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Original Article

Time to antibiotics administration and outcome in community-acquired pneumonia: Secondary analysis of a randomized controlled trial

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ABSTRACT

Background: The association between early antibiotic administration and outcomes remains controversial in patients hospitalized for community-acquired pneumonia.
Methods: We performed a secondary analysis of a randomized controlled trial comparing two antibiotic treatment strategies for patients hospitalized for moderately severe CAP. The univariate and multivariate associations between time to antibiotic administration (TTA) and time to clinical stability were assessed using a Cox proportional hazard model. Secondary outcomes were death, intensive care unit admission and hospital readmission up to 90 days.
Results: 371 patients (mean age 76 years, CURB-65 score ≥ 2 in 52%) were included. Mean TTA was 4.35 h (SD 3.48), with 58.5% of patients receiving the first antibiotic dose within 4 h.
In multivariate analysis, number of symptoms and signs (HR 0.876, 95% CI 0.784–0.979, $p = 0.020$), age (HR 0.986, 95% CI 0.975–0.996, $p = 0.007$), initial heart rate (HR 0.992, 95% CI 0.986–0.999, $p = 0.023$), and platelets count (HR 0.998, 95% CI 0.996–0.999, $p = 0.004$) were associated with a reduced probability of reaching clinical stability. The association between TTA and time to clinical stability was not significant (HR 1.009, 95% CI 0.977–1.042, $p = 0.574$). We found no association between TTA and the risk of intensive care unit admission, death or readmission up to 90 days after the initial admission.
Conclusion: In patients hospitalized for moderately severe CAP, a shorter time to antibiotic administration was not associated with a favorable outcome. These findings support the current recommendations that do not assign a specific time frame for antibiotics administration.

1. Background

Timely administration of appropriate antibiotic treatment is a critical determinant of success in the care of patients with severe sepsis or septic shock [1]. Community-acquired pneumonia (CAP) is the most frequent cause of sepsis and septic shock, and there is a consensus that patients with severe CAP should be treated as soon as possible. However, the link between time to antibiotic (TTA) and outcomes in patients presenting with moderately severe CAP (requiring hospital but not Intensive Care Unit admission) is debated. Earlier antibiotic administration might mitigate host inflammatory response and organ damage by reducing bacterial load. Nevertheless, historical studies have shown that antibiotics take several days to impact on outcomes among patients with pneumococcal pneumonia [2]. A few observational studies have reported an association between delayed treatment and worse outcomes in CAP [3–4]. However, since delayed administration of antibiotics is also related to patient characteristics, illness presentation, and quality of care, a causal link remains uncertain and this association might be due to confounding. The evidence supporting a causal relation between time to antibiotic administration and patient outcomes is low and the potential benefit of early antibiotic treatment may be balanced by an increase in CAP misdiagnosis and antibiotic overuse [5–6]. Moreover, competing needs in a busy emergency department demand prioritization of interventions clearly benefitting patient's outcome.

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These uncertainties have led the Infectious Disease Society of America and American Thoracic Society to de-emphasize the importance of the time to antibiotic administration in their more recent guidelines and to recommend the administration of the first antibiotic dose while the patient is still in the emergency department, without time frame specification [7].

We aimed to further explore this controversial question in a secondary analysis of a randomized-controlled trial on CAP antibiotic treatment.

2. Methods

We performed a secondary analysis of a multicenter randomized-controlled trial (RCT) comparing two antibiotic treatment strategies for CAP patients admitted to the ward [8]. (ClinicalTrials.gov: NCT00818610) Pneumonia was defined as the presence of two or more symptoms or signs of respiratory tract infection and presence of a pulmonary infiltrate on chest x-ray. Patients with severe CAP (PSI category V, three or more minor criteria on the 2007 ATS rule [7], need for immediate intensive care unit admission), immunosupression or living in a nursing home, were excluded.

Time to antibiotics (TTA) was defined as the time between emergency department registration and time of administration of the first dose of antibiotics, expressed in hours.

The primary outcome, time to clinical stability (TCS) was defined as the time between the first antibiotic dose and the first time the following criteria were reached and maintained for a minimum of 24 h: heart rate <100 bpm, systolic blood pressure >90 mm Hg, tympanic temperature <38·0 °C, respiratory rate <24/min, and oxygen saturation by pulsoxymetry >90% on room air. Secondary outcomes were ICU admission, in hospital, 30-day and 90-day mortality, and 30-day and 90-day readmission. These outcomes were prospectively recorded as part of the primary study, as were demographic characteristics, co-morbidities, symptoms, vital signs and laboratory values. Signs and symptoms recorded were new or increasing cough, fever (>38.0C), purulent sputum, pleuretic chest pain, new or increasing dyspnoea, tachypnoea (>18/min), focal findings on chest auscultation. As the presence of a high burden of symptoms or typical signs of pneumonia is likely to influence both the rapidity of treatment and the prognosis, we defined a corresponding explanatory variable by simply adding one point for the presence of each of the aforementioned sign or symptom. Hypoxemia was defined as oxygen saturation ≤90% while breathing room air or need for supplemental oxygen.

