Pulmonary Pharmacology & Therapeutics 45 (2017) 191–201

Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

Individualizing duration of antibiotic therapy in community-acquired pneumonia

Stefano Aliberti [a, *], Julio Ramirez [b], Fabio Giuliani [a], Timothy Wiemken [b], Giovanni Sotgiu [c], Sara Tedeschi [d], Manuela Carugati [e], Vincenzo Valenti [f], Marco Marchioni [g], Marco Camera [h], Roberto Piro [i], Manuela Del Forno [j], Giuseppe Milani [k], Paola Faverio [l], Luca Richeldi [m], Martina Deotto [n], Massimiliano Villani [o], Antonio Voza [p], Eleonora Tobaldini [q, r], Mauro Bernardi [s], Andrea Bellone [t], Matteo Bassetti [u], Francesco Blasi [a]

[a] Department of Pathophysiology and Transplantation, University of Milan, Internal Medicine Department, Respiratory Unit and Cystic Fibrosis Adult Center, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[b] University of Louisville, School of Medicine, Department of Medicine, Division of Infectious Diseases, Louisville, KY, United States
[c] Clinical Epidemiology and Medical Statistics Unit, Department of Biomedical Sciences, University of Sassari - Research, Medical Education and Professional Development Unit, AOU Sassari, Sassari, Italy
[d] Infectious Diseases Unit, Department of Medical and Surgical Sciences, Sant'Orsola Malpighi Hospital, Alma Mater Studiorum University of Bologna, Italy
[e] Department of Biomedical and Clinical Sciences, Università degli Studi di Milano, Milan, Italy
[f] Department of Health Bioscience, University of Milan - Respiratory Unit, Policlinico di San Donato, IRCCS - San Donato Milanese, Milan, Italy
[g] ASST Carlo Poma, Mantova, Italy
[h] Clinica Malattie Infettive, DIPMI, DISSAL, IRCCS AOU San Martino-IST, Università di Genova, Genova, Italy
[i] Pulmonology Unit, Arcispedale Santa Maria Nuova-IRCCS, Reggio Emilia, Italy
[j] Respiratory and Critical Care, Sant'Orsola Malpighi Hospital, Alma Mater Studiorum, University of Bologna, Department of Specialistic, Diagnostic and Experimental Medicine (DIMES), Bologna, Italy
[k] UO Pneumologia, ASST Lariana Ospedale S.Anna, S. Fermo della Battaglia, Como, Italy
[l] School of Medicine and Surgery, University of Milan Bicocca, San Gerardo Hospital, Monza, Italy
[m] National Institute for Health Research Respiratory Biomedical Research Unit, Mailpoint 813, LE75 E Level, South Academic Block, University Hospital Southampton NHS Foundation Trust, Southampton, UK
[n] Division of Internal Medicine, Azienda Ospedaliero-Universitaria S. Maria della Misericordia, Udine, Italy
[o] Dipartimento Cardio-Respiratorio, Unità Operativa di Pneumologia, San Carlo Borromeo Hospital, Via Pio II, 3, 20153 Milan, Italy
[p] U.O. di Pronto Soccorso e Medicina d'Urgenza, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy
[q] Fondazione IRCSS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy
[r] Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy
[s] Semeiotica Medica, Policlinico Sant'Orsola Malpighi, Alma Mater Studiorum, University of Bologna, Bologna, Italy
[t] Department of Emergency Medicine, San Anna Hospital, San Fermo della Battaglia, Como, Italy
[u] Santa Maria Misericordia University Hospital, Infectious Diseases Division, Udine, Italy

ARTICLE INFO

Article history:
Received 6 March 2017
Received in revised form
24 June 2017
Accepted 26 June 2017
Available online 27 June 2017

ABSTRACT

International experts suggest tailoring antibiotic duration in community-acquired pneumonia (CAP) according to patients' characteristics. We aimed to assess the effectiveness of an individualized approach to antibiotic duration based on time in which CAP patients reach clinical stability during hospitalization. In a multicenter, non-inferiority, randomized, controlled trial hospitalized adult patients with CAP reaching clinical stability within 5 days after hospitalization were randomized to a standard *vs*. individualized antibiotic duration. In the Individualized group, antibiotics were discontinued 48 h after the patient reached clinical stability, with at least five days of total antibiotic treatment. Early failure within 30 days was the primary composite outcome. 135 patients were randomized to the Standard group and 125 to the Individualized group. The trial was interrupted by the safety committee because of an apparent inferiority of the Individualized group over the Standard treatment: 14 (11.2%) patients in the Individualized group experienced early failure *vs*. 10 (7.4%) patients in the Standard group, p = 0.200, at

* Corresponding author. Department of Pathophysiology and Transplantation, University of Milan, Internal Medicine Department, Respiratory Unit and Cystic Fibrosis Adult Center, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Francesco Sforza 35, 20122 Milan, Italy.
E-mail address: stefano.aliberti@unimi.it (S. Aliberti).

http://dx.doi.org/10.1016/j.pupt.2017.06.008

the intention-to-treat analysis. 30-day mortality rate was four-time higher in the Individualized group than the Standard group. Shortening antibiotic duration according to patients' characteristics still remains an open question.

1. Take home message

Shortening antibiotic duration according to clinical stability might not be effective in all CAP patients.

2. Introduction

Community-acquired pneumonia (CAP) is one of the leading causes of death from infectious diseases worldwide [1]. Due to the high CAP-related morbidity and mortality, healthcare providers are seeking practices and strategies aimed at improving patients' outcomes [2]. A key measure is represented by amelioration in the appropriateness of antibiotic prescriptions. During the past decades, scientific evidence on public health efficacy of this intervention has been published, particularly on drug selection, early antibiotic initiation, and prompt switch from intravenous to oral therapy [3,4]. However, very few and well-designed studies evaluated the appropriate duration of antibiotic courses [5,6].

International guidelines suggest tailoring duration of antibiotic therapy according to patients' characteristics [7]. According to the British Thoracic Society, duration should depend on clinical judgment and vary according to disease severity and rapidity of clinical recovery [8]. Notably, these recommendations are only based on a formal combination of experts' opinions following the missing experimental evidence in the field. This also reflects the worldwide use in clinical practice of a standard antibiotic duration in CAP, ranging from 10 to 14 days, regardless of patients' clinical response [9]. In view of the disagreement between experts' opinions and current clinical practice, a trial focused on an individualized approach to antibiotic duration according to patient's clinical response is needed.

The objective of this randomized, controlled, non-inferiority study was to assess the effectiveness and safety of an individualized approach to duration of antibiotic therapy based on time to clinical stability in comparison with a local standard approach in hospitalized patients with CAP.

3. Materials and methods

3.1. Study design

This was a multicenter, phase IV, non-inferiority, pragmatic, randomized, controlled clinical trial enrolling adult patients hospitalized because of a CAP episode in 18 centres across Italy from January 1st, 2012 to December 27th, 2014. Ethical committee approvals were obtained both at the coordinating centre (Policlinico Hospital, Milan) and at each study centre. All recruited patients provided written informed consent. The study was registered on ClinicalTrials.gov (#NCT01492387). No amendments after the ethical committee approval were performed.

