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Duration of Antibiotic Treatment in Community-Acquired Pneumonia
A Multicenter Randomized Clinical Trial

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IMPORTANCE The optimal duration of antibiotic treatment for community-acquired pneumonia (CAP) has not been well established.

OBJECTIVE To validate Infectious Diseases Society of America/American Thoracic Society guidelines for duration of antibiotic treatment in hospitalized patients with CAP.

DESIGN, SETTING, AND PARTICIPANTS This study was a multicenter, noninferiority randomized clinical trial performed at 4 teaching hospitals in Spain from January 1, 2012, through August 31, 2013. A total of 312 hospitalized patients diagnosed as having CAP were studied. Data analysis was performed from January 1, 2014, through February 28, 2015.

INTERVENTIONS Patients were randomized at day 5 to an intervention or control group. Those in the intervention group were treated with antibiotics for a minimum of 5 days, and the antibiotic treatment was stopped at this point if their body temperature was 37.8°C or less for 48 hours and they had no more than 1 CAP-associated sign of clinical instability. Duration of antibiotic treatment in the control group was determined by physicians.

MAIN OUTCOMES AND MEASURES Clinical success rate at days 10 and 30 since admission and CAP-related symptoms at days 5 and 10 measured with the 18-item CAP symptom questionnaire score range, 0-90; higher scores indicate more severe symptoms.

RESULTS Of the 312 patients included, 150 and 162 were randomized to the control and intervention groups, respectively. The mean (SD) age of the patients was 66.2 (17.9) years and 64.7 (18.7) years in the control and intervention groups, respectively. There were 95 men (63.3%) and 55 women (36.7%) in the control group and 101 men (62.3%) and 61 women (37.7%) in the intervention group. In the intent-to-treat analysis, clinical success was 48.6% (71 of 150) in the control group and 56.3% (90 of 162) in the intervention group at day 10 (P = .18) and 88.6% (132 of 150) in the control group and 91.9% (147 of 162) in the intervention group at day 30 (P = .33). The mean (SD) CAP symptom questionnaire scores were 24.7 (11.4) vs 27.2 (12.5) at day 5 (P = .10) and 18.6 (9.0) vs 17.9 (7.6) at day 10 (P = .69). In the per-protocol analysis, clinical success was 50.4% (67 of 137) in the control group and 59.7% (86 of 146) in the intervention group at day 10 (P = .12) and 92.7% (126 of 137) in the control group and 94.4% (136 of 146) in the intervention group at day 30 (P = .54). The mean (SD) CAP symptom questionnaire scores were 24.3 (11.4) vs 26.6 (12.1) at day 5 (P = .16) and 18.1 (8.5) vs 17.6 (7.4) at day 10 (P = .81).

CONCLUSIONS AND RELEVANCE The Infectious Diseases Society of America/American Thoracic Society recommendations for duration of antibiotic treatment based on clinical stability criteria can be safely implemented in hospitalized patients with CAP.

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Community-acquired pneumonia (CAP) continues to be a leading cause of morbidity and mortality worldwide.[1] The annual incidence of CAP ranges from 5 to 11 cases per 1000 adults and accounts for considerable health care costs.[2,3] During recent decades, strategies of early initiation and an early switch to oral therapy have been thoroughly evaluated.[4-6] However, the optimal duration of antimicrobial therapy is not well established.

Shortened antibiotic treatments have numerous advantages. First, they have been associated with lower rates of antimicrobial resistance among respiratory pathogens.[7] In fact, low doses of β-lactam antibiotics for more than 5 days have been associated with an increase in *Streptococcus pneumoniae* penicillin-resistant nasopharyngeal carriers.[7] Second, reducing the duration of antibiotic treatments could lead to cost savings.[8] Third, unnecessarily long treatments could result in higher rates of adverse effects.[9] Fourth, adherence may improve if treatment duration is shortened.[10,11]

Despite these clear benefits and a few meta-analyses[12,13] suggesting noninferiority of shorter treatments, reducing the duration of treatment remains challenging in clinical practice, probably because of physicians feeling a false sense of security with longer treatments. To date, no clinical trials have been conducted concerning duration of antibiotic treatment in a real-world setting where clinicians can prescribe their drug of choice among hospitalized patients with CAP with varying degree of illness.

