Title

Efficacy of high doses of penicillin versus amoxicillin in the treatment of adults with non-severe community-acquired pneumonia. A randomised controlled noninferiority trial.

Título

Eficacia de altas dosis de penicilina frente a amoxicilina en el tratamiento de la neumonía no complicada adquirida en la comunidad en adultos. Ensayo clínico controlado de no inferioridad.

Short running title

Penicillin versus amoxicillin in pneumonia.

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Competing interests

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Abstract

Introduction. In some northern European countries community-acquired pneumonia (CAP) is treated with penicillin. This study was aimed at evaluating whether high-dose penicillin V is as effective as high-dose amoxicillin for the treatment of non-severe CAP.

Design. Multicentre, parallel, double-blind, controlled, randomised clinical trial.

Setting. 31 primary care centres in Spain.

Participants. Patients from 18 to 75 years of age without significant associated comorbidity attending the physician with symptoms of lower respiratory tract infection and radiological confirmation of CAP were randomised to receive either penicillin V 1.6 million units or amoxicillin 1,000 mg thrice-daily during 10 days.

Main measurements. The main outcome was clinical cure at 14 days and the primary hypothesis was that penicillin V would be no inferior to amoxicillin with regard to this outcome, with a margin of 15% for the difference in proportions. EudraCT register 2012-003511-63.

Results. 43 subjects (amoxicillin: 28; penicillin: 15) were randomised. Clinical cure was observed in 10 (90.9%) patients assigned to penicillin and in 25 (100%) patients assigned to amoxicillin with a difference of – 9.1% (95% CI, - 41.3% to 6.4%; p=0.951) for noninferiority. In the intention-to-treat analysis amoxicillin was found to be 28.6% superior to penicillin (95% CI, 7.3% to 58.1%; p=0.009 for superiority). The number of adverse events was similar in both groups.

Conclusions. We observed a trend favouring high-dose amoxicillin versus high-dose penicillin in adults with uncomplicated CAP. The main limitation of this trial was the low statistical power because of the low number of patients included.

Eficacia de dosis altas de penicilina frente a amoxicilina en el tratamiento de la neumonía no complicada adquirida en la comunidad en adultos. Ensayo clínico controlado de no inferioridad.

Introducción. En algunos países la neumonía adquirida en la comunidad (NAC) se trata con penicilina. Este estudio tuvo como objetivo evaluar si penicilina V a dosis altas es igual de efectiva que amoxicilina a dosis altas en la NAC no complicada.

Diseño. Ensayo clínico paralelo, doble ciego, controlado y multicéntrico,

Emplazamiento. 31 centros de salud en España.

Participantes. Se reclutaron pacientes de 18 a 75 años de edad sin comorbilidad asociada importante con síntomas de infección respiratoria inferior y confirmación radiológica de neumonía, que fueron asignados aleatoriamente a 1,6M unidades de penicilina V o amoxicilina 1.000 mg, tres veces al día, durante 10 días.

Mediciones principales. La variable de resultado principal fue curación clínica a los 14 días y se planteó la hipótesis de que penicilina no era inferior a amoxicilina con un margen de 15% para la diferencia de proporciones. Registro EudraCT 2012-003511-63.

Resultados. Se aleatorizaron 43 personas (amoxicilina: 28; penicilina: 15). Se observó curación clínica en 10 pacientes asignados a penicilina (90,9%) y en 25 asignados a amoxicilina (100%), observándose una diferencia de -9.1% (IC95%: -41.3 a 6,4%; p=0,951) para no inferioridad. En el análisis por intención de tratar, amoxicilina fue 28,6% superior a penicilina V (IC95%: 7,3% a 58,1%; p=0,009 para superioridad). El número de eventos adversos fue similar en ambos grupos.

Conclusiones. Se observó una tendencia de un mayor beneficio de amoxicilina frente a penicilina en adultos con NAC no complicada. La principal limitación fue la baja potencia estadística debido al bajo número de pacientes incluidos.

Palabras clave: Neumonía adquirida en la comunidad; Ensayo clínico aleatorio; Penicilina; Amoxicilina; Adultos.

Introduction

Community-acquired pneumonia (CAP) remains a burden in the modern world [1]. Respiratory bacteria constitute the major group of causative organisms. In approximately 50% of the cases the pathogen cannot be identified; however, *Streptococcus pneumoniae* is the organism most frequently isolated throughout all the studies and settings, even among outpatients [2,3].

