

Management of Recurrent Preschool, Doctor-Diagnosed Wheeze

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Abstract Preschool wheeze occurs in half of the children before they reach 6 y of age and recurrence is also common. Recurrent preschool wheeze is classified as either typical or atypical. For typical recurrent preschool wheeze, the diagnoses are either asthma or bronchiolitis/bronchitis. Responsiveness to a properly administered bronchodilator confirms asthma, atopic or otherwise. All atypical preschool wheeze should be referred to pediatric respirologist for assessment. Lung function test by impulse oscillometry (IOS) before and after bronchodilator is helpful to confirm airway hyperresponsiveness, an essential feature of asthma. Assessment of atopy is important by either skin prick test or serum IgE level. Treatment of acute wheeze includes standard supportive care, bronchodilator for those diagnosed with asthma and hypertonic saline for those diagnosed as having acute bronchiolitis. Other treatments included nebulized adrenaline for acute bronchiolitis and systemic steroids for asthma. For those with significant respiratory distress, continuous positive airway pressure (CPAP) or heated humidified high flow should be considered. Daily or intermittent inhaled corticosteroid or intermittent montelukast would reduce asthma exacerbation rate. A significant proportion of preschool wheeze persists till school age. An early diagnosis of asthma would be important to allow early optimal management.

Keywords Asthma · Bronchiolitis · Bronchitis · Diagnosis · Management · Preschool · Wheeze

Introduction

Wheeze in preschool children (aged below the age of 6 y) occurs in up to 50% of preschool children [1–3]. There was a rising trend in different countries [4, 5]. In Hong Kong, an increasing trend of hospital admission for preschool wheeze was observed, from 9.9 per 1000 in 2004 to 19.1 per 1000 population in 2013 [6]. Preschool wheeze is classified as either typical or atypical. Atypical preschool wheeze (Table 1) should be referred to pediatric respiratory medicine (PRM) specialist for evaluation and management [7]. For typical wheeze in children younger than 24 mo of age, it may be due to either acute bronchiolitis or asthma. For those older than 24 mo of age, it may be due to either acute bronchitis or asthma.

There are different guidelines on preschool wheeze [1, 4, 8–10] which give different definitions and management regimes on this common condition. The authors aim to update the management of preschool wheeze in the current article.

Definitions

It is important to note that parents-reported wheeze is not reliable with around 60% accuracy and there is only 50% agreement between parents and doctors. Parents tend to misinterpret any noisy breathing from the airway or chest as wheeze [11–13]. The inaccuracy is increased in ethnic minorities. It is also noted that children with doctor-confirmed wheeze demonstrated greater resistance than parents-reported wheeze [14]. Hence, the term “wheeze” in the current paper refers to doctor-diagnosed wheeze. Recurrence is defined as more than 2 episodes of doctor-diagnosed wheeze and each episode could last for a few hours

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to a few days. Typical wheeze refers to absence of features listed in Table 1.

Early preschool wheeze occurs before 2 y of age and late preschool wheeze is defined as occurring between 2 y of age to before 6 y of age. Around 45% of infants had at least one episode of wheeze and 20.3% had recurrent wheeze, in a study of 30,000 infants [15]. A study of 53 infants aged 3–26 mo, who were investigated with infant pulmonary function tests and rigid bronchoscopy for severe respiratory symptoms including wheeze, reported no evidence of eosinophilic airway inflammation or re-modeling [16, 17]. Wheeze in this otherwise healthy age group was most likely due to airflow obstruction, reversible or otherwise, caused by viral infection of the lower airway or asthma triggered by viral infection of the upper respiratory tract. They were associated with maternal asthma, male gender and a history of rhinitis [2]. Late preschool wheeze was predictive of subsequent asthma hospitalization during school age [18].

Pathophysiology of Typical Preschool Wheeze

Bronchiolitis and asthma account for most, if not all early typical wheeze. The main difference between the two is the lack of overt airway hyper-responsiveness in bronchiolitis. Ducharme et al. suggested that the diagnosis of asthma could be made clinically [4]. The most readily available diagnostic criterion remains the finding of a reversible airway obstruction confirmed by a therapeutic trial with inhaled bronchodilators as suggested by the Global Initiative for Asthma [19]. The diagnosis requires the documentation of improvement of airflow obstruction as evidence by the breath sound and wheeze 30 min after inhalation of short-acting β_2 -agonists (SABA) by a trained health care practitioner during an acute exacerbation [20]. In the authors' unit, physician documents the resolution of wheeze, improvement in breath sound 30 min after bronchodilator in preschoolers with acute wheezy attack (Table 2). Patients who respond to bronchodilator for the first episode

are labelled as probable asthma. If there is more than one recurrence of salbutamol responsive wheeze episode, it is diagnosed as asthma.

