

Original Article

The combined treatment of imipenem cilastatin and azithromycin for elderly patients with community-acquired pneumonia

Jinhua Yang¹, Yan'e Gong², Yanfeng Zhao³

Departments of ¹Respiratory and Critical Care Medicine, ²Clinical Laboratory, Heping Hospital Affiliated to Changzhi Medical College, Changzhi 046000, Shanxi, China; ³Department of Thoracic Surgery, Shanghai Pulmonary Hospital Affiliated to Tongji University, Shanghai 200433, China

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Abstract: Objective: This study aimed to observe the clinical symptoms and signs of community-acquired pneumonia (CAP) treated with imipenem cilastatin and detect the changes of blood NLR, ESR, PCT and CRP in the elderly. Methods: Patients enrolled in this study were randomly divided into three groups: 71 in the imipenem cilastatin treatment group, 73 in the moxifloxacin treatment group, and 69 in the imipenem cilastatin combined with azithromycin treatment group (combination therapy group). General data were obtained and analyzed. The changes in body temperature, respiration, heart rate, blood pressure, white blood cell count, NLR, ESR, PCT, and CRP were measured before and 10 days after treatment. Results: There were no significant differences in patients' gender, age, weight, vital signs, length of stay, or the severity of pneumonia among different groups ($P>0.05$). Blood cell count, NLR, ESR, PCT, and CRP at 10 days were significantly decreased compared to those at 1 day post treatment ($P<0.05$). The combined treatment of imipenem cilastatin and azithromycin significantly shortened the recovery time, and significantly down regulated NLR, ESR, PCT, and CRP levels compared to imipenem cilastatin and moxifloxacin, respectively ($P>0.05$). Conclusion: The combined treatment of imipenem cilastatin and azithromycin significantly improve the clinical symptoms of elderly patients with community-acquired pneumonia via shortening the recovery time and decreasing NLR, ESR, PCT, and CRP levels compared to single use of imipenem cilastatin or moxifloxacin, which lays fundamental indications for future treatment against CAP in clinic.

Keywords: Imipenem cilastatin, community-acquired pneumonia, efficacy, blood parameters

Introduction

Community acquired pneumonia (CAP) is an infectious disease of the pulmonary parenchyma and interstitial lung, acquired outside of the hospital. It is one of the most common diseases in the respiratory system and poses a public threat to the health of elderly, contributing to one of the most common causes of death from infectious diseases in the world [1]. The incidence of community-acquired pneumonia in rural China is estimated to be about 4% higher than that in urban areas [2]. Community-acquired pneumonia is generally caused by a combination of multiple types of microorganisms, of which, pneumonia mainly accounts for about 80% [3]. With the decline of the physical fitness and the immune defense function in the elderly, the latent bacterial flora quickly

becomes a conditional pathogen, which increases the chance of infecting the lungs and causing lung infections [4]. In recent years, the rapid development of industrial pollution and the aging population further elevate the probability of respiratory infection. It has been indicated that respiratory diseases in China account for the most hospital infections, up to 40% [5]. In elderly people respiratory function, bronchial mucociliary function, lung tissue elasticity, all decrease, while the reduction of sputum function further adds to the chance of bacterial invasion of the lungs [6]. The community-acquired pneumonias are mostly caused by *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, etc. Antibacterial drugs play key roles in pneumonia treatment. However, the abuse of antibiotics gives rise to a certain

degree of drug resistance. Therefore, the appropriate and rational use of antibacterial drugs can guarantee the clinical efficacy, reduce the incidence of adverse reactions and bacterial resistance to community-acquired pneumonia treatment.

Moxifloxacin is the fourth-generation broad-spectrum antibacterial drug of quinolones [7]. Moxifloxacin presents favorable advantages against macrolide- and penicillin-resistant bacteria. *Toxoplasma* topoisomerase II and IV are effective inhibitors to prevent DNA replication and they have a potent ability to penetrate the cell membrane [8]. Due to their unique chemical structure, which allows them to have strong antibacterial ability, they are now widely used in the treatment of *Streptococcus pneumoniae* infection [9]. However, the incidence rate of drug resistance frequently increases in the elderly, the efficacy of moxifloxacin especially in the elderly community acquired pneumonia remains to be further studied.