In some European countries, mainly those in Northern Europe, pneumonia is treated with penicillin V since the resistance of pneumococci to this antibiotic is low [4]. However, in most European countries amoxicillin is the first-choice antibiotic for uncomplicated cases [5-7].

Four reasons justify the present study. Firstly, the cut-off points which determine whether a pneumococcus is susceptible or resistant to penicillin changed in 2008 [8], and according to some recently published studies pneumococcal resistance to penicillin (minimum inhibitory concentration [MIC] >2 µg/ml) has fallen drastically [9]. Secondly, there is no correlation between pneumococcal infection by a strain resistant to penicillin and therapeutic failure with β-lactams prescribed at adequate doses [10]. Thirdly, the use of narrow-spectrum antibiotics is needed because of the dearth of new antimicrobials and the link observed between the consumption of broad-spectrum antibiotics and the emergence and spread of antibacterial resistance [11]; and fourthly, no clinical study comparing amoxicillin and penicillin V in pneumonia in adults has been published to date. Thus, the aim of the present trial was to determine whether high-dose penicillin V was as effective as high-dose amoxicillin for the treatment of uncomplicated CAP in a Mediterranean adult population.

Material and methods

We performed a prospective, parallel-group, randomised, double-blind, trial in primary healthcare centres in Spain carried out from November 2013 to April 2016. All patients provided written informed consent. The study protocol has been published elsewhere [12].

Patients aged 18 to 75 without significant associated comorbidity attending a primary care physician with signs and symptoms of lower respiratory tract infection and radiological confirmation of the diagnosis of pneumonia were invited to participate. We permitted the

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inclusion and randomisation of patients without radiological confirmation if there was a high suspicion of pneumonia as suggested in previous studies [13], that is, patients with lower respiratory tract infection, temperature higher than 38.5ºC and productive cough; however, chest X-ray had to be done in the following 24 hours, and if there was no radiological confirmation of pneumonia, patients were excluded. Due to difficulties in the recruitment of patients an amendment to the previous protocol was made, broadening the age range of subjects, considering some other comorbidities and also taking into account patients who had taken urinary antiseptics in the previous days [12].

Exclusion criteria were subjects under 18 or over 75 years of age, severe impairment of signs (impairment of consciousness, respiratory rate >30 breaths/minute, heart rate >125 beats/minute, systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, temperature >40ºC, oxygen saturation <92%), hypersensitivity to β-lactams, important alteration on chest X-ray, such as alveolar infiltrate in more than one lobe or bilateral, pleural effusion and/or pulmonary cavitation, problems to comply with treatment at home, lack of tolerance to oral treatment, significant comorbidity including bronchial asthma, renal failure, hepatic cirrhosis, heart failure, chronic obstructive pulmonary disease, ischaemic heart disease, stroke and/or type 1 diabetes mellitus, immunosuppression, terminal disease, pregnancy or lactation, hospitalization in the last month, consumption of antibiotics in the last two weeks, difficulty to attend the programmed visits or refusal to participate in the study.

It was a double-blind two arms clinical study; participants and investigators remained blinded to the treatment received. Patients were randomly assigned to receive either penicillin V 1,600,000 IU (two 800,000 IU pills) or amoxicillin 1,000 mg (two 500 mg pills) thrice a day during 10 days. Subject numbers were assigned sequentially as each subject entered the study. The subjects were assigned to a study drug through a randomisation schedule based on the randomisation plan. Since this was a multicentre study a block procedure was planned for the allocation of the study medication. Each container included 66 pills (60 pills for the treatment plus 6 extra pills). The dose of penicillin used in the study was not marketed in our country, and consequently, the study drugs were entirely prepared and labelled by the Pharmacy Unit of the Hospital Universitari *Son Espases* (Palma de Mallorca). As the medication was prepared by a Pharmacy

Service, the batches were small and every batch required stability analysis every 6 months. Furthermore, two pills per intake were needed due to the high penicillin dose, meaning that we had to double the number of batches and 6-month stability analyses, thereby exceeding the initial budget. Considering the high dose of penicillin used, a data and safety monitoring board was created to ensure patient safety and treatment efficacy during recruitment.

