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Insights in pediatric pulmonology: 2021

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Insights in pediatric pulmonology: 2021

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Editorial: Insights in pediatric pulmonology 2021

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BPD (bronchopulmonary dysplasia), bronchiolitis, infections, CF (Cystic fibrosis), ACT (airway clearance techniques), lung function test, sleep disorders

Editorial on the Research Topic
Insights in pediatric pulmonology 2021

Respiratory diseases are the commonest cause of morbidity in paediatric age in developed countries (1). Paediatricians must increasingly gain the knowledge, skills and experience they will need to treat a broad range of conditions that vary from acute and chronic respiratory disorders in children and adolescents. Because there is the urgent need to keep up with the research, we aimed to highlight the latest news in Pediatric Pulmonology.

We know that the advances in neonatal intensive care have led to improved survival in preterm infants (2). The effect of this result is the increase of infants affected by chronic conditions that affect primary the lung, but also undermine the balance of the whole organism. Broncho-pulmonary dysplasia (BDP) is an example of a neonatal chronic lung disease responsible of significant morbidity and mortality in preterm newborns (3, 4). The most accepted definition of BPD is based on the requirement of oxygen supplementation either at 28 days postnatal age or 36 weeks postmenstrual age (5). The aetiology of BPD is multifactorial and involves disruption of lung development and injury due to antenatal and/or postnatal factors (6). Some studies support the hypothesis that the development of BPD begins before birth after the exposition to proinflammatory cytokines during the intrauterine life. The exposure to inflammatory mediators may disrupt lung development through several mechanism (increase of vascular permeability, protein leakage, and mobilization of neutrophils into the interstitial and alveolar compartments). The increase of pro-inflammatory cytokines and the decrease of the counterregulatory ones may lead to unregulated and persistent inflammation (5). Wang et al. carried out a retrospective study to establish the association between levels of inflammatory cytokines in cord blood and bronchopulmonary dysplasia (BPD) in preterm infants. The results of the analysis carried out on 147 premature infants with gestational age ≤32 weeks showed that IL-6 cord blood levels at birth are significantly higher in the BPD group than in the non-BPD group. Therefore, Authors concluded that increase levels of IL-6, as well as increase maternal white blood cell (WBC) count on admission and lower birth weight, increase the risk of BPD progression.

Infectious respiratory illnesses are more frequently reported by parents in the first years of life (7). Acute viral bronchiolitis is one of the leading causes of hospitalization in the first 12–24 months of life (8). Airway cleansing, oxygen support and rehydration represent the main strategy suggested by international guidelines to manage viral bronchiolitis (9). As recent studies describe different phenotype corresponding to specific endotypes, trial with bronchodilator has been proposed in children with phenotype of bronchiolitis more strongly associated with asthma features. As reported by Bottau et al., the last one is likely in those infants with the first viral induced wheezing and aged over 6 months.

Beyond viral respiratory infections, bacterial acquired pneumonia sustained by Mycoplasma pneumoniae (MP) is often reported in school aged children (10). MP infection can cause serious consequences. Qiu et al. carried out a retrospective study to find the risk factor for developing severe MP pneumonia (SMPP). Based on the results of this research study, the percentage of neutrophils, the platelets count, the levels of C-reactive protein (CRP), lactate dehydrogenase (LDH) and D-dimer are risk factors for SMPP. Among the above-mentioned factors, D-dimer is the best predictor for complications such as pleural effusion, myocardial and liver damage.

According to the World Health Organization (WHO) 1 million children per year have TB disease and many more have a latent form of infection (11). Though treatment is resolving, some children may develop pleural tuberculosis and sometimes tuberculous empyema (TE). As the cause of TE in TB infected patients is unknown, Wu and colleagues designed a retrospective study to assess the factors associated with the presence of TE in children. The Authors concluded that surgical treatment, lung cavitation, high pleural LDH level, and low temperature are risk factors of development of TE in children with pleural TB.

Long lasting respiratory symptoms, like chronic cough, can be troublesome for paediatricians, also in a specialized setting (12). Despite advances in diagnostic imaging e laboratory tests in the field of respiratory medicine, history taking remains a primary step in diagnosing children with chronic cough. Kantar et al. stressed this concept in their kindly and accurate review, confirming the motto "history is half the diagnosis".

Among respiratory conditions to consider in the differential diagnosis of chronic cough, cystic fibrosis (CF) is one of the most feared diseases to exclude especially in children with other associated symptoms like frequent expectoration, bronchiectasis on chest CT and growth failure (13).

Like reported by Galodé et al., wheezing is not infrequent in CF affected children aged under 6 years, and bronchodilator response (BDR) is most represented in the group of patients aged 6–8 years. Atopy and Pseudomonas aeruginosa colonization in CF pre-schoolers are not associated with risk of wheezing or BDR. Nevertheless, CF affected wheezers at the age of 6 years have a worse lung function when compared with CF peers without wheezing.

Airways clearance techniques (ACT) are certainly a key point treatment in CF affected children. Its usefulness in the long-term period is undisputed (14, 15). Vandervoort and colleagues questioned if a single ACT session using positive expiratory pressure (PEP) mask has a short-term positive effect on forced expiratory volume in 1 s (FEV_1) and lung clearance index (LCI) in children affected by CF and primary ciliary dyskinesia (PCD). Despite the small sample, the Authors concluded that single PEP mask session has no significant short-term effect on FEV_1 and LCI in the analysed groups.

Anyway, other airways clearance techniques can improve lung function and physical resistance, finding application in certain conditions including obesity (16). Indeed, Kaeotawee et al. compared the effect of threshold inspiratory muscle training (IMT) on functional fitness and respiratory muscle strength (RMS) with incentive spirometry in 60 obese children and adolescents aged 8–15 years. The Authors concluded that 8 weeks of IMT training distance improve six-minutes walking test (6-MWT) and maximal inspiratory pressure (MIP) in obese paediatric patients.

It is well known that pulmonary function tests are important tools to diagnose and monitor chronic lung diseases (17). Although Radics et al. claimed their utilization in newborns is still far from being defined, Chaya et al. verified that spirometry remains the commonest test used in school age also in low-middle income countries. When associated with salbutamol test, spirometry allows the detection of bronchial reversibility that is typical of asthmatic patients (18). Asthma is the most common chronic disease in childhood, affecting an estimated 7 million children (19). Although most patients have good control of asthma symptoms, some children attend emergency department (ED) for acute asthma attack (20). Usually, the poor adherence to prescribed therapies justifies the need to access the hospital for acute attack. As reported by Kennedy and colleagues, the periodical revision of correct inhaler technique and the drafting of a personalised care plan have proven to be effective to reduce the ED and the systemic steroids utilization for asthma exacerbation.

However, it is reported that asthma can remain severe in a subtype of children despite the optimization of treatment and good adherence. For this group of patients, understanding of underlying molecular mechanisms is useful to develop a target therapy (21, 22). To date, as suggested by Ghirardo et al., the same molecular approach used for asthma treatment may be considered to treat other paediatric respiratory diseases for which the molecular basis is known.

Finally, up to 50% of children will experience a sleep problem (23). Early identification of sleep disorders may

prevent negative effects of sleep disturbance, such as irritability, behavioral problems, daytime sleepiness and learning difficulties (24). Most studies on sleep disorders in paediatric age are related to children living in low altitude. Ucrós and colleagues proposed a recent review on sleep disorders in children living in high altitude. They concluded that central apnea index decreases with age, while obstructive apnea/hypopnea index has a biphasic course, and periodic breathing in the first months of life is more marked with increasing altitude.

Among sleep disorders, obstructive sleep apnea (OSA) occurs in 1%–5% of children (25). Continuous positive airways pressure (CPAP) is the standard treatment (26). However, devices that automatically adjust the pressure during sleep (automatic PAP) are available (27). Tovichien et al. investigated the adherence and tolerance to CPAP and automatic PAP in a subgroup of paediatric patients affected by OSA. They found no statistically significant differences in the adherence and tolerance of the children using these devices.

Conclusions

This Topic offers a comprehensive update about several common respiratory conditions. We have a very special reason to be proud of this Issue as it represents a useful tool for clinicians in their clinical practice, also in not specialized setting.

Author contributions

FP drafted the editorial; RC revised and approved the final manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Factors Associated With the Presence of Tuberculous Empyema in Children With Pleural Tuberculosis

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Background: Until now, the factor of tuberculous empyema (TE) in children with pleural tuberculosis (TB) remains unclear. Therefore, a retrospective study was conducted to assess the factors associated with the presence of TE in children.

Methods: Between January 2006 and December 2019, consecutive children patients (≤15 years old) with suspected pleural TB were selected for further analysis. Empyema was defined as grossly purulent pleural fluid. The demographic, clinical, laboratory, and radiographic features were collected from the electrical medical records retrospectively. Univariate and multivariate logistic regressions were used to explore the factors associated with the presence of TE in children with pleural TB.

Results: A total of 154 children with pleural TB (definite, 123 cases; possible, 31 cases) were included in our study and then were classified as TE ($n = 27$) and Non-TE ($n = 127$) groups. Multivariate analysis revealed that surgical treatment (age- and sex-adjusted OR = 92.0, 95% CI: 11.7, 721.3), cavity (age- and sex-adjusted OR = 39.2, 95% CI: 3.2, 476.3), pleural LDH (>941 U/L, age- and sex-adjusted OR = 14.8, 95% CI: 2.4, 90.4), and temperature (>37.2°C, age- and sex-adjusted OR = 0.08, 95% CI: 0.01, 0.53) were associated with the presence of TE in children with pleural TB.

Conclusion: Early detection of the presence of TE in children remains a challenge and several characteristics, such as surgical treatment, lung cavitation, high pleural LDH level, and low temperature, were identified as factors of the presence of TE in children with pleural TB. These findings may improve the management of childhood TE.

Keywords: tuberculous empyema, children, pleural tuberculosis, risk factor, tuberculosis

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INTRODUCTION

According to World Health Organization (WHO) report, in 2018, the global tuberculosis (TB) burden was estimated to be 10.0 million and 1.2 million deaths occurred due to TB (1). Children constitute a significant proportion and account for 11% of total TB cases (1). In addition, at least 200,000 children died from TB in 2018 worldwide. In China, although the incidence of TB in children decreases from 29 per 100,000 in 2008 to 19 per 100,000 in 2017, TB remained the most common bacterial infection in children (2). Due to the considerable TB burden in children, effective measures are important to improve the TB control in children and initiate the diagnosis and treatment of childhood TB at an earlier stage.

Currently, tuberculous empyema (TE) remains a serious threat in China. Our previous study demonstrated that in adults, empyema was reported in 8.9% of patients with pleural TB and significant associations between several clinical characteristics (such as sex, pleural adenosine deaminase (ADA), white blood cell (WBC), and pulmonary TB) and presence of TE were observed (3). In the past decades, the treatment and outcome of empyema in children have been well characterized in several studies. In general, treatments, such as surgical operation or drugs, remain dependent on the empyema stage. For example, the conservative approach remains effective in the management of empyema in children (4); likewise, in adults, surgical management for stage III pediatric empyema is safe, effective, and well tolerated by children (5–7). However, compared with childhood pleural TB without empyema, children TE remains a serious challenge due to the severity, cost, and outcome.

Unfortunately, due to the lack of evidence, the factor of TE in children with pleural TB remains unclear. Therefore, in this retrospective study, we aimed to assess the factors associated with the presence of tuberculous empyema in children with pleural TB. It enables health providers to identify the characteristics of TE in children and develop appropriate strategies to improve the management of childhood TE. Moreover, it would be useful to identify TE from children with pleural TB at a high risk, and then appropriate treatment may be provided timely.

MATERIALS AND METHODS

Between January 2006 and December 2019, consecutive children patients (≤15 years old) with suspected pleural TB were selected for further analysis. Empyema was defined as grossly purulent pleural fluid (8). Definite pleural TB was defined as positive mycobacterial culture (sputum, pleural effusion, or pleural tissue) or suggested by pathological evidences (such as caseous necrosis, or Langhans' giant cells). Possible pleural TB was diagnosed based on the combinations of clinical symptoms and TB assays (such as TB RT-PCR and acid-fast bacilli (AFB) smear). The demographic (such as age, sex, and weight), clinical (such as symptoms, vital signs, and underling disease), laboratory (such as blood count and chemistry), and radiographic features were collected from the electrical medical records retrospectively.

Statistical analysis was performed using SPSS version 16.0 (SPSS, Chicago, IL, USA). All data were presented as mean ± standard deviation (SD). Univariate logistic regression analysis was performed to assess factors for the presence of TE, and variables with P-value < 0.1 were included for multivariate logistic regression analysis. Multivariate logistic regression analysis was then performed and the corresponding odds ratios (OR) and 95% confidence interval (CI), adjusted by age and sex, were calculated (9). In addition, to allow a better clinical understanding, continuous variables were transformed into categorical variables according to receiver operating characteristic curve (ROC) analysis. The accuracy of the multivariate model was evaluated using the Hosmer-Lemeshow goodness-of-fit test. The associations between the parameters were estimated using the Spearman correlation test. All tests were 2-sided, and a P-value < 0.05 was considered significant.

RESULTS

Patient Characteristics

The demographic data, clinical characteristics, laboratory, and radiographic findings collected from enrolled patients were shown in **Tables 1**, **2**. A total of 154 children with pleural TB (definite, 123 cases; possible, 31 cases) were included in our study and then were classified as TE ($n = 27$) and Non-TE ($n = 127$) groups. The patients have a mean age of 12.4 ± 3.3 years, and boys accounted for 64.9% (100 patients). One hundred and three were tested for HIV status, and all were HIV-negative. The weight was measured with a mean of 46.1 ± 16.2 kg. Among the 154 children patients, 93 (60.4%) were from rural areas. The vital signs were as follows: temperature, 37.2 ± 0.9°C; heart rate, 97.6 ± 16.0 beats/min; respiratory rate, 22.5 ± 2.7 breaths/min; blood pressure, 111.4 ± 12.3/69.2 ± 8.5 mmHg.

Twenty (13.0%) patients had a TB contact history, and surgical techniques were employed in the 29 (18.8%) patients. Prior to the admission to our center, most of them (91, 59.1%) were treated at a teaching hospital, and the mean times of hospitalization were 2.0 ± 1.6. The most common symptom was fever (134, 87.0%), followed by cough (84, 54.5%), chest pain (69, 44.8%), dyspnea (42, 27.3%), and sputum production (29, 18.8%). Cavity and loculated effusion revealed by radiographic examinations were observed in 7 (4.5%, 7/154) and 27 (17.5%, 27/154) patients, respectively. In addition, 62 (40.3%, 62/154) patients had effusion on the left side, 74 (48.1%, 74/154) on the right side, and 18 (11.7%, 18/154) on the both-side. Out of the total of 154 study patients, 89 (57.8%) had pulmonary TB, 13 (8.4%) had tuberculous lymphadenitis, 7 (4.5%) had milliary TB, 4 (2.6%) had tuberculous meningitis, 3 (1.9%) had bronchial TB, and the remaining 38 (24.7%) were isolated pleural TB.

Other characteristics, such as clinical chemistry analysis (serum or pleural effusion), blood cell analysis, and flow cytometry analysis, were summarized in **Tables 1**, **2**.

Univariate and Multivariate Analysis

Table 1 shows the univariate analysis of risk factors, comparing patients with TE with patients without TE. It was found that the presence of empyema was associated with temperature (OR = 0.420, 95% CI: 0.225, 0.781), hospitalization times (OR = 1.431, 95% CI: 1.141, 1.793), surgical treatment (OR = 27.787, 95% CI: 9.739, 79.288), fever (OR = 0.326, 95% CI: 0.116, 0.917), loculated effusion (OR = 3.806, 95% CI: 1.497, 9.679), pleural glucose (OR = 0.606, 95% CI: 0.386, 0.951), pleural LDH (OR = 1.001, 95% CI: 1.000, 1.002), and erythrocyte sedimentation rate (ESR, OR = 0.977, 95% CI: 0.958, 0.996) (all $P < 0.05$).

To make the results as readily understandable as possible, continuous variables were converted into dichotomous categorical variables based on the cut-off points determined with ROC analysis, and the corresponding optimal cut-off values were 37.2°C, 29 mm/h, 2.98 mmol/L, and 941 U/L, for temperature, ESR, pleural glucose, and LDH, respectively. Further multivariate analysis (Hosmer–Lemeshow goodness-of-fit test: $\chi^2 = 2.780$,

TABLE 1 | Univariate analysis of the demographic data associated with TE in childhood pleural TB.

	Total (*n*)	TE (*n*)	Non-TE (*n*)	*P*-value	OR (95% CI)
N	154	27	127		
Vital signs					
Temperature (°C)	37.2±0.9	36.8±0.7	37.3±0.9	0.006	0.420 (0.225, 0.781)
Heart rate	97.6±16.0	94.8±16.4	97.3±16.0	0.310	
Respiratory rate	22.5±2.7	22.1±2.5	22.5±2.9	0.325	
Systolic pressure	111.4±12.3	114.2±10.0	111.0±11.8	0.191	
Diastolic pressure	69.2±8.5	70.8±9.1	68.1±7.7	0.275	
Medical history					
Contact history of TB	20 (13.0%)	1 (3.7%)	19 (15.0%)	0.147	
Transferred times	2.1±1.0	2.0±1.0	2.2±1.1	0.788	
Transferred from a teaching hospital	91 (59.1%)	16 (59.3%)	75 (59.1%)	0.984	
Times of hospitalization	2.0±1.6	2.9±2.5	1.7±1.3	0.002	1.431 (1.141, 1.793)
Treatment delay (days)	61.8±134.6	60.7±67.6	91.8±177.8	0.965	
Surgical treatment	29 (18.8%)	19 (70.4%)	10 (7.9%)	0.000	27.787 (9.739, 79.288)
Symptoms and complications					
Cough	84 (54.5%)	13 (48.1%)	71 (55.9%)	0.463	
Fever (>38°C)	134 (87.0%)	20 (74.1%)	114 (89.8%)	0.034	0.326 (0.116, 0.917)
Chest pain	69 (44.8%)	13 (48.1%)	56 (44.1%)	0.701	
Dyspnea	42 (27.3%)	6 (22.2%)	36 (28.3%)	0.518	
Sputum production	29 (18.8%)	5 (18.5%)	24 (18.9%)	0.964	
Cavity	7 (4.5%)	3 (11.1%)	4 (3.1%)	0.091	
Loculated effusion	27 (17.5%)	10 (37.0%)	17 (13.4%)	0.005	3.806 (1.497, 9.679)
Clinical chemistry (pleural effusion)					
Total Protein	48.5±7.2	45.9±8.0	49.4±7.3	0.215	
Total Bilirubin (mmol/L)	8.6±5.6	11.5±10.1	8.2±5.0	0.109	
Adenosine deaminase (U/L)	60.3±28.8	71.5±49.4	61.6±28.4	0.198	
Glucose (mmol/L)	3.3±1.5	2.3±1.7	3.4±1.7	0.029	0.606 (0.386, 0.951)
Lactate dehydrogenase (U/L)	876.7±642.8	1505.4±1308.1	842.1±491.9	0.010	1.001 (1.000, 1.002)
Amylase (U/L)	29.6±10.4	25.7±11.0	32.0±11.6	0.210	
Other analysis					
Erythrocyte sedimentation rate (mm/h)	40.8±26.4	29.6±26.0	42.4±27.6	0.021	0.977 (0.958, 0.996)

TB, tuberculosis; OR, odds ratio; CI, confidence interval.

$df = 8$, $P = 0.947$) revealed that surgical treatment (age- and sex-adjusted OR = 92.0, 95% CI: 11.7, 721.3), cavity (age- and sex-adjusted OR = 39.2, 95% CI: 3.2, 476.3), pleural LDH (>941 U/L, age- and sex-adjusted OR = 14.8, 95% CI: 2.4, 90.4), and temperature (>37.2°C, age- and sex-adjusted OR = 0.08, 95% CI: 0.01, 0.53) were associated with the presence of TE in children with pleural TB (**Table 3**).

DISCUSSION

Until now, factors that affect the presence of empyema remain uncertain. In this study, the associations between TE and clinical characteristics were assessed in a referral TB hospital. Our study found that surgical treatment, cavity, pleural LDH, and temperature were associated with the presence of TE in children with pleural TB. To our knowledge, this is the first report investigating factors of the presence of TE among children with pleural TB. Our findings may improve the management of childhood TE and help appropriate treatment to be initiated timely.

First, the cavity in the lungs was identified having an association with the presence of empyema. In fact, previously, it is thought that lung cavitation means a high TB burden, high infectivity, and is associated with TE (10). One possible explanation is that cavitation appears to first occur within the parenchymal consolidation and TE may result from an inadvertent rupture into the pleural space (11, 12). This situation is not uncommon (11). In addition, the association suggests an indirect evidence of the mechanism of pleural TB formation that TB strains in lungs disseminate into pleural space directly.

Second, in the study, surgical treatment was also associated with the presence of TE in children. This finding shows that in our study, most of childhood TE patients underwent surgical treatment. To treat the TE and minimize the morbidity and mortality, physicians were required to choose the appropriate procedure. However, the optimal treatment of childhood TE remains unclear (13). In addition, although most of children

TABLE 2 | Univariate analysis of the demographic data associated with TE in childhood pleural TB.

	Total (*n*)	TE (*n*)	Non-TE (*n*)	*P*-value
N	154	27	127	
Demographic characteristics				
Age (years)	12.4±3.3	12.9±3.0	12.3±3.4	0.366
Sex (male)	100 (64.9%)	17 (63.0%)	83 (65.4%)	0.813
Weight (Kg)	46.1±16.2	46.5±17.0	44.9±14.9	0.889
Rural area	93 (60.4%)	17 (63.0%)	76 (59.8%)	0.763
Effusion sites				
Left	62 (40.3%)	10 (37.0%)	52 (40.9%)	0.707
Right	74 (48.1%)	13 (48.1%)	61 (48.0%)	0.991
Both	18 (11.7%)	4 (14.8%)	14 (11.0%)	0.579
Comorbidity				
Pulmonary TB	89 (57.8%)	14 (51.9%)	75 (59.1%)	0.492
Tuberculous lymphadenitis	13 (8.4%)	4 (14.8%)	9 (7.1%)	0.200
Milliary TB	7 (4.5%)	2 (7.4%)	5 (3.9%)	0.439
Tuberculous meningitis	4 (2.6%)	1 (3.7%)	3 (2.4%)	0.693
Bronchial tuberculosis	3 (1.9%)	0	3 (2.4%)	0.999
Clinical Chemistry (serum)				
Total protein (g/L)	68.7±6.9	68.2±7.2	69.3±7.5	0.673
Albumin (g/L)	38.8±4.8	38.7±5.2	38.7±4.9	0.908
Blood urea nitrogen (mmol/L)	3.9±1.2	3.6±1.0	4.0±1.2	0.174
Creatinine (μmmol/L)	52.3±15.3	55.7±14.7	49.2±13.9	0.227
Glucose (mmol/L)	4.8±1.2	4.8±0.6	4.9±1.6	0.908
Lactate dehydrogenase (U/L)	219.8±71.1	220.6±82.2	208.8±54.0	0.951
Blood analysis				
White blood cell (10^9/L)	7.3±2.6	6.8±2.0	7.4±2.8	0.320
Red blood cell (10^{12}/L)	4.4±0.5	4.6±0.5	4.5±0.5	0.114
Hemoglobin (g/L)	121.2±14.2	124.2±18.4	120.4±14.0	0.238
Hematocrit	36.6±3.9	37.3±4.6	36.6±4.0	0.299
Mean corpuscular volume (fL)	82.4±5.1	81.5±5.5	82.3±5.0	0.304
Mean corpuscular hemoglobin (pg)	27.3±2.1	27.1±2.6	27.1±1.8	0.579
Mean corpuscular hemoglobin concentration (g/L)	331.3±12.7	332.2±13.3	329.1±10.3	0.707
Platelet (10^9/L)	352.8±129.0	333.2±122.8	359.5±146.9	0.393
Neutrophil (10^9/L)	5.1±6.2	4.2±1.5	4.7±2.3	0.263
Lymphocyte (10^9/L)	1.7±0.9	1.8±0.7	1.7±0.8	0.832
Monocyte (10^9/L)	0.8±0.4	0.7±0.3	0.8±0.4	0.307
Coefficient of variation of red cell distribution width (%)	13.9±1.8	14.4±2.1	14.1±2.0	0.129
Flow cytometry				
CD19+ (%)	24.8±20.1	19.4±9.5	25.8±19.7	0.432
CD3+ (%)	62.4±13.7	64.4±12.1	61.5±13.5	0.658
CD3+CD4+ (%)	33.1±9.1	35.8±7.8	34.1±9.5	0.379
CD3+CD8+ (%)	24.0±12.0	24.5±10.4	22.4±10.7	0.902
CD3-CD16+CD56+ (%)	11.8±6.2	10.9±5.7	11.6±6.9	0.657
CD4+/CD8+ (%)	2.8±3.9	1.9±1.4	2.8±3.7	0.531

TB, tuberculosis.

patients with empyema can be successfully treated with the conservative treatment, the conservative treatment has a disadvantage because of the long duration of hospital stay, especially in cases with advanced stages (4). Hence, surgical treatment, such as decortication, resection, and muscle flap closure, is still necessary in childhood pleural empyema (14). However, the choice of surgical approach may be determined by the stage of TE and the corresponding success rates may be influenced by the stage of the empyema, such as stage I and II (5, 6, 15, 16).

Third, pleural LDH, as a biomarker varied during the progression of pleural inflammation (17), is found to be

TABLE 3 | Age- and sex-adjusted OR for risk factors associated with TE in childhood pleural TB.

	Adjusted (age and sex) OR	*P*-value
Surgical treatment	92.0 (11.7, 721.3)	<0.001
Cavity	39.2 (3.2, 476.3)	0.004
Pleural LDH (>941 U/L)	14.8 (2.4, 90.4)	0.004
Temperature (> 37.2°C)	0.08 (0.01, 0.53)	0.009

TB, tuberculosis; OR, odds ratio; CI, confidence interval.

associated with the presence of TE in children. It is thought that the initial level of pleural LDH reflects the serum level of LDH due to the filtration into the pleural space. In contrast, an increased LDH level is thought to have a cellular origin rather than a filtration origin (18). Similarly, pleural LDH can be used as a biomarker in the diagnosis of empyema. For example, Chen et al. found pleural LDH (≥1000 U/L) to be a maker discriminating complicated parapneumonic pleural effusion and empyema from uncomplicated parapneumonic pleural effusion with an AUC of 0.949 (19). Besides the above mentioned, pleural LDH also was found to be correlated with the duration of fever in patients with empyema, which may reflect the inflammation process (20, 21).

Low temperature was considered as another risk factor of the presence of TE among children with pleural TB. As known, the rise in the temperature due to empyema is a favorable symptom which may aid to shorten the delay in the treatment of TE. Therefore, the progression of developing TE was then stopped or delayed. Similarly, previous studies showed that absence of fever was significantly associated with total delay in patients with TB disease (9, 22–25). Interestingly, in the study, temperature was included in the final model. However, fever was not included in it. This may be explained by that fever, as an initiation symptom, was recalled by the patient before the admission to the hospital and the temperature was measured on the admission. Therefore, disease progression and previous treatment may made a significant impact and lead to the different analysis result. In contrast, a history of prolonged fever was confirmed as a significant clinical predictor for empyema in children (26, 27). Moreover, a longer duration of fever was associated with complicated community-acquired pneumonia, another serious complication as empyema (27). Based on these mentioned, further studies are required to investigate the association between temperature (or fever) and empyema, especially the corresponding biological plausible mechanism.

Although this study gives an insight into the management of childhood TE, the results of this study should be interpreted with some caution. First, retrospective collection of data and smaller number of cases are a significant concern for our study. Second, the study was based on a single center experience and our findings may generalize to other children populations. Furthermore, as the study had a relatively small sample size, a large study of childhood TE may be required to confirm these results.

CONCLUSIONS

Our findings suggest that early detection of the presence of TE in children remains a challenge in practice. Several characteristics, such as surgical treatment, lung cavitation, high pleural LDH level, and low temperature, have been identified as risk factors for the presence of TE in children with pleural TB. These findings may help to improve the diagnosis of TE and initiate appropriate treatment earlier. Moreover, it would also aid in shaping strategies for preventive management of childhood TE.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

This study was conducted at the Shandong Provincial Chest Hospital and confronted for the Helsinki Declaration. The study protocol was approved by the Ethics Committee of Shandong Provincial Chest Hospital. Due to the retrospective nature of this investigation and the anonymous nature of the data collection, this retrospective study was exempt from the need for written informed consent by the Ethics Committee of Shandong Provincial Chest Hospital.

AUTHOR CONTRIBUTIONS

M-SW and J-LW: designed the study and supervised data collection. Y-HW: performed statistical analysis and drafted the initial manuscript. M-SW: collected data. All authors approved the final version of the report.

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Comparing Adherence of Continuous and Automatic Positive Airway Pressure (CPAP and APAP) in Obstructive Sleep Apnea (OSA) Children

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Objectives: The treatment outcomes of pediatric obstructive sleep apnea (OSA) are affected by positive airway pressure (PAP) therapy adherence, which may be affected by the type of device used. Continuous PAP (CPAP) devices deliver a continuous and fixed air pressure level, whereas automatic PAP (APAP) devices automatically adjust the pressure to meet changing needs during sleep. The adherence, tolerance and consistency of OSA-children's use of CPAP and APAP devices were compared.

Study design: One-year, observational cohort study.

Methods: Twenty-seven OSA-children were enrolled. Fourteen (52%) used CPAP, and 13 (48%) used APAP. The adherence, tolerance, and consistency of the PAP usage by the two groups were compared.

Results: Overall, 11 of the 27 children (41%) showed good PAP adherence. The CPAP patients averaged 4.9 h of device usage on the days used, for 60% of days, with 6 of 14 (43%) demonstrating good adherence. In comparison, the APAP patients averaged 3.2 h for 55% of days, with 5 of 13 (38%) exhibiting good adherence. The 2 groups showed no differences in their adherence, tolerance, or consistency of device usage (*P* values, 0.816, 0.609, and 0.720, respectively). Although the adherence of both groups improved in the second 6 months, it was without statistical significance (*P* values, 0.400 and 0.724). Age, sex, baseline apnea-hypopnea index, comorbidities, prescribed period, device type, mask type, and caregiver education-level were not risk factors for poor PAP adherence.

Conclusions : No differences in the adherence, tolerance, or consistency of the children's use of CPAP and APAP were revealed in this small inhomogeneous cohort study with limited resources.

Keywords: CPAP, APAP, CPAP adherence, CPAP tolerance, consistency of CPAP use, OSA (obstructive sleep apnoea), children

INTRODUCTION

CPAP adherence effects treatment outcome of OSA-children and types of CPAP device may affect adherence based on adult study. However, our study revealed no difference of adherence, tolerance and consistency of CPAP use between OSA-children using CPAP and APAP in contrast to previous adult study.

Obstructive sleep apnea (OSA) arises from recurrent episodes of airway collapse during sleep which disrupts sleep architecture, ventilation and cardiovascular homeostasis (1). It affects 1–4% (2) of children. OSA is a common serious cause of metabolic, cardiovascular and neurocognitive morbidity in children. Most OSA-children are successfully treated with adenotonsillectomy. However, some children still have residual OSA, especially in cases with obesity, or they are simply not suitable candidates for surgery. Such patients are commonly prescribed positive airway pressure (PAP) therapy. Innovations in the PAP interfaces for children have increased the success of PAP treatment, even for young children.

In adults, PAP therapy reduces snoring, daytime sleepiness, nocturia, and subjective sleep disruption (3). Patients with a greater number of hours of PAP use tend to have a stronger feeling of being refreshed in the morning, an improved memory function, and better survival rates than otherwise. Moreover, longitudinal studies also indicate that PAP decreases the cardiovascular burden of OSA in compliant user (4). In children, PAP reduces the nocturnal and daytime symptoms of OSA. Although no randomized controlled trial on children is presently available, PAP therapy might also improve metabolic syndrome and nonalcoholic fatty liver disease (5), as well as systolic blood pressure (6).

There are two types of PAP device: continuous PAP (CPAP) and automatic PAP (APAP). CPAP delivers a continuous, fixed, air pressure throughout the breathing cycle. In contrast, the pressure delivered by APAP varies with changes in airflow resistance during sleep. The level of resistance is related to factors such as posture, degree of nasal congestion, and airway obstruction during each stage of sleep. APAP devices analyse inspiratory flow and titrate the airway pressure accordingly to maintain a constant airflow. Varying the air pressure that is required to reduce sleep disturbance may improve user comfort, thereby enhancing therapy adherence. A 2019 Cochrane review of adult studies found that people probably used APAP for 13 min longer per night at about 6 weeks compared with average usage of about 5 h per night with CPAP (4).

Tolerating PAP treatment is a highly complex issue and determined by various factors. Physical factors include disease severity, symptom relieve from PAP, underlying neurological disease and nasal anatomy. Psychological factors include locus of control, anxiety and depression (7–9). Finally, device-related factors such as mask leak, skin abrasions and nasal congestion may also deter use (10, 11).

To date, there have been few studies on PAP therapy adherence by children, and the research findings have been varied. Developmental factors may influence children's understanding of the need for therapy and its likely benefits. Moreover, high numbers of children with intellectual disabilities require PAP treatment. The efforts made by the parents of those children to initiate and sustain PAP therapy is likely to influence the level of adherence. Previous studies revealed modifiable facilitators to PAP adherence such as caregiver support, caregiver self-efficacy, authoritative parenting style, stable family structure, knowledge of PAP benefits, early adaptation to PAP and PAP apart of bedtime routine. Barriers to PAP adherence in OSA-children included poor communication between caregivers and child, discomfort of PAP interface or tubing, weight of PAP device hindering portability, lack of symptom relief/ therapeutic benefits, embarrassed about using PAP, low maternal education and older age (adolescents) (12) In addition, the minimum hours of device usage needed to achieve therapeutic benefits may also differ for children because they have a greater requirement for sleep than adults (13).

The present study set out to compare the patterns of PAP adherence (percentage of patients using device at least 4 h/day for more than 70% of nights), PAP tolerance (average hours on days used), and consistency of PAP usage (percentage of days used) of pediatric OSA patients using CPAP and APAP devices. The secondary objective was to identify the risk factors for poor PAP adherence to enable clinicians to optimize implementation and maintenance strategies for PAP therapy for children.

MATERIALS AND METHODS

This prospective cohort study included all children prescribed PAP for OSA treatment at the Department of Pediatrics, Siriraj Hospital, between 2020–2021. Our CPAP/APAP program included children with residual OSA after adenotonsillectomy and OSA related to obesity, craniofacial abnormalities or neuromuscular disorders. We diagnosed OSA from both clinical symptoms and diagnostic polysomnography (PSG) result. OSA symptoms included snoring, labored, paradoxical or obstructed breathing during sleep, sleepiness, hyperactivity, behavioral or learning problems. Diagnostic PSG revealed AHI more than 5 episodes/hour. We excluded patients with nocturnal hypoventilation (e.g. end-tidal carbon dioxide tension (PCO_2) > 50 mmHg for > 25% of total sleep time or peak end-tidal PCO_2 > 55 mmHg) who BiPAP was preferred (14).

After receiving printed and verbal information regarding the study, all participants provided written informed assent. In addition, the parents of the participants gave written informed consent to their children's data being included in this study.

All of the cases of PAP therapy were prescribed by a pediatric pulmonologist to treat OSA. In all, 14 CPAP devices and 13 APAP devices were used, with individual allocations being made in accordance with the patients' preferences. No humidification was used because CPAP device is not included in our national health coverage and all parents prefer to buy the cheaper one without humidifier. During the first month of usage, the devices were provided to the families free of charge and on a trial basis. If the PAP therapy was tolerated with good adherence and the family wished to continue the treatment, a payment plan was arranged. The ongoing installments were met by either the family or a supporting fund.

Typically, our PAP-therapy implementation program involved an initial, 2-night, inpatient-education session in the pediatric ward for the children and their parents. During that

period, they were provided with an explanation of OSA; the principles of PAP treatment; and practical guidance on PAP desensitization, device usage, and device care. An experienced sleep technician performed the mask fitting, choosing the most appropriate mask type for each child and determining the size offering the best fit. The families were also taught how to use the ramp function of the devices. Patients with good PAP tolerance underwent a nocturnal polysomnography with CPAP titration to determine the final titration of CPAP. We used the minimal CPAP pressure able to improve the AHI to <5 episodes/h and without desaturation <90% including supine rapid eye movement (REM) sleep for therapeutic CPAP pressure. Children who accepted the placement of the mask and the trial PAP treatment then continued nocturnal home PAP at that optimum therapeutic pressure. Once home PAP-therapy had been initiated, telephone contact was made by the sleep technician once weekly to support families and troubleshoot any problems. Any side effects of the PAP therapy were identified and addressed by phone or in person as they arose. Sleep data stored in those PAP devices were downloaded each time a patient visited our clinic (every 3 months). The "hours of usage per night" were defined as the time spent at the prescribed PAP pressure. The hours were recorded for all nights of use from the first day of the PAP education session. Information from the downloaded data were used for our study. We defined "good adherence" as device usage of at least 4 h/day for more than 70% of nights.

Continuous data are presented as mean ± SD, and categorical data as frequency and percentage. The means of the groups were compared using the Mann–Whitney U test, while their proportions were compared using the chi-squared test. Data were analyzed using IBM SPSS Statistics for Windows (version 25.0; IBM Corp., Armonk, NY, USA). A $P < 0.05$ was deemed statistically significant. Before commencement of this research, its protocol was approved by the Siriraj Institutional Review Board.

RESULTS

During the study period, 27 patients who had been diagnosed with OSA by clinical symptoms and polysomnography were indicated for PAP treatment. Their mean age was 12.4 ± 3.2 years; they were mostly male (63%); and their mean body mass index was 27 ± 11 kg/m^2. Of those 27 children, 11 (41%) had adenotonsillectomies; 10 (37%) had obesity; 10 (37%) had Duchenne muscular dystrophy; 10 (37%) had allergic rhinitis; 7 (26%) had Down syndrome; 5 (19%) had asthma; and 11 (41%) had intellectual disabilities that might have impacted on their ability to understand PAP treatment. In addition, 85% were snorers; 41% had a neurocognitive dysfunction; 26% had daytime fatigue; and 0% had a family history of OSA. From the baseline polysomnographies, the mean apnea-hypopnea index (AHI) was 24 ± 19 events/hour, and the mean SpO2 was 96% ± 2%. Three children (11%) had moderate OSA (defined as an AHI of at least 5 events/h), while 21 (77%) had severe OSA (defined as an AHI of at least 10 events/h). Nine children (33%) had rapid eye movement (REM)-related OSA (defined as an AHI during REM sleep of at least double that during non-REM sleep). Eleven children (41%) had positional OSA (defined as an AHI during supine sleep of at least double that during non-supine sleep). Downloaded PAP data were available for all 27 patients. The demographic data of the subjects, the PAP device brands, and the types of interface (nasal and oronasal masks) are summarized in **Table 1**.

TABLE 1 | Demographic data.

Age (years), mean (SD)	12.4 (3.2)
Sex, *n* (%)	
Male	17 (63%)
Female	10 (37%)
Comorbidities, *n* (%)	
- Obesity	10 (37%)
- Duchenne muscular diseases	10 (37%)
- Allergic rhinitis	10 (37%)
- Down syndrome	7 (26%)
- Asthma	5 (19%)
Post-adenotonsillectomy	11 (41%)
Intranasal steroids	8 (30%)
Type of PAP devices, *n* (%)	
- CPAP	14 (52%)
- APAP	13 (48%)
Brand of PAP devices, *n* (%)	
- Philips	11 (41%)
- Resmed	7 (26%)
- Apex	6 (22%)
- Hoffrichter	2 (7%)
- Breas	1 (4%)
Interface, *n* (%)	
- Nasal mask	23 (85%)
- Oronasal mask	4 (15%)

TABLE 2 | Adherence, tolerance, and consistency of PAP usage of CPAP and APAP groups.

	CPAP ***N* = 14**	**APAP** ***N* = 13**	***P* value**
Good adherence	6 (43%)	5 (38%)	0.816
PAP tolerance (average hours on days used)	4.9 (2.6–6.6)	3.2 (1.0–6.6)	0.609
Consistency of PAP usage (percentage of day used)	60.0% (28.4–86.0%)	55.0% (14.5–86.8%)	0.720

Six of the 14 CPAP patients (43%) achieved good therapy adherence. The CPAP patients used their devices for an average of 4.9 h on the days used, and for 60% of days. As to the APAP patients, five of 13 (38%) showed good adherence. This group used their devices for an average of 3.2 h on the days used, and for 55% of days. The adherence (percentage of patients using device at least 4 hours/day for more than 70% of nights), tolerance (average hours on days used), and consistency of device usage (percentage of day used) by the CPAP and APAP patients did not differ (*P* values, 0.816, 0.609, and 0.720, respectively; **Table 2**).

The CPAP group used their devices for an average of 3 h on the days used during the first 6 months of the study year. However, the average rose to 5 h during the second half of the year. A similar increase was found with the APAP group. Usage climbed slightly from an average of 2.2 h during the first half of the study year to 2.5 h during the second half. Nevertheless, the trends shown by the CPAP and APAP groups toward increasing PAP adherence in the second half of the study year were without statistical significance (*P* values, 0.400 and 0.724, respectively).

Overall, 11 children exhibited good PAP-therapy adherence, whereas 16 showed poor adherence. Apart from discomfort arising from the use of a PAP device, all other characteristics of the patients in the two groups were similar (**Table 3**). The only risk factor for poor PAP-therapy adherence identified by this study was the discomfort associated with PAP device usage (**Table 4**). We interviewed the 16 children who had demonstrated poor therapy adherence to ascertain the underlying reasons. None reported that their poor adherence was related to complications such as congestion or skin problems.

TABLE 3 | Characteristics of users with good vs poor PAP-therapy adherence.

	Good adherence *N* = 11	Poor adherence *N* = 16	*P* value
Age (years)	12.54 (3.17)	12.31 (3.24)	0.855
Male, *n* (%)	6 (54%)	11 (69%)	0.687
Comorbidities, *n* (%)			
- Obesity	2 (18%)	8 (50%)	0.124
- Duchenne muscular diseases	5 (45%)	5 (31%)	0.687
- Allergic rhinitis	3 (27%)	7 (44%)	0.448
- Down syndrome	4 (36%)	3 (19%)	0.391
- Asthma	2 (18%)	3 (19%)	1.000
- Intellectual disability	6 (55%)	5 (31%)	0.264
Previous adenotonsillectomy, *n* (%)	5 (46%)	6 (38%)	0.710
Intranasal steroids use, *n* (%)	3 (27%)	5 (31%)	1.000
OAHI prior to treatment	20.5 (14.5–26.5)	17.5 (9.5–25.5)	0.651
Type of PAP devices, *n* (%)			
- CPAP	6 (54%)	8 (50%)	1.000
- APAP	5 (46%)	8 (50%)	
Brand of PAP devices, *n* (%)			
- Phillip	3 (27%)	8 (50%)	0.163
- Resmed	2 (18%)	5 (31%)	
- Apex	5 (46%)	1 (6%)	
- Hoffrichter	1 (9%)	1 (6%)	
- Breas	0 (0%)	1 (6%)	
Interface, *n* (%)			
- Nasal mask	9 (82%)	14 (88%)	1.000
- Oronasal mask	2 (8%)	2 (12%)	
Duration of PAP usage, median (IQR)	36.5 (19.3–46.6)	22.8 (10.4–47.9)	0.916
Parental involvement, *n* (%)	11 (100%)	13 (81%)	0.128
Parental education, *n* (%)			
- Primary school	1 (9%)	4 (25%)	0.632
- High school	2 (18%)	4 (25%)	
- Higher than bachelor's degree	8 (73%)	8 (50%)	
Discomfort from PAP, *n* (%)	0 (0%)	11 (69%)	<0.005*
Lack of clinical benefits, *n* (%)	0 (0%)	5 (31%)	0.060

**A p-value < 0.05 indicates statistical significance.*

TABLE 4 | Risk factors for poor PAP-therapy adherence.

	OR (95% CI)	*P* value
Age	0.98 (0.76–1.30)	0.850
Male sex	0.54 (0.11–2.67)	0.455
Baseline AHI	0.99 (0.95–1.03)	0.650
Oronasal mask	0.64 (0.76–5.42)	0.685
Lower maternal education	0.38 (0.07–2.00)	0.244
Discomfort from PAP	48 (2.37–973.97)	0.012*
Lack of clinical benefits	3.33 (0.32–34.83)	0.315

**A p-value < 0.05 indicates statistical significance.*

DISCUSSION

In adults, PAP usage for >4 h per night is associated with improvements in apnea-hypopnea indices and Epworth Sleepiness Scale scores. There is also a linear relationship between the hours of nightly PAP-device usage and improvements in OSA symptoms, with a leveling off at approximately 7 h of use and no further gains in benefits thereafter (15, 16).

In the case of children, PAP adherence rates are typically quite poor, with most studies having reported usage averages of between 3 and 4 h per night (12). However, Ramirez and associates observed high levels of PAP usage (>8 h per night). In their study, PAP therapy was implemented in a dedicated, pediatric, noninvasive ventilation unit, and the patients and caregivers were provided with clinical and behavioral support (17). Another study suggested that it may not be reasonable to apply the definition of adherence used for adults to children. This is because children have longer recommended and actual sleep durations than adults, and those durations vary with age (13). Drawing on this hypothesis, we designed our PAP education program to include family support. We then conducted this research to determine whether PAP-therapy adherence differed between patients using CPAP and APAP devices.

Our study supported the findings of previous studies that there is generally poor PAP-therapy adherence in overall children. Those investigations reported that between only 41 and 75% of children showed good adherence (defined as an average of at least 4 h on 70% of the nights) (18–21). Because our hospital has a center of excellence for neuromuscular diseases, many of our cases needed caregiver assistance in putting on the PAP interface. The efforts made by the caregiver to sustain PAP therapy is likely to influence the level of adherence.

The present work found no differences in the adherence, tolerance, or consistency of the PAP therapies of the CPAP and APAP groups. This contrasts with a meta-analysis of adult studies, which identified a statistically significant difference of 11 min per night favoring APAP (22).

Our results showed that the major barrier to good adherence was not associated with the baseline characteristics of the patients, PAP device, or complications of device usage. Instead, the major barrier was related to the discomfort associated with PAP device usage. Personalized desensitization programs and behavioral interventions were shown by a previous investigation to increase the hours of usage in a group of children who had poor PAP-therapy adherence (23–25). In the present work, the adherence of both groups tended to improve in the second half of the study year, albeit without statistical significance. Ways that could be utilized to improve PAP-therapy adherence include education about the benefits of PAP usage and desensitization techniques prior to therapy initiation, play therapy, cognitive behavioral therapy for older children, positive reinforcement, and parental support using tele-education and telemonitoring.

The clinical benefits of PAP therapy in adults are directly related to the hours of usage of the devices per night. Skipping a night of treatment leads to a return of daytime sleepiness. In the case of children, untreated OSA is known to have adverse neurocognitive and behavioral consequences. Furthermore, improvements in PAP adherence have been associated with improvements in the parent-reported symptoms in children receiving PAP therapy. The impact of PAP therapy on the symptoms that can be perceived by the children themselves may play a key role in adherence.

A previous study demonstrated a trend toward an association between high PAP adherence (in terms of hours of use per night) and a younger age, a high AHI at diagnosis, primary vs middle/high school attendance, and neurocognitive disorders at baseline (26). However, the predictors of poor adherence are probably specific to each population. Unfortunately, data are scarce on the long-term PAP-therapy adherence of children and the factors influencing that adherence.

As to our secondary objective, we did not find any predictors for poor CPAP adherence. More specifically, the following factors showed no association: age, sex, baseline AHI, comorbidities, a previous adenotonsillectomy, PAP-device type, interface type, and education level of the caregiver.

We observed no association between age and PAP-therapy adherence. However, this finding contrasts with the work of DiFeo and colleagues (27). Likewise, another study suggested that educational programs for pediatric patients and their families should differ with age to improve PAP adherence (25). Other research also concluded that it was particularly important that adolescents with OSA be well supported in their use of PAP therapy (28).

Some studies revealed that female sex, developmental delay (18), and maternal education (27) were associated with a good adherence. Like some other studies, no such associations were demonstrated in our study population (29).

We also observed no association between OSA severity and PAP adherence. This corresponded with the results of the retrospective study by Hawkin et al. (18). It reported that OSA (diagnostic AHI and degree of hypoxemia), therapeutic pressure, and residual AHI had no impact on PAP adherence.

Specific integrated care support at home serves as an important way to improve self-efficacy when starting PAP therapy in children with OSA (30).

We acknowledge that our study had a small inhomogeneous sample and might therefore lacked power to achieve statistical significance. We performed this study in a place with limited resources. Our national health coverage doesn't include cost of CPAP device. Parents had to buy CPAP on their own and most parents preferred to buy the cheaper one without humidifier. Although bi-level PAP device would be more efficient for children with Duchenne muscular dystrophy (DMD), we didn't have enough financial support for them. The diagnostic PSG of all children with DMD in this study had only moderate OSA without sleep-related hypoventilation. We repeated PSG of them annually and switched to BiPAP in case that we found progressive severity of OSA or evidence of sleep-related hypoventilation. The results must be considered in the light of this important limits.

CONCLUSIONS

No differences in the adherence, tolerance, or consistency of the PAP therapies of the CPAP and APAP groups were revealed in this small inhomogeneous cohort study with limited resources.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Siriraj Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

PT contributed to study conception, study design, statistical analysis, and manuscript preparation. AK recruited study participants, conducted fieldwork, and performed data collection. KU contributed to study conception and design. All authors contributed to the article and approved the submitted version.

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Biological Treatments and Target Therapies for Pediatric Respiratory Medicine: Not Only Asthma

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We present a description of pediatric pneumology biological medications and other target therapies. The article aims at introducing the importance of a molecular approach to improve treatments. The first item treated was T2-High asthma and its current biological treatment and prescribing indications to propose a flow-chart to guide the clinical choice. Molecular rationales of such treatments are used to introduce a more general description of the biological and molecular approach to target therapies application. We introduce a general interpretation approach to neutrophilic asthma using the molecular plausibility one in order to propose possible future treatments mainly targeting interleukin-1 (IL-1), IL-17, IL-12, and IL-23. Indeed, cytokines can be excellent targets for several biological treatments. Downregulation of specific cytokines can be crucial in treating autoinflammatory and rheumatological diseases with a pulmonary involvement. Such conditions, although rare, should be early recognized as they can involve significant improvement with a properly targeted therapy. We face these conditions in a cherry-picking fashion picturing SAVI (STING-associated vasculopathy with onset in infancy), CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature), and COPA (coat proteins alpha syndrome) syndrome pulmonary involvement. Such examples are functional to introduce molecular-based approach for patients with rare conditions. Molecular plausibility can be highly valuable in treating patients with not-approved but possibly highly effective therapies. Due to the rarity of these conditions, we stress the concept of basket trials using the example of cytokinin-directed immunosuppressive treatment. Lastly, we provide an example of augmentative therapy using the alpha1 antitrypsin deficiency as a model. In summary, the article presents a collection of the most recent achievements and some possible future developments of target therapies for pediatric pulmonary conditions.

Keywords: biologics, pediatric pulmonology, asthma, innovative therapies, advances in pediatric pulmonology, molecular treatments, monoclonal antibodies, target therapies

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INTRODUCTION

The article aims at providing a comprehensive overview, although necessarily incomplete, of current biological treatments for asthma and other pulmonary conditions in children. The main focus will be set on molecular mechanisms, and in doing so, we will also discuss treatments that may be clinically applied in the next future. We searched PubMed and Scholar databases, limiting our consultation to the past 20 years and publications in English.

We consider it necessary to provide an adequate definition of biological treatment. Biopharmaceuticals are considered those drugs derived from a biological source, comprising somesthesis as well. This broad definition includes blood components, hormones, cellular therapies, and even gene therapies (1). In this, we decided to discuss only biological and target therapies that present an accurate and well-known interaction with a specific pathway in a key-lock mechanism, such as monoclonal antibodies.

SEVERE ASTHMA AND ENDOTYPES

Approximately 4–5% of asthmatic children present a severe disease. Severe asthma is defined as the need for high doses of inhaled corticosteroids (ICS) plus a second treatment to achieve symptoms control, or the persistence of symptoms despite such treatments. Therefore, this step-up approach modulated on the symptoms severity and clinical response results sometimes unsatisfactory (2).

Asthmatic symptoms are the consequence of broncho-obstruction and airway inflammation. However, the causative mechanism could be different in each patient. On this basis, it was introduced the concept of endotype characterization, aimed at specifying the molecular pathway that underlays each phenotype (3). Therefore, patients with a poorly responsive asthma may need an *ad-hoc* therapeutic approach. The endotype is the complex of the molecular and pathobiological mechanisms leading to the disease, while the phenotype is the categorization based on its clinical features (4).

Two major endotype categories of asthma are usually considered. T-helper type 2 cell high endotype (T2-High) is characterized by a T-helper inflammatory response with IL-4 (interleukin-4) and Il-13 (interleukin-13) release. Such cytokines lead to IgE production (class E immunoglobulin) and IL-5 (interleukin-5), which are proliferative and act as survival factors for eosinophils. T2-High markers commonly considered in the clinical practice are high fractional exhaled nitric oxide (FeNO) values, and elevated eosinophils count in blood, sputum, and airways.

T-helper type 2 cell low endotype (T2-Low) is characterized by a neutrophilic or pauci-granulocytic inflammation, with normal levels of eosinophils in blood sputum and airways. IL-1, IL-8, IL-17, and Il-23 are the molecules implied in this endotype (5). Often eosinophilic, and allergic asthma overlap due to partially shared biological pathways.

T2-HIGH ASTHMA

T2-High asthma is characterized by the activation and abundance of T-helper 2 that plays a crucial role in generating and maintaining eosinophilic inflammation through IL-4, IL-5, and IL13 production (6). Th2 cells, once activated, present the epitopes of the antigen to B cells and, together with IL-4 production and CD40/CD40L co-stimulation, induce their activation, leading to plasma cells formation, isotype switching to IgE, and their production (7). IgEs in atopic patients are both soluble and linked to mastocytes membrane through FC fragment leading to mastocytes degranulation in the presence of the antigens (8). Therefore, IgE can be a possible target for asthma with the predominance of allergic components marked by IgE elevation.

Like mast cells, basophils liberate histamine and PGD2 (plated derived growth factor 2), but they produce IL-4 as well (4).

ILC2s (innate lymphoid cells of group 2) are those that respond to DAMPs (damage-associated molecular patterns) producing IL-5 and IL-13. Such response leads to eosinophilia without an allergen-specific stimulation (9). Therefore, such a pathway can be targeted, inhibiting its products IL-5 or IL-13 indirectly. This type of inflammation can be suggested by eosinophilia in the absence of IgE elevation.

IL-4, IL-13, PDGF2, histamine, eosinophils degranulation causes smooth cells contraction, hypertrophy, collagen deposition in airway walls leading to airway remodeling (4). Therefore, in the cases of mixed patterns without a clear predominance of allergic mediated T2-High inflammation, we consider a valid option the inhibition of both IL-4 and IL-13.