Azithromycin is a class of internal lipid antibiotics, and it exerts its functions mainly through the combination of cell ribosomes, which thereby inhibits its dependence on RNA protein synthesis [10]. Azithromycin has a certain effect on atypical pathogens and respiratory pathogens [11], but due to the narrow spectrum of gastrointestinal reactions and other side effects of azithromycin antibacterial spectrum, it may severely affect the health of older people.

Imipenem cilastatin is an important antibiotic for the treatment of pneumonia [12]. It belongs to carbapenems, and is a broad-spectrum β -lactam antibiotic. It refers to a class of antibiotics containing the chemical structure of a β -lactam ring, including penicillin antibiotics and cephalosporins [13]. Bacteriocins, atypical β -lactams, β -lactamase inhibitors mainly act as a hindrance to the action of the linear decapeptide disaccharide polymer, which can destroy the bacterial cell wall, and ultimately cause cell-associated necrosis.

It is of great importance to provide effective antibiotic treatment in time after the diagnosis of CAP. Due to the poor physical fitness, drug absorption and low sensitivity of multiple drugs, growing resistance to various antibiotics in the elderly, it is necessary to determine suitable treatment for pneumonia, especially in the elderly. At present, antibiotics used in the initial treatment of community-acquired pneu-

monia are mostly selected from respiratory quinolones (moxifloxacin), macrolides, and β -lactams [14]. This article aims to provide scientific reference and guidance for the clinical use of imipenem cilastatin in elderly patients with community-acquired pneumonia by observing the efficacy and safety of imipenem cilastatin, imipenem cilastatin, azithromycin, and moxifloxacin in the treatment of community-acquired pneumonia.

Patients and methods

Clinical materials

A total of 213 patients with bacterial community-acquired pneumonia were enrolled, aged 56 to 91 years, from June 2016 to April 2018 in Heping Hospital affiliated to Changzhi Medical College. All patients were diagnosed in accordance with Chinese Adult Communicable Acquired Pneumonia Diagnosis and Treatment Guide 2016 Edition the diagnostic criteria. The hospitalized patients with community-acquired pneumonia were randomly divided into three groups, imipenem cilastatin group (n=71, including 38 males and 32 females), moxifloxacin group as control (n=73, including 36 males and 37 females), imipenem cilastatin and azithromycin combined treatment group (n=69, including 33 males and 36 females). This study was pre-approved by the ethical committee of Heping Hospital affiliated to Changzhi Medical College. All subjects signed a consent form before recruitment in this study.

Inclusion and exclusion criteria

Inclusion criteria: Community-acquired pneumonia was diagnosed by clinical features (e.g., cough, fever, pleuritic chest pain) and by lung imaging, usually an infiltrate seen on chest radiography; Patients with complete clinical data; The study drugs were not used within 11 months prior; Time of admission or diagnosis <48 h; Informed consent was given by patients and their families.

Exclusion criteria: Patients with lung cancer, aspiration pneumonia and other lung diseases; Clear contraindications and history of allergies to the study drugs; Patients with severe heart, liver, or renal insufficiency.

Intervention therapy

In moxifloxacin group, intravenous infusion of moxifloxacin (Nanjing Youke Pharmaceutical

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Table 1. The sex distribution of the three groups of subjects

Classification	Combined treatment (n=69)	Moxifloxacin (n=73)	Imipenem cilastatin (n=71)
Sex (Male/Female)	33/36	36/37	38/32

