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Original Article

Treatment of severe pediatric pneumonia by antibiotic de-escalation therapy

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Abstract: Objective: To improve the clinical efficacy of severe pediatric pneumonia, antibiotic de-escalation therapy was evaluated in this study. Methods: One hundred and forty children with severe pneumonia in intensive care unit (ICU) were recruited in this study. The patients were randomly divided into antibiotic de-escalation group and control group. In control group, standard antibiotic treatment was employed. Clinical efficacy, time of antibiotic use, fever and cough clearance, dyspnea improvement were recorded. Also, average length and expenditure in ICU, rate of trachea cannula, average length of mechanical ventilation after trachea cannula, adverse reaction, and case fatality rate were measured in this study. The variations of procalcitonin (PCT), D-dimer (D-D), and C-reactive protein (CRP) levels were determined before and after the treatment. Results: Antibiotic de-escalation group showed significantly higher overall effective rate than standard treatment group for severe pediatric pneumonia. The clinical related index and case fatality rate of antibiotic de-escalation group were also significantly better than that of control group. There was no significant difference for adverse reaction between two groups. Conclusion: Antibiotic de-escalation therapy showed significantly better clinical efficacy than standard treatment. Lower antibiotics usage and pain of children could be achieved in this therapy.

Keywords: Antibiotics, de-escalation therapy, intensive care unit, severe pediatric pneumonia

Introduction

As the highest incidence in respiratory diseases, pneumonia occurs in people of all ages [1, 2]. Based on the low immunity and poor health consciousness, children are more likely to suffer pneumonia after pathogen infection [3]. The clinical characteristics of pediatric pneumonia are fever, cough, sputum, dyspnea, and so on [4]. It is likely to develop severe pneumonia for the patient if we don't keep the disease under control in time [5]. With the development of the pneumonia, other symptoms (including respiratory failure, heart failure, and multiple organ failure) or even death may appear [6, 7].

Antibiotics play the most important role in pediatric pneumonia therapy [8]. The step-up antibiotics strategy was employed as the routine treatment in the past. In this treatment, narrow-spectrum antibiotic was used firstly. Then the antibiotics escalate into broad-spectrum during the medication. The infection exists persistently in this approach. Antibiotics abuse, wastage of medical resources, and occurrence of drug-resistant strains are also could be induced by this treatment. Moreover, because the lower efficacy, children will suffer the disease for a long time. It will affect not only physical but also mental health of patient [9].

In the previous study, antibiotic de-escalation therapy showed the good efficacy including the decreasing in mortality of children, and the improvement of the prognosis after the treatment [10]. However, based on the limited index of assessment, most studies were unable to comprehensively evaluate the antibiotic de-escalation therapy [11].

The aim of this study was to evaluate the efficacy of the antibiotic de-escalation therapy

Table 1. Participant information of two groups

Items	Control group (n=70)	Antibiotic de-escalation group (n=70)	t/χ^2	P
Age	2.6±0.8	2.8±0.7	1.574	0.118
Gender			0.261	0.609
Male	41	38		
Female	29	32		
Lesion locations in lung			0.293	0.864
Left	20	22		
Right	23	24		
Both sides	27	24		
Type of pneumonia			0.716	0.398
HAP	36	31		
CAP	34	39		
Average duration of disease (day)	3.5±0.7	3.3±0.9	-1.468	0.144

Note: HAP indicates hospital acquired pneumonia. CAP indicates community acquired pneumonia.

though detailed index. In this study, 140 children with severe pneumonia in ICU were recruited. All participants were randomly divided into antibiotic de-escalation group and the control group. In the control group, standard antibiotic treatment was employed.

Materials and methods

Patients

This study got approval from local ethical committee. One hundred and forty children with severe pneumonia were recruited from February 2015 to February 2017. The participants were divided into antibiotic de-escalation group and control group (70 cases in each group) by random number table approach. There was no significant difference in age, gender, course of disease and disease type between the two groups (**Table 1**). Moreover, antibiotics were not employed in patients before the study.