3.2. Study population

Patients aged 18 years or older who met all of the following inclusion criteria were eligible for enrollment: (1) diagnosis of CAP; (2) appropriate empiric antibiotic therapy for CAP received within 24 h after hospital admission; (3) clinical stability reached within five days after hospital admission, in the absence of any changes of the initial empiric antibiotic therapy; (4) signed informed consent. Patients with healthcare associated pneumonia were included in the study, according to the latest recommendations of the European Respiratory Society [2,10].

Patients showing any of the following exclusion criteria were not recruited: (1) immunodeficiency; (2) concomitant infection on hospital admission requiring antibiotic therapy (i.e., urinary tract infection); (3) *S. aureus* bacteraemia proved by blood culture; (4) etiology of pneumonia due to fungi, *Mycobacterium* spp., or *Pneumocistis jiroveci*; (5) hospitalization in the previous 15 days.

3.3. Data collection

Patients' management, laboratory analyses, and antibiotic therapy (including switch from intravenous to oral route) were performed according to the current standard of care for CAP patients and following local standard operating procedures [2]. Patients were daily assessed during their hospital stay, at the follow-up visit after 30 days from CAP diagnosis and with a phone call performed 90 days after CAP diagnosis to assess patients' clinical conditions, see online data supplement.

3.4. Interventions

Patients randomized to the “standard” group were treated for the duration of therapy dictated by the primary care physician (local standard of care arm). Patients randomized to “individualized” group were treated according to clinical response: antibiotic therapy was discontinued 48 h after the patient reached clinical stability, with at least five days of total antibiotic treatment. Day 0 was the day of hospital admission. Clinical evaluation of patients was performed every morning during clinical round from Day 1.

In order to reach clinical stability, all the following criteria should have met by the patient during the same day of hospitalization in comparison with the previous day from Day 1 to Day 5: (1) improved clinical signs (cough, and shortness of breath), and/or decreased quantity and improved quality of respiratory secretions; (2) absence of fever for at least 24 h, without the exposure to any antipyretic drug; (3) absence of increased inflammatory markers (either white blood cells −WBC- or C-reactive protein −CRP- or procalcitonin −PCT-) used in local centres in comparison with baseline values; (4) hemodynamic stability defined as non-invasive systolic blood pressure $\geq$90 mm Hg [11].

3.5. Study outcomes

Early failure was the primary composite study outcome occurring within 30 days following CAP diagnosis and including any of the following conditions: (1) pneumonia-related complications (e.g., lung abscess, empyema); (2) clinical failure during hospitalization (definition in the online data supplement); (3) a new antibiotic course after discontinuation of antibiotic therapy prescribed for the pneumonia, (4) re-hospitalization from any reason; (5) death from any reason [12].

Secondary outcomes included: (1) Pneumonia-related early failure; (2) Days of antibiotic exposure at 30-day follow-up; (3) Late failure at 90-day follow-up; (4) Length of hospital stay; (5) Adverse events associated with the antibiotic treatment given for the episode of pneumonia at both 30- and 90-day follow-up after CAP diagnosis.

An independent data and safety monitoring board was established to monitor safety and tolerability during the trial. Outcome definitions and assessment are reported in the online supplement.

3.6. Sample size

To determine if early failure rate in the individualized approach arm was not inferior to the standard of care approach arm, 95% confidence intervals (CIs) were constructed. 95% CIs for the difference in early failure were calculated for the study sample. Non-inferiority was determined if the lower limit of the confidence interval was not less than −5. Regarding early failure, an α of 0.05 and a β of 0.2 were selected. A clinically acceptable non-inferiority margin, δ, was set at 0.05. Based on our prior work on pneumonia and published literature, once patients reach clinical stability within the initial five days of hospitalization, an early failure rate at 30 days after the diagnosis of pneumonia of approximately 10% is expected for each study arm [2,12,13]. A sample size of 892 patients (446 in each study arm) was required to be 80% confident that the upper limit of a one-sided 95% CI excludes a difference in favour of the standard treatment of more than 5% if there is truly no difference between the two study arms. The planned sample size would have been adjusted increasing the recruitment of other patients, having considered a drop-out rate of 10%.

3.7. Randomization and masking

Eligible patients were randomized to either the “standard” or “individualized” group after having signed the informed consent form. Allocation of patients was concealed and a 1:1 randomization ratio was planned. Unblinded study personnel was responsible for the randomization process (T.W.). Patients were randomized using envelopes: sequentially numbered, opaque, sealed envelopes were sent to each centre with the indication of treatment that should be applied. Only the study statistician knew the block size. Two interim analyses were planned.

Two main criteria were prespecified for the early interruption of the study: (1) the investigational approach would have shown its inferiority; (2) proven harm for patients included in both arms. If the non-inferiority for the primary outcome would have been proven, but not for secondary outcomes, the study would have not been interrupted.

From a statistical perspective, the non-inferiority would have not been met if the upper bound of the one-sided x 100% confidence interval for the investigational therapeutic approach would have not been below the predefined margin delta, with a specific first type error.

3.8. Statistical analysis

Demographic, epidemiological, clinical, and microbiological variables were collected and input in an ad-hoc dataset. Qualitative and quantitative variables were summarized with absolute and relative (percentage) frequencies and means (standard deviations −SD) or medians (interquartile ranges −IQR), in case of parametric or non-parametric distribution, respectively. Comparisons between the two study groups were carried out with a chi-squared test or Fisher exact test for qualitative variables, when appropriate; Student's t or Wilcoxon test was used for parametric or non-parametric quantitative variables. A two-tailed p-value less than 0.05 was considered statistically significant. STATA 13 statistical software was used to perform all the computations.

4. Results

4.1. Study patients

From January 1st, 2012 to December 27th, 2014, a total of 1450 patients were screened and 260 underwent randomization: 135 were assigned to the “standard” group and 125 to the “individualized” group, see Fig. 1. The follow-up period ended on March 27th, 2015. The trial was interrupted by the safety committee because of apparent inferiority of the Individualized group over the standard treatment in regard to the primary outcome. Follow-up data were available for 100% of the patients at both 30 and 90 days.

4.2. Intention-to-treat analysis

A total of 260 patients were included in the ITT analysis. Baseline characteristics were not different between the two study groups (Table 1). The median time to reach clinical stability was 4 (3–5) days in the individualized group and 3 (3–4) days in the standard group, $p = 0.006$. A total of 125 (92.6%) patients in the Standard group and 110 (88%) patients in the Individualized group received at least one endovenous antibiotic on admission (p-value = 0.209). Furthermore, 23 (17.0%) patients in the Standard group and 16 (12.8%) patients in the Individualized group were switched from endovenous to oral antibiotics after reaching clinical stability (p-value = 0.339).

Early failure occurred in 14 (11.2%) patients in the Individualized group and 10 (7.4%) patients in the Standard group ($p = 0.200$). No significant differences between the two study arms were observed in any component of the early failure outcome, see Table 2.