Unlike asthma, children with acute bronchiolitis show no bronchodilator response, as the cause of airway obstruction is unrelated to smooth muscle contraction. First episode of bronchodilator responsiveness raises the suspicion of asthma and recurrent, *i.e.* more than twice, bronchodilator responsive wheeze confirms the diagnosis of asthma in a preschool child with typical wheeze.

An alternative approach to the one by responsiveness to SABA was that by the ERS Task Force [21] that proposed classifying preschool wheeze to episodic viral wheeze or multiple trigger wheeze to guide treatment. Episodic viral wheeze (EVW) is defined as wheezes only at the time of a clinically diagnosed viral upper respiratory tract infection and is symptom-free between viral colds. Bronchoalveolar lavage (BAL) and endobronchial biopsy showed no evidence of eosinophilic airway inflammation [22]. There was less airway obstruction, less impairment of gas mixing, and lower FeNO than in multiple trigger wheeze [23]. Multiple trigger wheeze (MTW) is defined as wheeze at the time of viral colds and between viral colds with triggers like excited behavior, aeroallergen exposure, and cold, smoky atmospheres. These children were reported to have eosinophilic inflammation [16]. However as these phenotypes can change within an individual over time [24], its usefulness to guide current treatment is limited [1].

Acute Bronchiolitis

The definitions of bronchiolitis are different in different countries. In the USA/ Canada and Hong Kong, it is defined as wheeze in the presence of viral infection whilst in the UK and Australia, it is respiratory crackles in the presence of viral infection [4]. Respiratory syncytial virus (RSV) is the commonest etiology of acute bronchiolitis with a potentially

Table 1 Features suggestive of atypical preschool wheeze

Clinical Features	Probable Diagnoses
Ex-prematurity	Bronchopulmonary dysplasia
Persistent symptoms from birth	Structural airway lesions like trachea/bronchomalacia, extramural compression by vessels, tracheoesophageal fistula
Productive wet cough	Persistent bacterial bronchitis/ Cystic fibrosis / Bronchiectasis / Primary ciliary dyskinesia / Immunodeficiency / Tuberculosis
Failure to thrive	Cystic fibrosis / Immunodeficiency
Recurrent pneumonia	Recurrent aspiration secondary to gastroesophageal reflux /Cystic fibrosis / Immunodeficiency
Neurological disorders	Recurrent aspiration due to dysfunctional swallowing
Swallow problem <i>e.g.</i> , choking, gagging / vomiting	Dysfunctional swallowing, primary or secondary to structural lesions, like laryngeal cleft
Finger clubbing	Bronchiectasis / Tuberculosis

Table 2 Definition of clinical responsiveness to bronchodilator

Breath sound	Wheeze	Bronchodilator responsiveness
↑	↑	+
↑	↓	+
↑	→	+
→	↑	–
→	↓	+
→	→	–
↓	↓	–
↓	↑	–
↓	→	–

life-threatening course in young infants younger than 6 mo or those with co-morbidities like bronchopulmonary dysplasia or cyanotic heart disease [25, 26].

Chest Radiograph

Chest radiograph is helpful for children with recurrent preschool wheeze to diagnose less common but readily treatable diseases like foreign body aspiration.

Lung Function Tests

Spirometry is not possible in children less than 2 y of age but it is often possible in those older than 4 y. For children between 3 y and 4 y of age, measuring the airway resistance using tidal breathing technique such as impulse oscillometry (IOS) is often successful. IOS studies of airway resistance before and after SABA were shown to have good diagnostic efficacy [27]. For IOS, resistance at 5 Hz or R(5) reflects the resistance of the whole airway whilst resistance at 20 Hz or R(20)

reflects the resistance of the central airway. Hence R(5) minus R(20) reflects the peripheral airway resistance. Positive airway hyper-responsiveness is diagnosed if R(5) – R(20) decreases by >44% after 4 puffs of salbutamol delivered *via* a spacer [28].