The inclusion criteria were consisted of (A) the guardian understanding and signing the informed consent, (B) meeting the diagnostic criteria for severe pneumonia from WHO [12]. The exclusion criteria consisted of (A) congenital diseases, (B) diseases of the blood system, liver function, kidney function and other multi-organ failure diseases, (C) not curing from underlying diseases, (D) incomplete medical records, (E) not possible to complete this study due to the lack of compliance.

Therapeutic schemes

Allergic history of antibiotics was enquired before the treatment. Blood routine examination, sputum culture, drug susceptibility test and lung CT were assessed before and during the treatment.

All participants received basic treatment: blood pressure, respiration, pulse, body temperature, and other vital signs of patients were monitored in ICU. Sputum and blood culture, drug susceptibility test were also performed. The treatment for oxygen inhalation, ventilation function improvement, acid-base balance correcting, electrolyte disorder, nutritional support symptom, and other complications (combination of respiratory function failure when given mechanical ventilation, merge sepsis shock given liquid recovery) were employed for patient under certain condition.

Treatment in antibiotic de-escalation group: according to the causes of disease of children for empiric treatment from the previous studies, 20 mg/kg meropenem (broad-spectrum carbapenems antibiotics, from Ouyi, China) was added to 100 ml normal saline for intravenous drip (every 8 h) to control the infection quickly [13, 14]. After the alleviation of disease, every 12 h of intravenous drip was performed. After pneumonia symptoms showing effective control, and requiring bacteriology and drug susceptibility test results, narrow-spectrum antibiotic was selected for continuous treatment (5-7 days). Two days' consolidation treatment was employed after the clearance of pneumonia symptoms.

Standard treatment in control group: Routine antibiotic treatment was performed. According to the reason of disease of children for empiric treatment from the previous studies, third generation of cephalosporin antibiotics (such as 20 mg/kg cefotaxime in 100 ml normal saline)

Table 2. Comparison overall effective rates between two groups

Group	Cleared	Good	Fair	Invalid	Overall effective rate	χ^2	*P*
Control group (n=70)	28	20	13	9	68.57%		
Antibiotic de-escalation group (n=70)	31	28	8	3	84.29%	4.798	0.029

Table 3. Comparison clinical index between two groups

Items	Control group (n=70)	Antibiotic de-escalation group (n=70)	t	P
Length of antibiotic use (d)	18.80±4.57	14.60±3.72	-5.963	0.000
Fever clearance time (d)	6.10±0.42	3.50±0.73	-25.829	0.000
Cough clearance time (d)	11.90±1.14	7.80±1.32	-19.668	0.000
Breathing difficulties improvement (d)	7.90±1.09	6.10±1.12	-9.636	0.000
Average length in hospital (d)	26.50±3.21	21.90±3.01	-8.746	0.000
Average cost in hospital (RMB)	15,121±2,123.46	8,946±2,792.13	-14.73	0.000

was used for intravenous drip (every 12 h) [13, 14]. The dosage of antibiotics was adjusted based on the variation of disease condition.

Outcome measures

The therapy efficacy was measured as follows. Routine blood and urine, liver and kidney function, blood culture, sputum culture and drug susceptibility test of participants were recorded before and after the treatment for the assessment of clinical efficacy. The efficacy was determined according to the following criteria [15]. Cleared: the symptoms, signs, laboratory tests and the etiology of the children were all restored to normal. Good: the patient was significantly improved, but one of the four items did not return to normal level. Fair: the patient was improved after treatment, and did not achieve good level. Invalid: no significant improvement or even progressive aggravation was appeared for the participant after 72 h. Overall effective rate = (cleared + good)/total number of cases * 100%.

Time of antibiotic usage, fever and cough clearance, dyspnea improvement were recorded. Also, average length and expenditure in ICU, rate of trachea cannula, average length of mechanical ventilation after trachea cannula, and adverse reaction were measured in this study. The changes of procalcitonin (PCT), D-dimer (D-D), and C-reactive protein (CRP) levels were determined before and after treatment. Case fatality rates were compared between the two groups.

