Principles of antibiotic application in children with lobar pneumonia: Step-up or step-down

YAN LI[1], FENG HAN[1], YAN YANG[2] and JIANWEI CHU[2]

Departments of [1]Pharmacy and [2]Infectious Diseases, Maternal and Child Health Care Hospital of Zaozhuang, Zaozhuang, Shandong 277102, P.R. China

Received May 25, 2016; Accepted December 30, 2016

DOI: 10.3892/etm.2017.4319

Abstract. In order to provide a scientific basis for rational use of antibiotics, we studied and compared the therapeutic effects of step-down and step-up antibiotic treatment schemes in children with lobar pneumonia. Eighty cases of children with lobar pneumonia were enrolled in this study and were randomly divided into two groups: The observation group and the control group, with 40 cases in each group. In the observation group, there were 23 cases with mild and 17 cases with severe lobar pneumonia, and in the control group, 25 were mild and 15 were severe cases. Patients in the control group were treated with antibiotics using step-up therapy method, while patients in the observation group were treated using step-down antibiotic therapy. Our results showed no significant differences in white blood cell (WBC) reduction rate, the course of antibiotic treatment, disappearance time of pulmonary rales and total efficiency in children with mild lobar pneumonia in the observation group after 72 h of treatment. The level of high-sensitivity C-reactive protein (hs-CRP) and procalcitonin (PCT) in the observation group were significantly lower. After 72 h of treatment of children with severe lobar pneumonia in the observation group, the rate of WBC reduction accelerated significantly. Compared to the patients in the control group, the course of antibiotic treatment and disappearance time of pulmonary rales were shortened significantly, while the total efficiency of treatment was improved considerably in the observation group. Also in the observation group, hs-CRP and PCT levels were significantly lower than that in the control group. In severe cases, step-down therapy showed a better result in relieving the inflammatory reactions. The disappearance time of pulmonary rales and the effective rate of treatment was significantly higher than those of step-up therapy. It was obvious that for children with severe lobar pneumonia, step-down therapy produced better results in relieving the inflammatory reaction.

Correspondence to: Dr Feng Han, Department of Pharmacy, Maternal and Child Health Care Hospital of Zaozhuang, 25 Culture Road, Zaozhuang, Shandong 277102, P.R. China
E-mail: zzfyykk@163.com

Key words: lobar pneumonia, antibiotics, step-up therapy, step-down therapy

Introduction

Lobar pneumonia is a common disease in children with lower respiratory tract infection. It is characterized by respiratory symptoms and pulmonary patchy consolidation. *Streptococcus pneumoniae*, *Mycoplasma sp.*, *Staphylococcus aureus* and *Haemophilus influenzae* are the main pathogenic microorganisms that can cause lobar pneumonia in children (1). It has been shown that (2) the use of step-up therapy as the initial treatment for children with lobar pneumonia can reduce the pace of drug resistance rate. Results obtained from prior studies (3) revealed that step-down therapy is the best course of action for children with severe lobar pneumonia. In that study, broad-spectrum antibiotics were used as the initial treatment, and then narrowed down the antibiotic spectrum after the stabilization of symptoms. The guide titled 'Administration Guide for Children with Community-Acquired Pneumonia' (4) did not provide any clear recommendations on the best course of action for lobar pneumonia treatment. In this study, in order to provide a reference for rational use of antibiotics, we evaluated the curative effects of step-up and step-down therapy in sick children with lobar pneumonia.

Patients and methods

Patients. From January 2014 to December 2015, 80 cases of children diagnosed with lobar pneumonia were enrolled in this study. Patients were randomly divided into two groups: The observation group and the control group with 40 cases in each group. There were 23 mild cases and 17 severe cases in the observation group, and in the control group we had 25 cases of mild and 15 cases of severe lobar pneumonia. Baseline data of the two groups were comparable (Table I).

