Comparison of the efficacy of ambroxol hydrochloride and *N*-acetylcysteine in the treatment of children with bronchopneumonia and their influence on prognosis

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Abstract. The aim of the present study was to compare the efficacy of ambroxol hydrochloride and *N*-acetylcysteine in the treatment of children with bronchial pneumonia and their influence on prognosis. A total of 120 children with bronchial pneumonia, admitted to The Affiliated Yantai Yuhuangding Hospital of Qingdao University from July 2015 to August 2018, were enrolled in the study. Among them, 58 children were treated with *N*-acetylcysteine and comprised the experimental group, and 62 children were treated with ambroxol hydrochloride and comprised the control group. Children's physical signs (such as fever, short breath, cough and pulmonary rales) and the adverse reactions to treatment were observed, and the disappearance time of the signs was recorded. In addition, the cellular immune function indicators and the quality of life after treatment were investigated. There was no significant difference in clinical data between the two groups (P>0.05). The effective rate in the experimental group was significantly higher than that in the control group (P<0.05). The disappearance time of symptoms, such as fever, cough, asthma and rales in the lung, was significantly shorter in the experimental group than that in the control group (P<0.05). The hospitalization time of patients in the experimental group was shorter than that in the control group (P<0.05). After treatment, immunoglobulin A (IgA), immunoglobulin G (IgG), immunoglobulin M (IgM) and complement C3 were significantly increased in the experimental group (P<0.01), and the IgA and IgG in the experimental group were significantly higher than those in the control group (P<0.01). The incidence of adverse reactions in the experimental group was significantly lower than that in the control group (P<0.05). In conclusion, *N*-acetylcysteine has a significant effect on the treatment of bronchopneumonia in children providing a quick relief from symptoms, such as lung rales, and therefore is worthy of use in clinic.

Introduction

Bronchopneumonia is a common infectious disease among infants, and has a very high incidence in children (1). *Mycoplasma pneumoniae*, together with bacteria and viruses, is the most important cause of bronchopneumonia and there are also infections caused by both bacteria and viruses (2). The main effect of bacterial pneumonia is pulmonary parenchymal damage, whereas the main effect of viral pneumonia is interstitial involvement (2). The obstruction of ventilation is caused by the thickening of the respiratory membrane and the obstruction of the lower respiratory tract caused by pulmonary inflammation. The main signs are respiratory, such as fine rales, fever, cough, asthma and lung pain (3).

Oral antibiotics constitute the basic clinical treatment for bronchopneumonia. However, antibiotics cause great damage to the nervous system, blood system and liver function (4). In the present study, aerosol inhalation was used for the treatment of bronchopneumonia in order to convert liquid medicine into water mist through ultrasonic electronic high-frequency vibration. This method is convenient for children for active respiratory inhalation and as the drug directly targets lesions, and is also effective for expectoration, cough relief, anti-inflammation and spasmolysis (5). Intravenous injection of ambroxol hydrochloride is a common treatment for bronchopneumonia in adults (6). However, children often have fear of oral and injectable drugs, which affects treatment compliance and coordination, and requires long-term hospitalization, increasing the risk of iatrogenic infections (7). Therefore, in recent years, aerosol inhalation has been included in the treatment of pediatric bronchopneumonia, effectively reducing side effects and ensuring children's safety (8).

In clinical practice, commonly used drugs for bronchopneumonia are ambroxol hydrochloride and *N*-acetylcysteine, which are antitussive drugs, although *N*-acetylcysteine is an amino acid with strong mucus dissolution. In the present study, the efficacy of ambroxol hydrochloride and *N*-acetylcysteine aerosol inhalation were compared in the treatment of children with bronchial pneumonia, as well as their effect on immune function and prognosis.

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Patients and methods

General data. A total of 120 children with bronchial pneumonia admitted to The Affiliated Yantai Yuhuangding Hospital of Qingdao University (Yantai, China) from July 2015 to August 2018 were enrolled in the present study. Among them, 58 children treated with *N*-acetylcysteine were selected as the experimental group, and 62 children treated with ambroxol hydrochloride were selected as the control group. There were 38 boys and 20 girls in the experimental group, 1-7 years of age, with median age of 4.6±1.57 years; 39 boys and 23 girls in the control group, 1-7 years of age, with median age of 4.5±1.57 years. There was no significant difference in the general characteristics of the selected children, indicating that the two groups were comparable (P>0.05; Table I).

