Discontinuing β-lactam treatment after 3 days for patients with community-acquired pneumonia in non-critical care wards (PTC): a double-blind, randomised, placebo-controlled, non-inferiority trial

Aurélien Dinh, Jacques Ropers, Clara Duran, Benjamin Davido, Laurène Deconinck, Morgan Matt, Olivia Senard, Aurore Lagrange, Sabrina Makhloufi, Guillaume Mellon, Victoire de Lastours, Frédérique Bouchand, Emmanuel Mathieu, Jean-Emmanuel Kahn, Elisabeth Rouveix, Julie Grenet, Jennifer Dumoulin, Thierry Chinet, Marion Pépin, Véronique Delcey, Sylvain Diamantis, Daniel Benhamou, Virginie Vitrat, Marie-Christine Dombret, Bertrand Renaud, Christian Perronne, Yann-Erick Claessens, José Labarère, Jean-Pierre Bedos, Philippe Aegerter, Anne-Claude Crémieux, for the Pneumonia Short Treatment (PTC) Study Group

Summary

Background Shortening the duration of antibiotic therapy for patients admitted to hospital with community-acquired pneumonia should help reduce antibiotic consumption and thus bacterial resistance, adverse events, and related costs. We aimed to assess the need for an additional 5-day course of β-lactam therapy among patients with community-acquired pneumonia who were stable after 3 days of treatment.

Methods We did this double-blind, randomised, placebo-controlled, non-inferiority trial (the Pneumonia Short Treatment [PTC]) in 16 centres in France. Adult patients (aged ≥18 years) admitted to hospital with moderately severe community-acquired pneumonia (defined as patients admitted to a non-critical care unit) and who met prespecified clinical stability criteria after 3 days of treatment with β-lactam therapy were randomly assigned (1:1) to receive β-lactam therapy (oral amoxicillin 1 g plus clavulanate 125 mg three times a day) or matched placebo for 5 extra days. Randomisation was done using a web-based system with permuted blocks with random sizes and stratified by randomisation site and Pneumonia Severity Index score. Participants, clinicians, and study staff were masked to treatment allocation. The primary outcome was cure 15 days after first antibiotic intake, defined by apyrexia (temperature ≤37·8°C), resolution or improvement of respiratory symptoms, and no additional antibiotic treatment for any cause. A non-inferiority margin of 10 percentage points was chosen. The primary outcome was assessed in all patients who were randomly assigned and received any treatment (intention-to-treat [ITT] population) and in all patients who received their assigned treatment (per-protocol population). Safety was assessed in the ITT population. This study is registered with ClinicalTrials.gov, NCT01963442, and is now complete.

Findings Between Dec 19, 2013, and Feb 1, 2018, 706 patients were assessed for eligibility, and after 3 days of β-lactam treatment, 310 eligible patients were randomly assigned to receive either placebo (n=157) or β-lactam treatment (n=153). Seven patients withdrew consent before taking any study drug, five in the placebo group and two in the β-lactam group. In the ITT population, median age was 73·0 years (IQR 57·0–84·0) and 123 (41%) of 303 participants were female. In the ITT analysis, cure at day 15 occurred in 117 (77%) of 152 participants in the placebo group and 102 (68%) of 151 participants in the β-lactam group (between-group difference of 9·42%, 95% CI −0·38 to 20·04), indicating non-inferiority. In the per-protocol analysis, 113 (78%) of 145 participants in the placebo treatment group and 100 (68%) of 146 participants in the β-lactam treatment group were cured at day 15 (difference of 9·44% [95% CI −0·15 to 20·34]), indicating non-inferiority. Incidence of adverse events was similar between the treatment groups (22 [14%] of 152 in the placebo group and 29 [19%] of 151 in the β-lactam group). The most common adverse events were digestive disorders, reported in 17 (11%) of 152 patients in the placebo group and 28 (19%) of 151 patients in the β-lactam group. By day 30, three (2%) patients had died in the placebo group (one due to bacteraemia due to *Staphylococcus aureus*, one due to cardiogenic shock after acute pulmonary oedema, and one due to heart failure associated with acute renal failure) and two (1%) in the β-lactam group (due to pneumonia recurrence and possible acute pulmonary oedema).

Interpretation Among patients admitted to hospital with community-acquired pneumonia who met clinical stability criteria, discontinuing β-lactam treatment after 3 days was non-inferior to 8 days of treatment. These findings could allow substantial reduction of antibiotic consumption.

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Infectious Disease Unit (A Dinh MD, C Duran MSc, B Davido MD, M Matt MD, S Makhloufi MD, G Mellon MD, Prof C Perronne PhD) **and Pharmacy** (F Bouchand PharmD), **Raymond-Poincaré University Hospital, AP-HP, Paris Saclay University, Garches, France; Clinical research unit, Pitié-Salpêtrière University Hospital, AP-HP, Paris, France** (J Ropers PharmD); **Infectious Disease Department, Bichat University Hospital, AP-HP, University of Paris, Paris, France** (L Deconinck MD); **Infectious Disease Department, Marne La Vallée Hospital, GHEF, Marne La Vallée, France** (O Senard MD); **Pneumology Department, Pontoise Hospital, Pontoise, France** (A Lagrange MD); **Internal Medicine Department, Beaujon University Hospital, AP-HP, University of Paris, Clichy, France** (Prof V de Lastours PhD); **Emergency Department, Foch Hospital, Suresnes, France** (E Mathieu MD); **Internal Medicine Department** (Prof J-E Kahn PhD, Prof E Rouveix PhD), **Emergency Department** (J Grenet MD), **Pneumology Department** (J Dumoulin MD, Prof T Chinet PhD), **and Geriatric Department** (M Pépin PhD), **Ambroise Paré University Hospital, AP-HP, Paris Saclay University, Boulogne-Billancourt, France; Internal Medicine Department, Lariboisière Hospital, AP-HP, University of Paris, Paris, France** (V Delcey MD); **Infectious Disease Department, Melun Hospital, Melun, France**