However, the difficulties in drug preparation, the limited budget and the elevated number of centres opened to minimize the low inclusion rate made it impossible to maintain the 4 block per centre distribution, and finally the medication was allocated following a simple randomisation according to centre needs.

Use of antithermic drugs or analgesics (acetaminophen, acetylsalicylic acid or ibuprofen), bronchodilators or any other medication, except oral systemic antibiotics, that the patient was talking was allowed.

Variables

The main outcome was clinical cure at 14 days, defined as the absence of fever, resolution or improvement of cough, improvement of general well-being and resolution or reduction of crackles indicating that no other antimicrobial treatment was necessary. Any clinical result other than the anterior was considered as treatment failure. Secondary outcomes were efficacy at day 30 after the initiation of antibiotic treatment, radiological resolution or improvement one month after the initiation of the treatment, complete clinical resolution at day 14 defined as the total resolution of acute symptoms and signs related to the infection, and the presence of adverse events. The radiologists responsible for diagnosing pneumonia and confirming the radiological cure were blind to the clinical data and the treatment administered.

On fulfilling the inclusion criteria, the nature of the study was explained to the patient and informed consent was obtained. All the eligible patients had a chest X-ray (posteroanterior and lateral views) demonstrating pneumonic infection. The study scheme and the visit program were explained to the patients, and they were then randomised to one of the 2 treatment groups and the medication was given. At the first follow-up visit, scheduled at day 3 (by phone or at the

centre), worsening of the clinical situation was evaluated to determine whether a change in the antibiotic treatment was necessary. Likewise, compliance and possible secondary effects of the treatment were evaluated. At the second follow-up visit, at day 14, the clinical evolution of the signs and symptoms was evaluated. Likewise, possible secondary effects of the treatment were evaluated. On the last follow-up visit, scheduled at day 30, the clinical outcome of the signs and symptoms of the pneumonia was evaluated and a new chest X-ray was performed (posteroanterior and lateral views) to confirm radiological resolution. The medication was discontinued in the case of significant adverse events. The variables were registered in an electronic case report form designed by the *Fundació Institut Català de Farmacologia,* Barcelona.

Sample size calculation and statistical analyses

The objective of the study was to demonstrate that penicillin V was not inferior to amoxicillin. Considering a success rate of 85% for the group treated with amoxicillin [14,15], a total of 105 patients were required in each treatment group (total of 210) to detect a noninferiority margin of 15% at maximum between the two treatments with a minimum power of 80% considering an alpha error of 2.5% for a unilateral hypothesis and maximum possible losses of 15%.

The intention-to-treat (ITT) population included all randomised patients with confirmation of pneumonic infection receiving at least one dose of the study drug and the per-protocol (PP) population included patients adherent to protocol with adequate treatment compliance and absence of major protocol violations.

Descriptive results of the outcomes were reported as number and percentages. To evaluate the differences on baseline characteristics, Fisher's exact tests for categorical variables and non-parametric tests for continuous measures were carried out. Comparisons between groups were performed using exact binomial distribution for the efficacy endpoints and adverse events [16], 95% confidence intervals (CI) for the differences in success percentages were estimated and p-values provided. All analyses were conducted with R statistical package, version 3.2.5.

Ethics approval

The study was approved by the Institutional Review Board (IDIAP Jordi Gol Clinical Investigation Ethic Committee) and the Spanish Agency of Medicines and Health Products. Written informed consent was obtained from all participants. Trial registration: EudraCT number 2012-003511-63.

Results

The required sample size of 210 patients could not be achieved although 31 centres were opened (10 centres were initially planned). A total of 43 subjects were screened and randomised (28 patients in the amoxicillin arm and 15 patients in the penicillin arm) and constituted the safety population. The demographic and clinical characteristics of the randomised population were well matched between the groups (Table 1). A total of 4 patients were excluded from the ITT population: 3 had a normal chest X-ray and one more was mistakenly given expired medication and was withdrawn the following day. A total of 3 patients were lost during follow-up and were all excluded from the PP population. The flow of patients in the study and causes of exclusion are presented in the general scheme of the study.