Diagnostic criteria for lobar pneumonia were the following: i) Fever, with obvious symptoms of respiratory tract infection; and ii) chest X-ray showed a large area of high density shadow or pulmonary parenchymal infiltrative lesions in pulmonary lobe or pulmonary segment. Mild lobar

Table I. The comparison of the baseline data in two groups.

	Wild cases			Severe cases		
Groups	Male/Female	Age (years)	Courses (days)	Male/Female	Age (years)	Courses (days)
Control (n=40)	14/11	9.8±3.7	1.3±0.3	9/6	8.9±3.6	1.5±0.6
Observation (n=40)	13/10	10.1±4.5	1.2±0.4	10/7	9.2±3.5	1.4±0.5
χ^2/t-test	0.001	0.124	0.023	0.005	0.263	0.236
P-value	0.971	0.768	0.869	0.946	0.862	0.752

pneumonia patients had normal diet, no signs of dehydration, their axillary temperature was <38.5˚C and the increased respiratory rate was <50 bpm. In severe cases, we observed axillary temperature of ≥38.5˚C, increased respiratory rate ≥50-70 bpm, cyanosis, breath groan, signs of dehydration and patients refused their diet.

We excluded patients with allergy to β-lactam antibiotics, patients suffering from other systemic infections, patients with developmental malformations, patients with congenital weak immunity, patients with serious diseases and those with poor prognosis. This study was approved by the Ethics Committee of the Maternal and Child Health Care Hospital of Zaozhuang, and the parents of the patients signed the informed consent forms.

Research methods. Patients in the control group were treated with antibiotics using step-up therapy method, while patients in the observation group were treated using step-down therapy.

Step-up therapy: (i) For mild cases, we first administered amoxicillin or second/third generation cephalosporins or azithromycin as initial treatment. If this treatment was not successful then azithromycin combined with cefoperazone/sulbactam was administered intravenously as the step-up therapy; ii) for severe cases, cefoperazone/sulbactam was used as initial treatment and if this treatment proved to be unsuccessful then azithromycin combined with cefoperazone sulbactam was administered intravenously as the step-up therapy.

Glucocorticoid was applied using the following protocol: 0.25-0.3 mg/kg/day dexamethasone, followed by 0.5-1 mg/kg/day prednisone (orally). This was reduced gradually (therapy lasted for 7 to 10 days). Step-down therapy: Intravenous azithromycin combined with cefoperazone/sulbactam were used in both mild and severe lobar pneumonia cases. Depending on patient's condition, glucocorticoid was applied using the same protocol mentioned before. According to the etiology results or remission of symptoms, narrow spectrum antibiotics were used as step-down therapy.

Observation index. The following indexes were evaluated and compared between the two groups after 72 h of treatment: White blood cell (WBC) reduction rate, course of antibiotic treatment, disappearance time of pulmonary rales, total efficiency, high-sensitivity C-reactive protein (hs-CRP) and calcitonin peptide procalcitonin (PCT) levels.

Enzyme-linked immunosorbent assay (ELISA) method was used to evaluate the hs-CRP and PCT levels. We used ELISA kits (Shanghai Shenggong Biotechnological Ltd., Shanghai, China) and strictly followed the protocol provided by the manufacturer. To judge the curative effects of the treatment, we referred to 'The use guidelines of antibiotics for acute respiratory infection (Trial)' as our reference. Treatment was considered effective if the following condition were present after 48 h: Drop in body temperature and obvious improvement in systemic symptoms as well as respiratory symptoms. We considered the treatment to be ineffective if after 72 h there was no obvious improvement on symptoms.

Statistical analysis. SPSS 20.0 software (IBM SPSS, Armonk, NY, USA) was used for statistical analysis. Data were expressed as mean ± standard deviation. Independent samples t-test was used between groups, paired t-test was used among groups. Count data were expressed as cases or (%). A χ^2 test (correction) was used between groups, P<0.05 was considered to indicate a statistically significant difference. All the tests were two-sided.