Inclusion and exclusion criteria. Inclusion criteria: i) Children that did not resist the treatment. The children's immediate family members and/or guardians consented to their participation in the study by signing an informed consent form; ii) diagnosis was confirmed by chest X-ray and blood routine examination, referring to clinical diagnostic criteria for infants' bronchopneumonia (9), and iii) children with normal liver and kidney function and no history of allergy.

Exclusion criteria: i) Children with other diseases affecting survival, such as tumor and immune system diseases; ii) children that resisted the treatment, and iii) children with other serious medical conditions. The study was approved by the Ethics Committee of The Affiliated Yantai Yuhuangding Hospital of Qingdao University and all immediate family members and/or guardians of the children that participated in the study were informed and signed an informed consent form.

Methods. Patients in both the experimental and control group were treated with oxygen, anti-infection and fluid replenishment therapy [anti-infection therapy can improve clinical symptoms to a certain extent, thus, the two groups were treated with the same anti-infection therapy and were given penicillin 200,000-400,000 U/(kg×day) for 3 days]. The patients in the control group received ambroxol hydrochloride (Ambroxol™, specifications: 30 mg x20 tablets, batch no. 20130507; Shanghai Boehringer Ingelheim Pharmaceutical Co., Ltd.). One tablet of ambroxol was added into 3 ml of 0.9% sodium chloride, and the solution was inserted into the mask of atomizer which was connected to the oxygen device. After the oxygen flow rate was adjusted to 7 l/min, atomization inhalation was carried out: 2 ml/time, 2 times/day, with 1 week for a course of treatment, for a total of two courses. The patients in the experimental group were treated with *N*-acetylcysteine (Fulushi™, specifications: 600 mg x4 tablets, batch no. 20131016; Zambon Company S.p.A.). A total of 3 ml of *N*-acetylcysteine were added into ~3 mg of 10% sodium chloride, and the solution was inserted into a separate mask atomizer which was connected to an oxygen device. After the oxygen flow rate was adjusted to 7 l/min, atomization inhalation was performed: 3 ml/time, 2 times/day, 1 week for a course of treatment, for a total of two courses.

Observation indicators

Effective rate of treatments. To compare the effective rate of the clinical treatments, the following evaluation criteria of the

therapeutic effects were used: Significantly effective treatment, all clinical symptoms disappeared and clinical signs basically disappeared after treatment; Effective treatment, the clinical symptoms almost disappeared and the clinical signs significantly improved after treatment; Ineffective treatment, there was no difference between the indicators before and after treatment, and there was no improvement or aggravation of the clinical symptoms and signs after treatment. Total effective rate=[(no. of significantly effective cases + no. of effective cases)/no. of total cases] x100%.

Symptoms disappearance time. The disappearance time of symptoms, such as fever, cough, lung rale, asthma and lung X-ray shadow was recorded in the two groups, and the efficacy was evaluated according to the standard literature (4).

Detection of immune function. A total of 4 ml of fasting venous blood were collected from the patients of the two groups before and after treatment, and were divided into two samples of 2 ml each. The samples were placed into an anticoagulation tube, and after centrifugation at 3,000 x g for 15 min at 4°C, serum humoral and cellular immune functions were detected. The humoral immune function was detected by the immunorapid ejection turbidimetric method (10) and the related observation indicators immunoglobulin A (IgA), immunoglobulin G (IgG), immunoglobulin M (IgM), complement C3 and C4 were investigated. Flow cytometry was used for the detection of cellular immune function, and the related indicators CD3, CD4, CD8 and CD4/CD8 were detected and analyzed. The specific detection process was as follows: Anticoagulation treatment was first performed on the whole blood, and then 100 μl of whole blood were added into the tube. A total of 20 μl of CD4-FITC (1:500, cat. no. 561005), 10 μl of CD8-PE (1:500, cat. no. 560959) and 10 μl of CD3-PerCP (1:500, cat. no. 552851) monoclonal fluorescent antibodies (BD Biosciences) were added. The tube was placed in the dark for 15 min at room temperature, and 2 ml of hemolysin were added to dissolve the red blood cells. Each sample was mixed and left at room temperature for 10 min, and then centrifuged at 1,500 x g at 4°C for 10 min. The supernatant was discarded and PBS buffer containing 0.1% NaN$_3$ was added. After centrifugation at 1,500 x g at 4°C for 10 min, the supernatant was removed. Next, the cells were resuspended and FACSCalibur flow cytometer (BD Biosciences) was used for the detection. CellQuest software (BD Biosciences) was used for analysis.