(S Diamantis MD); **Pneumology Department, Bois-Guillaume University Hospital, Rouen, France** (D Benhamou MD); **Internal Medicine, Annecy Hospital, Annecy, France** (V Vitrat MD); **Pneumology Department, Bichat University Hospital, AP-HP, University of Paris, Paris, France** (M-C Dombret MD); **Emergency Department, Cochin University Hospital, AP-HP, Paris Centre University, Paris, France** (Prof B Renaud PhD); **Emergency Department, Princesse Grace Hospital, Monaco** (Prof Y-E Claessens PhD); **Quality of Care Unit, Grenoble University Hospital, Grenoble Alpes University, Grenoble, France** (Prof J Labarère PhD); **Intensive Care Unit, André Mignot Hospital, Versailles, France** (J-P Bedos MD); **UMRS 1169 VIMA, INSERM, Versailles Saint-Quentin University, Versailles, France** (Prof P Aegerter PhD); **Infectious Disease Department, Saint-Louis University Hospital, AP-HP, University of Paris, Paris, France** (Prof A-C Crémieux PhD)

Correspondence to:
Dr Aurélien Dinh, Infectious Disease Unit, Raymond-Poincaré University Hospital, AP-HP Paris Saclay University, 92380 Garches, France
aurelien.dinh@aphp.fr

See Online for appendix

Research in context

Evidence before this study

Community-acquired pneumonia is a major cause of antibiotic prescriptions. Although most guidelines recommend 5–8 days of antibiotic treatment, duration of treatment is not evidence based. We searched PubMed, with no language restrictions, for clinical studies published between Feb 28, 1947, and Aug 19, 2020, focusing on duration of antibiotic treatment for community-acquired pneumonia in adults using the terms "antibiotic duration" AND "community-acquired pneumonia" AND "randomized OR randomised" AND "adult". Among the 277 studies found, most randomised trials or randomised placebo-controlled trials focused on comparing treatment durations longer than or equal to 5 days in patients admitted to hospital. Only one clinical trial in 2006, with a small sample size (n=119), had studied a treatment duration of 3 days in adult patients admitted to hospital with few comorbidities. A randomised controlled trial with sufficient sample size was thus warranted to assess this short treatment duration in current practice among patients admitted to non-critical care units with community-acquired pneumonia.

Added value of this study

We found that 3 days of β-lactam therapy is non-inferior to 8 days of treatment among non-immunocompromised patients with moderately severe community-acquired pneumonia (ie, admitted to a non-critical care unit, without serious respiratory insufficiency, and without septic shock) and who met clinical stability criteria after 3 days of β-lactam monotherapy. These results appear to be consistent across subgroups of older patients and those at high risk of not being cured (Pneumonia Severity Index score of >91). Reducing treatment duration could have a beneficial effect on bacterial resistance, costs, and occurrence of adverse events.

Implications of all the available evidence

We provide clear evidence from a double-blind, randomised, placebo-controlled, non-inferiority trial that we can safely discontinue β-lactam treatment after 3 days if the patient meets clinical stability criteria.

Introduction

Lower respiratory tract infections are one of the most common indications for antibiotic use in community and hospital settings.[1,2] Community-acquired pneumonia results in 600 000–800 000 admissions to hospital annually in the USA, with the highest incidence in those aged 65 years and older.[3–5] The number of cases due to community-acquired pneumonia and the number of associated deaths have been increasing in parallel with the ageing of the global population over the past decade.[6]

US guidelines for adults with community-acquired pneumonia recommend no less than 5 days of antibiotic treatment, with discontinuation based on clinical stability criteria,[7–9] as supported by a 2016 study,[10] whereas according to European guidelines, 8 days of treatment is recommended.[11] Therefore, the optimal duration of antibiotic therapy is not well established, and in daily practice most physicians usually treat their patients for 7–10 days.[12,13] A few studies from the 1940s and 1970s among adult patients, which were underpowered and non-randomised,[14–16] and one study from 2006 that focused on mild cases of community-acquired pneumonia,[17] have suggested that antibiotic treatment for fewer than 5 days could be sufficient, but these data are insufficient to recommend this treatment duration in patients admitted to hospital for community-acquired pneumonia. Shortened treatment durations would lead to reduced antibiotic consumption at the individual and population level, thus probably restricting the emergence of bacterial resistance,[18,19] and would bring several other benefits, including reducing occurrence of adverse events and costs.[18,20]

We aimed to assess the need for an additional 5-day course of treatment with β-lactam treatment among patients admitted to hospital for community-acquired pneumonia, who were clinically stable after 3 days of β-lactam treatment.

Methods

Study design and participants

The Pneumonia Short Treatment (PTC) trial was a double-blind, randomised, placebo-controlled, non-inferiority trial with two parallel groups in 16 French hospitals (appendix p 3).

Patients were recruited in medical wards by investigators. Eligible patients were aged 18 years or older, with moderately severe community-acquired pneumonia, treated with β-lactam monotherapy according to European guidelines (ie, amoxicillin plus clavulanate [oral or intravenous] or parenteral third-generation cephalosporin [ceftriaxone or cefotaxime]),[11,21] and who after 72 h of treatment had a clinical response, defined by the presence of all stability criteria. Community-acquired pneumonia was defined as the presence of at least one acute clinical sign compatible with pneumonia (eg, dyspnoea, cough, purulent sputum, or crackles), temperature above 38°C in the 48 h before admission to hospital, and a new pulmonary infiltrate on chest x-ray or CT scan (on day 0 or within 3 days of admission to hospital). Severity of disease was defined by the nature of admission to hospital, with mild disease not requiring admission to hospital, moderately severe disease requiring admission to a non-critical care unit, and severe disease requiring admission to a critical care unit. Stability criteria were defined, according to Halm et al[22]

and the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) guidelines in 2007,[4] as apyrexia (temperature ≤37·8°C), heart rate below 100 beats per min, respiratory rate below 24 breaths per min, arterial oxygen saturation of 90% or higher, systolic blood pressure of 90 mm Hg or higher, and normal mental status.

