Original Article

The analysis of risk factors for recurrent wheezing in infants and clinical intervention

Liting Geng[1], Xiaoyu Tang[1], Li Hua[1], Haipei Liu[1], Shaolong Ren[2], Wenwei Zhong[1], Jianhua Zhang[1]

[1]Department of Pediatric Respiratory, Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China; [2]Department of Epidemiology, School of Public Health, Fudan University, Shanghai, China

Contributions: (I) Conception and design: L Geng, J Zhang; (II) Administrative support: L Hua, H Liu, W Zhong; (III) Provision of study materials or patients: L Geng, X Tang; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: L Geng, S Ren; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Wenwei Zhong, MD, PhD; Jianhua Zhang, MD, PhD. Department of Pediatric Respiratory, Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine, 1665 Kongjiang Rd., Yangpu District, Shanghai 200092, China. Email: zhww1208@163.com; zjh12195@126.com.

Background: Asthma is one of the most common chronic diseases affecting children's health, and recurrent wheezing in infants is closely related to childhood asthma. However, up to now, there is a lack of unified diagnostic criteria and interventions for recurrent wheezing in infants. By analyzing and discussing the risk factors of recurrent wheezing in infants and related intervention measures, we aim to take individualized treatment for different children and reduce the occurrence of recurrent wheezing in infants.

Methods: From January 2017 to December 2020, children under 3 years old who were admitted to the Department of Pediatric Respiratory of Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine with the chief complaint of wheezing for the first time and were clinically diagnosed with bronchiolitis, asthmatic bronchopneumonia and asthmatic bronchitis were retrospectively analyzed through telephone questionnaires. These children were divided into two groups based on whether the wheezing occurred again after discharge. The demographic characteristics, clinical treatment, imaging characteristics, and related interventions and outcomes after discharge were analyzed in both groups.

Results: Among the 523 children under 3 years old who were hospitalized due to wheezing, 264 (50.5%) did not have wheezing after discharge, and 259 (49.5%) still had wheezing after discharge. Both chi-squared test and multivariate analysis showed that male, history of eczema, history of rhinitis, history of wheezing before hospitalization, family smoke exposure, mycoplasma infection and inhalation allergen sensitization were risk factors for recurrent wheezing in infants and young children ($P<0.05$). Simultaneously, Cox survival curve showed that different intervention time and intervention methods would lead to different prognosis.

Conclusions: (I) Male, with a history of eczema, rhinitis, wheezing before hospitalization, family environment smoke exposure, mycoplasma infection and a history of inhalation allergy are high risk factors for recurrent wheezing in the recurrent wheezing group, and are more likely to have recurrent wheezing after discharge, with shorter days of wheezing control; (II) there was a significant interaction between mycoplasma infection and a history of inhalation allergy in infants with the risk of recurrent wheezing; (III) long-term intervention for children with wheezing for 4 weeks or more after discharge can reduce the probability of recurrent wheezing; (IV) for children of male, with a history of eczema or rhinitis, the most effective intervention to reduce the probability of recurrent wheezing is long-term inhaled corticosteroids (ICS) treatment after discharge.

Keywords: Wheezing; risk factors; infants and young children; wheezing treatment; treatment response

Submitted Jan 27, 2023. Accepted for publication Aug 02, 2023. Published online Oct 24, 2023.
doi: 10.21037/tp-23-45
View this article at: https://dx.doi.org/10.21037/tp-23-45

Introduction

Wheezing is one of the most common respiratory symptoms. The anatomy, physiology and immune functions of the airway in infants and young children are relatively special. These structural and functional characteristics lead to a high incidence of wheezing in infants and young children, which not only affects the development and health of children, but also has been a global public health problem, causing a heavy burden on public medical expenditure (1).

In the past decade, it has been reported that about 33–50% of children have wheezing at least once before the age of 3 years, and about 20% are recurrent wheezing (2). Another study found that asthma in more than 85% of children started before the age of 3 years, and the impairment of lung function in children with asthma usually occurred in preschool (3). The researchers also found that 60% of the children had at least one episode of wheezing by age 6, and at least 40% of those who had wheezing before age 3 still had episodes by age 6. At the same time, compared with other normal children, the outpatient visit rate of preschool children with wheezing episodes increased by 50%, the emergency visit rate increased by 2 times, and the hospitalization rate increased by 3 times (4). Therefore, it is necessary to identify infants with wheezing symptoms who may have recurrent wheezing or even develop bronchial asthma in the future.

For the diagnostic criteria of infantile asthma, scholars have revised the empirical diagnostic criteria for many times, and established a variety of asthma prediction tools for early diagnosis. However, up to now, there is still a lack of clear and unified diagnostic criteria for asthma in infants and young children at high risk of asthma. The Asthma Prediction Index (API) is the most widely used and earliest validated asthma prediction tool. Castro-Rodríguez *et al.* (5) in the United States used the questionnaire data of the Tucson Children's Respiratory Disease Birth Cohort Study (n=1,246), obtained the important predictive factors through univariate analysis, and proposed that API could be used to predict the diagnosis of childhood asthma. The specificity of strict criteria was 96.1–97.0%, and the sensitivity was 14.8–27.5% (6). Its specificity, sensitivity and diagnostic accuracy need to be improved, and the prediction tools used to identify children with asthma still need to be further improved. The latest pediatric asthma risk score (PARS) was proposed by Biagini Myers *et al.* (7) and Sherenian *et al.* (8). The research and verification results show that PARS has higher sensitivity and accuracy than API. It is easier to identify children with medium/low risk asthma. But PARS is limited in that it is a screening tool rather than a diagnostic tool. At present, few studies have considered the effect of treatment during hospitalization and asthma pre-intervention after discharge on wheezing recurrence. At the same time, symptoms, signs, and imaging findings are rarely combined in the evaluation of risk factors for recurrent wheezing. Thus extending current epidemiologic knowledge will help manage wheezing children and may reduce the incidence of long-term respiratory sequelae. Optimizing asthma management in preschoolers is critical because the incidence and health care utilization in preschoolers are currently disproportionate compared to school-aged children with asthma (9). Exploring the risk factors and intervention effects of infantile wheezing will not only help to improve the etiological diagnosis rate of infantile wheezing, but also bring important theoretical and practical application value for clinical treatment decision-making.

