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ORIGINAL RESEARCH

Short Duration of Antibiotic Therapy in Hospitalized Patients with Community-Acquired Pneumonia: Results from the CAPO International Cohort Study

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Abstract

Background: Experts suggest a short duration of antibiotic therapy (DOT) in responding patients with community-acquired pneumonia (CAP). The aim of this study was to evaluate clinical outcomes after hospital discharge among patients treated with short-course antibiotic therapy (SCT) vs. long-course antibiotic therapy (LCT) for CAP.

Methods: A secondary analysis of the Community-Acquired Pneumonia Organization (CAPO) database from January 2007 to June 2013 was performed, including hospitalized CAP patients who reached clinical stability within 5 days. Two groups were identified: patients who were treated with antibiotic therapy for a total duration of 5 days or less (SCT Group) vs. longer than 5 days (LCT Group). Rehospitalization and mortality were evaluated at 30 days after discharge.

Results: 1,849 patients were enrolled (58% males; median age: 65 years), 179 (10%) were included in the SCT and 1,670 (90%) in the LTC group. Median DOT was 5 days in the SCT and10 days in the LTC group, p<0.001. At 30-day follow-up, there were no deaths in the SCT group, while 8 patients (0.7%) died in the LCT group, p=0.488. A total of 13 (11%) rehospitalizations were detected at 30 days after discharge in the SCT group vs. 132 (11%) in the LCT group, p=0.879. Once adjusted for several confounders, a short duration of antibiotic therapy was not associated to either adverse outcomes (OR: 1.04; 95% CI: 0.54-1.99; p=0.912).

Conclusions: A duration of antibiotic therapy of $\leq$ 5 days does not adversely impact clinical outcomes at 30-days after discharge compared to > 5 days in patients who reached early clinical stability.

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1 Introduction

Community-acquired pneumonia (CAP) is the leading cause of death from infectious diseases in most western countries[1]. One of the options to reduce morbidity and mortality in patients with CAP is to optimize antibiotic usage[2]. Increasing evidence over the last ten years has strengthened recommendations of guidelines concerning antibiotic selection, early initiation of therapy and switch from intravenous to oral therapy[3]. However, the appropriate duration of antimicrobial treatment remains a matter of controversy.

In clinical practice, a standard 10-14 day approach is still used to decide duration of antibiotic therapy in CAP patients, although guideline recommendations suggest a short duration of antibiotic therapy for patients with an early clinical response[4,5]. Since most CAP patients become clinically stable within 3-7 days from hospital admission, the American Thoracic Society (ATS) guidelines suggest that longer durations of therapy are rarely necessary[5]. However, few studies have evaluated the individualized approach targeted on each patient's clinical response to treatment[5–8]. According to guidelines suggestions, it is conceivable that a short duration ($\leq$ 5 days) of antibiotic therapy in responding patients should lead to similar long-term outcomes in comparison to those treated for more than 5 days. In that sense, Uranga et al. published a randomized clinical trial of duration of therapy (DOT) in CAP subjects[9]. 312 patients were enrolled in the study. In the

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intervention group, treatment was at least 5 days, according to clinical improvement. In the control group, duration of therapy was according to physician decision. In the intervention group DOT was 5 days versus 10 days in the control group. The authors found no differences in pneumonia success rate at 10 or 30 days after admission. However, the expected outcome could not be proven.

In order to strengthen this hypothesis, we decided to evaluate clinical outcomes after discharge among hospitalized patients with CAP who reached clinical stability within 5 days after admission and received antibiotics for $\leq$ 5 days versus those who received antibiotics for $\geq$ 5 days.

2 Methods

2.1 Study Design

A secondary analysis of the Community-Acquired Pneumonia Organization (CAPO) database was performed. The database contains data retrospectively collected from 60 hospitals in over 30 countries, between January, 01 2007 to June, 30 2013 was performed. In each participating center, primary investigators selected adult nonconsecutively hospitalized patients diagnosed with CAP. All data was collected on a case report form and transferred electronically to the CAPO coordinating center at the University of Louisville (Louisville, KY, USA). Discrepancies and inconsistencies in the data were determined at the coordinating center. After queries were clarified, cases were entered into the electronic REDCap database. Local institutional review board approval was obtained for each study site.