Statistical analysis

SPSS 22.0 software was used for data analysis. The data was expressed by mean ± standard deviation (mean ± SD). The comparison between groups was conducted with independent sample t test. The counting data was tested by χ^2. $P<0.05$ indicated statistically significant difference.

Results

Comparison efficacy between different treatments for severe pediatric pneumonia

The overall effective rate of antibiotic de-escalation group (84.29%) was significantly higher ($\chi^2=4.798$, $P=0.029$) than that of control group (68.57%). The results were shown on **Table 2**).

Comparison clinical index between different treatments for severe pediatric pneumonia

The average length of antibiotic used, fever and cough clearance, dyspnea improvement and average length in ICU of the antibiotic de-escalation group were significantly shorter (all $P<0.05$) than that of control group. The expenditure in ICU of antibiotic de-escalation group (8,946±2,792.13 RMB) was also significantly less ($P<0.05$) than that of control group (15,121±2,123.46 RMB). See **Table 3**.

The rate of trachea cannula, average length of mechanical ventilation after trachea cannula, and adverse reaction of antibiotic de-escala-

Table 4. Comparison clinical index in ICU between two groups

Group	Endotracheal intubation rate (%)	Mechanical ventilation time after intubation (d)	Case fatality rate (%)
Control group (n=70)	25 (35.7%)	6.87±1.35	16 (22.86%)
Antibiotic de-escalation group (n=70)	14 (20.0%)	4.23±1.26	5 (7.14%)
χ^2	4.301	-11.961	6.779
P	0.038	0.000	0.009

Table 5. Comparison the PCT, D-D, and CRP levels between two groups

Items	Control group (n=70)	Antibiotic de-escalation group (n=70)	t	P
PCT (ng/ml)				
Before treatment	6.70±0.31	6.80±0.34	1.818	0.071
After treatment	2.76±0.52	0.82±0.09	-30.757	0.000
D-D (ug/ml)				
Before treatment	2.50±0.57	2.60±0.45	1.152	0.251
After treatment	1.60±0.36	0.70±0.28	-16.510	0.000
CRP (mg/ml)				
Before treatment	119.00±24.92	118.00±26.78	-0.229	0.819
After treatment	24.00±7.21	14.00±8.71	-7.399	0.000

Note: PCT: procalcitonin. D-D: D-dimer. CRP: C-reactive protein.

tion group (20.0%) were significantly shorter (all P<0.05) than that of control group (35.7%). The case fatality rate of antibiotic de-escalation group (7.14%) was significantly lower (P<0.05) than that of control group (22.86%). The results are shown on **Table 4**. The number of people who died during the study was treated as missing data in other analysis.

Comparison of variation of pct, d-d and crp levels in participants between different treatment groups

There was no significant difference (P=0.071, P=0.251, P=0.819, respectively) between two groups for the variation of PCT, D-D and CRP levels in patients before the treatment. However, after the treatment, the PCT, D-D and CRP levels in antibiotic de-escalation group were significantly lower (all P<0.05) than that in control group. The data was shown on **Table 5**.

Comparison rates of adverse reaction between different treatment groups

Two cases of slight nausea and vomiting were reported in the antibiotic de-escalation group. One case of skin rash and two cases of pruritus were also recorded. The adverse reactions were significantly recovered after drug discontinuation. The rate of adverse reactions incidence was 7.14%. There were 7 cases of slight nausea and vomiting in the control group. Two cases of skin rash, 1 cases of pruritus were also recorded. The rate of adverse reactions incidence was 14.29%. There was no significant difference in the incidence of adverse reactions between the two treatment groups (**Table 6**).