In this case-control study, we sought more comprehensive and reliable clinical information on risk factors for recurrent wheezing and more importantly, we innovatively explored the impact of different treatments received after discharge on the development of the disease. To this end, we selected children hospitalized for wheezing in the Department of Pediatric Respiratory, Xinhua Hospital Affiliated to

Highlight box

Key findings

- Different gender, past history, smoke exposure history, etc. lead to different prognosis. For children with risk factors, long-term intervention after discharge can reduce the probability of recurrence of wheezing, and finally benefit from this treatment method.

What is known and what is new?

- According to the diagnostic criteria of asthma in infants and young children, scholars have revised the empirical diagnostic criteria for many times, and established a variety of asthma prediction tools for early diagnosis.
- More comprehensive and reliable clinical information on the risk factors of recurrent wheezing in infants was explored, and more importantly, the effect of different treatments on the development of the disease after discharge was innovatively explored.

What is the implication, and what should change now?

- We need active long-term intervention after discharge for children with risk factors to benefit from this treatment.

Shanghai Jiaotong University School of Medicine from January 2017 to December 2020 as the research subjects. Through the combination of clinical case system records and telephone follow-up structured questionnaire, these hospitalized children were divided into two groups: Non-recurrent wheezing group and recurrent wheezing group after discharge. The demographic characteristics, clinical manifestations, imaging characteristics, and the effect of intervention measures were compared between the two groups to know whether the pre-intervention treatment of wheezing could reduce recurrence. We categorized continued intervention after discharge into long-term intervention, short-term intervention, and no intervention according to the duration of intervention. Long-term intervention was defined as continuing to receive intervention treatment for ≥4 weeks after discharge, short-term intervention was defined as continuing to receive treatment for ≥1 and <4 weeks after discharge, and no intervention was defined as no treatment or continuing to receive intervention treatment for <1 week after discharge. According to the intervention methods, the patients were divided into: (I) inhaled corticosteroids (ICS) treatment, the method was aerosol inhalation of budesonide suspension, 0.5 mg/time, 2 times/day, and then gradually reduced according to the condition; (II) the leukotriene receptor antagonist (LTRA) treatment was oral montelukast sodium, 4 mg/time, 1 time/day; (III) ICS combined with LTRA treatment: the dosage was the same as above. We present this article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-45/rc).

Methods

Patients and controls

We retrospectively studied 523 children with wheezing (cases: median age, 15.5 months; age range: 5–30 months; boy: 66.5%), hospitalized in the Department of Pediatric Respiratory, Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine from January 2017 to December 2020 due to wheezing. Inclusion criteria: infants aged 0–3 years; Infants and young children diagnosed with wheezing, wheeze bronchitis, wheeze bronchopulmonary pneumonia, and bronchiolitis. Exclusion criteria: incomplete clinical data; congenital laryngeal and tracheal chondrodysplasia, tracheal foreign body, acute laryngitis caused by wheezy; diseases caused by non-respiratory diseases: such as congenital heart disease, gastroesophageal reflux disease, mediastinal mass, and other serious underlying diseases such as leukemia, malignant tumors, severe malnutrition, and immune deficiency. Withdrawal criteria: children who could not cooperate with the investigation and follow-up in this study. For cases, on admission, we searched the clinical records for data on the following clinical and laboratory variables: days of wheezing on admission, days of fever, days of cough, family history of allergic diseases, past history of allergic diseases, birth history, severity of illness. Laboratory values recorded were first white blood cell count, eosinophil count, blood C-reactive protein (CRP) concentration, procalcitonin (PCT), respiratory pathogens. Imaging included chest computed tomography (CT), and chest X-ray. For the second part of the follow-up, we designed a structured questionnaire to seek demographic data. The study variables included gender, age, breastfeeding history, family history of asthma and allergy, family smoking habits, whether there was allergic eczema and rhinitis, whether intervention measures were taken after discharge, and the outcome of the disease, including whether there was continued wheezing after discharge and the number of wheezing, whether there was wheezing in the past year, the time of the last wheezing, and whether bronchial asthma had been diagnosed. Among them, breastfeeding refers to exclusive breastfeeding within 4 months after birth; history of eczema refers to a previous diagnosis of eczema made by a dermatologist; positive family report of allergen refers to specific IgE positive; family history of asthma refers to a history of asthma in first and second degree relatives; smoke exposure refers to passive smoking or smoking by family members who live together; severe means a diagnosis of severe pneumonia. Laboratory diagnosis of *Mycoplasma pneumoniae* (MP) infection: serum antibody titer ≥1:160 can be used as a reference standard for recent MP infection or acute MP infection. MP infection can be diagnosed when the titer of MP-igg antibody is increased or decreased by 4 times or more in the convalescent and acute phases. In addition, MP-DNA test or MP-RNA test can also assist the diagnosis. For hospitalized patients, we mainly use IgM detection to assist diagnosis during hospitalization. Due to the limitations of previous detection methods, the virus detection rate is not high. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine (No. XHEC-D-2023-006) and

Table 1 Frequency of recurrent wheezing in children at different follow-up times post-discharge

After discharge—follow-up time (years)	n	Age at follow-up (years)	The number of different recurrent wheezing episodes			
			0	1	2	≥3
<2	101	3.64±1.30	45 (44.6)	18 (17.8)	22 (21.8)	16 (15.8)
2–<3	125	4.24±1.13	52 (41.6)	10 (8.0)	23 (18.4)	40 (32.0)
3–<4	146	4.92±1.11	82 (56.2)	11 (7.5)	18 (12.3)	35 (24.0)
4–<5	124	5.59±1.02	72 (58.1)	12 (9.7)	16 (12.9)	24 (19.4)
≥5	27	6.22±0.82	13 (48.1)	3 (11.1)	3 (11.1)	8 (29.6)
Total	523	4.73±1.36	264 (50.5)	54 (10.3)	82 (15.7)	123 (23.5)

Data are shown as mean ± SD or n (%). SD, standard deviation.

informed consent was obtained from all patients' parents or legal guardians.