In 2007, the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) developed recommendations for the duration of antibiotic treatment based on stability criteria proposed by Halm et al.[14] The guidelines suggested a minimum of 5 days of treatment, patients achieving an afebrile state for 48 to 72 hours, and patients meeting no more than 1 CAP-associated instability criteria before therapy discontinuation.[15] A longer duration was recommended if the initial therapy was not active against the identified pathogen or if the patient's condition was complicated by extrapulmonary infection, such as meningitis or endocarditis. Most guidelines classify current recommendations as having weak evidence mainly based on expert opinions.[15-17] Despite these recommendations focused on clinical state, arbitrarily longer treatments remain common.[18] In an attempt to clarify this issue and validate the IDSA/ATS guidelines for duration of antibiotic treatment in patients with CAP, we conducted a multicenter randomized clinical trial to assess whether duration of antibiotic treatment based on IDSA/ATS criteria was as effective as conventional treatment.

Key Points

Question How long should antibiotic treatment last for patients with community-acquired pneumonia?

Findings In this randomized clinical trial that included 312 patients, the clinical success rate was 50.4% in controls and 59.7% in the intervention group at day 10 and 92.6% in controls and 94.4% in the intervention group at day 30 without significant differences. The community-acquired pneumonia symptom questionnaire scores at days 5 and 10 were similar between the groups.

Meaning Basing antibiotic treatment duration on clinical stability criteria leads to a significant reduction in treatment duration without increasing the rate of adverse outcomes.

Methods

Study Design

This multicenter, noninferiority randomized clinical trial was performed in all hospitalized patients diagnosed as having CAP in 4 teaching hospitals in the Basque Country in Spain. The trial protocol can be found in Supplement 1. Patients were assessed for eligibility from day 0 to day 5 and randomized by a researcher at day 5 to an intervention or control group using an assigned number generated by an SAS statistical software, version 9.4, computer program (SAS Institute Inc).

Patients in the intervention group were treated with antibiotics for a minimum of 5 days, and the antibiotic treatment was stopped at this point if their body temperature was 37.8°C or less for 48 hours and they had no more than 1 CAP-associated sign of clinical instability, defined as systolic blood pressure less than 90 mm Hg, heart rate greater than 100/min, respiratory rate greater than 24 /min, arterial oxygen saturation less than 90%, or Pa_{O_2} less than 60 mm Hg in room air.[15] In contrast, duration of antibiotics in the control group was determined by physicians as in clinical practice. In both groups, antibiotic type was chosen empirically by physicians according to local guidelines. The project was approved by the Basque Country Ethical Committee. All patients were informed of the study goals, and written informed consent was obtained before their inclusion in the study. All data were deidentified.

Setting and Study Population

Hospitalized patients diagnosed as having CAP were recruited from January 1, 2012, through August 31, 2013. Data analysis was performed from January 1, 2014, through February 28, 2015. Eligible patients were 18 years or older and hospitalized with a diagnosis of CAP. Pneumonia was defined as pulmonary infiltrate on chest radiography not seen previously plus at least 1 symptom compatible with pneumonia, such as cough, fever, dyspnea, and/or chest pain. Patients were excluded if they were infected by human immunodeficiency virus; had chronic immunosuppression (defined as immunosuppression for solid organ transplantation, having undergone a splenectomy, receiving ≥10 mg/d of prednisone or the equivalent for >30 days, taking other immunosuppressive agents, or having neutropenia, ie, a neutrophil count <1000/μL [to convert to $\times 10^9$/L, multiply by 0.001]); 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 before admission; required a longer duration of therapy because of an uncommon cause (*Pseudomonas aeruginosa* or *Staphylococcus aureus*, among others); required a chest tube; or had a condition complicated by extrapulmonary infection, such as

meningitis or endocarditis. Patients who died or were transferred to the intensive care unit before randomization or who declined to participate or give inform consent were also excluded.