Pneumonia-related early failure occurred in 4 (3.2%) patients in the Individualized group and in 3 (2.2%) patients in the Standard group ($p = 0.458$). Late failure occurred in 12 (9.6%) patients in the Individualized group and in 11 (8.1%) patients in the Standard group ($p = 0.680$). No significant differences were observed between the two study arms in any component of pneumonia-related early and late failure, see Table 2. Median (IQR) LOS was 7 (5–8) days in the Standard group and 7 (6–8) days in the Individualized group ($p = 0.648$). The median (IQR) length of antibiotic exposure at 30-day follow-up was significantly shorter in the Individualized group in comparison to the Standard group: 6 (5–7) days *vs.* 8 (6–10) days ($p < 0.0001$).

No significantly different rates of adverse events from antibiotic treatment given for the episode of pneumonia at both 30- and 90-day follow-up after the diagnosis of the pneumonia were detected, see Table 3.

4.3. Per protocol analysis

A total of 44 patients in the Individualized group underwent protocol violation: physicians did not discontinue antibiotic therapy in all the cases. A total of 216 patients were included in the PP analysis, 81 (37.5%) belonging to the Individualized group. Baseline characteristics were not significantly different between the two study groups (Table 4). The median (IQR) time to reach clinical stability was 4 (3–5) days in the Individualized group and 3 (3–4) days in the Standard group ($p = 0.092$).

Early failure occurred in 6 (7.4%) patients in the Individualized group and 10 (7.4%) patients in the Standard group ($p = 0.612$). No significant differences between the two study groups were observed in any component of the early failure, see Table 5.

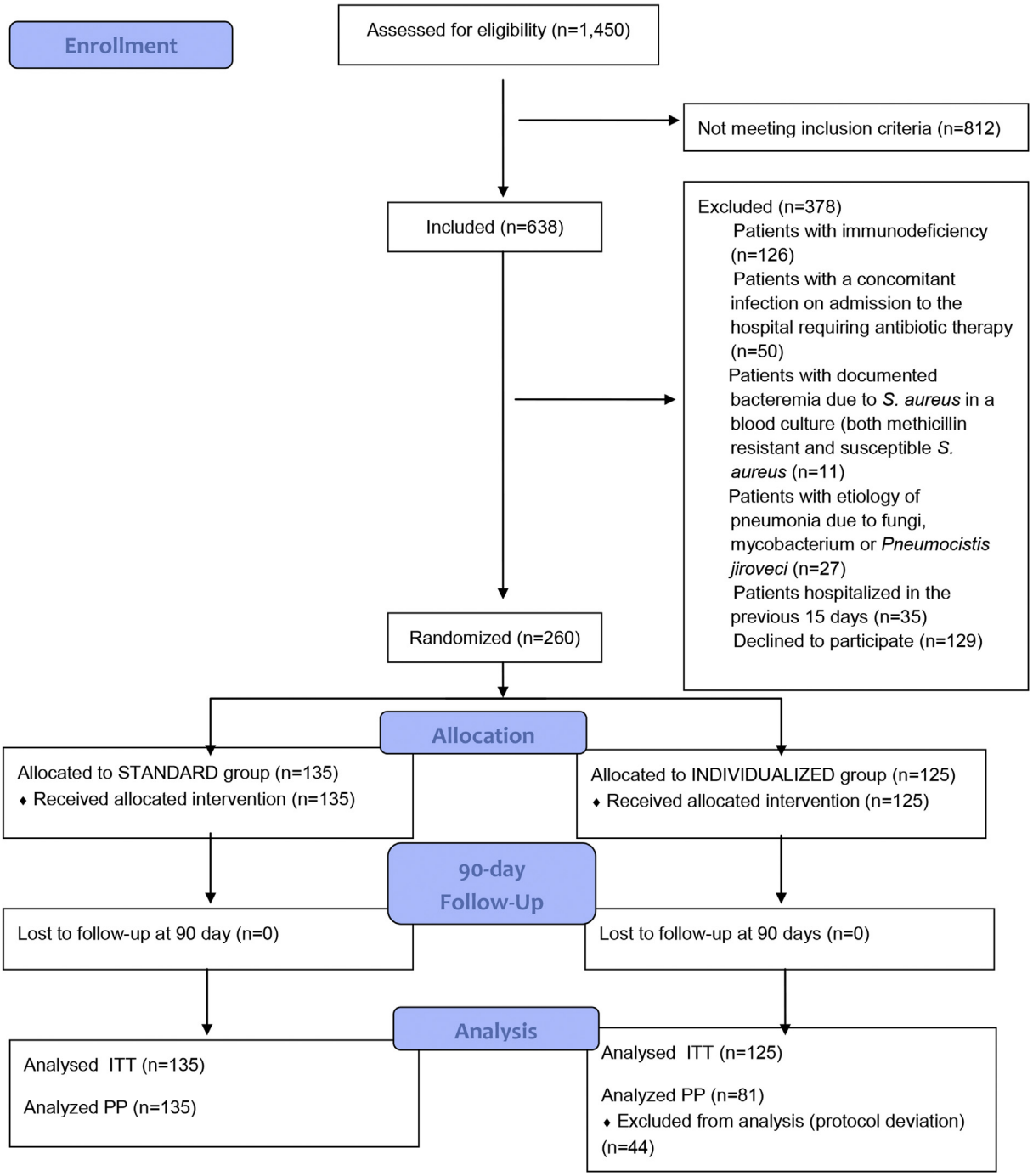

Fig. 1. Study flow-chart.

Pneumonia-related early failure occurred in 3 (3.7%) patients in the Individualized group and 3 (2.2%) patients in the Standard group ($p = 0.403$). Late failure occurred in 6 (7.4%) patients in the Individualized group and 11 (8.1%) patients in the Standard group ($p = 0.845$). No significant differences were observed in any component of pneumonia-related early and late failure, see Table 5. Median (IQR) LOS was 7 (5–8) days in the standard group and 7 (5–8) days in the Individualized group ($p = 0.724$). The median (IQR) length of antibiotic exposure at 30-day follow-up was significantly shorter in the Individualized group in comparison to the Standard group: 6 (5–7) vs. 8 (6–10) days ($p < 0.0001$).

No significantly different rates of adverse events from antibiotic treatment given for the episode of pneumonia at both 30- and 90-day follow-up after the diagnosis of the pneumonia were reported in the two study arms, see Table 6.

4.4. Characterization of patients who underwent protocol violation

Among patients randomized in the Individualized group, 44 underwent protocol violation (Group PV). They showed a worse primary outcome in comparison with 81 patients who followed the study protocol (Group SP): 8 (18.2%) vs. 6 (7.4%), $p = 0.066$. No significant differences were observed in any component of the primary outcome, see Table 7.

Table 1
Baseline demographics, comorbidities, disease severity, clinical, laboratory and radiological findings on admission, microbiology, and antibiotic therapy data of the study population according to the intention-to-treat analysis.