For infants less than 13 kg, infant lung function test can be considered. A rapid thoraco-abdominal compression (RTC) is applied at the end of a tidal breath inspiration which gives the maximal flow at functional residual capacity (VmaxFRC), a marker of peripheral airway resistance. The Tucson study reported a link between reduced VmaxFRC in the first weeks of life and subsequent onset of early preschool wheeze [2]. Another useful test is the raised volume rapid thoraco-abdominal compression (RVRTC) that allows measurement of forced expiratory volume at 0.5 s (FEV 0.5) and forced vital capacity (FVC). There was a significant reduction in z score for FEV 0.5, *i.e.*, –1.0 (95% CI from –0.5 to –1.5), in those with recurrent wheeze (> = 3 wheeze) compared with controls [29].

Assessment for Atopy

Personal and family history of atopy should be identified. Test for allergens sensitization carries management and prognostic purpose. A study on 463 children with preschool wheeze in the authors' department showed that preschool wheezers with positive skin prick test to aeroallergens had a greater risk of hospital admission for asthmatic attack after age of 6-y (OR = 2.83, 95% CI: 1.55, 5.18 with *p*-value <0.001) than children without sensitization [18]. The frequency of emergency admission for preschool wheeze, skin prick test (SPT) results and gender allows prediction of emergency asthma admission during school years (Table 3) [18]. Furthermore, children with positive skin prick test have 2 to 3 times higher risk for asthma preventer prescription during the school year.

Table 3 Probabilities of emergency asthma admission after the age of 6 y comparing children with various risk factors

Late preschool wheeze admission index[†]	0	0.5	1	1.5	2	2.5	3
Risk Factors							
Female							
SPT + ve Probability*	0.16	0.28	0.44	0.61	0.76	0.86	0.93
SPT-ve Probability*	0.07	0.13	0.22	0.37	0.54	0.70	0.83
Male							
SPT + ve Probability*	0.11	0.19	0.32	0.49	0.66	0.8	0.89
SPT -ve Probability*	0.04	0.08	0.15	0.26	0.42	0.59	0.74

* Probability of having asthma admission after the age of 6 y, [†] Number of admissions for preschool wheeze at age between 2 to 5.9 y divided by number of years, SPT Skin prick test

Treatment of Acute Attack

The basic supportive measures during acute wheeze include maintenance of hydration and nutrition, together with as-required oxygen supplement to maintain $\text{SpO}_2 \geq 92\%$ and one may consider heated humidified high flow nasal cannula with increased FiO_2 started at 8 L/min in moderate cases.

Bronchodilator should be tried during the acute treatment of preschool wheeze. A 2014 Cochrane review identified 30

studies assessing bronchodilators, predominantly salbutamol use in treatment of bronchiolitis and found no evidence of benefit in any outcomes for infants admitted to hospitals [30, 31]. However, children with asthma, in contrast, would respond to bronchodilator, *i.e.*, salbutamol 8 puffs through a spacer (Fig. 1).

Hypertonic saline was shown to be beneficial in reducing length of hospital stay. A meta-analysis of 24 trials and 3209 patients [32] showed a significant reduction in hospital length of stay of -0.45 d (95% CI -0.82 to -0.08 ; $p = 0.01$) compared