We cannot prove that penicillin V was not inferior to amoxicillin as clinical cure was observed in 10 patients assigned to penicillin (90.9%) and in 25 patients assigned to amoxicillin (100%) in the PP population with a difference of – 9.1% (95% CI, - 41.3% to 6.4%; p=0.951 for noninferiority). A total of 39 subjects (25 in the amoxicillin arm and 14 in the penicillin V arm) fulfilled all the criteria for the ITT population, and in this group amoxicillin was found to be superior to penicillin, with a difference of 28.6% (95% CI, 7.3% to 58.1%; p=0.009 for superiority) (Fig. 1).

All the results of this section refer to superiority comparisons in the ITT population (Fig. 1). Amoxicillin was found to be 28.6% superior to penicillin in terms of clinical resolution on day 30 (95% CI, 7.3% to 58.1%; p=0.009) and in terms of total resolution one month after the index visit (34.9% superior, 95% CI, 6.2% – 62.5%; p=0.002). Radiological resolution among patients assigned to amoxicillin was 27.3% superior to patients allocated to penicillin V (95% CI, 4.5% to

61%; p=0.027). A total of 4 adverse events were related to the study drugs: three cases among patients treated with amoxicillin and one case in the penicillin V group (10.7% vs. 6.7%, respectively) without any statistically significant differences. Three cases corresponded to epigastralgia and one corresponded to vaginal candidiasis.

Discussion

On the basis on the results obtained we cannot prove that high doses of penicillin V in adults with non-severe CAP are not inferior to high doses of amoxicillin – the currently recommended treatment – in patients under the age of 75 years, but because of the limited number of patients, the confidence intervals were wide. However, when we tested for the superiority of amoxicillin, we did find significant statistically differences, with amoxicillin being 28.6% superior to penicillin V in clinical resolution on day 14 (95% CI, 7.3% to 58.1%).

Limitations and strengths of the study

The major limitation of this study was the limited number of patients included. This can lead to false negative results because of the width of the confidence intervals. The approval from the Spanish Agency of Medicines and Health Products was delayed and we were not able to start recruiting until November 2013. Since the funding was only available until April 2016 we were only able to recruit patients for two and a half years. In addition, the diagnosis of CAP in primary care is challenging, since a positive X-ray for pneumonic condensation is required for correct diagnosis. In an attempt to increase patient recruitment to this study GPs were allowed to recruit patients with a high suspicion of pneumonia. These patients were then randomised before the chest X-ray was performed, with three patients being thereafter excluded from the ITT population because of normal radiological images. Patients with significant comorbidities, which is frequently observed in cases of pneumonia, were also excluded from the study. Many patients were also excluded because they had taken some doses of antibiotics, either because they had first bypassed the primary care professionals and gone to emergency departments, or

they had taken leftover doses stored at home, something which is still frequently done in our country [17].

A second limitation was the uneven number of patients per group. A proper block procedure randomisation plan was prepared, but it was not possible to follow it due to budget problems. To increase the number of candidates for the trial, many additional centres were included, but it was impossible to make enough medication to send an entire block to every centre, considering the small batches prepared by the pharmacy service and the stability analysis required per batch every six months. However, the probability of obtaining an imbalance greater than or equal to that observed (28 vs. 15 randomised patients) exceeds 6%, so that this disparity can be attributed to chance.

Another possible limitation of this study was the fact that microbiological studies were not taken into account. Bacterial eradication has been considered a secondary outcome in many studies undertaken up to now, but some experts recommend that this measure should not be considered in mild-moderate pneumonia [18]. Moreover, GPs judge the response to treatment with eminently clinical rather than microbiological criteria.

In this study, interventions and follow-ups were similar to clinical practice. We believe that the methodology used was very simple as it should be in primary care. The data collection was also simple enough to facilitate the inclusion of cases in primary care offices. Chest x-ray was absolutely necessary to confirm the diagnosis of pneumonia and was therefore an essential requisite for inclusion of the patients to thereby avoid the inclusion of patients who did not have the disease.

Comparison with other studies

To our knowledge, no study comparing oral penicillin and oral amoxicillin in CAP in adults has been carried out to date. Although some clinical trials have compared amoxicillin with penicillin, these were performed in children and with parenteral doses [19-23]. All these trials confirm that oral treatment with amoxicillin is equivalent to parenteral penicillin in children with CAP. Consequently, we cannot compare the results obtained in our randomised clinical trial with other

studies. In a recent Cochrane review, including 11 randomised clinical trials and 3,352 outpatients older than 12 years with a diagnosis of CAP, Pakhale et al observed that there is inadequate evidence to recommend one antibiotic class over another [24]. However, we demonstrated that amoxicillin is associated with better clinical outcomes than oral phenoxymethylpenicillin for the treatment of adults with uncomplicated CAP.