2.2 Inclusion and exclusion criteria

Patients $\geq$ 18 years of age and meeting the study definition of CAP and who reached clinical stability within 5 days after admission were included in this study. In order to investigate primarily the duration of antibiotic therapy prescribed only for the episode of CAP, patients who received antibiotic therapy for either <3 days or >28 days were excluded from the statistical analysis. Patients who died while receiving antibiotic therapy during hospitalization, as well as those for whom the duration of antibiotic therapy was missing from the database, were also excluded from the statistical analysis.

2.3 Study Definitions

CAP was defined as the presence of a new pulmonary infiltrate on chest radiograph at the time of hospitalization associated with at least one of the following: 1) new or increased cough; 2) an abnormal temperature (<35.6°C or >37.8°C) or 3) an abnormal serum leukocyte count (leukocytosis, left shift, or leukopenia defined by local laboratory values) [10].

Patients with healthcare-associated pneumonia (HCAP) (patients who were hospitalized in an acute care hospital for two or more days within 90 days of the infection; resided in a nursing home or long-term care facility; received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection; or attended a hospital or hemodialysis clinic) were also included in the study [11].

Time to clinical stability (TCS) was calculated as the number of days from the date of admission to the date the patient reached clinical stability criteria. Clinical stability was defined as follows: 1) improved clinical signs (improved cough and shortness of breath); 2) lack of fever for $\geq$ eight hours; 3) improving leukocytosis (decreased $\geq$ 10% from the previous day); 4) tolerating oral intake [12]. Criteria for clinical stability were evaluated daily during the first 7 days of hospitalization. The day that these four criteria were met was considered the day that patients reached clinical stability.

Duration of antibiotic therapy was analyzed as total duration of therapy and duration of intravenous and oral therapy. Total duration of therapy was calculated by subtracting the day the last antibiotic (either IV or oral) was discontinued from the day when the first antibiotic (either IV or oral) was started.

2.4 Study Groups and Outcomes

Among patients who reached clinical stability during the first 5 days of hospitalization, two study groups were defined: patients who were treated with antibiotic therapy for a total duration of 4-5 days for the short-course therapy group and those treated with antibiotic therapy for 6-28 days for the long-course therapy group.

Rehospitalization and mortality were evaluated as study outcomes during the follow-up after hospital discharge and up to day 30 after the initial diagnosis of pneumonia. Rehospitalization was defined as readmission to the hospital for any reason during follow-up. Mortality was defined as all-cause 30-day mortality during follow-up. Having either rehospitalization or mortality during follow-up was also evaluated as study outcomes.

2.5 Statistical Analysis

All statistical analyses were performed using SPSS (version 18.0; SPSS Inc., Chicago, IL, USA). Descriptive statistics were reported at baseline, with continuous data expressed as a median (25-75 interquartile range -IQR) and categorical data expressed as counts. Patient characteristics were compared between groups. Differences of continuous data between two groups were evaluated by Mann-Whitney U test (two groups). Differences of categorical variables between two or more groups were analyzed using the 2 test or Fisher's exact test where appropriate. Potential predictors of a combined adverse outcome that were considered of clinical relevance were investigated with the multivariable binomial logistic regression analysis. A P-value <0.05 was considered statistically significant.

3 Results

3.1 Study Population

A total of 3,324 patients were enrolled during the study period (male: 1,984; median age: 67 years), 1,475 were excluded (**Figure 1**). The final study population of patients who reached clinical stability within 5 days after hospital admission and were

