STUDY PROTOCOL

Suitability of Antibiotic Treatment for CAP (CAPTIME)

Purpose

The duration of antibiotic treatment in community-acquired pneumonia (CAP) lasts about 9-10 days, and is determined empirically. The last North American guideline for CAP recommends using clinical stability criteria as a reference to establish the duration of antibiotic treatment, which would result in about 5 days of antibiotic use for the majority of pneumonia cases. In order to validate this proposal we propose to carry out a randomized multicenter double-blind (until the 5th day) clinical trial with adult CAP patients admitted to 4 hospitals in Euskadi. A control group (with routine treatment) will be compared with an intervention group (antibiotic treatment for at least 5 days, which will be interrupted if temperature is =< 37,8ºC for at least 48 hours and no more than one sign of clinical instability is assessed), with regards to: clinical recovery by days 10 and 30, clinical improvement after days 5 and 10 as evaluated by PRO scales, duration of antibiotic treatment. A non-inferiority dichotomous sequential analysis will be performed (clinical recovery by day 10 and in follow-up at 30 days, clinical improvement after days 5 and 10, with PRO scales) as well as a superiority analysis for the duration of the antibiotic treatment. Stability criteria will be measured daily. The rest of the variables will be measured at admission and by telephone on days 10 and 30.

Study design

Study Type: Interventional

Study Design:	Allocation: Randomized

Endpoint Classification: Efficacy Study

Intervention Model: Parallel Assignment

Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)

Intervention group:

Patients randomized at day 5 to an intervention or a control group. Those in the intervention group are treated with antibiotics for a minimum of 5 days and the antibiotic treatment is stopped at this point if their body temperature is ≤37.8°C for 48 hours and they have no more than one CAP-associated sign of clinical instability defined as: systolic blood pressure <90 mmHg, heart rate >100 beats/min, respiratory rate >24 breaths/min, arterial oxygen saturation <90% or PaO_2 <60 mmHg in room air.

Control group:

Duration of antibiotics in the control group is determined by physicians as in routine clinical practice.

Eligibility

Patients ≥ 18 years old, hospitalized with a diagnosis of CAP. Pneumonia is defined as pulmonary infiltrate on chest X-ray not seen previously plus at least one symptom compatible with pneumonia such as cough, fever, dyspnea, and/or chest pain.

Exclusion criteria:

- Infected by the human immunodeficiency virus.

- Chronically immunosuppressed (defined as immunosuppression for solid organ transplantation, post-splenectomy, receiving ≥ 10 mg/day of prednisone or the equivalent for >30 days, being on other immunosuppressive agents, or having neutropenia, i.e., <1.0 x10^9/L netrophils)

- Lived in a nursing home

- Had been discharged from an acute care hospital, an onsite subacute care unit, or a palliative care unit within the previous 14 days.

- Had already taken antibiotics in the 30 days prior to admission.

- Required a longer duration of therapy due to an uncommon etiology (*P. aeruginosa,* or *S. aureus*, among others).

- Required a chest tube.

- Condition complicated by extrapulmonary infection, such as meningitis or endocarditis.

- Admitted to the Intensive Care Unit (ICU) before randomization.

- Declined to participate or give inform consent.

Primary Outcome Measures:

- Clinical cure [Time Frame: 10 days] [Designated as safety issue: No]:

resolution or improvement of symptoms and clinical signs related to pneumonia without a need for additional or alternative antibiotic treatment.

- Clinical cure [Time Frame: 30 days] [Designated as safety issue: No]:

resolution or improvement of symptoms and clinical signs related to pneumonia without a need for additional or alternative antibiotic treatment.

- CAP-related symptoms at days 5 and 10 measured with the 18-item CAP symptom questionnaire, a specific and validated patient-reported outcome measure, on which higher scores indicate more severe symptoms (range, 0 to 90).

Secondary Outcome Measures:

- Duration of the antibiotic treatment [Time Frame: 30 days] [Designated as safety issue: No]

- Days that the patient takes an antibiotic treatment, adding intravenous and oral.

- In-hospital mortality for any cause [Time Frame: 30 days] [Designated as safety issue: No]

- Mortality within 30 days after admission, whether related or unrelated to pneumonia.

- Readmission [Time Frame: 30 days] [Designated as safety issue: No]:

Readmission within 30 days after admission for reasons related or unrelated to pneumonia.

- Days needed to reach clinical stability [Time Frame: 30 days] [Designated as safety issue: No]

- Days off work due to disease.

- Days with restricted regular activity (work or recreation) due to pneumonia.

- Days with adverse effects due to medication.

- Recurrence [Time Frame: 30 days] [Designated as safety issue: No]

new (or worsening) symptoms and signs related to pneumonia and with a new infection of the respiratory tract in a patient considered cured on the 10th day visit.

- Duration of hospital stay [Time Frame: 30 days] [Designated as safety issue: No] days the patient needs to be hospitalized for pneumonia

- Days to return to normal activity [Time Frame: 30 days] [Designated as safety issue: No]days the patient needs to carry out their daily lives

Sample size estimation:

Based on the results of a similar study, we hypothesize that to achieve a 80% power to detect differences in the CAP-symptom mean score lower or equal the non-inferiority margin of 3 points, considering a one-side alpha error of .025, a mean of the CAP-Symptom score of 18 points in each group of patients, and a standard deviation in both groups of 11 units, we will require at least 142 patients in each branch of the study.

Statistical analysis:

For the descriptive analysis we will use averages, standard deviations, medians and ranks for the quantitative variables and percentages for the qualitative ones. The fundamental analyses will include: 1) first, and in order to make sure that randomization has been done correctly, the fundamental basal variables of the study will be compared between the intervention group and the control group to verify that there are no statistically significant differences between both groups in those variables. Intermediate analyses will be performed every three months of follow-up to see whether there are differences between both groups that may justify discontinuing the study. 2) To respond to the fundamental goals and hypotheses of the study univariate analyses will be performed comparing all the main and secondary dependent variables between the two groups of patients (main independent variable). A subanalysis with the most severe patients will also be conducted (PSI IV and V).

For the comparison of the quantitative variables between the control group and the intervention group Student's t test or Wilcoxon's non-parametric test will be used, depending on whether the studied variable follows a normal distribution or not. For the comparison of the qualitative variables a Chi-square test or Fisher's exact test will be used. In addition a comparative analysis of the basal characteristics of the lost and non-lost patients will be performed, using the same statistical tests previously mentioned.

Finally, multilevel analyses will be performed with mixed models to compare clinical primary outcomes between groups, including a hospital-level random effect.