Observational Study

Medicine®

OPEN

A retrospective study of azithromycin and ceftizoxime for the management of children with *Mycoplasma pneumoniae* pneumonia

Li-ping Han, MM[a], Han-yan Xiao, MM[b], Li-li Fang, MB[a,*]

Abstract

The aim of this study was to compare the clinical efficacy of azithromycin and ceftizoxime (AC) and erythromycin and amoxicillin/sulbactam (EAS) in the treatment of children with *Mycoplasma pneumoniae* pneumonia (MPP).

In this retrospective study, a total of 92 eligible children with MPP were included, and they were divided into a treatment group (n = 46) and a control group (n = 46). All patients were treated with intravenous ambroxol, and nebulized inhalation of budesonide and terbutaline. In addition, patients in the treatment group received AC. Patients in the control group underwent EAS. All patients in both groups were treated for a total of 10 days. Outcomes consist of erythrocyte sedimentation rate, C-reactive protein, serum lactate dehydrogenase, and interleukin 6, fever clearance time, time of cough disappearance, time of rale disappearance, time of signs disappeared by X-ray, and adverse events. All outcomes were measured after 10-day treatment.

After treatment, patients who received AC exerted better improvements in erythrocyte sedimentation rate ($P < .01$), C-reactive protein ($P < .01$), serum lactate dehydrogenase ($P < .01$), interleukin 6 ($P < .01$), fever clearance time ($P < .01$), time of cough disappearance ($P < .01$), time of rale disappearance ($P < .01$), and time of signs disappeared by X-ray ($P < .01$), than those in patients who received EAS. In addition, there were not significant differences in adverse events between 2 groups.

The results of this study showed that AC may benefit more than EAS for the children with MPP.

Abbreviations: AC = azithromycin and ceftizoxime, CRP = C-reactive protein, EAS = erythromycin and amoxicillin/sulbactam, ESR = erythrocyte sedimentation rate, IL-6 = interleukin 6, LDH = serum lactate dehydrogenase, MP = *Mycoplasma pneumoniae*, MPP = *Mycoplasma pneumoniae* pneumonia.

Keywords: azithromycin, ceftizoxime, *Mycoplasma pneumoniae* pneumonia

1. Introduction

Mycoplasma pneumoniae pneumonia (MPP) is a common respiratory disease resulted from mycoplasma infection, especially in pediatric population.[1–3] It accounts for about 10% to 40% of all pediatric community-acquired pneumonia in children and young adult population,[4–8] and 18% to 20% of them require hospitalization.[9–11] Its typical symptoms and signs are fever and persistent dry cough.[12,13] It has been reported that the overall incidence of MPP varies from 7.1% to 54.4% in China.[14] Although it is a self-limited and benign condition, it still proceeds to severe complications, such as respiratory failure and hypoxia.

Considering that pediatric population with MPP are mostly under the phase of physical development, proper antibiotics are very important to manage this condition. Currently, macrolide antibiotics are the most commonly utilized medication for children with MPP. Studies have reported that erythromycin and amoxicillin/sulbactam (EAS) can effectively alleviate clinical symptoms, enhance lung function, and decrease the period of MPP in children.[15,16] However, other study has also reported that EAS has limited efficacy and causes gastrointestinal adverse events.[17] Additionally, it also results in pain on the local puncture site and phlebitis, which may lead to poor compliance in pediatric population.[17]

Azithromycin is often recommended as the first choice to effectively perform bacteriostatic and bacteriological cleaning.[18–21] It also has good tolerance and long half-life, which can reduce the management period.[22,23] However, it still suffers from unsatisfied efficacy and high risk of drug resistance.[24] Ceftizoxime is a highly resistant beta-lactam antibiotic, which is active against bacterial infections.[25,26] Thus, azithromycin combined ceftizoxime (AC) is highly suggested as the advanced treatment for children with MPP.

Presently, there is insufficient evidence to compare the efficacy and safety of AC and EAS for the treatment of pediatric population with MPP. Therefore, this study aims to compare the

Editor: Jorddy Neves Cruz.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Department of Pediatrics, The Second Affiliated Hospital of Mudanjiang Medical University, Mudanjiang, China, [b] Second Ward of Neurology Department, The Second Affiliated Hospital of Mudanjiang Medical University, Mudanjiang, China.

[*] Correspondence: Li-li Fang, Department of Pediatrics, The Second Affiliated Hospital of Mudanjiang Medical University, No. 15, Dongxiaoyun Street, Aimin District, Mudanjiang 157000, China (e-mail: yinxingzhong9298@126.com).