Follow-up

A follow-up questionnaire was designed. The questionnaire was combined with the section of personal and family history of respiratory diseases—original questionnaire for children in the Standard Health Questionnaire and Anthropometric Measures prepared by the National Institutes of Health of the United States. The authors interviewed the family members of the child using a standardized structured telephone questionnaire to find out whether the child had wheezing episodes since discharge from hospital in 2017–2020. If the child had experienced another episode of wheezing diagnosed by the pediatrician after discharge, the follow-up outcome was considered to be recurrent wheezing.

Statistical analysis

The measurement data were tested for normal distribution. The measurement data conforming to normal distribution were represented as mean ± standard deviation ($\bar{x}\pm s$), and the data not conforming to normal distribution were represented by median [interquartile range (IQR)]. *T*-test was used to compare the measurement data with normal distribution between the two groups, and rank sum test was used to compare the measurement data with non-normal distribution between the two groups. The count data were expressed as rate, and the comparison between groups was analyzed by χ^2 test or Fisher exact probability. Multivariate logistic regression analysis was performed using odds ratio (OR) and 95% confidence interval (CI), and all possible risk factors that were statistically significant in univariate analysis were included to determine the independent risk factors associated with recurrent wheezing. At the same time, the Kaplan-Meier curve was established to study the effect of different risk factors on the recurrence of wheezing (version 4.2.2). Cox regression analysis was used to explore the effects of different intervention time, intervention methods and methods on wheezing recurrence. P<0.05 was considered statistically significant.

Results

Risk factors for recurrent wheezing in infants and children younger than 3 years

Demographic characteristics and clinical presentation: in this case-control study, a total of 630 infants and children younger than 3 years hospitalized for wheezing were enrolled, of whom 523 (83%) were successfully followed up by telephone. These patients were divided into two groups: no recurrent wheezing group and recurrent wheezing group. Among them, 264 patients (50.5%) did not have wheezing again after discharge, and 259 patients (49.5%) still had wheezing after discharge. In the analysis cohort, the median age was 15.5 months. Frequency of recurrent wheezing in children at different follow-up times post-discharge has been listed (*Table 1*).

Analysis of age and gender composition of children

A total of 523 children with wheezing were divided into non-recurrent wheezing group and recurrent wheezing group. There was no significant difference in the Chi-squared test results of admission age between the two groups (P>0.05) (*Table 2*). However, the Chi-squared results for the gender distribution composition ratio found statistical difference between the two groups (P<0.05)

Table 2 Demographic data and comparison between non-recurrent wheezing and recurrent wheezing groups

Factors	Overall (N=523)	Non-recurrent wheezing (N=264)	Recurrent wheezing (N=259)	χ^2	P
Characteristics					
Age at enrollment (days)	464 [250–903]	496.5 [245.25–924]	455 [261–870]	422.657	0.482
Male sex	348 (66.5)	161 (61.0)	187 (72.2)	7.387	0.007
History of eczema	360 (68.8)	161 (61.0)	199 (76.8)	15.308	<0.001
History of rhinitis	245 (46.8)	97 (36.7)	148 (57.1)	21.851	<0.001
Previous wheezing before hospitalization	151 (28.9)	62 (23.5)	89 (34.4)	7.533	0.006
Parental history of asthma	31 (5.9)	15 (5.7)	16 (6.2)	0.058	0.810
Smoke exposure at home	186 (35.6)	73 (27.7)	113 (43.6)	14.565	<0.001
Mode of birth (caesarean delivery)	280 (53.5)	143 (54.2)	137 (52.9)	0.085	0.771
Prematurity (32–37 weeks)	64 (12.2)	32 (12.1)	32 (12.4)	0.007	0.935
Presentation and course at hospitalization for wheezing					
Received corticosteroids during pre-hospitalization visit	233 (44.6)	113 (42.8)	120 (46.3)	0.659	0.417
Days of fever	356 (68.1)	186 (70.5)	170 (65.6)	1.396	0.237
Days of cough	4 [2–10]	4 [2–8]	4 [2–10]	39.848	0.226
Days of wheezing before hospitalization					
White blood cells >10	165 (31.5)	87 (33.0)	78 (30.1)	0.488	0.485
CRP >8	199 (38.0)	101 (38.3)	98 (37.8)	0.010	0.921
Procalcitonin >0.05	350 (66.9)	178 (67.4)	172 (66.4)	0.061	0.805
Respiratory pathogens					
Mycoplasma infection	203 (38.8)	88 (33.3)	115 (44.4)	6.744	0.009
Virus infection	230 (44.0)	117 (44.3)	113 (43.6)	0.025	0.874
Allergic/inflammatory features					
Blood eosinophils >4%	55 (10.5)	29 (11.0)	26 (10.0)	0.124	0.724
Blood eosinophils (per mL)	48 (9.2)	23 (8.7)	25 (9.7)	0.139	0.710
sIgE sensitization	62.3 [22.4–191]	57.9 [20.7–176]	68.3 [26.95–227]	392.207	0.558
Food sensitization	112 (21.4)	53 (20.1)	59 (22.8)	0.568	0.451
Aeroallergen sensitization	81 (15.5)	22 (8.3)	59 (22.8)	20.846	<0.001
IgG + IgA + IgM ≥4	458 (87.6)	236 (89.4)	222 (85.7)	1.626	0.202
Clinical course					
Hospital length of stay (days)	6 [5–7]	6 [5–7]	6 [5–7]	13.158	0.661
Days of azithromycin use	3 [0–5]	3 [0–5]	3 [0–5]	6.753	0.873
Severe pneumonia	56 (10.7)	29 (11.0)	27 (10.4)	0.043	0.836
Chest radiograph/chest CT suggested lung consolidation	50 (9.6)	28 (10.6)	22 (8.5)	0.674	0.412

Data are expressed as % of positive cases (percentage of positive cases), or median [IQR]. P values are not corrected for multiple testing. Data were tested by χ^2 test. CRP, C-reactive protein; Ig, immunoglobulin; CT, computed tomography; IQR, interquartile range.

Table 3 Multivariable models of risk factors associated with recurrent wheezing

Risk factor	Standard error	OR	95% CI		P value
			Lower limit	Upper limit	
Male	0.204	0.543	0.364	0.811	0.003
History of eczema	0.209	1.772	1.176	2.670	0.006
History of rhinitis	0.193	2.001	1.371	2.922	<0.001
Previous wheezing before hospitalization	0.213	1.601	1.054	2.432	0.027
Smoke exposure at home	0.203	2.145	1.442	3.190	<0.001
Mycoplasma infection	0.197	1.475	1.002	2.171	0.049
Aeroallergen sensitization	0.285	2.586	1.478	4.522	0.001

OR, odds ratio; 95% CI, 95% confidence interval.