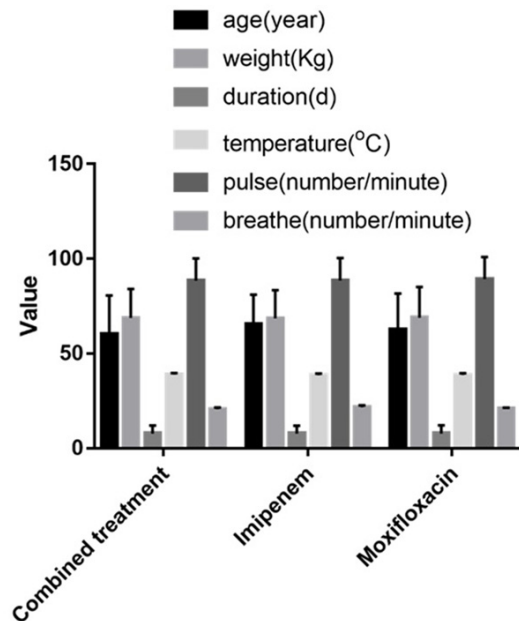


Figure 1. The comparison of age, weight, duration, body temperature, pulse and breathe between the day of admission and treatment in patients receiving imipenem cilastatin treatment, combination therapy, and moxifloxacin treatment ($P>0.05$).

Co., Ltd., Zhuozi H20130039, 20 mL:400 mg) 0.4 g, once daily, with course of treatment for 14 d. In imipenem cilastatin group, intravenous infusion of imipenem cilastatin (Zhejiang Hisun Pharmaceutical Co., Ltd., Zhuozi H200-67764, 0.5 g) 0.5 g was added to 100 mL of saline every 6 hours for 3 days. Later adjusted to every 8 hours after 3 days, with course of treatment for 14 days. In imipenem cilastatin and azithromycin combined treatment group, oral azithromycin tablets (Pfizer Pharm Co., Ltd.) were administered daily on the basis of the sub-groups of the imipenem cilastatin, 0.25 mg each time, twice daily.

Vital signs test

All patients received monitoring of body temperature, respiration, heart rate, blood pressure, and pulse oximetry (SpO_2) on the day of admission.

Inflammation index

The peripheral white blood cell count, NLR, ESR, PCT, and CRP were measured. All patients gave venous blood on the day of admission and on the 10th day, results of which were determined by the laboratory of our hospital.

Treatment indicators and efficacy criteria

The efficacy assessment was based on the criteria adopted in the Guiding Principles for Clinical Research of Antibacterial Drugs [15]: Abnormal lung signs completely disappeared without any abnormal changes seen by lung imaging; normal body temperature maintained for more than 3 days; no repeated judgments for cure during treatment; abnormal lung signs disappeared; abnormalities improved by lung imaging; and normal body temperature was maintained. Over 5 days was judged to be valid; if the above criteria were not met, the condition is judged to be invalid.

Statistical processing

Data in this study were presented as mean \pm standard deviation and cases (percentage), and Statistical Product and Service Solutions (SPSS) 19.0 software (SPSS Inc., Chicago, IL, USA) was used for data processing. t-test was used for the intergroup comparisons, chi-square test was used for enumeration data, and analysis of variance was used for the comparison among groups. $P<0.05$ suggested that the difference was statistically significant.

Results

General information

There were 71 patients in the imipenem cilastatin treatment group, including 38 males and 32 females. There were 73 patients treated with moxifloxacin as control, including 36 males and 37 females. There were 69 patients who received combined therapy of imipenem cilastatin and azithromycin, including 33 males and 36 females. There was no significant difference in gender, age, weight, and vital signs among the groups ($P>0.05$) (Table 1; Figure 1).

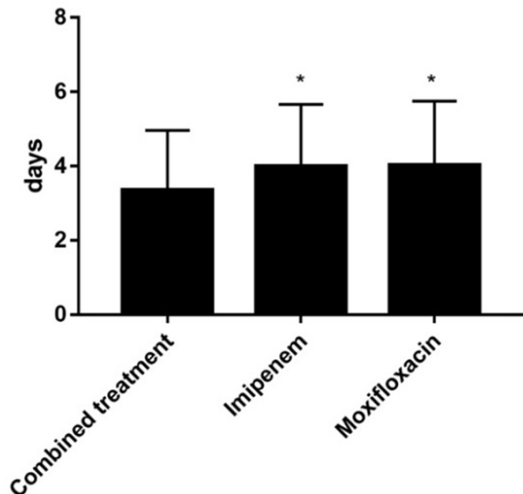


Figure 2. Duration of when the temperature returned to normal in patients from three groups. Compared with the combination therapy group, *P<0.05.