Data Collection

At baseline, demographic and clinical data for each patient were collected from medical records. Disease severity was determined with the Pneumonia Severity Index (PSI) calculated within the first 4 hours after diagnosis.[19] Comorbidities were measured with the Charlson Comorbidity Index[20] and patient independence in activities of daily living with the Katz Index.[21] The most abnormal values of vital signs (systolic blood pressure, heart rate, respiratory rate, and arterial oxygen saturation) were recorded daily from medical records and used to assess clinical stability.[15] Antibiotic treatment was assessed according to the Spanish Pulmonology and Thoracic Surgery Society guidelines.[22] Treatment adherence was monitored during hospitalization by nurses and by the electronic prescription support program once patients were discharged. Patients discharged before day 5 were trained to measure vital signs at home, being assessed at day 5 again in the hospital. All patients were provided with a telephone number at discharge. An etiologic diagnosis was made whenever the results of urinary antigen testing for *Legionella pneumophila* type 1 or *S pneumoniae*, serologic tests, or blood or sputum cultures were positive. All patients were evaluated at day 30 in a medical consultation.

Assessment of Outcomes

The primary outcomes were clinical success rate at day 10 and late follow-up (day 30) since admission, defined as resolution or improvement in signs and symptoms related to pneumonia without further antibiotics,[23] and CAP-related symptoms at day 10 measured with the 18-item CAP symptom questionnaire,[24] a specific and validated patient-reported outcome measure on which higher scores indicate more severe symptoms (range, 0-90). It was initially developed in English and then translated to 12 different languages, including Spanish.[24] Given our experience conducting the study, some of our primary outcomes differed from those we proposed in our registered protocol. Although all-cause mortality or major complications were planned as a primary outcome, as well as clinical cure, we found that there were too few events after day 5 to make this a good choice for the primary outcome.

Duration of antibiotic treatment, measured as days taking antibiotics from the first dose until the interruption of any antibiotic treatment during hospitalization and at late follow-up (to identify the use of any other antibiotic after hospital discharge), was listed as a principal outcome in the protocol, but we thought this was a more appropriate secondary outcome. Our other secondary outcomes were time until clinical improvement, defined as the number of days patients took to feel better after discharge, provided by a question asked of patients at day 30 about how long it took them to feel better; time to return to normal activity, defined as the number of days before patients returned to their routine, reported by patients at day 30 after hospital admission; radiographic resolution at day 30 after hospital admission, based on assessment of chest radiography performed at least at baseline and late follow-up; in-hospital mortality; mortality at day 30 after hospital admission; CAP recurrence, defined as new or worsening symptoms related to pneumonia or appearance of a new respiratory infection in a patient classified as cured at day 10; hospital readmissions up to day 30 from hospital admission; complications during hospitalization; number of days with adverse events (such as diarrhea or headache) attributable to antibiotics up to day 30 from hospital admission; and length of hospital stay, measured by subtracting date of admission from date of discharge.

Sample Size Estimation

Before starting the field study, on the basis of the results of a similar study,[25] we hypothesized that to achieve 80% power to detect differences in the CAP symptom questionnaire mean score lower or equal to the noninferiority margin of 3 points, considering a 1-sided α error of .025, a mean CAP symptom questionnaire score of 18 points in each group of patients, and an SD in both groups of 11 units, we required at least 142 patients in each branch of the study (sampsi procedure, STATA statistical software, version 10, StataCorp).