(*Table 2*), suggesting that male children were more likely to have recurrent wheezing.

Analysis of the patient's past history and birth history

Among the 523 children with wheezing, the general conditions of children in the non-recurrent wheezing group and the recurrent wheezing group were compared. The results showed that there were significant differences between the two groups in the history of eczema, rhinitis, wheezing before hospitalization, and smoke exposure in the home environment (P<0.05) (*Table 2*), while there were no significant differences between the two groups in the history of parental asthma, premature delivery, and natural labor (P>0.05) (*Table 2*).

Analysis of the manifestation and course of wheezing during hospitalization

Univariate analysis of case data: The results showed that there were significant differences between the non-recurrent wheezing group and the recurrent wheezing group in the presence or absence of mycoplasma infection and inhalation allergen sensitization (P<0.05) (*Table 2*). The Chi-squared results of the data included whether they had received corticosteroid treatment, fever before admission, days of wheezing before admission, white blood cell count, CRP, PCT, eosinophil percentage, absolute eosinophil count, serum IgE level, food allergen sensitization, temporary hypogammaglobulinemia, length of hospital day, days of azithromycin use, severe pneumonia and pulmonary consolidation found no statistical difference between the two groups (P>0.05) (*Table 2*).

Logistic regression analysis of risk factors

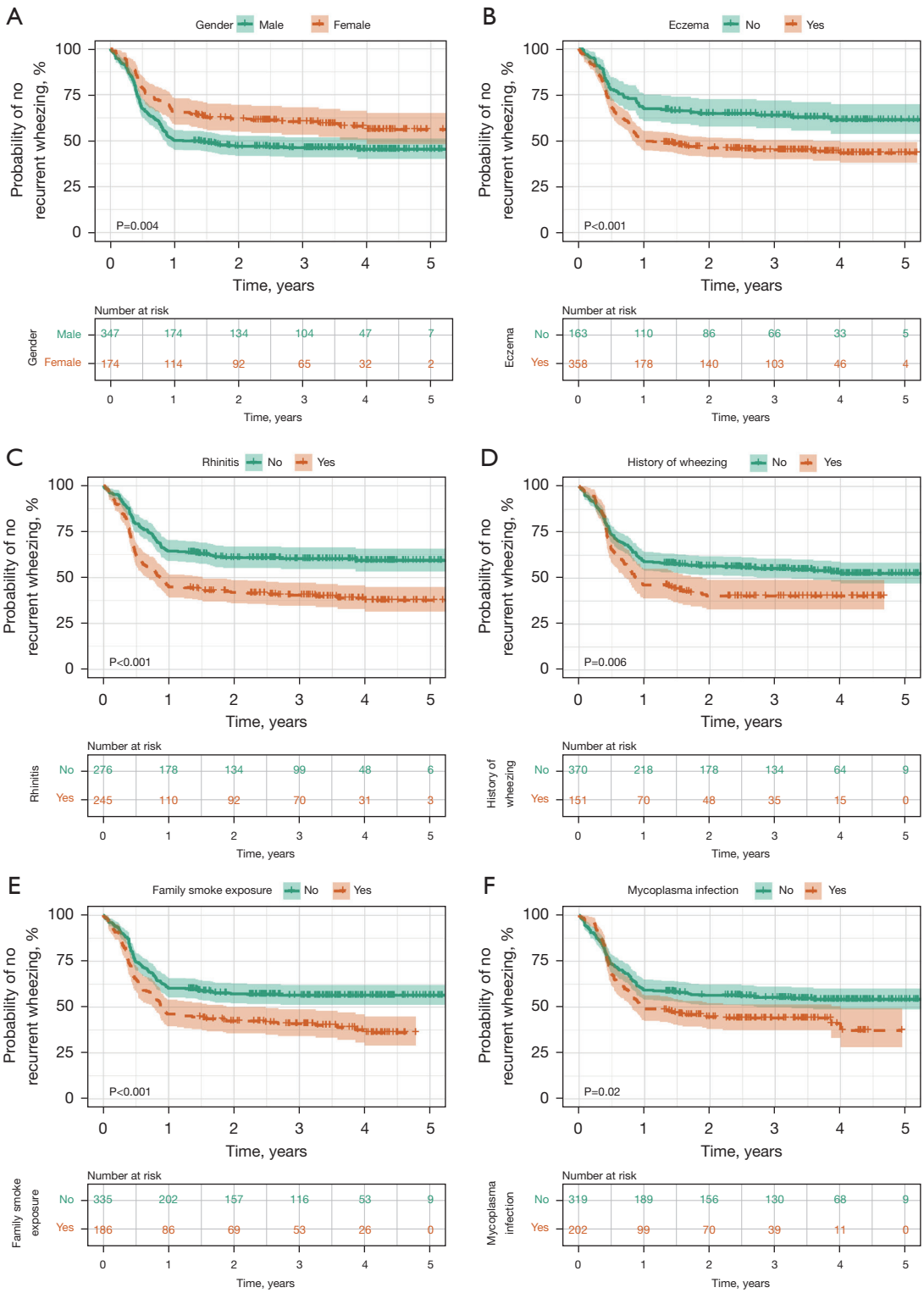
According to the results of univariate analysis, multivariate logistic regression analysis of seven statistically significant indicators showed that the risk factors associated with recurrent wheezing were male, history of eczema, history of rhinitis, history of wheezing before admission, family environmental smoke exposure, mycoplasma infection, and history of inhalation allergy (P<0.05) (*Table 3*).

Multivariate Cox proportional hazards model

On the basis of multivariate logistic regression analysis, in order to determine whether the risk factors of recurrent wheezing had an effect on the number of wheezing control days, we established a multivariate Cox proportional hazards model. The results showed that male (*Figure 1A*), with a history of eczema (*Figure 1B*), a history of rhinitis (*Figure 1C*), a history of wheezing before admission (*Figure 1D*), family environmental smoke exposure (*Figure 1E*), mycoplasma infection (*Figure 1F*), and a history of inhalation allergy (*Figure 1G*) were associated with an increased risk of recurrent wheezing (P<0.05), suggesting that the children with these risk factors were more likely to have recurrent wheezing after discharge and had a shorter wheezing control time.