	Individualized group n = 125	Standard group n = 135	P
Demographics			
Male, n (%)	77 (61.6)	79 (58.5)	0.612
Age, median (IQR) years	58.0 (43.8–79.5)	63.0 (46.0–77.0)	0.996
BMI median (IQR)	24.74.4	23.94.6	0.231
Healthcare-associated pneumonia, n (%)	6 (4.8)	9 (6.7)	0.519
Nursing Home Residency, n (%)	0 (0.0)	1 (0.7)	0.519
Comorbidities			
Neoplastic disease, n (%)	3 (2.4)	4 (3.0)	0.542
COPD, n (%)	25 (20.0)	25 (18.5)	0.762
Cerebrovascular accident, n (%)	7 (5.6)	11 (8.1)	0.419
Renal disease, n (%)	9 (7.2)	13 (9.6)	0.482
Chronic renal Failure, n (%)	7 (5.6)	11 (8.1)	0.419
Liver disease, n (%)	6 (4.8)	5 (3.7)	0.661
Arterial hypertension, n (%)	50 (40.0)	42 (31.1)	0.134
Coronary artery disease, n (%)	6 (4.8)	10 (7.4)	0.382
Congestive heart failure, n (%)	11 (8.8)	17 (12.6)	0.324
Atrial fibrillation, n (%)	11 (8.8)	18 (13.3)	0.246
Diabetes mellitus, n (%)	24 (19.2)	20 (14.8)	0.346
Hyperlipidaemia, n (%)	21 (16.8)	16 (11.9)	0.254
Prior acute myocardial infarction, n (%)	9 (7.2)	16 (11.9)	0.204
HIV infection, n (%)	5 (4.0)	4 (3.0)	0.452
Severity on admission			
Ventilatory support, n (%)	6 (4.8)	4 (3.0)	0.328
Blood pressure support[a], n (%)	0 (0.0)	1 (0.8)	0.513
Mental status change, n (%)	8 (6.5)	5 (3.7)	0.318
PSI Risk Class			0.434[b]
PSI Risk Class I, n (%)	30 (24.0)	32 (23.7)	
PSI Risk Class II, n (%)	29 (23.2)	36 (26.7)	
PSI Risk Class III, n (%)	40 (32.0)	30 (22.2)	
PSI Risk Class IV, n (%)	22 (17.6)	31 (23.0)	
PSI Risk Class V, n (%)	4 (3.2)	6 (4.4)	
PSI Risk Class IV and V, n (%)	26 (20.8)	37 (27.4)	0.214
CURB65 score			0.974[b]
CURB65 score 0, n (%)	46 (36.8)	48 (35.6)	
CURB65 score 1, n (%)	43 (34.4)	46 (34.1)	
CURB65 score 2, n (%)	23 (18.4)	29 (21.5)	
CURB65 score 3, n (%)	12 (9.6)	11 (8.1)	
CURB65 score 4, n (%)	1 (0.8)	1 (0.7)	
CURB65 score 5, n (%)	0 (0)	0 (0)	
CURB65 score 3-4-5, n (%)	13 (10.4)	12 (8.9)	0.680
Admission to intensive care unit, n (%)	1 (0.8)	0 (0.0)	0.481
Systemic steroids during the first 5 days after hospital admission	0 (0)	0 (0)	
Radiology			
Multilobar infiltrates, n (%)	38 (30.4)	47 (34.8)	0.448
Bilateral infiltrates, n (%)	35 (28.0)	44 (32.6)	0.421
Pleural effusion, n (%)	28 (22.4)	27 (20.0)	0.636
Clinical and laboratory data on admission			
Temperature, median (IQR)°C	37.5 (1.2)	37.6 (0.9)	0.463
Heart rate, median (IQR) bpm	94.3 (17.7)	92.7 (16.9)	0.457
Respiratory rate, median (IQR) bpm	20.0 (18.0–24.0)	20.0 (18.0–24.0)	0.454
Systolic blood pressure, median (IQR) mmHg	130.0 (115.0–140.0)	120.0 (110.0–140.0)	0.124
Diastolic blood pressure, median (IQR) mmHg	75.0 (68.0–80.0)	73.5 (67.0–80.0)	0.770
Oxygen saturation, median (IQR) %	95.0 (93.0–97.0)	95.0 (92.0–97.0)	0.159
White blood cells, median (IQR) cell/mm^3	10,580 (7900–15,340)	10,810 (7800–14,050)	0.743
Platelets, median (IQR) cell/L^{-1}	233,500 (178,000–278,750)	226,000 (169,000–281,000)	0.407
Haematocrit, median (IQR) %	38.3 (5.0)	38.6 (4.2)	0.926
Haemoglobin, median (IQR) mg/dL	12.9 (1.9)	12.9 (1.5)	0.914
Sodium, median (IQR) mmol/L	137.0 (135.0–139.0)	137.0 (134.0–140.0)	0.649
Potassium, median (IQR) mmol/L	4.0 (0.5)	3.9 (0.5)	0.223
Albumin, median (IQR) g/dL	3.4 (0.6)	3.3 (0.6)	0.483
Creatinine, median (IQR) mg/dL	0.9 (0.7–1.2)	0.9 (0.7–1.2)	0.714
Urea, median (IQR) mg/dL	32.5 (23.0–50.8)	32.0 (21.0–47.3)	0.581
Low density lipoprotein, median (IQR) mg/dL	90.5 (62.0–159.5)	85.0 (59.0–134.0)	0.675
High density lipoprotein, median (IQR) mg/dL	31.0 (17.3–47.0)	30.0 (16.5–43.5)	0.991
LDH, median (IQR) U/l	278.5 (215.5–419.0)	278.5 (215.5–419.0)	0.843
Cholesterol, meanSD mg/dL	142.1 (26.6)	143.5 (34.8)	0.853
Glucose, median (IQR) mg/dL	113.0 (99.0–136.8)	113.0 (99.0–137.5)	0.706
Aspartate Aminotransferase, median (IQR) U/l	20.0 (15.5–28.5)	20.0 (15.5–28.5)	0.415
Aspartate aminotransferase, median (IQR) U/l	21.0 (15.0–28.3)	21.0 (15.0–28.3)	0.264
Bilirubin, median (IQR) mg/dL	0.7 (0.5–1.2)	0.7 (0.5–1.2)	0.387

(*continued on next page*)

Table 1 (*continued*)

	Individualized group n = 125	Standard group n = 135	P
C-reactive protein, median (IQR) mg/dL	25.7 (10.6–123.8)	25.9 (10.7–124.0)	0.189
Procalcitonin, median (IQR) ng/mL	0.5 (0.2–3.1)	0.5 (0.2–3.1)	0.196
pH Mean (SD)	7.47 (0.06)	7.47 (0.06)	0.760
Bicarbonates, Mean (SD) mEq/L	25.4 (3.8)	24.9 (4.0)	0.491
PaO_2, Mean (SD) mmHg	63.9 (12.5)	65.3 (17.9)	0.568
Antibiotic treatment			
Patients receiving antibiotics before hospital admission, n (%)	40 (32.0)	39 (28.9)	0.586
Amoxicillin, n	2	0	–
Amoxicillin/clavulanate, n	8	7	–
Ampicillin/sulbactam, n	4	4	–
Azithromycin, n	46	47	–
Ceftazidime, n	1	1	–
Ceftriaxone, n	84	86	–
Ciprofloxacin, n	3	2	–
Clarithromycin, n	29	30	–
Levofloxacin, n	44	48	–
Meropenem, n	1	1	–
Piperacillin/tazobactam, n	13	15	–
Amikacin, n	2	1	–
Doxycycline, n	0	1	–
Microbiology			–
Patients with at least one isolated pathogen, n (%)	18 (14.4)	32 (23.7)	0.057
S. pneumoniae, n (%)	10 (8.0)	12 (8.9)	0.797
M. pneumoniae, n (%)	3 (2.4)	9 (6.7)	0.088
C. pneumiphila, n (%)	1 (0.8)	3 (2.2)	0.341
H. influenzae, n (%)	2 (1.6)	1 (0.7)	0.471
L. pneumophila, n (%)	0 (0.0)	3 (2.2)	0.138
S. aureus, n (%)	1 (0.8)	1 (0.7)	0.731
P. aeruginosa, n (%)	0 (0.0)	1 (0.7)	0.519
E. coli, n (%)	0 (0.0)	1 (0.7)	0.519
Enterobacteriaceae, n (%)	0 (0.0)	1 (0.7)	0.519
K. pneumoniae, n (%)	0 (0.0)	1 (0.7)	0.519
Influenza A, n (%)	1 (0.8)	0 (0.0)	0.481