In Scandinavian countries, where penicillin V is considered the first choice for uncomplicated pneumonia, high doses ranging from 1 million to 1.5 million IU thrice-daily are recommended [4,25]. According to data from the European Center for Disease Prevention and Control for the year 2014, resistant strains accounted for 20% of the pneumococci isolated in Spain [9]. However, most of this resistance rate corresponded to intermediate resistant organisms, against which higher doses of penicillin are recommended. From a microbiological standpoint, bacterial eradication is achieved when the concentration of antibiotic is above 40-50% of the time between β-lactams dose intervals. For partially resistant strains, it is recommended that this time be above 60% [26]. We know that the bioavailability of penicillin V is very variable, ranging from 25% and 60%. However, one study found that the MICs achieved with penicillin V were higher than with penicillin G administered parenterally [27]. In a study carried out in Sweden, Fredlund et al showed that oral penicillin V was as effective as parenteral penicillin in patients with CAP when the former was administered during 10 days [28]. Regarding the safety of the regimen of 1.6 million units (corresponding approximately to 1 gram of penicillin V) thrice-daily, this dose is not marketed in our country, although a presentation of 1.5 million IU is available in Scandinavian countries. In addition, the British National Formulary recommends doses of up to 1 gram of penicillin V every 6 hours [29]. For this reason, we think that the dose of 1.6 million units taken thrice daily was fully justified in this clinical trial.

The often-heard statement that resistant organisms lead to failure is now controversial. It is important to know that a large proportion of patients die because of the severity of their disease and the associated comorbidity but not due to failure of the antibiotic. Thus, the study by Pallarés et al provided evidence that the risk of death by pneumococcal pneumonia treated with benzylpenicillin or ampicillin was similar regardless of whether the patients were infected with germs resistant or not to penicillin [30]. In other studies evaluating the effectiveness of penicillin

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in monotherapy for the treatment of non-meningeal pneumococcal infections within the first 48 hours in adults, an increase in mortality was not observed when the infection was caused by a strain with an MIC <2 µg/ml [31]. However, in our study we demonstrated that amoxicillin is associated with better clinical outcomes than oral phenoxymethylpenicillin.

Some societies, such as the Spanish Society of Family Medicine, recommend amoxicillin as the first-choice antibiotic for non-severe CAP in countries where pneumococcal resistance is observed [5-7], and according to the results of the present study, there is no reason to change this recommendation.

References

1. Schnoor M, Hedicke J, Dalhoff K, Raspe H, Schäfer T; CAPNETZ study group. Approaches to estimate the population-based incidence of community acquired pneumonia. J Infect. 2007;55:233–9.

2. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. Thorax. 2012;67:71–9.

3. Drijkoningen JJ, Rohde GG. Pneumococcal infection in adults: burden of disease. Clin Microbiol Infect. 2014;20(Suppl 5):45–51.

4. Spindler C, Strålin K, Eriksson L, Hjerdt-Goscinski G, Holmberg H, Lidman C, et al. The community acquired pneumonia working group of the Swedish Society of infectious diseases. Swedish guidelines on the management of community-acquired pneumonia in immunocompetent adults – Swedish Society of Infectious Diseases 2012. Scand J Infect Dis. 2012;44:885–902.

5. Levy ML, Le Jeune I, Woodhead MA, Macfarlaned JT, Lim WS; British Thoracic Society Community Acquired Pneumonia in Adults Guideline Group. Primary care summary of the British Thoracic Society Guidelines for the management of community acquired pneumonia in adults: 2009 update. Endorsed by the Royal College of General Practitioners and the Primary Care Respiratory Society UK. Prim Care Respir J. 2010;19:21–7.

6. Woodhead M, Blasi F, Ewig S, Garau J, Huchon G, Ieven M, et al; 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 – Full version. Clin Microbiol Infect. 2011;17(Suppl 6):E1–59.