Quality of life. For the comparison of the quality of life of the patients in the two groups after 3 months of treatment, the Short Form (SF)-36 health survey (11) was used for evaluation, with 100 points in each scale (the higher the score, the higher the quality of life).

Adverse reactions. The adverse reactions of the two groups were recorded and compared, including vomiting, abdominal pain, rash, diarrhea and nausea.

Statistical analysis. Experimental data were analyzed by SPSS v20.0 statistical software (Shanghai Yuchuang Network Technology Co., Ltd.). The enumeration data were compared by χ^2 test, whereas the measurement data were expressed as the mean ± standard deviation and t-test was used for their comparison

Table I. Patient general characteristics [n (%), mean ± SD].

Factors	Experimental group (n=58)	Control group (n=62)	t/χ^2	P-value
Sex			0.089	0.765
Male	38 (65.52)	39 (62.90)		
Female	20 (34.48)	23 (37.10)		
Age (years)	4.6±1.57	4.5±1.57	0.349	0.728
WBC (x10^9/l)	17.68±2.45	16.37±2.97	1.844	0.068
CRP (mg/l)	29.38±5.62	28.46±6.03	0.863	0.390
Pulmonary auscultation				
Pulmonary rales	46 (79.31)	43 (69.35)	1.550	0.213
Tubular sound	12 (20.69)	19 (30.65)		
Fever				
Yes	51 (87.93)	55 (88.71)	0.018	0.894
No	7 (12.07)	7 (11.29)		
Cough				
Yes	56 (96.55)	61 (98.39)	0.417	0.520
No	2 (3.45)	1 (1.61)		
Asthma				
Yes	47 (81.03)	50 (80.65)	0.0001	0.976
No	11 (18.97)	12 (19.35)		
Hospitalization time (months)	1.96±2.34	2.16±0.05	0.498	0.619

WBC, white blood cell; CRP, C-reactive protein.

Table II. Comparison of treatment efficacy between the two groups [n (%)].

Group	No. of cases	Significantly effective	Effective	Ineffective	Total efficacy
Experimental group	58	35 (60.34)	20 (34.48)	3 (5.17)	55 (94.83)
Control group	62	30 (48.39)	21 (33.87)	11 (17.74)	51 (82.26)
χ^2		1.726	0.005	4.594	4.594
P-value		0.189	0.944	0.032	<0.05

between two groups. Paired t-test was used for the comparison of data at different time points. ANOVA and Least Significant Difference post hoc test were used for the comparison of data between multiple groups. The figures were generated using the GraphPad Prism 6 software (Emerald Biotech Co, Ltd.). P<0.05 was considered to indicate a statistically significant difference.

Results

Treatment efficacy. The total effective rate in the experimental group was 94.83%, which was higher than that in the control group (82.26%). The difference was statistically significant (P<0.05; Table II).

Changes in the immune function of children in the two groups. There was no significant difference in the humoral or cellular immune function indexes between the two groups before treatment (P>0.05). After treatment, IgA, IgG and complement C3 were significantly higher in both groups, compared with those before treatment (P<0.01). The experimental group had significantly higher IgM level after treatment compared with that before treatment; however, there was no significant difference between the IgM levels before and after treatment in the control group (P>0.05). In addition, there was no significant difference in complement C4 before and after treatment in the experimental group (P>0.05), whereas the complement C4 in the control group was significantly lower after treatment than that before treatment. However, there was no significant difference in C3 levels between the two groups after treatment (P>0.05; Fig. 1).