Discussion

Severe pediatric pneumonia is one of the leading causes of death in children [16]. According to the previous research, the improper use of antibiotics could increase the mortality during the treatment of severe pneumonia [17]. Thus, the clinical efficacy and prognosis can be improved through rational antibiotic treatment for severe pediatric pneumonia. In this study, 140 cases of severe pediatric pneumonia were selected and divided into antibiotic de-escalation group and standard antibiotic treatment group. The significantly higher overall effective rate (84.29%) of antibiotic de-escalation group indicated the better efficacy, which was conformed to the previous study [18].

The significantly shorter length of several clinical index (such as, fever and cough clearance, dyspnea improvement and average length in ICU in antibiotic de-escalation group, also indicated the higher inhibition the proliferation of pathogens in the early phase of disease. It also could decrease length in hospital, and the rate of super infection. For the significantly shorter length of antibiotic used and less expenditure in hospital in antibiotic de-escalation group,

Table 6. Comparison adverse reaction between two groups

Group	Nausea and vomiting (n, %)	Rash (n, %)	Pruritus (n, %)	Total (n, %)
Control group (n=70)	7 (10.00%)	2 (2.86%)	1 (1.43%)	10 (14.29%)
Antibiotic de-escalation group (n=70)	2 (2.86%)	1 (1.42%)	2 (2.86%)	5 (7.14%)
χ^2	0.150	0.341	0.341	0.255
P	0.698	0.560	0.559	0.614

indicated the decreasing use of antibiotics, and avoiding the overuse of antibiotics could be achieved through this treatment. Also, it could decrease the cost of treatment, which was conformed to another study [19].

In severe pneumonia, the accumulation of airway, alveolar and pulmonary inflammation can lead to serious ventilation and ventilation dysfunction [20]. In this study, the respiratory dysfunction appeared in participants in both two groups. Mechanical ventilation therapy was employed to cure the patients. The lower rate of endotracheal intubation and short length of mechanical ventilation in antibiotic de-escalation group was observed. The results demonstrated that the inflammation in lung was under control in a short time after the antibiotic de-escalation therapy.

The restored ventilation and ventilation function after alveolar dilatation induced the maintaining of normal oxygen saturation.

The antibiotic de-escalation therapy could control the development of disease at the early stage, then prevented multiple organ function failure (such as heart failure, toxic encephalopathy caused, shock and DIC) due to the severe pneumonia, and decreased the case fatality rate. These results indicated that the antibiotic de-escalation therapy could improve the prognosis of children, and increase survival rate, which was conformed to the previous study [21]. There were different results in the previous study from Viasus et al. for the case fatality rate of antibiotic de-escalation therapy, which showed no significant difference when compared with the routine treatment [22]. The reason of different results may be associated with the different type of patients in research. In the previous study, adult cases with better immunity and resistance to severe pneumonia and faster recover ability were assessed.

The results of PCT, D-D and CRP levels in different groups demonstrated that the effective improvement of hematology inflammation index using antibiotic de-escalation therapy, also indicated the efficacy and timeliness of this treatment.

Meropenem, which used in antibiotic de-escalation group, is an antibiotic of carbapenems. It inhibits the penicillin-binding proteins, then prevents cell wall stick peptide synthesis. Then the cell wall will break and result in the expansion of bacterial. The changes of cytoplasm osmotic pressure will also lead to the cytolysis and death of bacterial. This antibiotic has low toxicity, which hard to induce complications such as severe allergic reaction [23].

Compared the adverse reaction between antibiotic de-escalation group and standard treatment group, there was no significant difference, which indicated the similar safety between the two treatments. Meanwhile, the results in this study also demonstrated that, the antibiotic de-escalation therapy can increase the overall effective rate, and reduce the use of antibiotics, rate of complications and fatality.

Many clinical indexes were measured in this study, especially including the blood inflammation index, which provided the objective data for evaluation of antibiotic treatment. This study is limited to the cases and follow-up time, and the long-term prognosis is still incomprehensive. Thus, more research is needed in the future studies.

Disclosure of conflict of interest

None.

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