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Combination therapy in pediatric bronchitis: Examining mucolytic, bronchodilator and anti-inflammatory drug effects on secretion management and recovery time

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Abstracts: This study investigated the effectiveness of combining mucolytic agents (ambroxol hydrochloride), bronchodilators (terbutaline sulfate), and anti-inflammatory drugs (budesonide) in treating pediatric bronchitis. From September 2023 to February 2024, 410 pediatric patients were divided into two groups: A control group treated with bronchodilators and anti-inflammatory drugs, and a study group receiving the combined therapy. The results indicated that the study group exhibited significantly better clinical efficacy, with faster resolution of symptoms such as dyspnea, cough, and fever compared to the control group (P<0.05). Pulmonary function indicators, including tidal volume and respiratory ratios, also showed greater improvement in the study group (P<0.05). Additionally, serum levels of inflammatory markers (WBC, CRP, TNF-α, IL-6) were lower in the study group after treatment (P<0.05). Sleep quality improved more in the study group, with longer sleep duration and fewer awakenings (P<0.05). Airway secretion clearance function was also better in the study group, with lower sputum volume and viscosity (P<0.05). No significant difference in adverse reactions was observed between the groups (P>0.05). The findings suggest that the combined therapy of mucolytic agents, bronchodilators and anti-inflammatory drugs is highly effective in treating pediatric bronchitis, offering significant benefits in symptom improvement, pulmonary function enhancement, inflammatory reduction, sleep improvement, and airway clearance.

Keywords: Combination therapy, pediatric bronchitis, mucolytic agents, bronchodilators, anti-inflammatory drugs, secretion management, recovery time

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INTRODUCTION

Bronchitis is a clinical pediatric disease that often occurs due to viral and bacterial infections of the upper respiratory tract and is one of the common illnesses during infancy and early childhood (Patel *et al.*, 2021). In the infant and toddler stage, the immune system is not yet fully developed, making the ability to resist external pathogens relatively weak. Moreover, the respiratory tract of infants and toddlers is relatively narrow and the mucosa is thin, making them susceptible to infections that can lead to pediatric bronchitis (Li *et al.*, 2020). The primary site of lesion in pediatric bronchitis is the capillary bronchi in the lungs. It can arise as a complication of viral infections like the common cold or influenza, or be induced by bacterial infections. It is a prevalent acute lower respiratory tract infection, with capillary bronchitis and acute bronchitis being the most common types (Armstrong, 2021).

Pediatric capillary bronchitis is commonly seen in infants under 2 years old, especially in babies under 6 months old, with a typical course of 5-10 days. The main clinical manifestations include tachypnea, inspiratory retraction of the chest wall and expiratory wheezing (Lee *et al.*, 2023). Studies suggest that its pathogenesis may be closely related to environmental factors, genetic factors, immune function and viral infections, representing a clinical syndrome involving both infection and allergic reactions (Smith *et al.*, 2024). Capillary bronchitis is usually caused by viruses, with respiratory syncytial virus (RSV) being the most common pathogen (Hon *et al.*, 2023). Due to impaired ventilation and gas exchange function in pediatric capillary bronchitis, it can easily lead to cerebral hypoxia and carbon dioxide accumulation in affected children. Severe cases may further progress to heart failure and in extreme cases, respiratory failure (Jartti *et al.*, 2019). In addition, the disease is closely associated with recurrent wheezing symptoms in children in the future (Be'er *et al.*, 2022). Pediatric acute bronchitis is an acute inflammation of the bronchial mucosa, often secondary to upper respiratory tract infections. Initial symptoms include fever, paroxysmal dry cough, followed by an increase in sputum, which transitions from mucoid to purulent (Wopker *et al.*, 2020). Some children may experience vomiting and diarrhea and in severe cases, hypoxia and cyanosis may occur, leading to cerebral hypoxia and posing a serious threat to the child's life safety (Wopker *et al.*, 2021). Pediatric bronchitis has a high incidence and mortality rate, being the leading cause of infant mortality and also consumes a significant amount of healthcare resources, imposing a heavy economic burden on both society and families (Ferrante *et al.*, 2024). Therefore, implementing

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timely and effective clinical treatment measures is crucial for preventing recurrent episodes of pediatric bronchitis symptoms and the occurrence of its complications.