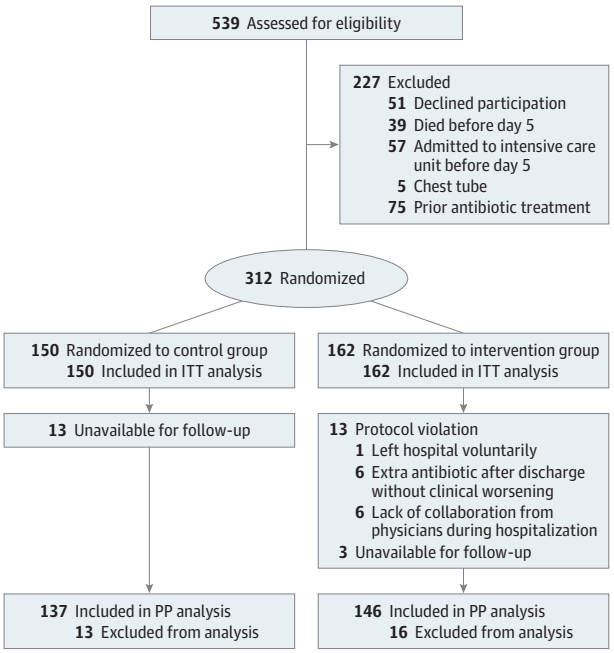
Statistical Analysis

Descriptive statistics included frequency tables, means (SDs), or medians (interquartile ranges). We compared baseline characteristics between patients who had protocol violations or who were unavailable for follow-up with those who did not. Baseline characteristics of the intent-to-treat population were compared between the control and intervention groups. Subsequently, vital signs at day 5, antibiotic treatment, and distribution of the causes in the per-protocol population were compared between the groups. Primary and secondary outcomes of the intent-to-treat and per-protocol populations were compared between the groups. Primary outcomes were compared between the groups stratified by PSI (classes I-III and IV-V), antibiotic group, or hospital. Categorical variables were compared with χ^2 and Fisher exact tests and continuous variables with unpaired, 2-tailed *t* tests or nonparametric Wilcoxon rank sum tests. Furthermore, Kaplan-Meier curves of return to normal activity until day 30 in the intent-to-treat and per-protocol populations were constructed for each patient group, and comparisons were performed with the log-rank test.

Finally, multilevel analyses were performed with mixed models to compare clinical primary outcomes between groups, including a hospital-level random effect. Linear mixed models were used to compare CAP symptom questionnaire scores at days 5 and 10 and generalized linear mixed models to compare clinical success at days 10 and 30. The dependent variable was the corresponding outcome, and independent variables were group (as the principal independent variable) and hospital (as the random effect).

All effects were considered significant at $P < .05$, unless otherwise stated. All statistical analysis was performed using

Figure. Study Flow Diagram



ITT indicates intent to treat; PP, per protocol.

SAS statistical software for Windows, version 9.2 (SAS Institute Inc), or S-Plus 2000 (MathSoft Inc).

Results

A total of 539 patients were assessed for eligibility (**Figure**). Before randomization, 227 patients did not meet the selection criteria, leaving 312 patients. Of these, 150 patients were randomized to the control group and 162 to the intervention group. The mean (SD) age of the patients was 66.2 (17.9) years and 64.7 (18.7) years in the control and intervention groups, respectively. There were 95 men (63.3%) and 55 women (36.7%) in the control group and 101 men (62.3%) and 61 women (37.7%) in the intervention group. Thirteen patients were later excluded for protocol violation (6 being treated with extra antibiotics within <1 week after discharge by their primary care physician without evidence of clinical worsening and 1 leaving the hospital voluntarily, whereas in 6 antibiotic treatment was not stopped during hospitalization despite clinical stability because of lack of collaboration by their physicians). In addition, 13 and 3 patients in the control and intervention groups, respectively, were unavailable for the late follow-up. However, the status of these 16 patients was checked through electronic medical records, and all but 1 was alive at late follow-up, whereas no information was found for the other patient. No differences were found in terms of age, sex, comorbidities, Katz Index, and severity of disease between those who violated the protocol or were unavailable for follow-up and those who did not.

Table 1. Baseline Characteristics of Study Participants[a]

Characteristic	Control Group (n = 150)	Intervention Group (n = 162)
Age, mean (SD), y	66.2 (17.9)	64.7 (18.7)
Sex		
Male	95 (63.3)	101 (62.3)
Female	55 (36.7)	61 (37.7)
Tobacco		
Current smoker	32 (21.3)	36 (22.6)
Never smoker	68 (45.3)	71 (44.7)
Former smoker	50 (33.3)	52 (32.7)
Alcohol consumption (yes)	24 (16.1)	17 (10.5)
Comorbidities		
Liver disease	4 (2.7)	4 (2.5)
Heart disease	38 (25.3)	39 (24.1)
Congestive heart failure	14 (9.3)	12 (7.4)
Cerebrovascular disease	16 (10.7)	9 (5.6)
Renal disease	12 (8.0)	12 (7.4)
COPD	21 (14)	27 (16.7)
Diabetes	25 (16.7)	21 (13.0)
Charlson Comorbidity Index, median (IQR)	1 (0-2)	1 (0-2)
Charlson Comorbidity Index, categorized		
0	61 (40.7)	70 (43.2)
1	37 (24.7)	47 (29.0)
>1	52 (34.7)	45 (27.8)
Katz Index, mean (SD)[b]	0.6 (1.6)	0.4 (1.3)
PSI class		
I-III	89 (59.3)	102 (63.0)
IV-V	61 (40.7)	60 (37.0)
PSI score, mean (SD)	83.7 (33.7)	81.8 (33.8)

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range; PSI, Pneumonia Severity Index.