n: number; IQR: 25–75 interquartile range; COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus; BMI: Body Mass Index; PSI: Pneumonia Severity Index;°either non-invasive or invasive mechanical ventilation.

[a] Use of vasopressors.

[b] Among the different risk classes/scores.

Table 2
Early failure occurring within 30 days, pneumonia-related early failure within 30 and late failure occurring within 90 days following the diagnosis of pneumonia in the two study groups according to the intention-to-treat analysis.

	Standard group n = 135	Individualized group n = 125	P
Early failure, n (%)	10 (7.4)	14 (11.2)	0.200
Single components of early failure			
Pneumonia-related complications, n (%)	1 (0.7)	2 (1.6)	0.471
Clinical failure during hospitalization, n (%)	1 (0.7)	5 (4.0)	0.090
A new course of antibiotics given for the pneumonia, n (%)	5 (3.7)	8 (6.4)	0.238
Re-hospitalization, n (%)	7 (5.2)	6 (4.8)	0.558
Mortality, n (%)	1 (0.7)	4 (3.2)	0.162
Pneumonia-related early failure, n (%)	3 (2.2)	4 (3.2)	0.458
Single components of pneumonia-related failure			
Pneumonia-related complications, n (%)	1 (0.7)	3 (2.4)	0.283
Clinical failure due to pneumonia occurring during hospitalization, n (%)	1 (0.7)	2 (1.6)	0.471
A new course of antibiotics given for a relapse of pneumonia, n (%)	3 (2.2)	4 (3.2)	0.466
Re-hospitalization due to a relapse of pneumonia, n (%)	1 (0.7)	2 (1.6)	0.471
Death due to pneumonia, n (%)	0 (0.0)	0 (0.0)	NA
New course of CAP, n (%)	3 (2.2)	4 (3.2)	0.458
Late failure, n (%)	11 (8.1)	12 (9.6)	0.680
Single components of late failure			
A new course of antibiotics for any reason after discontinuation of antibiotic therapy for pneumonia, n (%)	7 (5.2)	8 (6.4)	0.675
Re-hospitalization for any reason, n (%)	6 (4.4)	7 (5.6)	0.669
Death from any reason, n (%)	1 (0.7)	1 (0.8)	0.731

At baseline, no significant differences were observed between the two groups, but a lower rate of bilateral (7–15.9%- vs. 28–34.6%-, p = 0.026) and multilobar infiltrates (8–18.2%- vs. 30–37.0%-, p = 0.029) in the Group PV in comparison with group SP.

Table 3
Adverse events at both 30 and 90-day follow-up in the two study groups according to the intention-to-treat analysis.

	Standard group n = 135	Individualized group n = 125	P
At 30-day follow up			
Anaphylactic and allergic skin reactions, n (%)	1 (0.7)	0 (0.0)	0.519
QTc prolongation, n (%)	0 (0)	1 (0.8)	0.481
Nausea, n (%)	1 (0.7)	0 (0.0)	0.519
Diarrhoea, n (%)	4 (3.0)	4 (3.2)	0.596
Vomiting, n (%)	1 (0.7)	0 (0.0)	0.519
Abdominal pain, n (%)	1 (0.7)	0 (0.0)	0.519
At 90-day follow up			
Anaphylactic and allergic skin reactions, n (%)	1 (0.7)	1 (0.8)	0.731
QTc Prolongation, n (%)	0	1 (0.8)	0.481
Nausea, n (%)	1 (0.7)	0 (0.0)	0.519
Diarrhoea, n (%)	4 (3.0)	4 (3.2)	0.596
Vomiting, n (%)	1 (0.7)	0 (0.0)	0.519
Abdominal pain, n (%)	1 (0.7)	0 (0.0)	0.519

No adverse events including toxicity, convulsions, tendinopathies, peripheral neuropathy, at 30-day follow up and Clostridium difficile – associated colitis, toxicity, convulsions, tendinopathies, peripheral neuropathy at 90-day follow up were recorded in the study population.

No significant differences were detected between Group PV and Group SP in terms of median (IQR) time to clinical stability: 4 (4–5) days *vs*. 4 (3–5) days, respectively (p = 0.077). However, a higher prevalence of patients who underwent protocol violation was identified in the group of patients who reached clinical stability on day 4 or 5 after hospital admission in comparison with those who reached clinical stability in the first 72 h (34 patients, 41.5% vs. 10 patients, 23.3%, p-value = 0.043).

5. Discussion

The present trial was interrupted because of a higher prevalence at the ITT analysis of early failure at 30 days in hospitalized CAP patients treated with an individualized duration of antibiotic therapy according to time to clinical stability in comparison with those receiving a duration of therapy dictated by the treating physician. This difference (7.4% in the standard *vs*. 11.2% in the individualized group) was neither statistically significant nor was exceeding the 5% pre-planned delta. However, the monitoring and safety board committee decided to interrupt the study because, at the time of the conduct of the trial, this was the first trial ever evaluating clinical stability as a proxy to shorten antibiotic exposure in hospitalized CAP patients and because of the higher rate of 30-day mortality in the individualized group in comparison to standard group.

During the writing of the present study, a Spanish multicenter RCT was published suggesting that withdrawing antibiotic treatment based on clinical stability might be not inferior to standard duration in terms of resolution/improvement in signs and symptoms and CAP-related symptoms measured with an 18-item questionnaire [6]. This study has paved the way towards the need of individualized antibiotic treatment in CAP. Although, ours should be considered a study with unexpected negative outcomes, several teaching points might be retrieved, more from a research rather than a clinical point of view.

Firstly, criteria used by the monitoring and safety board committee to stop a non-inferiority trial are not very well defined in clinical research, especially in RCTs dealing with the outcome mortality. The pre-planned delta adopted in non-inferiority trial to define the sample size, usually refers to outcome data collected at the end of the study. It should be questioned what is the significant margin to be considered by the monitoring and safety board committee in order to stop a non-inferiority trial at different time points. In our case the decision of the monitoring and safety board committee might have been too conservative, introducing a bias in the conduction of the study. However, a four-fold increase in 30-day mortality registered in the individualized group in comparison with the standard one was considered an important, although not statistically significant, result for the trial interruption.