The commonly used medications for the treatment of pediatric bronchitis in clinical practice currently include bronchodilators, anti-inflammatory drugs and mucolytic agents. Sulfate terbutaline serves as an efficacious bronchodilator, primarily administered to manage bronchial spasms resulting from pulmonary disorders like bronchial asthma, chronic bronchitis and emphysema. It functions by selectively activating β2 receptors within the respiratory tract, leading to the relaxation of bronchial smooth muscles, ultimately achieving bronchodilation and mitigating airway spasms (Elkomy *et al.*, 2022). Terbutaline sulfate activates adenylate cyclase, increasing intracellular cAMP, which in turn reduces intracellular calcium ion concentration, leading to relaxation of bronchial smooth muscles (Sultan *et al.*, 2023). Budesonide is a glucocorticoid medication with significant anti-inflammatory effects, commonly used in the treatment of pediatric bronchitis (Daley-Yates *et al.*, 2023). Budesonide exerts its anti-inflammatory and immunosuppressive effects by inhibiting the production of inflammatory mediators, constricting blood vessels, suppressing cytokine expression and enhancing β2 receptor expression (Panettieri *et al.*, 2024). Studies have shown that budesonide has a significant anti-inflammatory effect, even when administered in microdoses through inhalation and is less likely to cause systemic adverse reactions (Huang *et al.*, 2021). Additionally, terbutaline sulfate is endorsed by the WHO as the preferred inhaled glucocorticoid for asthma treatment on the Model List of Essential Medicines for Children (intended for children aged 12 and younger). It has also been approved by the US FDA for use in children younger than 4 years, posing a relatively low risk (Krings *et al.*, 2023). Budesonide has also shown good efficacy in combination therapy regimens. Numerous clinical studies have demonstrated significant clinical effects of budesonide combined with terbutaline sulfate in the treatment of pediatric bronchitis, asthmatic bronchitis and other conditions (Chen *et al.*, 2020; Hardy *et al.*, 2019). Ambroxol hydrochloride, a commonly used mucolytic agent in clinical practice, can cleave the polysaccharide fibers of acidic glycoproteins in sputum, inhibit the synthesis of acidic glycoproteins in mucous glands and goblet cells, reduce the sialic acid content in sputum and decrease sputum viscosity. At the same time, it can stimulate the mucus cells of alveolar and bronchial mucosa glands to secrete smaller molecules with lower viscosity, namely mucins, thereby diluting the sputum and making it easier to expectorate (Cheng *et al.*, 2024). Theoretically, the combination therapy of terbutaline sulfate, budesonide and ambroxol hydrochloride has potential positive effects in improving the clinical efficacy of pediatric bronchopneumonia and promoting symptom improvement. However, the current research conclusions regarding the combined use of these three drugs in pediatric bronchitis are not definitive and their specific effectiveness still requires further research and validation.

Nebulization inhalation utilizes the principle of gas jet, combined with ultrasonic electronic high-frequency vibration, to convert liquid medications into an aerosol state, effectively moisturizing the respiratory tract, enhancing drug adsorption and improving therapeutic efficacy (Canto Mangana *et al.*, 2024). Currently, nebulization inhalation therapy is a commonly used and effective method for the treatment of pediatric bronchitis. The advantage of this treatment method lies in its administration via the respiratory tract, allowing it to directly act on the lungs and other target organs, achieving high local drug concentrations, rapid onset of action, low clinical dosage and effective assurance of both drug efficacy and treatment safety (Sorino *et al.*, 2020). Nebulization inhalation therapy has become one of the routine treatment methods for respiratory diseases, with high prevalence among both outpatient and inpatient populations, effectively reducing the economic burden on patients. Nebulization inhalation is convenient for children to inhale actively, reducing their fear of oral and injectable medications (O'Riordan, 2024). Therefore, in recent years, nebulization inhalation has been incorporated into the treatment regimen for pediatric bronchitis, effectively reducing side effects and ensuring the safety of children. Among the medications used in nebulization inhalation therapy, ambroxol hydrochloride, terbutaline sulfate and budesonide are commonly used. Based on clinical case practice, monotherapy has shown limited effectiveness, while combination therapy may yield better improvement. The aim of this study is to evaluate the efficacy of nebulization inhalation therapy in pediatric bronchitis patients and assess the clinical impact of a combination regimen comprising ambroxol hydrochloride, sulfate terbutaline and budesonide in treating 410 pediatric bronchitis cases admitted to our hospital between September 2023 and February 2024, with the goal of gathering further treatment insights.