7. Sociedad Española de Medicina Familiar y Comunitaria. Infecciones del aparato respiratorio inferior. En: Manual de Enfermedades Infecciosas en Atención Primaria. 3ª Ed. Barcelona: semFYC Ediciones, 2010; pp. 45–56.

8. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; eighteenth informational supplement. CLSI document M100-S18. Wayne, PA: Clinical and Laboratory Standards Institute; 2008.

9. European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe, 2014. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2015. Available at: http://ecdc.europa.eu/en/publications/publications/antimicrobial-resistance-europe-2014.pdf

10. Garau J. The hidden impact of antibacterial resistance in respiratory tract infection. Clinical failures: the tip of the iceberg? Respir Med. 2001;95(Suppl A):S5–11.

11. Saust LT, Monrad RN, Hansen MP, Arpi M, Bjerrum L. Quality assessment of diagnosis and antibiotic treatment of infectious diseases in primary care: a systematic review of quality indicators. Scand J Prim Health Care. 2016;34:258–66.

12. Llor C, Arranz J, Morros R, García-Sangenís A, Pera H, Llobera J, et al. Efficacy of high doses of oral penicillin versus amoxicillin in the treatment of adults with non-severe pneumonia attended in the community: study protocol for a randomised controlled trial. BMC Fam Pract. 2013;14:50.

13. Moberg AB, Taléus U, Garvin P, Fransson SG, Falk M. Community-acquired pneumonia in primary care: clinical assessment and the usability of chest radiography. Scand J Prim Health Care. 2016;34:21–7.

14. Aubier M, Verster R, Regamey C, Geslin P, Vercken JB. Once-daily sparfloxacin versus high-dosage amoxicillin in the treatment of community-acquired, suspected pneumococcal pneumonia in adults. Sparfloxacin European Study Group. Clin Infect Dis. 1998;26:1312–20.

15. Petitpretz P, Arvis P, Marel M, Moita J, Urueta J; CAP5 Moxifloxacin Study Group. Oral moxifloxacin vs high-dosage amoxicillin in the treatment of mild-to-moderate, community-acquired, suspected pneumococcal pneumonia in adults. Chest. 2001;119:185–95.

16. Wang W. On construction of the smallest one-sided confidence interval for the difference of two proportions. Ann Statistics. 2010;38:1227–43.

17. Llor C, Moragas A. Dificultades de selección en los ensayos clínicos en atención primaria. Cuando no se llega al tamaño muestral. Aten Primaria. 2013;45:71–3.

18. Gilbert DN. Clinical end points of therapy for patients with mild community-acquired pneumonia. Clin Infect Dis. 2008;47(Suppl 3):S140–4.

19. Atkinson M, Lakhanpaul M, Smyth A, Vyas H, Weston V, Sithole J, et al. Comparison of oral amoxicillin and intravenous benzyl penicillin for community acquired pneumonia in children (PIVOT trial): a multicentre pragmatic randomised controlled equivalence trial. Thorax. 2007;62:1102–6.

20. Addo-Yobo E, Chisaka N, Hassan M, Hibberd P, Lozano JM, Jeena P, et al. Oral amoxicillin versus injectable penicillin for severe pneumonia in children aged 3 to 59 months: a randomised multicentre equivalency study. Lancet. 2004;364:1141–8.

21. Tsarouhas N, Shaw KN, Hodinka RL, Bell LM. Effectiveness of intramuscular penicillin versus oral amoxicillin in the early treatment of outpatient pediatric pneumonia. Pediatr Emerg Care. 1998;14:338–41.

22. Rojas MX, Granados C. Oral antibiotics versus parenteral antibiotics for severe pneumonia in children (Review). Cochrane Database Syst Rev. 2006;(2):CD004979.

23. Agweyu A, Gathara D, Oliwa J, Muinga N, Edwards T, Allen E, et al; Severe Pneumonia Study Group. Oral amoxicillin versus benzyl penicillin for severe pneumonia among Kenyan children: a pragmatic randomized controlled noninferiority trial. Clin Infect Dis. 2015;60:1216–24.

24. Pakhale S, Mulpuru S, Verheij TJ, Kochen MM, Rohde GG, Bjerre LM. Antibiotics for community-acquired pneumonia in adult outpatients. Cochrane Database Syst Rev. 2014;(10):CD002109.