T2-LOW ASTHMA

Nowadays T2-High endotype of asthma can be treated with several possible biological therapies, hitting different targets in the T2-High inflammation cascade. On the contrary, T2-Low asthma endotype does not present any approved biological treatment right now. To date there are no approved biological treatments for the T2-Low asthma endotype (10). This dichotomic classification (T2-High and T2-Low) is still useful although highly simplified.

Endo-typing of asthma went beyond T2-High and T2-Low inflammation revealing a more complex reality than the dual system previously considered mainstream. Several factors contribute to defining the asthma endotype of each patient, and they can be classified on the most predominant inflammatory process or the most prevalent inflammatory cell. Grouping these entities, 4 types of inflammation were defined: allergic eosinophilic asthma, non-allergic eosinophilic asthma, non-allergic paucigranulocytic asthma, and neutrophilic inflammation. It should be stressed that these four forms of inflammation should not be considered mutually exclusive and that eosinophilic asthma may overlap with the neutrophilic one, forming a mixed complex inflammation that is more frequent in adulthood (11).

T2-HIGH TREATMENTS

Nowadays, the T2-High endotype of asthma has several possible biological therapies, hitting different targets in the T2-High inflammation cascade.

Even if there are no studies comparing the different biologic therapies for the T2-High endotype of asthma, the patient's characteristics and drug features could help choose the most appropriate treatment for each specific case. We suggest a possible flow-chart to help the choice between biological treatments in T2-High patients (**Figure 1**).

Anti IgE Treatment

Omalizumab was the first biological treatment approved for the treatment of severe asthma, and it is currently recognized for the treatment of children 6 years or older. Omalizumab is a humanized IgG1 monoclonal antibody administered subcutaneously every 14–28 days. Omalizumab binds free IgE, preventing IgE from activating their receptor on the mast cells and basophils, thus reducing inflammatory molecules release. Considering its action, Omalizumab is used in patients affected by severe asthma with confirmed allergic sensitization. Omalizumab showed to reduce the number of exacerbations and the dose of inhaled corticosteroids. Previous studies on adults showed a better efficacy in patients with high FeNo, periostin and eosinophil count values (12). The patient's IgE levels are predictive of individual response. Patients with low values of IgE will only marginally benefit from omalizumab administration, whereases extremely high values of IgE could overcome the omalizumab binding power, still leaving a high level of free IgE (2, 12, 13). Omalizumab reduces to a half the risk of a severe asthma exacerbation in patients with asthma classified as moderate to severe for a total reduction from 26 to 16% of patients having an asthma attack annually and a reduction in hospitalization rate for asthma attack from 3.1 to 0.5%. Similar results were found for children with a reduction in asthma attacks of 31% in one study, a reduction of 23.7% of days with asthma in another, and the achievement of a completely controlled asthma in 52.6% more cases in the omalizumab group compared to placebo. Adverse events were significantly fewer in the omalizumab treated group than in the control group except for local reactions (14). Dosage is based on weight and IgE levels at baseline.

Anti IL-5 Treatment

Mepolizumab is a monoclonal antibody that binds IL-5, avoiding its activating action on eosinophils, and is approved for patients 6 years or older and with a peripheral blood eosinophil count $\geq$ 150/microL. Mepolizumab is administered subcutaneously every month and is currently the antibody of choice for non-allergic eosinophilic asthma, that is quite rare, especially in children. It often represents a very difficult endotype to treat, requiring frequent oral corticosteroids. Mepolizumab reduces the number of exacerbations and the need for oral corticosteroids and is particularly effective in patients with marked eosinophilia. Mepolizumab's safety and pharmacodynamic were tested in patients 6–11 years with a good safety profile (15–18). The expected reduction in annualized exacerbation rate is reported to be 69% in children with severe asthma and eosinophilic phenotype (17), higher than the reduction reported for a similar population of adolescents and adults (19). Mepolizumab dose is 100 mg every 4 weeks except for patients aged 6–11 years with $<$40 kg of body weight who receive 40 mg of mepolizumab every 4 weeks (18). Other dosages of mepolizumab were tested effective and safe over the age of 12 administered intravenously (75, 250, and 750 mg every 4 weeks) (20).

Reslizumab has the same action as mepolizumab. It is administered intravenously 3 mg/kg of body weight every 4 weeks and has proved to be effective in reducing the number of asthmatic exacerbations by about a half. However, reslizumab is not approved in the pediatric population (21, 22).

Benralizumab is slightly different; it binds the IL5 receptor (IL-5R) on the eosinophils and basophils surface, inducing apoptosis. Benralizumab can be prescribed in patients older than 12 years, with a peripheral blood eosinophil count $\geq$ 150/microL. In SIROCCO study benralizumab obtained a 55% reduction of exacerbations and has shown to be more effective in patients with a high number of exacerbations per year. Benralizumab leads to profound eosinophils reduction. Like mepolizumab, benralizumab is administered subcutaneously but every 8 weeks (23–25).

Overall, in adolescents and adults, mepolizumab, reslizumab and benralizumab present a reduction in the number of severe asthma attacks of around 50%. The safety profile is optimal with no excess of severe adverse events and a similar discontinuation rate in the placebo groups, except for reslizumab that presents slightly more discontinuations in the treatment group (25).

Anti IL-4 and IL-13 Treatment

Dupilumab is a monoclonal antibody that binds the interleukin-4 receptor (IL-4R), inhibiting the IL-4 and IL-13 molecular pathways that present a pivotal role in the Th-2 differentiation. Dupilumab initially approved for atopic dermatitis, had recently obtained approval for its use in patients older than 12 years, with severe asthma and high FeNO or peripheral blood eosinophil count $\geq$ 150/microL. This biological treatment showed to reduce the asthmatic exacerbation rates and the dose of oral corticosteroids as opposed to placebo (26). Dupilumab is also effective in cases with elevated FeNo in the absence of eosinophilia, suggesting an IL-13 role in this kind of patient (27). A recent trial reported the efficacy and safety of dupilumab in moderate to severe asthma patients aged 6–11 years (28).

NEUTROPHILIC ASTHMA

Neutrophilic asthma is the most common form after the eosinophilic one. Two cytokines are commonly involved in neutrophilic asthma: IL-1 and IL-17 (11, 29, 30), possibly due to deficiency in anti-inflammatory mechanisms (31). Promisingly, IL-1 receptor antagonist (anakinra) administration reduces the rise of sputum neutrophilia in healthy adults exposed to endotoxin. Neutrophil reduction is associated with IL-6, IL-8, and IL-1β decrease (32). COVID-19 related concerns interrupted a trial investigating the administration of a single dose of anakinra immediately after the exposure to an allergen in

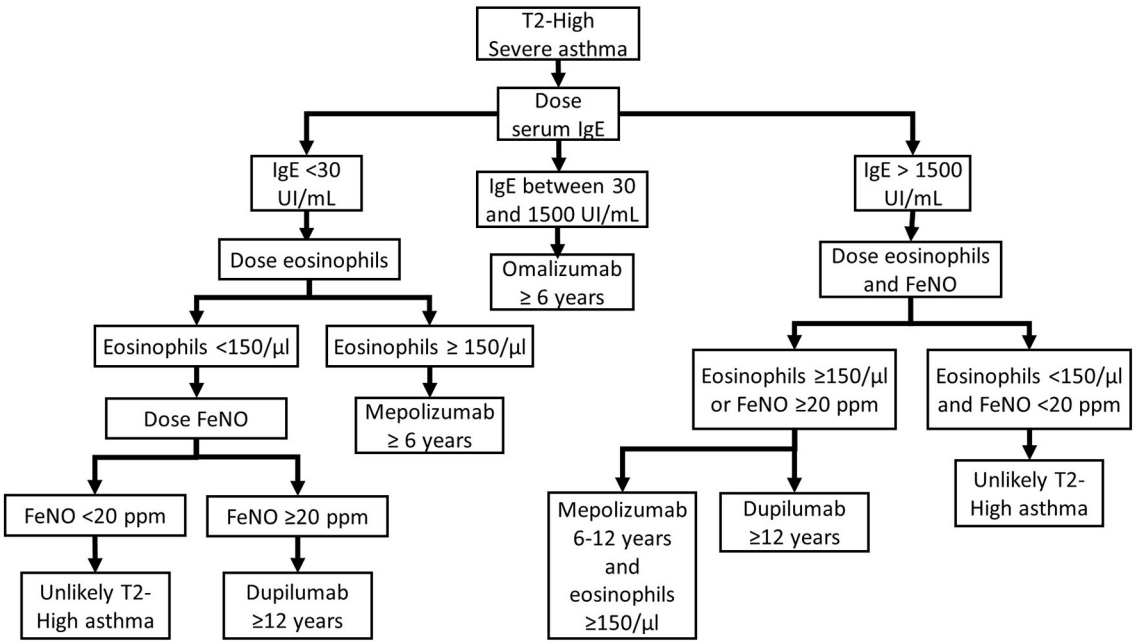

FIGURE 1 | T2-High asthma biologic treatment flow-chart.

adults affected by mild allergic asthma (https://clinicaltrials.gov/ct2/show/NCT03513458). Canakinumab was demonstrated to be effective in a similarly designed trial (33). It acts on the same pathway of anakinra, but directly locking the IL-1 with a remarkably longer half-life. Although the role of the inflammasome, and IL-1, is well recognized in acute allergic manifestations (34), allergic asthma remains mainly driven by IL-5 and IL-12. In our opinion, this evidence highlight the urge for randomized therapeutic studies outside the eosinophilic forms of asthma with inclusion and exclusion criteria focused on endotypes in adults and children.

ANTI-IL17 TREATMENT

As aforementioned, the IL-17 cascade is deeply involved in neutrophilic asthma (11). Technically speaking, IL-17 belongs to the family of proinflammatory cytokines highly conserved through different species that chemoattracts neutrophils and monocytes. IL-17 has a huge role in inducing and maintaining this type of inflammation, especially in autoimmune diseases, such as psoriasis and ankylosing spondylitis (35, 36). Different forms of IL-17 play different roles in the various phases of inflammation, with IL-17A prevalence as proinflammatory and IL-17F predominance during resolution (37). The different affinity for the various IL-17 receptors leads to the activation of different receptors and results in an opposite contribution of these molecules, part of the same family (38). IL-17A is produced by macrophage, mainly in response to IL23, which is fundamental for the differentiation and survival of T-helper lymphocytes-17 (Th-17) which, in turn, are pivotal in mucosal inflammation producing IL-17, IL-21, IL-22, and GM-CSF (39). Such kind of IL-17 driven inflammation is also involved in allergies and asthma (40) but it is possible to be secondary to the mucosal damage caused by T2-High inflammation. Because of this whole body of considerations, the IL-17 cascade is a remarkable target for future treatments of neutrophilic asthma, especially in children who present a high count and proliferation of Th-17 in the induced sputum (41). In September 2021, we started secukinumab in a patient affected by psoriasis who presented moderate-severe asthma with constantly low expiratory nitric oxide as a sign of non-eosinophilic asthma. After the start of the treatment, his quality of life improved, by reducing acute treatment needs (unpublished data). Secukinumab is a monoclonal antibody that binds IL17A approved for moderate to severe psoriasis, psoriatic arthritis, and some forms of spondylitis from 6 years (42).

ANTI-IL-12 AND ANTI-IL-23 TREATMENTS

Inhibition of IL23 with Risankizumab was proven ineffective and even harmful in adults with severe asthma (43). Once more, in this study, the eosinophilic inflammation was prevalent and confirmed the need for further studies focused on non-eosinophilic asthma.

Only one case was published, reporting a remarkable improvement in neutrophilic asthma receiving ustekinumab for severe psoriasis. Ustekinumab works upward in the IL-17 cascade and inhibiting IL23, lowering IL-17 production and the Th-17 recruitment. Ustekinumab binds IL12 as well, determining a reduction in Th1, natural killer, and cytotoxic lymphocytes activity making ustekinumab a possible effective drug for neutrophilic asthma (30).

INTERSTITIAL AND AUTOINFLAMMATORY DISEASES

Under the classification of children's interstitial lung diseases (chILD) fall hundreds of different conditions leading to interstitial involvement and are often extremely difficult to treat. A tiny minority of chILD present an underlying genetically determined systemic autoinflammatory disease (44). As we mentioned in the previous section, a treatment directed against specific cytokines or their receptors can shut down or mitigate specific inflammation forms. We will see three different conditions causing chILD, that share high levels of type I interferon. A summary of the molecular basis of such conditions is reported in **Figure 2**.

SAVI SYNDROME

STING (stimulator of interferon gene)-associated vasculopathy with onset in infancy (SAVI) is a systemic autoinflammatory disease caused by a mutation in the STING gene, causing its constitutive activation resulting in an autosomal dominant disease in nearly all cases. STING protein is located in the endoplasmic reticulum, and its activation is part of the early innate response to the viral infections (45) and bacterial infections, especially the intracytoplasmic ones (46). STING activation causes interferon type I releases (alpha and beta interferons) that bind the Janus Kinase (JAK) membrane receptor inducing its dimerization and activating the JAK-STAT pathway. JAK-STAT pathway has a broad action on several genes activation and transcription, determining the cellular response to interferons and other cytokines (45). SAVI syndrome is characterized by vasculitis urticaria that is usually severe, cold-sensitive, leaves scars, and is even worse on the extremities. Polyarthritis is so aggressive to induce ulcerations and, after that, autoamputations in most of the untreated cases. The pulmonary involvement is precocious, characterized by dry cough due to the chILD, and often jointly with the inflammatory status leads to a marked failure to treat (47, 48).

CANDLE SYNDROME

Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE), formerly known as Nakajo–Nishimura syndrome, is another monogenic condition caused by the PSMB8 gene encoding for a protein of the proteasome. PSMB8 encodes for immunoproteasome subunit β5i and, together with other mutations of the immunoproteasome, are grouped within the proteosome-associated autoinflammatory syndromes (PRAASs). PRAASs determine the ineffectiveness of the immunoproteasome with a consequent increase of old and misfolded waste proteins. Therefore, the cell responds by increasing interferons that usually activate and assemble the immunoproteasome. The lack of immunoproteasome effectiveness leads to a vicious circle in which type I interferon levels rise uncontrolled (49). CANDLE presents an autosomal recessive inheritance pattern and is clinically characterized by recurrent fever, neutrophilic dermatosis that leave purpuric scars, microcytic anemia, arthralgia leading to contractures in the long term. Lipodystrophy is usually severe and can be considered a landmark of the condition in the advanced stage of the disease (50). Pulmonary involvement is characterized by chILD and is usually less severe than for SAVI but may cause pulmonary hypertension. Early symptoms usually appear within the first weeks to 6 months of life (51).

COPA SYNDROME

Coat proteins alpha (COPA) syndrome is an autosomal dominant condition caused by a mutation in a gene encoding for a coatomer protein. More specifically, COPA participates in Coatomer Protein I (COPI) assembly, which is crucial for the backward trafficking of the proteins between the Golgi vesicles and from the Golgi apparatus to the endoplasmic reticule, leading proteins to stuck in the Golgi. An incorrect assembly of coated vesicles impairs the trafficking with a consequent intracellular stress and, therefore, interferon pathway activation, but also IL-1B and IL-6 release with Th-17 proliferation (52). Clinical features are dominated by arthritis and pulmonary fibrosis that may or may not arise before the articular symptoms and leads to progressive lung function decline. In nearly 50% of cases, pulmonary hemorrhage occurs, and it can be life-threatening. Both big and small articulations usually develop arthritis. Nephritis should always be searched and may lead to chronic kidney insufficiency. Occasionally optic neuromyelitis and avascular necrosis of the femoral head were described (53).

IDENTIFYING A SINGLE TARGET FOR ALL THREE DISEASES

Small molecules are usually designed to present a key-lock action, with very narrow or no effects on other pathways. Such medicines are generally obtained by full chemical synthesis and therefore are not biologics (54). Such a precise key-lock mechanism may lead to the misconception of a single extremely precise drug for each specific disease. On the contrary, the key-lock inhibition of a single molecule may be crucial for different pathways if they converge on the inhibited molecule (55). We will use the example of the three above-mentioned different genetic diseases caused by three different genes and clinically heterogeneous (SAVI, CANDLE, and COPA). All three share the type I interferon as a main standing effector of the inflammation in the final part of their cascade (56). Therefore, the inhibition of the interferon type I effector pathway was explored. Type I interferon acts through the JAK signal transducer and activation of transcription (STAT) pathway (JAK-STAT pathway) that is the effector of the cytokine receptors and several other receptors leading altogether to an extremely broad type of intracellular responses. JAK-inhibitors can specifically target a single type of JAK. In some cases, the inhibition of two JAKs type at once can be preferable

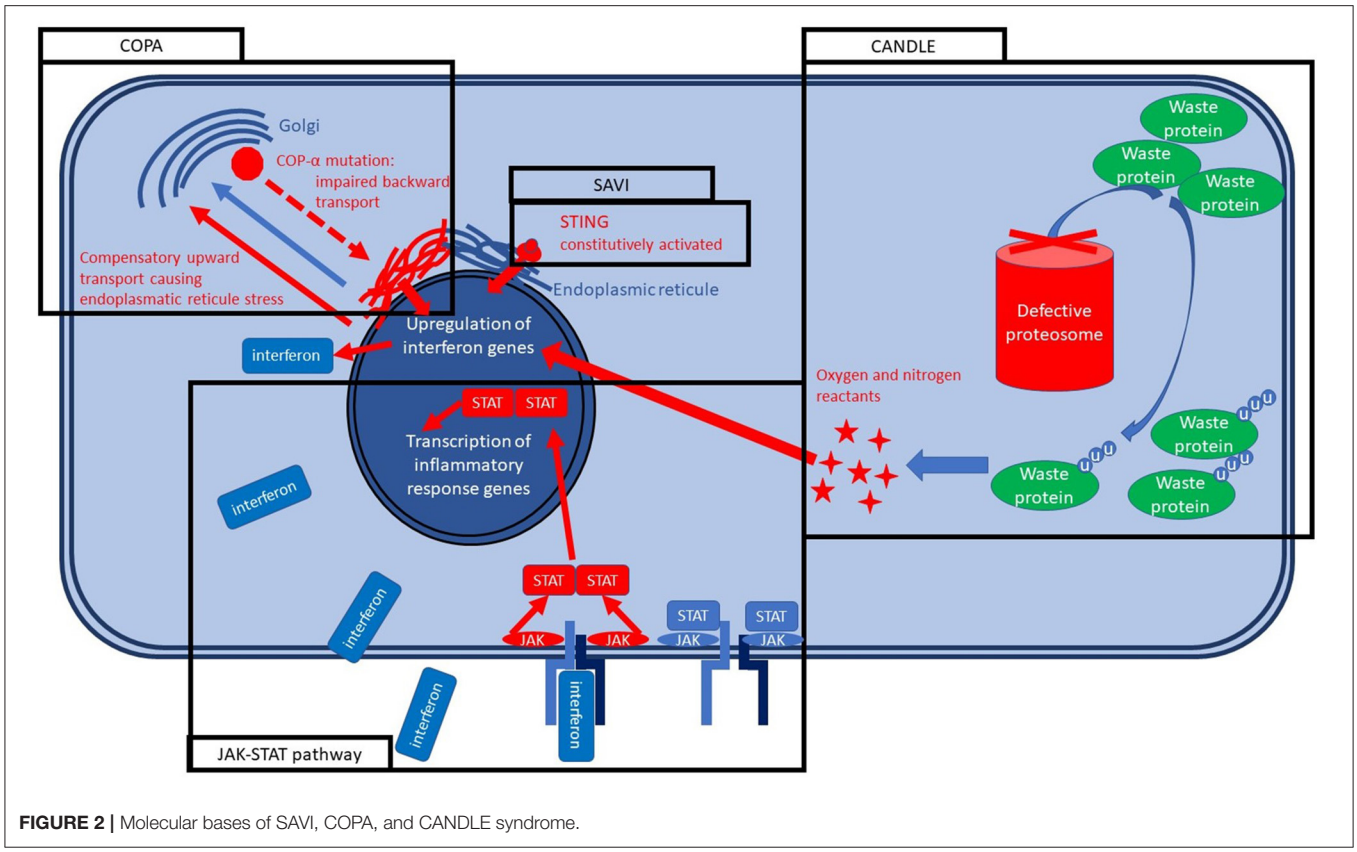

FIGURE 2 | Molecular bases of SAVI, COPA, and CANDLE syndrome.

as for baricitinib and ruxolitinib that inhibit both JAK1 and JAK2. Both were effectively tried in all three diseases with dramatic improvements.

BASKET TRIAL

This concept of inhibition of a single molecule key for several diseases went so further that recently trials were approved to test the effectiveness of one single target therapy for different diseases at once. Most of such trials are oncological ones, but IL-1inhibition was also tested in this specific study design called basket trial (57, 58).

AUGMENTATION THERAPY

Augmentation therapy provides a homologous of a defective molecule (usually an enzyme) to keep its function within a tolerable range to avoid the progression of the disease caused by a molecule deficiency. Such type of therapy is broadly diffused in metabolic medicine but is also used for some immunodeficiencies from hypogammaglobulinemia to the Adenosine DeAminase Severe Combined Immune Deficiency (ADA-SCID). Augmentation therapy is part of the common practice of adults' pneumologists to treat alpha-1 antitrypsin deficiency. This therapy is administered intravenously weekly when serum levels are confirmed under 11 μM (80 ng/mL), and FEV1 is reduced to 35-70% of the predicted value (59) or in the presence of a rapidly evolutive condition. Alpha-1 antitrypsin deficiency is usually clinically manifested due to hepatological involvement (60) but in rare cases, patients may present even severe pulmonary emphysema already in childhood. Specific mutations, null and Z, account for low or zero serological levels of alpha-1 antitrypsin, respectively (61), leading to an earlier onset of pulmonary emphysema. Very few pediatric cases of alpha-1 antitrypsin were treated with augmentation therapy (62).

CONCLUSIONS

Target therapies are rapidly changing pediatric pulmonology, causing a turning point in the patients' care. Such a shift in the mindset of clinical approach is ongoing and led to the need for a biologically precise diagnosis to administer the correct *ad-hoc* therapy that may be even more challenging. As a result, some of the classical randomized controlled trials designed to treat a disease may be inconclusive due to various underlying biological mechanisms. The obvious risk is the fragmentation of the study population with a consequent extreme difficulty in reaching the sample size for clinical studies exploring therapies for each biological cascade. Obtaining an adequate sample size will be even more challenging in the pediatric population. The concept of basket trial may be a possible partial answer to reach the necessary sample size for such studies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

SG, MM, AD, and FP drafted the manuscript. NU, MC, and RC reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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Breathing Patterns and Oxygenation Saturation During Sleep in Children Habitually Living at High Altitude in the Andes: A Systematic Review

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Background: Human respiratory physiology changes significantly in high altitude settings and these changes are particularly marked during sleep. It is estimated that 170 million people live above 2,500 m in environments where normal sleep parameters differ from those established at sea level or low altitude.

Methods: We conducted a systematic review of publications reporting sleep studies in healthy children living at high altitude. For this purpose, data from PubMed, EMBASE, SciELO and Epistemomikos bases were retrieved up to August 2021.

Results: Six articles met specified inclusion criteria; all reporting data were from South America involving 245 children (404 sleep studies) in children aged 0.6 months to 18 years, at altitudes between 2,560 to 3,775 m. The main results were: (1) Central apnea index decreased as the age increased. (2) The obstructive apnea/hypopnea index showed a bimodal profile with an increase in young infants up to age of 4 months, decreasing to 15 months of age, and then a second peak in children aged 4 to 9 years of age, dropping in older schoolchildren and adolescents. (3) Periodic breathing in the first months of life is more marked with increasing altitude and decreases with age.

Conclusions: There are few studies of sleep physiology in children living at high altitude. The international parameters defining normal apnea indices currently used at low altitude cannot be applied to high altitude settings. The interpretation of sleep studies in children living at high altitude is complex because there are important developmental changes across childhood and a wide range of altitude locations. More normative data are required to determine thresholds for respiratory pathology at a variety of high altitude settings.

Keywords: sleep, high altitude, apnea—hypopnea index, polysomnography, children

INTRODUCTION

In the last three decades sleep medicine has made great progress and normal sleep normal parameters for central and obstructive apneic events (both in terms of how they are defined as well as age-specific normal values) are well-established in children living at low altitude (1–3). These values, obtained through polysomnography or cardiorespiratory polygraphy (hereon termed "sleep studies"), are a basic tool for the diagnosis of sleep disordered breathing (SDB). However, these normative values cannot be applied to high altitude where sleep physiology changes (4–9). An estimated 170 million people live at high altitude that is, living 2,500 m or more above sea-level (10). In this paper we review sleep studies conducted in healthy children and adolescents at altitudes above 2,500 m in order to inform the medical evaluation and treatment of SDB in children resident at high altitude.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to perform this review (11). We identified published studies in MEDLINE, EMBASE, SciELO and EPISTEMONIKOS databases (up to August 2021), using the terms: "Sleep in children at high altitude" OR "Polysomnography in children at high altitude" OR "Polysomnography in children above sea level" OR "Respiratory sleep polygraphy in children at high altitude" OR "Respiratory sleep polygraphy in children above sea level" restricted to child (birth to 18 years old), without language restriction. Studies published solely in abstract form were excluded because the methods and results could not be fully analyzed.

To be included, studies had to meet all the following criteria: (I) cross-sectional or cohort studies; (II) inclusion of children from birth to 18 years of age) or in a mixed population (adults and children) if children were analyzed separately; (III) experimental or intervention studies where a polysomnography or polygraphy was undertaken in healthy children living above 2,500 m sea level. Exclusion criteria were studies of children with SBD, craniofacial malformations, genetic respiratory and neurological diseases. Only studies of children expected to be acclimatized were included, for this reason research related to sojourners was excluded. Reviews and letters to the editor (without data reports) were also excluded.

Data extraction and assessment of risk of bias: Titles, abstracts, and citations were independently analyzed by three authors (S.U., J.C.G, and J.C.R.). Based on the full text form, all the studies were evaluated for inclusion criteria, population included, study design, and outcomes. After obtaining full reports about potentially relevant studies, eligibility was assessed. Disagreements were discussed and resolved by consensus, and when necessary, advice was sought from the fourth reviewer (C.M.H.). A prespecified data analysis included year, location, number of participants, age, and type of sleep study (polysomnography/polygraphy). Parameters included were central apnea index (CAI), obstructive apnea/hypopnea index (OAHI), oxygen desaturation index (ODI) either of 3% or 4%, periodic breathing % (PB), microarousal index and CO_2 values, with their central and dispersion values. Additionally, we compared our data with sleep parameters from sea level or low altitude studies (1, 2, 12, 13).

RESULTS

One hundred and forty-four studies were retrieved from the databases, of which 6 were eligible for inclusion (**Figure 1**). All articles included were from research conducted in Andean regions of South America: two in Colombia, two in Ecuador, one in Argentina and one in Bolivia (4–9). The age range was 0.6 months to 16 years, and altitudes were between 2,560 to 3,775 m above sea level. A total of 245 children underwent 404 sleep studies (**Table 1**).

In **Tables 2–4** normal sleep parameters are presented according to age and altitude. During the first months of age the CAI increased as the altitude was higher and decreased with age, delivering the same normative values from the sea level in children 4 to 9 years old at 2,560 m, and in those 7 to 13 years old, at 3,650 m (**Table 2**). The OAHI showed a bimodal profile with an increase in young infants, in comparison with low altitude, a further decrease in infants up to 15 months, a new rise in children 4 to 9 years of age, and again a drop in older scholars and adolescents (**Table 3**). PB was only seen in the first 4 months of age, and it increased with increasing altitude (**Table 4**).

Oxygen desaturation index was higher in children 4–9 years old resident at high altitude at 2,560 m compared to similar age children at low altitude. In children 7–10 years of age living at 3,700 m a high ODI was also found (see **Supplementary Table 2**). With respect to CO_2, one study reported transcutaneous measures, with a median value of 39.4 in 32 children from 4 to 9 years of age at 2,560 m of altitude (see **Supplementary Table 2**). Two studies reported microarousals; at 2,640 m microarousals had a median of 19/h in infants 1.0 $\pm$ 0.3 months of age with a decrease to 9.5/h in those 13.2 $\pm$ 1.9 months old (6); at 3,650 m a median of 5.5 was found in a group of 26 children 7–10 and 13–16 years of age.

DISCUSSION

In this systematic review, we report sleep studies in healthy children resident at various high-altitude locations in the South American Andean region. Important differences were found in all indices compared to published normative values at low altitude, except for transcutaneous CO_2 values. As follows we discuss these findings and their implications.

Central apnea index was apparently increased in infants up to 4 months of age at 2,560 m, 2,640 m, and 3,200 m. Nevertheless, when the events associated with PB were discounted, the CAI values from sea level and high altitude were similar (see **Supplementary Table 1**); although at 3,650 m, where PB was not seen in schoolchildren and adolescents, a trend toward more central apnea was found (7). In relation to OAHI, values were higher than normative values in infants up to 6 months of age at 2,640 m (6), in children 4 to 9 years old at 2,560 m (9), and

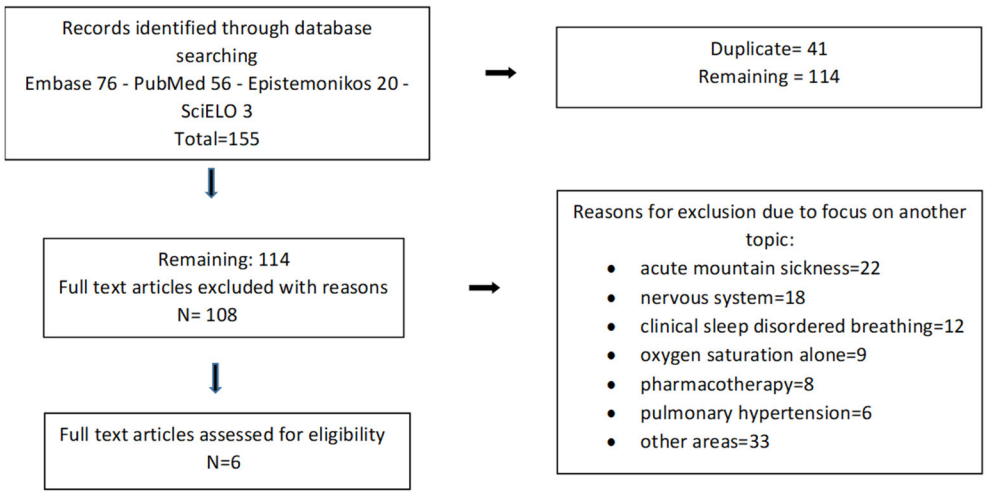

FIGURE 1 | Process of study selection.

TABLE 1 | Sleep studies in children living at high altitude.

References	Settlement	Altitude	*n*	Age	Study design	Type of sleep study	Scoring criteria
Alducín et al. (4)	San Antonio de Los Cobres—Argentina	3,775 m	12	0.6–7.7 months	Prospective cross sectional	Polysomnography	AASM, 1992
Ucrós et al. (5)	Cuenca—Ecuador	2,560 m	35	1–4 months	Prospective cross sectional	Polysomnography	AASM, 2012
Dueñas-Meza et al. (6)	Bogotá—Colombia	2,640 m	122*	0.7–15 months	Prospective cohort	Polysomnography	AASM, 2012
Hill et al. (7)	La Paz—Bolivia	3,650 m	26	7–10 years & 13–16 years	Prospective cross sectional	Polysomnography	AASM, 2007
Ucrós et al. (8)	Cañar—Ecuador	3,200 m	18	1–4 months	Prospective cross sectional	Polysomnography	AASM, 2012
Ucrós et al. (9)	Chiquinquirá—Colombia	2,560 m	32	4–9 years	Prospective cross sectional	Polygraphy	AASM, 2012

*Altitude given in meters above sea level. *Involved 281 sleep studies. AASM, American Academy of Sleep Medicine.*

TABLE 2 | Central apnea index (CAI) according to altitude and age.

References	Settlement	Altitude	Age	CAI/h—Median—Dispersion
Ucrós et al. (5)	Cuenca Ecuador	2,560 m	1–4 months	23.7 (p5 0.9–p95 130.2)
Ucrós et al. (9)	Chiquinquirá—Colombia	2,560 m	4–9 years	0.4 (p5 0–p95 2.4)
Dueñas-Meza et al. (6)	Bogotá—Colombia	2,640 m	1.0 ± 0.3 months	12.4 (p5 2.2–p95 65.4)
Dueñas-Meza et al. (6)	Bogotá—Colombia	2,640 m	3.6 ± 0.5 months	8.3 (p5 1.6–p95 50.7)
Dueñas-Meza et al. (6)	Bogotá—Colombia	2,640 m	6.6 ± 0.6 months	5.5 (p5 0.8–p95 17.8)
Dueñas-Meza et al. (6)	Bogotá—Colombia	2,640 m	13.2 ± 1.9 months	2.3 (p5 0.7–p95 8.7)
Ucrós et al. (8)	Cañar—Ecuador	3,200 m	1–4 months	30.5 (p5 8.8–p95 217.5)
Hill et al. (7)	La Paz—Bolivia	3,650 m	7–10 y 13–16 years	0.7 (IQR)

Altitude given in meters above sea level. p, percentile; IQR, interquartile range.

in older children and adolescents at 3,650 m (7). It has been proposed that this increase does not reflect genuine underlying airway obstruction, rather a lower threshold for categorization of hypopnoeic events that are scored when associated with oxygen desaturation. As children at high altitude have lower baseline SpO_2 values, smaller fluctuations in underlying respiratory physiology results in larger dips leading to more events reaching scoring criteria (9). This is further supported by our findings of an

TABLE 3 | Obstructive apnea/hypopnea index (OAHI) according to altitude and age.

References	Settlement	Altitude	Age	OAHI Median—Dispersion
Ucrós et al. (9)	Chiquinquirá—Colombia	2,560 m	4–9 years	8.8 (p5 1.21–p95 21.2)
Dueñas-Meza et al. (6)	Bogotá—Colombia	2,640 m	1.0 ± 0.3 months	6.8 (p5 0.6–p95 27.6)
Dueñas-Meza et al. (6)	Bogotá—Colombia	2,640 m	3.6 ± 0.5 months	3.5 (p5 0.3–p95 15.1)
Dueñas-Meza et al. (6)	Bogotá—Colombia	2,640 m	6.6 ± 0.6 months	0.9 (p5 0.0–p95 4.9)
Dueñas-Meza et al. (6)	Bogotá—Colombia	2,640 m	13.2 ± 1.9 months	0.5 (p5 0.0–p95 1.8)
Hill et al. (7)	La Paz—Bolivia	3,650 m	7–10 years & 13–16 years	2.1 (IQR 3.5)

Altitude given in meters above sea level. OAHI, Obstructive apnea/hypopnea index; p, percentile; IQR, interquartile range.

TABLE 4 | Periodic breathing (PB) values according to altitude and age.

References	Settlement	Altitude	Age	PB Median–Dispersion
Ucrós et al. (5)	Cuenca—Ecuador	2,560 m	1–4 months	4.9% (p5 0.2%–p95 46.8%)
Ucrós et al. (8)	Cañar—Ecuador	3,200 m	1–4 months	7.2% (p5 1.2%–p95 78.7%)
Dueñas-Meza et al. (6)	Bogotá—Colombia	2,640 m	1.0 ± 0.3 months	2.0% (p5 0%–p 95 21.9%)
Dueñas-Meza et al. (6)	Bogotá—Colombia	2,640 m	3.6 1 ± 0.5 months	0.9% (p5 0%–p 95 5.7%)
Hill et al. (7)	La Paz—Bolivia	3,650 m	7–10 y 13–16 years	0% (IQR)

Altitude given in meters above sea level. p, percentile 95; IQR, interquartile range.

increase in ODI at high altitude in comparison with low altitude in all the three studies which reported this value, increase that has even been reported at 1,600 m (12) (see **Supplementary Table 2**).

The rise in OAHI and ODI are particularly important in the age when adenoids and tonsils growth can be associated with obstructive apnea/hypopnea. Treatment thresholds for adenotonsillectomy are based on a combination of clinical findings and sleep study results. In children at high altitude the latter may be misleading if based on low altitude normative data. Normal OAHI and ODI values for age, and altitude where the child lives, should be used; otherwise, children with normal parameters will receive inappropriate treatment with all the inherent health and economic implications.

Only one study measured CO_2 using transcutaneous measures. Values were only slightly lower than those seen at 1,600 m (12) and at low altitude level (13) (see **Supplementary Table 2**). On the other hand, the CO_2 median (39.4 mm/Hg) was significantly higher than the value around 33.0 mm/Hg seen in blood gases in healthy adults at 2,640 m (14). This difference could be explained by different measurement techniques and the fact that the adult data were measured when awake while children were sampled during sleep. Further data is needed to determine normative values at high altitude, with calibration of transcutaneous or end-tidal measures with arterial values. This is particularly important to guide treatment in children monitored in high altitude pediatric intensive care settings.

Infants at high altitude experienced more PB than typically reported at sea level. During sleep at high altitude hypoxia may induce PCO_2 drops below the apneic threshold (15). PB is seen at low altitude in healthy infants in the first months of life and disappears after 4 to 6 months of age, both at low (3) and high altitude at least up to 2,640 m (6). This is probably related to central nervous system (CNS) maturation (3). However, in young infants living at high altitude, the percentage of PB is higher in comparison with low altitude (5, 6, 8). It has been suggested that some individuals are prone to PB because CNS oxygen receptors have increased chemosensivity to hypoxia (15). Although some authors classified high altitude PB as a disease (15, 16), there is no evidence that PB *per se* is a pathological condition in infants (3). It is also important to underline that high altitude PB should not has to be confused with idiopathic central sleep apnea, an extremely rare disorder (15). Information about microarousals during sleep in children living at high altitude is particularly scarce. What can be said is that the current international guidelines do not apply at 2,640 m, for young infants who had a median microarousal index of 19/h.

Regarding the issue of attention and neurocognition it is recognized that intermittent hypoxia is a key pathway by which obstructive sleep apnea/ hypopnea can cause impairment (17–20). Given the fact that SpO_2 decreases as altitude increases, and that the gap is wider during sleep (21), it would be expected this impairment would be a rule in children living at significant hypoxic environments. Nevertheless, the literature does not support this statement, as demonstrated by Virués-Ortega et al. (22) who reported in 41 children aged 6 to 16 years that attention skills did not differ significantly between low altitude and 3,700 m; indeed, only subtle neurocognitive differences impacts were seen. Only at higher altitudes of 4,100 m a negative outcome was found related with executive functions in a group of 8 children and 13 adolescents (22). This is perhaps surprising as the neurocognitive effects of SDB would be predicted to be more marked at high altitude due to the combination of an intermittent hypoxia in addition to basal hypoxia (7, 21, 23). The preliminary data infer a protective or adaptive mechanism in these high-altitude child populations (24).

Finally, it is important to underline that the interpretation of sleep studies at high altitude is complex because there are important developmental changes in sleep physiology and among the different ranges of altitude. Importantly however, the practice of applying normative data to interpret sleep studies based on American Academy of Sleep Medicine (25) and European Sleep Medicine guidelines (26) is flawed and such an approach would cause a significant proportion of healthy children to be erroneously diagnosed with SDB.

Limitations of This Review

This review was limited by the relative paucity of studies describing normal sleep parameters in children living at high altitude and by small sample sizes for most included studies. Secondly all the publications found were conducted in the Andes mountains in South America. This issue is important because evolutionary adaptation of the human being to high altitude differs in Asia in comparison with South America (27). The findings of this systematic review should not be extrapolated to regions different from South America but likely strengthens the findings for the Andean region. Third, one study used polygraphy instead of polysomnography (9), in consequence in this research a proportion of hypopnea events could have been missed leading to under-estimation of obstructive apnea/hypopnea indices.

CONCLUSIONS

There are few studies of sleep physiology in children living at high altitude. The parameters currently used at low altitude cannot be applied to high altitude. The interpretation of sleep studies in children living at high altitude is complex because there are important changes as across the different groups of age as well as across the ranges of altitude. Further large-scale populations studies are warranted at multiple altitude locations to confidently define normal parameters.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

SU and JC-R contributed to the study concept, literature search, data collection, and manuscript writing. JC-G contributed to the literature search. CH contributed to the literature search, review the manuscript, and incorporated significant thought. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2021.798310/full#supplementary-material

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Implementation of a Children's Safe Asthma Discharge Care Pathway Reduces the Risk of Future Asthma Attacks in Children–A Retrospective Quality Improvement Report

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Background: Many children attend Emergency Departments (ED) and Out of Hours (OoH) frequently for acute asthma. Follow up care is often suboptimal leaving these children at risk of a future attacks. We report on the development, implementation and evaluation of a safe asthma discharge care pathway (SADCP).

Methods: This is a retrospective report on the development, implementation and evaluation of outcomes of a SADCP. The pathway was based on the Teach-to-goal educational methodology that supported the mastery correct inhaler technique and ability to action the personalized asthma action plan (PAAP). Children with frequent asthma attacks were entered as they were discharged from the Emergency Department or ward. The first training session occurred within 1–3 weeks of the index asthma attack with 2 further sessions in the following 8 weeks. Children exiting the pathway were discharged either back to primary care or to a hospital clinic.

Results: 81 children entered the pathway (median age 5 years) with 72 discharged from the ED and 9 from the medical wards of the Royal Belfast Hospital for Sick Children. At pathway entry 13% had correct inhaler technique, 10% had a Personalized Asthma Action Plan (PAAP), and 5% had >80% (45% >50%) repeat refill evidence of adherence to inhaled corticosteroid over the previous 12 months. On pathway exit all children demonstrated correct inhaler technique and were able to action their PAAP. One year later 51% and 95% had refill evidence of >80% and >50% adherence. Comparisons of the 12 months before and 12 months after exit from the pathway the median number of emergency ED or OoH asthma attendances and courses of oral corticosteroids reduced to zero with >75% having no attacks requiring this level of attention. Similar findings resulted when the SADCP was implemented in a district general hospital pediatric unit.

Conclusion: Implementing an asthma care pathway, using Teach-to-Goal skill training methods and frequent early reviews after an index asthma attack can reduce the future risk of asthma attacks in the next 6 to 12 months.

Keywords: asthma attack, discharge care pathway, Teach-to-goal, inhaler technique, understanding action plan

INTRODUCTION

An asthma attack in the previous year is a predictor of a future asthma attack (1, 2). A significant percentage of children are re-admitted within a short time period after having an asthma attack which required hospitalization. In-addition, recurrent asthma attacks is a common reason for multiple crisis attendances at the Emergency Department (ED) (3, 4). The British Thoracic Society (BTS) asthma guidelines and National Review of Asthma Deaths (NRAD) report recommend that adults and children with asthma are seen in primary care within 1–2 days of an acute attack and by 4 weeks with a specifically trained asthma specialist in Secondary Care (5, 6). The NRAD reported that 10% of asthma deaths occurred within 28 days of hospital discharge and 21% had attended the ED in the previous year with more than half of these having attended more than once. Therefore, the NRAD report made the strong recommendation that follow-up arrangements should be made after every attendance at an ED or out-of-hours (OOH) service. Secondary care follow-up should be arranged after every hospital admission for asthma and for patients who have attended the ED two or more times with an asthma attack in the previous 12 months. Thus systems should be in place to facilitate the appropriate movement of patients from the acute setting into an asthma care program (6–8). Red flags for the prediction of potential asthma deaths in the NRAD report included; (a) incorrect inhaler technique, (b) non-adherence to preventer therapy, (c) absence of a Personalized Asthma Action Plan (PAAP), and (d) on-going exposure to asthma triggers. The basics of good asthma care that address these red flag are not in place for more than half of asthma patients in N Ireland and in even fewer in mainland Great Britain (9).

The regular use of inhaled corticosteroids taken with correct inhaler technique forms the pharmacological backbone of asthma therapy and ensuring the basics of asthma care are in place should bring both better day-to-day asthma control and reduce the risk of a future attack for most children (10). PAAPs typically state which treatments are required when the child is: (1) stable (e.g., regular adherence to preventer medication, Green zone), (2) action which should be taken at the start of an exacerbation or when asthma control has deteriorated (e.g., a head cold with increased coughing and the start of wheezing, Amber zone), (3) how to manage an acute attack of asthma (red zone). Having an up-to-date PAAP as part of supported self-management of asthma has previously been shown to be beneficial (11). It is important to ensure understanding of, and the ability to action, the written PAAP (green, orange, red zones) as well as understanding when and why to take each medication.

The Royal Belfast Hospital for Sick Children (RBHSC) provides tertiary pediatrics for N. Ireland (population approximately 1.9 million) and acute secondary care for the children of Belfast with typically 20–30 acute asthma admissions each winter month. On average 180 children with acute asthma attacks attend the ED in each of the winter months and more than 50 in each of the summer months. In 2009 the Public Health Agency of the Department of Health Social Services N Ireland (PHA, DHSSNI) conducted an audit of all the N Ireland E.D.s ($n = 14$) and 7 of the 8 acute Out of Hours (OoH) facilities. In this audit, covering a 2 week period, 14% of all attendances were for asthma attacks and about 20% of these cases were for repeat visits. Despite being advised to, only 8% of the adults and children attended their GP for follow up assessment within 2 weeks after the asthma attack (unpublished data) thus missing the opportunity to ensure good asthma preventative measures are in place. In addition, the RBHSC took part in an annual British Thoracic Society audit of acute asthma care. Like most other units we performed satisfactorily with the in-hospital acute management but we underperformed in the discharge process which was targeted at providing the child with a management programme (12). Children with frequent asthma attacks that require admission, attendance at the ED or OoH for crisis management are a group that requires more attention. An asthma attack is an important point of entry into an asthma care program so that the basics of asthma care can be implemented (7, 8).

We here report (retrospectively) on a Safe Asthma Discharge Care Pathway (SADCP) that we developed, implemented and then evaluated at the RBHSC and then applied the SADCP to a local children's District General Hospital unit.

METHODS

The PHA DHSSNI, as part of the "Transforming Your Care" initiative, agreed to facilitate the development of the children's Safe Asthma Discharge Care Pathway (SADCP) for N Ireland.

The SADCP aimed to use the acute asthma attack presentation at ED (with or without hospital admission), the index attack, as an opportunity to ensure the basics of asthma care were put in place for each child. It was planned to pilot and refine the pathway at both the RBHSC and at a local District General Hospital (Antrim Area Hospital, JLH, SB) and if beneficial then to have it rolled out to all pediatric units in N Ireland.

This is a retrospective narrative description of the development, implementation and service evaluation of

Abbreviations: ED, Emergency Department; OoH, Out of Hours; SADCP, Safe Asthma Discharge Care Pathway; DGH, District General Hospital.

our Safe Asthma Discharge Care Pathway. We include audits and checks on the outcomes and report the overall outcomes using a before/after design. The project was approved by the Standards Quality & Audit Department of the Belfast Health & Social Services Trust and was not deemed research (13).

Background Initiatives and Knowledge That Informed the Pathway Development

In 2012 we invited 52 consecutive children who were either being discharged after a hospital admission ($N = 40$) or who were frequent ED attenders (≥4 ED attendances for asthma attacks in the previous year, $N = 12$) to a new specialist asthma nurse (SB, GG) clinic. Twelve required more appropriate inhalers prescribed, all children were trained to use inhalers correctly at that clinic appointment (using the iterative Teach Back or Teach to Goal (TB/TTG) method, **Box 1**) (14–16). All children were given an updated written PAAP along with asthma education with emphasis on the need for adherence to the inhaled corticosteroid. We learned from this; (a) that the post discharge clinic should be held between 1 and 2 weeks following the index asthma attack (as all children attended) and (b) the nurses needed further follow up educational sessions in order to be sure the basics of asthma were being correctly implemented. Evidence suggests that one off educational sessions are inadequate and support the need for several educational sessions (17–19). In addition, we previously reported that children who had been trained to use inhalers correctly made critical errors while using their inhalers at home. Using remote video directly observed therapy (vDOT) it took up to 3 weeks with daily feedback before all children studied were able to demonstrate correct inhaler technique on a regular basis (20). Recent studies which used the TB/TTG teaching method showed that, while this technique is much better than simply demonstrating correct inhaler technique, the beneficial effects wane with patients relapsing back into incorrect inhaler techniques when assessed 4 weeks later (15, 16).

Following this initial pilot of a new nurse led asthma discharge clinic we believed that in order to ensure both mastery of correct inhaler technique and to ensure understanding and ability to correctly action the PAAP (for the green, amber and red asthma control zones, supported self-management) that we needed the following;

1) to make a follow up educational appointment soon after an index asthma attack.
2) to use the TB/TTG teaching method not only for training children to correct inhaler mastery but also to ensure their ability to action their PAAP (**Box 1**).
3) to provide 3 educational sessions 2–3 weeks apart in the 8–9 weeks post discharge after the index asthma attack. Several such teaching sessions ($N = 3$, each applying memory retrieval and spaced learning TB/TTG) aimed to address the waning over time of the learned skills (14–19, 21).

BOX 1 | Teach Back/Teach-to-Goal (TB/TTG) teaching technique. After iterative training on both correct inhaler technique and actions required to implement the PAAP zones (green, amber, and red), each child and their parent were required to retrieve from memory, teach back and demonstrate both correct inhaler technique and understanding of PAAP on 3 separately spaced occasions within each consultation.

	Inhaler technique	**Ability to action PAAP (green, amber, red zones)**
Initial Iterative training	On correct inhaler technique	Actions required to implement the PAAP zones
Teach back	Child/parent to explain back to trainer each step and reason why it is needed.	Explain back action required for each PAAP zone
Demonstrate back	Demonstrate that child can do each step correctly	
Repeat the above steps correctly on 3 separate occasions within each individual teaching session		

PHASE 1–DEVELOPMENT OF THE SAFE ASTHMA DISCHARGE CARE PATHWAY

A series of multidisciplinary team (MDT) meetings were arranged with representative children and their parents, primary and secondary care asthma nurses, general practitioners and pediatricians from both ED and respiratory medicine along with facilitators from the PHA, DHSSNI.

At the MDT meetings the following decisions were made;

Who to Target the Care Pathway

We agreed the following criteria for referral to/entry into the Safe Asthma Discharge Care Pathway (**Supplementary Material 1**).

- >1 years age (to avoid overlap cases with recurrent or persistent bronchiolitis symptoms).
- Children <15 years (the upper age that the RBHSC ED department accepted cases).
- Children with a doctor asthma diagnosis (those currently on preventer asthma medication).
- include those with frequent (<3) episodic viral wheeze episodes and currently treated with ICS and classic atopic asthma.
- >1 previous visit to A&E or hospital admission with wheeze in the previous 6 months.

First time wheezing episodes were therefore not to be included in this initial pilot period.

When Should the Children Be First Seen at the Asthma Nurse Clinic?

The MDT decided not to follow the BTS recommendation that children are seen within 1–2 days of discharge–as this was currently unachievable and likely the clinic visit would concentrate on whether the attack had completely

resolved. In addition, the recommended 4 week specialist review was considered too long a delay to wait as it was considered that the parental worry surrounding the acute attack may have faded increasing the possibility of reduced attendance. Given the excellent attendance at our initial pilot clinic (described above) review between 1 and 2 weeks following the index attack was considered as the optimal time.

Ensuring Immediate Safe Discharge From the ED or Wards and Referral to the Nurse Led Asthma Clinic

Given the intense workload and changing staff in the ED department an immediate safe discharge from ED department pathway proforma was developed. The aim being to prevent an early re-attendance during the next few weeks before the child could be seen at the asthma clinic. The child/parent would be informed that an appointment with a specialist asthma nurse would be organized between 1 and 2 weeks' time.

The same was true for discharge after a ward admission. Although the same asthma nurses (running the new pathway asthma clinic) may have had an opportunity to start the education process prior to ward discharge. Children are rapidly discharged once they no longer require oxygen and their breathless has subsided but often well before all wheezing has cleared up. Immediate discharge checklist proforma were developed (**Supplementary Materials 2A,B**) for the ED and hospital wards respectively. The same proforma was used as a referral document to the pathway Asthma Nurse and a printed copy given to the parents.

Each day the asthma nurse would collect the ED and ward referrals from the previous day and arrange the clinic review via the appointments office who sent out a letter inviting the child and parent to attend at the next available nurse led clinic in 1 and 2 weeks following their discharge.

What Was to Be Included in the Nurse Led Asthma Intervention of the SADCP and Why

We agreed that for this intervention to be effective the educational clinics needed to include the following features;

- Standard explanation of the nature of asthma, triggers and the roll of each type of medication (background education) with emphasis placed on the need for regular preventer inhaled corticosteroids (ICS) therapy irrespective of current symptoms.
- Training to mastery of inhaler technique using the Teach Back (or Teach to Goal) methodology (TB/TTG).
- Training to full understanding of the PAAP also using the TB/TTG approach–so that child and/or parent should be able to explain back to the asthma nurse the actions required for each of the green, amber and red zones in the PAAP.
- Each child should be offered 3 educational sessions over a 6–8 week period following the index asthma attack.
- Once mastery of the required skills had been achieved the asthma nurse would make the decision based on current asthma control to either request a] follow up by Primary Care or b] follow up at one of hospital based asthma clinics.

To allow time for comprehensive instruction, 45 min was allocated to new referral patients and 30 min for each follow-up review.

Figure 1 summarizes the final agreed Safe Asthma Discharge Care Pathway.

PHASE 2. IMPLEMENTATION OF THE SAFE ASTHMA DISCHARGE CARE PATHWAY

Ensuring Correct Patients Were Referred and Attended the Pathway Asthma Clinic

Asthma nurses introduced an ongoing system to educate medical and nursing staff rotating through ED and the medical wards regarding the Care Pathway. Initially there was a problem with both under and inappropriate referral. In order to improve the referral rate of appropriate cases every morning the consultant (BB, AF) in ED checked the entries for all the previous 24 h attendances and identified any potential missed cases, this acted as a safety net to ensure all suitable children had been referred. Inappropriate referral (mostly children with problem cough who were queried as having asthma or first time wheezers) was addressed by further education of the ED staff.

To help ensure families of children attended the asthma clinics they were told that they would be contacted and invited to a full and detailed asthma review on a specified date and time in the next 1 to 2 weeks. The importance of attendance was stressed explaining that the aim was to reduce the chances of their child having another acute attack.

Barriers and Issues Occurring During Implementation

(1) Prior to implementation of the pathway the most commonly used systemic oral corticosteroid used was prednisolone, however, during the implementation there was a transition to using single dose dexamethasone as the preferred oral steroid. The immediate discharge care pathway (**Supplementary Materials 2A,B**) therefore was changed to include Dexamethasone and local General Practitioners were informed that a second dose dexamethasone could be given to those whose symptoms had not adequately resolved after 2 days.

(2) Incompatibility of electronic records. Originally, it was planned that the immediate discharge checklist proforma for ED (**Supplementary Materials 2A,B**) would be placed on each child's N Ireland Electronic Record (NIECR) so that those in primary and secondary care would have access. However, it was not possible to link the ED department record with the NIECR and therefore paper copies were required to be printed. The child's pathway documentation and updated PAAP were therefore first uploaded onto NIECR at the time of the first pathway asthma clinic visit by the nurse.