How to cite this article: Han Lp, Xiao Hy, Fang Ll. A retrospective study of azithromycin and ceftizoxime for the management of children with Mycoplasma pneumoniae pneumonia. Medicine 2021;100:44(e27564).

Received: 23 January 2021 / Received in final form: 18 September 2021 / Accepted: 4 October 2021

http://dx.doi.org/10.1097/MD.0000000000027564

efficacy and safety of AC and EAS for the management of children with MPP.

2. Patients and methods

2.1. Ethical consideration

This retrospective study was approved by the Ethics Committee of The Second Affiliated Hospital of Mudanjiang Medical University. All patients provided written informed consent by their guardians.

2.2. Study design

This retrospective study analyzed a total of 92 eligible patient case records. All patients were performed between January 2018 and December 2019 at The Second Affiliated Hospital of Mudanjiang Medical University. They were assigned to a treatment group (n=46) and a control group (n=46). All patients in both groups received intravenous ambroxol, and nebulized inhalation of budesonide and terbutaline. In addition, patients in the treatment group received AC, whereas subjects in the control group underwent EAS.

2.3. Patients

In this retrospective study, 92 patients with confirmed diagnosis of MPP by biochemical and imaging examinations according to the guideline of "Expert Consensus on the Diagnosis and Treatment of Mycoplasma Pneumoniae Pneumonia in Children (2015 Edition)" were included.[27] In addition, patients were included if they had complete case record information; no treatment of hormone and antibiotics; aged between 3 and 10 years old; *Mycoplasma pneumoniae* (MP) antibody titer≥1:160 or a single MP-IgM antibody positive;[27] and provided written informed consent by their guardians.

Patients were excluded if they meet the following criteria: congenital immune dysfunction or deficiency; congenital heart disease, hereditary metabolic diseases; allergic to study medicine; abnormal function of liver or kidney; viral pneumonia, bacterial pneumonia, and tuberculosis; long-term use of immunosuppressive agents; no written informed consent was provided; and insufficient information of patient case records.

2.4. Treatment approach

All children in both groups received intravenous ambroxol (15-30 mg/each time (depending on different ages), once daily), and budesonide and terbutaline (budesonide 1 mg and terbutaline 0.1 mg/kg, nebulized inhalation twice daily). All medications were administered for a total of 10 days.

In addition, patients in the treatment group received azithromycin (5-10 mg/kg, once daily for 5 days), and ceftizoxime (50 mg/kg, twice daily for a total of 10 days). Patients in the control group underwent erythromycin (10 mg/kg, once daily for a total of 10 days), and amoxicillin/sulbactam (30 mg/kg, twice daily for a total of 10 days).

2.5. Outcome measurements

Outcomes include serum factors (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum lactate dehydrogenase (LDH), and interleukin 6 (IL-6)), symptoms and signs (fever clearance time, time of cough disappearance, time of rale disappearance, time of signs disappeared by X-ray), and adverse events. All outcomes were measured after 10 days treatment.

Table 1

Baseline characteristics between 2 groups.

Characteristic value	Treatment group (n=46)	Control group (n=46)	*P* value
Age (yr)	6.5 (2.1)	6.8 (2.4)	.52
Race (Asian Chinese)	46 (100.0)	46 (100.0)	–
Gender			
Boy	24 (52.2)	27 (58.7)	.53
Girl	22 (47.8)	19 (41.3)	.53
BMI (kg/m^2)	15.2 (2.0)	15.0 (2.3)	.66
Disease duration (d)	7.3 (1.9)	7.6 (2.0)	.46
Leukocytes (10^9/L)	10.7 (6.7)	10.8 (7.0)	.94
Platelets (10^9/L)	291.5 (115.4)	292.0 (113.9)	.98

Data are present as mean ± standard deviation or number (%).

2.6. Statistical analysis

This retrospective study utilized SPSS software (SPSS V.15.0, IBM Corp., Armonk, NY). All dichotomous data was presented as number and percentage, and was analyzed by χ^2 test or Fisher exact test. All continuous data was estimated as mean and standard deviation, and was appraised by *t* test or Mann–Whitney *U* test. A value of 2-side $P < .05$ indicates statistical significance.

3. Results

A total of 92 eligible patients with MPP were included in this retrospective study. Of those, 46 patients who received AC were assigned to the treatment group, whereas the other 46 subjects who underwent EAS were assigned to the control group. We presented all patient characteristics and demographics in Table 1. There were not significant statistical differences in age (year), race, gender, body mass index (kg/m^2), disease duration (day), leukocytes (10^9/L), and platelets (10^9/L) between 2 groups (Table 1).