[a] Data are presented as number (percentage) of study participants unless otherwise indicated. Percentages exclude patients with missing data. The percentage of missing data was 0% for all variables, except for the following: tobacco, 0.9%; alcohol consumption, 0.3%; and Katz Index, 0.9%.

[b] The Katz index assesses patient independence in activities of daily living, with higher values indicating more dependence (range, 0-6).

Baseline demographics and characteristics were similar in the control and intervention groups (**Table 1**). Mean (SD) PSI scores were 83.7 (33.7) and 81.8 (33.8) in the control and intervention groups, respectively (P = .55). Vital signs at day 5 were similar in both groups (eTable 1 in Supplement 2). Nearly 80% of patients in both groups underwent treatment with quinolones, whereas less than 10% were treated with a β-lactam plus macrolide. Etiologic diagnosis was made in 35 individuals (26.5%) in the control group and 28 (20.5%) in the intervention group (P = .25) (eTable 2 in Supplement 2).

Primary Outcomes

Clinical success rate at day 10 was 48.6% (71 of 150) in the control group and 56.3% (90 of 162) in the intervention group (P = .18) in the intent-to-treat analysis and 50.4% (67 of 137) in the control group and 59.7% (86 of 146) in the intervention

Table 2. Results for the Primary Study Outcomes

Outcome	Control Group	Intervention Group	*P* Value
Intent-to-Treat Analysis			
Total No. of participants	150	162	
Clinical success, No. (%)[a]			
At day 10	71 (48.6)	90 (56.3)	.18
At day 30	132 (88.6)	147 (91.9)	.33
CAP symptom questionnaire score, mean (SD)[b]			
At day 5	24.7 (11.4)	27.2 (12.5)	.10
At day 10	18.6 (9.0)	17.9 (7.6)	.69
Per-Protocol Analysis			
Total No. of participants	137	146	
Clinical success, No. (%)[a]			
At day 10	67 (50.4)	86 (59.7)	.12
At day 30	126 (92.7)	136 (94.4)	.54
CAP symptom questionnaire score, mean (SD)[b]			
At day 5	24.3 (11.4)	26.6 (12.1)	.16
At day 10	18.1 (8.5)	17.6 (7.4)	.81

Abbreviation: CAP, community-acquired pneumonia.

[a] Percentages exclude patients with missing data. In the intent-to-treat population, the percentage of missing data for each variable was as follows: clinical success at day 10, 1.9%; clinical success at day 30, 0.9%; CAP symptom questionnaire score at day 5, 3.8%; and CAP symptom questionnaire score at day 10, 4.4%. In the per-protocol population, the percentage of missing data was as follows: clinical success at day 10, 2.1%; clinical success at day 30, 1.0%; CAP symptom questionnaire score at day 5, 3.1%; and CAP symptom questionnaire score at day 10, 3.8%.

[b] On the CAP symptom questionnaire, which is a specific and validated patient-reported outcome measure based on 18 items, higher scores indicated more severe CAP-related symptoms (range, 0-90).

Table 3. Clinical Success Rates at Days 10 and 30 Among Different Severity Groups Defined by PSI Class[a]

	No. (%) of Participants		
PSI Class	Control Group	Intervention Group	*P* Value
Clinical Success at Day 10			
PSI classes I-III			
Intent to treat	41/86 (47.7)	58/101 (57.4)	.18
Per protocol	39/80 (48.8)	58/94 (61.7)	.09
PSI classes IV-V			
Intent to treat	30/60 (50)	32/59 (54.2)	.64
Per protocol	28/53 (52.8)	28/50 (56)	.75
Clinical Success at Day 30			
PSI classes I-III			
Intent to treat	83/88 (94.3)	93/102 (91.2)	.41
Per protocol	80/82 (97.6)	89/95 (93.7)	.29
PSI classes IV-V			
Intent to treat	49/61 (80.3)	54/58 (93.1)	.04
Per protocol	46/54 (85.2)	47/49 (95.9)	.10

Abbreviation: PSI, Pneumonia Severity Index.