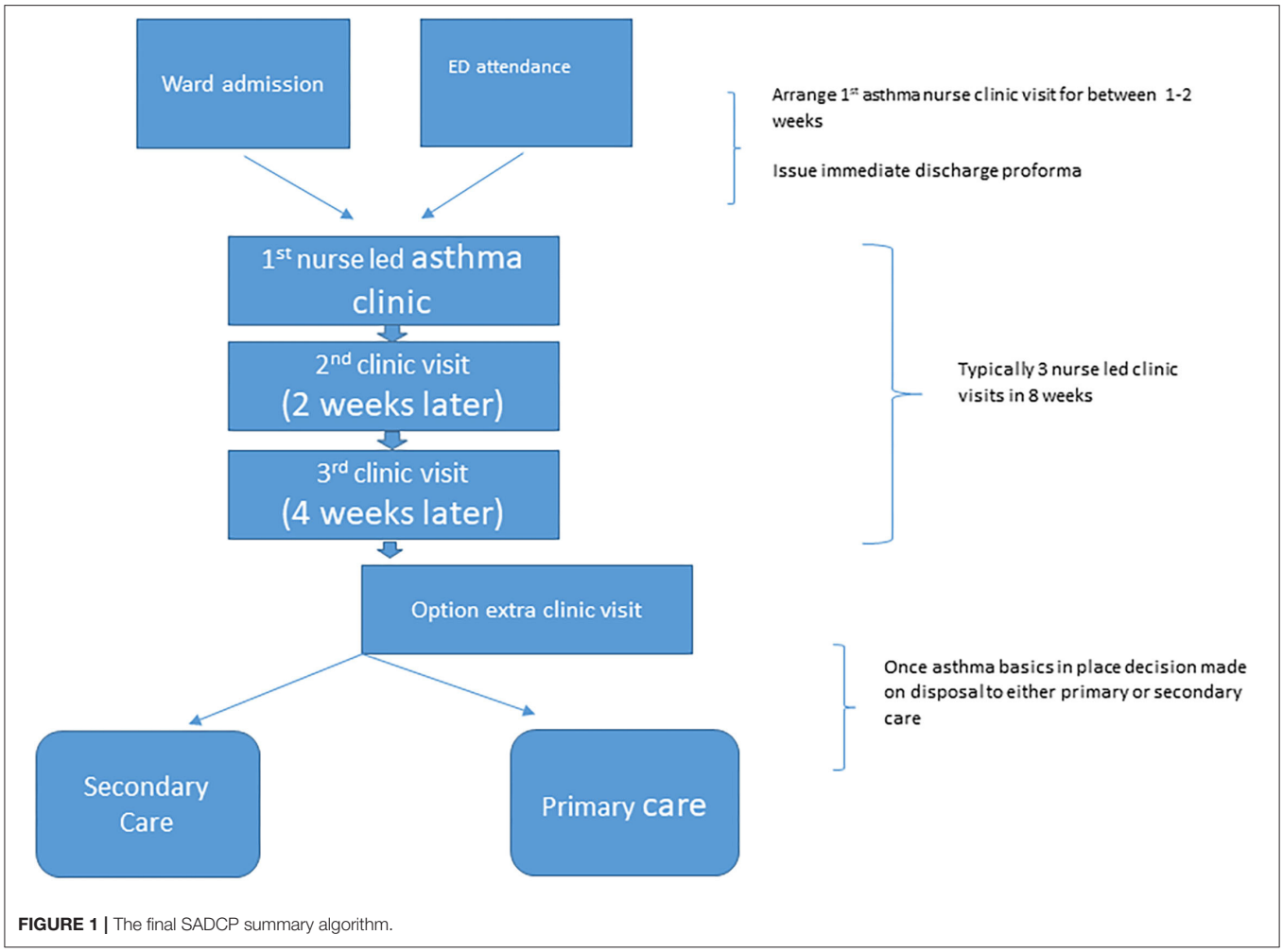

FIGURE 1 | The final SADCP summary algorithm.

(3) Teach Back or Teach to Goal (TB/TTG) methodology was used to ensure children had mastered correct inhaler technique and this required the use of trainer inhalers or placebo devices. The RBHSC organization does not allow the re-use of trainer inhalers or holding chamber devices (single patient use) and an adequate and ongoing supply of trainer/placebo inhalers needed to be obtained from Pharmaceutical companies. Hospital stock small volume holding chambers and, if used in training, were given to the child for future use.

PHASE 3-EVALUATION OF THE SAFE ASTHMA DISCHARGE CARE PATHWAY AS A SERVICE IMPROVEMENT

The PHA,DHSSNI requested that the final pathway (**Figure 1**) should be piloted and results audited prior to any decision regarding potentially rolling out the pathway across all N Ireland's pediatric units and consideration of modifying the pathway to suit adult asthmatics.

The clinically collected data was recorded in a fully anonymised spreadsheet for further analysis. We carried out the service evaluation to determine the impact of this SADCP once it had been established at both the RBHSC and Antrim Area Hospital pediatric units.

Data Collected

The numbers of child/parents engaging with the SADCP were recorded as well as the number dropping out. The number of asthma educational sessions required before the nurses considered that the "asthma basics" were correctly in place was recorded.

At the start of the clinic session the nurse assessed the child's current inhaler technique and understanding of their PAAP. Assessment of the inhaler technique was made using the manufacturer's checklist for each inhaler type.

The nurse classified each child's inhaler technique using a global assessment (20):

- "Correct" (all important steps carried out and nurse formed the opinion that the child would have received most of the expected dose).
- "Partial" (in which case the child made errors but the nurse felt that the child could have received at least some but not most of the dose).

- "Poor" technique (where critical errors were being made and the nurse formed the impression that likely little or none of the dose would be delivered to the lungs).

The nurse recorded whether the child already had a PAAP and if so assessed their understanding of this.

The N Ireland Electronic Care Record (NIECR) was used to record the acute asthma health care utilization of the first 81 children who were referred to and entered into the pathway and who had at least 12 months of follow up care (either in primary care or secondary) after exiting from the Safe Asthma Discharge Care Pathway. The number of acute courses of oral corticosteroids used, attendances at OoH and ED and any hospital admissions for acute asthma were recorded. In addition, an estimate of adherence to the inhaled preventer (ICS) was calculated from refills prescribed over the 12 months before and the 12 months following the child exiting the pathway. Before and after comparisons were made for the 12 months before with the 12 months after the index acute asthma attack for all children. We repeated the before/after analysis excluding those aged under 4 years who might be expected to have reduced wheezing over time.

On a separate sample of children currently on the pathway, an independent observer (OM) checked whether the child/parents had mastered the correct inhaler technique and had the ability to action the PAAP (green, amber, red zones) when leaving a pathway clinic visit.

A similar evaluation of a consecutive convenience sample of those entered into the care pathway at Antrim Area Hospital pediatric unit (the selected District General Hospital) was conducted by obtaining similar data on care pathway children for the 6 months before and after exiting the pathway.

Results of the Evaluations

The first 81 consecutive patients for whom 1 year of time had elapsed since exiting the SADCP at the RBHSC were studied. The median age was 5 years (IQR: 3 to 6 years, maximum 13 years). The majority were referred from ED ($N = 72$, 89%) and 9 were referred following a hospital admission. Those children/parents failing to attend the first appointment were telephoned to offer a new appointment and all children had attended by 3 weeks. Every child attended at least once with 10 having one single visit, 19 children had two clinic sessions and 37 had 3 sessions. For thirteen of the 19 children having only two clinic visits the third visit was deemed unnecessary as the nurses considered the children/parents had already mastered the asthma basics. However, 6 of the 19 did not attend further despite repeat phone calls. Unexpectedly, for sixteen children/parents the nurses considered they needed greater than the expected 3 training sessions and these children continued to be seen at the nurse led clinic until it was considered the skills could not be improved with further training.

Thirty-five children were classified as having a frequent episodic viral wheezing (43%) pattern while 46 fitted the multi-triggered wheeze pattern typically with day-to-day milder wheezing interspersed with acute attacks. Thirty-two had clinical atopy (mostly concomitant Allergic Rhinitis and /or atopic eczema). At baseline all children had previously been prescribed anti-asthma treatment with 34 on the BTS asthma guideline Step 2 and 47 on BTS Step 3.

Surprisingly in this cohort, few had obvious known trigger factors that could be easily avoided. Only 6 reported coming from homes where one or other parent smoked cigarettes, 6 had homes with damp and mold and 5 had pets which from the clinical history avoidance should have been considered. Advice was given about trigger avoidance whenever appropriate.

Improvements Made to Child's Care During the Safe Asthma Discharge Care Pathway

At the start of the Nurse led intervention only 13 of the 81 (16%) children had correct inhaler technique, 38 had partially correct technique and the remainder ($N = 30$) had poor technique and many of these required a change to a more age appropriate inhaler device. At baseline eight of the 81 (10%) children had evidence that they had been given a PAAP (**Table 1**). In the 12 months prior to the index asthma attack only 4 (5%) out of the 81 had evidence from prescription refills of >80% adherence (average calculated inhaler use based on refills collected over the previous 6 or 12 months) and for 33 (41%) the adherence was between 50 and 80%. At the end of the SADCP educational sessions all 81 were deemed to have mastered correct inhaler technique and had a good understanding of how to action their PAAP. In the 12 months post the intervention 42 (52%) of the 81 had evidence for GP prescriptions refills suggesting >80% adherence and 36 (44%) had refill adherence of between 50 and 80% (**Table 1**). The effectiveness of the pathway was demonstrated by statistically significant reductions in courses of OCS, attendances at out of hours and Emergency department visits and admissions for acute asthma (**Table 2**, **Figures 2A–D**). These improvements were observed for children both older and younger than 4 years.

Check of the Effectiveness of the Training Given to Child/Parents Attending at the Pathway Clinic

An independent assessor (OM) evaluated a separate convenience sample of children immediately before and again after leaving one of the pathway clinics. This aimed to determine if the children had mastered correct inhaler technique and whether the children/parents were able to explain what action they needed to take when the child's asthma control put them in the PAAP green, amber and red zones. The assessor sampled 26 child/parent units after their initial first clinic visit within the pathway and assessed

TABLE 1 | Changes made during the nurse led training sessions at the RBHSC.

	Baseline, on entry to care pathway	At end of pathway nurse led asthma intervention
Inhaler technique (*N*)		
Poor	30	0
Partial	38	0
Correct	13	81
Possession of up to date PAAP (*N*)		
No	73	0
Yes	8	81

TABLE 2 | For the RBHSC.

	12 months Pre-intervention	12 months Post-intervention	
Oral corticosteroids courses			
Median (IQR, range)	1 (IQR: 1–3, range: 1–10)	0 (IQR: 0–0, range: 0–4)	$P < 0.0001$
Out of Hours attendance			
Median (IQR, range)	1 (IQR: 0–2, range: 0–10)	0 (IQR: 0–0, range: 0–2)	$P < 0.0001$
ED attendances			
Median (IQR, range)	2 (IQR: 1–3, range: 1–11)	0 (IQR: 0–0, range: 0–4)	$P < 0.0001$
Admissions			
Median (IQR, range)	0 (IQR: 0–1, range: 0–3)	0 (IQR: 0–0, range: 0–1)	$P < 0.0001$
Adherence to ICS (*N*)			
<50%	44	4	
50–80%	33	36	
>80%	4	41	

Number of courses Oral Corticosteroids, Number of Out of Hours attendances, number of ED attendances and number of admissions for acute asthma attacks in the previous 12 months compared with the 12 months following the asthma nurse led intervention. The Wilcoxon paired test was used to assess whether this before/after improvement was statistically significant ($P < 0.05$). Adherence to inhaled corticosteroids (ICS) was calculated from primary care refills.

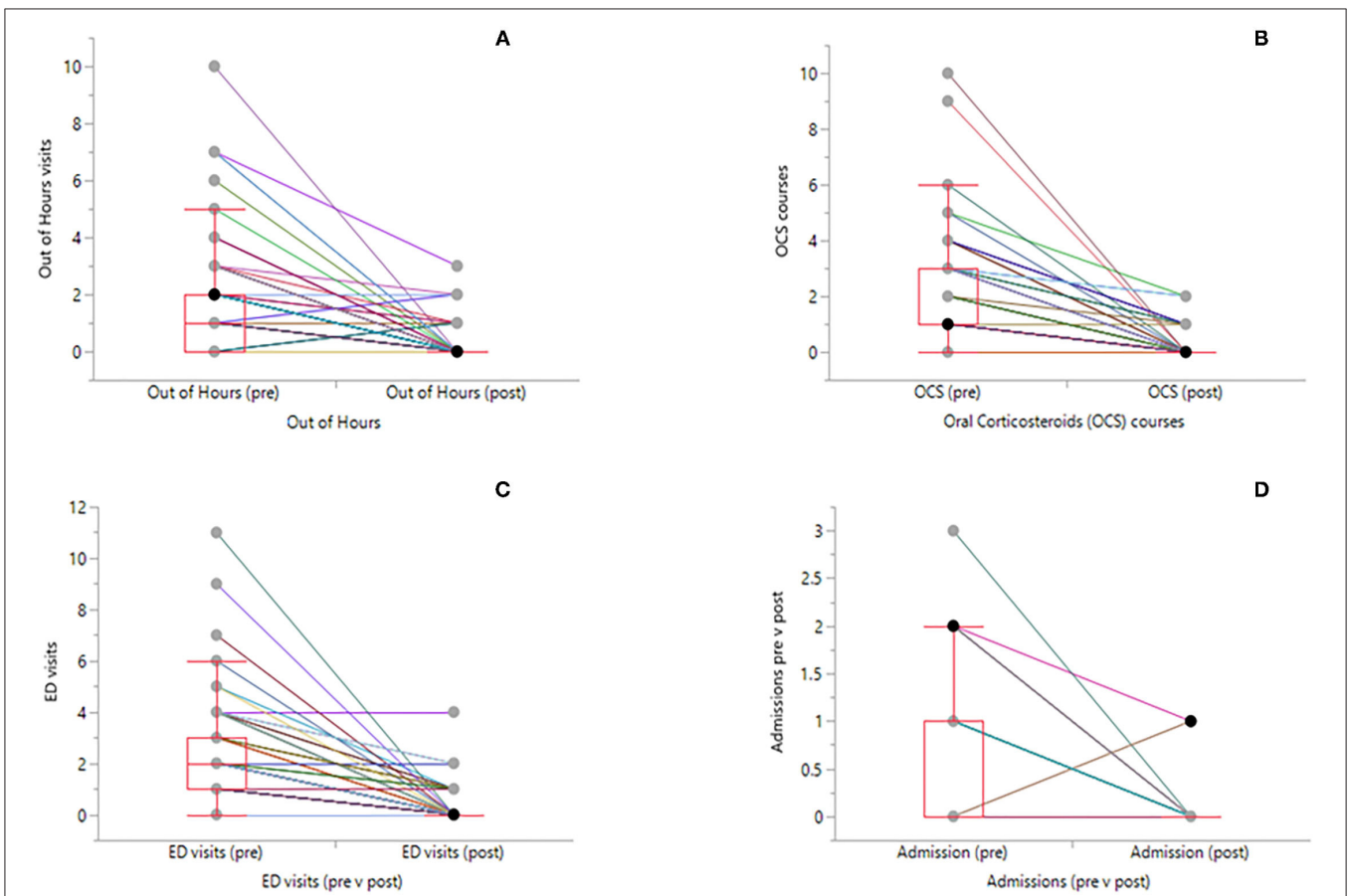

FIGURE 2 | Before and after Box plots with individual patients linked by solid lines. On the y-axis are number of OoH visits **(A)**, number of courses OCS **(B)**, number of ED visits **(C)** and number of admissions **(D)**. The center horizontal line in the box is the median, the upper horizontal box lines are the quartiles and dots above the upper whisker represent individual outliers.

a further 42 children who were having their 2nd or 3rd review. The assessor recorded inhaler technique steps and then formed a global assessment according to the 3 categories (correct, partial, poor technique) for both preventer and reliever inhalers. The

results are presented in **Table 3**. We checked for understanding of, and the ability to action, the given written PAAP after the same children/parents as above. We found that only 11 of the 26 (42%) of new patients attending their first visit on the care pathway already had a written PAAP. All the review patients had been given a PAAP but only 14 brought the PAAP to the review clinic making it difficult to confirm whether they had a written PAAP. After leaving the clinic all child/parent patients were able to describe what the medications did and when to use them. In addition, all patients were able to correctly describe what medications to use when the child's asthma control was in both the green and red zones of the PAAP. A number of patients were unclear regarding action to take when the child was entering the amber zone e.g., onset of a head cold and mild increase in cough and / or wheeze. Overall, this check audit of the nurse led clinics confirmed that using the TB/TTG technique for both training in mastery of correct inhaler technique and understanding of and ability to action the PAAP was working.

Implementing the Safe Asthma Discharge Care Pathway in a District General Hospital Pediatric Unit (Antrim Area Hospital Children's Unit)

The SADCP was evaluated at the children's unit of Antrim Area Hospital (JLH, SB). Antrim Area Hospital is a District General Hospital (DGH) with a pediatric and neonatal unit which covers the local area of County Antrim in N Ireland but which refers cases to the tertiary regional centre at the Royal Belfast Hospital for Sick Children.

We selected a convenience sample of 27 children who had been through the care pathway at least 6 months before so that we had data on the 6 months before and 6 months after exit from the care pathway. This included 14 children with multi-triggered atopic asthma and 13 children with episodic viral wheeze all of whom had previously been prescribed inhaled corticosteroids. Twenty-four children entered the pathway after an asthma ward admission and 3 were referred from the ED department. After completing the Care pathway 15 children were referred back to primary care and 12 referred to the local hospital asthma clinic. Four (15%) children entering the care pathway already had a written PAAP and 23 did not. All were given an updated PAAP after the first clinic visit. Five of the 27 patients only attended one clinic visit, 14 attended two clinics, 6 attended 3 clinics and 2 required 4 clinic visits. The outcomes of the before and after requirements for OCS, OoH attendances, ED attendances, admissions and calculated adherence to asthma preventer medication are summarized in **Table 4**.

DISCUSSION

We have developed and implemented a Safe Asthma Discharge Care Pathway (SADCP) that utilizes the index acute asthma attack as a window of opportunity to carry out and deliver an asthma management programme to children. This SADCP meets the recommendations suggested in the NRAD report (6). At least for the children exiting the SADCP the evaluation suggest this should reduce the risk for a future asthma attack, however, a full randomized controlled trial would be needed to confirm this. In addition, the benefits applied equally to those managed at the tertiary referral children's hospital and at a District General Hospital unit.

There are some important aspects of the asthma nurse led interventions within the SADCP that are worthy of emphasis. Firstly, we ensured that parents were aware that, shortly after discharge (from the ED or ward after the child's asthma attack), they would be invited to an arranged clinic appointment with the asthma nurse–the reason given was that we wanted to reduce the risk of a future attack. Informing and pre-arranging the follow up appointment may have led to better child attendance.

Secondly, we ensured that adequate time was set aside for the nurse led clinical sessions. We have observed that many children with asthma children receive frequent acute crisis care but are only offered short (e.g., 10 min) appointments in either primary or secondary care once or twice a year for their asthma reviews. We believe that it is impossible to do a comprehensive asthma assessment and provide training to mastery of inhaler skills in such short consultations.

Thirdly, we believe that use of the TB/TTG teaching methodology was important. Simply showing (brief instruction) a child/parent how to use an inhaler does not mean that correct inhaler technique will be carried out at home (21, 22). A recent systematic review of inhaler technique studies report no improvement for each of the last 4 decades despite improvements in inhaler device design (about 30% of asthmatics have correct technique) (23). Studies of using the TB/TTG technique show that this is a very do-able method of teaching within an asthma clinic setting, however, the beneficial effects wane by 28 days. In cognitive psychology it is recognized that re-testing and retrieval, as demonstrated by teach back are important to consolidate learning (24–27). The three clinic visits in 8 weeks help to reinforce memory retention through what has been called "spaced repetition." We provided 3 educational visits within an 8 week period in our SADCP asthma programme. Several studies have shown that 3 separate teaching sessions are needed typically 2–3 weeks apart to provide sustained good inhaler technique (17, 18). The effectiveness of spaced repetition in creating long-term memories and attenuating memory decay has been experimentally demonstrated in long-term memory formation (24–27). Finally, we extended the use of TB/TTG methodology to ensure that children/parents have a good understanding of how to utilize their PAAP. This is important because children experience asthma attacks even when the asthma basics of care are being correctly applied. Children and or parents were able to describe what action to take when the child's current asthma was in the green or red zones of the PAAP but some were less clear with what action to take at the start of an asthma exacerbation (amber zone). The reasons for this may include the numerous different individual scenarios that may not have been discussed and that the nurses themselves may not have had a clear view of specific action needed given this area has a conflicting evidence base (e.g., conflicting evidence regarding doubling the inhaled corticosteroids).

Our SADCP asthma management programme, like others, has multiple components and we unable to determine whether all aspects of the SADCP would be essential to have made similar

TABLE 3 | For the RBHSC.

	Total number (before training)	Total number (after training)	New (before training)	New (after training)	Review (before training)	Review (after training)
Preventer						
Correct	29	61	9	23	20	38
Partial	29	6	9	3	20	3
Incorrect	10	1	8	0	2	1
Reliever						
Correct	24	59	6	24	18	35
Partial	30	8	10	2	20	6
Incorrect	14	1	10	0	4	1

Global inhaler technique before and after TB/TTG inhaler education for both new and review children.

TABLE 4 | For AAH.

	6 months Pre-intervention	6 months Post-intervention	
Oral Corticosteroids Median (IQR, range)	1 (IQR: 1–2, range: 0–8)	0 (IQR: 0–1, range: 0–2)	$P < 0.001$
Out of Hours attendance			
Median (IQR, range)	0 (IQR: 0–1, range: 0–4)	0 (IQR: 0–0, range: 0–1)	$P = 0.03$
ED attendances			
Median (IQR, range)	2 (IQR: 1–2, range: 1–4)	0 (IQR: 0–0, range: 0–1)	$P < 0.001$
Admissions			
Median (IQR, range)	1 (IQR: 0–1, range: 0–3)	0 (IQR: 0–0, range: 0–1)	$P < 0.001$

Describes the number of courses Oral Corticosteroids, Number of Out of Hours, number of ED attendances and number of admissions for acute asthma attacks in the previous 6 months compared with the 6 months following the asthma nurse led intervention. The Wilcoxon paired test was used to assess whether this before/after improvement was statistically significant ($P < 0.05$).

improvements. However, from our experience and knowledge of the literature we applied the following; (1) utilized the acute attack as the window of opportunity, (2) ensured timely first entry into the SADCP i.e., between 1 and 2 weeks, (3) ensured each patient had adequate time with the asthma nurse, (4) used TB/TTG teaching methodology and (5) reviewed the child to provide re-inforcement of learning on 3 occasions in an 8 week time frame. We believe the SADCP as a package resulted in the improved outcomes for these children.

Although we have not performed a formal cost-benefit analysis the major extra costs required included in setting up this Safe Asthma Discharge Car Pathway were (1) having trained asthma nursing staff, and (2) allocating the asthma nurses with the clinic time (45 min per patient), equipment (e.g., single patient demonstration inhalers) and clinic space. The administration of the system was easily integrated into the work performed by the current administrative staff. Given that we found a large increase in preventer asthma medication (ICS and /or combination ICS+ beta2 agonist) adherence the cost of asthma medication would be an additional extra cost to the Health Service (prescriptions for children in N Ireland are free). The cost savings with in the hospital would be more difficult to calculate. The small reduction in ED attendances (e.g., 195 instead of 200 daily attendances) is only likely to result in reduced patient waiting times and a minimal drug cost saving (salbutamol plus oral steroid). Asthma attacks are one of the most feared consequences of having asthma and clearly the benefits to children and their families in reduced asthma attacks and potentially reduced risk of asthma death is self-evident and hard to cost.

LIMITATIONS

This is a before and after service improvement evaluation report. While the improvements in children's asthma outcomes seen are most likely due to the implementation of the asthma education programme a causal link cannot be confirmed. This would have required a Randomized Controlled Trial. It is well known that asthma varies over time and especially between seasons. However, as we recruited the children over a 1 year period, it is likely we would have equally caught children going from their bad to good season and vice versa. Younger children are more likely to have a transient episodic viral wheeze that resolves over time meaning that some improvements were due to natural resolution. The children in our study who had a symptom pattern in keeping with episodic viral wheeze had all previously been started on ICS suggesting that they were suffering frequent episodes. We found similar statistically significant improvements when we excluded those aged under 4 years from the analysis.

We did not collect data on the children's day to day asthma control over the period studied but only indices of acute asthma attacks and therefore we cannot comment on whether each child's

day-to-day symptom control was better. In addition, we were unable to find out whether, at 12 months post intervention, the parents had acted on the trigger avoidance advice suggested. We were surprised that fewer than expected children came from households with a parental smoker, how few houses were reported as having damp and mold and how few children had household pets to which they were allergic. Trigger avoidance is stressed in recent asthma guidelines but health care professionals can be uncertain as to how effective exclusions of an allergen can be and can feel that the efforts involved can be a futile exercise. In addition, there is very little information available on child / parent beliefs about trigger avoidance and motivation to make changes. This is an area that needs further research.

Finally, the recent Coronavirus (COVIT-19) pandemic has accelerated the use of Tele-Medicine as lockdowns and mandates meant that families and staff were less keen on face to face clinical meetings unless they were absolutely essential. While we believe face-to-face training is optimal it has been reported that inhaler instruction using the Teach-to-goal/Teach back technique is eminently possible via remote video consultation (28). Our SADCP therefore would lend itself to hybrid approaches with perhaps the first clinical assessment being face-to-face followed by some video consultations. Further research is needed into determining whether our care pathway could be further improved and streamlined using the combination of video consultations and video Directly Observed Therapy.

CONCLUSIONS

We found that implementing a nurse led safe asthma discharge care pathway (SADCP) following a child's acute asthma attack was feasible in both a major children's hospital and in a District General Hospital children's unit and for the children was followed by a reduced number of asthma attacks in the following year. Our SADCP could be modified and applied to adults after an asthma attack and also should be considered in primary care.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MS and JLH conceptualized and initiated the process for the development of the care pathway. LK, SB, BM, MS, JLH, BB, VV, and AF were the health care professionals (asthma, respiratory and emergency medicine) involved with the pathway development. LK, SB, GG, and CR delivered the care pathway. LK and SB collated the recorded data. OM and DO'D, performed the independent audit of the children's mastery of inhaler technique. MS analyzed the data. MS, JLH, DO'D, VV, and LK edited and wrote the initial draft manuscript. All authors have approved the paper.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.865476/full#supplementary-material

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Respiratory Oscillometry in Newborn Infants: Conventional and Intra-Breath Approaches

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Background: Oscillometry has been employed widely as a non-invasive and standardized measurement of respiratory function in children and adults; however, limited information is available on infants.

Aims: To establish the within-session variability of respiratory impedance (Zrs), to characterize the degree and profile of intra-breath changes in Zrs and to assess their impact on conventional oscillometry in newborns.

Methods: 109 healthy newborns were enrolled in the study conducted in the first 5 postpartum days during natural sleep. A custom-made wave-tube oscillometry setup was used, with an 8–48 Hz pseudorandom and a 16 Hz sinusoidal signal used for spectral and intra-breath oscillometry, respectively. A resistance-compliance-inertance (R-C-L) model was fitted to average Zrs spectra obtained from successive 30-s recordings. Intra-breath measures, such as resistance (Rrs) and reactance (Xrs) at the end-expiratory, end-inspiratory and maximum-flow points were estimated from three 90-s recordings. All natural and artifact-free breaths were included in the analysis.

Results: Within-session changes in the mean R, C and L values, respectively, were large (mean coefficients of variation: 10.3, 20.3, and 26.6%); the fluctuations of the intra-breath measures were of similar degree (20–24%). Intra-breath analysis also revealed large swings in Rrs and Xrs within the breathing cycle: the peak-to-peak changes amounted to 93% (range: 32–218%) and 41% (9–212%), respectively, of the zero-flow Zrs magnitude.

Discussion: Intra-breath tracking of Zrs provides new insight into the determinants of the dynamics of respiratory system, and highlights the biasing effects of mechanical non-linearities on the average Zrs data obtained from the conventional spectral oscillometry.

Keywords: infant oscillometry, respiratory resistance, respiratory reactance, respiratory compliance, nasal resistance, intra-breath method

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Motto:
"Accurate assessment of lung function in infants is no mean undertaking – requiring not only the highest specifications from equipment . . . but infinite patience and meticulous attention to detail from the operators."

Janet Stocks, 2004
Pediatric Anesthesia 14: 537–540

INTRODUCTION

The burdens of infant pulmonary function testing (PFT) imposed by the lack of active cooperation, the requirement for sleep, the obligatory nasal breathing, the high impedance of the respiratory system and several other factors have prevented the establishment of a gold standard in infant PFT. Respiratory oscillometry measures the mechanical impedance of the respiratory system (Zrs), and it has been shown as a promising method in different measurement settings (1). Recent work has demonstrated its feasibility in normally breathing unsedated infants with a high success rate (2–5). Additionally, a new tracking modality of oscillometry (6) has revealed disease-specific patterns of intra-breath changes in Zrs and has proven unique in predicting lower respiratory tract illness during infancy (7). However, a comprehensive analysis is still needed to fully characterize the intra-breath dynamics of Zrs in infants, with special regard to the substantial contribution of the upper airways (8–12). Confrontation of the novel intra-breath oscillometry with conventional spectral oscillometry is also lacking. While some data on the day-to-day Zrs changes in newborn infants are available (5, 13), the within-session reproducibility of oscillometry measures has not been studied.

The aims of the present study were (a) to measure Zrs in healthy term newborns to characterize the physiological flow (V')- and volume (V)-dependent changes *via* intra-breath oscillometry, (b) to examine the potentially confounding effects of intra-breath changes on average Zrs spectra obtained from conventional multi-frequency measurements and (c) to determine the within-session variability of conventional and intra-breath oscillometry variables.

MATERIALS AND METHODS

The study protocol was approved by the Institutional Clinical Ethics Committee of the University of Szeged (91/2011, renewed in 2017). A written informed consent and assent was obtained from all mothers prior to the subject recruitment. The data collection period started in January 2017 and ended in May 2017. All measurements were performed in the Neonatal Unit, Department of Obstetrics and Gynecology, University of Szeged.

Healthy term infants (> 37th week of gestation, birthweight > 2,500 g, APGAR score at 5 min ≥ 8, uninterrupted early adaptation) were included in the study. Lung function was measured between the 2nd–5th postpartum day on a single occasion, during natural sleep. Newborns were excluded from the study if steady-state breathing was not reached or leakage persisted around the face mask despite multiple trials.

Measurement Setup

Oscillometric measurement of input Zrs was made with a custom-made wave-tube setup (length: 20 cm, internal diameter: 8 mm), in a setting similar to that described previously (5, 7). Small-amplitude (0.5 hPa) oscillations were generated by the loudspeaker and superimposed on the breathing. Spectral oscillometric recordings were 30 s long, and five different pseudorandom signal specimens containing components at every 4 Hz between 8 and 48 Hz were applied. Intra-breath oscillometric recordings lasted for 90 s, and a single 16 Hz sinusoid was used. Multiple measurements were performed with both modalities in random order, without removing the face mask between recordings if the sleep stage was uninterrupted.

Airflow (V') was measured with a custom-made pneumotachograph. The wave-tube and the pneumotachograph were equipped with identical pressure sensors (Honeywell model 26PCAFA6D, Golden Valley, MN, United States). Single-use bacterial filter (Gibeck, Humid-Vent filter, small straight type, No. 19502 Teleflex Medical, Athlone, Ireland) and face mask (Hudson RCI, air-cushion mask with inflation valve, neonate size, No. 41277, Teleflex Medical) were attached to the setup. The equipment's dead space was flushed by medical air at a rate of 2 $L.min^{-1}$ to avoid hypercapnia.

Transcutaneous monitoring of peripheral hemoglobin oxygen-saturation was done (Edan M50, Bell Medical, Inc., St. Louis, MO, United States) during the recordings for safety reasons. No desaturation episode was detected during data collection. Oxygen saturation data were not stored for further analysis.

Signal Processing

Pressure and V' signals were sampled at a rate of 512 s^{-1}, bandpass filtered in the 4–50 Hz range for spectral oscillometry and the 14–18 Hz range for the intra-breath measurements. Zrs was calculated based on the auto- and cross-correlation spectra of the wave-tube's lateral pressures using the fast Fourier transform, and expressed as resistance (Rrs) and reactance (Xrs). The intra-breath Zrs values were computed for each oscillation cycle (0.0625 s) and a moving average was calculated over a time window of 0.25 s. The signals of volume (V) and volume acceleration (V"), respectively, were obtained by numerical integration and differentiation of V'.

Analysis of Zrs Spectra

An average spectrum was calculated from a minimum of 3 recordings of lowest Rrs. Recordings or segments thereof containing artifacts, such as glottis closure, vocalization, body movements and leaks around the mask were discarded. No criteria relating to tidal volume (V_T) were set and sighs *per se* were not considered as artifacts. A simple resistance (R)—compliance (C)—inertance (L) model (14) was fit to the average Zrs data, as described in detail previously (5). Conventional spectral oscillometry measures, such as the lowest-frequency (8-Hz) values of Zrs magnitude ($|Z_8|$), resonance frequency (f_{res}) and reactance area below f_{res} (Ax) were also calculated; the frequency

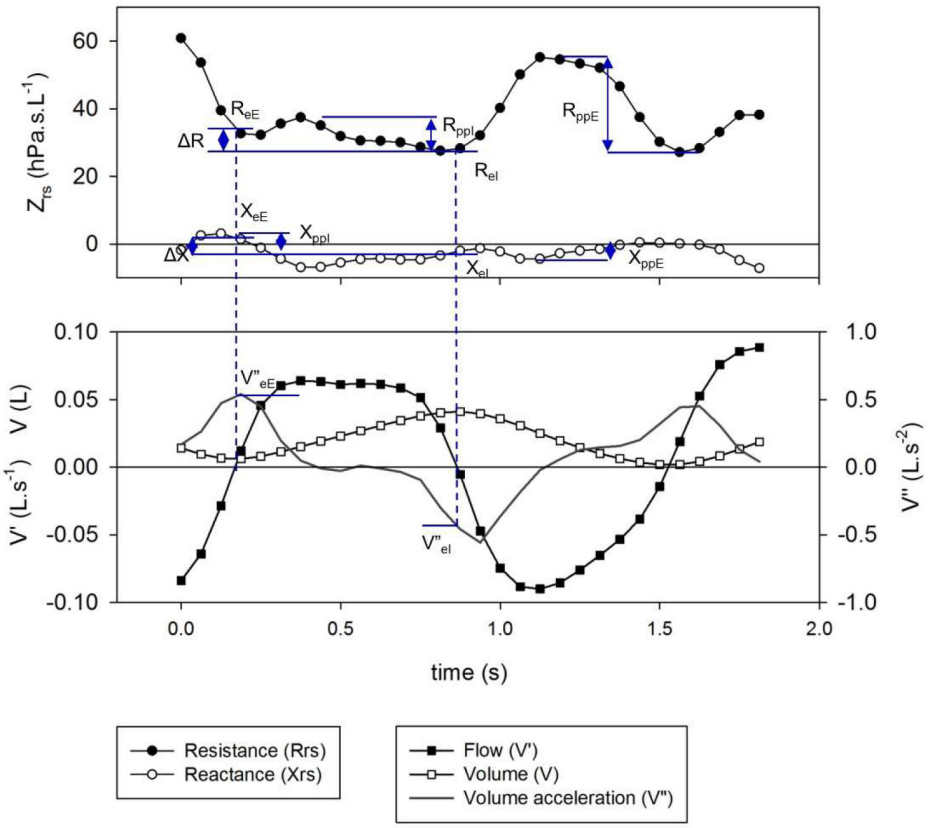

FIGURE 1 | Definition of specific intra-breath measures of resistance (Rrs) and reactance (Xrs). Shown are the time points of end inspiration (eI)- and end expiration (eE) (indicated by dotted lines), their differences (Δ) and peak-to-peak changes in inspiration (ppI) and expiration (ppE).

dependence of Rrs was characterized by the difference in Rrs between 8 Hz and 32 Hz (R_{8-32}).

Intra-Breath Measures

All regular artifact-free breaths (see previous section) except sighs were included in the analysis. Specific points of the respiratory cycle were selected to characterize the intra-breath dynamics of Zrs (**Figure 1**). Values of Rrs at end-expiration and end-inspiration (R_{eE} and R_{eI}, respectively) were calculated from the closest data points to zero V' obtained with linear interpolation. Tidal change in Rrs (ΔR) was determined as R_{eE}-R_{eI}. Peak-to-peak changes in Rrs during inspiration (R_{ppI}) and expiration (R_{ppE}) were determined. The corresponding parameters of Xrs (X_{eE}, X_{eI}, ΔX, X_{ppE} and X_{ppI}) and the average zero-flow impedance magnitude, $|Z_0| = |1/2(Z_{eE} + Z_{eI})|$ were also calculated.

Tidal Breathing Parameters

Simple tidal breath descriptors, such as V_T, respiratory rate (f_{br}), ratio of expiratory time over cycle time (T_E/T_{tot}), and the ratio of time to peak expiratory flow (V'_{maxE}) and T_E (T_{PTEF}/T_E) were obtained from the spirogram. Volume acceleration at end-expiration and end-inspiration ($V"_{eE}$ and $V"_{eI}$, respectively) were determined from pairs of V" data adjacent to the zero crossing.

Statistical Analysis and Graphics

Data are presented as mean ± standard deviation (SD). Two sample *t*-test, correlation analysis with Pearson's correlation coefficients were performed with the open-source RStudio software[1] based on R language (R.4.1). Cluster analysis was also performed in R using Euclidean distances and Ward's hierarchical method. Graphs were prepared with SigmaPlot 13.5 (Systat Software Inc., San José, CA, United States).

RESULTS

A total of 109 newborns were enrolled in the study. Six subjects were excluded due to technical reasons (see pre-defined exclusion criteria in the "Materials and Methods" section). Although the measurements were technically acceptable, 17 of the remaining 103 subjects were excluded on the basis of physiologically unrealistic values of Zrs parameters, such as negative L (n = 4), low C (< 0.5 mL.hPa^{-1}) (n = 6) or high RL product (>10 hPa^2.s^3.L^{-2}) suggestive for nasal obstruction (n = 7); in 4 of these 17 subjects, two exclusion criteria applied. Most of these subjects were also identified as

[1]https://www.rstudio.com

TABLE 1 | Comparison of anthropometry and spirogram data between subject groups of different patterns of flow dependence of reactance.

	All (n = 86)	Pattern A (n = 47)	Pattern B (n = 27)	Pattern C (n = 5)	Pattern D (n = 7)
GA (weeks)	38.7 ± 1.3	38.9 ± 1.2	38.6 ± 1.2	38.0 ± 2.1	38.3 ± 1.4
BL (cm)	49.5 ± 2.4	50.0 ± 2.5	49.3 ± 2.3	48.0 ± 2.7	47.7 ± 1.5**
BW (g)	3,269 ± 546	3,365 ± 569	3,293 ± 490	2,694 ± 491*	2,931 ± 210**
f_{br} (min^{-1})	62.0 ± 11.4	65.3 ± 12.2	58.2 ± 9.5**	57.9 ± 5.0*	57.5 ± 10.1
V_T (mL)	29.3 ± 5.5	29.3 ± 5.9	29.7 ± 4.6	26.2 ± 3.6	30.6 ± 6.5
V'_{maxE} ($mL.s^{-1}$)	90 ± 17	93 ± 17	81 ± 15**	77 ± 15	81 ± 16
T_E/T_{tot}	0.50 ± 0.03	0.50 ± 0.03	0.52 ± 0.03**	0.47 ± 0.03	0.51 ± 0.01
T_{PTEF}/T_E	0.47 ± 0.07	0.47 ± 0.07	0.45 ± 0.09	0.49 ± 0.07	0.49 ± 0.07
CoV[T_{tot}]	0.155 ± 0.058	0.155 ± 0.059	0.168 ± 0.055	0.132 ± 0.032	0.118 ± 0.058
CoV[V_T]	0.219 ± 0.092	0.231 ± 0.07	0.212 ± 0.069	0.162 ± 0.072	0.202 ± 0.097

Mean ± SD values.
Pattern A: minimal dependence of reactance (Xrs) on flow (V').
Pattern B: marked V'-dependent decrease in Xrs during expiration.
Pattern C: marked V'-dependent decrease during inspiration.
Pattern D: marked V'-dependent increases in Xrs.
GA, gestational age; BL, birth length; BW, birth weight; f_{br}, respiratory rate; V_T, tidal volume; V'_{maxE}, peak expiratory flow; T_E, expiratory time; T_{tot}, total respiratory cycle time; T_{PTEF}, time to peak tidal expiratory flow; CoV, coefficient of variation.
**$p < 0.05$ vs. Pattern A.*
***$p < 0.01$ vs. Pattern A.*

outliers during regression diagnostics, and therefore they were omitted from further analysis. Statistical analysis was performed on the data of the remaining 86 newborns (41 females, 45 males; spontaneous delivery: 41, caesarean section: 45) whose anthropometric characteristics are summarized in **Table 1**.

The mean total recording time in the 103 subjects was 14 min (range: 8–21 min); the recordings were suspended for 3–10 min in 13 subjects, and the measurements were successful only on the following day in 3 neonates. On the average, 48 (range: 15–105) respiratory cycles were analyzed from the intra-breath oscillometry in each newborn; these were collected as segments of steady-state breathing from a minimum of three 90-s recordings. The average values of spectral outcomes were calculated from 6 (3–11) recordings of a mean length of 26 s (12–30 s).

Overall, the intra-breath changes in Zrs, dominated by the V' dependence, were remarkably large. R_{ppE} and R_{ppI} amounted to 91.4 ± 33.3% and 55.9 ± 27.6%, respectively, of the average zero-flow impedance magnitude, i.e., $Z_0 = 1/2(Z_{eE} + Z_{eI})$. The maximum Rrs was usually located near the peak V', while the minimum was found around V' = 0. The corresponding changes in Xrs (X_{ppE} and X_{ppI}) were roughly half as large (44.9 ± 26.8% and 32.7 ± 19.3%, respectively). Tidal change in Rrs was on the average close to zero ($\Delta R = -0.4 \pm 6.5$ hPa.s.L^{-1}), with negative values of ΔR were observed in 51% of the subjects, whereas the decreases in Xrs between end expiration and end inspiration were more uniform ($\Delta X = 2.39 \pm 3.44$ hPa.s.L^{-1}).

Short-term changes in Zrs are illustrated with a few selected segments of intra-breath recordings (**Figure 2**). These examples are not intended to be exhaustive; they only highlight epochs where (i) regular intra-breath fluctuations in Rrs and Xrs are observed despite a slightly irregular spirogram (**Figure 2A**), (ii) a slow negative drift in Xrs occurs (**Figure 2B**) or (iii) increasing fluctuations in both Rrs and Xrs take place (**Figure 2C**) at virtually even tidal volumes, and (iv) the large expiratory increases in Rrs and decreases in Xrs are reduced following a sigh (**Figure 2D**).

Whereas Rrs exhibited positive V' dependences during inspiration and expiration, the intra-breath changes in Xrs were more diverse. Four typical patterns were determined qualitatively and are exemplified in **Figure 3** where Rrs and Xrs are plotted against V and V'. These patterns are characterized as minimal dependence of Xrs on V' (Pattern A), marked V'-dependent decrease in Xrs during expiration (Pattern B), marked V'-dependent decrease during inspiration (Pattern C) and marked V'-dependent increases in Xrs (Pattern D). Each newborn was classified into one group according to the V'-dependence of Xrs by cluster analysis, presuming that four different patterns exist (**Figure 4**). Subjects with the lowest V'-dependence in Xrs (Pattern A) were considered the control group. **Tables 1–3**, respectively, contain the anthropometrical and tidal breathing data, the spectral oscillometry measures and the intra-breath variables in the 4 clusters. Slightly lower body measures were found in the Pattern C and D groups and lower f_{br} values in Pattern B-D groups compared to the Pattern A data (**Table 1**). L was the highest while f_{res} and Ax were the lowest in the positive V' dependence (Pattern D) group (**Table 2**). L was significantly ($p < 0.05$) lower and Ax was higher in subjects with negative expiratory swings in Xrs (Pattern B) compared to Pattern A. Unlike the values of X_8, parameter C was found to be not different between groups. The overall fitting error of the R -C-L model to the Zrs data was 7.4 ± 2.8%; its components broken down to Rrs and Xrs were 6.3 ± 2.7% and 3.7 ± 1.6%, respectively.

Comparison of intra-breath measures (**Table 3**) revealed mild elevations in R_{eE} and R_{eI} in the C and D groups but no differences in ΔR between the different patterns. ΔX reached significantly higher values in the Pattern B group than in the rest of groups. Differences in the V' dependence of Rrs measures (R_{ppE} and R_{ppI}) were milder between groups than that of Xrs

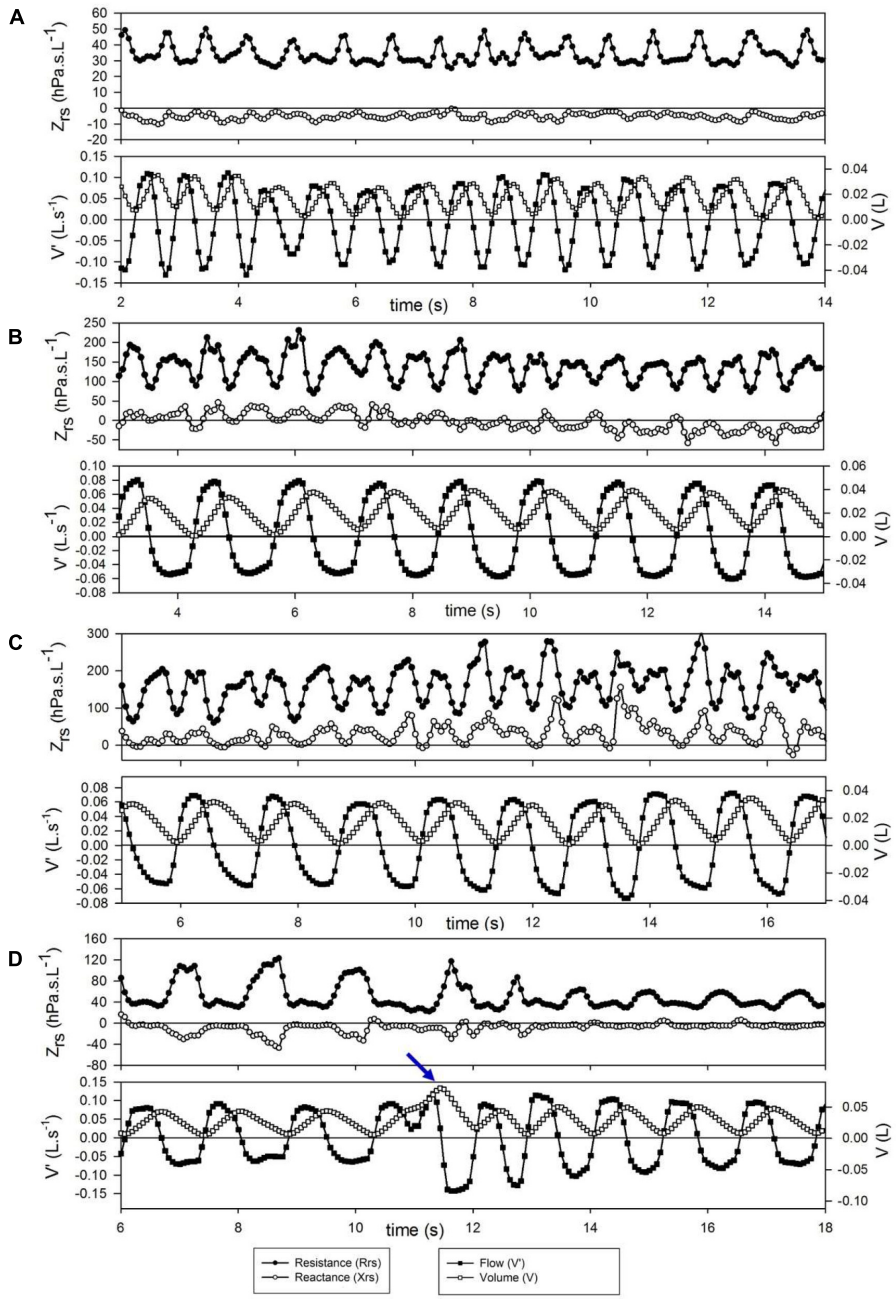

FIGURE 2 | Examples of short term changes in impedance (Zrs) and breathing pattern. Each graph represents a 12-s period. **(A)** Slightly irregular tidal flow but stable and low Zrs. **(B)** Slow downward drift in reactance (Xrs) during regular breathing. **(C)** Increasing flow dependence of Zrs during steady-state breathing; this probably reflects spontaneous development of nasal obstruction. **(D)** Transient decrease of expiratory flow limitation after a spontaneous sigh (arrow).

measures (X_{ppE} and X_{ppI}) as the latter are related to the clustering variables (**Figure 4**).

Figure 5 gives an overview on the correlations between selected indices of the spirogram, spectral oscillometry and intrabreath analysis. Among the between-category comparisons, high correlation coefficients were found between R and the intra-breath Rrs measures and between the spectral (L, f_{res} and Ax) and intra-breath Xrs measures, except C which was most correlated with Ax and X_8 but not with intra-breath Xrs data. A weak although statistically significant (r = 0.39, $p < 0.001$) linear correlation was found between ΔR and $|V''_{eE}/V''_{eI}|$. T_{PTEF}/T_E was not correlated with any of the spectral and intra-breath Rrs or Xrs outcomes, but exhibited a very strong relationship (r = 0.84, $p < 0.001$) with $|V''_{eE}/V''_{eI}|$, apparently unrelated to the pattern of V' dependence of Xrs (**Figure 6**).

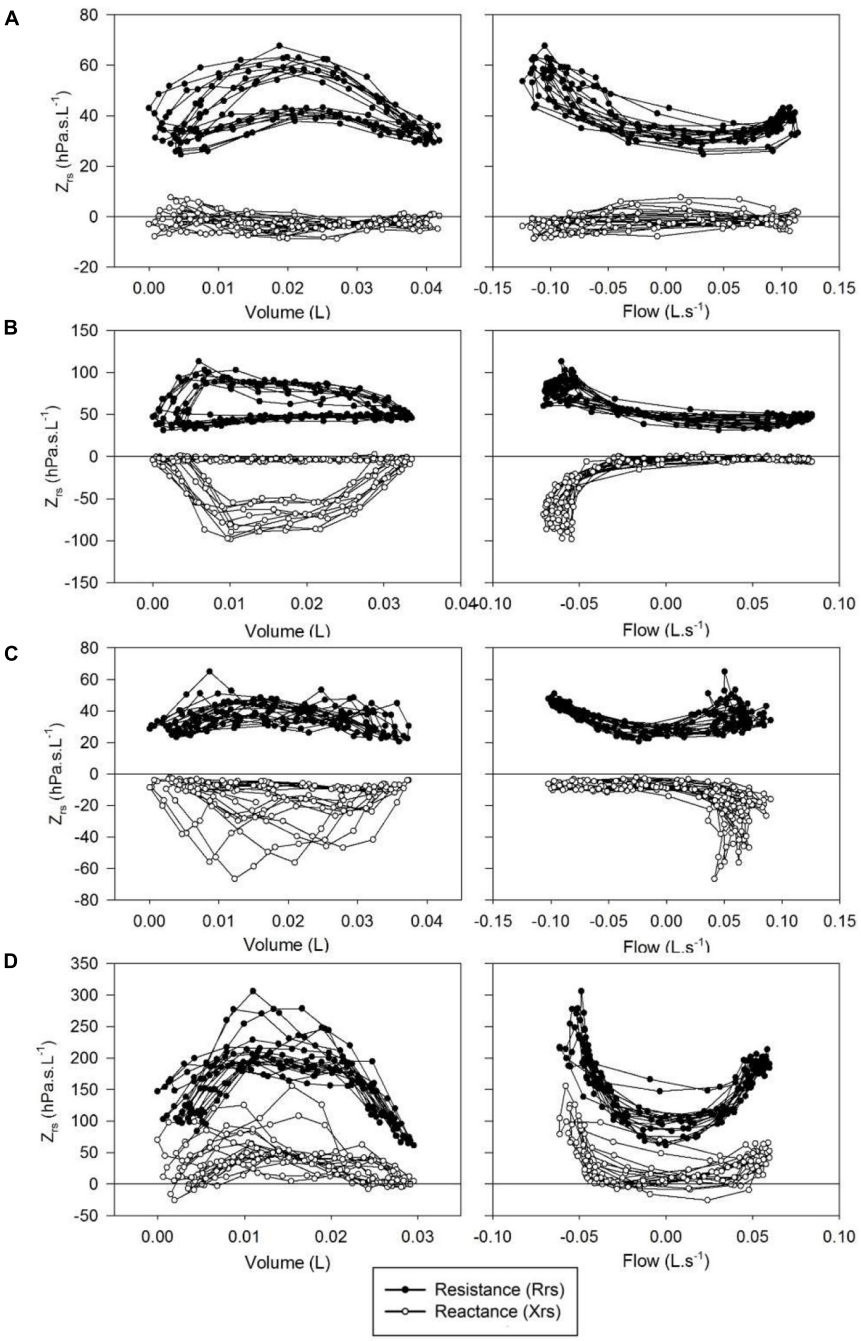

FIGURE 3 | Typical patterns of intrabreath changes in respiratory impedance (Zrs). **(A)** Insignificant changes in reactance (Xrs) and mild flow non-linearity in resistance (Rrs); **(B)** marked fall in Xrs and increase in Rrs during expiration; **(C)** marked fall in Xrs in inspiration; **(D)** increases in Xrs and Rrs with both inspiratory and expiratory flow.

DISCUSSION

The 94% success rate in the present study confirms earlier observations on the feasibility of oscillometry in unsedated newborns (5) and infants (2, 4, 7) although its outstanding value can largely be attributed to the favorable environmental and time allocation circumstances in the neonatal ward. These factors enabled a more detailed assessment of short-term variability of Zrs in healthy term neonates.

Intra-Breath Changes in Rrs

The characteristic effect of V' on Rrs was documented in early studies using single-frequency oscillations in orally breathing adult subjects (15, 16). These biphasic changes in

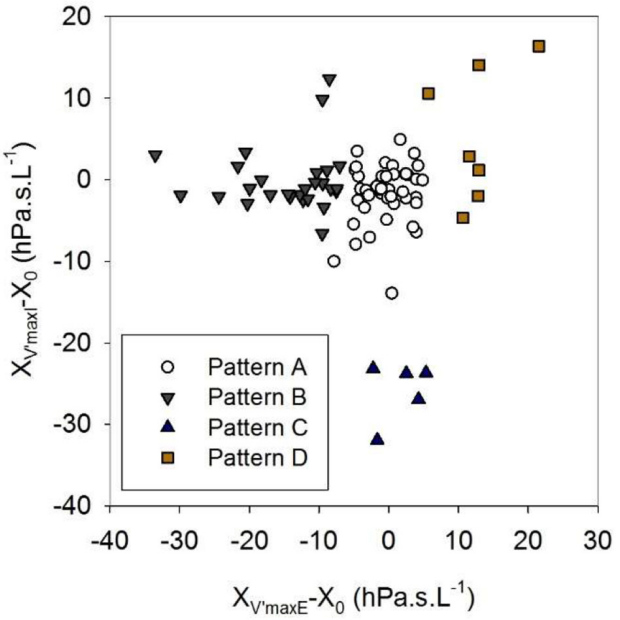

FIGURE 4 | Clusters established in the relationships between inspiratory and expiratory flow dependences of reactance. $X_{V'maxI}$ and $X_{V'maxE}$ are reactance values at peak inspiratory and expiratory flows, X_0 is the average zero-flow value of reactance. For definitions of Patterns A-D, see text or the legend to **Table 1**.

