Biomarkers

What is Their Benefit in the Identification of Infection, Severity Assessment, and Management of Community-acquired Pneumonia?

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KEYWORDS

• Biomarkers • Procalcitonin • C-reactive protein • Duration of therapy
• Community-acquired pneumonia • Severity of illness

KEY POINTS

- Information from measurement of levels of inflammatory biomarkers such as procalcitonin (PCT) at the time of admission with radiographic community-acquired pneumonia (CAP) can help to define the need for antibiotic therapy because levels are high with bacterial infection but not with viral infection.
- Measurement of PCT levels on admission and serially can help to define the prognosis of CAP and the likelihood of developing pneumonia complications.
- Serial measurement of PCT levels can be used to define the optimal duration of antibiotic therapy in CAP, and a PCT-guided approach has led to good outcomes, with a shorter duration of therapy than a standard clinical approach.
- Measurement of PCT levels may not be valuable in the setting of partially treated CAP and cannot always recognize whether influenza is complicated by secondary bacterial pneumonia.
- In patients with CAP and a low PCT value on admission, treatment in the intensive care unit (ICU) may not be necessary, even if the patient falls into the high-risk group by traditional prognostic scoring tools.
- Cardiac biomarkers may be more valuable than inflammatory biomarkers for predicting the long-term mortality risk in patients with CAP.

CAP is one of the most common reasons for hospitalization and is associated with significant morbidity and mortality. It is one of the most common infections for which antibiotics are prescribed and is the leading cause of death from infection in the United States. The annual incidence of CAP is between 5 and 11 per 1000 population, with the

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frequency rising in elderly patients. In 2006, 1.2 million people in the United States were hospitalized with pneumonia and 55,477 people died of the disease.[1] The mortality varies according to the severity of disease. Among outpatients, the mortality is less than 5%, whereas in the hospital, the mortality increases to more than 10%, but can exceed 30% when patients are admitted to the ICU.[2,3]

Early identification of patients with CAP with severe illness can lead to proper site-of-care decisions, and recent data have shown that delayed transfer to the ICU is a risk factor for poor outcome.[4] The Joint Commission on Accreditation of Healthcare Organizations and the Centers for Medicare and Medicaid services have in the past included rapid treatment of CAP as a performance measure, which has added pressure to start antibiotics rapidly, in the emergency department (ED), often before a firm diagnosis is established, and this practice has led to antibiotic complications such as *Clostridium difficile* colitis.[5] At present, we rely on several clinical scoring systems to define the severity of illness, and we use clinical and radiographic assessment to define the presence of pneumonia, the severity of illness, and the need for antibiotic therapy. Several new biomarkers have been developed that can supplement the current approach, by helping to define the presence of pneumonia, assisting in the assessment of disease severity, and guiding the duration of antibiotic therapy.[6,7] It remains controversial whether the use of biomarkers to manage patients with CAP is an improvement over the standard approach, using clinical assessment.

USING BIOMARKERS TO DIAGNOSE THE PRESENCE OF CAP AND THE NEED FOR ANTIBIOTIC THERAPY

Available Biomarkers and Their Advantages

Biomarkers include several proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6, which can not only reflect the degree of acute inflammation in the patient with CAP but also be direct stimulants of acute-phase reactants such as C-reactive protein (CRP) and PCT (**Box 1**). The levels of antiinflammatory cytokines can also be measured and include IL-1 receptor antagonist and IL-10. PCT is currently one of the most widely studied biomarkers and is produced in large quantities by parenchymal cells such as the liver in response to bacterial toxins or proinflammatory cytokines, but is downregulated in the presence of viral infection.[8] Serum levels of PCT rise within 2 hours of a bacterial infection stimulus, which is faster than the rise in CRP levels. The appeal of studying a biomarker in patients with CAP, when compared with a clinical assessment (fever, white blood cell [WBC] count, chest radiograph, and vital signs) is that it may give accurate information, rapidly, that is specific to bacterial infection and at an early time point in illness. Clinical features of CAP vary with the host inflammatory response, which can be a reflection of either the type of patient infected or the etiologic pathogen, and the data may not be specific for infection. In addition, clinical features can be attenuated by the presence of prior antibiotic therapy and may not be valuable early in the course of illness, as is the case in patients with initial chest radiographs with negative results in early CAP. In trying to use clinical features and laboratory testing to separate viral from bacterial CAP, Gram stain could be helpful, but its result needs to be correlated with cultures of sputum and other microbiological data such as blood cultures, which can take at least 24 to 48 hours to yield results. On the other hand, biomarkers measured in serum may give an indication about the presence of bacterial infection in a rapid and reliable manner, guiding the need for antibiotic therapy. In addition, as therapy leads to clinical improvement, levels of inflammatory biomarkers may decline, and serial monitoring can be used to guide when to stop antibiotic therapy.