Before treatment, there were not significant differences in ESR ($P=.64$), CRP ($P=.48$), LDH ($P=.59$), and IL-6 ($P=.77$) between 2 groups (Table 2). However, after 10-day treatment, children with MPP in the treatment group found more improvement in ESR ($P<.01$), CRP ($P<.01$), LDH ($P<.01$), and IL-6 ($P<.01$), than those of children in the control group (Table 3).

Table 2

Comparison of outcome measurements before treatment.

Outcome measurements	Treatment group (n=46)	Control group (n=46)	*P* value
CRP (mg/L)	29.8 (11.2)	31.6 (13.4)	.48
ESR (mm/h)	52.4 (23.6)	54.1 (21.9)	.64
LDH (IU/mL)	395.2 (115.7)	408.5 (120.3)	.59
IL-6 (pg/mL)	7.7 (3.2)	7.9 (3.4)	.77

Data are present as mean ± standard deviation.

CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, IL-6 = interleukin 6, LDH = serum lactate dehydrogenase.

Table 3

Comparison of outcome measurements after treatment.

Outcome measurements	Treatment group (n = 46)	Control group (n = 46)	*P* value
CRP (mg/L)	5.3 (2.6)	6.9 (3.1)	<.01
ESR (mm/h)	12.1 (3.4)	17.6 (5.3)	<.01
LDH (IU/mL)	297.2 (80.7)	355.9 (102.4)	<.01
IL-6 (pg/mL)	5.1 (2.3)	6.6 (3.0)	<.01

Data are present as mean ± standard deviation.
CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, IL-6 = interleukin 6, LDH = serum lactate dehydrogenase.

Table 5

Comparison of adverse events between 2 groups.

Adverse events	Treatment group (n = 46)	Control group (n = 46)	*P* value
Local pain	2 (4.3)	4 (4.7)	.41
Rash	2 (4.3)	4 (4.7)	.41
Gastrointestinal reaction	3 (6.5)	5 (10.9)	.46
Nausea	3 (6.5)	5 (10.9)	.46
Vomiting	2 (4.3)	3 (6.5)	.65
Total adverse events	12 (26.1)	21 (45.7)	.05

Data are present as number (%).

After treatment, children who received AC also showed better efficacy in fever clearance time ($P < .01$, Table 4), time of cough disappearance ($P < .01$, Table 4), time of rale disappearance ($P < .01$, Table 4), and time of signs disappeared by X-ray ($P < .01$, Table 4), than those in children who received EAS.

In addition, there were not significant differences in incidence of each adverse event (local pain, $P = .41$; rash, $P = .41$; gastrointestinal reaction, $P = .46$; nausea, $P = .46$; vomiting, $P = .65$; Table 5), and total incidence of adverse events ($P = .05$, Table 5) between 2 groups.

4. Discussion

MP infection is the major pathogenic factor of MPP in pediatric population.[3] Its incidence presents an increasing tendency in recent years.[14] Macrolide antibiotics are the essential selected medications for the treatment of MPP.[15] Of those, erythromycin is a frequent drug for patients with MP.[15,16] Although, erythromycin alone can control the condition of MPP to a certain extent in pediatric population, its clinical efficacy is still limited, which may impact their prognosis. In addition, it may also accompany a variety of adverse events, such as gastrointestinal reactions, including nausea, vomiting, abdominal pain and diarrhea, especially for long-term administration.[17] Fortunately, EAS are reported to have more powerful clinical efficacy and shorter treatment course for children with MPP.

Azithromycin is the other macrolide antiotic, which has a good activity against MPP, and plays a very essential role in antimicrobial activity,[18,19] especially for the treatment of MPP in pediatric population. However, there is restricted clinical efficacy and drug resistance, which may affect its utilization to the clinical practice.[24] Luckily, ceftizoxime is reported to solve such issue. Thus, AC is found to be more effective intervention for children with MPP.

Studies report that azithromycin is superior to erythromycin in treating children with MPP.[28,29] One study reported that the total effective rate of azithromycin was much higher than erythromycin in children with MPP.[28] The other study found that azithromycin was much better than erythromycin in time of cough relief and rale in pediatric patients with MPP.[29] In addition, study also reported the tolerance rates of azithromycin were less than those of erythromycin in treating MPP.[30] However, there is still insufficient data to compare the clinical efficacy and safety of AC and EAS for the treatment of MPP in pediatric population.