Moreover, there was no significant difference in CD3, CD4, CD8 and CD4/CD8 between the two groups before treatment. After treatment, CD3, CD4, and CD4/CD8 were significantly increased in both groups, compared with those before treatment; however the CD8 levels were significantly decreased in both groups (P<0.05). The levels of CD3, CD4, CD4/CD8 after treatment were significantly higher in the experimental group compared with those in the control group (P<0.05), whereas CD8 was significantly lower in the experimental group than that in the control group (P<0.05; Fig. 2).
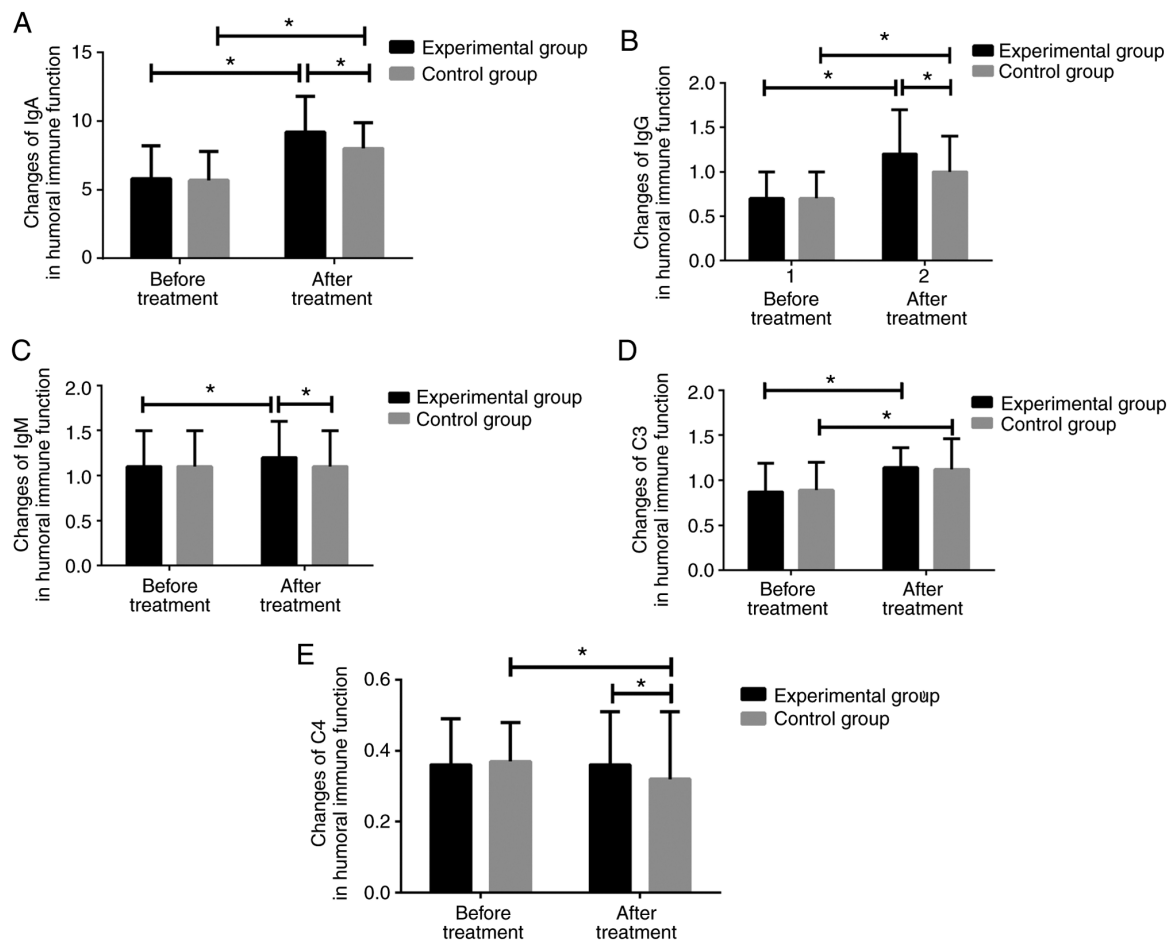
Figure 1. Changes of IgA, IgG, IgM, C3 and C4 in humoral immune function of children with bronchial pneumonia. The changes in the levels of (A) IgA, (B) IgG, (C) IgM, (D) C3 and (E) C4 in the humoral immune function of the children with bronchial pneumonia in the experimental and control groups are presented before and after treatment. *P<0.01. IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M.