Rrs, characterized by minimum values at zero V' and local maxima at peak inspiratory and expiratory V' (V'$_{maxI}$ and V'$_{maxE}$, respectively) were a marked feature in the neonates of this study, with the non-linearity in expiration usually exceeding that of inspiration. Previous observations suggest that the non-linear, V'-dependent increase in Rrs originates from the upper airways (12, 17, 18), obeying the classical empirical description by Rohrer (19).

An unexpected finding in the present investigation was the fact that R_{eI} was higher than R_{eE} (i.e., ΔR was negative) in almost half of the subjects. This is in contrast to previous intra-breath studies where the typically positive ΔR values were attributed to the tidal dilatation of the pulmonary airways (7, 20, 21). One important specific factor in infancy is the large contribution of the extrathoracic pathways to Rrs, whose transmural pressures are dependent on V' rather than V and are opposite to that of the pulmonary airways; this may lead to narrowing of the upper airways during inspiration and possibly some residual constriction at end inspiration. Another factor, also augmented in nasal breathing is the non-steady flow patterns that develop at fast transitions of V' in the upper airways of irregular geometry. This leads to extra dissipation, which has been shown to depend on the rate of change in V' (i.e., on V") (12, 17, 18), and would add to the true "zero-flow" values of R_{eE} and R_{eI}. In the present study, the asymmetry of respiratory phase change (as characterized by the ratio V"$_{eE}$/V"$_{eI}$) was shown to correlate with ΔR. Since the transition from inspiration to expiration is usually faster than *vice versa*, it can lead to low, or even negative values in ΔR. These factors discussed above suggests that the contributions of the upper airway to ΔR may mask the change in pulmonary airway caliber. Nevertheless, the near-zero mean value of ΔR is at variance with the results of the intra-breath measurements in infants (7) where an average of 4.43 hPa.s.L^{-1} (IQR: 0.65–8.13 hPa.s.L^{-1}) was observed. Since the same custom-made wave-tube device was employed in both studies and the spectral Zrs measures are similar, differences between the 2 populations, such as ethnic (Caucasians vs. Black Africans), age (newborns vs. 6 week old infants), gestational age (term vs. term + late preterm) and other characteristics may explain the different ΔR values.

Intra-Breath Changes in Xrs

While the changes in Rrs within the respiratory cycle are dominated by the "U" shape in V' dependence of different degrees and asymmetry, Xrs exhibited qualitatively more distinct intra-breath patterns. We defined a group with the lowest V'-dependent changes in Xrs (pattern A) and considered it the control group. The rest (45%) of the examined neonates exhibited diverse and strong V' dependences of Xrs. Three additional typical V'-dependent patterns were identified qualitatively and verified by cluster analysis. Inference to the underlying mechanisms of each pattern is burdened by the lack of

TABLE 2 | Comparison of spectral oscillometry data between subject groups of different patterns of flow dependence of respiratory reactance.

	All (n = 86)	Pattern A (n = 47)	Pattern B (n = 27)	Pattern C (n = 5)	Pattern D (n = 7)
R (hPa.s.L^{-1})	48.7 ± 12.9	46.0 ± 12.6	48.7 ± 11.5	59.9 ± 17.4	58.3 ± 9.4*
C (mL.hPa^{-1})	1.08 ± 0.30	1.13 ± 0. 32	1.01 ± 0. 29	1.05 ± 0.28	1.06 ± 0. 15
L (hPa.s^2.L^{-1})	0.068 ± 0.028	0.071 ± 0.027	0.057 ± 0.023*	0.047 ± 0.031	0.102 ± 0.020**
R_8 (hPa.s.L^{-1})	63.2 ± 16.8	59.6 ± 16.3	64.6 ± 16.4	77.3 ± 22.1	72.0 ± 11.2*
X_8 (hPa.s.L^{-1})	−14.9 ± 5.4	−13.9 ± 5.1	−16.7 ± 5.8*	−17.1 ± 5.8	−13.3 ± 4.2
R_{8-32} (hPa.s.L^{-1})	18.6 ± 7.3	16.9 ± 6.4	20.6 ± 8.5	24.7 ± 5.9*	17.6 ± 5.0
f_{res} (Hz)	21.4 ± 5.9	20.1 ± 5.2	23.7 ± 4.7**	29.2 ± 11.9	16.3 ± 1.9**
Ax (hPa.L^{-1})	103.1 ± 59.6	90.7 ± 55.1	124.8 ± 58.5*	157.0 ± 80.3	64.0 ± 20.8*

Mean ± SD values. For definitions of Patterns A-D, see text or the legend to ***Table 1****. R, resistance (model fitting); C, compliance (model fitting); L, inertance (model fitting); R_8, resistance at 8 Hz; X_8, reactance at 8 Hz; R_{8-32}, resistance difference between 8 and 32 Hz; f_{res}, resonance frequency; Ax, reactance area below f_{res}.*
**$p < 0.05$ vs. Pattern A; **$p < 0.01$ vs. Pattern A.*

TABLE 3 | Comparison of intra-breath oscillometry data between subject groups of different patterns of flow dependence of respiratory reactance.

	All (n = 86)	Pattern A (n = 47)	Pattern B (n = 27)	Pattern C (n = 5)	Pattern D (n = 7)
R_{eE} (hPa.s.L^{-1})	41.7 ± 11.3	38.7 ± 10.1	41.9 ± 9.0	53.3 ± 16.0	52.7 ± 13.2*
R_{eI} (hPa.s.L^{-1})	42.1 ± 13.5	38.5 ± 13.4	43.7 ± 11.7	51.3 ± 15.8	53.5 ± 11.2*
X_{eE} (hPa.s.L^{-1})	−1.35 ± 3.98	−1.55 ± 3.55	−1.516 ± 3.14	−6.74 ± 2.84*	4.53 ± 3.86**
X_{eI} (hPa.s.L^{-1})	−3.73 ± 4.21	−3.14 ± 3.54	−5.45 ± 3.69*	−8.05 ± 4.23	1.92 ± 3.92*
ΔR (hPa.s.L^{-1})	−0.40 ± 6.48	0.23 ± 6.30	−1.83 ± 7.48	2.03 ± 2.43	−0.81 ± 5.16
ΔX (hPa.s.L^{-1})	2.39 ± 3.44	1.58 ± 3.30	3.93 ± 3.72**	1.30 ± 1.74	2.62 ± 2.36
$R_{ppE}/\|Z_0\|$	0.91 ± 0.33	0.80 ± 0.26	1.08 ± 0.32**	0.67 ± 0.20	1.25 ± 0.43*
$R_{ppI}/\|Z_0\|$	0.56 ± 0.28	0.52 ± 0.24	0.50 ± 0.22	0.87 ± 0.21*	0.85 ± 0.46
$X_{ppE}/\|Z_0\|$	0.45 ± 0.27	0.32 ± 0.13	0.70 ± 0.31**	0.28 ± 0.08	0.50 ± 0.14**
$X_{ppI}/\|Z_0\|$	0.32 ± 0.19	0.30 ± 0.13	0.28 ± 0.09	0.90 ± 0.28**	0.33 ± 0.14

Mean ± SD values. For definitions of Patterns A–D, see text or the legend to ***Table 1****. R_{eE}, resistance at end expiration; R_{eI}, resistance at end inspiration; X_{eE}, reactance at end expiration; X_{eI}, reactance at end inspiration; ΔR, tidal change in resistance (R_{eE}-R_{eI}); ΔX, tidal change in reactance (X_{eE}-X_{eI}); R_{ppE}, peak-to-peak resistance difference in expiration; R_{ppI}, peak-to-peak resistance difference in inspiration; X_{ppE}, peak-to-peak resistance difference in expiration; X_{ppI}, peak-to-peak resistance difference in inspiration; $|Z_0|$, impedance magnitude at zero flow [1/2($|Z_{eE}|$ + $|Z_{eI}|$)].*
**p < 0.05 vs. Pattern A; **p < 0.01 vs. Pattern A.*

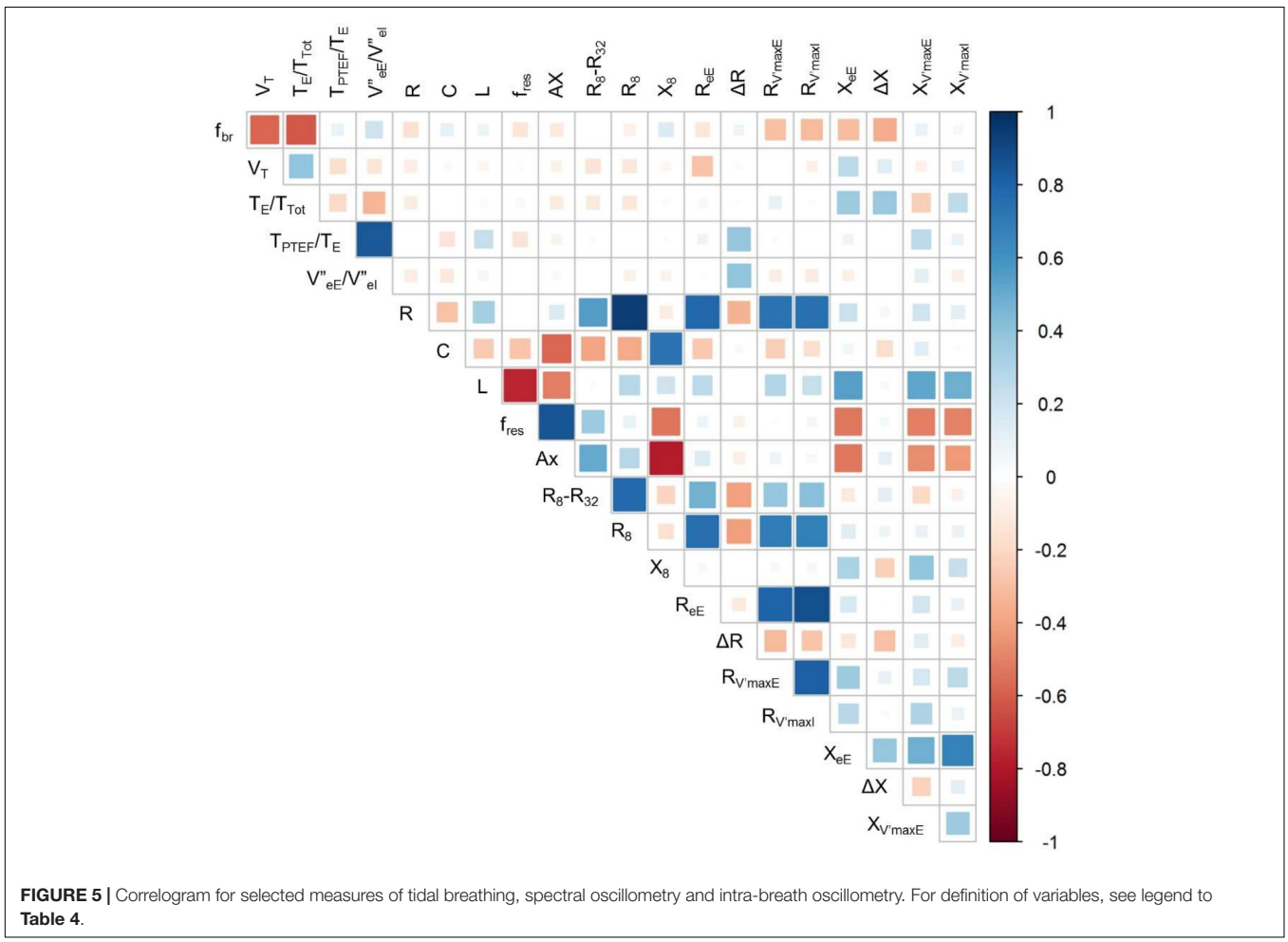

FIGURE 5 | Correlogram for selected measures of tidal breathing, spectral oscillometry and intra-breath oscillometry. For definition of variables, see legend to **Table 4**.

additional signals (e.g., nasopharyngeal pressure) unavailable in the non-invasive setting of the current study. Nevertheless, a decrease in Xrs during expiration (pattern B) is most likely caused by glottic braking that help maintain the end-expiratory lung volume in the early phase of postnatal lung and chest wall development (22). The small but highly significant increase in the T_E/T_{Tot} ratio in this group (**Table 1**) supports the above argument. Intuitively, a similar change in Xrs but in inspiration

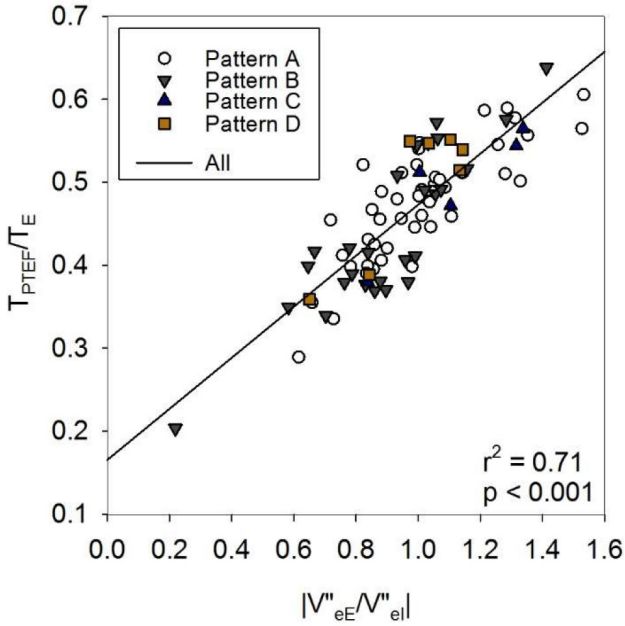

FIGURE 6 | Effect of asymmetry in volume acceleration (V") ratio on T_{PTEF}/T_E. eE: end expiration; eI: end inspiration; T_{PTEF}: time to peak tidal expiratory flow; T_E: expiratory time. For definitions of Patterns A–D, see text or the legend to **Table 1**.

TABLE 4 | Within-session variability presented as coefficient of variation (in%) of tidal breathing, spectral oscillometry and intra-breath oscillometry indices.

f_{br}	14.0 (3.9–38.2)
V_T	21.9 (7.8–42.3)
T_E/T_{tot}	7.9 (3.3–13.8)
T_{PTEF}/T_E	19.6 (11.1–44.4)
R	10.3 (1.9–29.7)
C	20.3 (3.3–88.4)
L	26.6 (3.6–154.0)
$\|Z_8\|$	13.6 (5.3–30.7)
R_{8-32}	26.5 (5.2–64.6)
f_{res}	15.7 (1.9–67.6)
Ax	37.9 (7.5–186.1)
$\|Z_{eE}\|$	19.6 (5.3–117.7)
$\|Z_{eI}\|$	23.1 (4.9–100.6)
$\|Z_{V'maxE}\|$	23.6 (4.3–71.0)
$\|Z_{V'maxI}\|$	22.2 (5.5–58.0)

Mean (range) values. f_{br}, respiratory rate; V_T, tidal volume; V'_{maxE}, peak expiratory flow; T_E, expiratory time; T_{tot}, total respiratory cycle time; T_{PTEF}, time to peak tidal expiratory flow; R, resistance (model fitting); C, compliance (model fitting); L, inertance (model fitting); $|Z_8|$, impedance magnitude at 8 Hz; R_{8-32}, resistance difference between 8 and 32 Hz; f_{res}, resonance frequency; Ax, reactance area below f_{res}.; $|Z_{eE}|$, impedance magnitude at end expiration; $|Z_{eI}|$, impedance magnitude at end inspiration; $|Z_{V'maxE}|$, impedance magnitude at maximum expiratory flow; $|Z_{V'maxI}|$, impedance magnitude at maximum inspiratory flow.

(Pattern C) can be attributed to the negative pressure swings in the glossopharyngeal area, which lead *via* deformation of soft tissues to inspiratory V' limitation and are augmented by the large nasal component of Rrs. This suggests that the nasal impedance is not only a significant additive component in Zrs (8, 11, 23) but it may modulate the transmural pressures in the compliant structures of distal extrathoracic airways more than in the case of oral breathing. Whereas Patterns B and C describe temporary changes in Xrs, pronounced in mid-expiration or mid-inspiration, respectively (**Figure 3**), Pattern D is characterized by marked positive increases in Xrs with both inspiratory and expiratory V'. This is likely to be associated with the increased impedance of the nasal pathway, in terms of both resistance and inertance, as reflected by the higher values of R and L in this group (**Table 2**), also manifested in the significant elevations in zero-V' Xrs (X_{eE} and X_{eI}, **Table 3**). Note that while the relatively low numbers of Pattern C and Pattern D subjects warrant considerations in their statistical assessments, the frequency of these patterns can be regarded as an inherent feature of the studied healthy term infants. Importantly, Xrs patterns suggesting intrapulmonary expiratory flow limitation observed in the South African cohort of 6-week-old infants (7) were not detected in the present study.

The respiratory pattern can undergo gradual or abrupt changes in a relatively short time (**Figure 2**). After examination of individual recordings, it can be concluded that a V'-dependent Xrs pattern is not a permanent characteristic of a newborn, but a temporary feature. Sudden changes in the V'-non-linearities might explain the huge day-to-day variability of spectral oscillometry (5). Therefore, measurements of both intra-breath and spectral oscillometry in the same session are recommended to detect and explain the short term changes in respiratory mechanics.

Within-Session Variability of Oscillometry Measures

The 90-s recordings allowed us to have a closer look into the short-term changes in intra-breath Zrs, which sometimes even disclosed transitions from one pattern of V' dependence into another. The within-session variability of intra-breath Zrs measures was slightly larger than that of the breathing pattern descriptors, which were obtained from the same recordings (**Table 4**). Although this may suggest that fluctuations in the spirogram cause changes in the intra-breath parameters, correlation analysis did not confirm such a relationship; similarly, no direct correlations were found between the tidal breathing pattern and the within-session variability of spectral oscillometry (data not reported).

The fact that the most stable spectral measures were R and $|Z_8|$ is somewhat surprising, as we expected a large variability contributed by the nasal pathway. Explanations based solely on our non-invasive measurement data would be speculative; however, there is indication that the nasal and the distal pulmonary resistances can change in opposite direction to maintain a relatively constant total resistance (23). The highest variability was observed in Ax, which is widely considered as a robust measure of elastic properties of the respiratory system (24). However, as the area of the negative Xrs domain is terminated by f_{res}, changes in the dominant nasal inertance would strongly influence the Ax values.

Indeed, the intra-breath analysis revealing the patterns of V' dependence indicated that Ax was biased by changes in Xrs (**Table 2**), whereas the model fitting of Zrs spectra accounted for the changes in L and resulted in remarkably constant estimates of C for all patterns in spontaneously breathing infants. The model-based approach supported by intra-breath analysis thus makes the values of C less influenced by the strong upper airway compartment and more specific to the elastic properties of the lungs.

Implications in Oscillometry Procedures in Infants

Technical standards and protocols of spectral oscillometry have been developed for cooperating children and adults (25, 26); these include reproducibility criteria based on repeated measurements that are separated by intervals when the subject is detached from the device. This protocol is clearly impractical to adopt in infant studies, primarily because of the removal and replacement of the face mask may alter the breathing pattern and the sleep stage *via* excitation of the facial nerves (27). Additionally, a minimum of 3 measurement epochs whose lowest-frequency Rrs values have a CoV of $\leq$ 10% (adults) or $\leq$ 15% (children) has been suggested as the reproducibility criterion (25). The wide ranges of within-session CoV values of tidal breathing and Zrs parameters observed in the present study (**Table 3**) may reflect a higher degree of natural variability in respiratory mechanics in neonates (28) compared with older subjects. Therefore, more permissive reproducibility criteria combined with the equally important Xrs measures and based on longer recordings should be established for infants. On the other hand, inclusion of the nasal passages in the infant oscillometry requires careful inspection of the patency of this pathway; congestion may lead to extreme values in R and L and associated with the Xrs pattern D, as in the current measurements.

Instrumentation Requirements

The spectral measures of Zrs in the present study, as expressed by the R, C and L parameter values (**Table 2**), are very close to that obtained with the same technique previously (2, 4, 5) and correspond to an impedance magnitude of 40–60 hPa.s.L^{-1}. Far above these values representing *averages* for whole breathing cycles, huge *peak values* in Zrs were identified by the intra-breath tracking to occur at instances of V'_{maxE} and V'_{maxI}. As illustrated in **Figures 2**, **3**, and quantified by the R_{ppI}/Z_0 and R_{ppE}/Z_0 data in **Table 2**, Zrs often exceeded 200 hPa.s.L^{-1} in the healthy term newborns of this study. This highlights the need for accurate measurements at peak values of Zrs and not only in intra-breath analysis, as the average values obtained in the conventional spectral oscillometry would also be distorted if an upper range of Zrs is misestimated. The wave-tube principle (29) employed in the present work is particularly advantageous in the measurements of high Zrs, and it was considered as the gold standard technique in the comparison of commercially available oscillometry devices (30). Device dependence might have been the primary reason for the large differences in the Rrs and Xrs values reported recently (13, 31), compared with that from the present and previous measurements with the wave-tube technique (2, 4, 5, 7).

Implications in Tidal Breathing Analysis

Comparative analysis of tidal breathing and oscillometry indices has revealed generally modest interrelationships (**Figure 5**) but pinpointed a strong connection between T_{PTEF}/T_E and an asymmetry measure of V" ($V"_{eE}/V"_{eI}$). T_{PTEF}/T_E can be obtained in relatively simple measurement settings and it has often been considered as a useful index to detect airway obstruction (32–34), although the assessment of T_{PTEF}/T_E as a surrogate of mechanical tests is controversial in the literature.

In the current study, T_{PTEF}/T_E did not correlate with the intra-breath Rrs or Xrs variables, and was not different between groups of V' dependence of Xrs. However, the mean values of $V"_{eE}/V"_{eI}$ of the subjects and the corresponding T_{PTEF}/T_E data covered wide ranges (**Figure 6**) with a strong linear relationship. This suggests that in healthy term newborns, such as those in the present study, marked differences in the activity of the respiratory control mechanisms rather than airway obstruction exist and determine the values of T_{PTEF}/T_E (35, 36).

Limitations

(i) The spectral and intra-breath oscillometry data were derived from recordings collected separately. In order to minimize systematic errors, the two modalities were alternated and, whenever possible, without the removal/repositioning of the face mask. Although there was good agreement in the mean 16-Hz Zrs data collected from the two modalities, the unchanged status of the respiratory mechanical system could not be guaranteed.

(ii) Although sleep state can be an important factor when interpreting lung function measurements in sleeping infants, addressing the relationship between the sleep state and respiratory mechanics was beyond the scope of the current study. Sleep states such as the active (rapid eye movement – REM) sleep and the quiet (non-REM) sleep typically last for 50–70 min in healthy newborns (37), and while we cannot exclude the possibility that a transition between sleep states took place during the measurements, it was more likely that the same state persisted during our recording sessions of typically 14-min duration. Since the estimated ratio of active and quiet sleep is approximately 2:1 in healthy term newborns (37), we can assume that a non-negligible portion of recordings was collected during active sleep. Regularity of the respiratory pattern is also known to be different during active and quiet sleep (38, 39); from the present data it can only be inferred that the variability of T_{tot} and V_T was independent of the Xrs pattern of V' dependence (**Table 1**).

(iii) The measurement device imposes some impedance against the breathing, which may alter the pattern of tidal breathing without this load. In the present study, the total load including the bacterial filter, the wave-tube, the pneumotachograph and the breathing tube amounted to 6.5 hPa.s.L^{-1}, i.e., roughly 10–15% of Rrs. Even if this additional load does not interact with the breathing pattern significantly, it increases the flow-dependent changes in the glossopharyngeal area and may augment the upper airway non-linearities.

CONCLUSION

The impedance tracking employed in the present study revealed marked intra-breath changes in Rrs and Xrs in healthy term neonates during natural sleep in the first few days of life. These changes were dominated by the increases in Rrs with V' in both inspiration and expiration, whereas Xrs exhibited different patterns of change, such as inspiratory and expiratory flow limitation. It is suggested that these intra-breath non-linearities are of upper airway origin, with fundamental contributions from the nasal pathways. Intra-breath changes exert a biasing effect on the conventional measures of the multi-frequency oscillometry that are intended to characterize pulmonary mechanics. It is recommended that the measurements of Zrs in infants cover longer study intervals than that required from cooperative subjects to account for the variable mechanical status of the developing respiratory system. Use of intra-breath oscillometry is proposed to gain more insight into the mechanisms determining Zrs and to properly interpret the results of conventional spectral oscillometry in infants.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Clinical Ethics Committee of the University of Szeged (91/2011, renewed in 2017). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

BR, ZGy, and ZH: study design and evaluation of measurements. BR and ZGy: impedance measurements. GM, ZGy, and ZH: design of the infant oscillometry system. BR, GM, ZGy, DC, and ZH: development of the infant intra-breath analysis. BR, DC, and ZH: interpretation of results. BR and ZH: drafting of the manuscript. All authors contributed to the article and approved the submitted version.

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The Relationship Between Cord Blood Cytokine Levels and Perinatal Characteristics and Bronchopulmonary Dysplasia: A Case–Control Study

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Objective: To establish the association between serial levels of inflammatory cytokines in cord blood and perinatal characteristics and bronchopulmonary dysplasia (BPD) in preterm infants.

Methods: 147 premature infants with gestational age ≤32 weeks who were born and hospitalized in the First Affiliated Hospital of Zhengzhou University between July 2019 and August 2021 were enrolled in this retrospective case–control study. Multiple microsphere flow immunofluorescence was used to detect seven cytokines in cord blood collected within 24 h of birth. Demographics, delivery characteristics, maternal factors, neonatal characteristics, and clinical outcomes were collected for the two groups. An unconditional logistic regression model was used in this study to assess the clinical variables.

Results: IL-6 cord blood levels at birth were significantly higher in the BPD group than in the non-BPD group, but the odds ratio (OR) was very small (OR = 1). No differences in other cytokine concentrations were observed between the two groups. Multivariable logistic regression analysis demonstrated that increased maternal white blood cell (WBC) count on admission and lower birth weight increased the risk of BPD progression.

Conclusions: Increased IL-6 cord blood levels at birth in preterm infants may have trivial significance for predicting BPD. Furthermore, higher maternal WBC count on admission and lower birth weight increased the risk of BPD.

Keywords: cord blood, cytokines, maternal, perinatal factors, bronchopulmonary dysplasia

INTRODUCTION

In 1967, Northway et al. first introduced the term bronchopulmonary dysplasia (BPD) to describe pulmonary injury in premature infants with respiratory distress syndrome (RDS) due to oxygen therapy and mechanical ventilation that showed imaging evidence of chest abnormalities at 36 weeks post-menstrual age (1). The prevalence of BPD has not decreased proportionately with advances in neonatal intensive care health care for respiratory management, including surfactant administration, perinatal steroids, and protective mechanical ventilation strategies, such as non-invasive positive pressure ventilation or high-frequency oscillatory ventilation, which have significantly improved the survival rate of preterm infants (2). BPD continues to be a common chronic respiratory disorder of preterm infants that affects ∼20–40% of very-low-birthweight infants (3). BPD causes long-term pulmonary morbidities and places an enormous economic burden on society and families (4). BPD is correlated with an increased incidence of clinical sequelae during hospitalization and after discharge, prolonged hospital stay, recurrent respiratory infections, and adverse neurodevelopmental outcomes throughout infancy (5). Consequently, identifying a useful biological marker that predicts BPD in premature infants and conducting timely treatment intervention are essential to reduce pulmonary complications in premature infants with BPD.

Several studies have shown that perinatal, neonatal, and postpartum factors are related to the onset of BPD, and little is known about antenatal factors. Our research has shown that a high maternal white blood cell (WBC) count on admission increases the risk of BPD, which suggests that perinatal factors related to systemic inflammation predispose patients to the development of BPD. Many factors, including preterm birth, exposure to supplemental oxygen, mechanical ventilation, proinflammatory mediators with inflammation, perinatal infection, inherited genetic factors, and postnatal infection, are involved in the progression of BPD (6). Among these factors, pulmonary inflammation plays a crucial role in the pathologic process of BPD. Lung tissue inflammation is exacerbated by mechanical ventilation and oxygen exposure, and the release of proinflammatory cytokines into lung tissue during the inflammatory process further aggravates lung injury in preterm infants (7). Previous studies have revealed that proinflammatory cytokine concentrations in the serum and bronchoalveolar fluid lavage of preterm infants that were obtained within 24 h of birth are correlated with increased incidence of BPD (8). It is difficult to collect samples of amniotic fluid and tracheal aspirate from premature infants, whereas cord blood is easy to obtain for measurement of cytokine levels. In some studies, cytokine levels in umbilical cord samples obtained after birth were analyzed in relation to major neonatal complications, including BPD (9). Few studies have been performed thus far on the relationship of inflammatory cytokine concentrations in cord blood samples obtained at birth and maternal characteristics and BPD.

Accordingly, this study aims to analyze the value of cytokine concentrations from cord blood samples obtained within 24 h of birth as a non-invasive biomarker and to determine clinical variables for identifying independent risk factors for the occurrence of subsequent BPD in premature infants.

METHODS

Study Design and Population

We performed a retrospective case–control study that was approved by the ethics committee of the First Affiliated Hospital of Zhengzhou University and for which informed parental consent was provided by all participants. The inclusion criteria were as follows: (1) a gestational age at birth below 32 weeks, (2) admission immediately after birth to our neonatal intensive care unit from July 2019 to August 2021 and survival until discharge, and (3) detection of cytokines within the first day of birth. The exclusion criteria were as follows: (1) major congenital malformations (e.g., congenital heart disease, multiple malformations, and chromosomal abnormalities), (2) incomplete data, and (3) death before discharge. Among 147 preterm infants with a gestational age of ≤32 weeks that were hospitalized in our institution during the study period, 60 developed BPD, corresponding to an incidence of 40.8%.

Data Collection

Clinical data on demographics, delivery characteristics, and maternal and neonatal factors were retrospectively obtained from the hospital's electronic medical record system. The demographic and delivery characteristics included gestational age (GA), birth weight (BW), small for gestational age (SGA), sex, mode of delivery, placental abnormalities (including placenta previa, implantation and abruption), meconium-stained amniotic fluid, and 1- and 5-min Apgar scores. Data on maternal characteristics were also collected, including maternal age, multiple pregnancies, gestational hypertension, gestational diabetes mellitus (GDM), antenatal steroid administration, tocolytic treatment (e.g., progesterone), premature rupture of membranes (PROM), intrauterine growth restriction, embryo transfer, and maternal WBC count on admission. Neonatal characteristics and the presence of neonatal morbidities, including continuous positive airway pressure, mechanical ventilation, surfactant therapy, respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), patent ductus arteriosus (PDA), and sepsis, were obtained and recorded.

BPD was defined as a requirement for >21% supplemental oxygen at 28 postnatal days, which was consistent with the standards of the National Institutes of Health (10). RDS and IVH were diagnosed according to corresponding criteria (11, 12). PDA was identified as an infant needing indomethacin or ligation to close the ductus arteriosus. Echocardiography was the standard used to diagnose PDA (13). Infants with symptoms of sepsis and blood cultures showing bacterial growth were evaluated as having sepsis. Gestational age was estimated according to the last menstrual time and ultrasound diagnosis. A birth weight (BW) <10th percentile of the average weight for the respective gestational age was classified as small for gestational age (SGA) (14). PROM was defined as the occurrence of natural membrane rupture before delivery at a gestational age ≤37 weeks (15).

TABLE 1 | Demographic and delivery characteristics of the controls and infants with BPD.

	BPD group ($n = 60$)	Control group ($n = 87$)	OR (95%CI)	*P*-value
Gestational age (wks), [median (IQR)]	29.30 (28.13, 30.20)	30.30 (29.10, 31.00)	0.939 (0.818, 1.078)	0.373
Birth weight (g), mean ± SD	1,178.83 ± 278.77	1,332.76 ± 315.03	0.998 (0.997, 0.999)	0.004*
SGA, *n* (%)	13 (21.7)	14 (16.1)	0.693 (0.300, 1.605)	0.392
Male sex, *n* (%)	26 (43.3)	37 (42.5)	0.968 (0.498,1.880)	0.923
Mode of delivery, cesarean, *n* (%)	44 (73.3)	53 (60.9)	0.567 (0.277, 1.160)	0.120
Placental abnormalities, *n* (%)	18 (30)	18 (20.7)	0.609 (0.285, 1.298)	0.199
Meconium-stained amniotic fluid, *n* (%)	14 (23.3)	21 (24.1)	1.045 (0.482, 2.267)	0.910
1 min Apgar score, [median (IQR)]	8 (6.25, 9)	8 (6.9)	0.965 (0.822, 1.134)	0.666
5 min Apgar score, [median (IQR)]	9 (8.10)	9 (8.10)	0.974 (0.781, 1.214)	0.816

Values are expressed as mean ± SD, median (IQR), or n (%).
IQR, Interquartile range; OR, odds ratio; CI, confidence intervals.
P-values were determined by univariate unconditional logistic regression analysis.
**Indicated statistical significance.*

Gestational hypertension was defined as a systolic blood pressure of 140 mmHg or more, a diastolic blood pressure of 90 mmHg or more, or both after 20 weeks of gestation (16). GDM was defined according to the guidelines of the American Diabetes Association (17).

Cytokine Determinations

An early blood sample from the umbilical cord was collected within the first 24 h of life, and the concentrations of cytokines (IL-4, IL-6, IL-10, IL-12p70, IL-17, TNF-α, and IFN-γ) in the cord blood were detected by multiple microsphere flow immunofluorescence (using FACSCanto II flow cytometers produced by the BD Company, Qingdao, China). The cytokine detection reagent was provided by Qingdao Raisecare Biotechnology Co, Ltd., Qingdao, China (Lot Number: 2019801) according to the manufacturer's recommendations. The normal ranges of IL-4, IL-6, IL-10, IL-12p70, IL-17, and TNF-α were 0–8.56, 0–5.4, 0–12.9, 0–3.4, 0–21.4, 0–16.5, and 0–23.1 (pg/ml), respectively.

Statistical Analysis

Unconditional logistic regression analysis was used to analyze clinical parameters significantly correlated to the onset of BPD. Quantitative data were obtained by performing a normality test (the Shapiro–Wilk test), and continuous variables were represented as by the mean ± SD if normally distributed and by medians and interquartile ranges otherwise. Qualitative data were analyzed by the χ^2-test and reported as frequencies (n) and percentages (%). The data were analyzed using IBM SPSS Statistics v. 25 software. All analyses were performed using 2-sided tests, and $p < 0.05$ was regarded as statistically significant.

RESULTS

A total of 147 premature infants with gestational ages below 32 weeks were enrolled in our study, including 60 infants in a BPD group and 87 infants in a non-BPD group.

Based on demographic and delivery characteristics (**Table 1**), the birth weight [1,178.83 (278.77) vs. 1,332.76 (315.03), $p = 0.004$] of the BPD group was lower than that of infants without BPD. There were no significant differences in other clinical variables, including gestational age (GA), small for gestational age (SGA), sex, delivery mode, placental abnormalities, meconium-stained amniotic fluid, and 1- and 5-min Apgar scores.

The maternal perinatal data and clinical variables were comparable in both groups of infants as assessed by univariate analysis (**Table 2**). Mothers delivering preterm infants that developed BPD had a higher mean WBC count on admission than mothers delivering infants without BPD [11.74 × 10^9/L vs. 10.23 × 10^9/L; odds ratio (OR), 1.121; $p = 0.02$]. The difference remained insignificant in maternal age, multiple pregnancies, gestational hypertension, GDM, antenatal steroid administration, tocolytic treatment, PROM, intrauterine growth restriction, and embryo transfer rates between the two groups.

Insignificant differences in both groups of infants in terms of neonatal characteristics and clinical outcomes could be detected, including main clinical therapeutic strategies, such as continuous positive airway pressure, mechanical ventilation, and surfactant therapy, as well as major clinical outcomes, including RDS, IVH, PDA, and sepsis (**Table 3**).

The IL-6 cord blood levels were significantly higher (median 102.69 vs. 25.07 pg/ml, $p = 0.02$) in the BPD group than in infants without BPD, but the OR was very small, and for every 1-pg/ml increase in the cord blood IL-6, there was a relatively small risk increase in the development of BPD [OR = 1; 95% confidence interval (CI), 1.000–1.000]. An insignificant difference was observed from cord blood samples in terms of other inflammatory cytokine concentrations (IL-4, IL-10, IL-12p70, IL-17, TNF-a, IFN-γ) between the BPD and non-BPD groups (**Table 4**).

The results of the aforementioned univariate analysis showed significant differences in the birth weight, maternal WBC count on admission, and IL-6 cord blood levels between the two groups of infants. All variables with a p-value < 0.05 were included in the multivariate logistic regression analysis, and the

TABLE 2 | Univariate regression analysis of perinatal factors of infants With BPD and controls.

	BPD group ($n = 60$)	Control group ($n = 87$)	OR (95%CI)	P value
Maternal age, [median (IQR)]	31 (28.35)	31 (29.34)	1.018 (0.954–1.085)	0.593
Multiple pregnancies, *n* (%)	13 (21.7)	26 (29.9)	1.541 (0.716–3.317)	0.269
Gestational hypertension, *n* (%)	21 (35)	29 (33.3)	0.929 (0.464–1.857)	0.834
Gestational diabetes mellitus, *n* (%)	12 (20)	20 (23)	1.194 (0.533–2.673)	0.666
Antenatal steroid, *n* (%)	8 (13.3)	15 (17.2)	1.354 (0.535–3.430)	0.523
Antenatal tocolytics, *n* (%)	25 (41.7)	23 (26.4)	0.503 (0.250, 1.014)	0.055
PROM, *n* (%)	18 (30)	25 (28.7)	0.941 (0.457–1.936)	0.868
IUGR, *n* (%)	5 (8.3)	5 (5.7)	0.671 (0.185–2.426)	0.543
Embryo transfer, *n* (%)	16 (26.7)	13 (14.9)	0.483 (0.212–1.099)	0.083
Maternal WBC count on admission (*10^9/L), mean ± SD	11.74 ± 4.04	10.23 ± 3.29	1.121 (1.021–1.232)	0.017*

Values are expressed as mean ± SD, median (IQR), or n (%).
PROM, Premature rupture of membranes; IUGR, intrauterine growth restriction.
P-values were determined by univariate unconditional logistic regression analysis.
**Indicated statistical significance.*

TABLE 3 | Univariate regression analysis of neonatal characteristics and clinical outcomes of infants with BPD and controls.

	BPD group (n =6 0)	Control group ($n = 87$)	OR (95%CI)	*P*-value
CPAP, *n* (%)	24 (40)	36 (41.4)	1.059 (0.542–2.069)	0.867
MV, *n* (%)	19 (31.7)	19 (21.8)	0.603 (0.286–1.270)	0.183
Surfactant use, *n* (%)	12 (20)	29 (33.3)	2.000 (0.922–4.336)	0.079
RDS, *n* (%)	57 (95)	82 (94.3)	0.863 (0.198–3.757)	0.845
IVH, *n* (%)	46 (76.7)	62 (71.3)	0.755 (0.354–1.610)	0.467
PDA, *n* (%)	14 (23.3)	21 (24.1)	1.045 (0.482–2.267)	0.910
Sepsis, *n* (%)	9 (15)	10 (11.5)	0.736 (0.280–1.937)	0.535

Values are expressed as n (%).
CPAP, continuous positive airway pressure; MV, mechanical ventilation; RDS, respiratory distress syndrome; IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus.
P-values were determined by univariate unconditional logistic regression analysis.

results demonstrated that an elevated maternal WBC count on admission (OR = 1.112; 95% CI, 1.006–1.229; $p = 0.04$) and low birth weight (OR = 0.998; 95% CI, 0.996–0.999; $p = 0.003$) were significantly associated with the development of BPD (**Table 5**).

DISCUSSION

It was demonstrated in this study that IL-6 cord blood levels within 24 h of birth were higher in the BPD group than in infants without BPD, and the difference was significant. An elevated maternal WBC count on admission was independently related to the occurrence of BPD. A multivariable regression analysis showed that this correlation remained after adjusting for other confounding factors, which has not been previously reported and suggests that the role of maternal perinatal inflammation may be critical for the pathologic process of BPD. In addition, low birth weight was independently associated with BPD occurrence. This result has been reported in previous studies (18).

IL-6 is a proinflammatory mediator that can induce lung lesions, aggravate long-term ventilation-induced barotrauma, and accelerate pulmonary inflammatory progression in the premature population, thus promoting pulmonary remodeling and the development of chronic lung disease (19, 20). IL-6 also increases inflammatory cytokine production (21). Elevated concentrations of the proinflammatory cytokine IL-6 have been demonstrated in both serum and tracheal aspirate (TA) samples collected on the first day of life of infants who subsequently developed BPD (22, 23). The results of our case–control study are more likely to demonstrate the true relationship between cytokine concentration profiles for cord blood obtained within 24 h of birth and BPD than previous reports. These findings indicate that among the investigated cytokines, cord blood values of IL-6 obtained within 24 h of birth are correlated with a higher incidence of BPD, which is consistent with previous findings (24). Although the *p*-value obtained from the multivariable logistic regression analysis showed a significant statistical difference in the IL-6 in cord blood obtained within 24 h of birth for the two groups, the OR was very small; thus, for every 1-pg/ml increase in cord blood IL-6, the impact on the increased risk of BPD was negligible, which suggests that IL-6 may have limited predictive value for the onset of BPD because the upper limit of 95% CI of the IL-6 level was close to 1.0.

At present, there is no relevant article on the relationship between umbilical cord blood IL-6 level within 24 h after birth and neonatal diseases. In our study, we found that the level of IL-6 cord blood at birth in the BPD group was significantly higher than that in the non-BPD group, but the OR was very small (OR = 1). This may be related to the late occurrence of BPD and the small gestational age of the cases we enrolled in the statistical analysis. In other words, the time span between the detection of umbilical cord blood IL-6 level within 24 h after birth and the occurrence of BPD is large, resulting in a smaller OR. In

TABLE 4 | Univariate regression analysis of umbilical cord cytokine levels in infants with and without BPD.

	BPD group ($n = 60$)	Control group ($n = 87$)	OR (95%CI)	*P*-value
IL-4, pg/mL	0.59 (0.30–1.30)	0.43 (0.22–1.16)	1.006 (0.989–1.023)	0.482
IL-6, pg/mL	102.69 (14.16–1,129.19)	25.07 (3.66–116.39)	1.000 (1.000–1.000)	0.016*
IL-10, pg/mL	2.43 (1.08–3.82)	2.01 (0.79–6.51)	0.997 (0.985–1.008)	0.569
IL-12p70, pg/mL	0.76 (0.29–1.24)	0.65 (0.23–1.40)	0.899 (0.701–1.153)	0.401
IL-17, pg/mL	0.77 (0.22–1.35)	0.53 (0.23–1.35)	0.915 (0.720–1.162)	0.466
TNF-a, pg/mL	0.60 (0.20–2.59)	1.20 (0.24–2.65)	0.901 (0.770–1.054)	0.192
IFN-γ, pg/ml	2.32 (1.03–4.89)	3.03 (1.19–8.21)	0.966 (0.913–1.021)	0.221

Values are expressed as median (IQR).
P-values were determined by univariate unconditional logistic regression analysis.
**Indicated statistical significance.*

conclusion, to some extent, this suggests that cord blood IL-6 levels within 24 h after birth are associated with BPD.

This research demonstrated that maternal factors related to perinatal inflammation, such as an elevated maternal WBC count on admission, were correlated with BPD and have not been mentioned in previous literature, which suggest that the occurrence of BPD is associated with antenatal intrauterine inflammation to some extent. It is well known that an elevated WBC count indicates maternal infection. Maternal infections may have an impact on the state of neonates. Premature neonates are particularly vulnerable to infections because of immature immune defense systems, incompletely developed skin barriers, and frequent requirements for invasive operations (25). Fetal exposure to maternal infection has also been demonstrated to interrupt normal pulmonary vascular development and predispose preterm infants to the subsequent onset of BPD. This hypothesis is supported by a previous observation that perinatal maternal inflammation increases the expression of inflammatory factors in the fetal lung, which in turn affects the formation of alveoli and microvessels (26). However, in the case of maternal systemic infection, the exact pathogenesis of BPD is not completely understood. According to the current study and previous observation (27) demonstrating that proinflammatory cytokines scarcely pass through the placenta, maternal serum levels of IL-6, IL-8, TNF-α, and IFN-γ are not increased in preterm infants, suggesting that maternal inflammation status has limited predictive value for intrauterine infection and the development of BPD. Nevertheless, maternal exposure to inflammatory bacterial products can compromise neonates' innate immune systems, which has a tendency to exacerbate inflammation and infection. This finding provides further support for the hypothesis that maternal lipopolysaccharide administration might aggravate fetal inflammatory responses by triggering the production of reactive oxidative agents, leading to fetal proinflammatory cytokine expression (28). Proinflammatory mediators may contribute to the progression of BPD (29). The inflammatory response in the developing lung mediated by proinflammatory cytokines impacts normal alveolarization and impairs microvascular development (30).

The pathogenesis of BPD is multifactorial. However, a continuous inflammatory response may be a major contributor to the development of chronic lung disease (31). Cytokines are the principal regulators of intercellular communication and participate in mediating the inflammatory response, which are also involved in pulmonary vascular development, the mediation of acute lung lesions, and aggravate ventilator-induced lung injury (32, 33). High oxygen exposure appears to contribute to lung injury in premature infants, leading to the activation of proinflammatory cytokines (34). However, there is contradictory evidence demonstrating the cytoprotective role of IL-6 under exposure to hyperoxia (35). IL-6 can increase mortality, DNA damage, and apoptosis under exposure to hyperoxia and regulate angiogenesis in newborns (36). In summary, these observations indicate that the incidence of BPD may be multifactorial, and further investigation is needed to assess the function of IL-6 induced by hyperoxia exposure.

TABLE 5 | Multivariable logistic regression analysis showing the relationship between independent variables and the risk of BPD in infants with BPD and control groups.

	OR	95%CI	*P*-value
Birth weight, g	0.998	0.996–0.999	0.003*
Maternal WBC count on admission, $\times 10^9$/L	1.112	1.006–1.229	0.037*
IL-6, pg/mL	1.000	1.000–1.000	0.010*

P-values were determined by multivariable unconditional logistic regression analysis.
**Indicated statistical significance.*

In previous studies, the IL-6 level in cord blood samples obtained at birth has been used as a predictor of the occurrence and progression of BPD in premature infants, and elevated IL-6 levels have been reported to suggest intrauterine infection (37). The rate of intrauterine infection is increased in PROM cases (38). Premature rupture of membranes is accompanied by an increase in the incidence of preterm birth (39). Premature infants have immature innate and adaptive immune responses that are characterized by insufficient synthesis of IgG, inadequate regulation and phagocytosis of pathogens, and higher activation of Th1 cells than Th2 cells, which may increase susceptibility to BPD (15). This indicates that the level of interleukin 6 in cord blood is related to the development of BPD.

Furthermore, cord blood samples can potentially be used as a non-invasive biological marker to predict the risk of major

neonatal outcomes, including retinopathy of prematurity (40), RDS (41), necrotizing enterocolitis (42), sepsis (43), IVH (44), and hyperbilirubinemia (45). In this study, cord blood samples collected within 24 h of birth were used to predict the progression of BPD, and the results provide evidence of the predictive value of umbilical cord blood samples for neonatal diseases. However, cord blood cytokine concentrations may not reflect the lung cytokine concentration, as well as tracheal aspirate (TA) and amniotic fluid; therefore, an evaluation of human lung tissue is crucial to better ascertain the disease status (46). Further research is needed to explore this aspect.

In this study, low birth weight was implicated as an important factor for BPD. This result was in agreement with those of several studies (47). This result is also supported by previous reports that low-birth-weight infants are prone to develop BPD due to an immature antioxidative stress defense system resulting from exposure to hyperoxia at birth and a lack of surfactant (48). Insufficient surfactant can enhance susceptibility to RDS, thus increasing the incidence rate of BPD (49). Furthermore, studies have shown that birth weight is negatively correlated with the severity of BPD (50). This result further demonstrates that low birth weight is responsible for a high incidence of BPD.

This study has some potential limitations. First, the case–control design made it difficult to avoid selection bias and recall bias in the enrolled study population. Second, the relatively small sample led to low statistical efficiency of the research results, such that the reliability of the conclusion needs to be confirmed. Therefore, we cannot rule out the occasionality of a significant difference in cord blood interleukin 6 levels between the two groups of infants. Further studies on large samples are also needed to investigate an association between cord blood cytokine concentrations and the progression of BPD in premature infants. Limited by its retrospective nature, most of the data (such as maternal and other perinatal factors) used in this study were collected from an electronic medical record system before enrollment of subjects. Therefore, all the clinical indices were accurately recorded, and maternal pregnancy outcomes were assessed during data collection. The present study had several strengths. First, the researchers who collected samples, recorded clinical indexes, and measured cytokine levels were blind to each other, which reduced the possibility of selection bias. Second, as foreign populations were investigated in previous studies, the Chinese population investigated in our study fills a gap in this field.

CONCLUSION

Our study demonstrates that inflammatory cytokine levels in cord blood obtained on the 1st day after birth may have limited predictive ability for the development of BPD. In addition, maternal characteristics associated with perinatal inflammation, such as elevated maternal WBC count on admission, have been found to be correlated with the onset of BPD. Therefore, further research on a larger number of enrolled infants is needed to investigate a potential association between measured concentrations of multiple cytokines in blood samples of premature infants and BPD. The role of interleukins as pulmonary biomarkers in the development of BPD and even timely therapeutic interventions during pregnancy also need to be investigated in the future.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

QZ, MW, and CL designed the main purposes and methods of this study. MW wrote the article and QZ revised the article. ZS, XC, and ML participated in the index design and preliminary statistical analysis. WC, JZ, JG, MS, WD, YZ, and MZ participated in the data collection and critically reviewed the contents of the article. All authors agree to submit the final article and agree to be responsible for all aspects of the work.

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D-dimer: The Risk Factor of Children's Severe Mycoplasma Pneumoniae Pneumonia

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Objective: Mycoplasma Pneumoniae (MP) is an important cause of community-acquired pneumonia in children, which can cause serious consequences. There has been some research into predicting Severe Mycoplasma Pneumoniae Pneumonia (SMPP) primarily focused on pre-treatment time by macrolide, pre-hospital course, CRP and LDH et.al. while seldom reporting on concoagulation status. We designed this retrospective study to compare the difference between SMPP and Non-severe MPP (NSMPP) with an attempt to find the risk factors, with a special focus on concoagulation status.

Method: We performed a retrospective study of 786 MPP patients who were hospitalized from January 1, 2016 to December 31, 2018, age ranging from 28 days to 18 years old. All patients were divided into SMPP group and NSMPP group. A univariate analysis was conducted between both groups. The factors with statistical differences were included in logistic regression analysis to summarize the predictors of SMPP. Next, the predictive value of each risk factor was calculated from the receiver operating characteristic curve (ROC curve). Patients who had D-dimer records were divided into the elevated D-dimer group (D-dimer > 308ug/L) and the control group (D-dimer ≤ 308ug/L), and the clinical manifestations were compared.

Results: There was no significant difference in gender, age, pre-treatment time by macrolide, the white blood cell counts (WBC), Fibrinogen (FIB), Activated Partial Prothrombin Time (APTT), Prothrombin Time (PT) and Thrombin Time (TT) between SMPP and NSMPP. Compared with NSMPP, the pre-hospital course of SMPP was longer ($P < 0.05$), the neutrophil ratio (N%), platelet Count (PLT), C-reactive Protein (CRP), Lactate Dehydrogenase (LDH) and D-dimer were significantly higher ($P < 0.01$). The binary logistic regression analysis showed that the N%, PLT, CRP, LDH and D-dimer were the key predictors for SMPP, the N% > 67%, OR = 3.233, PLT > 445×10^9 /L, OR = 2.589, LDH > 354U/L, OR = 4.335 and D-dimer level > 403 ug/L, OR = 7.316. The D-dimer possessed the best predictive value. The incidence of complications such as pleural effusion, myocardial and liver damage of MPP was higher in the elevated D-dimer group than that in the control group ($P < 0.05$).

Conclusion: The N%, PLT, CRP, LDH and D-dimer were risk factors for SMPP. D-dimer was the best predictor among them. MPP patients with D-dimer > 308ug/L had more complications such as pleural effusion, myocardial and liver damage. More attention should be given in the treatment for this group.

Keywords: mycoplasma pneumoniae, pediatrics, risk factor, D-dimer, concoagulation status

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INTRODUCTION

Mycoplasma Pneumoniae (MP) is an important cause of community-acquired pneumonia in children, accounting for 10% to 40% of the community-acquired pneumonia in all hospitalized children (1, 2). MPP is usually a self-limiting disease, yet it can also progress into refractory or severe pneumonia. With the increasing resistance to macrolides of MP in recent years, the incidence of SMPP is also increasing. SMPP could be complicated with pleural effusion, atelectasis and necrotizing pneumonia, etc. In severe cases, respiratory failure and hypoxemia may occur, requiring mechanical ventilation, support of extracorporeal membrane oxygenation, and may even result in death (3, 4). Children with MPP can also show a wide range of extra-pulmonary manifestations (5, 6). In recent years, there have been increasing reports of MP with thrombosis, including cerebral embolism, pulmonary embolism and DIC, etc. (6), which can result in serious consequences. There has been some research into predicting SMPP mainly focused on pre-treatment time by macrolide, pre-hospital course, CRP and LDH et al. (7, 8), while seldom reporting on concoagulation status. We designed this retrospective study to compare the difference between SMPP and NSMPP with an attempt to find the risk factors, with a special focus on concoagulation status.

MATERIALS AND METHODS

Setting and Patients

We performed a retrospective study at the Children's Hospital Affiliate to Capital Institute of Pediatrics, a tertiary referral children's hospital in Beijing, China from January 1, 2016 to December 31, 2018. The study was approved by the Research Ethics Board of this hospital.

Diagnostic Criteria

MPP diagnosis is as follows: acute respiratory infection symptoms (fever, cough or wheezing), physical examination and chest imaging with infiltrates and laboratory confirmed MP infection that include: serum Mycoplasma pneumoniae antibody $\geq$ 1:320, or serum Mycoplasma pneumoniae antibody $\geq$ 1:160 and the MP polymerase chain reaction (PCR) positive, or MP antibody titer of recovery phase and acute phase increased or decreased by 4 times or more (9, 10).

Severe MP pneumonia that is defined as MP pneumonia with one of the following: poor general conditions, significant increase in breathing rate (RR $>$ 70 breaths/min in infants, and 50 breaths/min in older children), Cyanosis; dyspnea, $\geq$ 2/3 of the lobe or multilobe involvement, pleural effusion, pulse oxygen saturation $\leq$ 92%, extra-pulmonary complications.

Inclusion criteria: The patients diagnosed with MPP ranging from age $\geq$ 28 days to 18 years old.

Exclusion criteria: (1) evidence of co-infection, including bacteria, viruses, fungi and tuberculosis, etc. (2) pre-existing chronic respiratory disease such as asthma, congenital bronchopulmonary abnormalities, bronchiectasis, etc. (3) Pre-existing other systemic diseases, such as congenital heart disease, chronic kidney disease, connective tissue disease, tumors and hematological diseases, immunodeficiency, etc.