MATERIALS AND METHODS

Design

This research is a randomized controlled clinical trial featuring two parallel groups and rigorously conforms to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Prior to participation, parents or legal guardians of all involved children provided informed consent, safeguarding the study's legality and ethical integrity. Additionally, the study has obtained formal approval from the hospital's ethics committee, with all research protocols adhering strictly to the ethical principles stipulated in the Declaration of Helsinki. The institutional ethics committee ensured that all participants had read and fully understood the relevant content before approving the study protocol and consent form. Throughout the study, all

collected data remained anonymous and were securely stored in a database, with strict confidentiality measures in place for patients' personal information.

Subjects

Between September 2023 and February 2024, 410 children with pediatric bronchitis were recruited as study subjects. The following inclusion criteria were applied: diagnosis of pediatric bronchitis confirmed by laboratory and imaging examinations, in accordance with the diagnostic criteria for pediatric bronchopneumonia revised by the World Health Organization; all patients were hospitalized for treatment; patients were aged between 0 and 6 years; relatively high treatment compliance and cooperation; patients had typical clinical symptoms such as cough, wheezing and shortness of breath; and received nebulization inhalation as adjunctive therapy. Exclusion criteria included: allergy or contraindication to the therapeutic drugs used in this study; use of bronchitis-related treatment drugs within 1 month prior to enrollment in this study; presence of severe congenital diseases; presence of other respiratory diseases; presence of mental disorders, making communication impossible; and patients who were physically weak and critically ill.

Intervention

After admission, both groups of children received conventional treatments such as oxygen inhalation, sputum suction and cardiac tonics. Based on this, the treatment protocols for the two groups were as follows: the control group received a regimen of sulfate terbutaline and budesonide, whereas the study group underwent a treatment plan incorporating ambroxol hydrochloride, sulfate terbutaline and budesonide. Budesonide Suspension for Inhalation (specification: 2 ml: 0.5 mg, National Medical Product Approval Number: HJ20140474, AstraZeneca Pty Ltd) was administered twice daily, morning and evening, at a dose of 0.25 mg each time. Terbutaline Sulphate Solution for Nebulization (specification: 2 ml: 5 mg, Imported Drug Registration Number: H20140108, AstraZeneca AB) was administered twice daily, morning and evening, at a dose of 2.5 mg each time. Ambroxol Hydrochloride Solution for Inhalation (specification: 2 ml: 15 mg, National Medical Product Approval Number: H20223050, Yingu Pharmaceutical Co., Ltd.) was administered twice daily, morning and evening, at a dose of 7.5 mg for children aged 0 to 2 years and 15 mg for children aged 2 to 6 years. Both groups used the PARI JuniorBOY nebulizer for nebulization and inhalation, with continuous treatment for 2 weeks.

Outcome measurements

Main results

Both groups were monitored for the timing of clinical symptom relief, specifically the duration for breathlessness to improve, cough to cease, pulmonary moist rales to disappear and fever to subside. The MSA-70 fully automatic pulmonary function tester was used to measure various pulmonary function indicators, including tidal volume, time to peak ratio, peak volume ratio and respiratory ratio. An automated biochemical analyzer was employed to assess serum inflammatory markers in both groups, such as WBC, CRP, TNF-α and IL-6 levels. The comparison between the two groups involved their sleep quality, specifically sleep duration and number of awakenings. Additionally, the treatment outcomes were evaluated, categorizing them as marked effectiveness, effectiveness and ineffectiveness. (1) Marked effectiveness: After treatment, all clinical symptoms such as cough and shortness of breath disappeared completely and both pulmonary rales and rhonchi disappeared entirely, with imaging examinations showing no shadows in the lungs; (2) Effectiveness: After treatment, symptoms of shortness of breath and cough were alleviated to some extent and some pulmonary rhonchi and rales disappeared, with imaging examinations showing a reduction in pulmonary shadows; (3) Ineffectiveness: After treatment, there was no change in any clinical symptoms and signs, or even deterioration.

