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.