Data Sources

The data source for analysis of patient information was collected from electronic medical records of the hospital. The evaluation indicators include pre-treatment time by macrolide, pre-hospital course, clinical symptoms and signs, intrapulmonary and extrapulmonary complications, laboratory and imaging findings. The laboratory tests include hemoglobin, WBC counts, neutrophil ratio (N%), PLT, CRP, LDH, D-dimer (ELISA method with the normal rang $<$ 243 ug/L), FIB, APTT, PT, TT, procalcitonin (PCT), alanine aminotransferase (ALT), aspartate aminotransgerase (AST), blood urea nitrogen (BUN), blood electrolytes, creatinine kinase, MB isoenzyme (CK-MB) and cardiac troponin T (CTnT). Serum mycoplasma pneumoniae antibody and MP PCR were performed to determine whether MP infection was present. Blood, pleural effusion and nasopharyngeal aspirate/bronchoalveolar lavage fluid cultures, virus antigen detection assays (respiratory syncytial viruses, adenovirus, metapneumovirus, influenza and parainfluenza), interferon-γ release assays and T cell spot tests (T-SPOTs) for a tuberculosis infection were performed to exclude co-infection. A plain chest radiograph or chest CT was performed before or during hospitalization. An electrocardiogram (ECG), echocardiography and abdominal ultrasound were performed. If the patient was suspected to have a fungal infection, bronchoalveolar lavage fungal cultures and blood (1,3)-β-D-glucan and galactomannan detection were performed.

Statistical Analysis

The continuous variables that followed a normal distribution were expressed as $x \pm s$, and the non-conformities were expressed as median $\pm$ quartile. If the continuous variables of the two groups both followed a normal distribution and the variances were equal, the T test was used. If they did not follow a normal distribution or the variances were not equal, the Mann–Whitney U test was used. The categorical variables were analyzed by Pearson Chi-squared test. The factors with $P < 0.05$ were included in a binary logistic regression model to assess predictors for SMPP. Some continuous variables, such as neutrophil ratio, PLT counts, CRP, LDH and D-dimer levels were categorized into the 30th percentile, 60th percentile and 90th percentile. Afterwards, the accuracy of predictive factors was calculated by ROC curve. All tests were two-tailed and P values < 0.05 were considered significant. All statistical analyses were performed using SPSS Statistics Version 25.0.

RESULTS

General Information

According to the inclusion and exclusion criteria, 786 patients were enrolled, 403 were male and 383 were female with the ratio of 1: 0.97. The age ranged from 1.3–17.4 years old, with an average age of 7.9 ± 3.0 years, of which children aged 5–9 years accounted for 56.5%, younger than 5 years old accounted for 30.3%, and 10–17 years old accounted for 13.2%.

Clinical Characteristic Comparison Between SMPP and NSMPP

Univariate Analysis Between SMPP and NSMPP

According to the criteria, 540 patients were diagnosed as SMPP and 246 were diagnosed as NSMPP. There was no significant difference in gender, age, pre-treatment time by macrolid, WBC counts, neutrophil counts, FIB, APTT, PT, TT, PCT, ALT, AST and blood BUN between the two groups ($P > 0.05$). All of PCT value of the including patients were normal. Compared with NSMPP, the pre-hospital course of SMPP was longer ($P < 0.05$), the N%, PLT, CRP, LDH and D-dimer were significantly higher ($P < 0.01$) (**Table 1**).

Binary Logistic Regression Analysis and ROC Curve Between SMPP and NSMPP

The binary logistic regression analysis was conducted for the pre-hospital course, the N%, PLT, CRP, LDH and D-dimer. It turned out that the N%, PLT, CRP, LDH and D-dimer were the predictive factors for SMPP. The N% > 67% (OR = 3.233), PLT > 445 × 10^9/L (OR = 2.589), LDH > 354U/L (OR = 4.335) and D-dimer level > 403 ug/L (OR = 7.316) (**Table 2**).

Subsequently, the cut-off values of the N%, PLT, CRP, LDH and D-dimer were calculated by ROC Curve as 41%, 361 × 10^9/L, 22 mg/L, 307 U/L and 308 ug/L respectively. The D-dimer possessed the best predictive value with a sensitivity of 57.2% and specificity of 78.6%. The total predictive accuracy rate of the four factors was 77.1% (**Table 3**, **Figure 1**).

Comparison of Complications Between MPP With Elevated D-dimer Group and Control Group

According to the above results, D-dimer possess the highest predictive value for SMPP. We divided the patients who have the D-dimer record into the elevated D-dimer group (D-dimer > 308 ug/L) and the control group (D-dimer ≤ 308 ug/L), with 54 patients without D-dimer results eliminated. The complications were compared between two groups. The results showed that in the elevated D-dimer group, the incidence of pleural effusion, myocardial and liver damage, and electrolyte disturbances was significantly higher than that in the control group, while there was no significant difference in the incidence of atelectasis, rash, anemia and otitis media between the two groups (**Table 4**).

DISCUSSION

It is generally believed that MPP is the most common community acquired pneumonia in school-age children. Previously, MPP was rare in infants and young children, even with the evidence of mycoplasma pneumoniae infection. A survey conducted between 2010 and 2012 showed that the incidence of MPP in 5 years and older children was higher than that in younger children (19 vs. 3%) (2). In our study, the patients under 5 years old accounted for 30.3% of all included patients, which was significantly higher than that in the study by Jain et al. (2), indicating that the incidence of MPP is trending toward a younger age range in recent years.

In the past, older children were more susceptible to severe mycoplasma pneumonia (11), while in this study, there was no significant difference in age between SMPP and NSMPP. The PCT level of all patients in severe and non-severe groups were normal, so it could not be used to diagnose MPP or determine the severity. Chan and Izumikawa observed that there was a delay in the administration of effective antibiotics in patients with SMPP, with an average delay of 9.3 days and 15 days, respectively. They believed that this might be the most important cause of fatal respiratory failure (12, 13). Some studies have also found that even if the medication was given within 3 days of onset, respiratory failure still developed. In our study, there was no difference in pre-treatment time by macrolide between SMPP and NSMPP group, so we could not conclude that the delayed use of antibiotics was a risk factor for SMPP. This might be due to the high resistance of mycoplasma

TABLE 1 | Clinical characteristic univariate analysis between SMPP and NSMPP.

Variable	SMPP ($n = 540$)	NSMPP ($n = 246$)	*P*
Age (year)	6.8 (4)	6.3 (5)	0.248
Sex (male/female)	267/273	128/118	0.713
Pre-hospital time (d)	7 (4)	7 (4)	0.036
Pre-treatment time (d)	4.6 ± 2.8	4.4 ± 2.8	0.301
WBC(×10^9/L)	8.23 (2.94)	7.97 (3.29)	0.370
N%	0.58 (0.14)	0.54 (0.16)	0.000
PLT (×10^9/L)	404 (160)	360 (141)	0.000
CRP (mg/L)	21 (27)	15 (22)	0.000
LDH (U/L)	326 (108.5)	299 (74.5)	0.000
D-dimer (ug/L)	332.5 (460)	216.5 (139)	0.000
FIB (g/L)	3.82 ± 0.66	3.81 ± 0.71	0.971
APTT (s)	32.3 (5.4)	32.7 (4.9)	0.113
PT (s)	11.6 (1.1)	11.5 (1.2)	0.322
TT (s)	15.1 (1.6)	15.1 (1.7)	0.308

Data are presented as means ± SDs or median (quartile).

TABLE 2 | Binary logistic regression analysis between SMPP and NSMPP.

Variables	OR	95%CL	*P* value
N% (<55%)	1		
55–67%	1.428	1.015–2.008	0.041
> 67%	3.233	2.186–4.784	0.00
PLT (<348 × 10^9 /L)	1		
348–445 × 10^9 /L	1.656	1.167–2.35	0.005
> 445 × 10^9 /L	2.589	1.779–3.767	0.000
CRP (<12 mg/L)	1		
12–27 mg/L	1.409	1.002–1.982	0.049
> 27 mg/L	3.491	2.355–5.174	0.000
LDH (<295U/L)	1		
295–354 IU/L	1.789	1.269–2,521	0.001
> 354 IU/L	4.335	2.89–6.502	0.000
D-dimer (<219ug/L)	1		
219–403 ug/L	1.562	1.114–2.191	0.010
>403 ug/L	7.316	4.598–11.642	0.000

TABLE 3 | Cut off value between SMPP and NSMPP.

Variables	Cut-off value	AUC	Sensitivity (%)	Specificity (%)
N%	**41%**	**0.663**	**0.649**	**0.765**
PLT	361 × 10^9/L	0.631	0.682	0.521
CRP	22 mg/L	0.638	0.488	0.739
LDH	307 U/L	0.695	0.692	0.609
D-dimer	308 ug/L	0.721	0.572	0.786

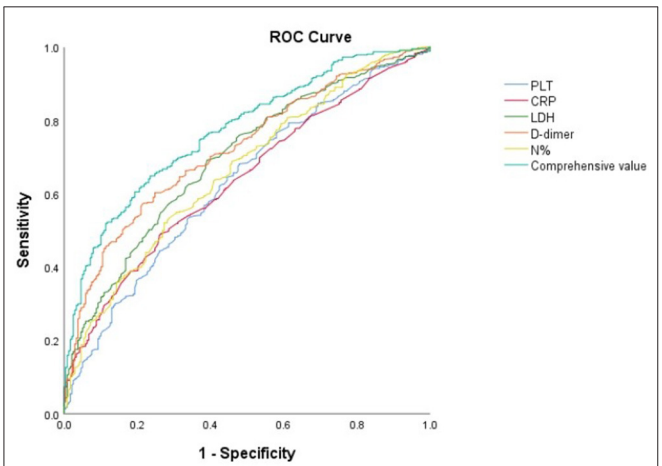

FIGURE 1 | ROC curve between SMPP and NSMPP.

TABLE 4 | Complications comparison between elevated D-dimer group and control group.

Complications	Elevated D-dimer Group (n = 333)	control Group (n = 153)	*P*-value
Pleural effusion	137 (41.1%)	33 (21.6%)	0.001
Atelectasis	29 (8.7%)	11 (7.2%)	0.699
Liver damage[a]	57 (17.1%)	3 (2.0%)	0.001
Myocardial damage[b]	70 (21.0%)	11 (7.2%)	0.003
Rash	30 (9.0%)	5 (3.3%)	0.079
Otitis media	6 (1.8%)	0 (0%)	0.185
Blood electrolytes disturbances	23 (6.9%)	1 (0.6%)	0.05
Anemia	23 (6.9%)	5 (3.3%)	0.281

[a]*Liver damage is defined as ALT or AST 2 times higher than normal value.* [b]*Myocardial damage is defined as CK-MB, CTnT or ECG abnormal.*

pneumoniae (14), which affected the efficacy of macrolides. Neutrophils are major effectors of acute inflammation. Cacciotto et al. (15) Confirmed that Mycoplasma pneumoniae can induce the production and activation of neutrophils, thus promoting the pathogenesis of mycoplasma infection. In our study, SMPP patients have significantly higher the N% than NSMPP patients.

It is currently believed that the over-activated immune response is associated with lung injury in MPP (16, 17). When pneumonia occurs, MP and its toxins, inflammatory mediators and hypoxia can cause damage to vascular endothelium, which lead to activation, aggregation and excessive consumption of platelets. At this time, megakaryocytes in the bone marrow are activated and produce more platelets to compensate for the loss. Mirsaeidi found that the platelet counts were positively related to the length of hospital stay, the mortality and prognosis of pneumonia (18), we found that a platelet count was an independent factor for SMMP, when higher than 445 × 10^9/L with OR = 2.589 ($P < 0.01$).

CRP was a non-specific marker of inflammation, which could rapidly increase within 4–6 h of infection. Its elevation was positively related to the degree of infection and inflammatory response (19). In our study, it is also shown that SMPP patients have higher CRP level than NSMPP patients (21 vs. 15), but not as high as an infection of bacteria.

Saraya et al. confirmed that the most significant pathological change of MPP was the accumulation of lymphocytes, neutrophils and alveolar macrophages in the area around the Bronchial Blood Vessels (PBVAs) in alveolar space (20). The continuous exudation of inflammatory cells was induced by cytokines and other inflammatory mediators (21), of which IL-8 and IL-18 played the most important role. Various studies have shown that IL-18 was directly related to the severity of MPP and could be used as a predictor of SMPP (22). Oishi and Miyashita found there was a significant correlation between serum IL-18 and LDH levels (8, 23). In this study, LDH was also found to be significantly higher in the SMMP group than in the NSMMP group and it was an independent variable used to predicte SMMP.

Studies have shown that in severe pneumonia, the interactions of inflammation and the coagulation system could aggravate lung injury. In recent years, there have been continuous reports of MPP complicated with systemic arterial and venous thrombosis, and even DIC (24). Once it occurs, it is acute and critical, with high mortality and disability rate, resulting in more serious consequences than pneumonia. D-dimer is a degradation product of cross-linked fibrin. Its increase indicates the presence of thrombosis and secondary fibrinolysis in the blood, which has an early and rapid diagnostic value for the hyper-coagulation state. Previous studies have shown that D-dimer was a predictor for 30-day mortality, the need for mechanical ventilation and circulatory support of severe pneumonia.

In our study, D-dimer in SMPP group was significantly higher than that in NSMPP group. D-dimer > 403 ug/L, the risk to become SMMP was 7 times higher than D-dimer within normal range, and its sensitivity to predicted SMPP was higher than the N%, PLT, CRP and LDH elevation. MPP with elevated D-dimer, possessed significantly more incidence of pleural effusion, myocardial and liver damage. This may reflect the mutual promotion of inflammation and coagulation, which aggravates systemic inflammation.

Some studies also found that SMPP was often accompanied by increased anti-phospholipid antibody (APA) titers, especially in children with thrombosis (25). Moreover, similar with the antiphospholipid antibody syndrome, children with MPP are prone to both venous and arterial thrombosis, suggesting that

APA may be one of the mechanisms of SMPP thrombosis. Unfortunately, we did not detect APA in this study.

In summary, the N%, PLT, CRP, LDH and D-dimer were risk factors for SMPP. When D-dimer level > 403 ug/L, the patient will have more risk to be SMPP (OR = 7.316). D-dimer was the best predictor among other indicators. MPP patients with D-dimer > 308 ug/L had more complications such as pleural effusion, myocardial and liver damage. More attention should be paid to D-dimer during diagnosis. The above conclusions illustrates the important role of inflammation and hypercoagulation state in the pathogenesis of MPP.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by 首都儿科研究所附属儿童医院伦理委员会. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

JQ, JG, and LC contributed to conception, design of the study, and wrote sections of the manuscript. JQ organized the database, performed the statistical analysis, and wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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MINI REVIEW
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Something Is Changing in Viral Infant Bronchiolitis Approach

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Acute Viral Bronchiolitis is one of the leading causes of hospitalization in the first 12–24 months of life. International guidelines on the management of bronchiolitis broadly agree in recommending a minimal therapeutic approach, not recommending the use of bronchodilators. Guidelines, generally, consider bronchiolitis as a "unique disease" and this runs the risk of not administering therapy in some patients who could benefit from the use of bronchodilators, for instance, in those who will develop asthma later in their life and face first episode in the age of bronchiolitis. Today, there is growing evidence that bronchiolitis is not a single illness but can have different "endotypes" and "phenotypes," based on age, personal or family history of atopy, etiology, and pathophysiological mechanism. There is evidence that some phenotypes of bronchiolitis are more strongly associated with asthma features and are linked to higher risk for asthma development. In these populations, possible use of bronchodilators might have a better impact. Age seems to be the main feature to suggest a good response to a bronchodilator-trial, because, among children > 6 months old with bronchiolitis, the presence of a subset of patients with virus-induced wheezing or the first episode of asthma is more likely. While waiting for new research to define the relationship between therapeutic options and different phenotypes, a bronchodilator-trial (using short-acting β2 agonists with metered-dose inhalers and valved holding chambers) seems appropriate in every child with bronchiolitis and age > 6 months.

Keywords: bronchiolitis, guideline, viral bronchiolitis phenotype, bronchodilator, valved holding chambers

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INTRODUCTION

Acute Viral Bronchiolitis is one of the leading causes of lower respiratory tract infection and hospitalization in the first 12–24 months of life (1, 2). Several guidelines have been published on the diagnosis and management of bronchiolitis; these guidelines have different reference ages in the diagnosis (<24 months in United States and <12 months in Europe), but basically agree in recommending a minimal therapeutic approach without the use of bronchodilators (3–6).

Accumulating evidence has revealed that bronchiolitis is not a single disease but can have different "endotypes" and "phenotypes" based on age of presentation, personal or family history of atopy, etiology, pathophysiological mechanism and clinical presentation (7–10). Therefore, today something seems changing in the viral infant bronchiolitis approach: in some phenotypes, drug treatment may be effective.

In this review, we try to address these topics, evaluating the different etiopathogenetic, clinical and therapeutic aspects of acute viral bronchiolitis.

PATHOGENETIC MECHANISMS

Bronchiolitis is more often described as inflammation and oedema of the bronchioles caused by respiratory viruses that invade the epithelial cells of the small airways. Although the exact mechanism is unknown, epithelial cells become necrotic and are sloughed off with an excessive amount of mucus. This condition leads to obstruction of the bronchioles and varying degrees of bronchospasm and air trapping (11).

Bronchiolitis is mostly associated with respiratory syncytial virus (RSV), that is detected in 50–80% of the hospitalized bronchiolitis cases (1, 12, 13). Other viruses can also be associated with bronchiolitis: rhinovirus (RV), human bocavirus, metapneumovirus, parainfluenza virus, influenza virus, adenovirus, coronavirus. Viral co-infections (usually with RSV and RV) are detected in 10–40% of severe cases (12). RSV is an RNA virus with two antigenically different subtypes (A with 11 genotypes and B with 23 genotypes) (14). RSV infection can be transmitted through direct inoculation of contaminated secretions in the nasal and conjunctival mucosa or by inhalation of large respiratory droplets (2, 15). Reinfections in young children are possible and are usually mild, although severe cases have been reported (16).

RSV binds to epithelial cells and replicates, causing epithelial necrosis and ciliary destruction. After being infected by RSV, the epithelial cells are sloughed to lower respiratory tract, where the virus infects the ciliated epithelial cells of the bronchioles mucosa and pneumocytes in the alveoli. Viral attachment to the target cell is mediated by F and G RSV surface glycoproteins. Epithelial cells necrosis results in the inflammatory response, by increasing the production of cytokines, including alarmins, chemokines, and growth factors. This inflammatory milieu attracts innate lymphoid cells, dendritic cells, and granulocytes to the site of infection (17, 18).

A strong induction of antiviral type I and type III interferons and interferon-induced genes is the primary response of the RSV infected mucosa, but RSV has developed the capacity to evade this innate interferon (INF) response through RSV-NS1/2 proteins, which are able to reduce both IFN-I and INF-III responses (19, 20). The disease state following RSV infection is associated with an increase in IL-17 production. This cytokine is more prominent in neonates, thus contributing to more severe clinical aspects (21, 22).

Intraluminal airway obstruction is caused by cellular infiltration of the peribronchiolar tissue, mucus overproduction, sloughing of infected epithelial cells and inefficient ciliary beating (15). Air trapping and varying degrees of lobar collapse can be caused by plugs composed of cellular debris and mucus in the bronchiole lumens (1). Viral clearance is permitted by innate and adaptive immune responses and the bronchiolar epithelium begins to regenerate within 3–4 days after the symptoms resolution. Currently, many studies indicate an association between RSV bronchiolitis and subsequent development of asthma (8).

Three RSV genotypes have been identified: NA1, ON1, and BA, respectively. The NA1 genotype infects young infants and is related to a more severe clinical course; the BA genotype is associated with eosinophilia and family history of asthma, while, in general, the ON1 genotype is associated with less severe symptoms (23). Interestingly, Harford et al. found that RSV infection resulted in dysregulation of β2-adrenergic receptor (β2AR) function, position and number. This dysregulation can explain the ineffectiveness of β2 agonists in treating obstruction in RSV infected patients (24).

The second most common virus causing bronchiolitis during infancy is RV. Its detection frequently occurs in children over 12 months of age. RV is an RNA Enterovirus belonging to the Picornaviridae family.

Lower respiratory tract infections are typically due to a RSV infection, particularly in very young children; on the contrary, RV infections are more common in slightly older children, in those with atopic predisposition in particular, and can cause severe wheezing (17). Lower respiratory tract infection is usually caused by RV type A, while severe wheezing is more commonly linked to RV type C infection (13, 25).

A partial defect in mucosal antiviral innate interferon responses may be related to a higher risk of severe RV infection and wheezing in young children with a family history of allergy and asthma. Cadherin-related family member 3 (CDHR3) has recently been identified as a unique receptor for RV-C (26), thus explaining the high pathogenic potential of RV-C. It is important to underline that an increased risk of childhood asthma has been associated with a polymorphism in the CDHR3 gene (27). RV infections seem to induce a milder epithelial inflammation than RSV, but in RV infections the expression of IFN type I decreases, with a predominant Th2 immune response (28).

Recently, a group of Italian researchers has demonstrated the presence of differing Th1/Th2 balance in patient hospitalized during the peak epidemic months or out of this period. The latter group was found to have a higher Th2 polarization in the immune response with a greater production of IL-4 and lower levels of IFNγ; therefore, they hypothesize the presence of two phenotypes of bronchiolitis: the first with RSV infection during the peak period and the second with a possible genetic predisposition to atopy and hospitalized during the non-peak season (29).

In conclusion, bronchiolitis is due to direct viral cytotoxic injury in conjunction with a robust host inflammatory response, but the relative contribution remains uncertain and is probably related to the type of virus involved and to the variability of the individual immune response. The role of the underlying genetic mechanisms is not yet clearly understood.

CLINICAL PRESENTATION

Diagnosis of acute bronchiolitis is clinical, supported by epidemiological and virological data. The term is generally applied to the first episode of wheezing in infants younger than 12–24 months of age (2, 5, 8). Peak incidence occurs between 3 and 6 months of age (1). After an incubation period of 4–6 days, infants show signs of upper respiratory tract infection (2): cough, runny nose, and fever are followed by lower respiratory distress characterized by nasal flaring, tachypnea, increased work of breathing with intercostal, subcostal or supraclavicular

retractions, use of abdominal muscles and grunting in the next 1–3 days (1, 8). Multiple respiratory sounds can be heard: respiratory crackles and bilateral wheezing are typical (1). Acute viral bronchiolitis is a quite dynamic disease: clinical severity usually peaks around 3–5 days from the symptoms onset, and the minute-to-minute variation in clinical findings is characteristic, as mucus and debris are cleared from the airways by coughing or as the child becomes asleep or agitated; thus, several examinations are recommended (1). Clinical assessment is also possibly confounded by nasal congestion, the resolution of which, with nasal discharge, can help ascertain whether respiratory sounds come from lower respiratory tract (2). Fever can be present in almost 30% of infants and usually occurs early in the course of disease (30).

Most infants have a mild clinical form that resolves in 10–14 days and can be managed at home; cough usually resolves within 2–3 weeks (31). Infant aged <3 months, born pre-term or with cardiopulmonary (e.g., chronic lung disease or congenital heart disease), immunodeficiency or neuromuscular disorders are at greater risk of severe disease, with complications including apnoea or bacterial infection (32). In particular, preterm infants are at a higher risk of apnoea (with a reported rate from 1 to 24%) (2), especially if with a corrected age of <2 weeks, birth weight <2.3 kg, respiratory rate <30 or >70 at presentation, and SpO_2 of 90% or less at presentation (33).

RSV infection is typically associated with an increased severity of presentation, while other viruses cause milder phenotypes (26, 34). In a retrospective cohort of previously healthy RSV-infected patients, respiratory failure was associated with lethargy, grunting, and a $PaCO_2 \geq 65$ mmHg at initial emergency department presentation (35, 36).

Hospitalization is usually recommended when children present with poor feeding, severe retractions, oxygen saturation of 92% or less, a respiratory rate higher then 60/min and in the presence of significant social risk factors (e.g., poor parental reliability or inadequate home environment) (35). Severity Scoring tools have been developed and validated to be used in clinical settings and can be useful for an objective measure. In general, these scores should be integrated with other measures and repeated to obtain clinical assessment to guide practical decisions (1, 7).

Finally, attempts have recently been made to characterize the clinical phenotype of bronchiolitis. Dumas et al. identified several clinical profiles from a multicenter study on children admitted to hospital with bronchiolitis: Profile A with high probability of RV etiology, history of wheezing and wheezing at presentation, eczema, and older age of the patient; profile B: wheezing at presentation, but no history of wheezing or eczema and high probability of RSV infection; profile C: the most severely ill group, with a longer hospital stay, and a high probability of RSV infection; profile D: the less severe illness, including non-wheezing children with a shorter length of hospitalization (26). A clinical respiratory assessment of the first bronchiolitis episode based on lung-X-rays, respiratory outcomes (hypoxemia, wheezing, and/or sub-costal retractions), nasal protein levels of antiviral and type 2 cytokines (IFNγ, IL-10, IL-4, IL-13, IL-1β, and TNFα) was conducted also by Arroyo et al. (37) in 2020 to define mild, hypoxemia or wheezing phenotypes.

These studies provide informations about outcomes, disease patterns and underlying airway immunobiology and, above all, they may be the evidence of the need of a tailored clinical and therapeutic approach (8, 27).

THERAPEUTIC OPTIONS

Among international guidelines, there is broad agreement on the role of support therapy; it is well-established that bronchiolitis management should be focused on guarantying proper hydration and oxygenation of the child. Intravenous or nasogastric fluid administration is recommended to ensure hydration whenever oral route is non-viable. Moreover, the enteral route should be preferred to the intravenous route (1). Oxygen therapy is recommended in children with peripheral oxygen saturation below 92% (1, 38) and should be performed through standard oxygen therapy (SOT) or *via* high flow nasal cannula (HFNC), providing heated and humidified air (39, 40).

Drug administration is ground for controversy, as corticosteroids, nebulized hypertonic saline, and nebulized epinephrine are mostly not recommended, while β2 agonist bronchodilators are contemplated in some guidelines and object of a long-lasting debate (1, 41–43). Although several guidelines advise against bronchodilators administration (4–6), in some countries, such as in Italy (3), the β2 agonist trial is considered as a possibility in selected cases as well. The recommendation of some guidelines on minimal handling of bronchiolitis (3–6) may result in several concerns of pediatric care providers and in the lack of adherence to the guidelines themselves (7, 44).

The indication on the utility of bronchodilators is mainly based on Gadomski and Scribani Chochrane systematic review, which states that albuterol administration does not result in a significant reduction in hospitalization or disease duration in non-hospitalized children. However, these same authors point out that some children may benefit from the administration of bronchodilators (45). As Wall suggests (42), it may be possible that some children, who will develop asthma later in their life, may experience their first episode in the age range of bronchiolitis and, thus, be indistinguishable from children with "pure" bronchiolitis (4, 42). This could be the reason why older patients (>6–12 months) with history of personal or familiar atopy, moderate to severe respiratory distress and wheeze as predominant auscultatory feature (i.e., no crackles) may improve with an asthma type therapy (42). Common practice as well suggests that clinical features of bronchiolitis in infants under 3 months of age are quite different from infants 8–12 months old. These data have been confirmed by two Italian studies, that noted how bronchiolitis in infants under 6 months of age is different from that in infants older than 6 months (46, 47).

Recent evidence noted that several pathogenetic clusters based on age, viral agents, immune phenotype, presence of wheeze and crackles, disease severity and risk of recurrent wheezing and asthma may underlie bronchiolitis (7–10). One group may be formed by very young infants (<6 months of age) with

RSV infection and increased risk of recurrent wheezing; instead, another group may comprise older children (>6 months of age) with RV infection, atopic predisposition, high risk of developing asthma (8) and, probably, a better response to bronchodilators. Although much more evidence is required, proposals were put forward for a more personalized treatment, based on the hypothesis of different entities of bronchiolitis (8, 48). An interesting recent study by Rodríguez-Martínez et al. (49) found out that therapeutic options based on a phenotypic-guided strategy are also more cost-effective than a guideline-guided strategy.

Considering all these data, there is evidence that some phenotypes of bronchiolitis are more strongly associated with asthma features and are linked to higher risk for asthma development. In these populations, use of bronchodilators might have a better impact. More specifically, we propose that an inhaled bronchodilator trial could be considered particularly in children older than 6 months of age, but two specific conditions must be advised. The first is that in these infants, that we can consider as "viral wheezers," bronchodilators should be administrated by metered-dose inhalers and valved holding chambers, as recommended by current guidelines, since this method is more effective and with less side effects than nebulized therapy (50, 51). The second is the indication to observe a clinical improvement with clinical scores after the bronchodilator trial (52). The dose and the time when to re-evaluate the clinical picture are still debated, perhaps the treatment scheme of worsening asthma in children younger than 5 years proposed by the GINA 2021 guidelines (short-acting β2 agonist: 2–4 puff every 20′ for three times in the first hour and review) can be applied (51).

Similarly to bronchodilators, the use of corticosteroid is not recommended in the management of infant bronchiolitis (1), but is part of the treatment of viral wheezing or asthma, so we agree that a course of corticosteroid could be indicated in moderate to severe clinical pictures, when the bronchodilators trial gave a positive result (42, 53–56).

These several data and considerations stress the necessity of subtype-specific studies, in order to evaluate the clinical response to different treatments and meet the need for a more personalized precision therapy.

DISCUSSION AND CONCLUSION

Bronchiolitis is one of the major health problems in infants around the world, but unfortunately, to date, no therapy has been validated for the management of this disease. Many guidelines have been published by various scientific societies, which agree on minimal handling (i.e., hydration and the administration of oxygen as the only treatment options) (3–6). Unfortunately, this approach risks excluding some patients who might benefit from the bronchodilator treatment (48). However, as pointed out by the American Academy of Pediatrics, guidelines are intended to assist clinicians in decision making and are not intended to "*replace clinical judgment or establish a protocol for the care of all children with bronchiolitis*" (5). In light of the data emerging from the scientific literature, acute bronchiolitis should no longer be considered as a single disease but rather as characterized by different phenotypes and endotypes (7–10, 26). In particular, it seems that the phenotype characterized by older age, type 2 immune response, personal or family (first-degree) history of atopy, RSV genotypes (ON1 and BA) or RV etiology and infection during non-RSV-predominant or non-peak viral months may have a good response to a trial with bronchodilators (48).

Evaluating all the evidence, age seems to be the main feature that may suggest a good response to the bronchodilator-trial. For instance, in the research by Dumas et al., the "profile A" (patient with personal or family history of wheezing and eczema, wheezing at clinical presentation, and RV infection) is often >6 months, probably have initial sign of asthma and may respond to a short-acting β2 agonist-trial (26, 57). Probably, the "true" bronchiolitis (in which therapy is useless) affects the child <6 months. This hypothesis may be supported by epidemiological data (1, 4), showing that bronchiolitis reaches its peak of incidence between 3 and 6 months, and by other studies suggesting that bronchiolitis in infants under 3–6 months of age is quite different from that in infants >6 months old (46, 47).

In a recent multicenter study with the objective of identifying factors associated with the use of albuterol among infants hospitalized for bronchiolitis, Condella et al. found that there is a subgroup of patients to whom clinicians preferentially administer albuterol. Characteristics of these infants mainly include presentation with wheeze and older age (>6 months), and these children may be similar to those affected by viral wheezing or their first episode of asthma (58).

This knowledge suggests that among infants >6 months with bronchiolitis, there could be a subset of patients who may have a virus-induced wheezing or their first episode of asthma and may respond to the bronchodilator-trial (4, 42).

To conclude, there is evidence that some phenotypes of bronchiolitis are more strongly associated with asthma features and are also linked to higher risk for asthma development. In these populations, use of bronchodilators might have a better impact.

Looking forward to future RCTs targeted to assess the utility of short-acting β2 agonists in different bronchiolitis phenotypes, a bronchodilator-trial (using short-acting β2 agonists with metered-dose inhalers and valved holding chambers) could be performed in infants with bronchiolitis and age > 6 months.

AUTHOR CONTRIBUTIONS

PB and LL designed the review. PB, LL, EL, AP, and CC performed literature search and draft the manuscript. PB, LL, and EC review and editing. LS and SC supervision the manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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History Taking as a Diagnostic Tool in Children With Chronic Cough

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Chronic cough is a common symptom of many underlying respiratory and non-respiratory disorders and may be associated with less serious causes, such as gastroesophageal reflux and nasal diseases. Chronic cough in children differs from that in adults with respect to its etiologies and management since it can indicate a symptom of an underlying disease in children. Guidelines for managing chronic cough in children are based on recording the history, followed by physical examination, chest radiography, and spirometry. Thus, taking accurate respiratory history for coughing helps delineate the pathophysiological basis of the cause of chronic cough. Detailed history taking enhances the evaluation and treatment, and facilitates a tailored diagnostic identification of likely diagnoses. While studies have described evidence-based red flags in children with chronic cough, the value of skilled physicians regarding history taking has received less attention for the best patient care. In the present article, we outline the major questions comprising a detailed history taking for chronic cough in children.

Keywords: chronic cough, children, history taking, diagnosis, red flags

INTRODUCTION

Coughing in children is one of the most common symptoms primarily resulting from respiratory tract disorders, but may also be associated with a variety of extra-pulmonary causes. Since the underlying pathology can indicate either a benign or more severe condition, an accurate and efficient diagnosis is required to identify effective treatments. Thus, guidelines for evaluating chronic cough in children have been developed to help healthcare practitioners. These guidelines have proven efficacious in improving the quality of life and achieving cough resolution earlier (compared to that in controls) in children presenting to specialist clinics (1) and in those presenting with acute cough who then developed chronic cough (2). These guidelines consist of a thorough history, physical examination, chest radiography, and spirometry (3). History-taking is justified

based on its high diagnostic yield, which guides subsequent diagnostic or therapeutic approaches (4, 5).

Over the centuries, knowledge of the anatomy and mechanisms underlying symptoms and signs has been gathered and related to the observed patterns of classical respiratory illnesses. This has made history and examination central and most important in determining a diagnosis and identifying correct investigations and treatment (6). Surprisingly, no studies addressed how medical history data aids chronic cough evaluation in children. While few studies have identified evidence-based red flags or pointers in children with chronic cough, the diagnostic value of skilled history taking has received less attention. Poor knowledge of the key diagnostic features of patient history may lead to inappropriate investigations, resulting in a delay in the diagnosis and management of the disease. Accurate history can efficiently aid clinicians in diagnosing and treating children with chronic cough. The present review aimed to explore the role of expert history taking and evidence-based red flags in diagnosing chronic cough in children and adolescents. The majority of the data presented refer to children/adolescents aged ≤14 years (hereafter referred to as "children").

THE ART OF HISTORY-TAKING

In children, chronic cough is the symptom of an underlying disease (3), and accurate history taking helps identify the cause of the cough as a complete history has a much higher diagnostic yield than that of conventional testing. The art of history taking requires a step-by-step approach, focusing on details and discrepancies, following a thorough review of the history. Keys to the successful history taking of chronic cough include [a] being meticulous and taking sufficient time with the patient, [b] having a calm relaxed setting, and [c] listening carefully to both the patient and family members. Clinicians must have excellent communication skills to gather patient stories, be objective, unprejudiced, and empathic (7). Racial and ethnic minorities report less partnership with physicians, less participation in medical decisions, and lower levels of satisfaction with care. Knowledge of cultural beliefs, behaviors about health and wellbeing and practices of different non-majority groups improve the patient-provider interaction. Current cough guidelines promote specific pointers to direct clinicians to initiate a workup plan often according to the limb of the algorithm (8–10). Moreover, a warning red flag alerts the clinician regarding the presence of a potentially serious problem or those requiring specific immediate action. Clinical years of experience has formed the basis of many specific pointers and red flag alerts in chronic cough, many of which can be identified during history taking, and are of great importance in the diagnosis of children with cough. Recent evidence-based studies have determined the sensitivity, specificity, and likelihood ratios of specific cough pointers and red flag alerts (**Table 1**).

AETIOLOGICAL CAUSES OF CHRONIC COUGH

In the last 15 years, researchers have reconsidered the aetiology of chronic cough in children. Grouping cough into distinctive classes based on pathophysiology is vital to facilitate a diagnostic approach (11). We present a grouping of nine pathological classes that encompass the most prevalent causes of chronic cough (**Table 2**). These classes can present as a single aetiology of cough or combinations of more than one such as airway infection due to airway aspiration.

Childhood post-infectious cough (typically with natural resolution over time) is a common aetiology in various age groups (12). After viral or bacterial infection of the airway, cough reflex hypersensitivity may continue for weeks (13, 14). In this category, the cough is dry, with no other symptoms (9). This entity belongs to the non-specific cough classification, where watchful waiting is the recommended approach (9, 10). Many cases of post-infection are likely associated with prolonged cough hypersensitivity that takes time to resolve (15). Cough was reported among the most common respiratory symptoms in children 3.2 ± 1.5 months after a SARS-CoV-2 infection (16).

Protracted, recurrent, or persistent airway infections include protracted bacterial bronchitis (PBB), chronic suppurative lung disease, bronchiectasis, cystic fibrosis, immune deficiency, ciliary dyskinesia, alpha-1 antitrypsin deficiency, and tuberculosis. The list is not exhaustive, as any untreated pulmonary infection can cause a chronic cough.

Airway anomalies include primary and secondary tracheobronchomalacia or other congenital airway malformations associated with various respiratory symptoms, such as chronic cough (17). These airway anomalies seem to be predisposed to and are closely associated with chronic recurrent airway infection and consequent inflammation. For example, a recent case-control study demonstrated that the presence of tracheomalacia (defined by European Respiratory Society as >50% expiratory reduction in the cross-sectional luminal area seen on flexible bronchoscopy) is an independent risk factor for bronchiectasis with an adjusted odds ratio of 24.4, and a 95% confidence interval (CI) of 3.4 to infinity (18).

Airway inflammation, such as various asthma phenotypes and eosinophilic inflammation in other airway infections, represent a common aetiology in both children and adults. Typically, mediators released during inflammation in allergic airway diseases can alter the function of the sensory and parasympathetic nervous systems, innervating the airways (19). The effect of inflammation on cough neural processing occurs at multiple peripheral and central sites within the nervous system (20). Moreover, allergen-induced bronchoconstriction and airway eosinophilia are associated with increased cough reflex sensitivity to capsaicin (21).

The airway aspiration class covers primary (during swallowing) and secondary (related to gastroesophageal reflux) airway aspiration and undiagnosed or retained foreign body aspiration (22–24).

TABLE 1 | Utility of specific cough pointers in differentiating specific coughs from non-specific coughs in children with chronic cough.

Pointer	Reference	Design	Setting	Population	Reference standard	Sensitivity	Specificity	PPV	NPV	PLR	NLR
Wet cough	Marchant et al. (8)	Prospective cohort	Single tertiary hospital in Australia	100 children with CC without known lung or other serious medical conditions (median age 2.8 years)	Specific cough (all causes)	96%	26%	74%	73%	1.29	NR
	Chang et al. (9)	Prospective cohort	Multi-centers in Australia	326 children with CC without a previous diagnosis confirmed by objective tests (asthma, CF, or BE) (mean age 3.3 years)	Specific cough (all causes)	65% (60–71%)	98% (85–100%)	99% (97–100%)	28% (21–37%)	26.15 (3.77–181.48)	0.36 (0.30–0.42)
Wet cough not resolved after 4 weeks	Chang et al. (9)	as above	as above	as above	Specific cough (all causes)	3% (2–7%)	100% (89–100%)	100% (65–100%)	13% (9–16%)	Infinity	0.97 (0.94–0.99)
Wheeze or reversible airway obstruction	Chang et al. (9)	as above	as above	as above	Specific cough (all causes)	21 % (17–26%)	100% (89–100%)	100% (92–100%)	15% (11–20%)	Infinity	0.79 (0.74–0.84)
Exertional dyspnea	Marchant et al. (8)	as above	as above	as above	Specific cough (all causes)	38%	65%	70%	32%	1.06	NR
	Chang et al. (9)	as above	as above	as above	Specific cough (all causes)	3% (2–6%)	100% (90–100%)	100% (63–100%)	10% (10–20%)	Infinity	1.0 (0.9–1.0)
Chronic dyspnea	Marchant et al. (8)	as above	as above	as above	Specific cough (all causes)	7%	97%	83%	32%	2.25	NR
Recurrent pneumonia	Marchant et al. (8)	as above	as above	as above	Specific cough (all causes)	7%	94%	71%	31%	1.12	NR
	Chang et al. (9)	as above	as above	as above	Specific cough (all causes)	3% (2–7%)	100% (89–100%)	100% (66–100%)	12% (9–17%)	Infinity	0.96 (0.94–0.99)
Hemoptysis	Marchant et al. (8)	as above	as above	as above	Specific cough (all causes)	7%	97%	83%	32%	2.25	NR
Cough associated swallowing	Marchant et al. (8)	as above	as above	as above	Specific cough (all causes)	25%	71%	65%	30%	0.85	NR
Failure to thrive	Chang et al. (9)	as above	as above	as above	Specific cough (all causes)	0% (0–2%)	100% (89–100%)	100% (5–100%	13% (9–17%)	Infinity	1.0 (0.99–1.00)
Feeding difficulties	Chang et al. (9)	as above	as above	as above	Specific cough (all causes)	6% (3–9%)	100% (89–100%)	100% (76–100%)	13% (9–17%)	Infinity	0.94 (0.92–0.97)
Chest pain	Chang et al. (9)	as above	as above	as above	Specific cough (all causes)	0% (0–2%)	100% (89–100%)	100% (5–100%)	13% (9–17%)	Infinity	1.0 (0.99–1.00)
Any cough pointer	Chang et al. (9)	as above	as above	as above	Specific cough (all causes)	100% (98–100%)	95% (82–99%)	99% (97–100%)	100% (89–100%)	20 (5.18–77.21)	0 (0–0.03)

CC, chronic cough; PPV, positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio; NLR, negative likelihood ratio; NR, not reported; FBA, foreign body aspiration.

TABLE 2 | Major aetiological causes of chronic cough in children* and examples.

1	**Post-infectious**: typically shows spontaneous resolution over time
2	**Airway infections (protracted/recurrent/persistent)**: Protracted bacterial bronchitis, chronic suppurative lung disease, bronchiectasis, cystic fibrosis, immune deficiency/ciliary dyskinesia, alpha-1 antitrypsin deficiency, other chronic infections e.g., tuberculosis and atypical mycobacteria
3	**Airway anomaly**: Primary or secondary tracheobronchomalacia, congenital airway and pulmonary malformation
4	**Airway inflammation:** Asthma, eosinophilic bronchitis, environmental pollutants
5	**Airway aspiration**: Primary airway aspiration, secondary aspiration owing to gastroesophageal reflux, foreign body aspiration
6	**Upper airway associations**: Rhinitis, sinusitis
7	**Tic and somatic syndrome**
8	**Extra-pulmonary:** Drug-induced, cardiac, vagal nerve branches stimulation (e.g., Arnold's ear reflex)
9	**Other specific diseases associated with chronic cough**: Interstitial lung disease or tumors

**Some overlap, for example, chronic cough related to primary ciliary dyskinesia can be both infection and inflammation.*

Somatic or tic cough is not an uncommon cause of chronic cough in children. Tics usually develop before 10 years of age and exhibit a waxing and waning course, but may increase as the age advances. Tics are prevalent in approximately 1% of children and adolescents (25).

Extra-pulmonary causes of cough include the use of angiotensin-converting enzyme (ACE) inhibitors or conditions that promote stimulation of the vagal branches. Arnold's nerve ear wax, cholesteatoma, or foreign bodies have are reported causes of chronic cough in children and adults (26, 27). Although rare, coughs induced by cardiac pathologies, mostly arrhythmias, have been reported in adults but not in children (28, 29).

Other specific cough aetiology includes specific types of cough, which are not yet diagnosed but correlate with interstitial lung diseases or tumors (30). In this class, numerous heterogeneous signs and symptoms have been reported. As cough can be a common symptom of airway and parenchymal abnormalities, it is not possible to list all of the causes in this paper.

THE CHRONIC COUGH HISTORY

Identification of symptoms and signs is the first goal of history taking to establish if specific pointers can help the clinician determine the etiological classification the patient most likely fits, and the algorithm for the treatment most appropriate to follow (10). A structured cough history should be conducted, which includes the mode of onset, severity, cough characteristics, time course/trajectory, and effects of previous treatment. The next stage is to identify the associated respiratory symptoms (breathlessness, wheezing/stridor/snoring, chest pains, haemoptysis) and other extrapulmonary symptoms (e.g., gastroesophageal reflux symptoms). The social context of the child with chronic cough is explored based on the child's age, birth history, and family history, which also includes the impact of cough on children and their families.

KEY FEATURES OF THE CHRONIC COUGH HISTORY

Age of Onset

A key element of chronic cough history in children is the onset of the cough.

Neonatal Onset

Chronic cough that started in and has continued since the neonatal period suggests that specific conditions need to be identified. These include (1) dysfunctional swallowing, (2) airway anomalies (e.g., laryngeal cleft, tracheoesophageal fistula), or (3) primary ciliary dyskinesia. Furthermore, in the context of the management of prematurity, injury to the lung by oxygen toxicity, mechanical ventilation, or infections increases the risk of long-lasting pulmonary impairment. Therefore, clinicians must explore neonatal respiratory distress syndrome, meconium aspiration, neonatal pneumonia, bronchopulmonary dysplasia, and treatment modalities, as well as corticosteroids, surfactants, and advanced respiratory care. Furthermore, congenital cardiac abnormalities, diaphragmatic hernia, tracheoesophageal fistula, or esophageal atresia are associated with long-term sequelae, such as tracheobronchomalacia or bronchiectasis (17, 31).

Pre-school Children

Common causes of cough in the preschool age are post-infectious airway infections, airway anomalies, or asthma (32). However, PBB is more common in preschool-aged children and marginally more common in males (33, 34). A study (35) that recruited 903 children presenting with acute cough and followed-up for development of chronic cough found that the risk factors for PBB were: childcare attendance [adjusted relative risk (aRR) = 2.32, 95% CI 1.48–3.63], prior history of chronic cough (aRR = 2.63, 95% CI 1.72–4.01), and age <2-years (<12-months: aRR = 4.31, 95% CI 1.42–13.10; 12-<24 months: aRR = 2.00, 95% CI 1.35–2.96). Factors that decreased the risk were baseline diagnoses of asthma/reactive airway disease (aRR = 0.30, 95% CI 0.26–0.35) or bronchiolitis (aRR = 0.15, 95% CI 0.06–0.38) (35).

School Children and Adolescents

The causes of chronic cough among older children and adolescents become more similar to those of adults with asthma, upper airway associations, and gastroesophageal reflux becoming more prominent (11). Additionally, cough can result from chronic suppurative lung disease and bronchiectasis in children who suffered recurrent lower respiratory infections during early childhood.

Mode of Onset

Abrupt Onset

Determining the onset of cough is vital for all children, regardless of how long they have been coughing (**Table 3**). This is crucial to rule out FB inhalation. Retained inhaled FB is common in young children between 0 and 3 years, and this may be unrecognized

TABLE 3 | Mode of onset and potential diagnostic category.

Mode of onset		Diagnostic category
Abrupt		Airway foreign body aspiration
Gradual	Progressing	All causes
	Stuttering	

TABLE 4 | Cough trajectory and potential diagnostic category.

Cough trajectory	Diagnostic category
Continuous	All causes
Subsiding	Post-infectious
Recurrent acute cough	Recurrent respiratory infections, all causes
Relentlessly progressive or static but on-going	Airway infection
	Airway anomaly
	Airway aspiration
	Other specific diseases

because a detailed history of the mode of onset was not explored. It is important to remember that the choking/spluttering episode may not have been observed by parents, or the inhalation event may not cause marked symptoms. The abrupt onset of coughing in a healthy child is thus a red flag that alerts the clinician about the possibility of an inhaled FB. The key clinical diagnostic feature is penetration syndrome, corresponding to respiratory defense reflexes (expulsive cough and laryngeal spasm) in response to a FB. There may also be asphyxia elements, such as cyanosis associated with coughing (36). Symptoms vary according to FB site in the airways. When the FB is trapped in the larynx or trachea diagnosis is immediately suggested owing to respiratory distress or stridor. In comparison, a positive diagnosis of FB bronchial may be challenging when few or no symptoms are identified. Kiyan et al. calculated the sensitivities, specificities, and positive and negative predictive values of clinical history, symptoms, physical examination findings, and radiological findings in patients with suspected FB aspiration (37). The sensitivity and specificity of the clinical history were 90.5 and 24.1%, respectively. Moreover, the sensitivity and specificity of symptoms reported were 97.8 and 7.4%, physical examination findings were 96.4% and 46.3%, and radiological findings were 71.7 and 74.1%, respectively (37). The outcomes of the literature review of 12,979 cases revealed that most patients with aspirated FB are children younger than 3 years of age (38). A history of abrupt cough is highly sensitive to FB aspiration (varied from 41 to 93.4%), but not specific, with reported specificity ranging from 8.3 to 55.3%) (38). However, a history of cyanosis (98.1–100%) or stridor (65.5–100%) at the onset is very specific to FB but not very sensitive (38).

Gradual Onset

If the onset of cough is progressive or stuttering, it will be difficult to attribute it to a specific category. If parents could accurately recollect the history, a child with a runny nose when the cough started may signify an upper respiratory tract infection, with the most likely cause being an airway infection resulting in a post-infectious cough.

Cough Trajectory

Continuous (or Static but On-Going) Chronic Cough

Children with chronic cough present with cough daily, but the cough may worsen when there is a new respiratory tract infection. The cause of this chronic cough can fall into any diagnostic category **(Table 4)**.

Recurrent Acute Cough

Chronic cough occurs when coughing is continuous and unceasing. Many children frequently experience recurrent coughing when they have upper respiratory tract infections. Children aged 2–5 years may experience several episodes of respiratory tract infections annually, especially if they attend day-care (39). Distinguishing recurrent acute cough due to recurrent infections is vital to historical details, assisting in delineating a chronic cough history. Further, in many respiratory infections, cough is often the last symptom that disappears. Problem coughing with each respiratory viral infection with only a short period of resolution may blend into the next infection and can be reported erroneously as chronic cough (40).

A careful history and enquiry on the timing of coughing can help in the differential diagnosis, asking for the parents to recall "when the child had days free of cough?" This is related to the onset of new upper respiratory tract infection symptoms, such as rhinorrhoea. The observation of coughing after the child's withdrawal from day-care or holidays often confirms the diagnosis.

Subsiding Cough

Many children with prolonged coughing (for longer than 4 weeks), after an upper respiratory tract infection, suffer from what is identified as a post-infectious cough. When the trajectory course of coughing suggests that it is waning and no other signs and symptoms are present, further observation should be made to ensure that the cough resolves completely.

Relentlessly Progressive Coughing

Prolonged coughing, which progressively worsens, requires further investigation and management. Potential causes vary and may include: (a) a retained FB, (b) *Bordetella pertussis* infection, (c) an expanding airway compressive lesion, for example, malignancy, and d] progressive airway infection (e.g., mycobacteria or fungi).

Type of Cough

Coughing is a sudden expulsion of air from the airways, which is characterized by a typical sound. The sound of a cough is associated with the vibration of larger airways and laryngeal structures during turbulent flow during expiration (41). This sound is specific and helps to identify cough, which is distinct from other vocal manifestations. The coughing sound

TABLE 5 | Cough sound and potential diagnostic category.

Cough sound	Diagnostic category
Barking/brassy seal-like	Airway anomaly
	Tic and somatic syndrome
Whooping/Paroxysmal/spasmodic	Post-infectious (pertussis)
	Other specific diseases
Staccato	Post infectious (Chlamydia)
	Other specific diseases
Honking	Tic and somatic syndrome

TABLE 6 | Type of cough and potential diagnostic category.

Type of cough	Diagnostic category
Dry	Post-infectious
	Airway inflammation
	Tic and somatic syndrome
	Extra-pulmonary
	Other specific diseases (e.g., tumors)
	Upper airway associations
Wet	Airway infection
	Airway aspiration
	Airway anomaly
	Upper airway associations
	Other specific diseases

is an important symptom, which is different from hundreds of diseases. Changes in its characteristics may have considerable value in identifying the mechanisms of airway pathology in respiratory diseases.

Cough Sounds

The cough sound provides information about the pathophysiological mechanisms of coughing by indicating the structural nature of the tissue that leads to certain patterns of cough. Under certain pathological conditions, cough sounds can help in the diagnosis (**Table 5**). For example, barking/brassy seal-like cough sounds are indicative of airway anomalies, such as tracheobronchomalacia or somatic cough. In many tracheobronchomalacia cases, parents report that they can identify the type of cough by hearing their children's coughing. Paroxysmal spasms of severe cough followed by an inspiratory whooping sound can be characteristic of pertussis. Barking honking cough is typical of somatic cough syndrome and tic cough. In infants, a staccato cough is indicative of chlamydia infection.

Cough Quality – Wet or Dry?

An essential component of a cough history includes determining if the cough is wet/productive or dry, which is vital information concerning the pathology of the disease (**Table 6**). When the cough is mixed (sometimes dry and sometimes wet), it is considered a wet cough.

Cough is a vital mechanism for removing mucus from the airways. Cough sound is effective in detecting mucus in the larger airways, as opposed to the smaller airways, because the rheological properties of mucus influence cough sounds. Additionally, shear stress through mucus secretions from the airways contributes to these sounds. In healthy adults, the area occupied by the mucus gland constitutes approximately 12% of the bronchial wall. However, in children, it is approximately 17% of the bronchial wall (42), leading to greater mucus secretion during childhood. The difference in composition suggests that mucus gland hypertrophy is more significant in children than in adults. After the accumulation of mucus in the lung, clearance of mucus by the high-velocity airflow associated with cough often becomes the sole mechanism for mucus clearance (42). In a normal cough, the high airflow velocity creates high shear stress, which clears the foreign matter and secretions off the bronchial wall, propelling them toward the larger airways and trachea.

Cough constitutes an important backup mechanism to the mucociliary escalator, which has been the primary mechanism to remove mucus from the lungs of patients with lung disease. A cough initiated deeply from the lungs is associated with an initial deep inspiration that allows air to get behind secretions within the distal airway. However, cough initiated from the upper larynx is not associated with an initial deep inspiration.

If a child's cough is wet, a phlegmy, rattly sound with the cough is emitted, suggesting the presence of secretions in the airways. Airway secretions are always present in wet cough. Moreover, wet cough in children, as determined by clinicians and parents, has good clinical validity (41). However, clinicians should interpret parental reports of a child's cough with some caution, in that one person's "dry" cough may very well be another's "wet" cough. Indeed, Morey et al. observed the unreliability of a 24 h history of reported cough quality (wet/dry) by carers of indigenous children compared with objectively recorded cough (43). Hence, clinicians should endeavor to hear the cough themselves either during the consultation or ask the parents to record it (44). Smart mobile phones are increasingly being employed to record cough, which greatly helps physicians identify the type of cough sound.