Comparison of symptom disappearance time between the two groups. The disappearance time of symptoms such as fever, cough, asthma, shadow of the lung X-ray, time of a cough disappearing and lung rales in the experimental group were significantly shorter than those in the control group (P<0.001 or <0.05; Table III).

Comparison of adverse reactions between the two groups of patients. After statistical analysis, the total number of patients with adverse reactions in the experimental group of patients, treated with *N*-acetylcysteine, was significantly lower than that of the control group of patients, treated with bromate hydrochloride (P<0.05; Table IV).

Comparison of quality of life between the two groups after 3 months of treatment. The quality of life of patients in the experimental and control group after 3 months of treatment was investigated, including physiological functioning, somatic pain and general health status. The scores of physiological functioning, somatic pain, general health status and vitality of the experimental group were significantly higher than those of the control group (P<0.001). However, there was no significant difference in social role functioning, emotional role functioning and mental health between the two groups (P>0.05; Table V).

Discussion

In recent years, with the opening of policies, as the birth rate has increased, the incidence of bronchopneumonia in children, which is mainly related to the immature lung development and immune system (low defense ability of the body), is higher than the incidence of neonatal diarrhea. When the cough frequency caused by pneumonia is too high, patients experience pain in the bilateral costal cartilage, accompanied by the occurrence of choking and other conditions. In infants, the bronchial tissue support and rebound elasticity are relatively weak, and the ciliary movement ability is not strong, thus, the secretions in the respiratory tract cannot be discharged in time. Another important reason for obstructing the airway is that the airway smooth muscle is weak, and cough response is insufficient, further reducing secretion excretion (12). As a result, the course of disease in some children is prolonged, and even secondary complications, such as respiratory failure, heart failure or toxic intestinal paralysis pose serious threats to life. At present, the clinical treatment of bronchopneumonia in infants mainly relies on anti-infection therapies and elimination of inflammation and the curative effect is still good, although the course of treatment required for the improvement of symptoms is long. Therefore, the focus of clinical research is to effectively
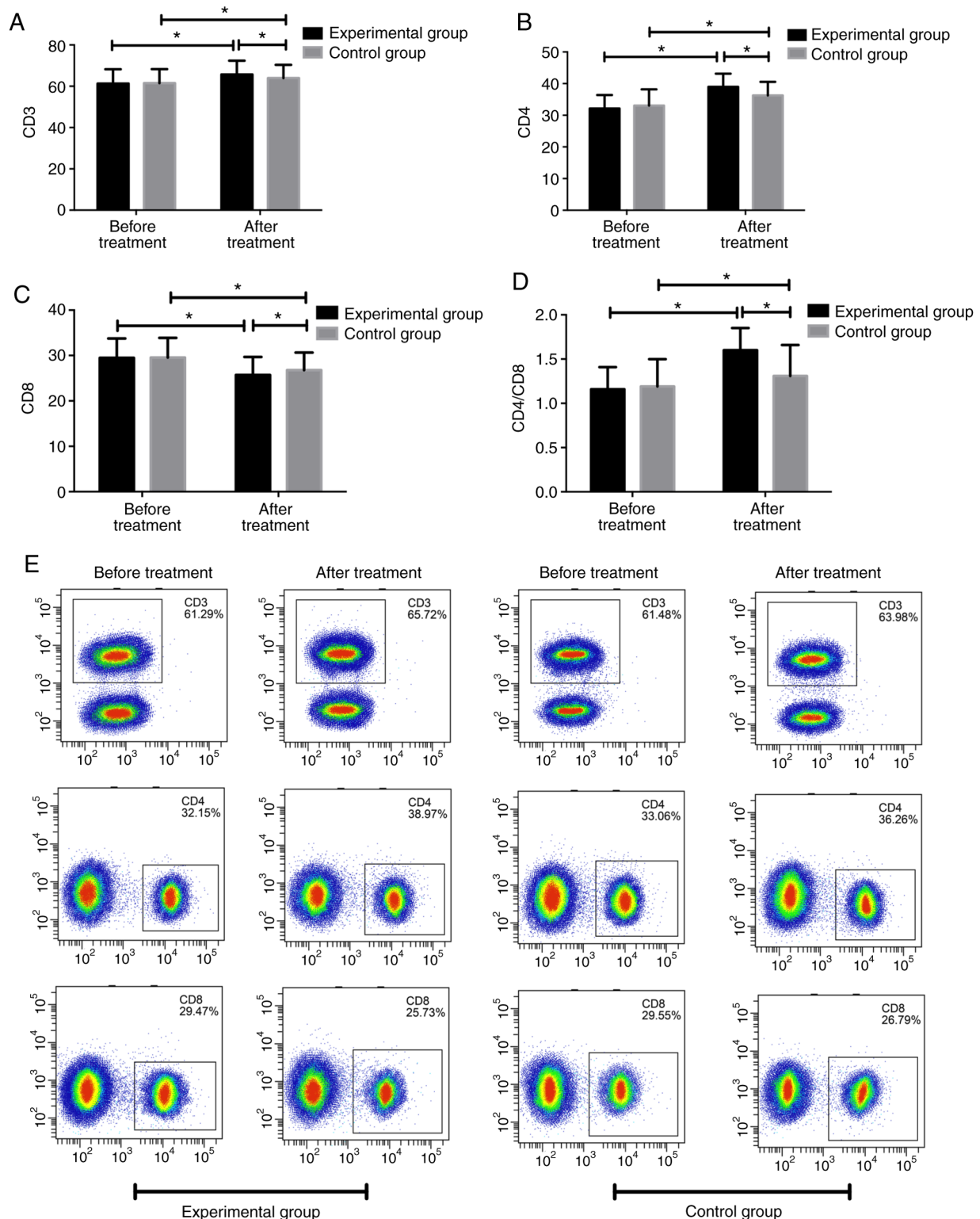
Figure 2. Cellular immune function changes of CD3, CD4, CD8 and CD4/CD8 in two groups of children with bronchial pneumonia. The cellular immune function changes of (A) CD3, (B) CD4, (C) CD8 and (D) CD4/CD8 in the experimental and control groups of children with bronchial pneumonia are presented before and after treatment. (E) The plots of the flow cytometry are shown. *$P<0.05$.