Key exclusion criteria were signs of severe or complicated community-acquired pneumonia (ie, abscess, massive pleural effusion, serious chronic respiratory infection), known immunosuppression, health-care-associated pneumonia or suspicion of aspiration pneumonia, any other infection necessitating concomitant antibiotic treatment, suspected or confirmed legionellosis, and infection due to intracellular microorganisms. Additional inclusion and exclusion criteria are listed in the appendix (pp 6–7).

The trial was approved by the Versailles/Saint-Germain-en-Laye ethics committee (Comité de Protection des Personnes number 13024), The French National Agency for Safety of Medicines and Health Products (number 130931A-41), and the French Data Protection Agency and was overseen by an independent Data Monitoring Safety Board. The study was done in accordance with the ethical principles of the Declaration of Helsinki and the Guidelines for Good Clinical Practice. All participants provided written informed consent.

Randomisation and masking

After 72 h of β-lactam treatment, patients who met all eligibility criteria were randomly assigned (1:1), using a web-based system (CleanWeb, Telemedicine Technologies, Boulogne-Billancourt, France) with permuted blocks of random block size with no size limits and stratified by randomisation site and Pneumonia Severity Index (PSI) score (≤70 or >70),[23] to receive either oral amoxicillin plus clavulanate treatment (β-lactam group) or matched placebo. The randomisation sequence was generated by an independent statistician. Sets of prepared study medication packages containing 30 pills of amoxicillin plus clavulanate or placebo tablets were kept in the pharmacy of each centre. The placebo tablets were indistinguishable from the amoxicillin plus clavulanate tablets in the study in terms of blister packaging, colour, taste, and design. Each package was given a randomisation number to ensure masking of the patients, treating physicians, investigators, pharmacists, and study coordinators.

Procedures

Patients assigned to the β-lactam group were given two pills of 500 mg of amoxicillin plus 62·5 mg of clavulanate orally three times a day for 5 days (from 2014 to September, 2017, the pills used were produced by Mylan, Canonsburg, PA, USA; and from October, 2017, to February, 2018, by Sandoz, Holzkirchen, Germany), and patients in the placebo group were given matched placebo (Bertin Pharma, Orléans, France) on the same schedule.

At the inclusion visit—ie, day 3 of β-lactam treatment—whether the patient met all the community-acquired pneumonia stability criteria was determined by the investigator before enrolling the patient. The patients' vital signs and community-acquired pneumonia score (scored using a validated short questionnaire, presented in the appendix [pp 12–13])[24] were recorded. Biological and microbiological assessments were done at the discretion of the treating physicians. Demographic, clinical, and radiological data, results of usual blood tests, and disease severity determined with the PSI score at the start of antibiotic treatment (day 0) were collected retrospectively from medical records for each patient.[23] Pneumonia-related symptoms were also scored retrospectively for day 0 using the community-acquired pneumonia score.

On day 3, after random allocation to treatment, patients were given their allocated medication and discharged at the treating physician's discretion. Compliance to treatment and side-effects were recorded during medical interviews and by self-report in the study booklet during the study treatment period (days 3–8). The study coordinator at each centre telephoned each patient on day 8 to ensure that they were following the study procedures and to collect their community-acquired pneumonia score questionnaire and any adverse events since discharge. Patients were asked to return the study drug blister packaging on day 15 to assess compliance. Face-to-face visits with the investigator in charge of the patient were planned 15 days and 30 days after the start of antibiotic treatment, and clinical data (stability criteria, community-acquired pneumonia score, and side-effects) were recorded. On day 30, a chest x-ray was done, and recovery time (with recovery defined as return to work or usual activities, or both) was collected. A telephone call on day 15 and day 30 could be done to collect the necessary data if the patient was unable to attend a face-to-face meeting.

Adverse events are reported according to the Common Terminology Criteria for Adverse Events (version 4.03).

After all data were collected, an independent adjudication committee, whose members were masked to treatment assignments, adjudicated the prespecified clinical outcomes. The committee consisted of an experienced intensivist and a specialist in infectious diseases. Both members independently reviewed the data extracted from the electronic case report forms. In case of disagreement, the patient record was reviewed jointly by the two physicians during a formal meeting to find a consensus (details are in the appendix [pp 18–20]).

Outcomes

The primary outcome was cure 15 days after the start of antibiotic treatment with β-lactam therapy. Cure was defined by the following criteria: apyrexia (temperature ≤37·8°C); resolution or improvement of clinical signs or symptoms (coughing frequency or severity, sputum production, dyspnoea, crackles); and no additional

antibiotic treatment (for community-acquired pneumonia or any reason) since the last follow-up visit. Patients not fulfilling all the above criteria were classified as not being cured.

The secondary outcomes were: cure at day 30; all-cause mortality on day 30; frequency and severity of adverse events during follow-up (with severity defined as serious *vs* non-serious); patient's pneumonia symptoms and quality of life assessed using the community-acquired pneumonia score at days 0, 3, 8, 15, and 30; and length of hospital stay assessed at day 15. Recovery time (ie, delay to return to usual activities) was self-assessed at day 30.