Differences in mycoplasma infection—recurrent wheeze association by inhaled allergen sensitization status during infancy

In addition, there was a significant interaction between mycoplasma infection and inhalation allergy history in infancy and early childhood on the risk of recurrent



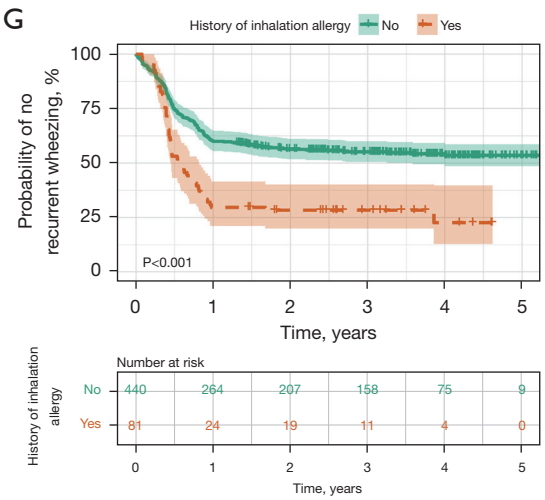


Figure 1 Multivariable Cox proportional hazards model for the effect of risk factors on wheezing recurrence. (A) Male was associated with an increased risk of recurrent wheezing; (B) a history of eczema was associated with an increased risk of recurrent wheezing; (C) a history of rhinitis was associated with an increased risk of recurrent wheezing; (D) a history of wheezing before admission was associated with an increased risk of recurrent wheezing; (E) family environmental smoke exposure was associated with an increased risk of recurrent wheezing; (F) mycoplasma infection was associated with an increased risk of recurrent wheezing; (G) a history of inhalation allergy was associated with an increased risk of recurrent wheezing.

wheezing (P<0.05), indicating that the magnitude of the mycoplasma-recurrent wheezing association varied according to inhaled allergen sensitization status (*Figure 2A*). In contrast, among infants who were not sensitized with inhaled allergens at enrollment, there was no significant difference in the risk of recurrent wheezing between the mycoplasma infection groups (*Figure 2B*). Among infants who were sensitized with inhaled allergens at enrollment, the risk of recurrent wheezing differed significantly between the mycoplasma groups.

Analysis of the effect of intervention treatment for children with recurrent wheezing after discharge

Differences in the association between long-term intervention and recurrent wheezing

In order to study whether long-term intervention treatment of wheezing after discharge has an effect on the recurrence of wheezing, we used SPSS statistical software (25.0.0; https://www.ibm.com/docs/zh/spss-statistics) for multivariate Cox regression statistical analysis. In this study, they were divided into long-term intervention, short-term intervention and no intervention according to the intervention time node. Long-term intervention was defined as continuing intervention for ≥4 weeks after discharge, short-term intervention was defined as receiving short-term treatment for ≥1 and <4 weeks after discharge, and no treatment or continuing treatment for <1 week after discharge without intervention. Compared with the children without intervention after discharge, the risk of recurrent wheezing after discharge was significantly reduced in the children who received long-term intervention (P<0.05) (*Figure 3*). The children who received only short-term intervention after discharge had a slightly lower risk of recurrent wheezing than those who received no intervention, but the difference was not statistically significant (P>0.05) (*Figure 3*), suggesting that the risk of recurrent wheezing was similar between the two groups. Intervention methods for different follow-up time in wheezy children post-discharge have been listed (*Table 4*).

Differences in the correlation between different treatment methods and recurrent wheezing in long-term intervention

The commonly used drugs for the intervention or control of asthmatic diseases in children include glucocorticoids, leukotriene modulators, antihistamines, etc. Antihistamines typically refer to H1 receptor antagonists, including first and second generation antihistamines. It is mainly used in the treatment of mild seasonal asthma combined with

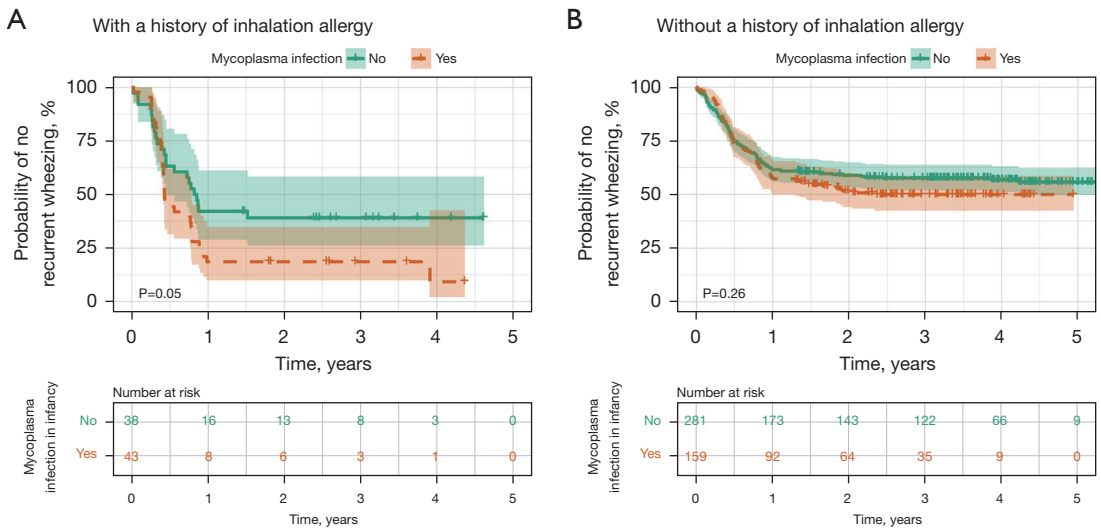


Figure 2 Interaction between mycoplasma infection in infancy and a history of inhalation allergy leading to recurrent wheezing. (A) Mycoplasma infection in infancy with a history of inhalation allergy was associated with an increased risk of recurrent wheezing; (B) mycoplasma infection in infancy without a history of inhalation allergy was not associated with an increased risk of recurrent wheezing.