Results

WBC reduction rate, course of antibiotic treatment and disappearance time of pulmonary rales. There were no significant differences in term of WBC reduction rate, course of antibiotic treatment, disappearance time of pulmonary rales in children with mild lobar pneumonia after 72 h of treatment (P>0.05). After 72 h of treatment in children with severe lobar pneumonia, the rate of WBC reduction accelerated considerably and the course of antibiotic treatment as well as disappearance time of pulmonary rales shortened considerably. Differences were statistically significant (P<0.05) (Table II).

Total efficiency of treatment. Compared to the control group, there was no significant difference in the total efficiency of treatment in children with mild lobar pneumonia in the observation group (P>0.05). The total efficiency of treatment in children with severe lobar pneumonia was considerably higher than that in the control group, and the difference was statistically significant (P<0.05) (Table III).

The comparison of hs-CRP and PCT level in serum of two groups. There were no significant differences in hs-CRP and PCT levels in mild and severe children in the groups before treatment (P>0.05). After treatment, hs-CRP and PCT levels decreased more significantly in the observation group compared to the control group, the differences were statistically significant (P<0.05) (Table IV).

Table II. The comparison of WBC reduction, course of antibiotic treatment and disappearance time of pulmonary rales in two groups.

	Wild cases			Severe cases		
Groups	WBC decrease ($x10^9$/l)	Course of antibiotic treatment (days)	Disappearance time of pulmonary rales (days)	WBC decrease ($x10^9$/l)	Course of antibiotic treatment (days)	Disappearance time of pulmonary rales (days)
Control	2.7±0.9	7.4±1.3	5.2±2.5	3.1±1.2	14.2±4.1	7.3±2.5
Observation	2.6±0.4	7.2±1.1	4.9±2.4	4.2±1.5	11.1±3.7	6.0±2.2
t-test	0.493	0.575	0.424	4.632	4.963	5.203
P-value	0.636	0.463	0.529	0.037	0.035	0.032

WBC, white blood cells.

Table III. The comparison of total efficiency of treatment of two groups [cases (%)].

		Wild		Severe	
Groups	Cases	Effective	Invalid	Effective	Invalid
Control, n (%)	40	20/25 (80.0)	5/25 (20.0)	5/15 (33.3)	10 (66.7)
Observation, n (%)	40	19/23 (82.6)	4/23 (17.4)	12/17 (70.6)	5/17 (29.4)
χ^2		0.000		4.441	
P-value		1.000		0.035	

Table IV. The comparison of serum hs-CRP and PCT levels in two groups.

	Wild cases				Severe cases			
	hs-CRP (mg/l)		hs-CRP (mg/l)		hs-CRP (mg/l)		hs-CRP (mg/l)	
Groups	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control	10.5±4.1	7.5±1.6	7.2±2.3	5.3±1.5	16.8±3.6	10.3±3.8	12.3±3.0	8.2±2.6
Observation	11.2±4.6	5.2±1.5	7.5±2.4	3.5±1.0	17.2±3.8	6.9±2.6	12.6±3.2	6.2±2.5
t-test	0.235	6.230	0.264	6.201	0.426	6.965	0.352	6.835
P-value	0.754	0.027	0.724	0.028	0.629	0.020	0.729	0.022

hs-CRP, high-sensitivity C-reactive protein; PCT, procalcitonin.