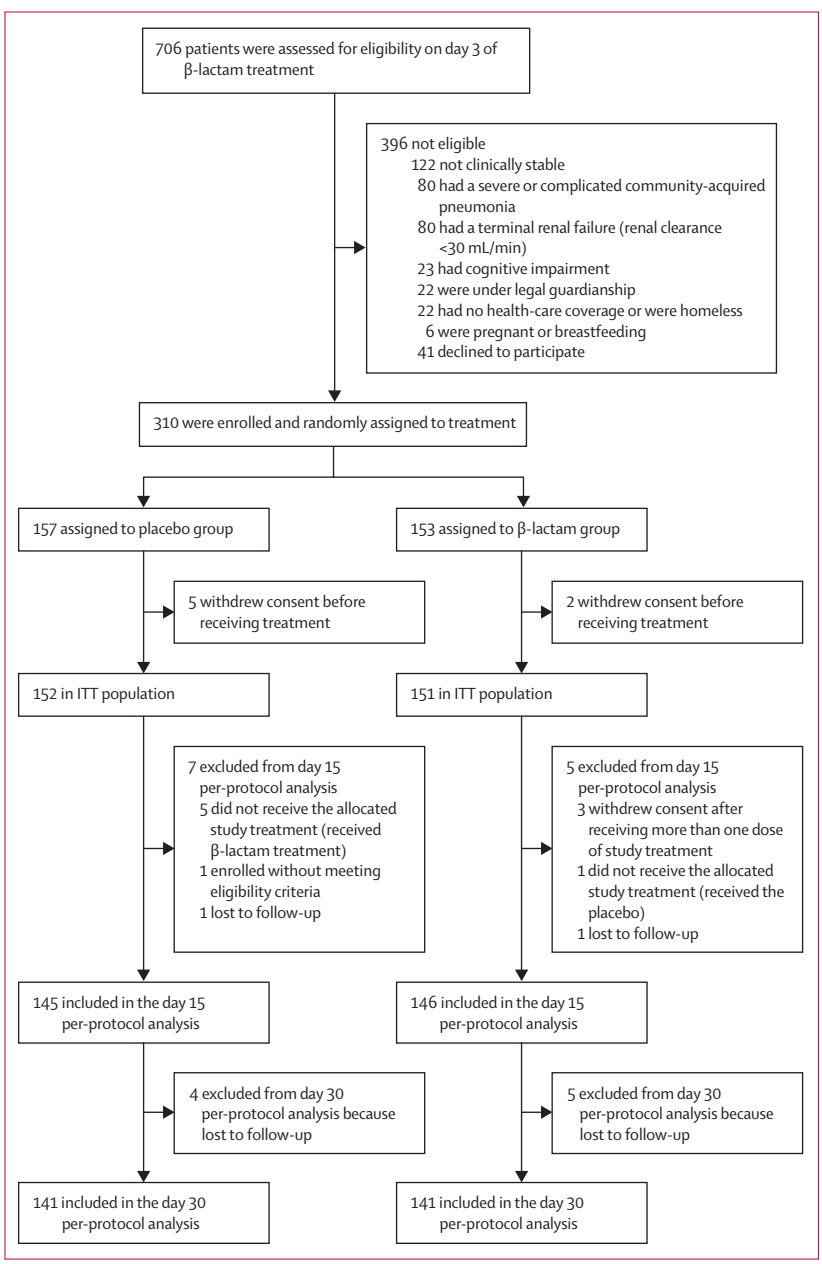

Figure 1: **Study flow chart**

Compliance to treatment, assessed at day 15, was added as a post-hoc outcome in all patients who were cured by day 15.

Statistical analysis

The study was designed as a non-inferiority trial to determine whether 3 days of antibiotic treatment was non-inferior to 8 days in patients reaching clinical stability after 3 days of treatment. We anticipated that 90% of patients in each group would be cured by day 15. We chose a non-inferiority margin of 10 percentage points (appendix p 5). We determined that including 310 patients would provide 80% power to show non-inferiority using the lower bound of the two-sided 95% CI of the percentage difference in proportions of patients who are cured. Statistical inference for non-inferiority was based on the lower bound of the 95% CI of the difference in cure proportions accounting for randomisation stratification factors (centre and PSI score).[25]

We present quantitative variables as mean (SD), continuous variables as median (IQR), and categorical variables as numbers with proportions. For secondary endpoints, we used the χ^2 test to compare the distributions of categorical variables, and we used Student's *t* tests to compare the distributions of quantitative continuous variables. We present the frequency of adverse effects in both groups. We did post-hoc sensitivity analyses of subgroups of patients at high risk of not being cured (ie, aged <60, ≥65, and ≥75 years, with a PSI score of <70, ≥70, <91, and ≥91). We assessed the primary outcome in both the intention-to-treat (ITT) population (ie, all patients randomly assigned to treatment and who received at least one dose of any treatment) and the per-protocol population (ie, all patients randomly assigned to treatment, not erroneously included, who received their assigned treatment, and received at least 80% of this treatment, except if discontinuation was due to worsening of their condition; excluding those who withdrew consent after more than one dose of study treatment, and those lost to follow-up, except if they received additional treatment since day 3). We assessed the secondary outcome of cure at day 30 in both the ITT and the per-protocol populations, and the endpoints of all-cause mortality on day 30; frequency and severity of adverse events during follow-up; patient's pneumonia symptoms and quality of life assessed using the community-acquired pneumonia score at days 0, 3, 8, 15, and 30; length of hospital stay; and recovery time at day 30 in just the ITT population. Additionally, we did a worst-case scenario analysis on missing data in the per-protocol population, in which we classified patients with missing outcomes in the β-lactam group as having been cured (appendix p 11). In all other analyses, patients with missing data in both groups were considered as not cured.

We considered p values of 0·05 or less to be significant. We did all analyses using R (version 3.6.1). This study is registered with ClinicalTrials.gov, NCT01963442.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Dec 19, 2013, and Feb 1, 2018, 706 patients were assessed for eligibility, of whom 310 were eligible and randomly assigned to either the placebo group (n=157) or the β-lactam group (n=153; figure 1). Seven patients withdrew consent before initiating study medication, five in the placebo group and two in the β-lactam treatment group, leaving 303 in the ITT population (figure 1). 291 (96%) of 303 patients were included in the per-protocol analysis at day 15. Six patients did not receive the allocated study treatment, instead receiving the other study group treatment, three patients withdrew their consent after receiving more than one dose of study treatment, two patients were lost to follow-up, and one patient was wrongly included (figure 1). 282 patients completed 30-day follow-up; nine patients were lost to follow-up between day 15 and day 30 (figure 1).