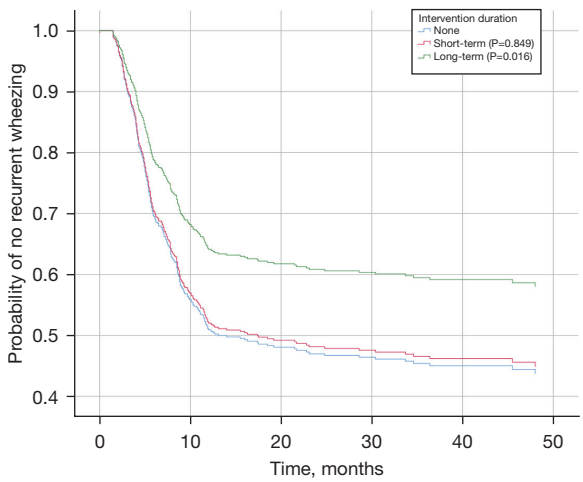


Figure 3 Differences in the association between long-term intervention and no recurrent wheezing.

allergic rhinitis, and the commonly used representative drugs in clinical practice are loratadine, cetirizine, etc. During the follow-up, we found the following problems in the application of cetirizine and loratadine: (I) among the 523 samples, there was no case of using antihistamines alone after discharge; (II) among the 523 samples, the duration of intervention involving antihistamines was less than one week, which did not meet the definition of long-term intervention; (III) most second-generation antihistamines suggested that they should only be used in children >2 years old. Loratadine and cetirizine were also considered to be safe for children ≥6 months old, but there was a lack of evidence for children <6 months old. Therefore, through telephone follow-up, we finally summarized the three most common long-term interventions in clinical practice: (I) ICS treatment; (II) LTRA treatment; (III) ICS combined with LTRA. Cox regression analysis was used to analyze the relationship between different intervention methods and recurrent wheezing. Comparing the three different long-term intervention modalities with no intervention and short-term intervention, the results showed that long-term ICS treatment can reduce the probability of recurrent wheezing compared with no intervention and short-term intervention, and the difference was statistically significant (P<0.05) (*Figure 4*). Compared with no intervention and short-term intervention, long-term LTRA treatment had a trend of decreasing the risk of wheezing recurrence, but the difference was not statistically significant (P>0.05) (*Figure 4*). Long-term ICS combined with LTRA treatment tended to reduce the risk of wheezing recurrence compared with no intervention and short-term intervention, but the difference was not statistically significant (P>0.05) (*Figure 4*).

Different responses to treatment strategies under different risk factors

We further explored the differences in the association

Table 4 Intervention methods for different follow-up time in wheezy children post-discharge

After discharge—follow-up time (years)	n	Age at follow-up (years)	Number of persons without intervention	Short-term intervention	Long-term intervention number		
					ICS	LTRA	ICS + LTRA
<2	101	3.64±1.30	26 (25.7)	40 (39.6)	22 (21.8)	4 (4.0)	9 (8.9)
2–<3	125	4.24±1.13	18 (14.4)	41 (32.8)	44 (35.2)	6 (4.8)	16 (12.8)
3–<4	146	4.92±1.11	29 (19.9)	58 (39.7)	37 (25.3)	5 (3.4)	17 (11.6)
4–<5	124	5.59±1.02	27 (21.8)	45 (36.3)	32 (25.8)	6 (4.8)	14 (11.3)
≥5	27	6.22±0.82	8 (29.6)	12 (44.4)	7 (25.9)	0 (0.0)	0 (0.0)
Total	523	4.73±1.36	108 (20.7)	196 (37.5)	142 (27.2)	21 (4.0)	56 (10.7)

Data are shown as mean ± SD or n (%). ICS, inhaled corticosteroids; LTRA, leukotriene receptor antagonist; SD, standard deviation.

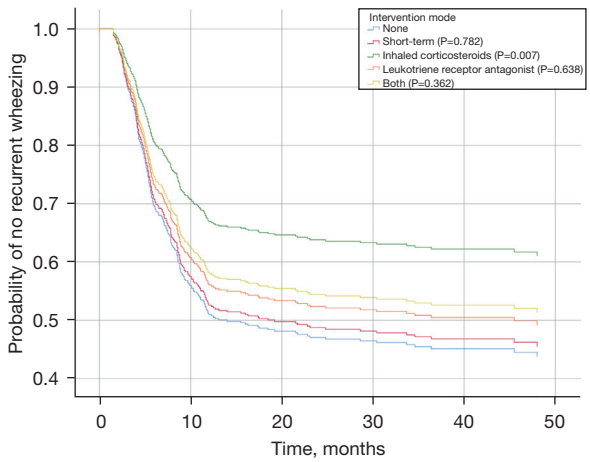


Figure 4 Differences in the correlation between different treatment methods and no recurrent wheezing in long-term intervention.

between different interventions and recurrent wheezing under different risk factors. Of 523 children with data that could be evaluated, 210 (40.2%) received long-term intervention (≥4 weeks), which was divided into three treatment modalities: daily ICS, daily LTRA, and daily ICS plus daily LTRA. The children had different responses to the three treatments. Overall, daily ICS was associated with a lower risk of wheezing recurrence and a longer duration of wheezing control than either daily ICS plus daily LTRA or daily LTRA, but the P value for this statistic was >0.05 (*Figure 5A*). To further examine whether there were differences between different interventions under different risk factors, in subsequent stratified analyses, we found that male infants (*Figure 5B*), infants with a history of eczema (*Figure 5C*), or infants with a history of rhinitis (*Figure 5D*) had the best response to the long-term daily ICS treatment strategy (P<0.05). Studies have found that children with wheezing who have the above risk factors should be treated with long-term intervention after discharge, and daily ICS therapy can obtain more beneficial results. However, there was no significant difference between the children with a history of wheezing, mycoplasma infection, a history of inhalation allergy, and family smoke exposure (P>0.05), suggesting that for these children, the time of pre-intervention for wheezing is more important than the way.

Discussion

Children with wheezing are a heterogeneous patient group with significant morbidity and health care utilization, but the same treatment is challenging (1,10,11). Initial drug selection and timing of administration are subject to much controversy. Given the limited number of studies in this age group, the overall quality of the evidence was low (12). There are no studies that can accurately assess how phenotypic features and biomarkers can be used to assess the possibility of pre-intervention for wheezing. In this case-control study, we followed 523 children hospitalized for wheezing. By combining clinical case records with a structured questionnaire during telephone follow-up, these hospitalized children were divided into two groups: no-recurrent wheezing group and recurrent wheezing group after discharge. Among them, 264 patients (50.5%) did not have wheezing again after discharge, and 259 patients (49.5%) still had wheezing after discharge.