Discussion

Lobar pneumonia in children generally has acute onset and severe symptoms, it can be diagnosed without laboratory examination and microbiological evidence. Clinicians mostly rely on personal experience and local epidemiological evidence to diagnose and treat lobar pneumonia (5). Several controversies exist about the initial course of treatment for children with lobar pneumonia. A prior study confirmed that (6) the outcome of infectious diseases depended on the interaction among antibiotics, patients' immunity and pathogenic microorganisms. Severe infantile lobar pneumonia has been shown to have acute onset and rapid progress. Due to weak immunity in children, pathogenic microorganisms can enter blood through lungs and cause septicemia and septic shock. A broad spectrum antibiotic therapy with powerful activity must be given to patients in early stage to strive for time for the upper sequential treatment (7). For severe infantile lobar pneumonia, step-down therapy has shown to be more effective than conventional and experimental antibiotic therapy (8). Results obtained from our study revealed that compared to the control group, children with severe lobar pneumonia in the observation group had higher rate of WBC reduction, shorter course of antibiotic treatment, shorter disappearance time of pulmonary rales, improved total treatment efficiency and lower levels of hs-CRP and PCT aftr 72 h of treatment. For severe cases of

lobar pneumonia, step-down therapy, compared to step-up therapy, could better relieve the inflammatory reaction, reduce the days of antibiotics use, reduce the disappearance time of pulmonary rales, and significantly improved the treatment efficiency. Our results showed that children with wild lobar pneumonia had no significant reduction in WBC count after 72 h of treatment. Also, no obvious changes in disappearance time of pulmonary rales and total efficiency of treatment were detected in those cases after 72 h of treatment. hs-CRP and PCT levels in the observation group was significantly lower than that in the control group. It has been shown that the effects of step-down therapy on controlling inflammatory reactions, days of antibacterial drug use, disappearance time of pulmonary rales and treatment effective rate were comparable to those observed in step-up therapy (9). It has been shown that lobar pneumonia caused by *Streptococcus pneumoniae* and *Mycoplasma pneumoniae* accounted for 30.0 to 60.0% of all lobar pneumonia cases, which was obviously higher than infections caused by other bacteria and viruses (10).

Other studies showed that clinical symptoms were atypical and chest X-ray examination showed atypical consolidation (10). Therapeutic effect of azithromycin combined with cefoperazone/sulbactam on the treatment of lobar pneumonia was as high as 80.0-90.0% that was higher than azithromycin combined with amoxicillin clavulanic acid and the third generation cephalosporin class (11). Prior studies showed that with the increase in drug-resistance among pathogenic bacteria, the application rate of broad-spectrum antibiotics such as imipenem has increased by about 40.0-65.0%. Also, the initial application time was shortened, and the period of application was extended (12). The drug resistance rate for the third generation cephalosporin and broad-spectrum penicillin could reach as high as 53.5-75.0%. The mixed infection rate increased by 30.0-50.0% in children suffering from lobar pneumonia combined with other bacterial infections.

Administration of cefoperazone/sulbactam combined with azithromycin for treating children with lobar pneumonia produced promising results and could be used as the first choice of treatment for lobar pneumonia. Cefoperazone/sulbactam, which has strong antibacterial properties, contains a β-lactamase inhibitor called sulbactam. Azithromycin has been shown to have significant therapeutic effects on infections caused by *Mycoplasma pneumoniae*, *Haemophilus influenzae* and *Streptococcus pneumoniae* (13-15).

In conclusion, the specific treatment plan for lobar pneumonia in children should combine different types of data including: local bacteriological data and epidemiological data on lobar pneumonia. We concluded that, most probably, the best way to treat severe cases of lobar pneumonia in children is step-down antibiotic therapy, while for mild lobar pneumonia infections, step-up antibiotic therapy may be the better choice.

There were few limitations associated with this study, for example the sample size used in the study was relatively small, and the economic benefits associated with each of the two schemes used in this study was not evaluated. Also, children's compliance level was not studied here. Certainly, more research in this field is warranted.