Box 1
Advantages and disadvantages of using biomarkers to help in CAP management

Advantages

Provides information that is specific to infections needing antibiotic therapy

- Levels can be high with bacterial infection and not viral infection
- Levels rise rapidly with bacterial infection
- Response is usually not organism dependent
- May be more specific for bacterial infection than clinical assessment

Results available rapidly

Levels may be abnormal early in the course of illness, before abnormal clinical and radiographic findings

Can help define short-term and long-term prognoses

Can supplement the information provided by prognostic scoring tools

Can help define the response to therapy

Can help determine the need for continuing antibiotic therapy

- Can reduce antibiotic usage without adverse consequences

Disadvantages

Results may be misleading and conflict with careful clinical assessment

Prior (effective) antibiotic therapy can lower levels rapidly and lead to false-negative findings

May not always distinguish atypical pathogen pneumonia from viral pneumonia

Cannot always recognize if influenza is complicated by secondary bacterial infection

Cannot separate aspiration chemical pneumonitis from aspiration bacterial pneumonia

Using Biomarkers to Define the Need for Antibiotic Therapy in CAP

In one study, patients with confirmed CAP were compared with those with respiratory tract infection (RTI) without CAP and to a group of healthy controls. Serum levels of CRP were highest in the CAP group, but those with pneumococcal or *Legionella* infection had higher CRP levels than those with viral or atypical pathogen infection and than those with negative results of microbiologic tests.[9] In this early study of biomarkers, there was also a correlation of CRP levels with the severity of illness, with the levels being higher in those who were hospitalized than in those treated at home. Many investigators have used CRP to define the need for antibiotic therapy in patients with CAP, but most of the recent data have come from studies of PCT, which seems to be more sensitive and specific for this purpose than CRP.

A group of Swiss investigators have carefully studied several biomarkers in patients with RTI, but have relied heavily on PCT levels measured with the highly sensitive Kryptor assay.[10–12] This assay is based on using a sheep polyclonal antibody, which can detect levels as low as 0.06 μg/L, which is far more sensitive than the previously popular commercially available Immunoluminometric assay (LUMI assay), which detected levels only as low as 0.3 to 0.5 μg/L. The group has performed several randomized interventions, including the Pro RESP, Pro CAP, and Pro HOSP studies, which studied patients with RTIs coming to the ED, patients with CAP, and patients with RTIs seen in the ED, respectively.[10–12] In the Pro RESP study, there were 87 patients with CAP and fewer who were randomized to PCT guidance received antibiotic therapy than those

randomized to standard care. Also, 1 patient with radiographic CAP received no antibiotics based on the PCT results, and recovered, in spite of being bacteriologically positive.[10] The safety of using serum PCT levels to guide antibiotic therapy led to the next study, the Pro CAP study, in which 302 patients with radiographic CAP were randomized either to receive standard care or to use admission and serial PCT levels guide the use of antibiotics. In the PCT group, therapy was strongly discouraged for levels less than 0.1 μg/L, discouraged if the value was 0.25 μg/L or less, encouraged if the level was greater than 0.25 μg/L, and strongly encouraged if the level was greater than 0.5 μg/L. However, clinical judgment was always allowed to override the guidance suggested by measurement of PCT levels. In the study, 15% with radiographic CAP had antibiotics withheld in the PCT group, compared with 1% in the standard care group, with no adverse outcomes in those not receiving therapy.[11] This observation led the investigators to suggest that PCT levels could be used to separate bacterial from nonbacterial causes of lung infiltrates; that patients with a favorable clinical picture, and a PCT level less than 0.25 μg/mL, could safely have antibiotics withheld; and that this decision was more reliably made when adding a biomarker to clinical assessment than by using clinical judgment alone. The Pro HOSP study extended the data from the earlier findings, which came from a single center, by including 6 different Swiss hospitals in a multicenter intervention study. This study also confirmed that by using PCT levels to guide the use of antibiotics less therapy was initiated, compared with standard care.[12]