By comparing the demographic characteristics, clinical test characteristics, imaging characteristics, and the effect of intervention measures, it was determined that male, history of eczema, history of rhinitis, history of wheezing

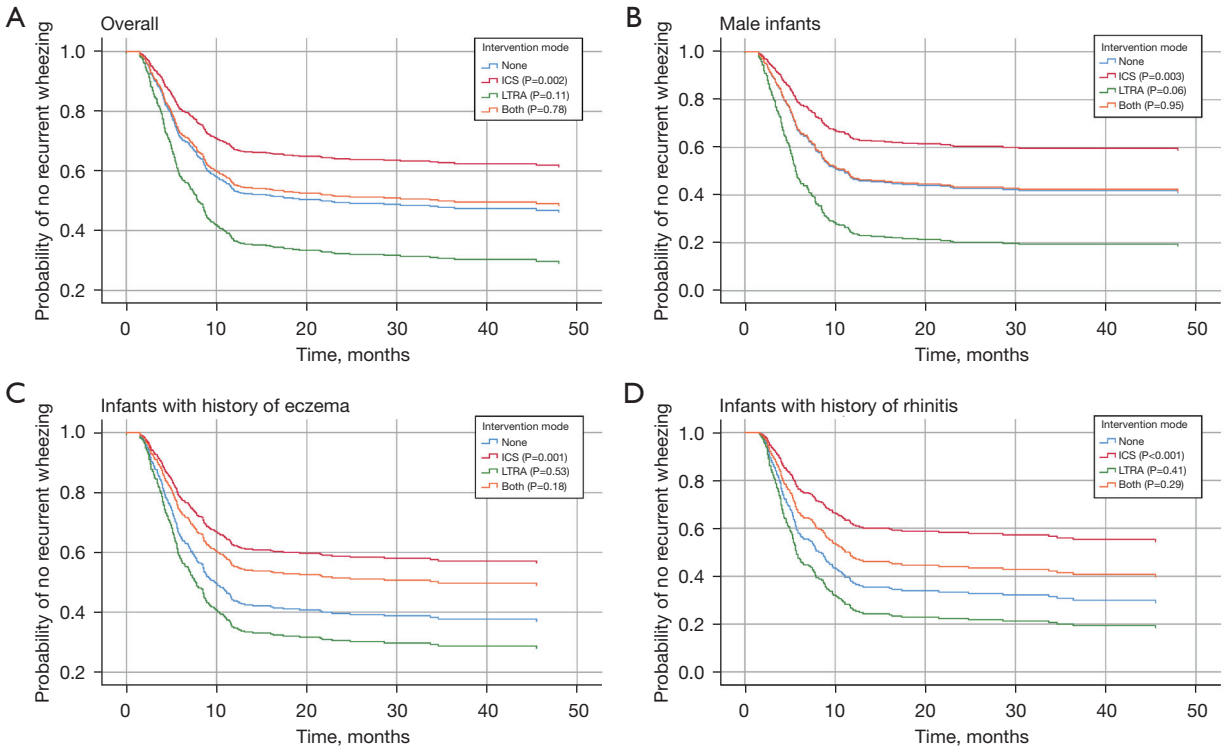


Figure 5 Differences in correlation between different intervention modes and different risk factors for recurrent wheezing. (A) Differences in the correlation between different treatment methods and recurrent wheezing in long-term intervention; (B) children who are male should choose daily ICS; (C) children who have previous history of eczema should choose daily ICS; (D) children who have previous history of rhinitis should choose daily ICS. ICS, inhaled corticosteroids; LTRA, leukotriene receptor antagonist.

before admission, family environmental smoke exposure, mycoplasma infection, and history of inhalation allergy were the risk factors for recurrent wheezing after discharge. The relationship between recurrent wheezing associated with mycoplasma infection and the status of history of inhalation allergy was also found.

Previous studies have found that male, a history of eczema, a history of rhinitis, and family environmental smoke exposure are closely related to recurrent wheezing (13-16). But little is known about the association between mycoplasma infection in early life and recurrent wheezing. Emerging evidence suggests that mycoplasma infection in early life is strongly associated with the development of chronic respiratory diseases. MP is one of the most common pathogens causing community-acquired pneumonia in children (17,18). MP pneumonia is a childhood pneumonia caused by atypical pathogens that was previously thought to be more common in adolescents and older children. However, MP infection has been more common in younger children in recent years, and there have been many infections in infants, most of them 9 to 12 months of age. This study found that mycoplasma infection can increase the probability of recurrent wheezing, and there is an interaction between mycoplasma infection and a history of inhalation allergy. This association remained significant in infants sensitized with inhaled allergens during infancy. For example, mycoplasma infection increased the risk of recurrent wheezing among infants who were sensitized with a history of inhaled allergies, whereas there was no significant difference in the presence or absence of mycoplasma infection among infants who were not sensitized with inhaled allergens. MP has common antigens with most organs in the body. After infection with MP, the body can produce autoantibodies to form immune complexes, cause cross immune responses, and cause damage to the lung and other tissues (19). This may be related to the tendency of wheezing children to relapse wheezing again in the later period. It is suggested that a child with inhaled allergen positive and mycoplasma infection will increase the probability of recurrent wheezing.