[a] Percentages exclude patients with missing data. The percentage of missing data in the intent-to-treat and per-protocol populations was as follows: clinical success at day 10, 1.9% and 2.1%, respectively; and clinical success at day 30, 0.9% and 1.0%, respectively.

group (*P* = .12) in the per-protocol analysis. At day 30, it improved to 88.6% (132 of 150) and 91.9% (147 of 162) in the control and intervention groups, respectively, in the intent-to treat analysis (*P* = .33) and to 92.7% (126 of 137) and 94.4% (136 of 146) in the control and intervention groups, respectively, in the per-protocol analysis (*P* = .54). The CAP symptom questionnaire scores were similar in the 2 groups on day 5 (24.7 [11.4] and 27.2 [12.5] in the control and intervention groups, respectively; *P* = .10 in the intent-to-treat analysis; and 24.3 [11.4] and 26.6 [12.1] in the control and intervention groups, respectively; *P* = .16 in the per protocol analysis). At day 10, the CAP symptom questionnaire scores decreased in both groups (18.6 [9.0] and 17.9 [7.6] in the control and intervention groups, respectively; *P* = .69 in the intent-to-treat analysis; and 18.1 [8.5] and 17.6 [7.3] in the control and intervention groups, respectively, *P* = .81 in the per protocol analysis) (**Table 2**). Within different PSI severity groups, clinical success rate at day 10 was comparable in the 2 groups. In the intent-to treat analysis, patients with more severe disease achieved clinical success at day 30 more frequently in the intervention group than in the control group. No differences were observed in the per-protocol analysis (**Table 3**). Primary study outcomes by type of antibiotics and by hospitals are given in eTable 3 and eTable 4, respectively, in Supplement 2.

Table 4. Results for Secondary Study Outcomes in the Per-Protocol Analysis[a]

Outcome	Control Group (n = 137)	Intervention Group (n = 146)	*P* Value
Time, median (IQR), d			
Taking antibiotics	10 (10-11)	5 (5-6.5)	<.001
Not taking antibiotics	21 (10-27)	25 (5-32)	.001
Taking intravenous antibiotics	2 (1-4)	3 (2-4)	.22
Until clinical improvement	12 (8-18)	12 (7-15)	.41
Return to normal activity	18 (9-25)	15 (10-21)	.36
Radiographic resolution at day 30	93 (73.2)	112 (81.2)	.12
In-hospital mortality	2 (1.5)	3 (2.1)	>.99
30-d Mortality	3 (2.2)	3 (2.1)	>.99
Recurrence by day 30	6 (4.4)	4 (2.8)	.53
Readmission by day 30	9 (6.6)	2 (1.4)	.02
In-hospital complications			
Pleural effusion	10 (7.3)	5 (3.4)	.15
Treatment failure[b]	2 (1.5)	3 (2.1)	>.99
Respiratory failure[c]	26 (19.0)	31 (21.2)	.64
Severe sepsis[d]	7 (5.1)	8 (5.5)	.89
Renal failure[e]	5 (3.7)	6 (4.1)	.85
ICU admission	2 (1.5)	1 (0.7)	.61
Use of invasive mechanical ventilation	2 (1.5)	1 (0.7)	.61
Use of noninvasive mechanical ventilation	3 (2.2)	2 (1.4)	.67
Need for vasopressors	2 (1.5)	3 (2.1)	>.99
Antibiotic adverse effects by day 30	18 (13.1)	17 (11.7)	.72
Time with antibiotic adverse effects, mean (SD), d	3 (2.8)	1.7 (2.1)	.24
Length of hospital stay, mean (SD), d	5.5 (2.3)	5.7 (2.8)	.69

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

[a] Data are presented as number (percentage) of study participants unless otherwise indicated. Percentages exclude patients with missing data. The percentage of missing data was 0% for all variables, except for the following: days taking antibiotics, days taking intravenous antibiotics, and days to return to normal activity, 1.4%; days until clinical improvement, 7.0%; radiographic resolution at day 30, 6.3%; recurrence by day 30, readmission by day 30, treatment failure, renal failure, ICU admission, and antibiotic adverse effects by day 30, 0.3%; and use of mechanical ventilation and need for vasopressors, 0.7%.