We used frequencies, proportions, medians with interquartile range (IQR) and means with standard deviation (SD) for descriptive statistics. Hypothesis testing used two-sided tests and a significance level of 0.05. Differences between proportions were tested using Fisher's exact test or Chi square test as needed. Differences between means were tested by ANOVA.

Associations between TTA and characteristics of the population are provided in a descriptive purpose. The association between TTA and the primary outcome (TCS) was tested using univariate and multivariate Cox proportional hazard models. Potential confounding variables associated in univariate with time to clinical stability with a $p < 0.10$ were introduced in the multivariable model together with TTA. CURB-65 score was used to control for the severity of disease [9]. Heterogeneity of the relation between TTA and time to clinical stability in different severity strata was tested by introducing an interaction term in the model.

Some of the predictor variables (initial heart rate, respiratory rate, and hypoxemia) are also components of the independent variable, time to clinical stability, which can lead to incorporation bias. We therefore conducted a sensitivity analysis excluding these variables from the multivariate model. A second sensitivity analysis was conducted excluding patients treated with oral antibiotics before admission, or with inappropriate initial antibiotic treatment, defined as patients with an identified pathogen who was resistant to the treatment initially prescribed.

For the secondary outcomes, we stratified the population using a TTA of more or <4 h, a cut-off used in several studies and near the mean TTA of our population. Differences between strata were tested using Fisher's exact test or Chi square test as needed.

3. Results

Time of antibiotic administration was available in two of the six centers participating to the original study, one university hospital and one university-affiliated community hospital. The two hospitals included a total of 371 patients (64% of the original population), who form the population of the present analysis. Two hundred and eight of them were women (56.1%) and mean age was 76 years (IQR 65–84). Twenty-one patients (5.7%) had been treated with oral antibiotics before admission, for <24 h. CURB-65 score was ≥2 in 192 patients (52%). Twenty-nine patients (7.8%) had bacteraemia. Mean TTA was 4.35 h (SD 3.48), with a median of 3.3 h (IQR 2.1–5.9). TTA was longer than eight hours in 53 patients (14%). Two hundred and seventeen patients (58.5%) received the first antibiotic dose within four hours after arrival. The initial treatment was found inappropriate in 16 patients (4.3%).The presence of fever was associated with a significantly shorter TTA. The association between patient characteristics and TTA is reported in Table 1.

Mean time to clinical stability was 6.0 days (SD 6.2), with a median of 4 days (IQR 2.0–7.5). Univariate and multivariate associations between predictor variables and time to clinical stability are displayed in Table 2. Eight variables were associated with time to clinical stability with a p value < 0.10 in univariate: CURB-65 score, number of co-morbidities, number of symptoms and signs, age, heart rate, respiratory rate, presence of hypoxemia, and platelets count. The hazard ratio (HR) was less than one in all the significant variables, implying a decreased probability of reaching stability for each increment of these variables. Conversely, no significant association was observed between TCS and TTA in univariate analysis (HR 1.015; 95%CI 0.985 to 1.046).Other

Table 1
Characteristics of the patients and time to antibiotics (TTA).

Variable (number)	Mean TTA in hours (SD)	*P* value
Age by quartile (years)		0.149
21–65 (100)	4:50 (3:58)	
66–76 (96)	3:49 (2:58)	
77–83 (81)	4:42 (4:34)	
84–101 (94)	4:59 (3:38)	
Number of co-morbidities		0.462
0 (138)	4:17 (3:28)	
1 (116)	4:53 (4:04)	
2 or more (117)	4:37 (3:46)	
CURB 65 score[a]		0.591
0 (50)	4:41 (3:26)	
1 (129)	4:47 (4:13)	
2 (140)	4:14 (3:17)	
3 or more (52)	4:54 (4:24)	
Temperature (°C)		0.002
≤37.0 (56)	5:10 (4.17)	
37.1–38.0 (109)	5:31 (4:10)	
38.1–38.5 (93)	4:15 (3:36)	
≥38.6 (113)	3:40 (3.04)	
Heart rate		0.070
≤85 (93)	5:23 (3:45)	
86–97 (93)	4:38 (3:45)	
98–110 (95)	4:20 (4:01)	
≥111 (90)	3:56 (3:37)	
Respiratory rate		0.433
≤20 (108)	4:42 (4:04)	
21–24 (94)	4:55 (3:52)	
25–28 (86)	4:21 (3:36)	
≥29 (75)	4:00 (3:34)	

[a] CURB-65: one point for each of confusion, urea > 7 mmol/L, respiratory rate > 30/', blood pressure < 90 mm Hg (systolic) or 60 mm Hg (diastolic), and age ≥ 65 years

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