Secondary outcomes

The airway secretion clearance function was compared. All participants had a 3 mL blood sample collected from the elbow vein in the morning after an overnight fast, at 8:00 AM the next day. The samples were then processed in a centrifuge to separate the serum. Twenty millicuries (mCi) of technetium-99m-diethylenetriaminepentaacetic acid (99mTC-DTPA) were dissolved in the separated 3 mL of 0.9% serum and nebulized at a rate of 7 L/min. Gamma-ray imaging equipment was used to assess the distribution and clearance efficiency of 99mTC-DTPA in the early stages of inhalation. By observing the radioactive distribution in the lungs, the patency of the airways could be determined. The results of the lung ventilation imaging were analyzed by two experienced nuclear medicine physicians using a double-blind method. The evaluation criteria were: normal (0): uniform radioactive distribution in both lungs; mild abnormality (+): slight radioactive deposition in the large airways and/or uneven radioactive distribution in the lung fields, but less than 25% of the area of both lung fields; moderate abnormality (++): excessive radioactive deposition in the large airways and/or uneven radioactive distribution in the lung fields, covering 25% to 50% of the area; severe abnormality (+++): significant radioactive deposition in both the large and small airways and/or reduced or deficient radioactive distribution in more than 50% of the lung fields. During the treatment period, the total 24-hour sputum volume was collected from the children, weighed using a scale, blotted dry with filter paper and then re-weighed to calculate the dry/wet weight ratio. The sputum viscosity was measured using a cone-plate viscometer at a high shear rate of 100/s, with the average of three consecutive measurements taken as the final value. Adverse reactions in the children were monitored during the treatment process in both groups, including nausea, vomiting, diarrhea, dizziness, palpitations, xerostomia, allergic rash, etc.

Table 1: Comparison of baseline demographic and clinical characteristics

Characteristics	Control group (n=195)	Study group (n=215)	$\chi^2/t/Z$	*P*
Gender (n, %)				
male	96 (49.23)	93 (43.26)	1.469	0.225
female	99 (50.78)	122 (56.74)		
Age [M (Q1,Q3), years]	4 (3, 5)	4 (3, 6)	-1.417	0.157
Duration [M (Q1,Q3), days]	5 (4, 6)	6 (4, 7)	-1.463	0.144
Post-hospitalization temperature ($\overline{x}\pm s$, °C)	37.99±1.39	38.05±1.26	-0.470	0.639
Post-admission BSS score ($\overline{x}\pm s$, points)	15.39±3.69	15.40±4.14	-0.013	0.989

Table 2: Comparison of time to disappearance of clinical symptoms [M (Q1,Q3), days]

Characteristics	Control group (n=195)	Study group (n=215)	*Z*	*P*
Breathing improvement time	5 (4, 6)	4 (4, 5)	-9.480	0.000
Cough disappearance time	5 (5, 6)	4 (3, 4)	-12.143	0.000
Disappearing time of lung moist rales	7 (6, 7)	5 (4, 6)	-7.995	0.000
Fever disappearance time	3 (2, 3)	2 (2, 2)	-11.085	0.000

Table 3: Comparison of lung function indexes ($\overline{x}\pm s$)

Characteristics	point of time	Control group (n=195)	Study group (n=215)	*t*	*P*
Tidal volume (mL/kg)	pre-treatment	5.77±1.32	5.84±1.14	-0.637	0.524
	post-treatment	6.63±1.36	7.20±1.39	-4.221	0.000
Peak time ratio (%)	pre-treatment	17.27±3.35	17.22±3.17	0.171	0.864
	post-treatment	23.18±3.25	29.37±3.06	-19.853	0.000
Peak volume ratio (%)	pre-treatment	19.54±4.20	19.58±4.14	-0.115	0.908
	post-treatment	24.84±4.60	29.82±4.84	-10.645	0.000
Respiratory ratio (%)	pre-treatment	0.61±0.06	0.60±0.06	0.426	0.670
	post-treatment	0.76±0.08	0.83±0.07	-9.191	0.000