[b] Treatment failure was defined as clinical deterioration based on the presence of any of the following: hemodynamic instability, demonstrated respiratory failure or the appearance of it, need for mechanical ventilation, demonstrated radiographic progression of pneumonia or the appearance of a new infectious foci, and absence or delay in achieving clinical stability after first 72 hours.

[c] Respiratory failure was defined as Pao_2 to fraction of inspired oxygen ratio less than 250 mm Hg.

[d] Severe sepsis was defined as sepsis associated with organ dysfunction and perfusion abnormalities. One of the following criteria had to be met: pH less than 7.30, systolic blood pressure less than 90 mm Hg, pneumonia-associated altered mental status, Pao_2 to fraction of inspired oxygen ratio less than 250 mm Hg, acute renal failure (creatinine level >2 mg/dL [to convert to micromoles per liter, multiply by 88.4]), disseminated intravascular coagulopathy, or hematocrit less than 25%.

[e] Renal failure was defined as a creatinine level greater than 2 mg/dL.

Multilevel analyses with mixed models revealed that, even including a hospital-level random effect, differences between the intervention and control groups in clinical success at days 10 or 30 were not significant (odds ratio, 1.54; $P = .11$; and odds ratio, 1.38; $P = .52$, respectively, considering the control group as the reference group). Regarding the CAP symptom questionnaire, we found significant differences between the 2 groups at day 5, with scores being higher in the intervention group ($\beta = 2.71$, $P = .0497$) but did not find significant differences at day 10 ($\beta = 0.12$, $P = .89$).

Secondary Outcomes

Secondary outcomes in the intent-to treat analysis are summarized in eTable 5 in Supplement 2. Time receiving antibiotic treatment was significantly longer in the control than the intervention group (median, 10 days [interquartile range, 10-11] vs 5 days [interquartile range, 5-6.5], respectively; $P < .001$). Four patients (2.9%) and 101 patients (70.1%) from the control and intervention groups, respectively, were receiving antibiotics for only 5 days ($P < .001$). No significant differences were found between groups in time until clinical improvement and days to return to normal activity measured at day 30, radiographic resolution at day 30, or adverse effects by day 30 (**Table 4**). Furthermore, no significant differences were found between groups using Kaplan-Meier survival curves of return to normal activity (eFigure in the Supplement 2) until day 30 (mean time to return to normal activity, 16.6 and 15.4 days in the control and intervention groups, respectively; log-rank test, $P = .16$).

In-hospital and 30-day mortality, in-hospital complications, recurrence by day 30, and length of hospital stay were similar in the 2 groups (Table 4). However, readmission by day 30 was significantly more common in the control group than in the intervention group (9 [6.6%] vs 2 [1.4%]; $P = .02$). Calling

by telephone after discharge was less common in the control group than the intervention group (38 [27.7%] vs 58 [39.7%]; $P = .03$).

Discussion

This study indicates that withdrawing antibiotic treatment based on clinical stability criteria after a minimum of 5 days of appropriate treatment is not inferior to traditional treatment schedules in terms of clinical success. Hence, we conclude that IDSA/ATS guidelines concerning duration of antibiotic treatment can be safely implemented among hospitalized patients with CAP.[15] Clinical cure rates at late follow-up were 92.7% and 94.4% in the control and intervention groups, respectively, which is consistent with published data.[26-28] Specifically, we were able to safely limit the duration of antibiotic treatment to 5 days in 101 patients (70.1%) in the intervention group.

This is the first study, to our knowledge, to validate the IDSA/ATS guideline recommendations for duration of antibiotic treatment. Determining the duration of antibiotic treatment based on clinical response appears to be a better strategy than using arbitrary treatment lengths. Shorter treatments also led to less antimicrobial resistance, fewer adverse effects, lower cost, and improved adherence. In agreement with previous data,[29] most of our patients reached stability by day 3. Given that the IDSA/ATS guidelines recommend[15] antibiotic treatment should be discontinued after 48 hours of stability, this implies no more than 5 days of treatment in most cases, although this does not currently happen in clinical practice.