More importantly, through the analysis of the effect of intervention treatment for children with wheezing after discharge, we concluded that after discharge of children with wheezing, continuing to give more than 4 weeks of intervention treatment can reduce the probability of wheezing again. We proceeded to classify the different intervention modalities into the following three types: daily ICS, daily LTRA, and daily ICS combined with daily LTRA. We found that after the inclusion of risk factors, different treatment modalities showed possible differences in prognosis. Of these, 154 (29.4%) were treated with daily ICS (≥4 weeks), of whom 86 (55.8%) were free from wheezing after discharge. Overall, the Cox survival curve showed that the order of different interventions with good prognosis was: daily ICS > daily ICS combined with daily LTRA > daily LTRA, but the P value of this statistic was >0.05. It seems that compared with different intervention methods, the length of intervention is more important. For children with high-risk factors, long-term intervention for ≥4 weeks is more effective in reducing the recurrence rate of wheezing. In subsequent stratified analyses, we found that sex, previous history of eczema and previous history of rhinitis could be used to predict the drug strategy associated with the best response in these infants. The study found that children with these risks should choose daily ICS or daily ICS combined with daily LTRA. These results are clinically important given that the rate of Ed visits and hospitalizations is almost two to three times higher in infants compared to older children. Recent studies have shown that treatment with bronchodilators or glucocorticoids is reasonably effective in infants with moderate to severe respiratory distress, particularly those with asthma risk factors (20). We can use phenotypic features and biomarkers to assess the benefit of pre-intervention treatment for wheezing. For example, for an infant hospitalized for wheezing, who is male, has a history of eczema, a history of rhinitis, a history of wheezing before admission, smoke exposure in the home environment, mycoplasma infection, and a history of inhalation allergy, long-term intervention for more than 4 weeks after discharge can reduce the probability of recurrent wheezing and ultimately benefit from this treatment.

Conclusions

Different gender, past history and smoke exposure history lead to specific clinical manifestations and disease outcomes during wheezing in infants and young children. In the case of male, eczema history, rhinitis history, wheezing history before admission, smoke exposure in family environment, mycoplasma infection, and inhalation allergy history, long-term intervention (more than 4 weeks) after discharge can reduce the probability of recurrent wheezing. Ultimately, it benefits from this treatment.

Acknowledgments

Funding: This work was supported by grants from the National Natural Science Foundation of China (No. 82170025), and the Shanghai Municipal Health Commission (No. 202040164).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-23-45/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-23-45/dss

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-23-45/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-45/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine (No. XHEC-D-2023-006) and informed consent was obtained from all patients' parents or legal guardians.

References

1. Akinbami LJ, Moorman JE, Bailey C, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. NCHS Data Brief 2012;(94):1-8.
2. Alvarez-Alvarez I, Niu H, Guillen-Grima F, et al. Meta-analysis of prevalence of wheezing and recurrent wheezing in infants. Allergol Immunopathol (Madr) 2018;46:210-7.
3. Ducharme FM, Tse SM, Chauhan B. Diagnosis, management, and prognosis of preschool wheeze. Lancet 2014;383:1593-604.
4. Stokes JR, Bacharier LB. Prevention and treatment of recurrent viral-induced wheezing in the preschool child. Ann Allergy Asthma Immunol 2020;125:156-62.
5. Castro-Rodríguez JA, Holberg CJ, Wright AL, et al. A clinical index to define risk of asthma in young children with recurrent wheezing. Am J Respir Crit Care Med 2000;162:1403-6.
6. Leonardi NA, Spycher BD, Strippoli MP, et al. Validation of the Asthma Predictive Index and comparison with simpler clinical prediction rules. J Allergy Clin Immunol 2011;127:1466-72.e6.
7. Biagini Myers JM, Schauberger E, He H, et al. A Pediatric Asthma Risk Score to better predict asthma development in young children. J Allergy Clin Immunol 2019;143:1803-1810.e2.
8. Sherenian MG, Biagini Myers JM, Martin LJ, et al. The pediatric asthma risk score (PARS): making the move to the most accurate pediatric asthma risk screening tool. Expert Rev Clin Immunol 2019;15:1115-8.
9. Nuolivirta K, Törmänen S, Teräsjärvi J, et al. Post-bronchiolitis wheezing is associated with toll-like receptor 9 rs187084 gene polymorphism. Sci Rep 2016;6:31165.
10. Karaca-Mandic P, Jena AB, Joyce GF, et al. Out-of-pocket medication costs and use of medications and health care services among children with asthma. JAMA 2012;307:1284-91.
11. Fitzpatrick AM, Jackson DJ, Mauger DT, et al. Individualized therapy for persistent asthma in young children. J Allergy Clin Immunol 2016;138:1608-1618.e12.
12. Chong J, Haran C, Chauhan BF, et al. Intermittent inhaled corticosteroid therapy versus placebo for persistent asthma in children and adults. Cochrane Database Syst Rev 2015;2015:CD011032.
13. Lukkarinen M, Koistinen A, Turunen R, et al. Rhinovirus-induced first wheezing episode predicts atopic but not nonatopic asthma at school age. J Allergy Clin Immunol 2017;140:988-95.
14. Daines M, Pereira R, Cunningham A, et al. Novel Mouse Models of Fungal Asthma. Front Cell Infect Microbiol 2021;11:683194.
15. Nicolai A, Frassanito A, Nenna R, et al. Risk Factors for Virus-induced Acute Respiratory Tract Infections in Children Younger Than 3 Years and Recurrent Wheezing at 36 Months Follow-Up After Discharge. Pediatr Infect Dis J 2017;36:179-83.
16. Hasegawa K, Mansbach JM, Bochkov YA, et al. Association of Rhinovirus C Bronchiolitis and Immunoglobulin E Sensitization During Infancy With Development of Recurrent Wheeze. JAMA Pediatr 2019;173:544-52.
17. Wang M, Wang Y, Yan Y, et al. Clinical and laboratory profiles of refractory Mycoplasma pneumoniae pneumonia in children. Int J Infect Dis 2014;29:18-23.
18. Cho HK. Consideration in treatment decisions for refractory Mycoplasma pneumoniae pneumonia. Clin Exp Pediatr 2021;64:459-67.
19. Zhu R, Mao S, Shi W, et al. A prediction study of IL-18 and IFN-γ in glucocorticoid treatment response in infants and young children with severe Mycoplasma pneumoniae pneumonia. Transl Pediatr 2022;11:738-47.
20. Rodríguez-Martínez CE, Castro-Rodriguez JA, Nino G, et al. The impact of viral bronchiolitis phenotyping: Is it time to consider phenotype-specific responses to individualize pharmacological management? Paediatr Respir Rev 2020;34:53-8.

Cite this article as: Geng L, Tang X, Hua L, Liu H, Ren S, Zhong W, Zhang J. The analysis of risk factors for recurrent wheezing in infants and clinical intervention. Transl Pediatr 2023;12(10):1810-1822. doi: 10.21037/tp-23-45