Wet cough is associated with increased airway infections, airway anomalies, airway aspiration, and other less common specific diseases. Conversely, dry cough is associated with post-infectious conditions, tic and somatic syndrome, extra-pulmonary cough, or other less common specific diseases. In some cases, cough sounds may alternate between dry and wet; in this case, the cough is considered to be wet. Chang et al. argued that wet cough is categorized as a specific cough (those that require treatment) and non-specific cough (likely to resolve without treatment) (9). Wet cough has a positive likelihood ratio (LR) of 26.2 (95%CI 3.8–181.5) (9). Although the absence of other pointers (associated signs and symptoms of coughing illness discussed below) did not significantly change the pre-test probability (negative LR close to 1). The absence of all pointers (including wet cough) had a strongly negative LR of 0 (95% CI, 0–0.03) (**Table 1**). Hence, chronic dry cough without any cough-specific pointers in children, based on the outcome of normal chest radiographs, can be safely managed using the watchful waiting approach.

Presence of Expectorated Sputum

Some children (mainly older children) can expectorate or cough up sputum, and questioning about the properties of the mucous/sputum should be included (**Table 7**). Mucous within the airways can be associated with airway inflammation or infection, which can be eosinophilic or neutrophilic, both, or lymphocytic. Identification is vital during the diagnosis (45). In adults, purulent sputum, a yellow to green color, is associated with neutrophilia and possible bacterial infections (46, 47). In children, the color (and amount) of airway secretions observed during bronchoscopy is associated with bacterial infection (48). Therefore, bacteriological testing is recommended. A purulent expectorate can be associated with airway infection, airway aspiration, or other specific diseases, and in some cases, airway anomalies.

Collecting sputum specimens is not feasible in small children, and the risk of obtaining low-quality sputum culture is high; however, these can be obtained in older children (49). Induced sputum may be feasible for young children. A clear expectorate indicates excess secretions that may be related to airway aspiration or upper airway disease.

True haemoptysis is a characteristic of severe underlying conditions. Examples include airway infection (e.g., undiagnosed tuberculosis), bronchiectasis, and other specific diseases (e.g., arteriovenous malformation, tumor). It is important to remember that a child spitting out some blood with a cough is not necessarily true haemoptysis–blood can originate from the throat or indeed from cheek biting.

The cough with expectoration of branching airway casts is characterized by plastic bronchitis. Pediatric cardiothoracic surgeries, infections, and inflammatory processes are among the conditions associated with cast formation (50).

TABLE 7 | Expectorate and potential diagnostic category.

Characteristics of the expectorated sputum	Diagnostic category
Absent	No specific indication
Clear	Airway aspiration
	Upper airway associations
	Other specific diseases
	Non-infective airway inflammatory process
Purulent	Airway infection
	Airway aspiration
	Chronic suppurative airway disease
	Airway anomaly
Haematic	Airway infection
(haemoptysis)	Bronchiectasis
	Arterio-venous malformation
	Other specific diseases (e.g., hereditary haemorrhagic telangiectasia)
Casts	Other specific diseases (plastic bronchitis)

Triggers of Cough

Events that immediately precede and seem to trigger a cough or worsen cough should be recorded, which can help arriving at a specific diagnosis for the cough (**Table 8**). Parents and older children should be asked if they can identify symptoms that worsen the cough, such as exercise in cold air, changes in season, meals/feeding, or lying down or body position. Cough can be triggered at the time of meals and feeding points, leading to aspiration syndrome. Cough triggered by physical activity is typically caused by airway inflammation and associated hyperreactivity (asthma). Cough triggered by an allergen is often caused by airway inflammation or upper airway associations. Cough triggered by a change in body position can be caused by airway aspiration, airway anomalies, or other specific diseases. Stress can trigger cough in children with motor or phonic tics or Tourette syndrome.

Environmental triggers can exacerbate cough and must be addressed by clinicians. For example, a history of exposure to tobacco, e-cigarettes, and environmental smoke (51, 52) can trigger a cough. Parental reporting of cough is less accurate if parents are smokers (53), which may be the reason behind the child's continuous cough. In many developing countries, indoor cooking and heating may contribute to the development of lung disease. Hobbies, such keeping or working with birds, may present a risk of pulmonary infection (54).

TABLE 8 | Triggers of cough and potential diagnostic category.

Trigger	Diagnostic category
Physical activity	Any cause
	Airway hyper-reactivity/asthma phenotype
	Eosinophilic airway inflammation
	Upper airway associations
Feeding/meals	Airway aspiration
	Airway anomaly (e.g., tracheo-esophageal fistula)
Allergens	Upper airway associations
	Airway inflammation
Pollution (indoor or outdoor)	Upper airway associations
	Airway inflammation
	Post-infectious
Tobacco smoke and e-cigarettes	Upper airway associations
	Airway inflammation
	Post-infectious
Fog	Upper airway associations
	Airway inflammation
	Post-infectious
Body position	Airway anomaly
	Airway aspiration
Stress	Tic and somatic syndrome
Temperature (cold)	Airway hyper-reactivity/asthma phenotype

TABLE 9 | Variability during the day and potential diagnostic category.

Variability pattern		Diagnostic category
Only diurnal		Tic and somatic syndrome
Pre-dominantly diurnal	Uniformly throughout day	All causes
	Mostly morning	Airway infection/Bronchiectasis
		Airway aspiration
Pre-dominantly nocturnal		Airway aspiration
		Airway inflammation–asthma
		Other specific diseases
Diurnal and nocturnal		All causes

TABLE 10 | Prior therapeutic intervention.

Prior therapeutic interventions (drug/dosage/duration/delivery method/response)
Antibiotics: type, dosage and duration
Oral or inhaled corticosteroids
Bronchodilators
Anti-gastroesophageal reflux drugs
Anti-histamines
Mucoactive drugs
Narcotics
Cough suppressants

Variability Pattern of Cough Over Day and Night

A history of the variability of cough during the day and night can provide clinicians with important information about the cough and guide them toward a likely diagnosis (**Table 9**). An exclusively dry diurnal cough in the absence of red flags and normal chest radiography can signal somatic cough, while the presence of night-time cough rules out a diagnosis of somatic cough (10). A pre-dominantly morning wet cough is highly suggestive of chronic airway infections, such as bronchiectasis. A pre-dominant night cough is often attributed to airway aspiration or airway hyper-reactivity/eosinophilic airway inflammation related to asthma. However, clinicians should be aware that nocturnal cough is often inaccurately reported when compared to objective recordings (55, 56).

Response to Prior Cough Treatments

Evaluating the response to pharmacological and non-pharmacological interventions before treatment may help identify the cause of cough. The medication type, dosage, duration, and method of delivery are all important factors when discussing a response to prior cough treatments (**Table 10**). For example, when assessing response to inhaled corticosteroids, the method of delivery, technique of inhalation, dose, frequency, and duration of the trial should be assessed as a short duration (e.g., 3 days) or suboptimal delivery represents an inadequate treatment trial.

An appropriate medication trial over a certain period may help to exclude diagnosis and reduce the scope of the investigation. An absence of response to an appropriate antibiotic for an appropriate period with the correct dose (typically an appropriate dose for a minimum of 2 weeks or 4 weeks) suggests that the diagnosis may not be simply PBB (57). Goyal et al. demonstrated that among 105 children with persistent cough, 88 (83.8%) had bronchiectasis despite at least 4 weeks of antibiotic treatment. Of the 24 children whose cough resolved after antibiotic treatment, only six (25.0%) were diagnosed (adjusted OR 20.9; 95% CI 5.36–81.8) (58). The authors concluded that further investigations, including a multi-detector computerized tomography scan, should be considered in a child with a chronic wet cough that persisted after 4 weeks of oral antibiotics. However, reducing the likelihood of underlying bronchiectasis and responding to a single prolonged course of antibiotics does not completely exclude this diagnosis.

Oral or inhaled steroids are effective in treating eosinophilic inflammation (59, 60). Thus, ineffective treatment (assuming it has been correctly delivered) can exclude the presence of eosinophilic inflammation. If narcotics or cough suppressants are used, they must be stopped, and cough should be re-evaluated.

In adult patients with chronic cough, ACE inhibitors are considered wholly or partially the cause (61). Remarkably, the prevalence of ACE inhibitor-induced cough in adults is in the range of 5–35%; in children, it is reported sporadically. Alharbi et al. (62) found that such instances increased with age until a plateau was attained in middle adulthood (40–59 years). The incidence of cough in children receiving ACE inhibitors, as reported by Baker-Smith, was low (3.2%), similar to that in children receiving angiotensin receptor blockers (1.8%) (63).

OTHER KEY FEATURES OF HISTORY

Associated Symptoms and Signs

Apart from cough, questions on any associated symptoms and signs form part of the history taking as it can help to determine the cause of chronic cough and/or the need to undertake further investigations (10). Their presence or absence provides key elements for establishing a diagnostic algorithm (**Table 11**). Most of these associated symptoms are considered to be red flags. Dyspnoea, chest pain, cyanosis, haemoptysis, haematemesis, fever, and apnoea are red flags to airway infection, airway anomalies, airway aspiration, or other specific diseases. Choking, regurgitation, spitting, vomiting, epigastric pain, and heart pain indicate aspiration syndrome. Neck posturing may indicate an airway anomaly or aspiration syndrome. Wheezing is indicative of airway inflammation (i.e., asthma), airway anomaly (i.e., tracheomalacia), or other specific diseases (9).

Concomitant Disease Conditions

The presence of a disease may be the underlying cause of chronic cough, and its investigation is vital (**Table 12**). Moreover, previous hospitalisations or treatment for pulmonary diseases

TABLE 11 | Associated symptoms and potential diagnostic category.

Associated symptoms	Diagnostic categories
Dyspnoea (at rest or exertional)	Airway anomaly Airway inflammation Airway infection Other specific diseases (any pulmonary cause)
Chest pain	Airway anomaly Airway inflammation Airway aspiration Other specific diseases
Cyanosis	Airway anomaly Airway inflammation Airway aspiration Other specific diseases
Stridor	Airway anomaly Other specific diseases (e.g., laryngeal abnormality)
Fever	Airway infection Other specific diseases
Regurgitation/Spitting/ vomiting	Airway aspiration
Choking during feeding*	Airway aspiration Other specific diseases
Haematemesis	Airway infection Other specific diseases
Haemoptysis	Airway infection Other specific diseases
Apnoea	Airway anomaly Airway aspiration Other specific diseases
Wheezing	Airway anomaly Airway inflammation Airway infection Other specific diseases
Hoarseness	Airway aspiration Other specific diseases (e.g., laryngeal abnormality)
Epigastric pain	Airway aspiration Other specific diseases
Heartburn	Airway aspiration Other specific diseases
Neck posturing (dystonic, spontaneous hyperextension)	Airway aspiration Airway anomaly Other specific diseases

TABLE 12 | Concomitant disease conditions and potential diagnostic categories.

Concomitant disease conditions	Diagnostic categories
Congenital anomalies of the aero-digestive tract	Airway aspiration Airway anomaly Other specific diseases
Cardiac abnormalities	Airway anomaly Other specific diseases
Neurodevelopmental abnormalities	Airway aspiration Airway anomaly Other specific diseases
Immunodeficiency/ Immunosuppression conditions	Airway infection
Congenital syndromes	Airway anomaly Other specific diseases
Weight loss	Airway infection Other specific diseases
Failure to thrive	Airway infection Airway aspiration Other specific diseases
Tumor	Airway anomaly Other specific diseases
Chronic rhinitis/sinusitis	Upper airway associations Airway inflammation Other specific diseases

should be questioned. Congenital anomalies of the aero-digestive tract after surgical intervention, cardiac anomalies, and congenital syndromes are associated with airway infections, airway anomalies, or other specific diseases. Neurodevelopmental anomalies are frequently associated with airway aspiration or other diseases. Diagnosed immunodeficiency, primary or secondary airway anomalies, airway aspiration, or other specific diseases can cause airway infections and chronic cough. Moreover, rhinitis, sinusitis, and allergic diseases are upper airway coughs.

Tumor and its therapeutic management are associated with cough. The presence of other tic-related symptoms (e.g., excessive blinking of eyes and twirling of hair) should raise the suspicion of a tic-associated cough. Weight loss and failure to thrive are red flags indicating airway infection, airway anomalies, airway aspiration, or other diseases (9).

Risk Due to Exposure to Infections

Epidemiological factors must be considered when evaluating chronic cough (**Table 13**). Non-vaccinated children are at a higher risk of developing infectious diseases. Since this is the case with immunization, natural *B. pertussis* infection may fail to permanently protect patients against pertussis (64). Numerous studies have documented that a second episode of pertussis can occur after a few years. Moreover, the emergence of mutated strains *of B. pertussis* can cause re-infection (65). Visiting or living in an endemic area that can increase the risk of contagious diseases, such as tuberculosis, HIV, or parasitic infections, should be investigated.

A further factor to consider when discussing chronic cough with parents is the child's exposure to viral infections. Children who attend childcare have a higher risk of recurrent respiratory infections. As mentioned above, among other factors, childcare attendance was an independent risk factor for the diagnosis of PBB (aRR = 2.32, 95% CI 1.48–3.63) (35).

TABLE 13 | Questioning about risks of exposure to infections.

Risk factors of exposure to infections
Day-care attendance
Lack of vaccinations
Cough in family members/relatives
Traveling to endemic areas
Epidemiological risk factors e.g., pollution, settings with high TB prevalence

FAMILY HISTORY

Family history provides key clues to the presence of genetic pulmonary diseases, such as cystic fibrosis, alpha 1-antitrypsin deficiency, hereditary haemorrhagic telangiectasia, immotile cilia syndrome, situs inversus, spontaneous pneumothorax, atopy, asthma, and immunodeficiency syndromes (66). Moreover, careful history taking can uncover more common familial diseases. Family history should encompass at least three generations to account for sex-linked traits. Family history can also identify exposure to tuberculosis or other contagious diseases.

IMPACT OF COUGH

The cough history should also include an evaluation of the impact of cough on children and their families. This includes the most troubling aspects (e.g., sleep) and the impact of the cough on the child (e.g., schooling/preschool) and their parents (e.g., work). Understanding these aspects will assist counseling. Validated parent and child chronic cough specific quality of life questionnaires (PC-QoL (67) and CC-QoL (68), respectively) are available. The short-form of PC-QoL (PC-QoL-8), consisting of only eight questions (56), can be used in the clinic setting. Alternatively, a simple visual analog score (1–10) (56) can also be used to assess the impact and response.

SUMMARY

Effective evaluation of children with chronic cough is vital, and the use of management pathways specific to children (10) is efficacious. Determining the underlying diagnosis is one of the primary goals in the management of chronic cough in children, followed by targeted investigations or, in some cases, treatment trials. This is contrary to what has been proposed by some groups in adults, where chronic cough itself is considered a syndrome.

Based on the existing guidelines on chronic cough in children, the initial step of management consists of history taking followed by physical examination, chest radiography, and spirometry (in older children who are cooperative). Meticulous and thorough history taking is a cornerstone to this process, for which the primary cost is the clinician's time. Acquiring the necessary history requires exhaustive questioning, leaving sufficient time and careful listening. Physicians should assemble diagnostic clues through unhurried history taking to make a presumptive diagnosis. The process is different from on-the-spot rapid diagnosis, a popular "protocol-driven" medicine. A step-by-step approach is needed, paying attention to details and discrepancies by meticulously reviewing history.

After robust history taking, physical examination, chest radiography, and spirometry may confirm or raise diagnostic reliability. Once a diagnostic probability of the cough is undertaken, the next step in the guidelines includes evidence-based treatment pathways that include PBB (57), bronchiectasis (69), airway aspiration (23), somatic and tic cough (70), pertussis (71) or asthma (72). These management pathways guide clinicians in identifying children who require immediate referral to tertiary care or at which stage to refer to others.

The burden of chronic cough in children is high, with over 80% of children having five or more doctor visits within 12 months, and 53% have more than doctor visits within the same period (73). Stress is the primary contributor to parent's emotional distress. A thorough chronic cough history taking may decrease the burden on families by allowing accurate and timely diagnosis in primary care for some children, and more appropriate early referral to tertiary care.

Some limitations were identified in our history-taking approach, which included patients who presented an overlap of symptoms of more than one diagnostic class. Furthermore, the symptoms of a secondary diagnosis, described as a pathological condition whose treatment does not result in the resolution or improvement of the cough, should be carefully considered (74). In these cases, it is critical to differentiate between primary and secondary diagnoses. In a prospective study in children with chronic cough, Marchant et al. (74) reported that in children with a primary diagnosis of PBB, 55% had a secondary diagnosis (e.g., airway malacia and gastroesophageal reflux).

Chronic cough in children remains a diagnostic challenge in clinical practice. Although new diagnostic tools have been introduced in the field of respiratory medicine, allowing the severity, frequency, and timing of cough to be measured objectively using automated cough measurement devices (75, 76). Nevertheless, history taking remains a primary step in diagnosing children with chronic cough. A combination of a thorough history and the use of cough management protocols or algorithms is likely to improve clinical outcomes and decrease the burden on these children and their families.

AUTHOR CONTRIBUTIONS

AK, JM, and AC: study conception and design. W-JS: analysis and interpretation of data. AK, JM, MS, GC, AZ, and AM: draft manuscript preparation. All authors reviewed the results and approved the final version of the manuscript.

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Prevalence and Determinants of Wheezing and Bronchodilatation in Children With Cystic Fibrosis: A Retrospective Cohort Study

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Background: Many patients with cystic fibrosis (CF) wheeze, and are dubbed as having CF-asthma. Understanding the determinants of such wheezing may avoid unnecessary treatments and open newer treatment avenues.

Objectives: Main: To evaluate the prevalence and characteristics of wheezing and a positive bronchodilatory response (BDR) in children with CF. Secondary: To identify the predictive markers and the impact of current wheezing a positive BDR.

Methods: A retrospective single-center study in children with CF. We determined the characteristics of physician-reported wheeze in patients <6 years, and a BDR in patients aged 6–17 years. Anthropometric, lung function, laboratory, genetic and microbiological data were recorded in all groups. Variables were compared using the Chi^2 and Student *t*-tests, and ANOVA.

Results: 125 preschool and 69 school-aged children and adolescents with CF were included in the study. 71.2% of patients <6 years of age had had at least one episode of wheezing: 26.3% of patients were Transient Early Wheezers, 12.6% Late Onset Wheezers and 37.9% were Persistent Wheezers. The prevalence of a positive BDR was 73.5, 48.5, and 52.9% in the 6–8 years, 10–12 years, and 15–17 years age groups, respectively. Allergic factors were not predictive of wheezing in preschoolers. In the 6–8 years age group, the sum of wheal diameters of allergic skin prick tests (SPT, house dust mite + cat + dog dander) was greater in those with a BDR vs. no BDR (4 [2.0–8.8] vs. 1 [0–7.0] mm, $p = 0.01$). The presence of *Pseudomonas aeruginosa* in the bronchial secretions before 3 years of age was not significantly associated with either the presence of wheezing at the age of 6 years or a BDR in school-aged children and adolescents. The proportion of homozygous p.F508del patients was significantly lower in the group of patients who had wheezed by 6 years of age (60% vs. 72.7%, $p = 0.009$), but higher in the 6–8 years old group with a BDR vs. no BDR (64% vs. 36%, $p = 0.04$). Current wheezers at 6 years had a lower mean FEV_1 vs. the non-current wheezers (91.5 ± 4.4%

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vs. 100.9 ± 2.4%; $p = 0.047$). Similarly, forced vital capacity (FVC) was significantly lower in the 6–8 years old group with BDR vs. no BDR (85 ± 19 vs. 101 ± 21%, $p = 0.015$).

Conclusion: Wheezing and BDR are very frequent findings in children with CF. Current wheeze at the age of 6 years was associated with worse lung function. Labeling wheezing in CF as "CF-Asthma" is misleading since the determinants are different, and may lead to inappropriate prescriptions of inhaled steroids.

Keywords: asthma, wheezing, bronchial hyperresponsiveness, cystic fibrosis, respiratory function tests

INTRODUCTION

Cystic fibrosis (CF) is one of the most frequent and severe genetic diseases affecting European populations. Clinical manifestations can vary from mild to severe forms, and prognosis depends to a large extent on the severity of respiratory impairment. This associates chronic bronchial inflammation and infection, and the presence of very thick mucus, a consequence of the absence or dysfunction of the CFTR channels present on the apical surface of bronchial epithelial cells. Bronchiectasis will ensue, followed by chronic respiratory failure.

Asthma and CF are both chronic inflammatory diseases of the lung, but their pathophysiology is quite different. Airway inflammation is mostly eosinophilic in allergic asthma, whereas it is predominantly neutrophilic in CF (1, 2). Wheezing is very common in asthma. A prevalence of 30–50% has been reported in preschool children, in whom less than half will undergo persistent symptoms (1). Wheezing, whether in patients with asthma or CF, is classically the consequence of airway obstruction due to inflammation, bronchospasm, non-discharged secretions and/or small airways.

Morphologically, the bronchi of patients with asthma and CF share common features, such as the development of bronchial remodeling, including hyperplasia of the bronchial smooth muscle (3, 4). Bronchial hyperresponsiveness (BHR) is also observed in both conditions. This is usually demonstrated by the onset of bronchoconstriction induced by a specific or non-specific stimulus, and/or reversibility after exposure to a bronchodilator (5). Up to half of all patients with CF have measurable BHR, which does not appear to be related to the patient's atopic status (6–8). According to Weinberger BHR in CF shows characteristics which are different from asthma, e.g., bronchodilation on exertion (9).

Alterations in the signaling pathways regulating airway smooth muscle (ASM) contractility in CFTR-deficient patients have been described. As an example, persistent bacterial infection, especially by *Pseudomonas aeruginosa*, stimulates the release of interleukin-8 from the airway epithelium, resulting in neutrophilic inflammation. Increased neutrophilia and CFTR-deficient T-helper cells create an inflammatory environment characterized by high levels of Tumor Necrosis Factor (TNF). The presence of high levels of TNFα, Interleukin-8 and Interleukin-13, may contribute to increased ASM contractility which participates in wheezing and BHR (10).

Predictive indices and scores have been proposed to identify which of the early non-CF wheezing children are at risk of persistence (of wheezing) at school age. Two of these have been validated in different populations: the PIAMA score (11, 12) and the Asthma Predictive Index (API) (13). A positive API index indicates a 2.6–9.8 greater risk of current asthma during school age (6 and 13 years) (14). According to the PIAMA score the risk of asthma from age 6 to 8 years is as follows: <5% (score 0–7); 6–22% (score 8–15); 25–60% (score 16–23) (12).

There is a lack of such data in children with CF. Our primary objective was therefore to evaluate the prevalence and characteristics of wheezing and a bronchodilatory response (BDR) to short-acting beta-agonists as a marker of airway lability in a population of children with CF followed in a single large CF center. The secondary objectives were to identify the factors associated with wheezing and a positive BDR, and to determine the impact of current wheezing at the age of 6 years.

MATERIALS AND METHODS

We conducted a retrospective, analytic, single-center study in children with CF, aged less than 18 years, followed at the Regional Pediatric CF-center in Bordeaux University Hospital, France. In this retrospective study French regulatory legislation requires that the protection of personal data is ensured, and this was applied in our study (15). The Bordeaux University Hospital Institutional Research Ethics Board authorized the conduct and publication of this research (Reference CERBDX-2022-03).

The ***first part*** of the study involved children aged less than 6 years, recruited from February 2016 to June 2016. The primary objective was to determine the overall frequency of wheezing in such children. The secondary objectives were to describe the characteristics of wheezing according to the TUCSON clinical phenotypes as described by Martinez et al. (16), to determine predictive markers for the persistence of wheezing at school age (6 years), and to describe the consequences of wheezing particularly with respect to lung function at 6 years. Children were assigned to four categories according to their history of wheezing: those who had no recorded lower respiratory tract illness with wheezing during the first 3 years of life and had no wheezing at 6 years of age (NW); those with at least one lower

Abbreviations: ASM, airway smooth muscle; BDR, bronchodilatory response; BHR, bronchial hyperresponsiveness; IgE, type E immunoglobulin; API, Asthma Predictive Index; IS, induced sputum; LW, late (onset) wheezers; NW, never wheezers; PW, persistent wheezers; PIAMA, prevention and incidence of asthma and mite allergy; SPT, skin prick tests; TW, transient (earlier) wheezers.

respiratory tract illness with wheezing during the first 3 years of life but no wheezing at 6 years of age (those with transient early wheezing, TW); those who had no lower respiratory tract illness with wheezing during the first 3 years of life but who had wheezing at 6 years of age (those with wheezing of late onset, LW); and those who had at least one lower respiratory tract illness with wheezing in the first 3 years of life and had wheezing at 6 years of age (those with persistent wheezing, PW) (16).

Data collected over the first 6 years of life were the following: Demographic (age, weight, and gestational age), family (asthma and atopy, *in utero* and postnatal cigarette smoke exposure), respiratory function (best lung function (LFT) results between age 6 and 7 years), immunological (allergic Skin Prick Tests and total IgE or specific IgE to the most common respiratory allergens: (house dust mite, cat or dog dander)), bacteriological (pathogens found in the sputum) and therapeutic (treatments prescribed for respiratory symptoms. From these data, we scored the Asthma Predictive Index, the PIAMA score and determined the "TUCSON" wheezing phenotypes (16).

The ***second part*** of the study involved children aged 6–17 years from 2002 to 2011 and focused on the presence of a BDR. The preschool children shown in the above section were not included in this >6 years age school age study group. Three age ranges were selected: ≥6 years to <8 years, ≥10 years to <12 years, and ≥15 years to <17 years. For each patient, anthropometric, clinical, allergic (total IgE, blood eosinophils, and allergic skin tests), bacteriological, genetic, and spirometric data were collected. LFT criteria regarding bronchial obstruction and the BDR were reported according to the ATS/ERS recommendations. The criteria for a positive BDR were: improvement in ppFEV1 by at least 12%, of $ppFEF_{25-75}$ or ppFEV1 by at least 35%; decrease in ppRV (and/or ppRV/TLC) by at least 20%, decrease in R_{aw} by at least 35%. The BDR was analyzed either based solely on ppFEV1 criteria, or on all the above-mentioned criteria (positive BDR if at least one of the functional reversibility parameter was present).

Current wheezing at 6 years of age was defined as children who had presented at least one episode of wheezing in the previous 12 months.

Regarding continuous variables, data are presented as medians and interquartile ranges, or means and standard deviations, according to their distribution. The statistical analysis was

TABLE 1 | Population characteristics according to the TUCSON phenotypes in preschool children aged less than 6 years.

	Total	NW	TW	LW	PW
N	125	22	25	12	36
Gender (G/F)	56/69	10/12	10/15	6/6	13/23
Age (years)	9.9 ± 4.9				
Genotypes					
Homozygous p.Phe508del	44 (55/125)	72.7 (16/22)#/##	32 (8/25)##	53 (7/12)	41.7 (15/36)#
Heterozygous p.Phe508del	45.6 (57/125)	27.3 (6/22)	48 (12/25)	41.7 (5/12)	44.4 (16/36)
Others	10.4 (13/125)	0 (0/22)	20 (5/25)	0 (0/12)	13.9 (5/36)
Birth weight (g)	3,158 ± 587	3,070 ± 126	3,228 ± 118	2,942 ± 171	3,131 ± 99
Full-term birth	92 (115/124)	95.4 (21/22)	92.0 (23/25)	91.6 (11/12)	91.6 (33/36)
≥1 parent with asthma	20.3 (25/123)	27.3 (6/22)	16.6 (4/24)	16.6 (2/12)	28.6 (10/35)
Smoking					
in utero	25.6 (31/121)	14.3 (3/21)	33.3 (8/24)	16.6 (2/12)	35.3 (12/34)
Postnatal	59.5 (72/121)	61.9 (13/21)	66.6 (16/24)	58.3 (7/12)	50 (17/34)
Personal allergy before age 6 years*					
Eczema	20 (24/120)	9.1 (2/22)	34.8 (8/23)	25.0 (3/12)	18.2 (6/33)
Rhinitis	9.2 (11/120)				
Respiratory sensitization before age 6					
SPT positive** House Dust Mite	6.7 (5/74)				
Cat	4.0 (3/75)				
Dog	2.7 (2/73)				
Sum specific IgE (HDM+Cat+Dog) (kUI/l)	2.0 [0.5–134.9]				
Food sensitization before age 6 years					
SPT** and/or RAST*** positive	23.4 (29/124)	18.6 (4/22)	20.8 (5/24)	16.7 (2/12)	33.3 (12/36)
Positive API at age 3 years	80.4 (41/51)	0	83.3 (10/12)	80.0 (8/10)	76.2 (16/21)
BMI *z*-score at age 3 years	−0.39 ± 0.09	−0.38 ± 0.19	−0.40 ± 0.17	−0.90 ± 0.25	−0.19 ± 0.16
Bacteriology					
S. aureus 0–3 years	87.7 (93/106)	89.5 (17/19)	90.0 (18/20)	88.9 (8/9)	86.2 (25/29)
P. aeruginosa 0–3 years	42.6 (46/108)	55 (11/20)	52.4 (11/21)	22.2 (2/9)	44.8 (13/29)
P. aeruginosa (chronic) 0–3 years	17.6 (19/108)	25.0 (5/20)	23.3 (5/21)	0 (0/9)	10.3 (3/29)

n/N; mean ± standard deviation; % (n/N); median [min, max].
**Reported by parents.*
***SPT positive if papule >3 mm.*
****RAST positive if >0.1 kUI/l.*
NW, never wheezers; TW, transient wheezers; LW, late wheezers; PW, persistent wheezers.
#NW vs. PW (p = 0.037); ##NW vs. TW (p = 0.009).

performed using NCSS software (Kaysville, Utah). The qualitative variables were compared using the Chi^2 test. Quantitative variables were compared using a Student's *t*-test if two groups were studied and by analysis of variance (ANOVA) in the presence of >2 groups (with a Bonferroni test to determine statistical differences between groups). A *p*-value < 0.05 was considered statistically significant.

RESULTS

One hundred and twenty-five patients aged less than 6 years of age and 69 patients above 6 years of age were included in the study.

Preschool Children (<6 Years)

Demographic Data

Mean age of patients at the time of the retrospective data collection was 9.9 ± 4.9 years. The M:F sex ratio was 1:1.2 [girls: 69/125 (55.2%)]. These patients were full-term babies in 92% of cases, exposed to cigarette smoke *in utero* and postnatally in 25.6% and 59.5% of cases, respectively, and had at least one asthmatic parent in 20.3% (25/123) of cases. The p.Phe508del mutation was present in 87% (110/126) of cases (**Table 1**).

Prevalence of Wheezing

The cumulative yearly frequency wheezing is shown in **Figure 1**. At least one episode of wheezing during the first 6 years of life was recorded in 71.2% (89/125) of cases. Regarding 115 children who had attained the age of 3 years, 66.1% (76/115) had had at least one episode of wheezing. In patients reaching the age of 6 years the cumulative prevalence of children having wheezed at least once was 76.8% (73/95) and 48.4% (46/95) had wheezed at least three times.

Prognostic Scores

The API index was available in 72 of 73 children who had wheezed at least once from birth to the age of 6 years. A positive API between 0 and 3 years of age was present in 77.3% (34/44) of cases. The yearly cumulative frequency of a positive API is shown in **Figure 1**. **Figure 2** indicates the PIAMA risk score.

Phenotypes

Twenty-two (23.2%) children had never wheezed by 6 years of age (NW). The distribution of 73 children with wheezing was as follows: 25 (26.3%) TW, 12 (12.6%) LW, and 36 (37.9%) PW (**Figure 3**).

Predictive Markers

These are shown in **Table 2**. Homozygous p.Phe508del mutations were present in 72.7% of the children in the NW group compared to 32% in the TW group ($p = 0.009$) and 41.7% in the PW group ($p = 0.037$).

Impact on Respiratory Function at 6 Years

The prevalence of "current" wheezers at the age of 6 years was 28.8% (21/73). The impact of wheezing in children according to their wheezing profiles or the existence of "current" wheezing at the age of 6 years is summarized in **Tables 2**, **3**.

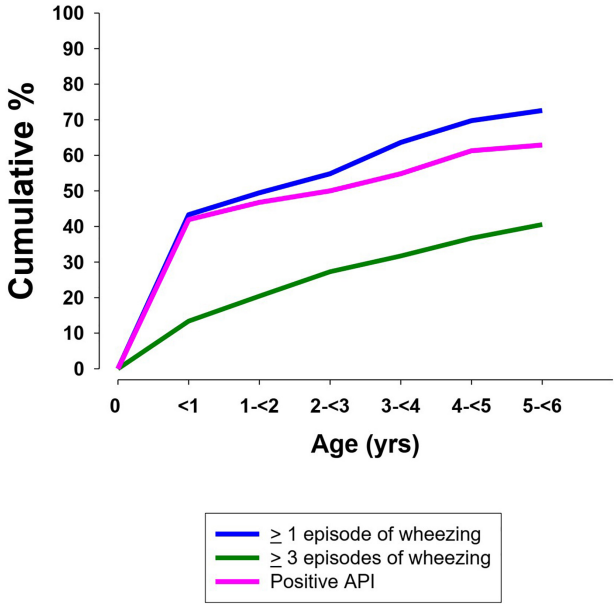

FIGURE 1 | Cumulative frequency of wheezing and a positive Asthma Predictive Index in preschool children (<6 years) with CF (13).

One of the main consequences of preschool wheezing was its impact on respiratory function. In the present cohort patients who had never wheezed had a mean $ppFEV_1$ of 107.8 ± 3.4% vs. 98.0 ± 2.2% in those who had had at least one episode between birth and 6 years of age ($p = 0.027$, **Figure 4**). **Figure 4** shows the ppFEV1 and $ppFEF_{25-75}$ according to the types of wheezing profiles. FEV_1 and forced vital capacity (FVC) values according to the different TUCSON phenotypes were as follows: NW > TW > PW > LW (NS).

Treatments

Prescriptions of short-acting bronchodilators and inhaled corticosteroids were significantly more frequent in symptomatic children (TW < LW < PW) compared to the NW groups (**Table 3**). At 6 years of age "current" wheezers had received more bronchodilator therapy ($p = 0.039$) and inhaled corticosteroids (NS) vs. non-current wheezers.

School-Age Children and Teenagers (>6 Years)

Demographic Data

Sixty-nine patients were included in this group (**Table 4**). The M:F sex ratio was 1:1. A Phe508del homozygote genotype was present in 71% (49/69) of cases. Forty-nine children had had at least one annual checkup between ≥6 years and <8 years, 33 children between ≥10 years and <12 years, and 17 children between ≥15 years and <17 years.

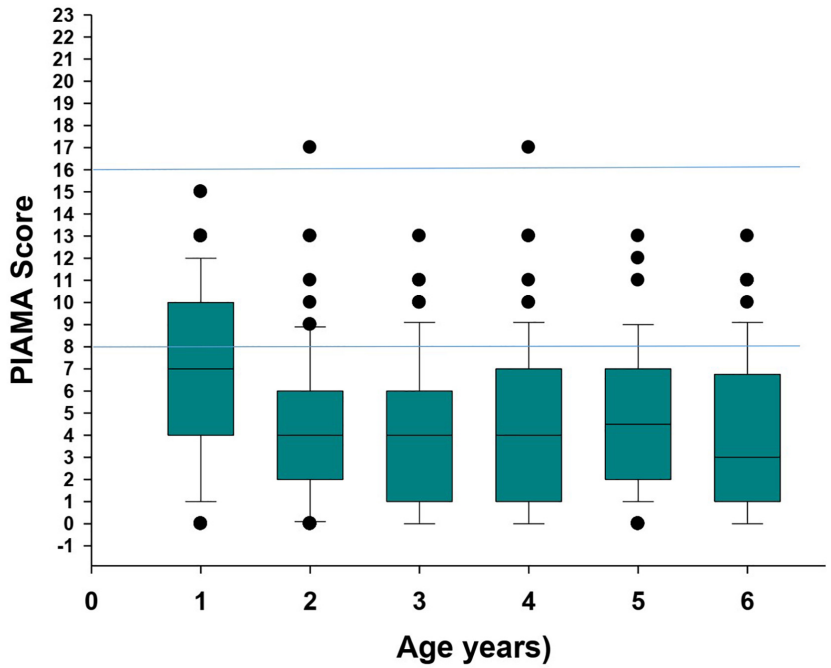

FIGURE 2 | PIAMA* score in children with CF. Box and whisker indicating the median (horizontal line) and the upper and lower quartiles of the PIAMA* score. The black dots indicate the outliers. The blue horizontal lines indicate the risk of asthma in non-CF patients between 6 and 8 years of age according to the PIAMA* score: 0–7: low; 8–15: medium; 16–23: high. *PIAMA, prevention and incidence of asthma and mite allergy (12).

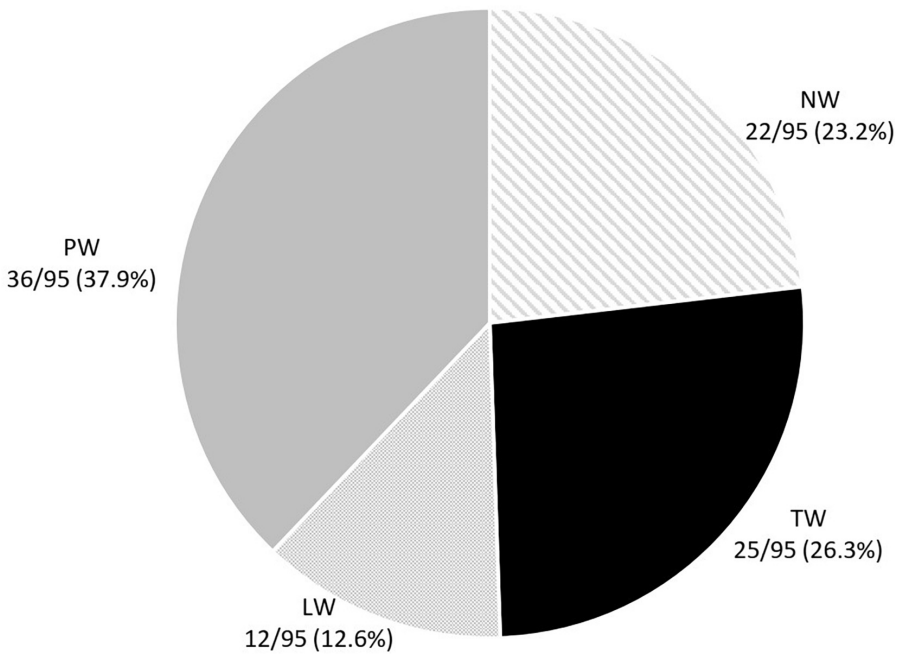

FIGURE 3 | Distribution of the preschool wheezing phenotypes according to the TUCSON* phenotypes. *Tucson phenotypes: TW, transient earlier wheezers; NW, never wheezers; LW, late onset wheezers; PW, persistent wheezers (16).

Prevalence of a Positive Bronchodilatory Response

A positive BDR was found in 73.5, 48.5, and 52.9% of children between 6 and 8 years, 10 and 12 years, and 15 and 17 years, respectively (**Table 5**). Longitudinally, among the 36 patients with early BDR (at 6–8 years), 8 out of 14 (57%) retained this BDR at 10–12 years, and 3/5 at 15–17 years (**Table 5**). Among the 13

TABLE 2 | Consequences of pre-school wheezing according to the TUCSON phenotypes.

Data	Total	NW	TW	LW	PW
BMI					
6 years (*z*-score)	0.08 ± 0.11	−0.18 ± 0.22	−0.28 ± 0.20	−0.57 ± 0.33	0.28 ± 0.18
ppFEV$_1$					
6–7 years % theoretical value	100.4 ± 1.9	**107.8 ± 3.8**	98.4 ± 4.0	97.7 ± 5.0	**97.9 ± 3.0***
ppFVC					
6–7 years % theoretical value	98.4 ± 1.9	105.9 ± 4.9	97.6 ± 3.9	91.2 ± 4.9	96.7 ± 2.9
ppFEF$_{25-75}$					
6–7 years % theoretical value	87.0 ± 2.9	**99.6 ± 5.6**	**82.6 ± 5.9***	93.6 ± 7.4	**79.1 ± 4.1***
Bacteriology					
S. aureus 0–6 years	95.5 (86/90)	95.5 (21/22)	100.0 (21/21)	81.8 (9/11)	97.2 (35/36)
P. aeruginosa 0–6 years	62.2 (56/90)	68.2 (15/22)	72.7 (16/22)	54.5 (6/11)	54.3 (19/35)
At least once chronic infection	18.9 (17/90)	27.3 (6/22)	31.8 (7/22)	0 (0/11)	11.4 (4/35)
Treatment received from 0–6 years					
Inhaled bronchodilators	74.5 (70/94)	**31.8 (7/22)****	**75 (18/24)***	**83.3 (10/12)***	**97.2 (35/36)***
Inhaled corticosteroids	74.5 (70/94)	**40.9 (9/22)**	**75 (18/24)***	75.0 (9/12)	**94.4 (34/36)*/****

Mean ± SD; % (n/N).
TW, transient earlier wheezers; NW, never wheezers; LW, late onset wheezers; PW, persistent wheezers.
**p < 0.05 vs. NW; **p < 0.05 TW.*
Bold values indicate the significant difference between the two groups p < 0.05.

patients without early BDR criteria, 3 of 6 (50%) progressed to a positive BDR response at the age of 10–12 years.

Using FEV_1 as a sole criterion, a positive BDR was demonstrated in 34.7, 6.1, and 5.9% of the children between 6 and 8, 10 and 12, and 15 and 17 years of age, respectively (**Table 5**).

Predictive Markers

The homozygous Phe508del genotype was more frequent in the BDR + group compared to the BDR- group (64% vs. 36%, $p = 0.041$) in 6- to 8-year-olds (**Table 6**). The body mass index in the BDR + group was greater vs. the BDR- group in children aged 10–12 years ($p = 0.01$). The sum of the diameters of the prick test papules for 3 pre-defined common respiratory allergens was greater in the BDR+ patients at all ages, but this was significantly in the 6–8 years age group only ($p = 0.005$). The blood eosinophil counts were significantly lower in the BDR+ group of patients at the age of 10–12 years only ($p = 0.013$). The number of *Aspergillus* precipitation arcs was also lower in the BDR+ group at the age of 10–12 years ($p = 0.05$) (42).

TABLE 3 | Consequences of current' wheezing at the age of 6 years.

Data	Current wheezers	Not current wheezers	*P*
BMI 6 years (*z*-score)	*n* = 16 0.15 ± 0.26	*n* = 48 −0.11 ± 0.15	NS
ppFEV$_1$	*n* = 20 **91.5 ± 4.4**	*n* = 45 **100.9 ± 2.4**	**0.047**
ppFVC	*n* = 20 89.9 ± 4.2	*n* = 45 98.6 ± 2.4	NS
ppFEF$_{25-75}$	*n* = 19 77.7 ± 5.6	*n* = 45 85.0 ± 3.6	NS
Bacteriology			
S. aureus 0–6 years	95 (19/20)	95.8 (46/48)	NS
P. aeruginosa			
P. aeruginosa at 6 years	70.0 (14/20)	56.3 (27/48)	NS
Chronic infection	5.0 (1/20)	20.8 (10/48)	NS
Treatment			
Short-acting beta-2 agonists	**100 (21/21)**	**82.4 (42/51)**	**0.039**
Inhaled corticosteroids	90.5 (19/21)	82.4 (42/51)	NS

Mean ± SD; % (n/N).
Bold values indicate the significant difference between the two groups p < 0.05.

Impact of a Positive Bronchodilatory Response on Lung Function

FVC and FEV1 values of BDR + patients at the age of 6–8 years were lower than those of BDR- patients, with a significant difference regarding FVC only (85% vs. 101%, $p = 0.015$, **Table 6**).

DISCUSSION

The present study indicates that wheezing is a common phenomenon in preschool children with CF. Wheezing was not associated to p.Phe508del homozygosity, allergic factors or chronic *Pseudomonas aeruginosa* colonization. Persistent wheezing was associated with lower lung function at the age of 6 years. A positive BDR in older children with CF was also a common finding, and was associated with lower lung function between 6 and 8 years of age, increased BMI between 10 and 12 years of age, and a greater sum of the diameter of allergic prick test papules for three common respiratory allergens. In this study, we did not find identify allergic bronchopulmonary aspergillosis as a cause of wheezing.

The reported rate of wheezing in CF is variable. In a large population of patients with CF in the United States and Canada, the cumulative percentage of patients reaching onset of persistent

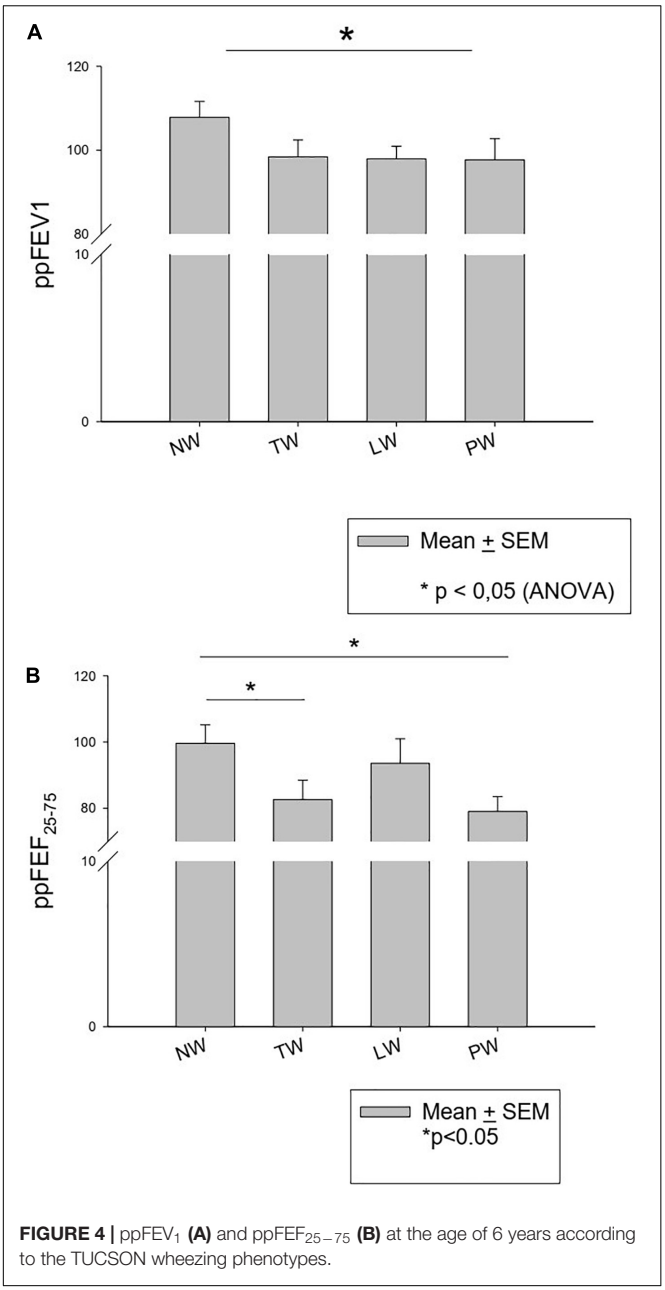

FIGURE 4 | $ppFEV_1$ **(A)** and $ppFEF_{25-75}$ **(B)** at the age of 6 years according to the TUCSON wheezing phenotypes.

wheezing was approximately 30% at the age of 6 years and 50% at the age of 15 years (17). In contrast, the European CF Epidemiologic Registry (ERCF) reported a rate of asthma of 14% in children with CF less than 6 years of age. Ren et al. showed that wheezing during the first 6 years of life was associated with lower lung function at the age of 6–8 years (18, 19). Based on the different TUCSON phenotypes (16), they reported that persistent wheezers (PW) had significantly lower FEV1 than never wheezers (NW) (19). Levine et al. showed that 39% of children aged 14.4 (4–76) years, median (range), with CF had reversible bronchial obstruction (20).

Physicians tend to extrapolate asthma treatment to the management of wheezing in CF. We and others (1, 17, 20) raise concerns regarding the abuse of inhaled steroids and bronchodilators which are too often prescribed in patients with CF. According to the French 2019 CF registry, 36.3 and 59.3% of patients received inhaled corticosteroids and bronchodilators, respectively (21). Our work confirmed the widespread use of these agents: short-acting bronchodilators were prescribed in 97.2% of PWs and 94.4% of such wheezers received inhaled corticosteroids. Ren et al. reported that 89.1% of PW received bronchodilators vs. 73.2% of NW ($p < 0.05$). Kent et al. (22) pointed out that there was little evidence for the efficacy of asthma therapy in CF. A Cochrane review concluded that no study has been able to demonstrate that the use of inhaled corticosteroids decreases lung inflammation in CF (23). In France, a Delphi study recommended restricting the use of inhaled corticosteroids in CF due to an insufficient level of evidence (24). According to Smith and Edwards neither long-acting beta-2 agonists nor long-acting muscarinic antagonist bronchodilators demonstrate improvement in FEV1 in CF (25). Moreover, the side effects of inhaled corticosteroids are not negligible. They can cause oral fungal infections and at high doses may negatively impact growth. Overall, under close supervision, teams caring for patients with CF may safely stop prescribing inhaled corticosteroids in these patients (26).

Preschool Children (<6 Years)

Wheezing in children with CF is more frequent compared to non-CF children [33.6% at 3 years of age and 48.6% at 6 years of age in the TUCSON Cohort (16)]. McColley et al. (17) found that children diagnosed by neonatal screening had a reduced risk of early onset of wheezing. The early diagnosis of the disease (associated with appropriate overall management by pediatric expert centers) is of vital importance to preserve the respiratory status in CF (14).

Predictive Markers

In our study, a positive API between 0 and 3 years of age was not significantly associated with any TUCSON wheezing phenotype, or with "current" wheezing at the age of 6 years. The PIAMA score was also not contributory. Personal allergic diseases (eczema, allergic rhinitis, etc.) were relatively uncommon and non-discriminatory. There was a 2 to threefold lower prevalence of eczema in the NW than in the 3 other subgroups (NS). No other criteria (birth weight, gestational age, parental asthma, allergic SPT, and smoking) was significantly associated with a particular TUCSON wheezing profile. The "protective" role of p.Phe508del homozygote mutations representing 72.7% of the children in the NW group compared to 32% in the TW group ($p = 0.009$) and 41.7% in the PW group ($p = 0.037$) was not found by Ren et al. (19). Chronic colonization with *P. aeruginosa* at 3 years of age was not associated with "current" wheezing at 6 years of age ($p = 0.044$). Interestingly, McColley et al. (17) found that the presence of *P. aeruginosa* and/or *Staphylococcus aureus* seemed to be "protective" for the occurrence of crackles and chest congestion. They suggested that the treatments and more stringent follow-up when these bacteria were present may have played a "protective" role.

Consequences of Preschool Wheezing in Cystic Fibrosis

In our study, $ppFEF_{25-75}$ was significantly greater in NW compared to PW ($p = 0.027$). Ren et al. also reported higher FEV_1 and FVC values in NW compared to the other phenotypes (19). Preschool wheezing had a significant impact on lung function at school age in our study. In current wheezers at the age of 6 years $ppFEV_1$ was impaired [91.5% vs. 100.9% in non-wheezers since 12 months ($p = 0.047$)], as shown in previous reports (16, 19). Preschool wheezing did not significantly affect Body Mass Index at 6 years of age even though "current" wheezers had a −0.52 lower BMI z-score compared to the "non-current" wheezers, or the microbiological status in the sputum.

School-Age Children and Teenagers (≥6 Years)

We did not specifically study the prevalence of wheezing in school-age children. However, we did demonstrate that BDR was a common phenomenon involving approximately half of the patients studied. Mitchell et al. reported BHR after methacholine challenge in 51% of children with CF, compared to 98% in asthmatic control children (7). Mellis and Levison identified 24% of histamine responders among CF patients, compared to 90% in asthmatic control patients (27). In addition, there appears to be two categories of CF patients: those with symptoms of asthmatic disease, clinically diagnosed on the basis of recurrent acute exacerbations of wheezing, with a very high efficacy of bronchodilators and/or systemic corticosteroids; and those with some degree of "isolated" BHR (non-asthmatics) (9, 47).

Bronchial responsiveness to bronchodilators is an integrated physiological response involving airway epithelium, nerves, mediators and bronchial smooth muscle. In 1993, an *ad hoc* ATS committee recommended that the diagnosis of asthma be based either on methacholine/histamine challenges, or repeat spirometry after beta-adrenergic agonists or steroid trials (5). This suggests that bronchoconstrictor responsiveness (BCR) and BDR may be considered physiological opposites in chronic obstructive airways disease. In many LFT laboratories, provocation tests have been replaced by bronchodilator tests in the assessment of cases of airways obstruction. However, the correlation between bronchoconstriction and bronchodilator response is imperfect and it is not possible to infer with certainty the presence of one from the other (28). In COPD symptoms were more associated with the presence of a BCR, but not a BDR, indicating that they are two different phenotypic markers that are not interchangeable (29).

In the present study, a greater sum of allergic SPT HDM + Cat + Dog papules, lower lung function values and homozygous Phe508del genotypes were associated with a positive BDR in 6–8 year-old children. BDR+ patients aged 10–12 had lower blood eosinophil counts and *Aspergillus* precipitin arcs, as well as a higher body mass index, compared with BDR-children. In a similar study, Levin et al. showed that reversible obstruction ($\Delta ppFEV1 \geq 12\%$) was associated with

TABLE 4 | Population characteristics of school-aged children (≥6 years) and teenagers.

Data	Total (*N* = 69)
Age (years)	12.2 ± 3.6
Sex ratio (M:F)	34/35
Age at diagnosis (months)	4.3 [0.3–57.8]
BMI	
6–8 years	15.5 ± 1.6
10–12 years	16.8 ± 2.2
15–17 years	19.6 ± 2.2
Genotype	
DF508 homozygous	49 (71)
Heterozygous	15 (21.7)
Others	5 (7.3)
ppFEVl	
6–8 years	89.7 ± 20.4
10–12 years	85.7 ± 15.9
15–17 years	75.2 ± 20.9
Positive skin prick test (at least one)	
6–8 years	43/49 (87.8)
10–12 years	29/33 (87.9)
15–17 years	17/17 (100)
Pseudomonas aeruginosa	
6–8 years	4/49 (8.2)
10–12 years	7/33 (21.2)
15–17 years	7/17 (41.2)
Staphylococcus aureus	
6–8 years	19/47 (40.4)
10–12 years	15/33 (45.5)
15–17 years	11/17 (64.7)
Haemophilus influenzae	
6–8 years	7/47 (14.9)
10–12 years	4/33 (12.1)
15–17 years	2/17 (11.7)

Values expressed as mean ± standard deviation, median [interquartile] or n/N (%).

TABLE 5 | Prevalence of bronchodilatory responses (BDR).

Profile	6–8 years	10–12 years	15–17 years	*N*
Early BDR	+	+	−	2
	+	+		6
	+	−	+	2
	+	−		4
	+		+	1
	+			21
Absence of early BDR	−	+		3
	−	−	−	1
	−	−		2
	−			7
Other		+	+	1
		+		4
		−	+	1
		−	−	2
		−		5
			+	4
			−	3
Total BDR	36/49	16/33	9/17	69
n/N (%)	(73, 5)	(48, 5)	(52, 9)	

p = 0.02 (6–8 vs. 10–12 years).
BDR according to age (>1 positive lung function BDR criteria, upon annual assessment).
+, present; −, absent.

younger age (p = 0.01) and a severe genotype (p = 0.02), but not with a family history of asthma, serum IgE, blood eosinophils, pancreatic status, ppFEV1 < 40%, *Aspergillus* or *Pseudomonas* infection (20). In a study by Van Haren et al. including 20 children with CF, 40% of patients had histamine BHR, mainly among the youngest, and this was correlated with positive allergic SPTs (30). In children with CF, the prevalence of positive markers of respiratory allergy is significantly higher than in the general population (9). In a study including 31 adult patients with CF, such sensitization was found in 65% of patients with BHR (31). In three other studies performed in adults after challenge testing, BHR was also not correlated with allergic SPT positivity (7, 27, 32). Our study allowed us to observe the BDR with a longitudinal perspective. Regardless of the criteria used, the prevalence of a BDR was greater in the youngest patients and had decreased by the age of 10–12 years. Overall, allergy appears to be inconsistently associated with BHR and BDR + in CF.