shorten the duration of symptoms and improve the overall curative effect of treatment (13).

The main purpose of the present study was to compare the clinical efficacy and effect on prognosis of ambroxol hydrochloride and *N*-acetylcysteine treatments in children with bronchopneumonia. The results showed that the clinical symptom relief time in children who received *N*-acetylcysteine aerosol inhalation treatment was significantly shorter than that of the control group, and the total clinical effective rate was 94.83%, which was higher than that of the control group (82.26%) ($P<0.05$). This result is consistent with the study of Trastotenojo *et al* (14), who demonstrated

Table III. Comparison of symptoms disappearance time between the two groups (mean ± SD, days).

Group	No. of cases	Fever	Cough	Asthma	Lung X-ray shadow	Lung rales	Time of a cough disappearing
Experimental group	58	2.1±0.5	4.2±0.3	3.7±0.6	5.7±0.4	4.12±1.23	4.31±1.46
Control group	62	2.6±0.4	5.5±0.3	5.2±0.5	6.1±0.5	6.87±1.69	6.84±1.42
t		6.068	17.12	14.91	4.818	10.13	9.621
P-value		<0.001	<0.001	<0.001	<0.001	<0.05	<0.05

Table IV. Comparison of adverse reactions after treatment between the two groups [n (%)].

Group	No. of cases	Vomit	Abdominal pain	Erythema	Diarrhea	Nausea	Total
Experimental group	58	1 (1.72)	1 (1.71)	0 (0.00)	0 (0.00)	0 (0.00)	2 (3.45)
Control group	62	2 (3.23)	2 (3.23)	1 (1.61)	1 (1.61)	2 (3.23)	8 (12.90)
χ^2		0.277	0.277	0.943	0.943	1.903	4.409
P-value		0.599	0.599	0.331	0.331	0.168	0.037

Table V. Comparison of quality of life between the two groups after 3 months of treatment (mean ± SD).