Secondly, the major finding of a 17% of protocol violation with a substantial difference in primary outcome in the ITT *vs*. PP analysis lead us to draw three main conclusions. (a) A "pragmatic" RCT might not be the perfect design to evaluate duration of antibiotic therapy in CAP. This study showed that, even if in a RCT, when physicians are dealing with duration of antibiotic therapy, they still tend to prolong it up to eight days, as previously documented in an observational study [9]. (b) The 5-day cut off for TCS we selected as an inclusion criterion might not be appropriate. We found: (1) a higher prevalence of patients who underwent protocol violation among those who reached clinical stability on day 4 or 5, in comparison with those who reached clinical stability in the first 72 h after hospital admission; (2) a significant one-day difference in TCS of 3 vs. 4 days between the standard and individualized group. In light of these results, someone could speculate that the 5-day cut-off for TCS could not be appropriate as an inclusion criterion for this type of studies and that a 3-day cut-off should be considered for future similar RCTs. (c) Time to clinical stability might not be the perfect marker to individualized antibiotic duration in hospitalized patients with CAP, or at least not for all of them. The rate of protocol violation of patients who underwent a longer duration of therapy and who experienced worse outcomes during the study might support this hypothesis. In a secondary analysis of the database, no clinically and statistically significant differences were detected between patients who did or did not undergo protocol violation. Thus, no specific characteristics of patients who might or might not benefit of an individualized duration of antibiotic therapy based on time to clinical stability might be proposed so far. One important limitation of the present study is that no objective report from the investigators of the reasons for protocol violation has been included in the study design. Finally, our results raise a question mark on international experts' opinions recommending to shorten antibiotic duration in all patients with CAP.

Thirdly, we should acknowledge that 129 (20%) patients declined to participate in a study proposing them to discontinue antibiotic therapy. A feeling of "protection" can be felt by the patient under antibiotic therapy than when the antibiotic

Table 4
Baseline demographics, comorbidities, disease severity, clinical, laboratory and radiological findings on admission, microbiology, and antibiotic therapy data of the study population according to the per protocol analysis.

	Standard group n = 135	Individualized group n = 81	P
Demographics			
Male, n (%)	79 (58.5)	48 (59.3)	0.915
Age, median (IQR) years	63.0 (46.0–77.0)	56.0 (43.5–76.5)	0.355
BMI, Mean (SD)	23.94.6	24.74.4	0.341
Healthcare-associated pneumonia, n (%)	9 (6.7)	2 (2.5)	0.149
Nursing Home Residency, n (%)	1 (0.7)	0 (0.0)	0.625
Comorbidities			
Neoplastic disease, n (%)	4 (3.0)	2 (2.5)	0.597
COPD, n (%)	25 (18.5)	15 (18.5)	1.000
Cerebrovascular accident, n (%)	11 (8.1)	2 (2.5)	0.075
Renal disease, n (%)	13 (9.6)	6 (7.4)	0.577
Chronic renal Failure, n (%)	11 (8.1)	5 (6.2)	0.592
Liver disease, n (%)	5 (3.7)	3 (3.7)	0.653
Arterial hypertension, n (%)	42 (31.1)	29 (35.8)	0.477
Coronary artery disease, n (%)	10 (7.4)	6 (7.4)	1.000
Congestive heart failure, n (%)	17 (12.6)	9 (11.1)	0.746
Atrial fibrillation, n (%)	18 (13.3)	6 (7.4)	0.180
Diabetes mellitus, n (%)	20 (14.8)	14 (17.3)	0.630
Hyperlipidaemia, n (%)	16 (11.9)	14 (17.3)	0.264
Prior acute myocardial infarction, n (%)	16 (11.9)	8 (9.9)	0.655
HIV infection, n (%)	4 (3.0)	3 (3.7)	0.526
Severity on admission			
Ventilatory support, n (%)	4 (3.0)	5 (6.2)	0.212
Blood pressure support, n (%)[a]	1 (0.8)	0 (0.0)	0.615
Mental status change, n (%)	5 (3.7)	6 (7.4)	0.236
Pneumonia Severity Index	37 (27.4)	17 (21.0)	0.291
Risk Class IV and V, n (%)			
CURB65 score 3-4-5, n (%)	12 (8.9)	6 (7.4)	0.703
Admission to intensive care unit, n (%)	0 (0.0)	0 (0.0)	–
Radiology			
Multilobar infiltrates, n (%)	47 (34.8)	30 (37.0)	0.741
Bilateral infiltrates, n (%)	44 (32.6)	28 (34.6)	0.766
Pleural effusion, n (%)	27 (20.0)	18 (22.2)	0.697
Clinical and laboratory data on admission			
Temperature, mean (SD)°C	37.6 (0.9)	37.4 (1.2)	0.217
Heart rate,, mean (SD) bpm	92.7 (16.9)	94.5 (18.1)	0.473
Respiratory rate, median (IQR) bpm	20.0 (18.0–24.0)	20.0 (18.0–24.0)	0.788
Systolic blood pressure, median (IQR) mmHg	120.0 (110.0–140.0)	130.0 (110.0–140.0)	0.343
Diastolic blood pressure, median (IQR) mmHg	73.5 (67.0–80.0)	71.0 (65.0–80.0)	0.449
Oxygen saturation, median (IQR) %	95.0 (92.0–97.0)	96.0 (92.8–98.0)	0.121
White blood cells, median (IQR) cell/mm^3	10,810 (7800–14,050)	10,530 (7680–15,990)	0.591
Platelets, median (IQR) cell/L^{-1}	226,000 (169,000–281,000)	235,000 (187,000–289,000)	0.383
Haematocrit, median (IQR) %	38.6 (4.2)	38.3 (5.2)	0.993
Haemoglobin, median (IQR) mg/dL	12.9 (1.5)	12.9 (1.9)	0.865
Sodium, median (IQR) mmol/L	137.0 (134.0–140.0)	137.0 (134.0–139.0)	0.568
Potassium, median (IQR) mmol/L	3.9 (0.5)	4.0 (0.5)	0.300
Albumin, mean (SD) g/dL	3.3 (0.6)	3.4 (0.7)	0.808
Creatinine, median (IQR) mg/dL	0.9 (0.7–1.2)	0.9 (0.7–1.1)	0.762
Urea, median (IQR) mg/dL	32.0 (21.0–47.3)	32.0 (21.8–45.5)	0.922
Low density lipoprotein, median (IQR) mg/dL	85.0 (59.0–134.0)	98.0 (73.0–153.5)	0.573
High density lipoprotein, median (IQR) mg/dL	30.0 (16.5–43.5)	29.0 (20.5–46.5)	0.780
LDH, median (IQR) U/l	278.5 (215.5–419.0)	266.0 (235.5–395.0)	0.848
Cholesterol, mean (SD) mg/dL	143.5 (34.8)	147.1 (25.9)	0.694
Glucose, median (IQR) mg/dL	113.0 (99.0–137.5)	107.0 (95.5–139.0)	0.457
Aspartate Aminotransferase, median (IQR) U/l	20.0 (15.5–28.5)	25.5 (20.0–35.0)	0.096
Aspartate aminotransferase, median (IQR) U/l	21.0 (15.0–28.3)	29.0 (15.5–41.8)	0.181
Bilirubin, median (IQR) mg/dL	0.7 (0.5–1.2)	0.6 (0.4–0.9)	0.753
C-reactive protein, median (IQR) mg/dL	25.9 (10.7–124.0)	33.3 (15.8–137.5)	0.323
Procalcitonin, median (IQR) ng/mL	0.5 (0.2–3.1)	0.5 (0.1–1.6)	0.523
pH mean (SD)	7.47 (0.06)	7.47 (0.07)	0.796
Bicarbonates, median (IQR) mEq/L	25.0 (23.0–26.7)	24.8 (22.9–27.7)	0.321
PaO_2, mean (SD) mmHg	65.3 (17.9)	63.9 (13.9)	0.675
Antibiotic treatment			
Patients receiving antibiotics before hospital admission, n (%)	39 (28.9)	24 (29.6)	0.908
Amoxicillin, n	0	1	
Amoxicillin/clavulanate, n	7	4	
Ampicillin/sulbactam, n	4	2	
Azithromycin, n	47	31	
Ceftazidime, n	1	1	
Ceftriaxone, n	86	58	
Ciprofloxacin, n	2	2	