We found no differences in length of stay between the groups probably because the day of discharge is determined primarily by when antibiotics are switched from intravenous to oral, not the overall length of treatment.[6] In our study, length of intravenous antibiotic treatment was similar in both groups. As previously reported,[27] no differences were observed in adverse effects probably because of similarities in prescribed antibiotics in both arms. Surprisingly, a higher readmission rate was observed in the control group. All patients were provided with a telephone number at discharge, leading to a higher rate of telephone calls in the intervention group, which could have avoided readmissions among this group.

Another notable characteristic of this study is the distinctive design under real-world conditions in which physicians are free to choose the most appropriate antibiotic. We followed this strategy in an attempt to mimic clinical practice.

To date, most studies[12,13] have evaluated outcomes in terms of clinical success. However, patients are known to be more concerned about other variables, such as time until clinical improvement and return to normal activity. In relation to this, we evaluated both outcomes, as reported by patients, and no significant differences were found between short and long courses. In addition, in an attempt to obtain more accurate information and unlike most previous research,[30-33] we assessed symptom severity with the CAP symptom questionnaire, observing decreases in scores from day 5 to day 10 in both groups.

An important strength of this study is that severely ill patients were included. Although patients admitted to the intensive care unit were excluded, we allowed inclusion of those with PSI scores greater than 130 (class V). There are few data on shortened antibiotic treatment in severe CAP. Choudhury et al[34] conducted a prospective, observational study in patients with severe CAP and did not find significant differences in 30-day mortality, need for mechanical ventilation and/or inotropic support, or major complications between short and long regimens. Similar to our study, they excluded patients who died within 7 days, were admitted to the intensive care unit, developed complicated pneumonia, failed to reach clinical stability, or had positive culture results for microorganisms requiring prolonged treatment. Still, little is known about how shortened treatments work in critically ill patients. In a double-blind (until day 8) randomized clinical trial that compared 15- and 8-day courses in adults with ventilator-associated pneumonia, Chastre et al[35] found that there was no clinical benefit to extending antibiotic treatment beyond an 8-day course to 15 days in patients who had received appropriate initial empirical therapy, with the possible exception of those with nonfermenting gram-negative *Bacillus* infections.

Regarding pharmacodynamic parameters, quinolones are known to have concentration-dependent killing activity. Thus, high-dose regimens would tend to increase the area under the concentration-time curve and peak plasma concentration, making shortened antibiotic treatments safe in terms of efficacy. In relation this, Dunbar et al[27] found that 750 mg of levofloxacin for 5 days was at least as effective as 500 mg of the same drug for 10 days in patients with mild to severe CAP. Interestingly, our study found similar clinical success rates even without our patients being prescribed a higher dose of quinolones. A few studies[31,33,36] have drawn attention to macrolides, which are known to have a long half-life and elevated pulmonary concentrations. D'Ignazio et al[37] observed similar success rates when comparing a single dose of azithromycin microspheres with 500 mg of levofloxacin for 7 days in outpatients with CAP.

Our study has several limitations. First, almost 80% of the patients received quinolones. Physicians selected the antibiotic, leading to a high rate of prescription of quinolones, as is usual in Spain.[38] Hence, the results probably cannot be extrapolated to other countries where β-lactams are widely used, such as the United Kingdom.[39] Second, because of the open design after day 5, there could have been an effect on physicians' decisions concerning antibiotic duration in the control group. Nevertheless, this does not seem to have happened because treatments were markedly longer in the control group. Third, few patients with severe disease (PSI class V) were included in this study. Fourth, patients who received previous antibiotic treatment, lived in nursing homes, were immunosuppressed, or needed a chest tube or longer therapy for disease of an

uncommon bacteriologic origin were excluded from the study; thus, results cannot be generalized to such patients. Fifth, the study was conducted in 4 teaching hospitals in the Basque Country, which could limit generalization of the results to other countries. However, patient demographic and baseline characteristics, disease severity on admission, process of care, and outcomes were similar to those described in other studies.[40-42]

Conclusions

Our study indicates that the IDSA/ATS recommendations for shorter duration of antibiotic treatment based on clinical stability criteria can be safely implemented in hospitalized patients with CAP, leading to a significant reduction in treatment duration.

ARTICLE INFORMATION

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