Mechanisms of Wheezing and Bronchial Hyperresponsiveness in Cystic Fibrosis

According to McCuaig and Martin, deficient ion transport across CFTR in patients with CF cannot be solely responsible for the altered ASM physiology, as there is as much smooth muscle hypertrophy in pediatric CF patients as in those with non-CF bronchiectasis (10). Both CF and non-CF bronchiectasis are diseases characterized by high levels of neutrophils in the lungs, suggesting an important contribution of the inflammatory environment to ASM alterations. The presence of a bacterial infection, particularly *Pseudomonas*, will promote the secretion of IL-8 and TNF-alpha, leading to bronchial remodeling. In addition, CFTR-deficient T cells will be directed to type 2 T-helper cells, which will cause a pro-allergic response (10). In addition, calcium responses are altered in CFTR-deficient ASM at a very early stage, as confirmed by studies in CFTR−/− neonatal pigs. Ca^{++} is a crucial second messenger in smooth muscle contraction, activating myosin light chain (MLC) kinase through the formation of a Ca^{++} and calmodulin complex. The release of Ca^{++} and the activation of Cl- channels in the sarcolemma of ASM may be of importance in the smooth muscle contraction in CF, in contrast to asthma (33). Other possible causes of wheezing include antenatal cigarette smoke exposure (16), small or floppy airways (34, 35), excess intraluminal mucus (34), gastro-intestinal reflux (36), and oxidant-antioxidant species imbalance (37). Gastro-esophageal reflux, one of the most common gastrointestinal manifestations of CF, probably plays a role in the pathogenesis of the airway disease by inducing repeated micro-aspiration and bronchospasm (36).

TABLE 6 | Predictive markers and factors a positive bronchodilatory response (BDR) in patients aged >6 years.

	BDR+ (6–8 years)			**BDR+ (10–12 years)**			**BDR+ (15–17 years)**		
	Yes	**No**	***P***	**Yes**	**No**	***P***	**Yes**	**No**	***P***
$ppFEV_1$	87 ± 20	98 ± 21	NS	87 ± 12	84 ± 19	NS	80 ± 21	70 ± 21	NS
ppFVC	**85 ± 19**	**101 ± 21**	**0.015**	91 ± 10	84 ± 12	NS	83 ± 15	80 ± 16	NS
FEV_1/FVC	102 ± 9	98 ± 13	NS	96 ± 9	100 ± 14	NS	95 ± 12	86 ± 16	NS
Eos/mm^3	0.13 [0.11–0.21]	0.20 [0.03–0.46]	NS	0.29 [0.08–0.29]	0.28 [0.21–0.34]	NS	0.23 [0.06–0.43]	0.15 [0.10–0.28]	NS
Eos %	2.35 [1.83–4.00]	2.45 [1.85–5.00]	NS	**2.90 [1.60–3.70]**	**5.20 [2.75–7.40]**	**0.013**	2.20 [0.80–5.23]	1.70 [0.93–2.80]	NS
IgE (kUI/l)	37 [14–132]	20 [3–225]	NS	41 [27–121]	178 [30–670]	NS	35 [21–251]	89 [36–352]	NS
Sum SPT (mm)	**4 [2.0–8.8]**	**1 [0–7]**	**0.012**	4 [2–7.8]	3 [0.5–8.5]	NS	7 [5.5–8.5]	6 [1.5–7.8]	NS
Asp. Arcs (number)	0.47 ± 0.08 0 [0–0]	0.55 ± 0.15 0 [0–0]	NS	**0.0** ± **0.0** 0 [0–0]	**0.9 ± 1.7** 0 [0–1.7]	**0.05**	1.6 ± 2.5 0 [0–3]	0.5 ± 0.7 0 [0–l]	NS
Pa (log CFU/ml)	0.2 ± 0.7 0 [0–0]	0.6 ± 2.1 0 [0–0]	NS	1.2 ± 3.9 0 [0–0]	1.4 ± 2.8 0 [0–1.5]	NS	4.8 ± 7.6 0 [0–7.5]	1.1 ± 1.6 0 [0–2.8]	NS
Sa (log CFU/ml)	2.6 ± 3.4 0 [0–7]	2.5 ± 3.4 0 [0–7]	NS	2.9 ± 3.2 0 [0–6]	3.0 ± 3.9 0 [0–8]	NS	2.7 ± 2.8 3 [0–5.5]	4.0 ± 3.5 4 [0.3–7]	NS
Hi (CFU/ml)	0.7±1.9 0 [0–0]	0.9 ± 1.9 0 [0–l]	NS	0.4 ± 1.7 0 [0–0]	1.2 ± 2.8 0 [0–0]	NS	0.0 ± 0.0 0 [0–0]	1.8 ± 3.4 0 [0–3.8]	NS
Sum log CFU Pa+Sa+Hi	3.3 ± 4.2 0 [0–7]	3.8 ± 1.0 5 [0–7]	NS	4.6 ± 6.4 2 [0–7.5]	5.6 ± 5.6 6 [0–8.5]	NS	7.4 ± 6.5 6 [4–9]	6.9 ± 5.5 7 [2–8.8]	NS
LABA	14/35 (40)	4/13 (31)	NS	6/16 (37)	8/17 (47)	NS	4/8 (50)	6/8 (75)	NS
Macrolide	18/35 (51)	7/13 (54)	NS	9/16 (56)	12/17 (71)	NS	9/9 (100)	6/8 (75)	NS
Wheezing	–	–	–	–	–	–	–	–	–
Phe508del (Homozygote)	**16/25 (64)**	**9/25 (36)**	**0.041**	11/17 (65)	6/17 (35)	NS	3/7 (43)	4/7 (57)	NS
Body weight (kg)	21.5 ± 4.3	21.9 ± 4.2	NS	36.7 ± 8.9	31.4 ± 7.3	NS	53.2 ± 6.0	50.3 ± 14.5	NS
Height (m)	1.17 ± 0.08	1.18 ± 0.06	NS	1.43 ± 0.11	1.40 ± 0.09	NS	1.64 ± 0.06	1.6 ± 0.12	NS
BMI	15.5 ± 1.6	15.6 ± 1.8	NS	**17.8** ± **2.1**	**15.8** ± **1.9**	**0.01**	19.8 ± 1.5	19.4 ± 3.0	NS

Mean ± SD; % (n/N).

BMI, Body Mass Index; Eos, blood eosinophils; IgE, immunoglobulin type E; SPT, skin pricks tests; Arc Asp., arcs Aspergillus; Pa, Pseudomonas aeruginosa; Sa, Staphylococcus aureus; Hi, Haemophilus influenzae; LABA: long-acting beta 2 agonists.

Bold values indicate the significant difference between the two groups p < 0.05.

An altered redox environment with a low concentration of antioxidants, in particular glutathione, contrasting with high levels of 8-isoprostane in the epithelial surface liquid contributes to progressive lung damage (37).

Study Limitations

This study was retrospective and monocentric. This explains the small number of patients compared to other similar studies. However, missing data were limited since we have used prospective standardized national CF Registry procedures and dedicated software (MucoDomeos).[1]

Overall, based on the different data from the literature and from our own study the following hypothesis can be proposed: most children with CF behave like non-specific asthmatic patients, with a high prevalence of BHR and/or response to bronchodilators. They would then evolve toward a form of chronic obstructive airway disease with a lower prevalence of BHR. This raises the question as to which are the most appropriate treatments of BHR in CF. At the present time, the most promising agents are CFTR modulators. VX-809/770, reduces the ASM cell proliferation and normalizes calcium reuptake kinetics (38); Ivacaftor rapidly improves airflow obstruction, air trapping and airway distensibility (39); Lumacaftor-ivacaftor improves LCI (−1.6, 95% CI −2.6 to −0.5; $P < 0.01$), airway microbiota and inflammation, as well as MRI morphology (−1.3, 95% CI −2.3 to −0.3; $P < 0.05$) and perfusion score (−1.2, 95% CI −2.3 to −0.2; $P < 0.05$) (40). Ribeiro and Gentzsch have suggested that CF airway epithelial inflammation may enhance the efficacy of CFTR modulators, and this could have clinical implications regarding the presence of wheezing (41).

CONCLUSION

While wheezing is very common in children with CF, no major determinants in children below 6 years of age could be clearly identified. Current wheezing at age 6 years was significantly associated with lower lung function. In children older than 6 years, allergic factors, genetics (p.F508del homozygosity) and higher BMI were significantly associated with the presence of a positive BDR but this varied between age groups. In 6–8 years old children with a BDR, baseline lung function was significantly lower. Our results suggest that the "CF-Asthma" designation may be misleading in a vast majority of cases, and may lead to inappropriate treatment with inhaled steroids, especially in preschool wheezers.

[1] https://www.vaincrelamuco.org/2019/05/09/mucodomeos-un-logiciel-adapte-aux-besoins-des-crcm-2684

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical approval was not provided for this study on human participants because not yet, processing. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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The Short Term Influence of Chest Physiotherapy on Lung Function Parameters in Children With Cystic Fibrosis and Primary Ciliary Dyskinesia

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Airway clearance therapy (ACT) is one of the cornerstone treatment modalities to improve mucociliary clearance for patients with bronchiectasis. The progression of lung disease in patients with bronchiectasis can be evaluated by spirometry and multiple breath washout (MBW) and it is advised to monitor these on a regular basis. However, the short term effect of ACT on spirometry and MBW parameters is insufficiently clear and this variability may impact standardization. For cystic fibrosis (CF), available literature refutes a short time effect on spirometry and MBW parameters in children, however, for primary ciliary dyskinesia (PCD) no data are available. We performed a single-center, prospective cross-over study to evaluate the short term effect of a single ACT session using positive expiratory pressure mask on forced expiratory volume in 1 s (FEV_1) and lung clearance index (LCI), derived from MBW, compared to no ACT (control) in pediatric patients with CF and PCD. A total of 31 children were included: 14 with PCD and 17 with CF. For the whole group, there was no difference in median change of FEV_1 pp between the treatment and the control group (p 0.969), nor in median change of LCI (p 0.294). For the CF subgroup, the mean change in FEV_1 pp with ACT was −1.4% (range −9 to + 5) versus −0.2% (range −6 to + 5) for no ACT (p 0.271), the mean change in LCI with ACT was + 0.10 (range −0.7 to + 1.2) versus + 0.17 (range −0.5 to + 2.8) for no ACT (p 0.814). In the PCD subgroup, the mean change in FEV_1 pp with ACT was + 1.0 (range −7 to + 8) versus −0.3 (range −6 to + 5) for no ACT (p 0.293) and the mean change in LCI with ACT was −0.46 (range −3.7 to + 0.9) versus −0.11 (range −1.4 to + 1.3) for no ACT (p 0.178). There was no difference between PCD and CF for change in FEV_1 pp after ACT (p = 0.208), nor for LCI (p = 0.095). In this small group of pediatric patients, no significant short-term effect of chest physiotherapy on FEV_1 pp nor LCI in PCD and CF values nor variability was documented.

Keywords: airway clearance, physiotherapy, bronchiectasis, primary ciliary dyskinesia, cystic fibrosis

INTRODUCTION

Mucociliary clearance (MCC) is one of the most important defense mechanisms of the human airway against infections or inhaled pollution (1). Cilia lining the respiratory epithelium are an essential part of the MCC and move the mucus layer toward the pharyngeal cavity. Disorders of the MCC such as primary ciliary dyskinesia (PCD) and cystic fibrosis (CF) result in chronic airway inflammation, infection and eventually airway damage (2). This results in the formation of bronchiectasis with chronic cough and sputum production (1).

Cystic fibrosis (CF) is caused by biallelic mutations in the Cystic Fibrosis Transmembrane conductance Regulator (*CFTR*) gene (3), which translates to the CFTR protein, a transmembrane chloride channel mainly present in the respiratory and gastro-intestinal epithelium. Impaired chloride and water transport disturb the airway MCC by altering the periciliary liquid layer and the viscosity of the mucus layer. The defective MCC causes chronic airway infection and obstructive lung disease worsening with age, leading to respiratory insufficiency in young adults.

Primary ciliary dyskinesia (PCD) is a more rare inherited disease caused by abnormalities in the function and/or structure of the motile cilia, especially in the upper and lower respiratory tract. Patients suffer from chronic upper and lower respiratory tract infections, and almost half of them have situs inversus (4). While CF is characterized by a "chemical" disturbance of the MCC, in PCD the MCC disturbance has a "mechanical" origin (1).

The respiratory treatment for both disorders mainly consists of enhancement of the mucociliary clearance by physiotherapy and inhaled mucolytics combined with antibiotic treatment for acute and chronic infections (5, 6). Current physiotherapy management of CF is multifaceted, inclusive of a combination of inhalation therapy, airway clearance therapy (ACT), physical education/exercise and ongoing education about the disease and its treatment. ACT has the goal to facilitate mucus expectoration from the airways, by applying manual compression techniques, autogenic drainage and stimulating cough and huff (open glottis): by increasing the expiratory flow, secretions are more easily moved toward the oropharynx.

Positive expiratory pressure devices are used to prevent airway collapse and to recruit non-ventilated areas with occluded airways and to facilitate mucociliary clearance.

As progressive worsening of obstructive lung disease is frequent in patients with bronchiectasis, strict monitoring of disease progression with regular lung function assessment is advocated as good clinical practice (2).

Spirometry is the most frequently used, and a well standardized technique to monitor airway disease. Progressive decline in forced expiratory volume in 1 s (FEV_1) is observed in both disorders (7) and related to morbidity and mortality. In recent years, measures of ventilation heterogeneity such as lung clearance index (LCI) measured by the multiple breath washout test (MBW), have gained more attention. LCI seems to be more sensitive than spirometry for early airway disease (8, 9) and correlates with the risk of respiratory exacerbations (10, 11).

Standardization of lung function measurements is of utmost importance for correct assessment of a treatment effect, both for long-term follow-up of lung disease, and for use in clinical trials. Guidelines for standardization of spirometry and MBW report on required quality criteria for acceptability, repeatability and variability (12, 13). However, the timing of measurements in relation to ACT is not mentioned and not well studied. Previous studies in patients with CF showed heterogeneous results, with a significant effect on FEV_1 mainly in adults with advanced disease, but not on LCI (14–17). In PCD, there is only one small study in children that showed a heterogeneous change in FEV_1 after exercise (18).

The reported studies were characterized by different designs, different ACT techniques and their combination with for instance a bronchodilator or a treadmill. In addition, most studies lacked a control group.

As stimulation of mucus clearance may change the airflow obstruction and ventilation inhomogeneity, assessment of the effect of ACT on FEV_1 and LCI is clinically relevant. A proper control arm is important, as sputum expectoration is stimulated by the lung function maneuvers itself.

The aim of the present study was to study the short-term influence of ACT, more specifically using a positive expiratory pressure (PEP) mask, on spirometry (FEV_1) and measures of ventilation heterogeneity (LCI by MBW) in children with CF and PCD, in a cross-over study.

We hypothesize a significant short-term effect of ACT on lung function measurements in PCD, as the disturbance in MCC is of a mechanical character. In CF, where the defect is more of a chemical nature, we expect less impact of ACT to induce changes in lung function parameters.

MATERIALS AND METHODS

Subjects

Children between 6 and 18 years of age with a confirmed diagnosis of CF or PCD and able to perform spirometry were recruited in the Pediatric Pulmonology Department of the University Hospital of Leuven for a prospective cross-over clinical trial between June 2020 and June 2021. The diagnosis of CF was confirmed by a sweat chloride value $\geq$ 60 mmol/L and/or the presence of two disease causing mutations in the *CFTR* gene. All patients were pancreatic insufficient and had lung disease. The diagnosis of PCD was confirmed according to the European guidelines (19). A nasal punch biopsy, including a cell culture to exclude secondary defects was performed in all patients for functional evaluation of ciliary motility with high speed videomicroscopy and ultrastructural evaluation with transmission electron microscopy (20). Genetic analysis was performed in most patients.

Patients had to be respiratory stable at the time of inclusion, defined as "no change in sputum, no fever, no change in therapy for 30 days prior to inclusion, no more than 10% change in FEV_1 pp since the last visit."

Height, weight and body mass index (BMI) were expressed as z-scores according to the Flemish reference equations (21).

The study was approved by the research ethics committee UZ/KU Leuven (s55766). Informed consent/assent was obtained from the patients (if > 12 years) and/or their parents.

Study Design

We performed a single-center, prospective, randomized cross-over study. Patients were recruited at the time of a scheduled routine visit. At the first visit, patients were randomly assigned to the intervention (airway clearance therapy, ACT) or the control group (**Figure 1**). Due to the nature of the intervention blinding was not possible. Cross-over to the second visit after 6 months (= next scheduled visit) resulted in paired data for each individual patient.

The intervention consisted of a standardized session of ACT: a positive expiratory pressure (PEP) mask was used with the help of a physiotherapist. Three series of PEP were executed, each with 20 expirations followed by a minimum of three huffs and expectoration of mucus. Manual external compression of the chest by the physiotherapist was added to stimulate the process of mucus clearance. Every patient used his/her personal PEP mask with corresponding resistance to ensure comfort and custom-fit material. The resistance used was the one for which the patient could sustain a pressure of 15 cm of water for about 2 min of tidal breathing. No bronchodilators or other inhaled drugs were administered prior or during the ACT. Patients did not perform prior physiotherapy on the day of the study.

For the control condition, patients were allowed a period of 30 min of rest.

Outcome Measures

The spirometry-derived parameters FVC and FEV_1 were assessed using a hand held spirometer (Spirobank II® Smart) and performed according to the ATS/ERS guidelines (12). The software program Winspiro was used for visualization and display of results. The results were expressed as percent predicted, according to GLI reference values (22). The best FVC and FEV_1 of at least three technically acceptable measurements was used.

Nitrogen Multiple breath washout (MBW) measurements were performed using the Exhalyzer D (Eco Medics AG, Spiroware Version 3.2.1) and conform the consensus guidelines

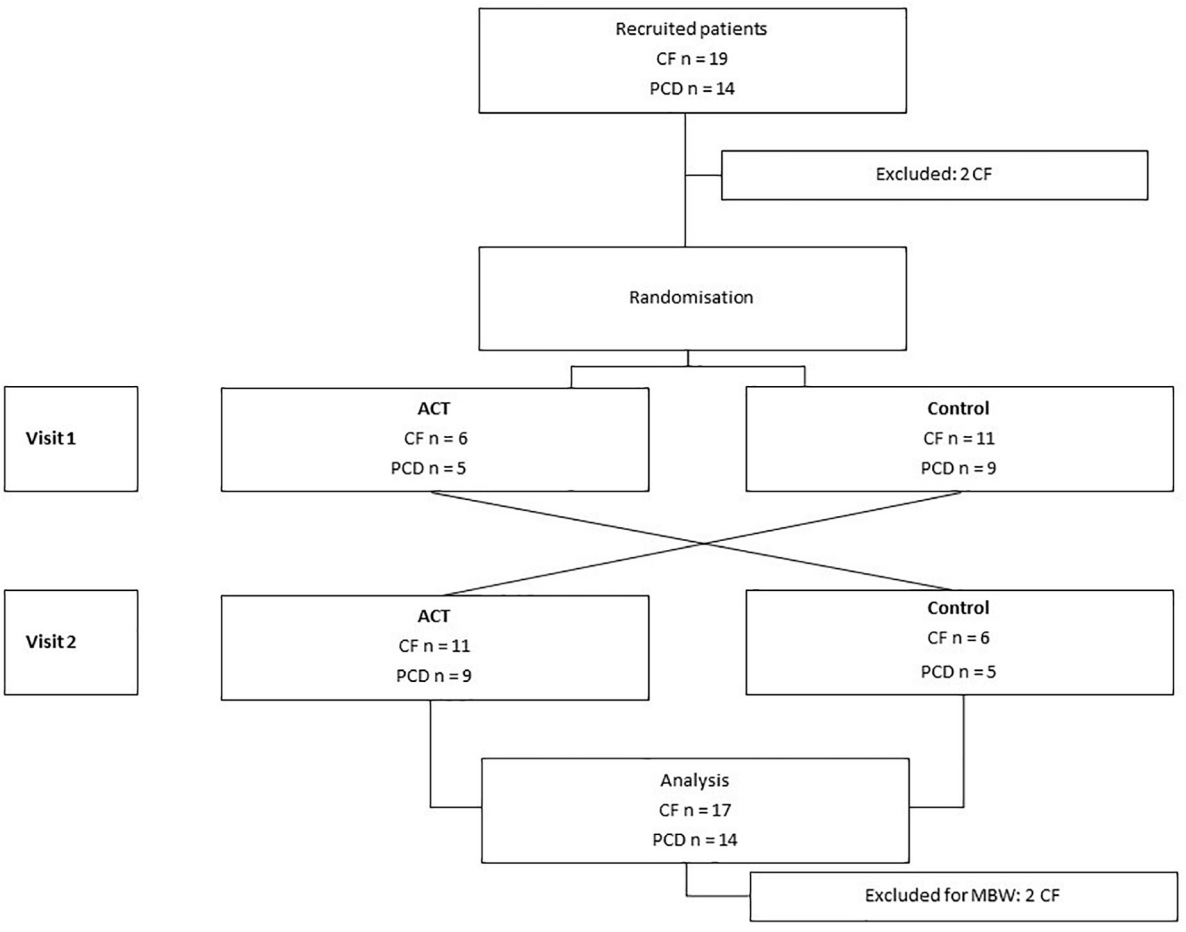

FIGURE 1 | Study overview. A total of 33 patients were recruited to participate in the study: 19 with CF, 14 with PCD. Two patients with CF were excluded. Patients were randomly selected before visit 1 for ACT or the control visit. After the first visit, cross-over to the other study intervention was done. In total, data from 17 patients with CF and 14 with PCD were available for spirometry, 15 with CF and 14 with PCD for MBW.

(13). The lung clearance index (LCI), the functional residual capacity (FRC) and the index of convection-dependent inhomogeneity multiplied by the tidal volume (s_{cond}*VT) were calculated from MBW maneuvers. The mean of at least two technically acceptable measurements with maximal variation of 10% in FRC was used. Reference values for LCI provided by the software were used (Houltz and Robinson et al.). The mean normal LCI value was 6.54, the upper limit of normal 7.17. As we didn't expect physiotherapy to have an impact on the acinar airways, we didn't compare the change in S_{acin}*VT (a measure of diffusion convention-interaction-dependent inhomogeneity in the acinar airways, distal from the terminal bronchioles, in the zone were gas exchange begins) between ACT and no ACT.

Each visit consisted of 2 MBW and 2 spirometry measurements. The lung function tests were performed in a fixed order: MBW was performed at first, followed by spirometry. Then, the intervention was performed: either a 20 min ACT session followed by a rest period of 30 min or 30 min rest without ACT. After the intervention, MBW and spirometry were repeated.

Statistics

All variables were described using mean and standard deviation if normally distributed, otherwise median and range were used. Data were checked for normal distribution using Kolmogorov-Smirnov test. Changes in lung function parameters were calculated by substraction of the value before the intervention from the value after the intervention and reported as Δparameter. The variability of the measurements induced by the intervention was calculated as the absolute value of Δparameter, | Δparameter|. %LCI change was calculated as the relative change of LCI to control for higher variability at elevated values (23): substraction of LCI before the intervention from LCI after the intervention divided by the LCI before the intervention. Paired samples t-tests were used to assess differences within patients. Differences between both patient groups (CF and PCD) were calculated using a Mann–Whitney U test for continuous variables and Fisher's Exact for categorical variables.

Bland-Altman plots were used to visualize the change and bias in lung function parameters induced by the intervention; the difference of the parameter before and after the intervention was plotted against the mean of the parameter before and after the intervention.

An Anova analysis with repeated measures was used to evaluate differences in lung function parameters between CF and PCD, with treatment group as within subject factor and patient group as between subject factor.

No formal power calculation was performed as we felt that no data were available in the literature to estimate the possibly expected change in lung function (both FEV_1 and LCI) due to ACT. Therefore, the sample size was exploratory.

Statistical analysis was performed using IBM SPSS statistics version 28 and Prism version 8. A 95% confidence interval was used for all results, significance set at alfa = 0.05 without correction for multiple measures.

RESULTS

Thirty-three subjects (CF n = 19, PCD n = 14) were included in the study. A total of two patients with CF were excluded from the analysis (one did not show up, one received a bronchodilator during the test moment). For MBW, two additional subjects with CF were excluded from the analysis because of insufficient test repeatability. Spirometry analyses were available for 31 subjects (CF n = 17, PCD n = 14) and MBW results for 29 subjects (CF n = 15, PCD n = 14).

Baseline characteristics were similar in both groups, with a predominance of boys (**Table 1**). Patients with CF were significantly shorter than those with PCD. There was no difference in baseline FVC pp and FEV_1 pp, nor in LCI between both groups.

There was no change in baseline characteristics between the first and the second visit: height z-score (p 0.640), weight z-score (p 0.481), BMI z-score (p 0.401), FVC pp (0.401), FEV_1 pp (0.814), LCI (p 0.348) nor FRC (0.280) did change significantly. This was also the case when analyzing the subgroups of patients with PCD and CF separately.

We did not observe significant differences in ΔFVC pp, ΔFEV_1 pp, ΔLCI, %LCI change, ΔFRC and Δs_{cond}*VT between ACT and the control condition. For the total patient group (n = 31), the mean ΔFEV_1 pp was −0.4 (range −9 to + 8) for ACT, −0.2 (range −6 to + 5) for the control condition (**Figure 2**); the mean ΔLCI was −0.17 (range −3.73 to + 1.17) for ACT, + 0.03 (range −1.42–+2.78) for the control condition (**Figure 3**). The results were similar in the subgroups of PCD and CF separately. Detailed results are presented in **Table 2**, graphs for ΔFVC, ΔFRC and Δs_{cond}*VT are available in the online supplements. When data from patients with normal values for FEV_1 and LCI (n = 5) were excluded, all comparisons remained similar (data not shown).

Bland-Altman plots illustrate the change in FEV_1 (**Figure 4**) and LCI (**Figure 5**) before and after the intervention in patients with CF and PCD, both in the ACT (a) and control group (b).

The variability of the measurements induced by the intervention were not different between the ACT and control group in the whole group of patients; |ΔFVC pp| (p = 0.593), |Δ FEV_1 pp| (p = 0.219), |ΔLCI| (p = 0.721) and |Δscond*VT|

TABLE 1 | Baseline characteristics of the study participants.

	Total	CF	PCD	Difference (p-value)
Subjects (n)	31	17	14	
Male sex (n, %)	20 (65%)	11 (65%)	9 (64%)	0.636
Age (year) (mean, SD)	11.7 (3.1)	10.7 (2.8)	12.8 (3.3)	0.077
Height (z-score) (mean, SD)	−0.6 (1.0)	−1.0 (1.0)	−0.1 (0.9)	0.015
Weight (z-score) (mean, SD)	−0.6 (0.7)	−0.7 (0.7)	−0.5 (0.8)	0.653
BMI (z-score) (mean, SD)	−0.4 (0.6)	−0.2 (0.6)	−0.6 (0.6)	0.200
Bronchiectasis (n, %)	25 (81%)	13 (76%)	12 (86%)	0.517
FVC baseline (pp) (mean, SD)	96.6 (12.9)	96.5 (15.4)	96.6 (9.6)	0.953
FEV_1 baseline (pp) (mean, SD)	93.0 (14.3)	94.0 (16.8)	91.9 (11.1)	0.739
LCI baseline (mean, SD)	8.6 (1.3)	8.6 (1.4)	8.6 (1.2)	0.847

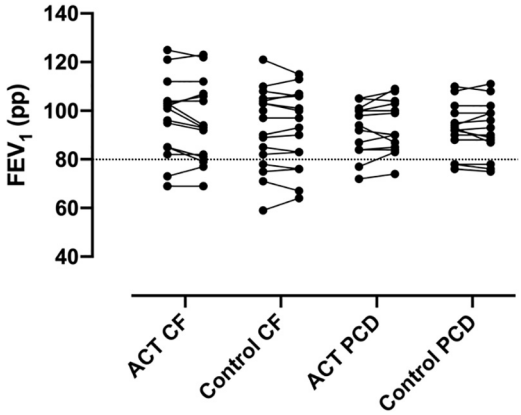

FIGURE 2 | Change in FEV_1 pp after ACT in patients with CF and PCD, compared to the control condition. No significant changes were observed, nor were significant differences observed between CF and PCD. The dashed line indicates the lower limit of normal for FEV_1 pp.

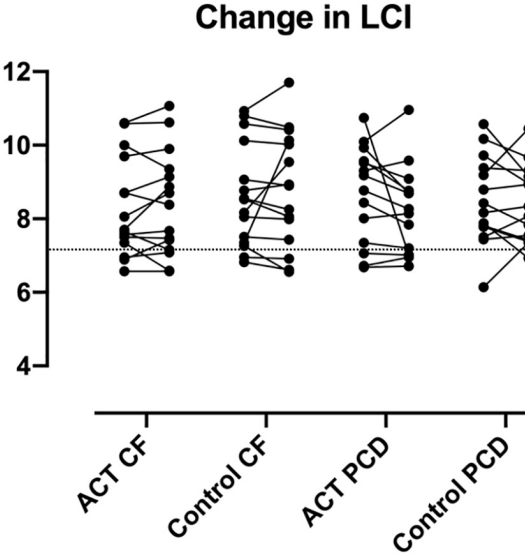

FIGURE 3 | Change in LCI after ACT in patients with CF and PCD, compared to the control condition. No significant changes were observed, nor were significant differences observed between CF and PCD. The dashed line indicates the upper limit of normal for LCI.

(p = 0.106). Only |ΔFRC| was lower in the control group compared to the ACT group (p = 0.008). Results were similar in the subgroup of CF and PCD separately (only no significant difference in |Δ FRC| for CF).

When evaluating the difference between CF and PCD using ANOVA with repeated measures, no significant difference was found for FVC (p = 0.500) (effect of treatment p = 0.098), FEV_1 (p = 0.208) (effect of treatment p = 0.949), neither for LCI (p = 0.095) (effect of treatment p = 0.287), FRC (p = 0.244)

TABLE 2 | Changes in lung function parameters in ACT group versus control.

	Total group (n = 31)			CF (n = 17)			PCD (n = 14)		
	ACT	Control	Comparison	ACT	Control	Comparison	ACT	Control	Comparison
ΔFVC pp	0.5 (3.1; −6 to + 6)	−0.7 (2.7; −6 to + 4)	0.089	0.4 (3.2; −6 to + 6)	−1.1 (3.1; −6 to + 4)	0.188	0.8 (3.2; −4 to + 6)	−0.4 (2.2; −4 to + 4)	0.313
ΔFEV1 pp	−0.4 (4.0; −9 to + 8)	−0.2 (2.8; −6 to + 5)	0.969	−1.4 (4.1; −9 to + 5)	−0.2 (3.0; −6 to + 5)	0.271	1.0 (3.7; −7 to + 8)	−0.3 (2.6; −6 to + 5)	0.293
ΔLCI	−0.17 (0.9; −3.73 to + 1.17)	0.03 (0.8; −1.42 to + 2.78)	0.294	0.10 (0.5; −0.76 to + 1.17)	0.17 (0.8; −0.47 to + 2.78)	0.814	−0.46 (1.1; −3.73 to + 0.87)	−0.11 (0.8; −1.42 to + 1.26)	0.178
%LCI change	−1.6 (8.9; −34.7 to + 15.2)	0.7 (10.5; −13.4 to + 37.8)	0.384	1.2 (6.5; −10.3 to + 15.2)	+ 2.1 (11.5; −9.6 to +37.8)	0.924	−4.6 (10.3; −34.7 to + 8.6)	−0.7 (9.4; −13.4 to + 19.7)	0.169
ΔFRC (l)	0.03 (0.2; −0.37 to + 0.74)	0.02 (0.1;−0.21 to + 0.30)	0.610	−0.10 (0.1; −0.28 to + 0.25)	0.00 (0.1; −0.08 to + 0.30)	0.841	0.08 (0.3; −0.37 to + 0.74)	0.03 (0.1; −0.21 to + 0.25)	0.405
ΔScond*VT	−0.002 (0.02; −0.06 to + 0.04)	0.003 (0.02; −0.03 to + 0.05)	0.207	0.000 (0.02; −0.03 to + 0.04)	0.002 (0.02; −0.03 to + 0.04)	0.833	−0.005 (0.02; −0.06 to + 0.04)	0.006 (0.02; −0.03 to + 0.05)	0.115

Data are presented as mean (SD; range). Comparison between groups was performed with paired t-test.

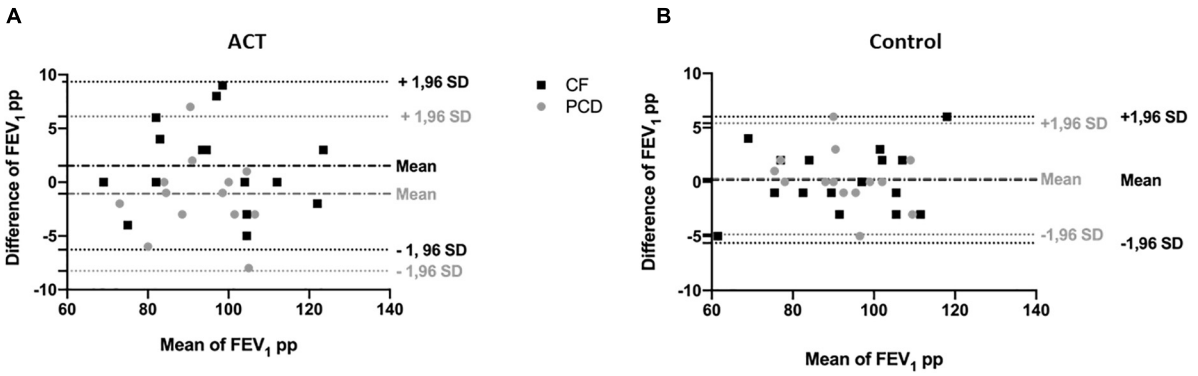

FIGURE 4 | Bland and Altman plot for FEV_1 pp in the ACT condition **(A)** compared to the control condition **(B)**, in patients with CF (black) and patients with PCD (gray). The difference of FEV_1 pp is plotted against the mean of FEV_1 pp to illustrate the change of the measurement after the intervention. There is no significant difference in change with ACT compared to the control condition.

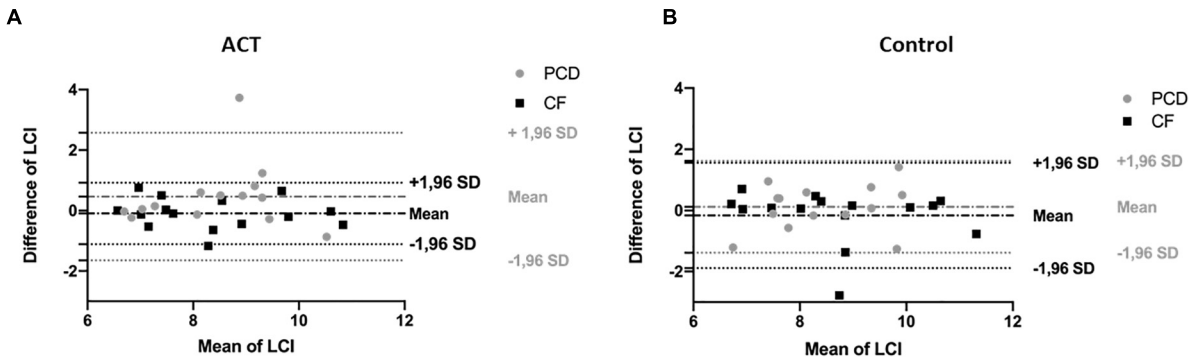

FIGURE 5 | Bland and Altman plot for LCI in the ACT condition **(A)** compared to the control condition **(B)**, in patients with CF (black) and patients with PCD (gray). The difference of LCI is plotted against the mean of LCI to illustrate the change of the measurement after the intervention. There is no significant difference in change with ACT compared to the control condition.

(effect of treatment $p = 0.594$) or s_{cond}*VT ($p = 0.920$) (effect of treatment $p = 0.196$).

DISCUSSION

In this study, we observed no short-term effect of ACT on lung function parameters in children with CF and PCD. We could not confirm differences between PCD and CF.

Our findings in CF are consistent with the literature. A significant effect of ACT on FEV_1 was found in some studies (16, 17), but only in adults with severe disease, and in combination with salbutamol administration (16). All other studies reported no effect of ACT on FEV_1. But, only one study included a control condition to compare the variability after an intervention to the natural variability (14). A few studies also included MBW/LCI, and all showed no change after ACT. For PCD, no reliable data were available until now.

We hypothesized that ACT could potentially have a short-term effect on lung function parameters in PCD, as ACT has the aim of mechanical complementation of the impaired MCC. The hypothesis was not confirmed, possibly because all children were treated with regular ACT and evaluated outside exacerbations, and therefore only little amounts of mucus can be expectorated per session of ACT.

One of the strengths of our study is the cross-over design with the inclusion of a control condition. In this way, each patient could serve as his own control, in stable conditions. The variability induced by the ACT was compared to the variability without intervention (within-test variability) and we showed that an ACT intervention doesn't increase the within-test variability of both FEV_1 and LCI. Additionally, the within- and between-test variability shown in our study, was similar to what was previously shown (23). This information is important for correct interpretation of lung function parameters in long term follow-up, and for design of clinical trials where FEV_1 and LCI are used as outcome measures.

Assignment to either ACT or control at the first visit was random. However, patients nor study personnel could be blinded for the intervention. For the first time, patients with PCD were included, and compared to patients with CF and similar disease severity. We didn't include children with other

etiologies of bronchiectasis, such as post-infectious, immune deficiency-related or idiopathic bronchiectasis. In adults with non-CF bronchiectasis (including patients with PCD), a change in LCI but not FEV_1 after ACT has been documented (24). As non-CF non-PCD bronchiectasis may have a broad range of pathophysiological mechanism causing dysfunction of the MCC, these findings cannot be extrapolated without caution to children with non-CF non-PCD bronchiectasis.

The limitations of our study were a small study sample, and the absence of adult patients and/or patients with severe lung disease. Especially in patients with PCD and advanced disease, lung function parameters could be influenced by ACT. This should be further studied in the future. No hypertonic saline inhalation or other mucolytic was used in combination with ACT, as is often done in clinical practice for home treatment. Because we wanted to study the influence of ACT alone and because mucolytic or expectorant drugs can also influence MCC, we decided not to use inhaled drugs in combination with ACT. Because of the COVID pandemic inclusion was temporarily interrupted and several patients were not willing to participate. The time between both visits was rather long for a cross-over design, but in this way all visits could be combined with clinical visits and reduced the study burden for the patients. We realize the study was very time-consuming and tiring for the patients with at least six spirometry maneuvers and 4 MBW measurements in total per visit. Additionally, the stable baseline characteristics between both visits confirms the participating patients were stable.

Based on our findings, the timing of lung function measurements in relation to ACT doesn't seem to have a relevant impact on the interpretation of the results in stable children. Especially for use as outcome parameter in clinical trials, no specific attention needs to be given to the timing of ACT.

CONCLUSION

In this study, no significant short-term effect of ACT was found on lung function parameters in stable children with CF and PCD. Further research with a larger sample size, adult patients and other chronic lung diseases is needed.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the University Hospitals Leuven, Belgium. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

BV, DD, EH, MS, and MV performed the study measurements. MB, TT, MV, and EH designed the study. MB, FV, and MP recruited the patients. BV, DD, and MB performed the statistical analysis. BV and DD drafted the manuscript. MB designed the final manuscript. All authors read and approved the final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.858410/full#supplementary-material

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Lung Function in Preschool Children in Low and Middle Income Countries: An Under-Represented Potential Tool to Strengthen Child Health

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Background: The burden of respiratory disease is high in low-middle income countries (LMIC). Pulmonary function tests are useful as an objective measure of lung health and to track progression. Spirometry is the commonest test, but its use is limited in preschool children. Other lung function methods have been developed but their use in LMIC has not been well described.

Aim: To review the use of preschool lung function testing in children in LMIC, with particular reference to feasibility and clinical applications.

Methods: Electronic databases "PubMed", "Scopus"," Web of Science", and "EBSCO host" were searched for publications in low and middle income countries on preschool lung function testing, including spirometry, fractional exhaled nitric oxide (FeNO), oscillometry, interrupter technique, tidal breathing and multiple breath washout (MBW), from 1 January 2011 to 31 January 2022. Papers in English were included and those including only children ≥6 years were excluded.

Result: A total of 61 papers from LMIC in Asia, South America, Africa, Eurasia or the Middle East were included. Of these, 40 included spirometry, 7 FeNO, 15 oscillometry, 2 interrupter technique, and 2 tidal breathing. The papers covered test feasibility (19/61), clinical application (46/61) or epidemiological studies (13/61). Lung function testing was successful in preschool children from LMIC. Spirometry was the most technically demanding and success gradually increased with age.

Conclusion: Preschool lung function testing is under-represented in LMIC for the burden of respiratory disease. These tests have the potential to strengthen respiratory care in LMIC, however access needs to be improved.

Keywords: spirometry, fractional exhaled nitric oxide, oscillometry, interrupter technique, tidal breathing, multiple breath washout

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INTRODUCTION

Childhood respiratory disease is a common cause of morbidity and mortality globally (1). The burden of acute and chronic respiratory disease is especially high in low-middle income countries (LMIC) (2), may result in impaired lung function and set a trajectory for chronic illness into adulthood (3, 4). However, access to respiratory diagnostic and management tools such as lung function are limited in many LMIC (5).

Lung function attained in early life is important for respiratory health, with low lung function associated with subsequent risk of respiratory disease (6). Pulmonary function tests are an objective measure of lung health which can be used to diagnose and track lung disease and assess response to treatment. In recent years non-invasive tests have been developed and guidelines produced for preschool children, facilitating its use in assessing respiratory health in early life (7, 8).

Lung function tests used in preschool children include spirometry, bronchial response testing, multiple breath washout (MBW), fractional exhaled nitric oxide (FeNO), oscillometry and other tests which measure resistance, including the interrupter technique (Rint). and plethysmography. With increased recognition of the importance of maximizing early life respiratory health and the growing availability of tools to do so, their use in LMIC is of particular interest.

Of the preschool lung function tests, spirometry is the most commonly used and most widely available. Even though use is limited in very young or uncooperative children, it is feasible in children as young as 3 years (9). Spirometry measures lung volumes at maximal expiration and is able to assess airflow obstruction, response to bronchodilator therapy and lung volumes on forced expiration. The commonly reported measures are the forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), FEV_1/FVC and forced expiratory flow between 25 and 75% of FVC (FEF_{25-75}). (10). Spirometry predominantly reflects airflow in large and medium sized airways, and is a poor measure of peripheral small airways or early lung disease (11). Current international recommendations for spirometry collection and interpretation in young children are available (10, 12).

Oscillometry (or the forced oscillation technique, FOT). is a simple, non-invasive technique which is performed during tidal breathing. Minimal co-operation is required thereby making this a popular measurement in preschool children. This measures the impedance of the respiratory system, which includes resistance and reactance across a range of frequencies reflecting the entire respiratory system including the small airways (13). The novel intra-breath measurement may be a more sensitive measure of small airway disease, thus allowing early detection of disease (14, 15). Recent international recommendations for oscillometry have been published on methodology, technical standards and future developments for use in children (7, 16, 17).

The interrupter technique measures the resistance of the respiratory system requiring minimal cooperation. The technique involves a sudden interruption of flow during tidal breathing, this allows for alveolar and pressure at the mouth to equilibrate therefore alveolar pressure can be estimated (18, 19). Different methods have been used to perform the test making the comparison of results difficult thus highlighting the need for test standardization. Furthermore, research is still required to determine the best algorithm to calculate pressure at the mouth during occlusion and the cut-off value for Rint post bronchodilator needs to be established (7).

Multiple breath washout (MBW) is used to assess ventilation homogeneity. It measures the functional residual capacity (FRC) and the lung clearance index (LCI) in preschool children (8). It is more sensitive than spirometry for the detection of peripheral airway disease and has been successfully used in the monitoring of children with cystic fibrosis (CF) and primary ciliary dyskinesia (PCD) (7, 20). It correlates with high resolution CT scan in CF patients as well as in children with asthma, bronchiolitis obliterans or chronic lung disease of prematurity (8, 21).

Fractional exhaled nitric oxide (FeNO) is a non-invasive marker of T-helper cell type 2 (TH2). eosinophilic airway inflammation. Tests can be performed with high repeatability and accuracy (22–24). Its main use is an adjunct to the diagnosis of TH2 type asthma and guiding the use of inhaled corticosteroid (ICS) treatment. In addition, FeNO can also assist in the differential diagnosis of other conditions such as cystic fibrosis (CF), PCD, scleroderma, obstructive sleep apnoea syndrome and hepatopulmonary syndrome. Fractional exhaled nitric oxide levels are low in PCD; however measurement of nasal NO improves the diagnostic accuracy and is a useful screening tool for PCD (23, 25). Normal values for FeNO are published for children from 4 years of age (24), as well as international applications and the use of FeNO (23, 24, 26). However, there are limited data on the use and feasibility of such measures in LMIC, despite the high burden of lung disease and need for objective tools to diagnose and monitor these.

We aimed to review the use of preschool lung function testing in children in LMIC, with reference to feasibility and clinical applications, to identify opportunities for optimizing diagnosis and management of childhood respiratory disease in these settings.

METHODS

We reviewed published literature of preschool lung function testing in LMIC, which included children between the ages of 3 to 5 years. We included published papers from 1 January 2011 to 31 January 2022 that included lung function testing in the preschool age group from a World Bank defined LMIC.

The search was conducted on the following electronic databases: PubMed, Scopus, EBSCOhost (Cinahl, Africa wide information, Health source- Nursing/Academic Edition). and Web of Science including the search terms: Respiratory Function Test*" OR "Lung function test*" OR "pulmonary function test*" OR "respiratory function test*" OR "multiple-breath washout" OR "Forced oscillation technique" OR" tidal breathing" OR "fractional excretion of nitric oxide" OR Spirometry OR Oscillometry OR "impulse oscillometry" OR "interrupter technique" OR "interrupter resistance" AND "preschool child*". Full search strategy can be seen in **Supplementary Table S1**. Reviews, editorials, case reports and conference proceedings were excluded. Any papers including only children $\geq$ 6 years were excluded. Abstracts of identified documents were reviewed and screened by SC, with second author DG assisting with inclusion queries. All included papers were reviewed by SC.

RESULTS

A total of 626 papers were screened of which 61 were eligible for inclusion, **Supplementary Figure S1**. They included papers from

4 regions: 30 (49.2%) from Asia, 17 (27.9%) from South America, 9 (14.7%) from Africa and 5 (8.2%) from Europe and the Middle East. Five lung function tests were most commonly reported: 40 (65.6%) spirometry, 7 (11.5%) FeNO, 15 (24.6%) oscillometry, 2 (3.3%) interrupter technique and 2 (3.3%) tidal breathing measurements. There were no papers including MBW. The papers covered test feasibility (19, 31.1%), clinical applications (46, 75.4%) and epidemiological studies (13, 21.3%). Clinical studies focused on development of reference tools (19/46, 41.3%). and on specific diseases: asthma (15/46, 32.6%), of which 4 papers in addition to asthma included allergic rhinitis, air pollution, obesity and allergic bronchopulmonary aspergillosis (ABPA); CF (5/46, 10.9%); 1 bronchiolitis obliterans, 1 recurrent wheeze, 1 systemic sclerosis. Epidemiological studies assessed the impact of air pollution (10/13, 77%); electronic waste (e-waste) (2/13, 15.4%) (27, 28) and the effect of antenatal omega 3 fatty acid supplementation (1/13, 7.7%) on lung function. E-waste is accumulated discarded or broken electronic devices which is becoming the largest amount of waste in the world (27, 28). As spirometry, FeNO, oscillometry or tidal breathing were most commonly used they were the focus of this review.

Spirometry

The majority (40, 68%) of papers included spirometry, (**Table 1**). Spirometry was used to develop reference equations, diagnose and manage respiratory diseases including asthma or CF, assess the impact of air pollution, electronic exposures (e-exposures) or socio-economic status on lung function. Twenty (50%) studies were from Asia, 9 (22.5%) from South America, 7 (17.5%). from Africa and 4 (10%) from Europe and the Middle East.

Success rates for spirometry in preschool children increased with age (29). Children between 4–6 years of age achieved a success rate between 82–85%, (30–32). while children between 3–5 years and 3–6 years of age, success rates were 68.4% and 42% respectively (29, 33).

A number of reference ranges were generated for individual population groups in LMIC, which were compared to either local reference ranges and/or The Global Lung Function Initiative (GLI) 2012 equation (32–39). Many resulted in an over estimation/underestimation of lung function for the population assessed, highlighting the complexity of population differences in lung function. A Nigerian study determined reference equations for children with sickle cell anemia (40). Published international equations also used arm span to determine height for spirometry (41). The GLI 2012 "Caucasian" provided a reasonable fit for Jordanian children (29). When assessing spirometry in two groups of healthy children with Indian ancestry, one living in UK and the other in India, the GLI equations for best fit differed: the "GLI-Black" equation was most useful for interpreting the South-Asian data and "GLI-Other" for North Indian data (42). Similarly in a South Africa population the GLI 2012 "GLI-Caucasian" provided a good fit for the Caucasian population, "GLI-Black " and "GLI-Southeast Asian" was a good fit for the Indian population and "GLI-Other" fit the Black African and Mixed ancestry populations well (43). These findings highlight the importance of multiple factors, including environment and socioeconomic exposures that impact population differences (42, 43).

Numerous environmental factors were reported to impact on lung function. Children living in rural areas or exposed to poorer socio-economic circumstances had lower lung function compared to those in urban areas (42, 44). Exposures to volatile organic compounds, particulate matter 10 (PM_{10}) or carbon monoxide (CO) were associated with a decrease in FEV_1 and FVC in exposed preschool children (45–47).

In a study in Guatemala, where CO was used as a proxy for $PM_{2.5}$, timing of chimney stove installation was compared to cooking over open fires, and showed a decrease in PEF of 173 ml/min/year (95% CI −341 to −7). with chimney stove installation at 18 months compared to installation at birth (48). A Chinese study failed to demonstrate any significant association between $PM_{2.5}$ exposure and any of the spirometry lung function measures, however an increase in oscillometry resistance was noted suggesting that oscillometry may be a more sensitive measure (49). In addition to air pollution, e-waste is a growing concern. Chinese children living in e-waste exposed areas had significantly lower birth weight, chest circumference and spirometry lung function compared to those in unexposed areas (27, 28).

The majority of included papers used spirometry in the clinical diagnosis and management of pediatric obstructive lung disease including asthma and CF. The studies investigated genetic predisposition to asthma, and management of acute, poorly controlled and cough-variant asthma (CVA). and the impact of obesity (50–53). Genes associated with increased susceptibility to asthma and lower spirometry indices were identified in Chinese and Egyptian children (54, 55). One study assessed current definitions of BDR, suggesting that a BDR of >7.5% may be more valuable in young children rather than the adult defined 12% (56). Another study included assessing impact of ABPA on spirometry of asthmatic children (57). In a Chinese study acute asthma did not respond to adding montelukast to the regular regimen (58), however it was noted that in children with CVA, cough associated with chronic airway allergic inflammation without wheeze, had a significant improvement in FEV_1, FVC, and PEF ($p < 0.001$). with montelukast and budesonide compared to budesonide alone, while another study noted that FEV_1/FVC was normal in CVA compared to patients with asthma ($p < 0.001$) (51, 52).

Spirometry was also used in South American, Turkish and South African children to monitor lung function in cystic fibrosis (59), and showed good correlation between CT scan Bhalla score and FEV_1, FVC, FEF_{25-75} (60).

Fractional Exhaled Nitric Oxide

Of the 7 papers using FeNO, 4 (57%) clinical studies measured FeNO to assess risk and treatment response of asthma or recurrent wheeze; and 3 epidemiological studies assessed the impact of IAP on airway inflammation in children. These included studies mainly from Asia (5 from China, 1 from Thailand) and 1 from Ecuador, South America. There were no

TABLE 1 | Details of included studies using spirometry ($n = 40$).

