Incidence, Etiology, Timing, and Risk Factors for Clinical Failure in Hospitalized Patients With Community-Acquired Pneumonia*

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Background: **The etiology of clinical failure in hospitalized patients with community-acquired pneumonia (CAP) may be related or unrelated to pulmonary infection. The objective of this study was to define the incidence, etiology, timing, and risk factors associated with clinical failures related to CAP vs those unrelated to CAP.**

Methods: **Observational retrospective study of consecutive CAP patients. All patients who experienced clinical failure were identified. Cases were presented to a review committee that defined, by consensus, etiology, timing, and risk factors for clinical failures related to CAP.**

Results: **Among 500 patients who were enrolled in the study, clinical failure was identified in 67 (13%). Clinical failure was related to CAP in 54 patients (81%). The most common etiologies for clinical failure related to CAP were severe sepsis (33%), acute myocardial infarction (28%), and progressive pneumonia (19%). All cases of severe sepsis occurred in the first 72 h of hospitalization. The most common etiology for clinical failure unrelated to CAP was the development of hospital-acquired pneumonia (45%). At the time of hospital admission, factors associated with clinical failure related to CAP were advanced age, congestive heart failure, hypotension, abnormal gas exchange, acidosis, hypothermia, thrombocytopenia, and pleural effusion.**

Conclusions: **The development of severe sepsis early during hospitalization is the primary etiology for clinical failure related to CAP. To achieve early treatment intervention, physicians should maintain a high index of suspicion for severe sepsis in hospitalized patients with CAP. To decrease the number of clinical failures unrelated to CAP, interventions need to be developed at the local level to improve the processes of care for patients with pneumonia.** ***(CHEST 2008; 134:955–962)***

Key words: pneumonia; respiratory failure; septic shock

Abbreviations: APACHE = acute physiology and chronic health evaluation; ATS = American Thoracic Society; CAP = community-acquired pneumonia; CURB-65 = confusion, urea level > 7 mmol/L, respiratory rate ≥ 30 breaths/min, systolic BP < 90 mm Hg or diastolic BP ≤ 60 mm Hg, or age ≥ 65 years; IDSA = Infectious Diseases Society of America; LOS = length of stay; PSI = pneumonia severity index

Up to 5.6 million cases of community-acquired pneumonia (CAP) occur annually in the United States, and > 1 million patients require hospitalization.[1] Once antimicrobial treatment has been initiated, patients who have been hospitalized with CAP can improve and reach clinical stability or can experience a lack of clinical response.[2] Among those with a lack of response, patients in whom clinical deterioration develops are characterized as experiencing clinical failure. The incidence of clinical failure in patients with CAP ranges from 6 to 24%,[3–7] and can reach up to 31% in patients with severe CAP.[8] When a lack of treatment response occurs in patients with CAP, it significantly increases the risk of complications, length of hospital stay, and death, especially in patients with severe CAP.[3,8]

Although clinical failure and mortality are the most relevant outcomes in patients with CAP, there

is little discussion in the literature about incidence and etiology. A review of the current literature indicated that investigators have used different approaches to evaluate the etiology of clinical failure and mortality in patients with CAP. Using a microbiological approach, clinical failure has been characterized as having an infectious vs a noninfectious etiology.[3,6] An approach based on the interactions among the host, the pathogen, and the drug has been used[7] to characterized clinical failure as being host related, pathogen related, or drug related. Using a pathophysiologic approach, mortality has been characterized[9] as CAP related vs CAP unrelated, considering the role that the pulmonary infection and inflammatory response played in the development of the outcome. The authors found that CAP-related mortality was significantly different from CAP-unrelated mortality regarding timing and risk factors. Based on these findings, it was suggested that future studies evaluating the quality of pneumonia care should use a strategy to differentiate between pneumonia-related and pneumonia-unrelated outcomes. No prior investigation has characterized clinical failure as being related to CAP vs unrelated to CAP; therefore, we designed a study with the objective of defining the incidence, etiology, timing, and risk factors associated with clinical failure related to CAP and unrelated to CAP.

Methods and Materials

Study Design and Study Patients

This was an observational, retrospective study of consecutive patients who were admitted with a diagnosis of CAP to the Veterans Affairs Medical Center of Louisville, KY, between June 2001 and March 2006. Patients enrolled in this study are part of the Community-Acquired Pneumonia Organization database.[10] The study protocol and data collection form are available on the study Web site (www.caposite.com). The institutional review board of the Veterans Affairs Medical Center approved the study. Patients who were ≥ 18 years of age and satisfied the criteria for CAP were included in this study.

The records of all enrolled patients were reviewed. Data, including demographic information, clinical data on hospital admissions, radiologic findings, and laboratory values, were collected. The severity of pneumonia was evaluated by the pneumonia severity index (PSI)[11] and CURB-65 (confusion, urea level > 7 mmol/L respiratory rate ≥ 30 breaths/min, systolic BP < 90 mm Hg or diastolic BP ≤ 60 mm Hg, or age ≥ 65 years) scores[12]; microbiological and in-hospital treatment data; and autopsy results.

A microbiological workup with testing of sputum samples, blood cultures, testing of tracheal aspirates, testing of pleural fluid, BAL, serology for atypical organisms and urine antigens for Legionella spp and *Streptococcus pneumoniae* were performed according to standard clinical practice. The identification of microorganisms and susceptibility testing were performed according to standard methods.[13] The empirical antibiotic treatment was evaluated for compliance with the American Thoracic Society (ATS)/ Infectious Diseases Society of America (IDSA) guidelines for CAP.[2]

Study Definitions

CAP was defined as the presence of a new pulmonary infiltrate on a chest radiograph at the time of hospitalization that was associated with at least one of the following: (1) new or increased cough; (2) an abnormal temperature (< 35.6°C or > 37.8°C); (3) an abnormal serum leukocyte count, which is considered to be present if the patient had leukocytosis (leukocyte count, > 10.500 cells/μL), leucopenia (leukocyte count, < 4.500 cells/μL), or left shift (> 5% immature neutrophils). *Severe CAP* at the time of hospitalization was defined according to the latest ATS guidelines.[2]

The time to clinical stability was calculated as the number of days from the date of hospital admission to the date that the patient met clinical stability criteria. *Clinical stability* was defined according to the ATS guidelines for CAP.[2] The criteria for clinical stability were evaluated daily during the first 7 days of hospitalization.

Length of stay (LOS) was calculated as the number of days from the date of hospital admission (day 0) to the date of hospital discharge. LOS was censored at 14 days in an effort to capture only CAP-related LOS.

In-hospital mortality was defined as death by any cause during hospitalization. Patients were followed up from the day of hospital admission to day 28; those patients who remained hospitalized for > 28 days were considered to be alive.

Clinical failure was considered if any of the following took place after the patient was transferred from the emergency department to the ward or to the ICU, and after initial stabilization: (1) acute pulmonary deterioration with the need for either invasive or noninvasive mechanical ventilation; (2) acute hemodynamic deterioration with the need for aggressive fluid resuscitation (*ie*, > 40 mL/kg colloids or crystalloids), vasopressors, or invasive procedures (*eg*, pericardial drainage or electrical cardioversion); and (3) in-hospital death up to 28 days after hospital admission. The presence of severe CAP or septic shock at the time of the hospitalization was not considered to be a criterion for clinical failure.

Early clinical failure was defined as clinical failure occurring ≤ 3 days after hospital admission. *Late clinical failure* was defined are clinical failure occurring > 3 days after hospital admission.

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