In the ITT population, the median age was 73·0 years (IQR 57·0–84·0), 123 (41%) of 303 participants were female, and 73 (24%) patients had at least two comorbidities (table 1). Median temperature at day 0 was 38·7°C (IQR 38·3–39·3) and 119 (39%) of 303 patients needed oxygen therapy. Median PSI score was 82·0 (IQR 57·5–104·0). The treatment groups were well matched with regards to their demographic and clinical characteristics and the results of routine blood tests at day 0 (table 1). Before enrolment, most patients in the two groups were given amoxicillin plus clavulanate as β-lactams during the first 3 days of hospital stay (98 [64%] of 152 in the placebo group and 98 [65%] of 151 in the β-lactam group; appendix p 8). Median community-acquired pneumonia score at day 0 was 44·38 (IQR 28·40–55·03) in the placebo group and 46·15 (26·04–60·36) in the β-lactam group. Instead of a face-to-face visit, five patients had a telephone call visit to collect data to assess endpoints at day 15 (three in the placebo group, and two in the β-lactam group) and 13 at day 30 (seven in the placebo group, and six in the β-lactam group). Microbiological analysis was done for 260 patients, and 31 (12%) samples were positive, including positive identification in 14 (11%) of 130 patients in the placebo group and 17 (13%) of 130 patients in the β-lactam group (appendix p 9).

In the ITT analysis, on day 15, 117 (77%) of 152 participants in the placebo group, and 102 (68%) of 151 participants in the β-lactam group were determined to have been cured (figure 2). The between-group difference was 9·42% (95% CI –0·38 to 20·04), indicating non-inferiority.

In the per-protocol analysis, on day 15, 113 (78%) of 145 participants in the placebo treatment group, and 100 (68%) of 146 participants in the β-lactam treatment group were determined to have been cured, with a between-group difference of 9·44% (95% CI –0·15 to 20·34), indicating non-inferiority (figure 2). In the subgroup analyses, the 95% CIs were wide because of the small number of patients in each subgroup. Nevertheless, the lower bound of the 95% CI of the between-group difference was above the –10% margin in each subgroup analysis, except for the per-protocol subgroup analysis for patients younger than 65 years and with a PSI score of more than 91.

In the ITT analysis on day 30, 109 (72%) of 152 participants in the placebo group and 109 (72%)

	Placebo group (n=152)	β-lactam group (n=151)
Age, years	72·5 (54·0–85·3)	74·0 (58·0–83·0)
Sex		
Female	66 (43%)	57 (38%)
Male	86 (57%)	94 (62%)
Temperature, °C	38·8 (38·3–39·3)	38·7 (38·3–39·3)
Oxygen therapy	60 (39%)	59 (39%)
Comorbidities*	34 (22%)	39 (26%)
Liver disease	5 (3%)	2 (1%)
Heart failure	30 (20%)	33 (22%)
Cerebrovascular disease	13 (9%)	10 (7%)
Renal disease	13 (9%)	11 (7%)
Coronary insufficiency	24 (16%)	20 (13%)
Diabetes	24 (16%)	32 (21%)
Chronic obstructive pulmonary disease	31 (20%)	40 (26%)
At least two comorbidities	34 (22%)	39 (26%)
Active smoking	30 (20%)	25 (17%)
PSI score	80·5 (57·0–103)	83·0 (58·0–104)
Risk class 2 (<70)	56 (37%)	55 (36%)
Risk class 3 (71–90)	39 (26%)	34 (23%)
Risk class 4 (91–130)	45 (30%)	56 (37%)
Risk class 5 (≥131)	12 (8%)	6 (34%)
Community-acquired pneumonia score at day 0	44·4 (28·4–55·0)	46·2 (26·0–60·4)
Laboratory values at admission		
Haemoglobin, g/dL	12·8 (11·9–13·9)	13·1 (11·9–14·3)
Leucocyte, G/L	11·5 (8·05–16·0)	11·7 (8·70–15·2)
Absolute neutrophil count, G/L	9·81 (6·57–14·4)	9·68 (6·87–12·9)
Urea, mmol/L	6·70 (4·80–8·80)	5·90 (4·70–8·00)
Glucose, mmol/L	6·20 (5·40–7·00)	6·20 (5·33–7·50)
Creatinine, µmol/L	78·0 (65·0–100)	79·0 (63·0–96·0)
C-reactive protein, mg/L†	134 (59·0–234)	104 (46·8–200)
Procalcitonin, µmol/L‡	0·55 (0·20–2·23)	0·20 (0·10–0·60)
Radiological examination results		
Multilobar	30 (20%)	23 (15%)
Pleural effusion	11 (7%)	16 (11%)

Data are n (%) or median (IQR). For laboratory values, data are given to three significant figures or two decimal places as appropriate. PSI=Pneumonia Severity Index. *Some patients had more than one comorbidity. †Obtained for 235 patients (placebo group: n=117; treatment group: n=118). ‡Obtained for 107 patients (placebo group: n=50; treatment group: n=57).