Factors	Experimental group (n=58)	Control group (n=62)	t	P-value
Physiological functioning	81.36±10.96	69.29±11.25	5.947	<0.001
Somatic pain	88.05±10.49	69.23±12.54	8.885	<0.001
General health status	83.66±9.81	71.07±12.14	6.223	<0.001
Vitality	83.14±10.26	73.79±13.79	4.191	<0.001
Social role functioning	63.21±10.67	63.54±11.37	0.164	0.8703
Emotional role functioning	72.63±12.09	69.98±12.04	0.232	1.202
Mental health	83.62±10.48	81.18±10.46	1.276	0.2045

the distinct advantages of nebulized inhalation therapy with *N*-acetylcysteine. *N*-acetylcysteine is a derivative of acetyl group of cysteine and has a free radical scavenging effect. Because of its strong mucilage dissolving effect, *N*-acetylcysteine is a solution with good solubility which can be used as an expectorant in clinic (15). In-depth research has also revealed that: i) *N*-acetylcysteine is an antioxidant, which can effectively reduce reactive oxygen species and inhibit the activity of nuclear factor in disease-causing cells *in vivo* (16); and ii) the fiber in the concentrated sputum is cut off by the sulfhydryl group contained in the *N*-acetylcysteine molecule, so that the sputum is easily liquefied and removed from the body (15). The experimental results showed that all immune factors were significantly improved after treatment except for C3 and CD8. Hermeyer *et al* (17) pointed out that the key link in the occurrence and development of bronchial pneumonia was inflammatory reaction. With the aggregation of granulocytes into the inflammatory area and the release of a large number of free radicals, lipid peroxidation of the cell membrane occurs, leading to cell autolysis and tissue necrosis. *N*-acetylcysteine has good cell membrane penetration after entering the cell, and therefore plays an antioxidant role and doesn't cause aggravation or tissue cell damage. In

clinical practice, ambroxol hydrochloride atomization inhalation has a good clinical effect in the adjuvant treatment of pediatric bronchopneumonia, indicating that atomization inhalation has a good effect in drug delivery. In the present study, the results showed that, compared with hydrochloric acid, *N*-acetylcysteine atomization inhalation effects are more significant. In order to further explore the curative effect of *N*-acetylcysteine atomization inhalation therapy the cell and humoral immunity function in the two groups of children were investigated. The results showed that the immune function of the two groups of children was obviously affected after treatment, with the immune function showing a certain degree of recovery, which was more apparent in the patients of the experimental group (18). The reason for the failure of the bronchopneumonia treatment is that the main antibody against infection is significantly reduced during the anti-inflammatory reaction and the incomplete development of the immune function in children makes it impossible to be replenished in time. In the present study the SF-36 scoring system was also used to measure the quality of life of the two groups of patients after treatment, including the assessment of physiological functioning, somatic pain, general health status, vitality, social functioning, emotional functioning and mental health. The

results revealed that the patients treated with *N*-acetylcysteine had significantly higher scores than the patients treated with ambroxol hydrochloride. *N*-acetylcysteine dissolves sputum, reduces sputum adhesion force, increases the cilia movement and inhibits the growth of pathogenic bacteria, reducing the local inflammation reaction, thus, impairing the immunity system, so that the body's humoral immunity gradually returns to normal. In the present study, the number of patients selected was small, and the experimental results are therefore limited. The reliability of the presented data needs to be further verified by future studies with a greater sample size.

In summary, the present study showed that the total effective rate, cellular immune function, humoral immune function and the quality of life in the two groups of children were significantly improved after the different treatments except for C4. Inhalation of *N*-acetylcysteine can effectively improve the clinical symptoms and signs, as well as the immune function of children with bronchial pneumonia, and the curative effect is remarkable, suggesting that *N*-acetylcysteine treatment is worthy of use in clinic.

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Availability of data and materials

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

Authors' contributions

HL wrote the manuscript, analyzed and interpreted the patient data. WW designed the study and performed the flow cytometry and immunoturbidimetric assay. XG was responsible for the analysis and interpretation of the data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of The Affiliated Yantai Yuhuangding Hospital of Qingdao University (Yantai, China). Patients who participated in this research had complete clinical data. Signed written informed consents were obtained from all children's immediate family members and/or guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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