Authors, Year	Country	Age	No. of patients	Study type	Theme	Main finding
Zhu et al. (63)	China	5–12yr; little group-divided into groups 5–7 years	121		asthma, allergic rhinitis	Spirometry was used to assess factors associated with FeNO. A greater peak expiratory flow in addition to a greater age, height/weight and level of total IgE are related to higher FeNO levels
He et al. (49)	China	5–13 years	43		air pollution	No significant associations were noted between personal $PM_{2.5}$ exposure and spirometry.
Kang et al. (56)	China	4–12 years	286-asthma, 301-control		asthma	A BDR threshold of $\geq$ 7.5% may be more valuable compared to $\geq$ 12% in childhood asthma
Leung et al. (55)	China	2–7 years	1341		asthma	The minor allele SNP (rs408223), of CDHR3 was associated with lower $FEV_{0.5}$ ($\beta = -2.411$, $P = 0.004$), and $FEV_{0.5}$/FVC ($\beta = -1.292$, $P = 0.015$)
Sun et al. (52)	China	3–10 years	112	experimental study	asthma	Pulmonary function indices (FVC, FEV_1 and PEF), were significantly higher ($p < 0.001$), in the observational group (treated with montelukast and budesonide), than the control group (budesonide alone), Treating cough variant asthma with montelukast combined with budesonide is more effective than budesonide alone.
Wang et al. (58)	China	2–5 years	120	randomized, double-blind placebo-controlled trial	acute asthma	Treating acute asthma exacerbation with montelukast compared to placebo demonstrated no significant difference in the PEF and FeV_1.
Zeng et al. (28)	China	5–7 years	206		e-waste exposure	Taken together, birth weight and chest circumference may be good predictors for lung function levels in preschool children
Zeng et al. (27)	China	5–7 years	206		e-waste exposure	Children living in the exposed area have lower lung function (FVC and FEV_1). Levels compared to unexposed children. Haemoglobin levels may be a good predictor for lung function- one unit of haemoglobin (1 g/L). Decline was associated with 5 mL decrease in FVC and 4 mL decrease in FEV_1
Jian et.al. (35)	China	4– 80 years	7115	cross-sectional study	reference equation	This study established new reference values for the Chinese population 4 to 80 years. The "South East Asian" and "North East Asian" GLI reference equations under or overestimated the FEV_1, FVC, and FEV_1/FVC. Local Chinese equations underestimated FVC and FEV_1
Sonnappa et al. (44)	India and UK	5–12 years	1039	prospective cross-sectional study	socio-economic circumstance	Spirometry differences were assessed between children from urban, semiurban, and rural schools. There were significant reductions in FEV1 and FVC in Indian-semiurban and Indian-rural children when compared with Indian-urban children.
Kumari et al. (57)	India	5–15 years	106	cross-sectional	asthma, ABPA	Percentage predicted values of FEV_1 and FEF_{25-75} were lower in asthmatic children with allergic bronchopulmonary aspergillosis (ABPA). Compared to no ABPA, but this did not reach statistical significance. PEF that was significantly higher in children with aspergillus sensitization (AS). Compared to those without AS (P= 0.046).
Kumar et al. (50)	India	5–18 years	620	cross-sectional study	asthma, obesity	Obese children with asthma (Group 1). Had significantly lower lung function compared to non-obese asthmatic children(Group 2). FEV_1,

(Continued)

TABLE 1 | Continued

Authors, Year	Country	Age	No. of patients	Study type	Theme	Main finding
						FVC, $FEF_{25-75\%,}$ PEF for Group-1 were 66.3 ± 9.9,63.5 ± 4.2,54.2 ± 5.7,67.4 ± 8.4. FEV1, FVC, $FEF_{25-75\%,}$ PEF for Group-2 were 74.07 ± 3.5,77.4 ± 7.2, 60.1 ± 2.1, 71.6 ± 2.4. P values were < 0.001, < 0.001, < 0.001, < 0.05 respectively.
Gulla et al. (92)	India	138–120 months	46	retrospective control study	cystic fibrosis	Children with viral infection (Group I). Had adverse outcome in form of greater worsening of Shwachman clinical scores, number of pulmonary exacerbations requiring antibiotic usage, need for intravenous antibiotics, hospitalization rates and mortality. Spirometry decreased in both groups decrease in lung function in both groups but was not significant
Bolla et al. (37)	India	5–15 years	790	cross-sectional study	reference equation	Separate equations in males and females were generated with age, weight and height as predictors. No comparison to other reference equations were made.
Lum et al. (42)	India and UK	5–17 years	8124	observational	reference equation	"GLI-Black" equations were most useful for interpreting South-Asian data and "GLI-Other" for North Indian data. When using GLI-predicted values from White Europeans, FEV_1 and FVC in South-Asian children were approximately 15% lower. There was an association between socio-economic circumstances (SEC), and lung function. Lung volumes were significantly lower in those living in rural areas or exposed to poorer SEC.
Asrul et al. (45)	Malaysia	5 and 6 years	120	cross-sectional comparative study	air pollution	There was a significant difference in indoor air quality between urban and suburban preschools. FVC and FEV_1 among urban children were significantly lower compared to the suburban children. Exposures to indoor air pollutants, especially $PM_{2.5}$ increases the risk of getting lung function abnormalities.
Choo et al. (46)	Malaysia	4–6 years	630	cross-sectional comparative study	air pollution	Urban area preschools have higher CO, PM_{10} and $PM_{2.5}$ concentration compared to from suburban and rural areas. FVC, FEV_1, FVC% predicted and FEV_1% predicted values were significantly lower among children from urban and suburban area preschools compared to rural preschools.
Kamaruddin et al. (93)	Malaysia	5–6 years	100	cross-sectional comparative study	air pollution	Significant associations between PM10 and VOCs with FEV_1% were noted (PR = 5.55, 95% CI = 2.189–14.07), (PR = 6.15, 95% CI = 2.565–14.73), respectively in exposed compared to unexposed children.
Rawi et al. (47)	Malaysia	5–6 years	11	cross sectional study	air pollution	Studied preschools had a significantly higher PM and CO concentration compared to the comparative preschools. FVC, FEV_1, FVC% and FEV_1% predicted values were significantly lower among studied group.
Asif et al. (39)	Pakistan	5–14 years	3275	cross-sectional study	reference equation	Reference range equations were developed with predictors that included age, height, and weight. Separate equations for males and females were generated. No comparisons made to other studies.
Ventura et al. (59)	Brazil	1–15 years(median age 3.75 years)	38 with CF,31 control	longitudinal study	cystic fibrosis	Pasclerosisrticipants with higher C-reactive protein/albumin ratio at the baseline had higher odds of FEV1 ≤ 70% after three years of follow-up.

(Continued)

TABLE 1 | Continued

Authors, Year	Country	Age	No. of patients	Study type	Theme	Main finding
Veras et al. (31)	Brazil	6 years and younger	74	cross-sectional descriptive	feasibility	The spirometry success rate was 82%. Performance improved with age.
França et al. (32)	Brazil	4–6 years	195		reference equation	Reference range generated using height as a predictor. One equation for males and females. No comparison to GLI 2012
Jones et al. (34)	Brazil	3–12 years	1990	cross-sectional observational study	reference equation	Equation generated significantly from those currently in use in Brazil-Underestimate FVC and FEV1 values.
Burity et al. (33)	Brazil	3–6 years	425	prospective study	reference equation	Full expiratory curves are more difficult to obtain in preschool children. In addition to height, gender also influenced the measures of FVC and FEV_1
Matos et al. (53)	Brazil	4–12 years	1129	cross-sectional study	asthma	Overweight children have less respiratory capacity, and was associated with lower FEV_1/FVC ratios (PR =1.37; 95% CI 1.14, 1.64)
França et al. (30)	Brazil	4–6 years	47		asthma	83% success rate for performing spirometry
Ardura-Garcia et al. (64)	Ecuador	5–15 years	264	cohort study	asthma	Spirometry did not predict asthma recurrence.
Heinzerling et al. (48)	Guatemala	5–8 years	506	prospective cohort study	air pollution	A significant decrease in PEF [173 mL/min/year (95% CI −341 to −7)], and a non-significant decrease in FEV1 growth were observed with later stove installation at 18 months compared with stove installation at birth
Bougrida et al. (38)	Algeria	5–16 years	208		reference equation	Several predictors in the reference range and these include height, weight, age, gender BSA, BMI. Separate equations for males and females. There were significant differences in FeV_1 between the measured and predicted values from published reference equations except for a USA reference equation.
Jiffri et al. (54)	Egypt	1–15 years	120 asthma,120 controls		asthma	There is an association between the TNFA −308G>A polymorphism and susceptibility to asthma. Spirometry used to classify patients into asthma severity namely mild intermittent asthma, mild persistent asthma, moderate persistent asthma, or severe persistent asthma
Akodui et al. (40)	Nigeria	5–12 years	100	cross-sectional study	sickle cell anaemia, reference equation	Preferred proxy for spirometry indices in children with sickle cell anaemia may be arm span
Thacher et al. (94)	Nigeria	5–11 years	299	cross-sectional study	asthma, air pollution	The relationship between smoke exposure and airway obstruction in households that did and did not use firewood daily was not significant (mean FEV1/FEV6 of 0.95 and 0.97, respectively; $P = 0.41$). There was a significant decline in predicted FEV_1 with age ($p < 0.001$)
Corten et al. (95)	South Africa	5–8 years	12	cross-sectional study	cystic fibrosis	There were significant correlations between PEF and manual dexterity and between FVC % predicted and balance scores Poorer lung function may affect motor development.
Smith et al. (43)	South Africa	5–95 years	4223	cross-sectional population-based study	reference equation	GLI2012 "Other" had the best fit for Black African individuals and Mixed Ethnicity group when using z-scores. The Caucasian individuals demonstrated a good fit with the GLI2012 "Caucasian" equation and participants of Asian ancestry demonstrated a good fit to the "Southeast Asian" and "Black" equation.
Sibanda et al. (96)	Zimbabwe	1–94 years	240 (49 between 1- 16 years of age)	observational study	systemic sclerosis	The mean FEV_1/FVC ratio for all the patients combined was Significantly higher than predicted for age, gender, ethnicity, and BMI

(Continued)

TABLE 1 | Continued

Authors, Year	Country	Age	No. of patients	Study type	Theme	Main finding
						suggesting a restrictive pattern. The severity of the restrictive changes varied with the types of autoantibodies detected.
Ghasempour, M. et al. (51)	Iran	5–15 years	73	description-observation	asthma	The average FEV_1/FVC parameter in the cough variant asthma group was 89.44 ± 13.07, and 72.35 ± 8.47 in the classic asthma group, with a significant difference between the two groups ($p < 0.05$). Patients with cough variant asthma $FEF_{25-75\%}$ were lower than expected. Spirometry can be used in the diagnosis of cough variant asthma.
Tabatabaie et al. (36)	Iran	4–10 years	495		reference equation	Reference range equations were generated for both males and females using height and age as predictors. When compared to previous published international equations significant differences were noted.
Al-Qerem et al. (29)	Jordan	3–5 years	765	random sampling	reference equation	The GLI 2012 for Caucasians is a reasonable fit for Jordanian preschool aged children.
Sasihuseyinoglu et al. (60)	Turkey	mean age7.83 years	80	retrospective study	cystic fibrosis	There were significant correlations between the Bhalla score and FEV_1, FVC, and $FEF_{25-75\%}$

PR, Prevalence Ratio; CI :Confidence Interval; PM, particulate matter; $PM_{2.5}$:particulate matter 2.5; PM_{10}, particulate matter 10; PEF, peak expiratory flow; SNP, single-nucleotide polymorphism; FEV0.5, forced expiratory volume in 0.5-second; FVC, forced vital capacity.

published preschool studies from Africa. Included studies are summarized in **Table 2**.

The success rate for performing FeNO in preschool children ranged between 86–99%. Thai children living in a metropolitan area attending day care, average age of 50.1 months (range 29–72 months), achieved a success rate between 86–93% with data collected over 3 time points (61). A cohort of 507 Chinese children aged 5 years achieved a success rate of 99% (62). Over half of studies (57%) used a Niox Mino analyzer (Aerocrine, Solna, Sweden). to measure FeNO using the single breath technique. Most studies used the recommended normal standards (26). No studies have explored population differences in FeNO.

All 3 studies assessing impact of air quality on respiratory health found that environmental pollution, including benzene and $PM_{2.5}$, were associated with high FeNO (49, 61, 62).

Studies from China and one from South America, used FeNO measurement in the management of preschool asthma (63–65), noting the strong association with IgE mediated inflammation and ICS efficacy (63). However, it was also suggested that FeNO may be less useful in the preschool age group for detecting ICS response, as the mean FeNO level was significantly higher only in the "older" age group than the cut off values reported in other studies for the diagnosis of asthma (63). FeNO was not able to predict recurrence (64).

Oscillometry and Interrupter Technique

Oscillometry has been successfully used in LMIC to assess the impact of early life exposures and for clinical management of children with respiratory disease. These include: 6 studies from Asia, 6 from South America, 2 from West Africa and 1 from the Middle East summarized in **Table 2**. The studies used a range of commercially available equipment including both impulse oscillometry (IOS). and airwave oscillometry (AOS).

Oscillometry has proven to be effective in assessing the impact of early life exposures on preschool lung function (49, 66). An increase in household $PM_{2.5}$ exposure increased airway reactance in Nigerian children, similarly high personal exposure to $PM_{2.5}$ was associated with an increase in small airway resistance (R_{5-20}), total airway resistance (R_5). and resistance frequency dependence (R_{5-20}), representing small airway disease, in asthmatic Chinese children living outside Shanghai (49, 66).

In a Ghanaian longitudinal cohort, infants exposed to a less diverse nasopharyngeal microbiome had a higher small airway resistance compared to a more diverse microbiome at 4 years of age (67). Further, in a Mexican birth cohort study, prenatal omega 3 fatty acid supplementation in pregnancy did not influence preschool lung function at 36, 48 or 60 months (68).

Oscillometry was easily performed by preschool children with the overall success rate ranging between 74–98% in studies making it a particularly attractive option (69–73). As a clinical tool oscillometry for preschool children is supported by studies that are able to detect differences in prebronchodilator lung function of preschool children with respiratory symptoms compared to those without respiratory symptoms (74).

Reference data for Mexican, Thai, Turkish and Colombian children have been collected (70–72, 75–77), facilitating the use in diagnosis of respiratory disease. It is also a useful tool to assess airway reversibility in asthmatic children and cut off values for bronchodilator response were proposed (69, 73). A Chinese study in children with obstructive sleep apnea hypopnea syndrome (OSAHS). demonstrated an increase in total airway resistance in children with

TABLE 2 | Detail of included studies that assessed fractional exhaled nitric oxide ($n = 7$), oscillometry ($n = 15$), interrupter technique ($n = 2$). and tidal breathing ($n = 2$).

Authors, Year	Country	Age	No. of patients	Study type	Theme	Main finding
Fractional exhaled nitric oxide						
Zhang et.al (62)	China	5 years	507	cross-sectional study	air pollution	Indoor and outdoor PM2.5 levels in day care centres were associated with higher levels of FeNO. FeNO levels were also associated with current wheeze and physician diagnosed pneumonia.
Han et.al. (65)	China	4–11 years (4–6 and 7-11 years)	142	cross-sectional descriptive study	asthma	Family management (FM), describes how family members cooperate and integrate the management of childhood chronic disease into their daily family life. FM was closely related to asthma control and could significantly predict FeNO value and C- ACT score.
Li et al. (22)	China	32–48.7 months	88		recurrent wheeze	sRAGE may be a novel biomarker of inflammation of the respiratory tract. There was a significant negative correlation between serum sRAGE and FeNO ($p < 0.001$). In the high-risk asthma group, sRAGE levels increased significantly while FeNO decreased significantly after Pulmicort therapy
Zhu et al. (63).	China	5–12 yr;little group classified as 5–7 years.	121		asthma, allergic rhinitis	Height and total IgE are well correlated with FeNO in asthmatic children greater age, height/weight, peak expiratory flow (PEF), and higher level of total IgE ($p < 0.001$) are associated with higher FeNO levels
He et al. (49)	China	5–13 years	43		air pollution	An increase in 24-h personal $PM_{2.5}$ exposure one day prior to the clinic visit was associated with a significant increase in of FeNO (airway inflammation), of 9.6%
Siwarom et.al (61)	Thailand	29–72 months	436	randomised control study	air pollution	The mean FeNO levels were statistically different in each season ($p < 0.001$). FENO levels had a strong association with high benzene levels (OR 5.9; 95%CI 1.5–22.9; p-value = 0.01).
Ardura-Garcia, C.et al. (64)	Ecuador	5–15 years	264	cohort study	asthma	FeNO level did not predict asthma recurrence.
Oscillometry						
Zhang et.al. (78)	China	3–14 years	120	retrospective study	upper airway obstruction	R_5 in the OSAHS group was significantly higher than that in the non-OSAHS group ($P = 0.0025$)
He et al. (49)	China	5–13 years	43		air pollution	An increase in 24-h personal $PM_{2.5}$ exposure one day prior to the clinic visits was associated with a significant increase in total airway resistance (R_5) of 6.3%, small airway resistance (R_5–R_{20}) of 15.8%
Li et al. (82)	China	<14 years	42	case review	bronchiolitis obliterans	In children with bronchiolitis obliterans impulse oscillometry showed an increase in Z_5 (147.5 ± 19.3% of the predicted value, normal: less than 120% of the predicted value), R_5 (140.4 ±12.8% of the predicted value, normal: less than 120% of the predicted value), and X_5 (226.5 ± 13.4% of the predicted value, normal: less than 120% of the predicted value). This suggesting increased peripheral airway resistance.
Udomittipong et al. (70)	Thailand	3–7 years	291	cross-sectional study	reference equation	Reference values for respiratory impedance using FOT were generated using height and arm span were generated.
Udomittipong et al. (73)	Thailand	3–6 years	150		asthma	Cut-off values for evaluating bronchodilator response in FOT were determined: Rrs6: −23%, Rrs8: −20%, Rrs10: −20%, Xrs6: 36%, Xrs8: 60%, and Xrs10: 43%.

(Continued)

TABLE 2 | Continued

Authors, Year	Country	Age	No. of patients	Study type	Theme	Main finding
Gupta et al. (69)	North India	2–18 years	345	prospective interventional study	asthma	Oscillometry is a useful tool to assess lung function and airway reversibility in asthmatic children. It can provide an objective measurement in children unable to perform spirometry.
Medeiros et.al. (74)	Brazil	3–6 years	76	cross -sectional study	respiratory symptoms	IOS in children with respiratory symptoms were higher pre-bronchodilator for R_5 Hz and R_{5-20}Hz compared to those children without respiratory symptoms.
Duenas-Meza et al. (77)	Colombia	3–5 years	96	cross-sectional study	reference equation	Normal IOS reference range equations were determined, and height was the only predictor. A fall in R_5Hz of 28% or an increase in X_5Hz of 36% postbronchodilator can be considered as an upper limit of normal.
Gutiérrez-Delgado et.al. (68)	Mexico	birth cohort until 5 years	772	double blind, randomized, placebo-controlled study	Intervention with DHA	Prenatal DHA supplementation did not influence IOS values with respect to resistance and reactance at 6, 8, and 10 Hz
Gochicoa-Rangel et al. (71)	Mexico	2.7–15.4 years	283		reference equation	Reference range equations were derived for impulse oscillometry. Predictors include age and height. Marked differences were noted between the derived reference equation when compared to other studies. Separate reference ranges for male and females were generated.
Gochicoa-Rangel et.al. (75)	Mexico	4–15 years(mean age 8.6)	224	cross-sectional study	reference equation	Due to the robust adjustment of the equation derived from Gochicoa-Rangel et al. (71) this equation has been recommended for clinical and research purposes in a Mexican population.
Shackleton et al. (72)	Mexico	3–5.2 years	584	double-blind, randomised, placebo-controlled clinical trial	reference equation	Reference ranges for FOT were generated for Mexican children. Height was the only predictive factor and the same equation for males and females was used. An Australian reference range equation overestimate lung function in Mexican children.
Dubowski et.al. (67)	Ghana	4 years	112	prospective study	infection exposure	Infants exposed to a less diverse NPM (nasopharyngeal microbiota) had a higher small airway resistance (R5–R20 = 17.9%, 95% CI 35.6, 0.23; $p = 0.047$). Compared to a more diverse phenotype
Dutta et.al. (66)	Nigeria	2 years (mean age 2.9 years)	223	randomised control trial	air pollution	Increase in postnatal household air pollution ($PM_{2.5}$). were significantly associated with higher airway reactance at 5 Hz (X5 Hz; $P = 0.04$)
Er et al. (76)	Turkey	3–7 years	151		reference equation	Reference values for IOS in healthy Turkish children were determined. Resistance was significantly correlated with height and reactance was significantly correlated with age ($p < 0.05$–). Separate equations were derived for males and females.
Interrupter technique						
Rocha et al. (79)	Brazil	5 to 18 years (mean 10,79 years)	38	cross-sectional study	cystic fibrosis	Interrupter resistance (Rint). correlates well with spirometry. There was a strong correlation between inverse Rint and FEV1 ($r = 0.8$; $p < 0.001$), and moderate correlation between inverse Rint and FEF25–75% ($r = 0.74$; $p < 0.001$). Rint was not accurate in evaluating bronchodilator response.

(Continued)

TABLE 2 | Continued

Authors, Year	Country	Age	No. of patients	Study type	Theme	Main finding
Gochicoa et.al. (80)	Mexico	24 days to 6.6 years	264	prospective, cross-sectional descriptive study	reference equation	Reference values for interrupter technique (Rint), was determined in Mexican children. There was an inverse relationship between Rint and height. Females had a higher Rint than males ($P = 0.054$).
Tidal breathing						
Kumar et.al. (81)	India	3 years	310	prospective birth cohort study	acute respiratory infections	The ratio of tidal expiratory flow (TEF) at 25 or 50% of tidal expiratory volume to peak TEF (TEF50 or TEF25/peak TEF) at 3 years was significantly increased in children who had an acute respiratory infection in infancy.
Li et al. (82)	China	<14 years	42	case review	bronchiolitis obliterans	The tidal breathing analysis revealed a decreased tPTEF% tE (18.2 ± 0.26%, normal: more than 40%), or VPEF%VE (21.7 ± 0.32%, normal: more than 40%).

FeNO, fractional exhaled nitric oxide; OR, odds ratio; CI, 95% confidence interval;$PM_{2.5}$, particulate matter 2.5; C-ACT, Childhood Asthma Control Test; sRAGE, Receptor for Advanced Glycation End products; Z_5, magnitude of respiratory impedance; R_5 :total respiratory resistance; X_5:distal capacitive reactance; obstructive sleep apnea hypopnea syndrome (OSAHS); R5Hz, total resistance at 5 Hz; R20 Hz :central resistance at 20 Hz; R_5–R_{20} Hz, difference between resistance at 5Hz and 20 Hz; IOS, Impulse oscillometry; PM2.5:particulate matter 2.5; CI:95% confidence interval; Rrs6, Rrs8, Rrs10, Resistance at 6 Hz, 8Hz and 10Hz; Xrs6, Xrs8, and Xrs10, Reactance at 6 Hz, 8 Hz and 10Hz; DHA, docosahexaenoic acid; tPTEF% tE, ratio of time to reach peak tidal expiratory flow to total expiratory time VPEF%VE, ratio of volume to reach peak expiratory flow to total expiratory volume.

OSAHS compared to children with snoring but without OSAHS (78).

The interrupter technique was used in 2 South American studies, one of which looked at the development of reference values for newborn, infants and preschool children, while the other measured Rint in children with cystic fibrosis and found that Rint correlated well to spirometry FeV_1 and FEF_{25-75}, but not accurate in determining bronchodilator response (79, 80).

Tidal Breathing

Tidal breathing was used in 2 studies, one an Indian birth cohort and the other a Chinese retrospective cohort study (81, 82), (**Table 2**). Tidal breathing measurements were in keeping with an obstructive pattern in patients with bronchiolitis obliterans (82). Indian children who had an acute respiratory tract infection in infancy had increased ratios of tidal expiratory flow (TEF) at 25 or 50% of tidal expiratory volume to peak TEF (TEF50 or TEF25/peak TEF) at 3 years suggesting increased airway resistance (81).

CONCLUSION

Preschool lung function tests used in LMIC were feasible with high success rates. Success with spirometry increased with age (29), and oscillometry had higher feasibility compared to spirometry. All tests were useful for clinical application and epidemiological studies. Comprehensive preschool testing including spirometry, FeNO, oscillometry and tidal breathing were only reported from China, and only 19 countries of 137 registered LMIC (14%) were represented in the review, a large discrepancy as the majority (80%) of children live in LMIC, where the burden of early life respiratory disease and exposures known to cause illness are high. These include air pollution, maternal smoking, a high infectious load including tuberculosis, and high rates of preterm birth (2, 83–86). Lung functions tests assessing these vulnerable groups are lacking. A number of studies explored the effects of air pollution; and the studies suggest that air pollutants increase airway inflammation and may in part explain the association between household air pollution and recurrent wheeze (83). Given the burden of early life exposures and the need to identify preventative measure, priority should be given to strengthening access to lung function assessment tools.

The majority of clinical studies focussed on asthma diagnosis and management, including defining BDR in young children. The prevalence of asthma in LMIC is high, with a temporal increase in severe asthma (87). Of particular concern is that up to 40% of children in LMIC with severe symptoms are undiagnosed (87, 88). Oscillometry was useful, and more sensitive than spirometry, in measuring airway resistance and cut off values for BDR response was also determined. FeNO has been identified as a useful adjunct in diagnosis and informing treatment in asthmatic patients (89). Access to these tests to improve diagnosis and management is needed for the many children living in LMIC.

Other clinical uses have included management of chronic lung conditions like CF, bronchiolitis obliterans, OSAHS, obesity and systemic sclerosis all of which are associated with respiratory complications. Lung function tests assessing vulnerable groups such as children born preterm, those living with HIV or exposed in utero and those with a history of pulmonary TB and other early life lower respiratory tract infections are lacking in children from LMIC.

The importance of reference range equations were highlighted in these studies. A healthy standard is needed for lung function tests to distinguish between health and disease in different populations. The GLI reference equations attempt to address this, however unique environmental exposures including in-utero exposures influence lung development and this needs to be

considered when developing reference equations (90). Research studies assessing impact of exposures require appropriate patient samples and statistical modeling and should include both exposed and unexposed control groups.

There are currently no published data for MBW in preschool children in LMIC settings, however data on infant testing have been published in South Africa (3, 91). There is limited data on tidal breathing and the interrupter technique. Impulse and airway oscillometry use different input signals and this may impact results especially at high impedance, which is associated with disease. Furthermore, FeNO single breath and tidal breathing measures have different interpretation of normal ranges, and the results are not interchangeable. These factors may affect the interpretation and comparison of data.

Challenges to accessing lung function testing need to be addressed, these include lack of trained personnel as each lung function test requires specialized training skills and lack of financial resources to support development and implementation of these tests. Spirometry and oscillometry are relatively inexpensive, whereas FeNO and MBW are currently more expensive further limiting access. Equipment maintenance and poor access locally to consumables and technical support incur further costs. This reduces research outputs and lack of robust data to better diagnose, prevent and manage respiratory disease in these settings (5).

In conclusion, preschool testing in LMIC is feasible, both epidemiologically and clinically. It has the potential to be useful in strengthening the diagnosis, management and prevention of respiratory diseases in younger children but is underutilized. Spirometry still remains a key clinical and epidemiological tool in LMIC, however has limitations especially in young children. Understanding and addressing the challenges for improving access to these tools is needed in order to strengthen the prevention, early diagnosis and management of childhood respiratory disease in LMIC.

AUTHOR CONTRIBUTIONS

SC, DG, and HZ conceived the idea. SC and DG reviewed the literature and drafted the manuscript. HZ provided further input into the manuscript. All authors reviewed, contributed, and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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Effect of Threshold Inspiratory Muscle Training on Functional Fitness and Respiratory Muscle Strength Compared to Incentive Spirometry in Children and Adolescents With Obesity: A Randomized Controlled Trial

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Background: To determine the effect of threshold inspiratory muscle training (IMT) on functional fitness and respiratory muscle strength (RMS) compared to incentive spirometry (IS) in children/adolescents with obesity.

Methods: A total of 60 obese children/adolescents aged 8–15 years were randomized into the threshold IMT group (n = 20), the IS group (n = 20), or the control group (n = 20). The IMT group performed 30 inspiratory breaths with the intensity set at 40% of baseline maximal inspiratory pressure (MIP) twice daily for 8 weeks; the IS group performed 30 breaths with sustained maximum inspiration twice daily for 8 weeks; and, the control group was assigned no training device for 8 weeks. Six-min walk test (6-MWT), RMS, and spirometry were compared between baseline and 8 weeks.

Results: Six-MWT distance (528.5 ± 36.2 vs. 561.5 ± 35.2 m, p = 0.002) and MIP (121.2 ± 26.8 vs. 135.3 ± 32.1%Predicted, p = 0.03) were significantly improved after 8 weeks of IMT training. There was no significant difference in any evaluated pulmonary function parameters between baseline and 8 weeks in the IS or control groups; however, 6-MWT distance demonstrated a trend toward significant improvement in the IS group (526.9 ± 59.1 vs.549.0 ± 50.6 m, p = 0.10). No significant difference among groups was found for any variable relative to change from baseline to post-training.

Conclusion: Eight weeks of threshold IMT training significantly improved both inspiratory muscle strength (MIP) and functional fitness (6-MWT) in children/adolescents with obesity. Eight weeks of IS training yielded a trend toward significantly improved functional fitness.

Keywords: effect, threshold inspiratory muscle training, respiratory muscle strength, obese children and adolescents, incentive spirometer, 6-MWT, obesity

INTRODUCTION

Obesity is a major public health problem that affects children, adolescents,and adults worldwide, and that exerts adverse impact on many systems, including the respiratory, cardiovascular, and metabolic systems (1–3). The effects of obesity on the respiratory system include altered pulmonary function and exercise intolerance, and comorbid obesity can also worsen both asthma and obstructive sleep apnea (4). Several studies reported reduced functional fitness and reduced respiratory muscle strength (RMS) in children and adolescents with obesity (5–9), and these deficiencies may contribute to dyspnea on exertion. The principle pillar of treatment for obesity is weight reduction. Nutritional control and exercise are the main components of a weight loss program; however, some obese individuals experience exercise intolerance and/or limited functional fitness (10, 11) – both of which are obstacles to weight reduction.

Inspiratory muscle training (IMT) helps to improve both RMS and functional exercise capacity. The devices used for IMT mainly include pressure-based and volume-based loading type devices (12). Threshold IMT is a pressure-based loading device, and is the most commonly used inspiratory muscle trainer for improving the strength and edurance of the respiratory muscles (13). Incentive spirometer (IS) is a volume-based loading type device. IS is frequently used to increase lung volume and to prevent pulmonary complications after thoracic or abdominal surgery, and it is also employed for IMT *via* a technique known as sustained maximum inspiration (14). The IS device is less expensive than the threshold IMT device.

Many studies of threshold IMT (15–17) and IS (18, 19) training among obese adults reported substantial improvement in 6-min walk test (6-MWT) distance, inspiratory muscle strength, and spirometry. In children and adolescents, studies of the effect of threshold IMT (20–27) and IS (28–30) on pulmonary function were conducted in other diseases, including neuromuscular disease (NMD), cerebral palsy (CP), asthma, and cystic fibrosis (CF). To our knowledge, no study has investigated the effect of threshold IMT and IS on functional fitness, RMS, and spirometry in children and adolescents with obesity. In addition, no studies have compared the effects of these two devices on functional fitness and RMS in obese children and adolescents.

Therefore, the primary aim of this study was to investigate the effect of threshold IMT on functional fitness as measured by 6-MWT compared to IS in children/adolescents with obesity. The secondary objective of this study was to compare the effects of these 2 devices on maximal inspiratory pressure (MIP), which is a biomarker for RMS, and forced expiratory volumes and flows. We hypothesized that after 8 weeks of training, IMT by threshold IMT or IS would have more benefit on 6-MWT distance than no device, and that the benefit of threshold IMT would be superior to that of IS. If these devices can improve functional fitness in this patient population, we will have research evidence to recommend them as an alternative therapy for enhancing exercise capacity, which would facilitate weight loss.

MATERIALS AND METHODS

Study Protocol

This prospective randomized controlled trial (RCT) recruited children and adolescents aged 8–15 years who were diagnosed with obesity, which was defined as a body mass index (BMI) *z*-score $\geq$ 2 according to World Health Organization (WHO) reference criteria (31). Patients with a history of neuromuscular, cardiac, or pulmonary disease; history of smoking or environmental tobacco smoke exposure; respiratory tract infection within the preceding 4 weeks; and/or, inability to perform pulmonary function testing (PFT) were excluded. Collected data included gender; age; height and obesity indices, including body weight (BW), BMI, BMI *z*-score, chest circumference (CC), waist circumference (WC), and WC/height (Ht).

Study participants were randomly allocated into 1 of 3 groups (IMT group, IS group, or control group) by block randomization. The IMT group received 8 weeks of at-home threshold IMT, and the IS group received 8 weeks of at-home incentive spirometer training. Functional fitness (6-MWT), RMS parameters [MIP, and maximal expiratory pressure (MEP)], and spirometry were evaluated at baseline before training and at 8 weeks after training by the same trained technician.

Participants in the threshold IMT group were instructed to perform IMT at an intensity of 40% of their baseline MIP using the threshold IMT device (Threshold IMT®, Philips Respironics, Chichester, United Kingdom) with a resistance load of 9–41 cm H_2O. Subjects were trained to position themselves in a sitting position in a chair, and to apply the provided nose clip to prevent airflow through the nose. They then exhaled completely, placed the mouthpiece of the device into their mouth, and then inhaled with maximal force to open the valve of the device. Subjects in the IS group were instructed to use the incentive spirometer device (Pulmo-gain®, CA-MI, Langhirano (Parma), Italy) by performing a slow and deep inspiration until total lung capacity (TLC). Sustained maximum inspiration was set at approximately 3 s followed by expiration until achieving functional residual capacity (FRC). In both study device groups, a frequency of 3 sets of 10 breaths with a rest period of 1 min between each set was performed twice a day for 8 consecutive weeks. The control group did not receive any instruments for respiratory muscle training. Standard treatment for obesity, including recommendation for exercise, nutritionist consultation for dietary control, and evaluation of comorbidities, was given to study subjects in all 3 groups.

To improve the likelihood that study participants would adhere to their assigned training protocol (if they were in either the threshold IMT or IS groups), subjects were asked to complete a daily log indicating the date and time of their respiratory muscle training sessions. All participants were contacted weekly by the study assessment technician to ensure proper device use technique, to inquire about adverse events during interventions, and to inquire about adherence to the requested frequency of training.

This study was conducted at the Division of Pulmonology of the Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during October 2021–March 2022. The study protocol was approved by our center's Institutional Review Board (IRB) (approval no. Si 277/2021), and was registered in the Thai Clinical Trials Registry (TCTR) (TCTR20211124001). Informed consent or assent (when applicable) was obtained from study participants and/or their legal guardian(s) before study enrollment.

Anthropometric Evaluation

A standard scale (TANITA Corporation, Tokyo, Japan) was used to determine BW and height. BMI was calculated as body weight (kg) divided by height squared (m^2). BMI was also expressed as *z*-score (BMI *z*-score) adjusted for gender and age according to WHO growth reference (32, 33). CC was measured at nipple level, and WC was measured between the inferior margin of the last rib and the iliac crest. The WC (cm)/height (cm) ratio was calculated.

Spirometry

Spirometry was performed using a Vyntus^{TM} BODY instrument (Vyaire Medical, Mettawa, IL, United States) according to American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations (34). FEV1, FVC, FEV1/FVC ratio, forced expiratory flow rate within 25–75% of vital capacity ($FEF_{25-75\%}$), and peak expiratory flow (PEF) were collected and recorded. All parameters except FEV1/FVC were reported as percentage of predicted value (%predicted) from multi-ethnic global lung function equations (2012) (35).

Respiratory Muscle Strength

Inspiratory and expiratory muscle strength was assessed by MIP and MEP, respectively, using a Vyntus^{TM} BODY instrument (Vyaire Medical) according to ATS/ERS guidelines (36). MIP was measured with the subject breathing in from residual volume (RV) to TLC, and MEP was measured during forced expiration from TLC to RV. The measurement considered for data analysis was the highest value among 3 acceptable maneuvers (without leakage and lasting for at least 1 s), and at least 2 were reproducible (not different more than 10% from the second highest value). A maximum of 9 maneuvers for each MIP and MEP assessment was performed, and both values were expressed as absolute and %predicted based on reference equations (37).

6-Min Walk Test

Functional fitness was assessed by 6-MWT (distance in meters), which is a recommended performance-based tool according to ATS/ERS guidelines (38). Participants were instructed to walk as fast as they could without running or jogging for 6 min on a flat, straight, there-and-back walking course. The course was 30 meters in length, and clearly visible cones were placed at each end of the course. Participants were given words of encouragement during the test, and the time remaining was announced at different timepoints during the test. The total distance covered by each participant in 6 min was recorded. Complaints of physical discomfort were also recorded. Participant heart rate, respiratory rate, blood pressure, and peripheral oxygen saturation (SpO_2) were measured before and after the test. If a participant complained of heart palpitations, chest pain, or shortness of breath, the test was immediately stopped.

Sample Size Determination

The sample size for this study was calculated using data from a pilot study that we conducted in 12 obese children and adolescents. That pilot study yielded mean 6-MWT distances of 540, 520, and 490 m (pooled standard deviation: 27 meters) in the IMT, IS, and control groups, respectively. Using a power of 0.8, a two-sided alpha level of 0.05, and an effect size 0.58, a minimum sample size of 20 participants per group was required.

Statistical Analysis

SPSS Statistics for Windows version 18.0 (SPSS, Inc., Chicago, IL, United States) was the software used to analyze the data. The baseline characteristics of study participants are presented as mean plus/minus standard deviation for continuous data, and as number and percentage for categorical data. Paired *t*-test was used to analyze within group changes for normally distributed data. One-way analysis of variance (ANOVA) followed by Tukey's *post hoc* test was used to compare continuous data among 3 groups, and chi-square test was used to compare categorical data among 3 groups. A *p*-value less than 0.05 was considered statistically significant for all tests.

RESULTS

Of the 66 enrolled participants, 60 children and adolescents (20 participants per group) completed the 8 weeks of training with compliance over 80% and successful performance of all PFTs (**Figure 1**). The mean (±SD) age of control, IMT, and IS group subjects was 11.2 ± 2.55, 12.4 ± 1.92, and 12.5 ± 2.61 years, respectively. Age, gender, height, and obesity indices, including BW, BMI, BMI *z*-score, and CC, were statistically similar among the 3 groups at baseline; however, WC/Ht was significantly greater in the IMT group than in the IS or control groups ($p = 0.01$) (**Table 1**).

Following 8 weeks of respiratory muscle training, significant increases in 6-MWT distance [25.0 (0.75, 74.0) m, $p = 0.002$] and MIP [9.33 (2.94, 15.7) cmH_2O; $p = 0.01$, 9.40 (0.79, 13.0)%predicted; $p = 0.03$] were observed in the IMT group, but not in the IS or control groups (**Table 2** and **Figures 2**, **3**). However and importantly, there was a trend toward significant improvement in the 6-MWT distance in the IS group ($p = 0.10$). No significant differences were observed between before and after 8-weeks of respiratory muscle training in any of the 3 groups for the spirometric parameters FEV1, FVC, FEV1/FVC, $FEF_{25-75\%}$, and PEF. No significant difference among the IMT, IS, and control groups was found for any variable relative to change from baseline to after 8 weeks of respiratory muscle training (**Table 2**).

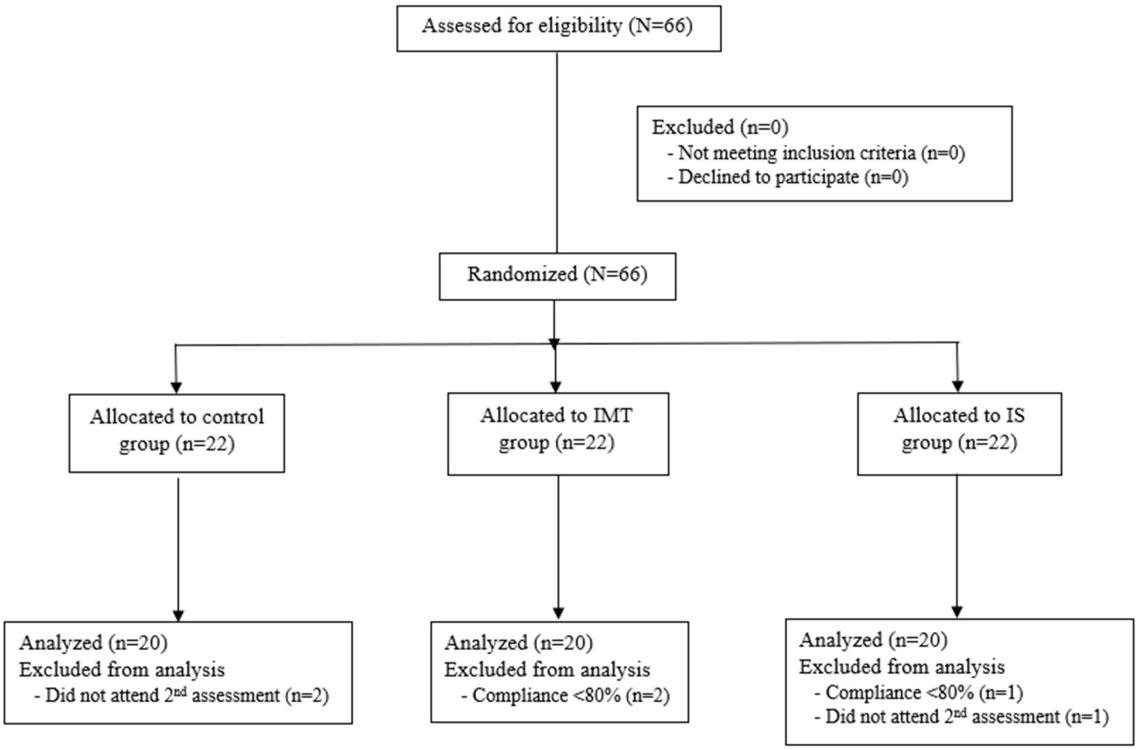

FIGURE 1 | Flowchart of patient enrollment, group allocation, and data analysis protocol (IMT, threshold inspiratory muscle training; IS, incentive spirometry).

TABLE 1 | Mean demographic data and obesity indices compared among the control, IMT, and IS groups.

	Mean ± SD			
Data	**Control group (*n* = 20)**	**IMT group (*n* = 20)**	**IS group (*n* = 20)**	***p***
Age (years)	11.2 ± 2.55	12.4 ± 1.92	12.5 ± 2.61	0.15
Male gender, *n* (%)	17 (85.0%)	13 (65.0%)	12 (60.0%)	0.19
Height (m)	1.51 ± 0.17	1.58 ± 0.1	1.57 ± 0.16	0.28
Body weight (kg)	73.8 ± 26.1	85.6 ± 22.6	78.4 ± 26.2	0.33
Body mass index (kg/m^2)	31.3 ± 5.83	33.9 ± 5.47	30.9 ± 7.1	0.27
Body mass index *z*-score	3.56 ± 0.85	3.50 ± 0.71	2.99 ± 0.9	0.06
Chest circumference (cm)	95.5 ± 14.2	101.4 ± 14.8	95.2 ± 15.2	0.33
Waist circumference (cm)	100.9 ± 14.6	110.4 ± 13.5	99.5 ± 16.6	0.05
Waist circumference/height	0.67 ± 0.06	0.70 ± 0.06	0.63 ± 0.08	***0.01***

A p-value < 0.05 indicates statistical significance. IMT, threshold inspiratory muscle training; IS, incentive spirometry. The bold italic means a p-value < 0.05.

DISCUSSION

The effects of threshold IMT on functional fitness and RMS have been investigated in adults with obesity, but not in children and adolescents with obesity. The present study is the first to study the effectiveness of threshold IMT on functional fitness, RMS, and spirometry, as well as the first RCT to compare the effects of threshold IMT and IS in obese children and adolescents. The results of this study demonstrated the benefit of an 8-week threshold IMT program for improving functional exercise capacity as measured by 6-MWT distance, and inspiratory muscle strength as measured by MIP in children and adolescents with obesity. The present study also observed a trend toward statistically significant improvement in the 6-MWT distance between before and after 8 weeks of respiratory muscle training in the IS group.

Several studies reported reduced RMS and functional fitness in children and adolescents with obesity (5–9). This is attributed to excessive fat deposition on the chest wall and abdomen, which contributes to dysfunction of the inspiratory muscles (especially the diaphragm), reduced chest wall compliance, reduced lung volume, and impaired lung mechanics that collectively lead to decreased functional fitness (8, 39).

The IMT device may benefit these patients by improving inspiratory muscle strength and endurance. Similar to our findings in children and adolescents, there have been many studies in adults that support the benefit of threshold IMT (15–17, 40) on inspiratory muscle strength and functional fitness. In contrast, studies of the IS device in obese adults are very limited. One study reported improved FEV_1, FVC, and maximum voluntary ventilation after IS training, but RMS and functional fitness were not mentioned (19). The other study found significant improvement in 6-MWT distance after IS training (18). The mechanism of increased RMS after IMT may be multifactorial (12). The proposed mechanisms include increased proportion and size of type II muscle fibers (16, 41, 42), promoted diaphragm hypertrophy, attenuated respiratory muscle metaboreflex, and enhanced respiratory muscle economy. Improved RMS augments respiratory capacity, promotes muscle oxygenation, reduces lactate production by respiratory muscles, and eventually reduces respiratory muscle fatigue, which enhances functional fitness that facilitates exercise (18, 42, 43).

According to results of our study, the use of threshold IMT rather than IS may be suitable for improving the submaximal exercise capacity in obese children and adolescents. The explanation for the observed difference in outcome between these two devices is that the mechanism of threshold IMT is pressure-based loading, and the principle of use is inspiration against a set resistance pressure. This mechanism is like weight or resistance training exercise for inspiratory muscles, which is similar to weightlifting for strengthening extremity muscles. The main advantages of resistance training include improving muscle strength and endurance, enhancing the oxygen uptake of exercising muscles, and reducing muscle fatigue – all of which will

TABLE 2 | Mean 6-min walk test distance, respiratory muscle strength, and spirometry before and after training compared among the control, IMT, and IS groups.

		Mean ± SD		
Data		**Control group (*n* = 20)**	**IMT group (*n* = 20)**	**IS group (*n* = 20)**
6-MWT distance (m)	Before	529.5 ± 52.2	528.5 ± 36.2	526.9 ± 59.1
	After	533.7 ± 44.0	561.5 ± 35.2	549.0 ± 50.6
	Difference	8.50 (-34.5,45.7)	25.0 (0.75,74.0)	14.5 (-25.5,47.2)
	p-value	0.71	***0.002***	0.1
MIP (cmH_2O)	Before	98.6 ± 33.2	113.0 ± 27.8	109.3 ± 26.4
	After	101.4 ± 28.0	126.3 ± 25.9	114.4 ± 28.2
	Difference	3.16 (-3.78,15.2)	9.33 (2.94,15.7)	7.17 (-2.40,12.9)
	p-value	0.52	***0.01***	0.21
MIP (%Predicted)	Before	112.7 ± 26.1	121.2 ± 26.8	119.9 ± 25.2
	After	116.1 ± 23.7	135.3 ± 32.1	125.7 ± 30.6
	Difference	2.48 (-5.29,20.7)	9.40 (0.79,13.0)	5.25 (-2.52,15.8)
	p-value	0.52	***0.03***	0.17
FVC (%Predicted)	Before	101.7 ± 14.5	106.4 ± 12.6	114.6 ± 10.3
	After	100.2 ± 13.4	107.3 ± 13.8	114.0 ± 11.8
	Difference	-1.00 (-8.25,4.75)	0.50 (-3.25.3.75)	0.50 (-5.00,3.75)
	p-value	0.38	0.46	0.68
FEV_1 (%Predicted)	Before	97.5 ± 16.8	100.1 ± 13.4	109.4 ± 11.2
	After	97.6 ± 15.8	101.2 ± 12.3	109.6 ± 13.8
	Difference	0.50 (-4.75,5.25)	0.50 (-2.00,3.75)	0.00 (-4.00,2.00)
	p-value	0.96	0.47	0.93
FEV_1/FVC (%)	Before	85.0 ± 7.67	84.3 ± 6.89	85.6 ± 7.41
	After	86.4 ± 7.84	84.2 ± 5.66	85.9 ± 6.02
	Difference	1.41 (-2.03,3.67)	-0.47 (-1.78,0.48)	-0.92 (-2.46,1.52)
	p-value	0.16	0.89	0.82
$FEF_{25-75\%}$ (%Predicted)	Before	90.6 ± 27.3	86.3 ± 25.5	99.3 ± 28.1
	After	94.0 ± 27.6	87.7 ± 18.0	97.8 ± 23.7
	Difference	2.50 (-6.75,16.5)	-2.00 (-10.7,10.0)	-4.00 (-7.50,3.25)
	p-value	0.36	0.70	0.80
PEF (%Predicted)	Before	79.7 ± 21.3	78.2 ± 15.0	91.0 ± 19.8
	After	83.4 ± 23.1	77.6 ± 17.5	89.8 ± 17.9
	Difference	3.50 (-4.50,13.0)	0.50 (-11.2,8.50)	-1.00 (-10.5,11.2)
	p-value	0.21	0.80	0.81

A p-value < 0.05 indicates statistical significance. IMT, threshold inspiratory muscle training; IS, incentive spirometry; 6-MWT distance, 6-min walk test distance; MIP, maximum inspiratory pressure; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; $FEF_{25-75\%}$, forced expiratory flow rate within 25–75% of vital capacity; PEF, peak expiratory flow rate. Difference: median (IQR). The bold italic means a p-value < 0.05.

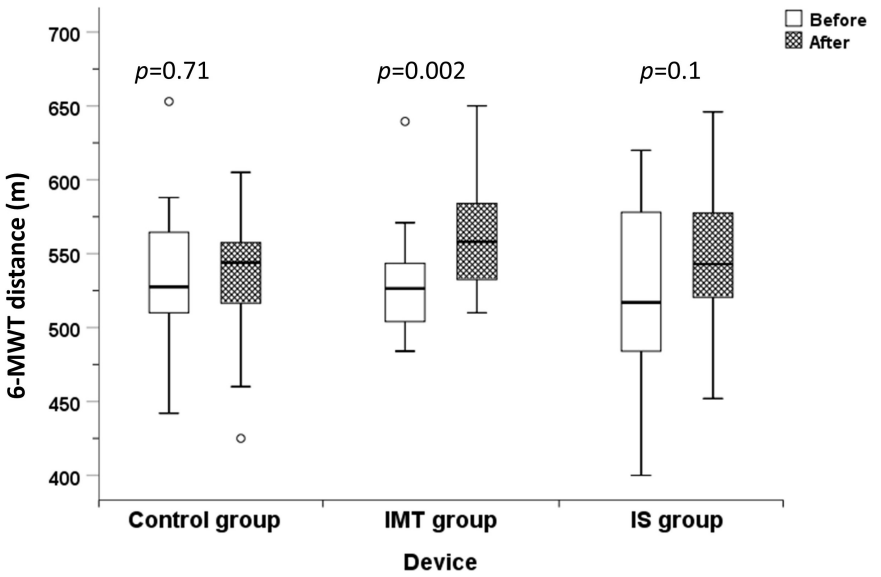

FIGURE 2 | 6-MWT distance before and after 8 weeks of training compared among the control, IMT, and IS group (6-MWT distance, 6-min walk test distance; m, meters; IMT, threshold inspiratory muscle training; IS, incentive spirometry).

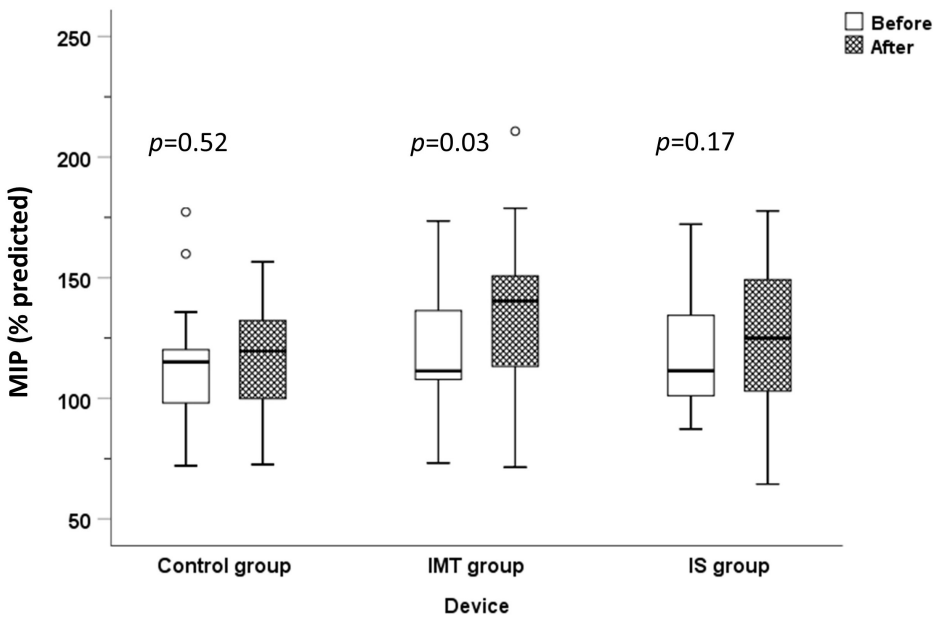

FIGURE 3 | Maximum inspiratory pressure before and after 8 weeks of training compared among the control, IMT, and IS group (MIP, maximum inspiratory pressure; IMT, threshold inspiratory muscle training; IS, incentive spirometry).

improve functional fitness (12, 42, 43). By way of comparison, the IS device is a volume-based loading device. Its principle of use is inspiration to the TLC level, but the inspiration is not against resistance. The effectiveness of the IS for respiratory muscle training is, therefore, inferior to the threshold IMT, which leads to less improvement in functional fitness.

Threshold IMT is a portable, simple, user-friendly, and safe respiratory muscle training device for improving RMS and functional fitness. The results of this study and previous studies suggest that this device should be incorporated as an adjunctive therapeutic modality together with standard therapy of nutritional control and exercise in obese individuals. Threshold IMT might also benefit obese individuals who cannot tolerate exercise training, or who cannot perform outdoor exercise in some situations or settings. Further clinical trials to determine the appropriate protocol (frequency, duration, and

resistance load) of threshold IMT in children and adolescents with obesity are needed. Previous RCTs in obese adults (15–17, 40) that reported substantial benefit after threshold IMT all commented on the importance of periodic adjustment of the training load to yield optimal training outcomes. Concerning other useful recommendations for improving respiratory muscles in clinical practice, Shei et al. (12) recommended that the training session be personalized, and to consider setting training goals, such as improving RMS and/or endurance, to facilitate longer training sessions.

Limitations

This study has some mentionable limitations. First, even though our data was prospectively collected, the data included in this study was collected from a single center. Second, our threshold IMT intensity level might be low (40% of baseline MIP), and there was no adjustment of intensity level. Third, the threshold IMT device that was used in this study had a pressure level that ranged from 9 to 41 cm H_2O; however, we used the only commercially available brand of threshold IMT device that is currently available in Thailand. Fourth and last, the 8-week duration of respiratory muscle training in this study may have been too short in this study population.

CONCLUSION

Eight weeks of threshold IMT training significantly improved both inspiratory muscle strength (MIP) and functional capacity (6-MWT) in children and adolescents with obesity. Eight weeks of IS training yielded a trend toward significantly improved functional capacity. These results suggest that threshold IMT can be recommended as an adjunct therapy together with nutritional control and increased physical activity in obese children and adolescents. Based on the assumption that threshold IMT would help to reduce exercise intolerance, increased exercise would contribute to weight reduction, which is a main target of obesity management.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Siriraj Institutional Review Board Faculty of Medicine Siriraj Hospital, Mahidol University Email: siiro@mahidol.ac.th. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

KU contributed to the study conception, study design, statistical analysis, and manuscript preparation. PK recruited the study participants, conducted the fieldwork, performed the data collection, interpreted the data, and wrote the first draft of the manuscript. AN and PT contributed to the study conception and design. AP recruited the study participants and conducted the fieldwork. PC and KM conducted the fieldwork and performed the data collection. All authors contributed to the article and approved the submitted version.

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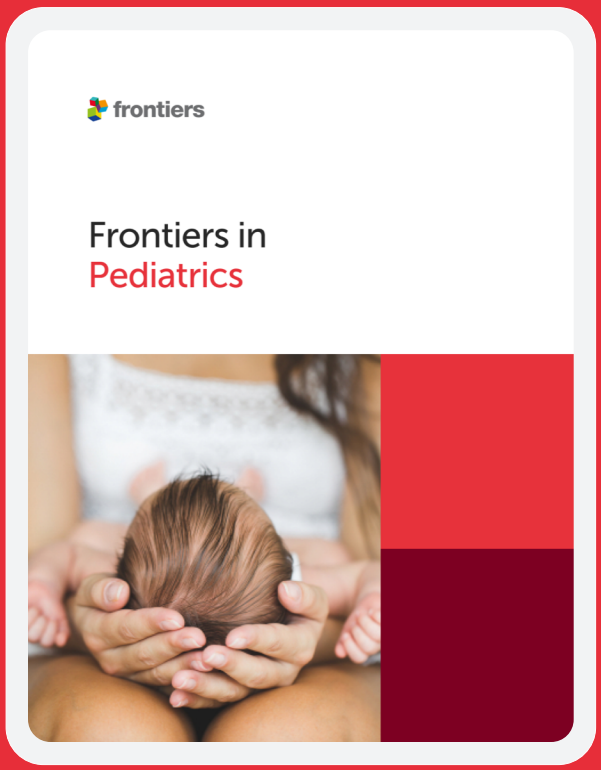

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