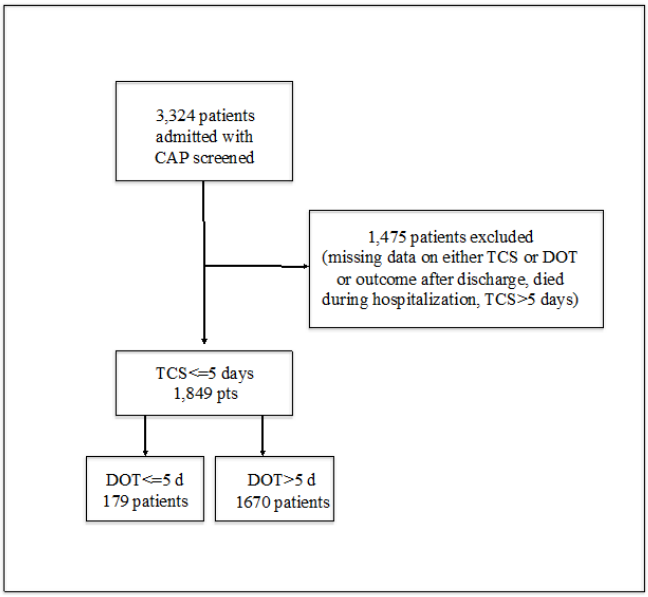

Fig. 1 Study flow diagram. CAP: community-acquired pneumonia; TCS: time to clinical stability; DOT: duration of treatment.

discharged alive accounted for 1,849 subjects. The median (IQR) TCS in the study population was of 3 (2-4) days. A total of 179 patients (10%) belonged to short-course group, and 1,670 patients (90%) to long-course group. No significant differences were found between the two study groups in terms of demographics, comorbidities, or severity of the disease on admission (**Table 1**). The median (IQR) TCS was 3 (1-4) days in the short-course therapy group and 3 (2-4) days in the long-course therapy groups; P=0.014. The median (IQR) duration of antibiotic therapy was 5 (4-5) days in the short group, and 10 (8-12) days in the long group; P<0.001. (**Table 2**) Median (IQR) DOT among patients undergoing empiric monotherapy was 9 (7-11) days vs. 10 (7-12) days for those undergoing combination therapy; P<0.001. The median (IQR) LOS in the entire study population was 7 (4-10) days. Median (IQR) LOS was 5 (4-6) days in the short group vs. 7 (5-10) days in the long group; P<0.001. DOT coincided with LOS in 380 patients (20%). DOT was longer than LOS in 1,002 patients (55%) and shorter in 456 patients (25%).

3.2 Clinical Outcomes

No patient died during follow-up in the short-course group, while 8 patients (0.7%) died in the long-course group; P=0.488. A total of 13 (11%) rehospitalizations were detected during follow-up in the short group vs. 132 (11%) in the long group, P=0.879 (**Table 2**).

Either outcome during follow-up was detected in 153 patients (12%) among the entire study population; 13 patients (11%) in the short vs. 140 patients (12%) in the long group; P=0.970.

Demographics, severity of disease, clinical, laboratory, and radiological findings with significant univariate association with either outcome during follow-up in the study population are shown in **Table 3**. The multivariable logistic regression model showed that HCAP (Odds Ratio (OR): 2.13; 95% CI: 1.31-3.47, P=0.002), and chronic obstructive pulmonary disease (COPD) (OR: 2.20; 95% CI: 1.45-3.35; P<0.001) on admission were independent predictors of adverse outcomes during follow-up. Once adjusted for several confounders, a short duration of antibiotic therapy (5 days) was not associated with either outcome (OR: 1.04; 95% CI: 0.54-1.99; P=0.912).

4 Discussion

Our study shows that among hospitalized patients with CAP who reached clinical stability within 5 days, and who received antibiotic therapy for 4 or 5 days had no significant differences in outcomes compared to those who received antibiotics for >5 days. Furthermore, adjusting for several confounders did not impact clinical outcomes. SCT was associated in our study with a significant reduction in LOS. From a clinical point of view, our findings support using shorter durations for antibiotics. Our results could help implementation of tailored protocols to determine antibiotic discontinuation in clinical practice, which could then have a great impact in reducing total antibiotic exposure, bacterial resistance and costs. Our findings also support that an individualized strategy, based on patients' clinical stability, can be considered the most comprehensive approach in determining the duration of antibiotic therapy.

The interaction between the host, the pathogen, and antibiotic factors characterize the clinical response in each single case of CAP, and determines the time in which a patient reaches clinical stability. At that point, the bacterial burden in the lung is greatly decreased due to a combination of the patient's immune

Table 1 Baseline demographics, comorbidities, severity of the disease, clinical, laboratory and radiological findings on admission, microbiology and antibiotic therapy data of the study population, according to the two study groups: short-course therapy, and standard-course therapy.