Table 4: Comparison of serum inflammatory indices ($\overline{x}\pm s$)

Characteristics	point of time	Control group (n=195)	Study group (n=215)	*t*	*P*
WBC ($\times 10^9$L)	pre-treatment	10.09±2.16	10.19±2.32	-0.483	0.630
	post-treatment	6.93±1.70	4.41±1.11	17.894	0.000
CRP (mg/L)	pre-treatment	21.93±3.98	21.52±4.36	0.977	0.329
	post-treatment	5.27±1.16	3.02±0.67	24.410	0.000
TNF-α (ng/L)	pre-treatment	27.56±5.97	27.09±6.60	0.748	0.455
	post-treatment	8.84±1.70	4.98±1.31	25.843	0.000
IL-6 (ng/L)	pre-treatment	57.19±6.06	57.44±5.81	-0.416	0.678
	post-treatment	42.59±5.31	29.97±3.80	27.859	0.000

Table 5: Comparison of sleep quality [M (Q1,Q3)]

Characteristics	point of time	Control group (n=195)	Study group (n=215)	*Z*	*P*
Sleep time (h/d)	pre-treatment	6 (5, 7)	6 (5, 7)	-1.070	0.285
	post-treatment	7 (7, 8)	8 (8, 9)	-7.959	0.000
Awakening times (times /d)	pre-treatment	2 (2, 2)	2 (2, 2)	-0.662	0.508
	post-treatment	0 (0, 0)	0 (0, 0)	-2.647	0.008

Table 6: Comparison of treatment effects

Grade	Control group (n=195)	Study group (n=215)	*Z*	*P*
Marked effectiveness	113	165		
Effectiveness	82	50	-4.063	0.000
Ineffectiveness	0	0		

Sample size

Since no similar studies had been conducted previously, this study utilized the Bronchiolitis Severity Score (BSS) data from the first 30 enrolled children to calculate the sample size. After estimation, the study concluded that to ensure the accuracy and reliability of the research (i.e., controlling the risk of type I error within 0.05 and achieving a statistical power of 90%), at least 117 children were needed in each group. This study selected 410 pediatric patients with bronchitis admitted from September 2023 to February 2024, with 195 patients in the control group and 215 patients in the study group, meeting the sample size requirements.

Ethical approval

This study was approved by the Ethics Committee of the Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (Ethical approval: KY-20230128).

STATISTICAL ANALYSIS

SPSS 25.0 statistical software was utilized for data analysis. Normally distributed continuous variables were reported as $\bar{x} \pm s$ and compared using the t-test. Non-normally distributed continuous variables are expressed as [M (Q1, Q3)] and analyzed with the Mann-Whitney U test. Categorical data were shown as n (%) and tested using the χ^2 test, adjusted χ^2 test, or Fisher's exact test. Ordinal data were performed using the Mann-Whitney U test. The statistical significance set at $P<0.05$.

RESULTS

Comparison of baseline characteristics

No statistically significant differences were observed in the baseline demographic and clinical characteristics between the two patient groups ($P>0.05$), thus ensuring the comparability of subsequent intervention effects. See table 1.

Comparison of time to resolution of clinical symptoms

The study group showed shorter times for improvement of dyspnea, resolution of cough, disappearance of pulmonary rales and resolution of fever compared to the control group ($P<0.05$). See table 2.

Comparison of pulmonary function indicators

Before treatment, there were no statistically significant differences across the two patient groups in terms of tidal volume, time to peak ratio, peak volume ratio and respiratory ratio ($P>0.05$), indicating good comparability across the two patient groups at baseline. After treatment, pulmonary function improved to varying degrees in both groups and the pulmonary function indicators of the study group, including tidal volume, time to peak ratio, peak volume ratio and respiratory ratio, were all better than those of the control group ($P<0.05$). See table 3.