The present study explored the efficacy and safety of AC compared with EAS in treating children with MPP. Our results are partly consistent with previous studies.[28,29] The results of this study showed that patients in the treatment achieved better improvements in ESR, CRP, LDH, IL-6, fever clearance time, time of cough disappearance, time of rale disappearance, and time of signs disappeared by X-ray, than those of patients in the control group. It indicates that AC may be better than EAS for the treatment of children with MPP. In addition, there is a similar safety profile between 2 groups in this study.

This retrospective study still has several drawbacks. Firstly, this study was only conducted at 1 center of The Second Affiliated Hospital of Mudanjiang Medical University, which may restrict the generalization of its findings to other hospitals. Secondly, this retrospective study did not employ approach of randomization and blinding to both patients and investigators, which may cause risk of bias of study selection. Thirdly, this study only assessed short-term of 10-day treatment, and no further evaluation was performed in this study. Fourthly, this study only analyzed all outcome data at the time point of 10-day posttreatment, and no outcome data at other time points were collected and analyzed, because of insufficient information and incomplete data at other time points. Fifthly, the sample size of this study is relatively small, which may affect the present findings. Finally, the last limitation is a retrospective study in nature. Thus, future studies should avoid above limitations.

Table 4

Comparison of symptoms relief between 2 groups.

Symptoms relief (d)	Treatment group (n = 46)	Control group (n = 46)	*P* value
Fever clearance time	3.2 (1.4)	5.3 (1.8)	<.01
Time of cough disappearance	7.8 (2.5)	9.4 (3.3)	<.01
Time of rale disappearance	5.3 (2.5)	7.5 (3.4)	<.01
Time of signs disappeared by X-ray	12.1 (3.4)	15.0 (5.1)	<.01

Data are present as mean ± standard deviation.

5. Conclusion

The results of the present study demonstrated that AC may exert more promising efficacy than EAS for the treatment of children with MPP.

Author contributions

Conceptualization: Li-ping Han, Han-yan Xiao, Li-li Fang.
Data curation: Li-ping Han, Han-yan Xiao, Li-li Fang.
Formal analysis: Li-ping Han.
Investigation: Li-li Fang.

Methodology: Li-ping Han.
Project administration: Li-li Fang.
Resources: Li-ping Han, Han-yan Xiao.
Software: Li-ping Han, Han-yan Xiao.
Supervision: Li-li Fang.
Validation: Li-ping Han, Han-yan Xiao, Li-li Fang.
Visualization: Li-ping Han, Han-yan Xiao, Li-li Fang.
Writing – original draft: Li-ping Han, Han-yan Xiao, Li-li Fang.
Writing – review & editing: Li-ping Han, Han-yan Xiao, Li-li Fang.

References

[1] Lee E, Cho HJ, Hong SJ, Lee J, Sung H, Yu J. Prevalence and clinical manifestations of macrolide resistant *Mycoplasma pneumoniae* pneumonia in Korean children. Korean J Pediatr 2017;60:151–7.

[2] Zhou Y, Zhang Y, Sheng Y, Zhang L, Shen Z, Chen Z. More complications occur in macrolide-resistant than in macrolide-sensitive *Mycoplasma pneumoniae* pneumonia. Antimicrob Agents Chemother 2014;58:1034–8.

[3] Pereyre S, Goret J, Bebear C. *Mycoplasma pneumoniae*: current knowledge on macrolide resistance and treatment. Front Microbiol 2016;7:974.

[4] Liu G, Talkington DF, Fields BS, Levine OS, Yang Y, Tondella ML. *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* in young children from China with community-acquired pneumonia. Diagn Microbiol Infect Dis 2005;52:7–14.

[5] Vervloet LA, Marguet C, Camargos PA. Infection by *Mycoplasma pneumoniae* and its importance as an etiological agent in childhood community-acquired pneumonias. Braz J Infect Dis 2007;11:507–14.

[6] Miyashita N, Fukano H, Mouri K, et al. Community-acquired pneumonia in Japan: a prospective ambulatory and hospitalized patient study. J Med Microbiol 2005;54:395–400.

[7] Waites KB, Balish MF, Atkinson TP. New insights into the pathogenesis and detection of *Mycoplasma pneumoniae* infections. Future Microbiol 2008;3:635–48.

[8] Atkinson TP, Balish MF, Waites KB. Epidemiology, clinical manifestations, pathogenesis and laboratory detection of *Mycoplasma pneumoniae* infections. FEMS Microbiol Rev 2008;32:956–73.

[9] Waites K. New concepts of *Mycoplasma pneumoniae* infections in children. Pediatr Pulmonol 2003;36:267–78.

[10] Rogozinski LE, Alverson BK, Biondi EA. Diagnosis and treatment of *Mycoplasma pneumoniae* in children. Minerva Pediatr 2017;69:156–60.