The length of time for the patient's average body temperature returned to normal

There was no significant difference in the duration of body temperature returning to normal between imipenem cilastatin and moxifloxacin groups (P>0.05). However, the combined treatment of imipenem cilastatin and azithromycin significantly shortened the recovery time compared to imipenem cilastatin and moxifloxacin (P<0.05) (**Figure 2**).

Monitoring results of vital signs

We monitored the vital signs of patients from different groups. The result showed that there was no significant difference in respiration, heart rate, blood pressure and blood oxygen saturation among the three groups at 1 and 10 days post treatment, respectively (P>0.05) (**Figure 3**).

The changes of blood and inflammatory markers in patients with different therapeutic strategies

We measured the levels of blood and inflammatory markers in patients with different therapeutic strategies. At 1 day post treatment, no statistical differences regarding peripheral white blood cells, NLR, ESR, PCT, and CRP were found among patients treated with imipenem

cilastatin, moxifloxacin, or combination of imipenem cilastatin and azithromycin. Of note, the levels at 10 days post treatment were significantly decreased compared to those at 1 day post treatment (P<0.05). In addition, the combined treatment of imipenem cilastatin and azithromycin significantly down regulated NLR, ESR, PCT, and CRP levels compared to imipenem cilastatin and moxifloxacin, respectively (P<0.05) (**Figure 4**).

The length of stay in hospital

We found a slight difference concerning the length of stay in the hospital for patient receiving imipenem cilastatin, moxifloxacin and combination of imipenem cilastatin and azithromycin, though the difference was not statistically significant (P>0.05) (**Table 2**).

Discussion

Community-acquired pneumonia (CAP) is a common respiratory diseases throughout the world, and it is one of the most common causes of infectious death in the world [16]. The incidence rate in China is increasing annually, and quinolones are generally given to patients with stable vital signs [17].

Macrolides can exert antibacterial activity against gram-positive bacteria, gram-negative bacteria, and atypical pathogens, mainly through the formation of irreversible binding of the bacterial inner ribosomal 50S, which prevents the translocation of mRNA and inhibits the synthesis of bacterial proteins [18, 19].

The mechanism of action of β-lactams is to inhibit cell wall mucin synthesis by blocking the synthesis of cell wall mucilage, thereby destroying the bacterial cell wall and lysing the integrity of the bacteria. Since atypical pathogens usually have no cell wall, β-lactams present special impeding function for such pathogens. Clinically, β-lactams and macrolides are commonly used to treat CAP. The quinolone antibacterial activity mainly works through DNA gyrase competition within the bacterial DNA binding sites. It blocks the DNA gyrase binding, resulting in the destruction of irreversible DNA damage. Moxifloxacin is a new generation of quinolones, widely used in clinical practice.

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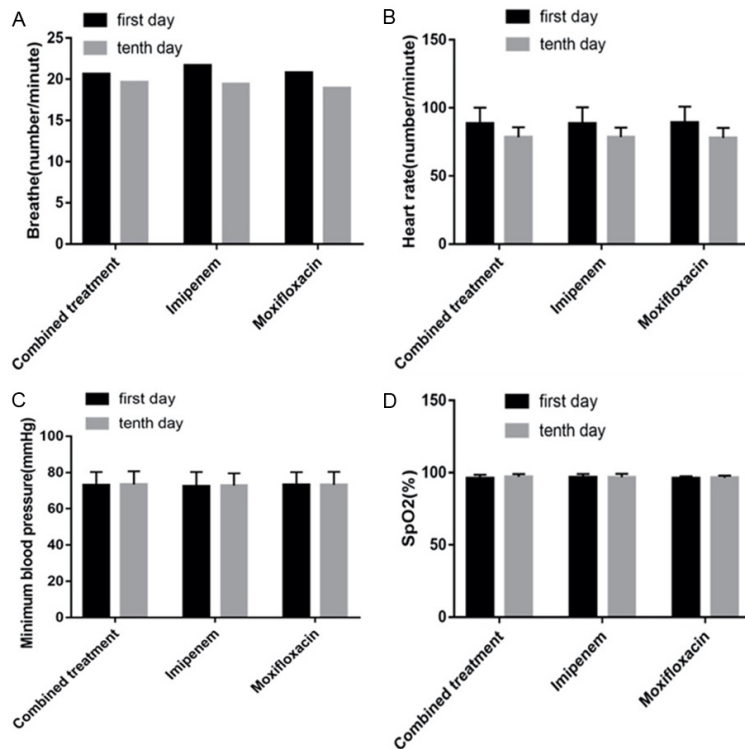


Figure 3. Vital signs of patients at 1 and 10 days post treatment. A. Respiratory status. B. Heart rate. C. Blood pressure. D. Blood oxygen conditions.