Comparison of serum inflammatory markers

In the comparative analysis of serum inflammatory factor levels before and after treatment for pediatric bronchopneumonia, this study observed that key indicators such as WBC, CRP, TNF-α and IL-6 showed no statistically significant differences across the two patient groups before treatment ($P>0.05$), ensuring baseline consistency among the study subjects. Subsequently, after implementing different treatment regimens, the levels of serum inflammatory factors decreased in both groups. Notably, the concentrations of key pro-inflammatory factors such as WBC, CRP, TNF-α and IL-6 were significantly lower in the study group compared to the control group after treatment and this difference was statistically highly significant ($P<0.05$). See table 4.

Comparison of sleep quality

Before treatment, statistical evaluation of the two key sleep parameters, sleep duration and number of awakenings, in both groups of children showed no significant differences ($P>0.05$), ensuring the comparability of baseline sleep status among the study subjects. With the implementation of the treatment regimen, this study observed positive changes in sleep quality in both groups, manifested as prolonged sleep duration and reduced number of awakenings. Furthermore, after receiving the triple-drug combination therapy, children in the study group showed significantly prolonged sleep duration and a markedly reduced number of awakenings compared to the control group ($P<0.05$). See table 5.

Comparison of treatment effects

After treatment, no ineffective cases were observed in either treatment group. The marked effectiveness rate was 76.74% in the study group, which was superior to the 57.95% in the control group ($P<0.05$), indicating that the treatment effect was better in the study group. See table 6.

Comparison of airway secretion clearance function

The lung ventilation imaging results showed that the airway secretion clearance function in the study group was better than that in the control group after treatment ($P<0.05$). See table 7.

Comparison of wet weight of sputum during treatment

After corresponding treatment, the sputum volume, dry/wet weight ratio of sputum and sputum viscosity in both groups of children showed significant decreases compared to before treatment ($P<0.05$). Further analysis revealed that, compared to the control group, children in the study group who received the triple-drug combination therapy showed a more significant reduction in sputum volume, a lower dry/wet weight ratio of sputum and a greater decrease in sputum viscosity ($P<0.05$). See table 8.

Comparison of adverse reaction occurrence in children

During the treatment period, when meticulously assessing the safety of different medication regimens in the treatment

Table 7: Comparison of airway secretion clearance function

point of time	Grade	Control group (n=195)	Study group (n=215)	*Z*	*P*
pre-treatment	0	0	0	-0.477	0.633
	+	18	21		
	++	107	121		
	+++	70	72		
post-treatment	0	154	188	-2.293	0.022
	+	35	23		
	++	6	4		
	+++	0	0		

Table 8: Comparison of wet weight of sputum between two groups ($\overline{x}\pm s$)

Characteristics	point of time	Control group (n=195)	Study group (n=215)	*t*	*P*
Sputum volume (g)	pre-treatment	36.07±8.75	36.49±8.67	-0.489	0.625
	post-treatment	8.59±2.01	5.78±1.31	16.890	0.000
Sputum dry/wet weight ratio	pre-treatment	0.61±0.12	0.63±0.12	-1.288	0.198
	post-treatment	0.41±0.11	0.36±0.11	5.000	0.000
Sputum viscosity ($\times10^{-2}$Pa·s)	pre-treatment	6.16±1.12	6.12±1.19	0.324	0.746
	post-treatment	3.87±0.68	3.05±0.45	14.506	0.000

Table 9: Comparison of the occurrence of adverse reactions in the two groups

Characteristics	Control group (n=195)	Study group (n=215)	χ^2	*P*
Nausea and vomiting	4	6	0.135	0.713
diarrhea	1	1		
dizziness	1	1		
palpitations	1	1		
xerostomia	3	4		
allergic rash	1	1		
Total incidence	11(5.64%)	14(7.44%)		

of pediatric bronchopneumonia, this study found that despite the different drug compositions of the two treatment regimens, statistical testing revealed no notable difference in the occurrence of adverse reactions between the two groups of pediatric patients (P>0.05). This result suggests that although the study group incorporated an additional mucolytic agent, it did not increase the risk of adverse reactions, indicating that the combined use of ambroxol hydrochloride, terbutaline sulfate and budesonide is acceptable in terms of safety. See table 9.