Table 4 (*continued*)

	Standard group n = 135	Individualized group n = 81	P
Clarithromycin, n	30	22	
Levofloxacin, n	48	35	
Meropenem, n	1	1	
Piperacillin/tazobactam, n	15	8	
Amikacin, n	1	0	
Doxycycline, n	1	0	
Microbiology			
Patients with at least one isolated pathogen, n (%)	32 (23.7)	13 (16.0)	0.180
S. pneumoniae, n (%)	12 (8.9)	6 (7.4)	0.703
M. pneumoniae, n (%)	9 (6.7)	2 (2.5)	0.149
C. pneumiphila, n (%)	3 (2.2)	1 (1.2)	0.518
H. influenzae, n (%)	1 (0.7)	2 (2.5)	0.316
L. pneumophila, n (%)	3 (2.2)	0 (0.0)	0.242
S. aureus, n (%)	1 (0.7)	1 (1.2)	0.610
P. aeruginosa, n (%)	1 (0.7)	0 (0.0)	0.625
E. coli, n (%)	1 (0.7)	0 (0.0)	0.625
Enterobacteriaceae, n (%)	1 (0.7)	0 (0.0)	0.625
K. pneumoniae, n (%)	1 (0.7)	0 (0.0)	0.625
Influenza A, n (%)	0 (0.0)	1 (1.2)	0.375

n: number; IQR: 25–75 interquartile range; COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus; BMI: Body Mass Index;°either non-invasive or invasive mechanical ventilation.

[a] Use of vasopressors.

Table 5
Early failure within 30 days, pneumonia-related early failure within 30 and late failure within 90 days following the diagnosis of pneumonia in the two study groups according to the per protocol analysis.

	Standard group n = 135	Individualized group n = 81	P
Early failure	10 (7.4)	6 (7.4)	0.612
Single components of early failure			
Pneumonia-related complications, n (%)	1 (0.7)	2 (2.5)	0.316
Clinical failure during hospitalization, n (%)	1 (0.7)	2 (2.5)	0.316
A new course of antibiotics given for the pneumonia, n (%)	5 (3.7)	5 (6.2)	0.302
Re-hospitalization, n (%)	7 (5.2)	3 (3.7)	0.616
Mortality, n (%)	1 (0.7)	2 (2.5)	0.316
Pneumonia-related early failure	3 (2.2)	3 (3.7)	0.403
Single components of pneumonia-related early failure			
Pneumonia-related complications, n (%)	1 (0.7)	1 (1.2)	0.610
Clinical failure due to pneumonia occurring during hospitalization, n (%)	1 (0.7)	1 (1.2)	0.610
A new course of antibiotics given for a relapse of pneumonia, n (%)	3 (2.2)	3 (3.7)	0.403
Re-hospitalization due to a relapse of pneumonia, n (%)	1 (0.7)	1 (1.2)	0.610
Death due to pneumonia, n (%)	0 (0.0)	0 (0.0)	NA
New course of CAP, n (%)	3 (2.2)	4 (3.2)	0.458
Late failure	11 (8.1)	6 (7.4)	0.845
Single components of late failure			
A new course of antibiotics for any reason after discontinuation of antibiotic therapy for pneumonia, n (%)	7 (5.2)	5 (6.2)	0.759
Re-hospitalization for any reason, n (%)	6 (4.4)	4 (4.9)	0.556
Death from any reason, n (%)	1 (0.7)	0 (0.0)	0.625

discontinuation is proposed for a trial.

Fourthly, 44% of the screened patients were recruited in the study and only 18% were randomized. This finding might significantly limit the inference of the results (too strict selection criteria). The present study being the first RTC ever on individualizing duration of antibiotic therapy on each patient's clinical stability, only immunocompetent patients who quickly responded to appropriate antibiotic therapy during the first five days of hospitalization were selected. This might represent a non-severe population of CAP patients who are usually managed as outpatients.

Fifthly, the choice of a composite outcome might be one of the limitations, in light of different weights that each single component of the primary endpoint have (e.g., mortality *vs*. disease-specific complications due to pneumonia). The choice of a hard endpoint should be suggested for future studies, although this might imply to be less conservative in selecting the study population and, thus, including patients with mild-to-moderate immunodepression. Finally, it would be important in future similar RCTs to collect specific cause of failure, rehospitalization or death.

In conclusion, this RCT was interrupted because of a higher prevalence of early failure, including mortality, at 30 days in hospitalized CAP patients treated with an individualized duration of antibiotic therapy according to time to clinical stability in comparison with those receiving a duration of therapy dictated by the treating physician. Further studies are needed to understand if shortening antibiotic duration can be safely applied in all hospitalized patients with CAP.

Table 6
Adverse events at both 30 and 90-day follow-up in the two study groups according to the per protocol analysis.

	Standard group n = 135	Individualized group n = 81	P
At 30-day follow up			
Anaphylactic and allergic skin reactions, n (%)	1 (0.7)	0 (0.0)	0.625
Nausea, n (%)	1 (0.7)	0 (0.0)	0.625
Diarrhoea, n (%)	4 (3.0)	1 (1.2)	0.379
Vomiting, n (%)	1 (0.7)	0 (0.0)	0.625
Abdominal pain, n (%)	1 (0.7)	0 (0.0)	0.625
At 90-day follow up			
Anaphylactic and allergic skin reactions, n (%)	1 (0.7)	1 (0.8)	0.625
Nausea, n (%)	1 (0.7)	0 (0.0)	0.625
Diarrhoea, n (%)	4 (3.0)	1 (1.2)	0.379
Vomiting, n (%)	1 (0.7)	0 (0.0)	0.625
Abdominal pain, n (%)	1 (0.7)	0 (0.0)	0.625

No adverse events including toxicity, convulsions, tendinopathies, peripheral neuropathy, QTc prolongation at 30-day follow up and Clostridium difficile – associated colitis, toxicity, convulsions, tendinopathies, peripheral neuropathy, QTc prolongation at 90-day follow up were recorded in the study population.