Due to the special clinical features of community-acquired pneumonia in the elderly, there is generally anti-biotin resistance, and poor physical fitness in the elderly, along with poor drug absorption rates. On account for different individuals, the actual effect of quinolones, macrolides, and β -lactams varies. A retrospective analysis reported that the efficacy of quinolones was comparable to that of β -lactams combined with macrolides. Moreover, quinolones may be safer, but the drug resistance and potential drug resistance are increased [20]. In 2016, evidence showed that β -lactams combined with macrolides in the treatment of CAP and β -lactams combined with quinolones were more effective than β -lactams and macrolides. In the combined quinolones treatment group, the recovery time and hospital stay were significantly shorter than those in the control group [21]. It has been indicated that combined treatment for community-acquired pneumonia in the elderly significantly decreased the Oxygen Index, C-reactive protein, and procalcitonin compared to single use of moxifloxacin. Also, imipenem cilastatin was superior to moxifloxacin in the treatment of

elderly patients with community-acquired pneumonia, with favorable safety [15].

In this study, 213 elderly patients with community-acquired pneumonia were studied; they received imipenem cilastatin, moxifloxacin or combined therapy of imipenem cilastatin and azithromycin group, respectively. The results of the study showed that the duration required for the body temperature of the combination therapy group returning to normal was significantly shortened compared to imipenem cilastatin or moxifloxacin-treated. In terms of inflammatory markers such as NLR, ESR, PCT and CRP, these levels in the combination treatment group were markedly reduced compared to the other two groups. It is speculated that β -lactam antibiotics act mainly

on the cell wall of the mucopeptide synthetase, and have the best effect on the bacteria during the breeding period, while it mainly blocks the mRNA displacement and destroys the synthesis of structural proteins in bacteria. The β -lactam antibacterial drugs and the macrolide synergistically impair the bacteria in the stationary phase and reproductive phase. The combination contributes to a synergistic effect and increases the drug's antibacterial activity.

The diagnosis and treatment guidelines for community-acquired pneumonia suggest that symptoms can improve significantly after the body temperature returns to normal 3-5 days later, and cannot be used as a discontinuation indication based on complete absorption of lung shadows. However, the specific treatment measures should be performed based on individual differences, infectious pathogens, and geographical circumstances. Our data propose that azithromycin combination therapy can be used as the first choice for the treatment of CAP in the elderly. The limitation in this study exists that no significant differences in the indexes of respiration, heart rate, blood pressure, and pulse oxygen saturation after distinct

