CHEST

Original Research

PNEUMONIA

Delayed Administration of Antibiotics and Atypical Presentation in Community-Acquired Pneumonia*

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Objectives: **The time to the first antibiotic dose (TFAD) has been adopted as a measure of quality of care in patients with community-acquired pneumonia (CAP) based on two retrospective studies of large Medicare databases. The mechanism by which a difference of a few hours in receiving antibiotics can be deleterious is difficult to understand given the historical data regarding how long it takes for antibiotics to influence outcome. We investigated the factors that predict a prolonged TFAD and their association with mortality.**

Design: **Prospective cohort study.**

Setting: **A large tertiary hospital.**

Patients: **Immunocompetent adults admitted to the hospital with CAP.**

Results: **A total of 451 patients with CAP were studied. A TFAD of > 4 h was associated with increased mortality ($p = 0.017$). Altered mental state ($p = 0.001$), absence of fever ($p = 0.02$), absence of hypoxia ($p = 0.025$), and increasing age ($p = 0.038$) were significant predictors of a TFAD of > 4 h. After adjusting for these factors, the association between TFAD and mortality was not statistically significant ($p = 0.131$). Similar findings were observed in patients who were ≥ 65 years.**

Conclusions: **A delay in administering antibiotics in patients with CAP is more common in patients who present with an altered mental state or minimal signs of sepsis. TFAD is likely to be a marker of comorbidities driving both an atypical presentation and mortality rather than directly contributing to outcome. Using TFAD as an indicator of quality of care in patients with CAP without significant additional clinical information is potentially misleading as the relationships among TFAD, comorbidities, and outcome are complex.** ***(CHEST 2006; 130:11–15)***

Key words: age; altered mental state; antibiotics; community-acquired pneumonia; presentation; time

Abbreviations: CAP = community-acquired pneumonia; CI = confidence interval; OR = odds ratio; PSI = pneumonia severity index; TFAD = time to first antibiotic dose

Community-acquired pneumonia (CAP) is a major health problem in the United States. As well as being the seventh leading cause of death, the estimated financial cost of treating CAP in the United States exceeds 12 billion dollars per year.[1]

Two retrospective analyses[2,3] of large Medicare databases identified the time between presentation to the hospital and the time to the first antibiotic dose (TFAD) as a significant predictor of outcome.

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Both of these studies have inconsistencies, particularly the higher mortality rate among those receiving antibiotics within 2 h. However, the findings of these studies have convinced national regulatory bodies in the United States to make TFAD a benchmark for quality of care in patients with CAP.[4]

A reasonable biological explanation for why a difference of a few hours in antibiotic administration should lead to a better outcome has not been established. Historical data strongly indicate that

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antibiotics take several days to impact on outcome from pneumococcal pneumonia.[5] Possible explanations include confounding factors inadequately accounted for in the retrospective database reviews and TFAD being a surrogate marker for other quality-of-care factors.

While the use of large Medicare databases has advantages with respect to statistical power and the ability to generalize findings across broader populations, clear disadvantages occur with respect to the loss of detailed individual clinical data and the loss of surety of diagnosis inherent in prospective clinical trials. We analyzed our prospectively collected cohort of patients with CAP specifically examining the clinical factors influencing TFAD.

Materials and Methods

Study Design

A prospective cohort of patients admitted to the Methodist Healthcare-Memphis Hospitals with CAP between November 1998 and July 2001 was recruited. Informed consent was obtained from all patients. The Methodist Healthcare Institutional review board approved the study.

Inclusion Criteria

Consistent with published guidelines,[6] CAP was defined as an acute illness (< 14 days of symptoms) in which the presence of a new chest radiographic infiltrate was confirmed by either a radiologist or a pulmonary/critical care physician, and having clinical features suggestive of acute pneumonia. The clinical features required for diagnosis were one feature from group A (fever [temperature of > 37.8°C], hypothermia [temperature of < 36°C], cough, and sputum production), or two features from group B (dyspnea, pleuritic pain, physical findings of lung consolidation, and leukocyte count of $> 12 \times 10$ cells/L or $< 4.5 \times 10$ cells/L).

Exclusion Criteria

Exclusion criteria included patients with HIV infection, those receiving chemotherapy or who had received immunosuppressive therapy in the past 60 days (including prednisolone, ≥ 20mg/d for > 7 days), nonambulatory nursing home residents, and patients who have been hospitalized within the past 30 days.

Definitions

The TFAD was defined as the time difference between the recorded time on presentation to triage in the emergency department and the recorded time of administration of the first dose of antibiotics by the nursing staff. Pneumonia severity index (PSI) scores[7] were calculated at the time of the patient's admission to the hospital. Septic shock was defined using American College of Chest Physicians/Society of Critical Care Medicine criteria.[8] Hypoxia was defined as an oxygen saturation of < 90% while breathing room air. An altered mental state was defined as any disorientation in time, place, or person including any Glasgow coma scale score of < 15.

Statistical Analysis

Logistic regression analysis was used to assess the impact of clinical factors on TFAD. Significant interactions were included in all models at a threshold of $p < 0.1$. Analysis was performed using a statistical software package (SPSS, version 11.5.0; SPPS Inc; Chicago, IL). A p value of < 0.05 was considered to be significant.

Results

A total of 451 patients were enrolled into the study. The cohort had a mean (±SD) age of 58.2 ± 19.2 years, 53.3% were women, and the severity breakdown by PSI grade was as follows: grade I, 11.3%; grade II, 22.2%; grade III, 18.9%; grade IV, 20.4%; and grade V, 8.7%. The mean TFAD was 285 ± 202 min, with 50.7% of patients not receiving their first dose within 4 h. Of those patients with a TFAD of < 4 h, 32.0% were given antibiotics within 2 h of presentation. Death occurred in 36 patients (8.0%).

We next analyzed the data points on the PSI predicting a TFAD of > 4 h. Table 1 summarizes the significant findings. Various age cutoffs were as-

Table 1—*Factors Predicting a Delay in Antibiotic Delivery of > 4 h*

Factor	OR (95% CI)	p Value
Altered mental state	2.89 (1.53–5.45)	0.001
Absence of hypoxia	1.82 (1.09–3.04)	0.022
Absence of fever	1.59 (1.06–2.40)	0.025
Age	1.01 (1.00–1.06)	0.038
Cerebrovascular disease	1.09 (0.56–2.14)	0.351
Congestive cardiac failure	0.79 (0.47–1.31)	0.791
Renal disease	0.87 (0.43–1.74)	0.406
Liver disease	0.89 (0.37–1.91)	0.851
Nursing home resident	3.24 (0.32–32.60)	0.294
Absence of shock	1.76 (0.46–6.72)	0.405
Tachycardia > 125 beats/min	1.30 (0.84–2.02)	0.245
Respiratory rate > 30 breaths/min	1.25 (0.71–1.86)	0.288

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