Table 7
Primary composite study outcome occurring within 30 days following the diagnosis of pneumonia in patients who underwent protocol violation (PV) and who followed the study protocol (SP) in the individualized group.

	Group PV	Group SP	p
Primary composite outcome, n (%)	8 (18.2)	6 (7.4)	0.068
Single components of primary outcome			
Pneumonia-related complications, n (%)	0 (0)	2 (2.5)	0.418
Clinical failure during hospitalization, n (%)	3 (6.8)	2 (2.5)	0.234
A new course of antibiotics given for the pneumonia, n (%)	3 (6.8)	5 (6.2)	0.582
Re-hospitalization, n (%)	3 (6.8)	3 (3.7)	0.355
Mortality, n (%)	2 (4.5)	2 (2.5)	0.441

Funding

This study was supported by an unrestricted grant from the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy. The funding source did not have any involvement in either collection, analysis and interpretation of the data, nor in the writing of the report, nor in the decision to submit the paper for publication.

Contributions

Study concept and design: SA, JR, FB. Acquisition of data: FG, ST, MC, VV, MM, MC, RP, MDF, GM, PF, LR, MD, MV, AV, ET, MB, AB, BM. Analysis and interpretation of data: SA, FB, JR, TW, GS. Drafting of the manuscript: SA, JR, FB, GS. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: SA, TW, GS. Study supervision: FB, JR. All authors read and approved the final manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication.

Declaration of conflict of interests

All the authors declare no competing interests.

Acknowledgments

The authors would like to acknowledge the assistance of Letizia Corinna Morlacchi and Nicola Montano (Policlinico Hospital, Milan), Sandro Amaducci (San Carlo Hospital, Milan), Paula Peyrani (University of Louisville, KY, USA), Fabio Franzetti (Luigi Sacco Hospital, Milan), Paolo Rossi and Silvia Duranti (Santa Maria della Misericordia Hospital, Udine), Giulia Bonaiti, Giulia Suigo and Alberto Pesci MD (San Gerardo Hospital, Monza), Stefano Nava, Silvia Libassi and Pierluigi Viale (Sant'Orsola Hospital, Bologna), Anna Maspero (San Fermo della Battaglia Hospital, Como), Elena Parazzini and Lucia Testoni (Humanitas Research Institute, Rozzano), Luigi Zucchi (Santa Maria Nuova Hospital, Reggio Emilia), Claudio Viscoli and Simone Dini (San Martino Hospital, Genova), Benedetta Cattaneo and Lisa Pancini (Policlinico San Donato, Milano), and Riccardo Fantini (Policlinico, Modena). No financial support has been received for this trial.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.pupt.2017.06.008.

References

[1] R.G. Wunderink, G.W. Waterer, Community-acquired pneumonia, N. Engl. J. Med. 370 (2014) 1863.
[2] M. Woodhead, F. Blasi, S. Ewig, J. Garau, G. Huchon, M. Ieven, A. Ortqvist, T. Schaberg, A. Torres, G. van der Heijden, R. Read, T.J. Verheij, Joint taskforce of the European Respiratory Society and European Society for clinical microbiology and infectious diseases. Guidelines for the management of adult lower respiratory tract infections, Clin. Microbiol. Infect. 17 (Suppl 6) (2011) E1–E59.
[3] J.A. Ramirez, S. Vargas, Brier ME. RitterGW, A. Wright, S. Smith, D. Newman, J. Burke, M. Mushtaq, 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, Arch. Intern Med. 159 (1999) 2449–2454.
[4] J.J. Oosterheert, M.J. Bonten, M.M. Schneider, E. Buskens, J.W. Lammers, W.M. Hustinx, M.H. Kramer, J.M. Prins, P.H. Slee, K. Kaasjager, A.I. Hoepelman, Effectiveness of early switch from intravenous to oral antibiotics in severe community acquired pneumonia: multicentre randomized trial, BMJ 333 (2006) 1193–1195.
[5] S. Aliberti, F. Giuliani, J. Ramirez, F. Blasi, How to choose the duration of antibiotic therapy in patients with pneumonia, Curr. Opin. Infect. Dis. 28 (2015) 177–184.
[6] A. Uranga, P.P. España, A. Bilbao, J.M. Quintana, I. Arriaga, M. Intxausti, J.L. Lobo, L. Tomás, J. Camino, J. Nuñez, A. Capelastegui, Duration of antibiotic

treatment in community-acquired pneumonia: a multicenter Randomized clinical trial, JAMA Intern Med. 176 (9) (2016) 1257–1265.
[7] L.A. Mandell, R.G. Wunderink, A. Anzueto, J.G. Bartlett, G.D. Campbell, N.C. Dean, S.F. Dowell, T.M. File Jr., D.M. Musher, M.S. Niederman, A. Torres, C.G. Whitney, Infectious diseases Society of America; American Thoracic Society. Infectious diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults, Clin. Infect. Dis. 44 (Suppl 2) (2007) S27–S72.
[8] W.S. Lim, S.V. Baudouin, R.C. George, A.T. Hill, C. Jamieson, I. Le Jeune, J.T. Macfarlane, R.C. Read, H.J. Roberts, M.L. Levy, M. Wani, M.A. Woodhead, Pneumonia Guidelines Committee of the BTS Standards of Care Committee. BTS guidelines for the management of community acquired pneumonia in adults: update 2009, Thorax 64 (Suppl 3) (2009) iii1–55.
[9] S. Aliberti, F. Blasi, A.M. Zanaboni, P. Peyrani, P. Tarsia, S. Gaito, J.A. Ramirez, Duration of antibiotic therapy in hospitalised patients with community-acquired pneumonia, Eur. Respir. J. 36 (2010) 128–134.
[10] American Thoracic Society; Infectious Diseases Society of America, Guidelines for the management of adults with hospital-acquired, ventilatory-associated, and healthcare-associated pneumonia, Am. J. Respir. Crit. Care Med. 171 (2005) 388–416.
[11] S. Aliberti, A.M. Zanaboni, T. Wiemken, A. Nahas, S. Uppatla, L.C. Morlacchi, P. Peyrani, F. Blasi, J. Ramirez, Criteria for clinical stability in hospitalised patients with community-acquired pneumonia, Eur. Respir. J. 42 (2013) 742–749.
[12] S. Aliberti, A. Amir, P. Peyrani, M. Mirsaeidi, M. Allen, B.K. Moffett, J. Myers, F. Shaib, M. Cirino, J. Bordon, F. Blasi, J.A. Ramirez, Incidence, etiology, timing, and risk factors for clinical failure in hospitalized patients with community-acquired pneumonia, Chest 134 (2008) 955–962.
[13] EA. Halm, MJ. Fine, WN. Kapoor, DE. Singer, TJ. Marrie, AL. Siu, Instability on hospital discharge and the risk of adverse outcomes in patients with pneumonia, Arch. Intern Med.;162:1278–1284.