In a subsequent analysis, the investigators combined patients from the Pro RESP and Pro CAP studies, which included 373 patients with radiographic CAP. Of these patients, 20 ultimately had noninfectious diagnoses and another 24 recovered without antibiotic therapy.[13] The investigators found that both PCT and highly sensitive CRP (hsCRP) were similarly accurate for predicting the presence of an abnormality in chest radiograph, with both being more useful than clinical signs such as fever, leukocyte count, abnormal lung examination, sputum production, cough, and dyspnea ($P<.001$). A clinical model alone had an area under the curve (of sensitivity vs 1 − specificity) of 0.79 to predict an abnormal result of radiography, compared with a value of 0.88 and 0.92, respectively, when PCT was added or when both PCT and hsCRP were added to the clinical assessment. PCT was more accurate than hsCRP or clinical features to predict the presence of bacteremia ($P<.01$) and to predict the severity of pneumonia, as defined by the Pneumonia Severity Index (PSI). Stolz and colleagues[14] have demonstrated that CRP levels can also predict radiographic pneumonia at a CRP cutoff value of 100 mg/mL with 91% specificity.[14] The advantages of using CRP include low cost, easy availability, historic use, and familiarity with the test, particularly in Europe, but currently, the data with PCT seem more robust for determining when to use antibiotic therapy in patients with suspected CAP.[13,15]

Limitations of Using Biomarkers to Define the Need for Antibiotic Therapy in CAP

Although the Swiss studies have shown that PCT may be able to separate patients with radiographic CAP who need antibiotics from those who do not, it is uncertain if PCT can reliably recognize the presence of atypical pathogen CAP versus bacterial CAP. A small study evaluated 30 patients with CAP, 20 with bacterial pneumonia, and 10 with infection involving *Chlamydophila pneumoniae, Mycoplasma pneumoniae*, or *Legionella pneumophila*.[16] Unlike the Swiss studies, this study used the less-sensitive LUMI assay for PCT, rather than the Kryptor assay. PCT levels were high for bacterial pneumonia versus atypical pathogen infection (7.64 vs 0.8 μg/L, $P = .03$). However, clinical parameters and CRP levels were not able to differentiate bacterial from atypical pathogen CAP, and from a practical perspective, one would want PCT data to recommend antibiotic therapy for patients with atypical pathogen CAP. The German Competence

Network, Community Acquired Pneumonia (CAPNETZ) study evaluated the cause of CAP in 1337 patients and did not find that PCT levels could reliably separate individual patients with bacterial CAP from those with atypical pathogen CAP, although groups of patients with bacterial CAP tended to have higher PCT levels than those with atypical pathogen infections.[17] In the recent H1N1 epidemic, PCT levels in patients with pure viral infection tended to be lower than in those with bacterial pneumonia, but still, some patients with severe viral pneumonia had relatively high levels, which overlapped with levels found in patients with bacterial infection.[18] Using a PCT level of 0.1 μg/mL as the threshold, pneumococcal pneumonia was 8.3-fold more likely than CAP due to atypical or viral cause if PCT was increased. Using a PCT level of 0.25 μg/mL as threshold was not as effective; however, the likelihood of *Streptococcus pneumoniae* CAP compared with the other causes was still more than threefold if PCT exceeded this level. There were no significant differences in PCT levels, CRP levels, and WBC count in patients with atypical or viral cause of CAP.

One of the reasons that PCT may not be useful in defining the cause of CAP in individual patients is that levels are influenced not only by the identity of the pathogen but also by the severity of illness, and thus patients with severe nonbacterial pneumonia may have relatively high levels. In The CAPNETZ study, in contrast to CRP levels and WBC count, there was a marked increase in PCT levels with increasing severity of CAP.[17] In addition, bacteremia may lead to an increased level of PCT, and in one CAP study, a cutoff value of 0.25 μg/L for the initial PCT measurement identified 96% of patients with positive results of blood cultures.[19] However, a low level, as discussed above, may still indicate the safety of withholding antibiotic therapy. A confounding factor to this general rule is the use of antibiotic pretreatment. Kruger and colleagues[20] have shown that PCT and copeptin levels (pro-arginine vasopressin, a cardiac biomarker) fall rapidly after antibiotic therapy, and thus the levels of these markers may be falsely low in the setting of treated bacterial pneumonia.

