Intern Med*. 2011;171(15): 1322-1331.
68. Agarwal R, Schwartz DN. Procalcitonin to guide duration of antimicrobial therapy in intensive care units: a systematic review. *Clin Infect Dis*. 2011;53(4):379-387.
69. Kopterides P, Siempos II, Tsangaris I, Tsantes A, Armaganidis A. Procalcitonin-guided algorithms of antibiotic therapy in the intensive care unit: a systematic review and meta-analysis of randomized controlled trials. *Crit Care Med*, 2010;38(11):2229-2241.
70. Heyland DK, Johnson AP, Reynolds SC, Muscedere J. Procalcitonin for reduced antibiotic exposure in the critical care setting: a systematic review and an economic evaluation. *Crit Care Med*. 2011;39(7):1792-1799.
71. Bafadhel M, Clark TW, Reid C, et al. Procalcitonin and C-reactive protein in hospitalized adult patients with community-acquired pneumonia or exacerbation of asthma or COPD. *Chest*. 2011;139(6):1410-1418.
72. Koutsokera A, Stolz D, Loukides S, Kostikas K. Systemic biomarkers in exacerbations of COPD: the evolving clinical challenge. *Chest*. 2012;141(2):396-405.
73. Saeed K, Dryden M, Bourne S, Paget C, Proud A. Reduction in antibiotic use through procalcitonin testing in patients in the medical admission unit or intensive care unit with suspicion of infection. *J Hosp Infect*. 2011;78(4):289-292.
74. Schuetz P, Batschwaroff M, Dusemund F, et al. Effectiveness of a procalcitonin algorithm to guide antibiotic therapy in respiratory tract infections outside of study conditions: a post-study survey. *Eur J Clin Microbiol Infect Dis*. 2010;29(3): 269-277.
75. Sponholz C, Sakr Y, Reinhart K, Brunkhorst F. Diagnostic value and prognostic implications of serum procalcitonin after cardiac surgery: a systematic review of the literature. *Crit Care*. 2006;10(5):R145.
76. Schuetz P, Affolter B, Hunziker S, et al. Serum procalcitonin, C-reactive protein and white blood cell levels following hypothermia after cardiac arrest: a retrospective cohort study. *Eur J Clin Invest*. 2010;40(4):376-381.
77. Gilbert DN. Use of plasma procalcitonin levels as an adjunct to clinical microbiology. *J Clin Microbiol*. 2010;48(7):2325-2329.
78. Jensen JU, Hein L, Lundgren B, et al. Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: a randomized trial. *Crit Care Med*. 2011;39(9):2048-2058.
79. Whitney CG, Farley MM, Hadler J, et al; Active Bacterial Core Surveillance Program of the Emerging Infections Program Network. Increasing prevalence of multidrug-resistant *Streptococcus pneumoniae* in the United States. *N Engl J Med*. 2000;343(26):1917-1924.
80. Woodhead M, Blasi F, Ewig S, et al; Joint Taskforce of the European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases. Guidelines for the management of adult lower respiratory tract infections—full version. *Clin Microbiol Infect*. 2011;17(suppl 6):E1-E59.