Table 1: **Demographic and clinical characteristics of trial participants at admission to hospital**

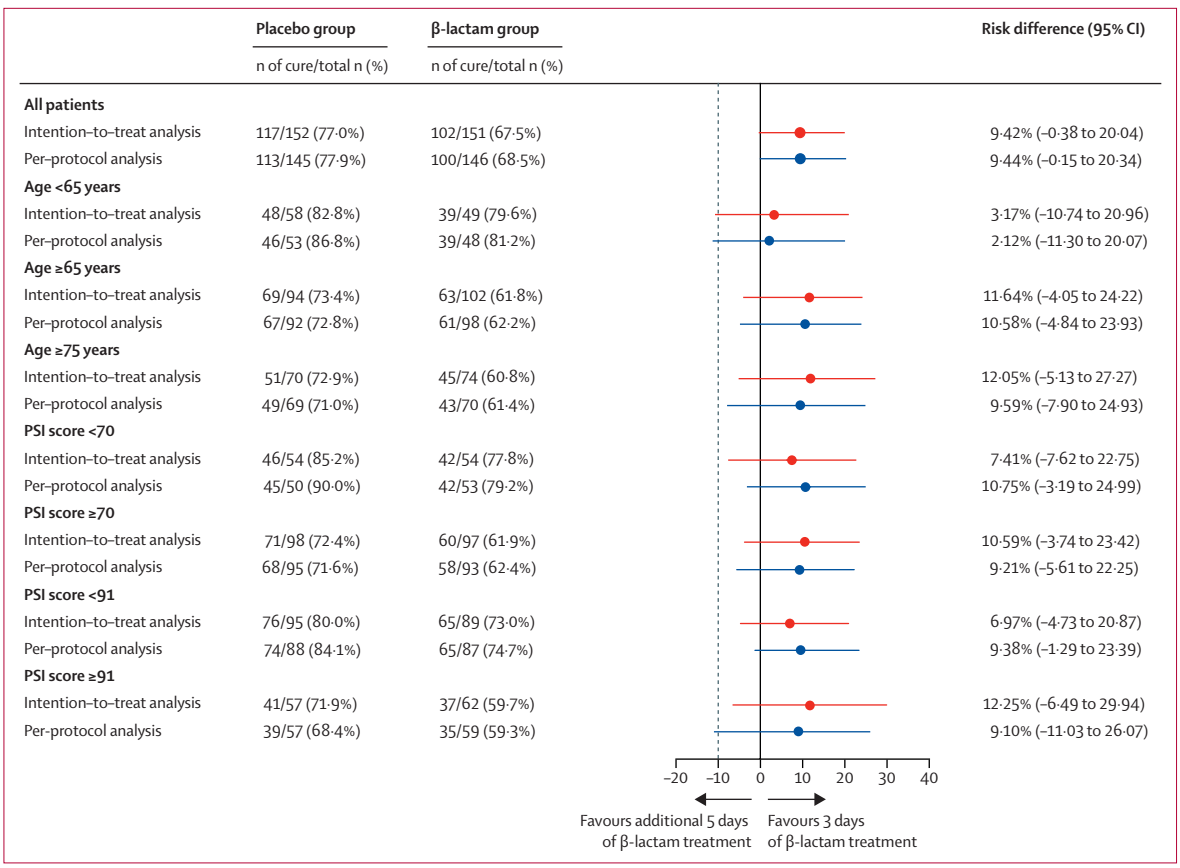

Figure 2: **Primary outcome of cure at day 15, in the intention-to-treat and per-protocol population, and post-hoc subgroup analyses**
Data are n/N (%) and risk difference with 95% CI in parentheses. Vertical dotted line indicates non-inferiority margin. PSI=Pneumonia Severity Index.

of 151 participants in the β-lactam group had been cured, with a between-group difference of –0·47% (95% CI –11·31 to 9·98; table 2).

In the per-protocol analysis on day 30, 105 (74%) of 141 participants in the placebo group, and 107 (76%) of 141 participants in the β-lactam group had been cured, with a between-group difference of –1·42% (95% CI –12·08 to 9·20).

No difference was seen in the death rate at day 30 (table 2). Three (2%) of 152 patients died in the placebo group, one due to bacteraemia due to *Staphylococcus aureus*, one due to cardiogenic shock after acute pulmonary oedema, and one due to heart failure associated with acute renal failure, and two (1%) of 151 in the β-lactam group due to pneumonia recurrence and possible acute pulmonary oedema. No difference was seen in the proportion of participants reporting at least one adverse event linked to treatment (22 [14%] of 152 in the placebo group *vs* 29 [19%] of 151 in the β-lactam group; p=0·29; table 2). All adverse events are detailed in table 3. The most common adverse events were digestive disorders, reported in 17 (11%) of 152 patients in the placebo group and 28 (19%) of 151 patients in the β-lactam group. Only two serious adverse events were reported: an episode of hepatitis in the placebo group, and an episode of skin rash in the β-lactam group. The median length of hospital stay was not significantly different between the two groups and neither was median recovery time (table 2). The main causes for not meeting cure criteria were no resolution or improvement of symptoms (in the ITT group: 24 [69%] of 35 in the placebo group and 38 [78%] of 49 in the β-lactam group), additional antibiotic treatment (six [17%] in the placebo group and two [4%] in the β-lactam group), and fever at day 15 (one [3%] in the placebo group and three [6%] in the β-lactam group; data for the per-protocol population are in the appendix [p 10]). The change in the community-acquired pneumonia score during follow-up to day 30 was also similar in the two groups (appendix p 14). Between-group differences in community-acquired pneumonia scores and quality of life will be reported elsewhere. 100% compliance to study medication was noted in 106 (94%) of 113 patients in the placebo group and 93 (93%) of 100 in the β-lactam group who were cured at day 15 (appendix p 15).

Post-hoc subgroup analyses showed no significant difference in the cure rate at day 15 between treatment

groups among patients younger or older than 65 years or 75 years, and patients with PSI scores of less than 70 or 70 or higher, and patients with PSI scores of less than 91 or 91 or higher, in both the ITT or the per-protocol populations (figure 2). The worst-case scenario analysis in the per-protocol population did not show any significant between-group difference in the cure rate at day 15 and day 30 either (appendix p 11).