One potential application of PCT would be in patients with suspected aspiration pneumonia, to separate chemical pneumonitis from bacterial pneumonia, the former possibly not requiring antibiotic therapy. In one study of 65 patients with aspiration syndrome, 32 were bacteriologically positive using bronchoalveolar lavage, but their PCT levels did not differ from that of the bacteriologically negative patients.[21] It is possible that PCT was not useful in this clinical setting, because even chemical pneumonitis is associated with a high level of inflammation, and some patients with initial chemical aspiration may still get subsequent secondary bacterial infection.[22]

BIOMARKERS TO HELP DEFINE PROGNOSIS AND SITE-OF-CARE DECISIONS IN PATIENTS WITH CAP

Predicting Prognosis and Complications

The most widely used prognostic scoring systems are the PSI and modifications of the British Thoracic Society rule, the CURB-65 and CRB-65 scores. Other tools, such as the Infectious Disease Society of America/American Thoracic Society (IDSA/ATS) criteria for severe CAP and the SMART-COP system are designed to assess the severity of illness along with the need for ICU admission or intensive respiratory and vasopressor support.[23] These systems are useful for assessing the short-term mortality of CAP, but there may also be long-term mortality consequences of this illness, which are not the result of acute infection and inflammation.[24] Several studies have evaluated the role of biomarkers alone and also in conjunction with scoring systems in predicting prognosis.

Some early investigations established the idea that PCT levels were highest in patients with more severe illness and in those who developed complications.[25] In

a group of inpatients and outpatients with CAP, PCT levels measured within 24 hours of admission were higher for those in the highest mortality risk groups (PSI classes III–V) than for those in the lowest mortality risk groups (classes I–II). In addition, PCT levels were higher in patients with pneumonia complications and mortality than in those without these consequences of infection. In general, PCT levels in this study were not influenced by the cause of CAP.[25] Similarly, serial measurements of PCT may have prognostic significance. In a study of 100 ICU-admitted patients with CAP, PCT levels were measured on days 1 and 3, and both levels were higher in nonsurvivors than in survivors.[26] In addition, levels increased over time in the nonsurvivors, whereas they decreased in survivors. In a multivariate model, an increase in PCT level from day 1 to day 3 was associated with a 4.5 odds ratio (OR) for death.

Another study examined 75 patients with radiographic CAP and found that initial PCT levels were highest in those with higher PSI class, pneumococcal infection, and bacteremia.[27] Those who developed complications (ICU admission or death) had higher PCT levels initially and serially than those who did not. In addition, midregional pro-Atrial Natriuretic Peptide (ANP), a cardiac biomarker, was better than PCT to predict mortality, and its levels also remained high on serial measurement in those with complications. The biomarkers in this study were comparable to clinical scoring systems (CURB-65 and PSI) for predicting mortality, and levels tended to be higher with higher clinical severity scores.

Levels of inflammatory biomarkers may also correlate with long-term outcomes in CAP. In a report of 1799 patients with CAP, Yende and colleagues[28] found that 17.1% died within 1 year of admission and that the risk of dying was associated with persistent inflammation at discharge, as reflected by high levels of IL-6 and IL-10. Menendez and colleagues[29] found a correlation between inflammation and treatment failure, with higher IL-6, PCT, and CRP levels on days 1 and 3 and higher IL-8 levels on day 3 as predictors of this specific complication. Similarly, Reade and colleagues[30] found that higher levels of IL-6 and IL-10 on admission correlated with a higher risk of mortality at 6 months, whereas higher TNF and d-dimer levels correlated with 1-year mortality. More recently, Kruger and colleagues[31] examined the 28-day and 180-day mortalities in 728 patients with CAP. Although PCT, CRB-65 scoring system, midregional pro-ANP, copeptin, and pro-endothelin were all predictors of mortality, the best predictor of both short-term and long-term mortalities was midregional pro-adrenomedullin (MR-proADM). MR-proADM was independent of the CRB-65 score for predicting short-term and long-term mortalities.[31] Adrenomedullin is a peptide biomarker with several biologic effects, including vasodilatation, immune modulation, and bactericidal activity and has been shown to be a prognostic marker in CAP. Levels of adrenomedullin are increased in sepsis, and levels of proADM are increased in heart failure. The finding that cardiac biomarkers, such as MR-proADM, were more predictive of mortality than inflammatory biomarkers is consistent with recent observations about the high frequency and importance of cardiac complications of CAP. Approximately 6% to 7% of patients with CAP have a concomitant myocardial infarction, and these patients have an increased mortality compared with patients without this type of event. The proinflammatory and procoagulant effects of infection may destabilize atheromatous plaque in the coronary arteries, and this may account for the high frequency of myocardial infarction and the usefulness of a cardiovascular marker such as MR-proADM for predicting long-term prognosis in patients with CAP.[32–34]