Characteristic	Short-course therapy	Long-course therapy	*P*
	n = 179	n = 1,670	
Demographics, n. (%)			
Male	94 (53)	974 (58)	0.135
Age, median (IQR) years	64 (46-79)	66 (49-79)	0.261
Health-care associated pneumonia	21 (12)	199 (12)	0.942
Comorbidities, n. (%)			
Congestive heart failure	25 (14)	232 (14)	0.978
Active Coronary artery disease	15 (8.4)	140 (8.4)	0.999
Essential hypertension	57 (32)	525 (31)	0.911
Chronic obstructive pulmonary disease	39 (22)	365 (22)	0.983
Neurological disease	23 (13)	249 (15)	0.459
Diabetes mellitus	29 (16)	295 (18)	0.624
Cerebrovascular accident	25 (14)	182 (11)	0.216
Renal disease	20 (11)	129 (7.7)	0.107
Liver disease	9 (5)	99 (5.9)	0.625
Neoplastic disease	17 (9.5)	173 (10)	0.718
Severity on admission, n. (%)			
Altered mental status	19 (11)	170 (10)	0.855
Admission to ICU	8 (4.5)	96 (5.7)	0.480
PSI Risk Class IV and V	81 (45)	846 (51)	0.169
CURB-65 score 4 and 5	6 (3.4)	69 (4.1)	0.615
Physical findings, median (IQR)			
Systolic Blood Pressure	130 (113-146)	125 (110-142)	0.162
Diastolic Blood Pressure	75 (65-80)	70 (60-80)	0.050
Heart rate, bpm	93 (80-107)	98 (85-110)	0.005
Respiratory rate, bpm	20 (18-24)	22 (18-26)	0.008
Alteration of gas exchange*	60 (34)	678 (41)	0.066
Laboratory values			
White blood cells count, cell	11,410 (8,000-16,000)	11,510 (8,000-15,800)	0.901
Arterial pH<7.35	3 (4.2)	52 (7.3)	0.324
Sodium <130 mmol/L	10 (6.1)	117 (7.2)	0.598
Hematocrit <30%	10 (5.7)	121 (7.5)	0.388
Blood urea nitrogen, mg/dL	16 (6-32)	23 (11-40)	<0.001
Microbiology, n. (%)			
Pathogen isolated	57 (32)	562 (34)	0.626
Mixed infection	4 (2.2)	47 (2.8)	0.653
Bacteremia	14 (14)	110 (9.1)	0.142
S. pneumoniae	15 (8.4)	257 (15.4)	0.012
MSSA	2 (1.1)	13 (0.8)	0.631
MRSA	3 (1.7)	16 (0.9)	0.606
H. influenzae	2 (1.1)	22 (1.3)	0.822
P. aeruginosa	1 (0.6)	6 (0.4)	0.680
M. catarrhalis	1 (0.6)	3 (0.2)	0.300
Legionella spp.	2 (1.1)	27 (1.6)	0.609
M. pneumoniae	2 (1.1)	17 (1.0)	0.900
K. pneumoniae	1 (0.6)	10 (0.6)	0.947
Antibiotic used, n. (%)			
Ceftriaxone	70 (41)	734 (44)	0.483
Levofloxacin	44 (26)	502 (30)	0.127
Azithromycin	61 (34)	490 (29)	0.188
Clarithromycin	35 (20)	309 (19)	0.732
Cefotaxime	1 (0.6)	7 (0.4)	0.787
Amoxicillin/clavulanate	31 (17)	182 (11)	0.011
Ampicillin/Sulbactam	10 (5.6)	129 (7.7)	0.303
Monotherapy	63 (35)	523 (31)	0.289
Time from arrival to first antibiotic dose, median (IQR) hours	4.5 (2.4-9.1)	4 (2.5-6.5)	0.556
Switched from intravenous to oral antibiotic	77 (43)	1161 (70)	<0.001