Discussion

We found that discontinuing β-lactam treatment after 3 days in patients with community-acquired pneumonia who were clinical stability resulted in outcomes that were similar and non-inferior to those in patients who continued their treatment for an additional 5 days. These data support the concept that antibiotic therapy can be safely discontinued in patients who have moderately severe community-acquired pneumonia who have early clinical response to therapy,[10,18] which could allow an important reduction in antibiotic exposure among patients being treated in hospital for community-acquired pneumonia.

In daily practice for community-acquired pneumonia, physicians still often prescribe 7–10 days of antibiotic treatment[12] out of habit inherited before the recognition of the threat of bacterial resistance.[26–28] This tendency is reinforced by the common belief that an extended course of antibiotics protects from reinfection and even antibacterial resistance.[18,28] However, short-course antibiotic treatments are one of the best ways to reduce selection pressure for antimicrobial resistance, and randomised trials are needed to identify the minimum length of treatment to ensure cure.[18,19,28,29] According to the French National Health Agency, third-generation cephalosporin and amoxicillin plus clavulanate are major drivers for bacterial resistance.[30]

Uranga and colleagues[10] found in their open-label, randomised, controlled, non-inferiority trial (n=310) that 5 days of antibiotic treatment among patients presenting with stable community-acquired pneumonia was similar to 10 days of treatment, which supports current US guidelines.[7] Until now, to our knowledge, only one randomised controlled trial has shown the non-inferiority of 3 days of antibiotic treatment (amoxicillin) compared with 8 days of treatment for community-acquired pneumonia in an adult population (n=119) with early response to antibiotics.[17] However, the smaller study population had less severe illness (52 [44%] of 119 were in PSI risk class 2) and were younger (median age of 54 years in the 3-day group and 60 years in the 8-day group) than our study population; hence, the findings were insufficient to affect practice for the majority of patients admitted to hospital with community-acquired pneumonia, who are often older people with one or more comorbidities.[5] By contrast, our study population had a median age of 73 years, which is similar to the usual average age of patients with community-acquired pneumonia.[10,31] Furthermore, our results were consistent across several subgroups, including older patients and those at high risk of not being cured.

Strengths of our study include its double-blind, randomised design and assessment by an independent blinded adjudication committee. Indeed, because primary outcomes in randomised controlled trials of community-acquired pneumonia are subject to debate, with the definition of cure often being subjective, we decided that cure should be assessed by two independent reviewers, with strong infectious disease expertise, and according to a predefined clinical outcome. Moreover, the sample size allowed a well powered statistical analysis of non-inferiority, and our results were confirmed in a worst-case scenario analysis.

	Placebo group	β-lactam group	Difference	p value
Cure at day 30				
ITT analysis	109/152 (72%)	109/151 (72%)	−0·47 (−11·31 to 9·98)	>0·99
Per-protocol analysis	105/141 (74%)	107/141 (76%)	−1·42 (−12·08 to 9·20)	0·89
Mortality at day 30	3/152 (2%)	2/151 (1%)	0·60 (−3·50 to 4·40)	>0·99
Patients with at least one adverse event related to treatment	22/152 (14%)	29/151 (19%)	−4·70 (−7·08 to 2·31)	0·29
Patients with at least one serious adverse event related to treatment	1/152 (1%)	1/151 (1%)	0·00 (0·00 to 0·99)	>0·99
Length of hospital stay, days,	5·00 (4·00 to 9·00)	6·00 (4·00 to 9·00)	−1·00 (−1·00 to 1·00)	0·74
Recovery time, days	15·00 (9·00 to 21·50)	15·50 (7·00 to 20·00)	−0·50 (−4·00 to 5·50)	0·33

Data are n/N (%), median (IQR) or between-group difference in percentage points, with 95% CI in parentheses. Unless otherwise stated, analyses are in the ITT population. χ^2 test was used to compare the distributions of categorical variables and Student's *t* tests to compare the distributions of quantitative continuous variables. ITT=intention-to-treat.

Table 2: **Secondary outcomes**

	Placebo group (n=152)	β-lactam group (n=151)
Patients	22 (1)	29 (1)
Digestive disorders	17	28
Diarrhoea	13	18
Mycosis	1	1
Skin rash	0	3 (1)
Headache	2	0
Hypoxia	0	1
Clostridioides difficile infection	1	0
Hepatitis	2 (1)	1
Epistaxis	1	0
Total	24 (1)	34 (1)

Data are number of events and data in parentheses are the number of serious adverse events. One patient could present with several adverse events.

Table 3: **Adverse events and serious adverse events associated with the study treatment**

Our study has several limitations. First, our results cannot be extrapolated to patients who do not respond after 3 days of β-lactam therapy, especially to those with infection due to intracellular bacteria, with severe community-acquired pneumonia (admitted to a critical care unit, with serious respiratory insufficiency or septic shock), or with advanced renal failure. Absence of stability criteria at day 3 was the reason for exclusion for 122 (31%) of 396 excluded patients, which is in line with other studies,[22] and 80 (20%) patients presented with a severe or complicated community-acquired pneumonia and another 80 (20%) had advanced renal failure, leading to their exclusion. 114 patients were excluded for reasons other than an absence of relevant signs and symptoms. Thus, a 3-day treatment regimen seems relevant for approximately 60% of patients (424 of 706) admitted to hospital with the strict definition of community-acquired pneumonia used for our study. Second, only patients treated with β-lactam monotherapy were enrolled in our trial, consistent with the usual European therapeutic approaches and guidelines,[11,21] which differ from US guidelines.[4,7] However, we believe that our results could be applied to dual antibiotic regimens in the studied population. Third, we aimed to reproduce as closely as possible the pragmatic therapeutic approach of a clinician confronted with a patient with suspected community-acquired pneumonia in real-world conditions. Accordingly, we made no effort to identify a causative microorganism,[5] although, when available, results of microbiological analysis were collected. As a consequence, a viral aetiology of pneumonia could not be ruled out, as is often the case in routine care. Most current diagnostic tests are not accurate enough to determine if a case of community-acquired pneumonia is solely due to a virus, although viruses could be involved in up to 30% of cases.[7] Nonetheless, if patients with viral infections had been included in our study population, they should be well balanced between the two treatment groups due to our randomisation methods. Moreover, in daily practice, if a viral infection is detected, antibiotics are often prescribed to treat any potential bacterial co-infection or superinfection.[32] Fourth, biomarkers such as C-reactive protein and procalcitonin analysis were not required in our study, and only collected when available, because collection is not recommended in daily practice.[7,8,11] Furthermore, as stated in the ATS and IDSA guidelines, duration of antibiotic therapy can be reduced in patients with community-acquired pneumonia with the use of procalcitonin, but in several studies the average length of treatment was much longer than was recommended in current guidelines.[7] Fifth, in our sample size calculations we anticipated a 90% cure rate; however, our actual cure rate was much lower. This difference might be due to the high variability in definitions of cure between studies leading to over-estimation in our calculations. Additionally, in our subgroup analyses, we found quite wide 95% CIs, which were probably due to the small number of patients in each subgroup.