Other investigations have established a role for biomarkers in predicting the prognosis of patients with CAP. Menendez and colleagues[7] evaluated the impact of adding biomarkers to prognostic scoring, using the PSI and CURB-65, in 453 patients with CAP. They found that measurements of levels of CRP at admission added to the

prediction of prognosis from scoring systems, whereas using PCT levels did not. However, they did find that PCT levels and CRP levels both increased significantly as the severity of illness increased, as measured by the PSI and CURB-65 scoring tools. Another study of 384 patients with CAP also found that CRP levels on admission had prognostic value and that levels were higher in patients with more severe illness, as measured by the PSI. An increment of 50 mg/L CRP on admission was associated with a 1.22-fold odds for a patient to be in PSI classes III–V as compared with classes I and II. In addition, levels were higher in patients with bacteremia than in those without and in those with complications (empyema, ICU admission, and death) than in those without.[35] In addition, if CRP levels were greater than 100 mg/L on day 4 after the admission, there was a significant increase in the rate of complications ($P<.01$).

Other studies of biomarkers to define the prognosis in CAP have evaluated the relative value of the prognostic information provided by PCT and CRP levels. One study found that among 1671 patients in the German CAPNETZ study, elevated PCT levels on admission helped to identify patients who had a high risk of dying up to 28 days and that the predictive value of PCT was comparable to that of CRB-65 and more accurate than measurements of levels of CRP.[36] In addition, PCT had a high negative predictive value, and when levels were less than 0.228 ng/mL, there was an almost 99% predictive value that the patient would not die. In addition, another study of 88 patients with CAP found that PCT levels on admission were more valuable than CRP levels to predict severity of illness.[37] In that study, although the sensitivity of CRP for predicting severe illness was higher than that of PCT, the specificity and positive and negative predictive values of PCT were substantially higher than the respective values for CRP. Similarly, a Korean study found that measurement of PCT in the ED was useful for predicting 28-day mortality and that it added to the predictive value of prognostic scoring tools to a much greater extent than measuring the levels of CRP was able to do.[38]

Thus, many studies have shown that measurement of levels of CRP on admission has limited prognostic information. However, as suggested above, serial measurements of CRP levels may be more valuable, especially in patients with severe CAP. Investigators from Portugal[39] have used serial measurements to define 3 patterns of CRP response to therapy: fast decline, slow decline, and nonresponse. They have found that survival was related to the rate of decline in CRP levels and that a level at day 5 that exceeds 50% of the level at day 1 was associated with increased mortality. In this study, of 191 patients in the ICU with CAP, 66 had a fast decline in CRP levels and a 4.8% mortality, 81 had a slow decline and a 17.3% mortality, and 44 had no response and a mortality rate of 36.4%.

Although PCT may be more valuable for predicting CAP prognosis than CRP, other biomarkers have also been studied and shown to be of value for this purpose. Studies have shown that increased levels of pro-adrenomedullin, copeptin, natriuretic peptides, and cortisol are significantly related to mortality in CAP, along with other prohormones such as pro-atrial natriuretic peptide and coagulation markers.[40] Bello and colleagues[41] performed a prospective study of 228 patients to assess the prognostic value of MR-proADM and found that levels of this biomarker increased with increasing disease severity and that the prognostic information provided was independent of the cause. PCT was the only biomarker that showed significant differences ($P<.0001$) between bacterial and viral/atypical CAP. In the study, MR-proADM predicted both short-term and long-term mortalities and was the only biomarker that discriminated between patients who died versus those who survived at 30, 90, and 180 days and 1 year. Thus, whereas PCT has value in deciding when to start antibiotics (with levels being higher in bacterial vs viral infection), MR-proADM cannot serve this purpose but provides much more discriminating information about the prognosis in CAP, both short and long term.