N: number; IQR: 25-75 interquartile range; ICU: intensive care unit; PSI: pneumonia severity index; CXR: chest radiograph; MSSA: methicillin-sensible *S. aureus*

response and the antibiotic activity. After a short time, the antibiotic could be discontinued. It is reasonable to suspect that as microorganisms are killed at the alveolar level, clinical improvement occurs. There is evidence supporting the idea of rapid clearance of pathogens from the lungs in pulmonary infections[13–17]. Between 1940 and 1960, some authors described rapid defervescence of pneumococcal pneumonia symptoms as early as 12 hours, with clinical cure after one to three days of therapy[13,14]. More recently, Dunbar et al. demonstrated that 5 days of levofloxacin are as effective as 10 days in patients with CAP[15]. In that way, El Moussaoui et al. showed that 3 days of amoxicillin was as effective as 8 days in patients with pneumonia who reach clinical stability by day 3[16]. Similarly, animal models showed us a rapid killing of microorganisms in the lung with adequate therapy[17]. Clearly, the most important concern about a short course treatment is the possibility of occurrence of complications and delayed clinical failure. However, in an earlier study by Halm et al., the authors demonstrated that if clinical stability is reached, the occurrence of unfavorable outcome is less than 1% in patients treated with standard duration of therapy[18]. These results are confirmed by other groups[19]. All this information taken together implies that in patients who reach clinical stability soon in the course of pneumonia, it is safe to shorten therapy, and this idea is supported by our results. It pointed out the need for a tailored duration of therapy according clinical evolution.

Several research groups have previously shown a strong correlation between defervescence of inflammatory response and favorable clinical outcomes[20,21]. In that sense, the inclusion of the demonstration of decreased levels of Procalcitonin or C-reactive protein (CRP) between day 1 and day 3 could help physicians to

Table 2 Patients experiencing adverse clinical outcomes after discharge and up to day 30 after the initial diagnosis of pneumonia in the study population, according to the two study groups.

Characteristic	Short-course therapy n = 179	Long-course therapy n = 1,670	*P*
Mortality, n	0	8 (0.7%; 95% CI: 0.2%-1.2%)	0.488
Rehospitalization, n	13 (11%)	132 (11%)	0.879
Combined outcomes*, n	13 (11%)	140 (12%)	0.970

*: Either death for any cause or rehospitalization after discharge and up to day 30 after the initial diagnosis of pneumonia

Table 3 Demographics, severity of disease, clinical, laboratory, radiological findings with significant univariate association with adverse outcome (either all-cause mortality or rehospitalization) after discharge and up to day 30 after the initial diagnosis of pneumonia in the study population.

Characteristic	Neither mortality nor rehospitalization n = 1,696	Either mortality or rehospitalization n = 153	*P*
Demographics			
Age, median (IQR) years	63 (47-78)	69 (53-82)	0.002
Health-care associated pneumonia, n. (%)	116 (9.9)	38 (25)	<0.001
Comorbidities, n. (%)			
Active Coronary artery disease	99 (8.4)	21 (14)	0.031
Essential hypertension	385 (33)	68 (44)	0.004
Chronic obstructive pulmonary disease	241 (21)	54 (35)	<0.001
Neurological disease	160 (14)	35 (23)	0.002
Neoplastic disease	92 (7.8)	22 (14)	0.006
Severity on admission, n. (%)			
Altered mental status	100 (8.5)	27 (18)	<0.001
Admission to ICU	52 (4.4)	12 (7.8)	0.063
PSI Risk Class IV and V	552 (47)	89 (58)	0.009
CURB-65 score 4 and 5	36 (3.1)	11 (7.2)	0.009
Laboratory values, median (IQR)			
Creatinine, mg/dL	1.0 (0.9-1.3)	1.0 (0.9-1.6)	0.021
Hematocrit, %	39 (35-42)	38 (34-41)	0.031
Empiric antibiotic therapy, n. (%)			
Monotherapy	388 (33)	60 (39)	0.126
Time from arrival to first antibiotic dose, median (IQR) hours	4 (2.5-6.5)	4 (2-7.5)	0.745

N: number; IQR: 25-75 interquartile range; ICU: intensive care unit; PSI: pneumonia severity index.

decide to shorten therapy. According to Menendez et al.[20], decreased levels of CRP below 100 mg/dl by day 3, and representing more than a 50% reduction between day 1 to 3 may be the clinical thresholds to shorten antibiotic therapy. In studies evaluating Procalcitonin, different safety cutoffs have been used and several aspects should be taken into account when interpreting this biomarker[22].