References

1. Noel G, Viudes G, Laporte R and Minodier P: Evaluation of the impact of pneumococcal conjugate vaccine on pediatric community-acquired pneumonia using an emergency database system. J Pediatric Infect Dis Soc 28: 12-13, 2016.
2. Cannavino CR, Nemeth A, Korczowski B, Bradley JS, O'Neal T, Jandourek A, Friedland HD and Kaplan SL: A randomized, prospective study of pediatric patients with community-acquired pneumonia treated with ceftaroline vs. ceftriaxone. Pediatr Infect Dis J: Apr 18, 2016 (Epub ahead of print).
3. Wendy LW, Dominic SD and Wim BW: Pneumococcal urinary antigen test: diagnostic yield and impact on antibiotic treatment. Clin Respir J 18: 17-18, 2016.
4. Subspecialty Group of Respiratory Diseases, The Society of Pediatrics, Chinese Medical Association; Editorial Board, Chinese Journal of Pediatrics: Guidelines for management of community acquired pneumonia in children (the revised edition of 2013) (I). Zhonghua Er Ke Za Zhi 51: 745-752, 2013 (In Chinese).
5. Kim L, McGee L, Tomczyk S and Beall B: Biological and epidemiological features of antibiotic-resistant *Streptococcus pneumoniae* in pre- and post-conjugate vaccine eras: a United States perspective. Clin Microbiol Rev 29: 525-552, 2016.
6. Gattarello S: What is new in antibiotic therapy in community-acquired pneumonia? an evidence-based approach focusing on combined therapy. Curr Infect Dis Rep 17: 501, 2015.
7. Janapatla RP, Hsu MH, Liao WT, Chien KY, Lee HY and Chiu CH: Low serum Fetuin-A as a biomarker to predict pneumococcal necrotizing pneumonia and hemolytic uremic syndrome in children. Medicine (Baltimore) 95: e3221, 2016.
8. Yayan J, Ghebremedhin B and Rasche K: No resistance to penicillin, cefuroxime, cefotaxime, or vancomycin in Pneumococcal pneumonia. Int J Med Sci 12: 980-986, 2015.
9. Yayan J: The comparative development of elevated resistance to macrolides in community-acquired pneumonia caused by *Streptococcus pneumoniae*. Drug Des Devel Ther 8: 1733-1743, 2014.
10. Saraya T: The history of *Mycoplasma pneumoniae* pneumonia. Front Microbiol 7: 364, 2016.
11. Agweyu A, Kibore M, Digolo L, Kosgei C, Maina V, Mugane S, Muma S, Wachira J, Waiyego M and Maleche-Obimbo E: Prevalence and correlates of treatment failure among Kenyan children hospitalised with severe community-acquired pneumonia: a prospective study of the clinical effectiveness of WHO pneumonia case management guidelines. Trop Med Int Health 19: 1310-1320, 2014.
12. Kalinogorskaya OS, Belanov SS, Volkova MO, Gostev VV and Sidorenko SV: Antibiotic resistance and serotype pattern of *Streptococcus pneumoniae* isolated from children in St. Petersburg in 2010-2013. Antibiot Khimioter 60: 10-18, 2015 (In Chinese).
13. Hu J, Sun X, Huang Z, Wagner AL, Carlson B, Yang J, Tang S, Li Y, Boulton ML and Yuan Z: *Streptococcus pneumoniae* and *Haemophilus influenzae* type b carriage in Chinese children aged 12-18 months in Shanghai, China: a cross-sectional study. BMC Infect Dis 16: 149, 2016.
14. Xia J, Zhang D, Xu Y, Gong M, Zhou Y and Fang X: A retrospective analysis of carbapenem-resistant Acinetobacter baumannii-mediated nosocomial pneumonia and the in vitro therapeutic benefit of cefoperazone/sulbactam. Int J Infect Dis 23: 90-93, 2014.
15. Kohno S, Tateda K, Kadota J, Fujita J, Niki Y, Watanabe A and Nagashima M: Contradiction between in vitro and clinical outcome: intravenous followed by oral azithromycin therapy demonstrated clinical efficacy in macrolide-resistant pneumococcal pneumonia. J Infect Chemother 20: 199-207, 2014.