[11] Waites KB, Talkington DF. *Mycoplasma pneumoniae* and its role as a human pathogen. Clin Microbiol Rev 2004;17:697–728.

[12] Izumikawa K. *Mycoplasma pneumoniae* pneumonia. Nihon Rinsho 2003;61(Suppl 2):536–41.

[13] Youn YS, Lee KY. *Mycoplasma pneumoniae* pneumonia in children. Korean J Pediatr 2012;55:42–7.

[14] Qin Q, Xu BP, Liu XY, Shen KL. Status of *Mycoplasma pneumoniae* pneumonia in Chinese children: a systematic review. Adv Microbiol 2014;4:704–11.

[15] Harris JA, Kolokathis A, Campbell M, Cassell GH, Hammerschlag MR. Safety and efficacy of azithromycin in the treatment of community-acquired pneumonia in children. Pediatr Infect Dis J 1998;17: 865–71.

[16] Wenzel RP, Hendley JO, Dodd WK, Gwaltney JM. Comparison of josamycin and erythromycin in the therapy of *Mycoplasma pneumoniae* pneumonia. Antimicrob Agents Chemother 1976;10:899–901.

[17] Li SL, Sun HM, Zhao HQ, et al. A single tube modified allele-specific-PCR for rapid detection of erythromycin-resistant *Mycoplasma pneumoniae* in Beijing. Chin Med J 2012;125:2671–6.

[18] Qiu JL, Huang L, Shao MY, et al. Efficacy and safety of azithromycin combined with glucocorticoid on refractory *Mycoplasma pneumoniae* pneumonia in children: a PRISMA-compliant systematic review and meta-analysis. Medicine (Baltimore) 2020;99:e20121.

[19] Li Q, Li ZY, Zhang J, et al. Xiyanping plus azithromycin chemotherapy in pediatric patients with *Mycoplasma pneumoniae* pneumonia: a systematic review and meta-analysis of efficacy and safety. Evid Based Complement Alternat Med 2019;2019:2346583.

[20] Fleming-Dutra KE, Demirjian A, Bartoces M, Roberts RM, Taylor THJr, Hicks LA. Variations in antibiotic and azithromycin prescribing for children by geography and specialty-United States, 2013. Pediatr Infect Dis J 2018;37:52–8.

[21] He HX, Zhang XQ. Clinical observation on self-made yiqixiaozhi decoction and azithromycin in the sequential treatment of mycoplasma pneumonia in children. J Sichuan Trad Med 2018;7:43–6.

[22] Zhang YN. Effect of reduning combined with Cefoxitin on children pneumonia. J Contemp Med 2017;15:158–9.

[23] Lu JY. Comparison of efficacy and safety of cefoxitin sodium and cefepime in the treatment of elderly patients with bronchopneumonia. J Contemp Med 2017;15:105–6.

[24] Gong L, Xu L, Diao M, et al. Clinical effect of treating secondary asthma attacks of children *Mycoplasma pneumoniae* with combined therapy of montelukast and azithromycin. Eur Rev Med Pharmacol Sci 2016; 20:5256–60.

[25] Li DD, Lang YM, Shi YX, Tian LY. Pathogen analysis of secondary bacterial infections in children with *Mycoplasma pneumoniae* pneumonia. J Clin Pediatr 2018;36:317–8.

[26] Wan SJ, Liu RZ, Lu YX. Discussion on the clinical features and treatment of severe mycoplasma pneumonia in children. Electro J Clin Med 2017;4:4232.

[27] Respiratory Group of Pediatrics Branch of Chinese Medical Association, Chinese Journal of Practical Pediatrics Editorial Committee.Expert consensus on the diagnosis and treatment of *Mycoplasma pneumoniae* pneumonia in children (2015 edition). Chin J Pract Pediatr Clin Med 2015;30:1304–8.

[28] Yang D, Chen L, Chen Z. The timing of azithromycin treatment is not associated with the clinical prognosis of childhood *Mycoplasma pneumoniae* pneumonia in high macrolide resistant prevalence settings. PLoS One 2018;13:e0191951.

[29] Tang XR. Clinical analysis of sequential azithromycin and erythromycin intravenous drip in the treatment of mycoplasma pneumonia in children. Guide Chin Med 2013;9:230–1.

[30] Peng JB, Chen BB, Deng CH. Efficacy of azithromycin and erythromycin in treatment of mycoplasma pneumonia and effects on immunoglobulins and lymphocyte subsets. Med Innov China 2015;12:54–7.