Our study has several limitations. In view of its retrospective design, neither selection biases nor other unapparent clinical information that could be important for clinical decision regarding duration of antibiotic therapy can be excluded. For instance, information for patients developing a complication, prolonging antibiotics despite achieving clinical stability are missing. Furthermore, the number of patients included in the SCT group might not have been enough to detect a significant difference in outcomes in comparison to patients in the LCT group. This study confirms the results of Uranga et al.[9], providing evidence of usual clinical practice, beyond a controlled clinical trial. Our results are strengthened by the large cohort of patients enrolled worldwide without strict exclusion criteria and this increases the generalizability of our findings. Furthermore, we used clinical information available in clinical practice to define a patient's response to therapy, which is used regularly by physicians and easy to define and interpret. Future research should be focused on the usefulness of biomarkers to determine clinical stability.

In conclusion, our data showed that among hospitalized patients with CAP who reached clinical stability within five days after admission, similar clinical 30-day outcomes might be detected between patients treated with five days of antibiotics versus those treated with more than five days.

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References

1 National Center for Health Statistics (US) *et al.*, "Health, united states, 2006: With chartbook on trends in the health of americans," 2006. [Online]. Available: http://www.cdc.gov/nchs/data/hus/hus06.pdf

2 M. Woodhead, F. Blasi, S. Ewig, G. Huchon, M. Leven, A. Ortqvist, T. Schaberg, A. Torres, G. van der Heijden, and T. Verheij, "Guidelines for the management of adult lower respiratory tract infections," *European Respiratory Journal*, vol. 26, no. 6, p. 1138, 2005.

3 J. A. Ramirez, S. Vargas, G. W. Ritter, M. E. Brier, A. Wright, S. Smith, D. Newman, J. Burke, M. Mushtaq, and A. Huang, "Early switch from intravenous to oral antibiotics and early hospital discharge: a prospective observational study of 200 consecutive patients with community-acquired pneumonia," *Archives of Internal Medicine*, vol. 159, no. 20, pp. 2449–2454, 1999.

4 S. Aliberti, F. Blasi, A. Zanaboni, P. Peyrani, P. Tarsia, S. Gaito, and J. Ramirez, "Duration of antibiotic therapy in hospitalised patients with community-acquired pneumonia," *European Respiratory Journal*, vol. 36, no. 1, pp. 128–134, 2010.

5 L. A. Mandell, R. G. Wunderink, A. Anzueto, J. G. Bartlett, G. D. Campbell, N. C. Dean, S. F. Dowell, T. M. File, D. M. Musher, M. S. Niederman *et al.*, "Infectious diseases society of america/american thoracic society consensus guidelines on the management of community-acquired pneumonia in adults," *Clinical infectious diseases*, vol. 44, no. Supplement 2, pp. S27–S72, 2007.

6 W. S. Lim, S. Baudouin, R. George, A. Hill, C. Jamieson, I. Le Jeune, J. Macfarlane, R. Read, H. Roberts, M. Levy *et al.*, "Bts guidelines for the management of community acquired pneumonia in adults: update 2009," *Thorax*, vol. 64, no. Suppl 3, pp. iii1–iii55, 2009.

7 L. A. Mandell and T. M. File, "Short-course treatment of community-acquired pneumonia," *Clinical Infectious Diseases*, vol. 37, no. 6, pp. 761–763, 2003.

8 M. S. Niederman, L. A. Mandell, A. Anzueto, J. B. Bass, W. A. Broughton, G. D. Campbell, N. Dean, T. File, M. J. Fine, P. A. Gross *et al.*, "Guidelines for the management of adults with community-acquired pneumonia: diagnosis, assessment of severity, antimicrobial therapy, and prevention," *American journal of respiratory and critical care medicine*, vol. 163, no. 7, pp. 1730–1754, 2001.

9 A. Uranga, P. P. España, A. Bilbao, J. M. Quintana, I. Arriaga, M. Intxausti, J. L. Lobo, L. Tomás, J. Camino, J. Nuñez *et al.*, "Duration of antibiotic treatment in community-acquired pneumonia: a multicenter randomized clinical trial," *JAMA internal medicine*, vol. 176, no. 9, pp. 1257–1265, 2016.