DISCUSSION

Children with bronchitis are prone to respiratory distress, which can lead to plasma osmosis and edema, subsequently increasing airway secretions, which ultimately obstruct the capillaries of the children, causing varying degrees of ventilation impairment (Berry and Mansbach, 2020; Fu *et al.*, 2023). Some children with bronchitis, after treatment with antibiotics and cough relievers, are prone to adverse reactions such as recurrent cough and the treatment effect is not significant (Andina Martínez *et al.*, 2024). Therefore, the key to treating children with bronchitis lies in maintaining airway patency. However, the tracheal and bronchial lumens of children are relatively narrow and ciliary movement is poor, making it difficult to expel mucous secretions. Therefore, the combined nebulized inhalation therapy of budesonide and terbutaline sulfate has relatively limited effectiveness and certain limitations (Murphy *et al.*, 2020; Strauss, 2020). On the other hand, ambroxol hydrochloride, a commonly used mucolytic agent, can reduce the viscosity of sputum by cleaving the polysaccharide fibers of acid glycoproteins in sputum and inhibiting the synthesis of acidic proteins in mucous glands and goblet cells, thereby making the sputum thinner and easier to expel (Li *et al.*, 2025). Additionally, ambroxol hydrochloride can stimulate the frequency and intensity of ciliary movement in the respiratory tract, enhancing the ciliary clearance capacity and thus helping patients to cough up sputum more effectively (Liu *et al.*, 2024). Because ambroxol hydrochloride exhibits the aforementioned clinical effects, its use in the treatment of bronchitis and related diseases can accelerate patients' recovery and achieve good clinical outcomes.

In this study, the combination of ambroxol hydrochloride, terbutaline sulfate and budesonide was used in the treatment of pediatric bronchitis, achieving satisfactory results. The findings indicated that the study group exhibited better clinical treatment outcomes,

shorter duration for symptom resolution, improved pulmonary function indicators and enhanced sleep quality compared to the control group. This suggests that nebulized inhalation therapy with terbutaline sulfate, budesonide and ambroxol hydrochloride can improve treatment efficacy, rapidly alleviate clinical symptoms, enhance pulmonary function in children, reduce their discomfort and improve sleep quality. The addition of nebulized ambroxol hydrochloride therapy can reduce sputum viscosity, making the sputum thinner and easier to cough up, effectively improve ciliary movement, enhance the function of cilia in clearing respiratory secretions, stimulate type II alveolar cells to secrete surfactant and improve alveolar ventilation and gas exchange function (Zhu. *et al.*, 2023). The combination of ambroxol hydrochloride with terbutaline sulfate and budesonide not only further improves ventilation status in children but also reduces the irritation of sputum on the airways, lowers the risk of infection and promotes the recovery of pulmonary function, achieving a more ideal therapeutic goal (Qiu *et al.*, 2022). Studies have shown that in some children with viscous sputum, the use of bronchodilators and anti-inflammatory drugs alone may not effectively improve ventilation function due to sputum obstruction in the airways. However, with the addition of ambroxol hydrochloride, sputum is eliminated, the airways are cleared and ventilation is better improved and it reduces nighttime cough and respiratory distress caused by sputum obstruction in the airways, thereby improving sleep quality (Yu *et al.*, 2021).