25. Knudsen JD, Odenholt I, Erlendsdottir H, Gottfredsson M, Cars O, Frimodt-Møller N, et al. Selection of resistant Streptococcus pneumoniae during penicillin treatment in vitro and in three animal models. Antimicrob Agents Chemother. 2003;47:2499–506.

26. Oakes M, Human RP, Meers PD. Serum-levels of four antibiotics administered orally to patients in general practice. Lancet. 1973;1:222–4.

27. Bryan CS, Talwani R, Stinson MS. Penicillin dosing for pneumococcal pneumonia. Chest. 1997;112:1657–64.

28. Fredlund H, Bodin L, Bäck E, Holmberg H, Krook A, Rydman H. Antibiotic therapy in pneumonia: a comparative study of parenteral and oral administration of penicillin. Scand J Infect Dis. 1987;19:459–66.

29. British Medical Association; Pharmaceutical Society of Great Britain: British National Formulary 59. London: BMJ Publishing Group Ltd and Royal Pharmaceutical Society, 2010; pp. 231–352.

30. Pallarés R, Linares J, Vadillo M, Cabellos C, Manresa F, Viladrich PF, et al. Resistance to penicillin and cephalosporin and mortality from severe pneumococcal pneumonia in Barcelona, Spain. N Engl J Med. 1995;333:474–80.

31. Metlay JP, Hofmann J, Cetron MS, Fine MJ, Farley MM, Whitney C, et al. Impact of penicillin susceptibility on medical outcomes for adult patients with bacteremic pneumococcal pneumonia. Clin Infect Dis. 2000;30:520–8.

Table 1. Baseline characteristics of the patients randomized into two groups to receive either amoxicillin or penicillin V. Values are numbers (percentages) unless stated otherwise.

	Amoxicillin (n=28)	Penicillin V (n=15)
Male sex	14 (50.0)	5 (33.3)
Age, mean (SD)	49.0 (14.3)	46.6 (17.4)
Smoking status:		
Current smoker	4 (14.3)	3 (20.0)
Former smoker	4 (14.3)	4 (26.7)
Non smoker	20 (71.4)	8 (53.3)
Excessive consumption of alcohol	3 (10.7)	1 (6.7)
High blood pressure	3 (10.7)	3 (20.0)
Diabetes mellitus	1 (3.6)	0 (-)
Hypercholesterolemia	7 (25.0)	3 (20.0)
Cough	28 (100)	14 (93.3)
Days with cough before randomization visit, mean (SD)	6.2 (4.7)	10.1 (8.7)
Joint and muscle aches	14 (50.0)	8 (53.3)
Expectoration	24 (85.7)	12 (80.0)
Sputum color:		
Uncolored	1 (3.6)	4 (26.7)
Yellow or green	21 (75.0)	6 (40.0)
Rust	2 (7.1)	1 (6.7)
Diarrhea	2 (7.1)	2 (13.3)
Dyspnea	8 (28.6)	6 (40.0)
Chest pain	13 (46.4)	7 (46.7)
General malaise	20 (71.4)	13 (86.7)

Clinical examination:		
Temperature, mean ºF (SD)	99.1 (33.8)	99.1 (33.3)
Systolic blood pressure, mean of mm Hg (SD)	128.0 (16.1)	125.1 (13.9)
Diastolic blood pressure, mean of mm Hg (SD)	77.9 (10.1)	74.7 (11.6)
Pulse, mean per minute (SD)	85.5 (14.9)	83.3 (9.0)
Respiratory rate, mean per minute (SD)	19.3 (4.0)	18.5 (3.6)
Pulse oximetry, mean of saturation (SD)	96.8 (1.7)	97.0 (1.7)
General crackles	1 (3.6)	1 (6.7)
Focal crackles	23 (82.1)	12 (80.0)
Ronchi	7 (25.0)	3 (20.0)
Wheezing	6 (21.4)	2 (13.3)
Treatment administered:		
Analgesics	21 (75.0)	14 (93.3)
Non-steroidal anti-inflammatory drugs	12 (42.9)	8 (53.3)
Antitussives	8 (28.6)	2 (13.3)
Bronchodilators	7 (25.0)	0 (-)
Mucolytics	6 (21.4)	4 (26.7)

SD: standard deviation