10 S. Aliberti, P. Peyrani, G. Filardo, M. Mirsaeidi, A. Amir, F. Blasi, and J. A. Ramirez, "Association between time to clinical stability and outcomes after discharge in hospitalized patients with community-acquired pneumonia," *CHEST Journal*, vol. 140, no. 2, pp. 482–488, 2011.

11 A. T. Society, I. D. S. of America *et al.*, "Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia." *American journal of respiratory and critical care medicine*, vol. 171, no. 4, p. 388, 2005.

12 S. Aliberti, A. M. Zanaboni, T. Wiemken, A. Nahas, S. Uppatla, L. C. Morlacchi, P. Peyrani, F. Blasi, and J. Ramirez, "Criteria for clinical stability in hospitalised patients with community-acquired pneumonia," *European Respiratory Journal*, vol. 42, no. 3, pp. 742–749, 2013.

13 W. S. Tillett, J. E. McCormack, and M. J. Cambier, "The treatment of lobar pneumonia with penicillin," *Journal of Clinical Investigation*, vol. 24, no. 4, p. 589, 1945.

14 E. H. Townsend JR and H. G. Decancq JR, "Pneumococcic segmental (lobar) pneumonia: its treatment with a single injection of procaine penicillin g," *Clinical pediatrics*, vol. 4, no. 2, pp. 117–122, 1965.

15 L. M. Dunbar, R. G. Wunderink, M. P. Habib, L. G. Smith, A. M. Tennenberg, M. M. Khashab, B. A. Wiesinger, J. X. Xiang, N. Zadeikis, and J. B. Kahn, "High-dose, short-course levofloxacin for community-acquired pneumonia: A new treatment paradigm," *Clinical infectious diseases*, vol. 37, no. 6, pp. 752–760, 2003.

16 R. el Moussaoui, C. A. de Borgie, P. van den Broek, W. N. Hustinx, P. Bresser, G. E. van den Berk, J.-W. Poley, B. van den Berg, F. H. Krouwels, M. J. Bonten *et al.*, "Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study," *BMJ*, vol. 332, p. 1355, 2006.

17 C. M. Luna, S. Baquero, S. Gando, J. R. Patrón, J. G. Morato, O. Sibila, R. Absi, A. Famiglietti, C. A. Vay, F. Von Stecher *et al.*, "Experimental severe pseudomonas aeruginosa pneumonia and antibiotic therapy in piglets receiving mechanical ventilation," *CHEST*, vol. 132, no. 2, pp. 523–531, 2007.

18 E. A. Halm, M. J. Fine, T. J. Marrie, C. M. Coley, W. N. Kapoor, D. S. Obrosky, and D. E. Singer, "Time to clinical stability in patients hospitalized with community-acquired pneumonia: implications for practice guidelines," *JAMA*, vol. 279, no. 18, pp. 1452–1457, 1998.

19 R. Menéndez, A. Torres, F. R. de Castro, R. Zalacaín, J. Aspa, J. J. M. Villasclaras, L. Borderías, J. M. M. Benítez, J. Ruiz-Manzano, J. Blanquer *et al.*, "Reaching stability in community-acquired pneumonia: the effects of the severity of disease, treatment, and the characteristics of patients," *Clinical Infectious Diseases*, vol. 39, no. 12, pp. 1783–1790, 2004.

20 R. Menéndez, R. Martínez, S. Reyes, J. Mensa, E. Polverino, X. Filella, C. Esquinas, A. Martínez, P. Ramirez, and A. Torres, "Stability in community-acquired pneumonia: one step forward with markers?" *Thorax*, vol. 64, no. 11, pp. 987–992, 2009.

21 R. Menéndez, R. Martinez, S. Reyes, J. Mensa, X. Filella, M. A. Marcos, A. Martinez, C. Esquinas, P. Ramirez, and A. Torres, "Biomarkers improve mortality prediction by prognostic scales in community-acquired pneumonia," *Thorax*, vol. 64, no. 7, pp. 587–591, 2009.

22 F. Blasi, D. Stolz, and F. Piffer, "Biomarkers in lower respiratory tract infections," *Pulmonary pharmacology & therapeutics*, vol. 23, no. 6, pp. 501–507, 2010.