The research also demonstrated that post-treatment levels of serum inflammatory markers (WBC, CRP, TNF-α, IL-6) were lower in the study group compared to the control group, indicating that the combination of the above three drugs can alleviate infection in pediatric bronchitis, reduce inflammatory stress damage, protect lung tissue and control the progression of the disease. In addition, after treatment, the airway secretion clearance function in the study group surpassed that of the control group and the sputum volume, dry/wet weight ratio of sputum and sputum viscosity in the study group were all lower than those in the control group. The control group was treated with terbutaline sulfate and budesonide. Terbutaline sulfate mainly exerts a bronchodilatory effect and has a relatively small direct impact on inflammatory factor levels (Ayed *et al.*, 2020). Budesonide is a glucocorticoid with potent anti-inflammatory effects, which can inhibit the activation, migration and proliferation of inflammatory cells such as eosinophils, mast cells and T lymphocytes and reduce the production of inflammatory mediators (Lipworth *et al.*, 2024). In this study, ambroxol hydrochloride was added to the treatment regimen based on terbutaline sulfate and budesonide. Its anti-inflammatory effect complements that of budesonide, enabling a more comprehensive inhibition of the inflammatory cascade reaction (Zhang *et al.*, 2024). This results in further reductions in the levels of serum inflammatory markers such as white blood cells, CRP, TNF-α and IL-6, alleviates pediatric bronchitis infection, reduces inflammatory stress damage, protects lung tissue and controls disease progression. Studies have shown that ambroxol hydrochloride can inhibit the release of histamine, leukotrienes and inflammatory cytokines from human leukocytes and mast cells, thereby reducing the levels of inflammatory factors in the serum, alleviating inflammatory stress damage and protecting lung tissue (Meng *et al.*, 2020). In addition, ambroxol hydrochloride has antioxidant effects, which can significantly reduce oxidative stress damage during disease progression and effectively delay airway remodeling. At the same time, it dissolves and dilutes sputum by increasing the water content of respiratory mucus and reducing its viscosity, making it easier for the ciliary system to clear the sputum, thereby reducing the residence time of sputum in the respiratory tract and lowering the risk of secondary infections. Moreover, there was no significant difference in the incidence of adverse reactions between the study group and the control group, indicating that the addition of ambroxol hydrochloride to the inhalation therapy of budesonide combined with terbutaline sulfate did not increase the risk of adverse reactions and the combined treatment regimen was safe. Ambroxol hydrochloride primarily improves sputum excretion by regulating respiratory mucus secretion and promoting ciliary movement. It has few adverse reactions on its own and its pharmacological mechanism supports its safety (Xue *et al.*, 2024). Furthermore, a meta-analysis showed that the inhalation of budesonide combined with ambroxol hydrochloride was effective in treating respiratory diseases such as asthma and bronchitis, without increasing adverse reactions, further validating the safety of the combination therapy (Shen *et al.*, 2023). This study provides important clinical reference, supporting that the combination therapy has high safety while ensuring efficacy.

CONCLUSION

This study found that in the treatment of pediatric bronchitis, the combined use of mucolytic agent (ambroxol hydrochloride), bronchodilator (terbutaline sulfate) and anti-inflammatory drug (budesonide) demonstrated significant advantages compared to the traditional treatment approach using only bronchodilators and anti-inflammatory drugs. The study group showed significantly better clinical treatment outcomes, not only rapidly alleviating symptoms such as shortness of breath, cough, wet rales in the lungs and fever, but also effectively improving various indicators of pulmonary function, reducing serum levels of inflammatory factors, improving sleep quality in children and enhancing the clearance function of airway secretions, resulting in more significant improvements in sputum volume, dry/wet weight ratio and viscosity. Additionally, the occurrence of adverse reactions

did not differ significantly between the two treatment approaches. This indicates that the combination therapy greatly improves treatment effectiveness while ensuring safety, has high clinical application and promotion value, provides a more effective strategy for the treatment of pediatric bronchitis and is worth widely applying in clinical practice.

Limitations of the study

This study provides valuable insights into the combination therapy for pediatric bronchitis, but it also has some limitations. Firstly, the study only selected 410 pediatric patients from one hospital, with a relatively limited sample size and a single source, which may not fully represent the entire pediatric bronchitis patient population. There may be differences in drug responses among patients from different regions, races and with different baseline health statuses and the limitation of the sample restricts the generality of the study results. Secondly, the study primarily focused on various indicators during and shortly after the treatment period, such as the time to resolution of clinical symptoms, pulmonary function indicators and serum inflammatory indicators, but lacked long-term follow-up data. The long-term effects of the combination therapy on patients' pulmonary function, growth and development and the likelihood of relapse are not yet clear. Thirdly, although the study clarified the therapeutic effectiveness of the combination therapy, it did not delve into the specific synergistic mechanisms when the mucolytic agent, bronchodilator and anti-inflammatory drug are used in combination. This may affect clinicians' precise understanding of the combined use of drugs and the further optimization of treatment regimens. Future research can address these limitations to improve the scientific validity and credibility of the study results, providing a more reliable basis for clinical practice.

Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

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