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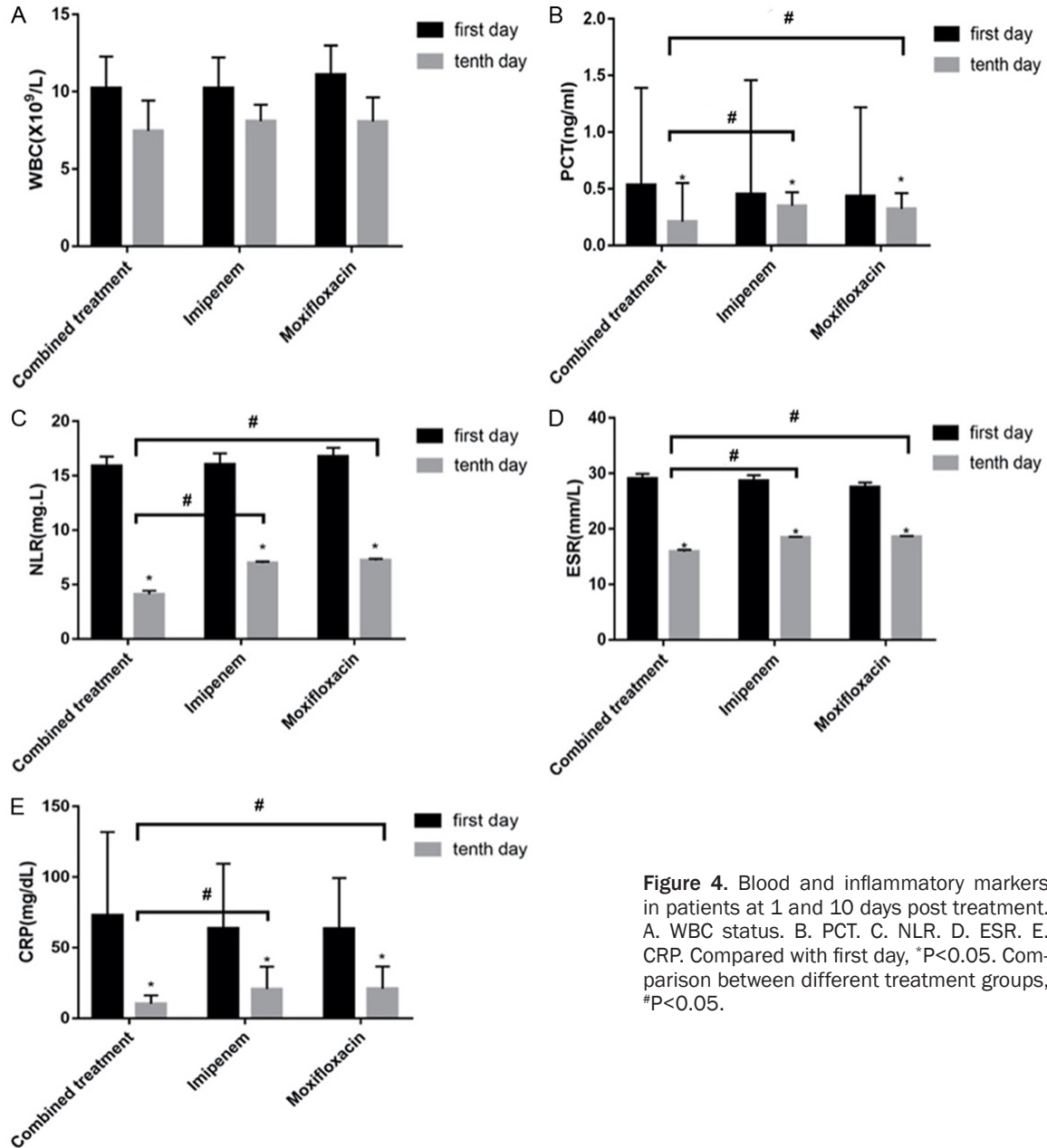


Figure 4. Blood and inflammatory markers in patients at 1 and 10 days post treatment. A. WBC status. B. PCT. C. NLR. D. ESR. E. CRP. Compared with first day, *P<0.05. Comparison between different treatment groups, #P<0.05.

Table 2. Comparison of three groups of antibiotics and duration in hospital for several days

Group	Treatment days		The number of days in hospital	
	($\bar{X} \pm S$)	M (min-max)	($\bar{X} \pm S$)	M (min-max)
Combined treatment	12.49 ± 2.87	12 (10-15)	17.56 ± 5.291	15 (10-21)
Moxifloxacin	13.25 ± 2.96	13 (10-16)	18.36 ± 5.38	15 (13-23)
imipenem cilastatin	13.47 ± 2.67	13 (10-17)	18.54 ± 5.97	15 (14-24)
P	0.354		0.562	

therapeutic strategies have been performed, while a longer period of observation after the treatment, along with larger size of cohort should be considered.

Conclusion

Our data demonstrate that the combination of imipenem cilastatin and azithromycin in the

treatment of elderly patients with CAP present favorable clinical effect compared to subcutaneous injections of imipenem cilastatin or moxifloxacin alone, which provides new leads for further therapy against CAP in elderly.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Jinhua Yang, Department of Respiratory and Critical Care Medicine, Heping Hospital Affiliated to Changzhi Medical College, 110 Yan'an South Road, Changzhi 046000, Shanxi, China. Tel: +86-0355-3128124; E-mail: jinhuayang159@163.com

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