Defining Site of Care

The ability of biomarkers to refine the prognostic information provided by scoring systems may also be valuable in deciding whether an admitted patient needs to be treated in the ICU or on a medical floor. Ramirez and colleagues[42] evaluated 627 patients with CAP admitted to a medical ward and 58 additional patients admitted to the ICU. The investigators found that admission levels of PCT, CRP, IL-6, and TNF-α were higher in patients in the ICU than in those in the ward. However, for predicting the need for ICU admission, the IDSA/ATS criteria were the most accurate, with an OR of 12, but of all the biomarkers, PCT (value >0.35 ng/mL) was the most accurate with an OR of 6.9. Interestingly, of the 78 patients who met 3 of the IDSA/ATS minor criteria for severe CAP, no patient needed ICU admission if the PCT level was less than 0.35 ng/mL, but 23% with elevated PCT levels in this group did need ICU admission. There were also 10 patients admitted to the ICU without severe CAP criteria present, and 8 of them had elevated PCT levels. Of the group admitted to the ICU, 36 were admitted directly and had a 17% mortality, compared with the 27% mortality in the 22 with delayed admission. The patients with delayed ICU admission had higher PCT values than those who remained in the ward. Thus, admission PCT levels might be examined along with other clinical criteria for ICU admission and could be used to potentially avoid delayed ICU admission for patients with high levels and also to avoid using the ICU for low-risk patients who have low PCT levels, in spite of the presence of other clinical signs of severe CAP.

The finding that low levels of biomarkers could be used to avoid ICU admission for patients who have clinical signs of more severe illness was also corroborated in several other studies. Kruger and colleagues[36] found that when the PCT level was 0.228 ng/mL or less, mortality was low, regardless of the score on the CRB-65 scale, and that the negative predictive value for mortality of PCT at this level was 98.9%. Similarly, Huang and colleagues[43] found 546 patients with CAP in PSI class IV and V, but there were 126 who had PCT levels in the lowest quartile (<0.1 ng/mL) and only 2 of these patients (1.6%) died. When MR-proADM levels were measured in the same population, the finding of a level in the lowest quartile was less useful than the finding of a PCT level in the lowest quartile for defining patients at low risk of death.[44]

USING BIOMARKERS TO GUIDE THE DURATION OF CAP THERAPY

As discussed, measurement of levels of biomarkers, especially PCT, can help clinicians decide when to use antibiotics in a patient with CAP and levels measured at the time of admission, and serially, can help to define prognosis and the likelihood of disease-related complications (**Table 1**). Because a reduction in PCT indicates a good prognosis and a good response to therapy, several studies have examined whether serial measurements of PCT can be used to define the optimal duration of antibiotic therapy for CAP. In general, these studies have shown that PCT guidance can reduce the duration of antibiotic therapy, without adverse effects on the patient, compared with the use of clinical assessment to define the duration of CAP therapy.[44,45]

In the ProCAP study, 302 patients with radiographic pneumonia in a single center were randomized to either PCT-guided duration of antibiotic therapy or a control group with clinical guidance only.[11] In the 151 PCT patients, duration of therapy was based on serial PCT levels measured on admission, at 6 to 24 hours (if therapy was initially withheld) and days 4, 6, and 8. Using PCT values, therapy was strongly discouraged if the level was less than 0.1 μg/L, discouraged if the levels was 0.25 μg/L, encouraged if the

Table 1
Randomized controlled trials of PCT to guide duration of therapy in patients with CAP seen in the hospital

Author (Year) (Reference)	Number of Patients PCT (P) Control (C)	Setting	Duration of Therapy PCT	Duration of Therapy Control	Mortality
Christ-Crain et al,[10] 2004	42 (P) 45 (C)	Single center, ED	90.4% given antibiotics	97.8% given antibiotics	<5% in both groups
Christ-Crain et al,[11] 2006	151 (P) 151 (C)	Single center, ED	5 days (median)	12 days (median)	10% (P) 10% (C) Pneumonia related
Schuetz et al,[12] 2009	460 (P) 465 (C)	6 hospitals ED	7 days (median)	10 days (median)	5.2% (P) 5.6% (C)
Bouadma et al,[46] 2010	79 (P) 101 (C)	7 ICUs, Infection suspect	5.5 days (P) (mean)	10.5 days (mean)	16.9% (P) 19.0% (C) Not all were pneumonia in these data