Finally, the diagnosis of community-acquired pneumonia is challenging. Radiological examination is necessary to establish parenchymal lung involvement. Our case definition required a chest x-ray to better suit everyday practice. However, our definition has some limitations and CT scan could be more accurate. Thus, to avoid misclassification, investigators were allowed to do a CT scan if needed. However, the number of patients who had CT scans to confirm their diagnosis was not recorded for our study.

In summary, in our trial, among patients requiring admission to hospital for moderately severe community-acquired pneumonia and who met clinical stability criteria after 3 days of β-lactam therapy, a strategy of discontinuation of antibiotic treatment proved to be non-inferior to 8 days of treatment. Community-acquired pneumonia and, more generally, lower respiratory tract infection are some of the most common indications for antibiotic use, and so our findings support the substantial reduction in consumption of antibiotics.

Contributors

AD and A-CC did the literature search. AD, A-CC, JL, Y-EC, JR, and PA were responsible for the study design. AD, CD, and JR collected the data. All authors interpreted the data. AD, A-CC, JR, PA, and AL analysed the data. AD, JR, CD, A-CC, and PA created the figures and drafted the manuscript. All authors revised and approved the final version of the manuscript for submission. AD, JR, and CD had full access to all the data in the study and all authors had final responsibility for the decision to submit for publication. JR and CD also had full access to and verified the underlying data.

Pneumonia Short Treatment (PTC) Study Group

France J Attal-Behar, S Beaune, T Chinet, T Cudennec, M De Laroche, A De Thezy, J Dumoulin, C Dupont, E Fercot, V Giraut, S Greffe, J Grenet, C Guyot, S Labrune, M Lachatre, S Moulias, C Naline, M Pepin, E Rouveix, M Sahut-D'izarn, A Sefssafi, L Teillet (Ambroise Paré University Hospital, AP-HP Paris Saclay University, Boulogne-Billancourt); J-P Bru, J Gaillat, V Gautier, C Janssen, L Pagani, V Vitrat (Annecy Hospital, Annecy); M Abderrahmane, J Camuset, C Legall, P Longuet-Flandres, A-M Menn (Argenteuil Hospital, Argenteuil); V De Lastours, G Prevost, M Lecronier (Beaujon University Hospital, AP-HP, Clichy); C Burdet, O Derradji, L Escaut, E Hinglais, P Lebras, E Lefevre, M Noaillon, P Rabier, M Raphael, E Teicher, C Verny, D Vittecoq, B Wyplosz (Bicêtre University Hospital, AP-HP Paris Saclay University, Le Kremlin-Bicêtre); M Ben Hayoun, F Brun-Vezinet, E Casalino, C Choquet, M-C Dombret, X Duval, N Houhou, V Joly, X Lescure, M Pogliaghi, C Rioux, Y Yazdanpanah (Bichât University Hospital, AP-HP, Paris); E Barros, B Begga, S Boukobza, H Bouredji, I Chouahi, I Delacroix, A Froissart, V Garrait, E Ngwem, C Phlippoteau, S Salehabadi, C Toper, F Vinas (Créteil University Hospital, Créteil); M Amsilli, O Epaulard, P Pavese, I Pierre, J-P Stahl (Grenoble Hospital, Grenoble); J Aulagnier, J Celerier, R Cojocariu, J-E Kahn, E Mathieu, C Rachline, Y Schoindre, T Sene, C Thierry (Foch Hospital, Suresnes); C Aparicio, V Delcey, A Lopes, M Morgand, P Sellier, G Simoneau (Lariboisière University Hospital, AP-HP, Paris); C Chakvetadze, S Diamantis, A Gauthier, K Jidar, B Jourdain (Melun Hospital, Melun); J-F Boitiaux, P Deschamps, E Devaud, B Philippe (Pontoise Hospital, Pontoise); R-O Calin, T Chroboczek, B Davido, L Deconinck, P De Truchis, A Lagrange, S Makhloufi, M Matt, G Mellon, O Senard (Raymond Poincaré Hospital, AP-HP Paris Saclay University, Garches); Dl Benhamou, C Chapuzet, L Chauffrey, M Etienne, L-M Joly, B Obstoy, M Salaun, L Thiberville, J Tillon (Rouen Hospital, Rouen); D Bollens, J Bottero, P Campa, G Cosqueric, B Lefebvre, Z Ouazene, J Pacanowski, D Pateron, N Valin (Saint-Antoine University Hospital, AP-HP, Paris);

C Compain, H Cordel, B Doumenc, E Fois, N Gambier, M-A Khuong, E Pasqualoni, M Poupard (Saint-Denis Hospital, AP-HP, Saint-Denis).

Declaration of interests
We declare no competing interests.

Data sharing
Because secondary analyses are ongoing, data collected for the study, including individual participant data and a data dictionary defining each field in the set, will not be made available to others.

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