levels 0.25 μg/L or more, and strongly encouraged if the level was 0.5 μg/L or more. In all instances, clinical assessment could be used to override the guidance suggested by the PCT measurement. Patients in the PCT group had a duration of therapy that was 55% shorter than that of the control population and the median duration was reduced to 5 days, compared with 12 days for the control population. After 4 days, approximately 50% of patients in the PCT group were receiving therapy, compared with over 90% in the control group; after 8 days, less than 20% in the PCT group were receiving therapy compared with greater than 80% in the control group. In patients with CAP of varying severity, PCT guidance led to a shorter duration of therapy than was seen in the control group, but for patients with mild CAP (PSI class I–III), duration of therapy was lower with PCT guidance than for patients with moderate to severe CAP (PSI classes IV and V) who had PCT guidance. At follow-up 4 to 6 weeks after admission, failure rates were the same for patients with PCT guidance as for the control group.

A similar randomized trial design was used in the multicenter (6 Swiss hospitals) proHOSP study, which included 925 patients with CAP.[12] When using PCT guidance, serial measures were used in the manner listed for the proCAP study and for patients with a high initial level, greater than 10 μg/L, therapy was urged to be stopped when the value decreased by more than 80% from the initial value. For patients with severe CAP, clinical assessment could lead to overriding the recommendation that followed from PCT measurement. In that study, 78% of the PCT-guided group and 90% of the control group, who were hospitalized, were initially treated with antibiotics. At day 5, 60% of the PCT-guided group and 90% of the control group were receiving antibiotics and the duration of therapy was reduced from 10.7 days for the control group to 7.2 days for the PCT group. Adverse outcomes occurred at the same rate in both groups, and mortality was low, approximately 5% to 6% in both groups. A similar approach has been used in a prospective randomized study of critically ill patients that included nearly 200 patients with CAP.[46] In that study, PCT guidance led to a reduction in antibiotic duration to 5.5 days, compared with 10.5 days for the control group.

In all these studies, there were no adverse events that could be related to the reduced duration of therapy that followed PCT guidance. Similarly, in a recent meta-analysis, Schuetz and colleagues[47,48] used individual patient data to perform a meta-analysis and concluded that in more than 2000 patients with CAP (inpatients and outpatients) studied with a randomized trial design, PCT guidance led to significantly fewer patients being started on antibiotics (90% vs 99%) as well as a substantial reduction in antibiotic use (7 days vs 10 days median duration), but that it had no impact on mortality and was associated with a significant reduction in the rate of treatment failure (19% vs 23.4%).

CONCLUSIONS: HOW AND WHEN TO USE BIOMARKERS IN CAP

Biomarkers are a promising tool for the management of CAP and can supplement the information provided by routine clinical assessment and commonly used prognostic scoring tools. Among the available biomarkers, PCT has been studied extensively in recent years, and several clinical trials have established its utility in CAP management, particularly if the highly sensitive Kryptor assay is used. PCT levels can be measured at the time of initial evaluation, and values can help to predict the presence of radiographic CAP and the need for antibiotic therapy. The latter is driven by the general finding that levels of PCT, an acute-phase reactant produced by many cell types, particularly the liver, rise with bacterial infection and fall with viral illness. However, PCT levels do rise with severe illness and may not be able to distinguish whether

influenza is, or is not, complicated by secondary bacterial infection, and similarly, may not be able to distinguish chemical from bacterial aspiration syndromes. In the management of pneumonia, serial measurements of PCT levels can be used to guide duration of therapy, and the use of PCT guidance has led to a reduction in antibiotic use and duration, without adverse consequences to the patient.

Several biomarkers have been measured on admission and serially, to define the prognosis of patients with CAP, and the findings can supplement the information provided by traditional prognostic scoring tools. Levels of biomarkers tend to be higher in patients with more severe illness, and the pattern of serial change may have prognostic value, a finding that has been demonstrated for CRP. When PCT levels are low, prognosis in CAP is generally good, regardless of the severity of illness as defined by prognostic scoring tools such as the PSI. In predicting the long-term prognosis of patients with CAP, cardiac biomarkers, such as MR-proADM, are more valuable than inflammatory biomarkers, pointing to the important interaction between pneumonia and secondary heart disease.

In the future, biomarkers may help to streamline the care of patients with CAP, but as with any laboratory tool, the findings need to be moderated by clinical assessment and the results of biomarker testing need to be ignored if in conflict with a careful clinical evaluation.

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