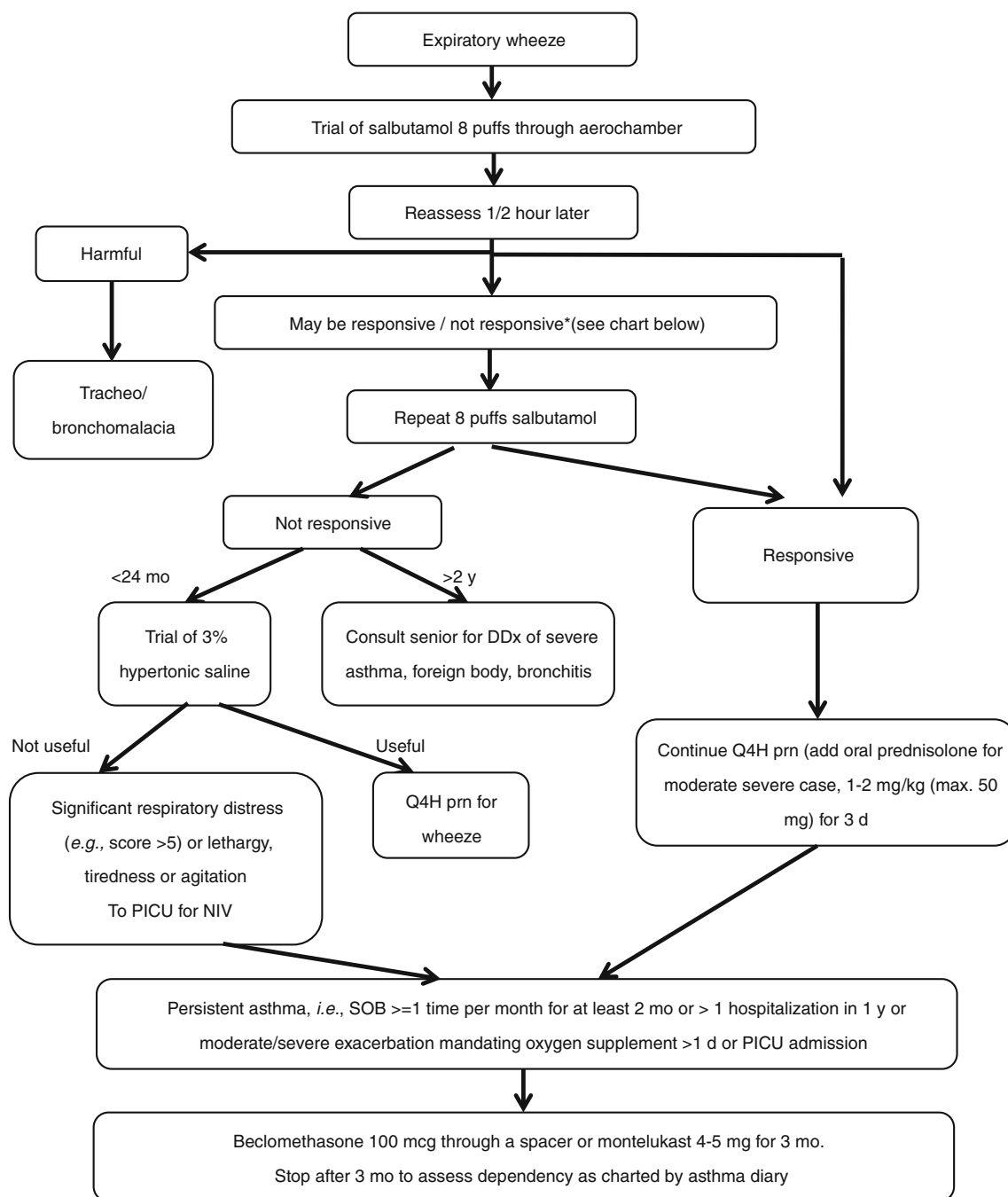


Fig. 1 Treatment algorithm for preschool wheeze. PICU Pediatric intensive care unit; NIV Non-invasive ventilation

with those receiving 0.9% saline or standard care. A second meta-analysis of 15 trials and 1922 patients found a smaller, but significant, decrease in length of stay by -0.36 d (95% CI -0.5 to -0.22 ; $p < 0.001$) in those who received hypertonic saline [33]. Both meta-analyses showed substantial heterogeneity across studies ($I^2 = 82.1\%$, $p < 0.001$; 91 and $I^2 = 77.08\%$, $p = 0.02992$). A recent re-analysis [34] of the 2 meta-analysis that removed the two outlying Chinese studies that accounted for imbalances in day of illness at presentation, produced summary estimates in support of the null hypothesis, *i.e.*, hypertonic saline was not effective in decreasing the length of stay, leading to the advice not to use hypertonic saline in the UK [9].

The main problem of all previous meta-analyses was the inclusion of studies that adopted different definitions of bronchiolitis, *i.e.*, wheeze only to wheeze and/or crackles to crackles only. If only the studies that defined bronchiolitis as wheeze only were included, hypertonic saline was found to be effective for Asians but not for Europeans (Fig. 2).

Hence, authors recommend an individualized basis on the use of hypertonic saline in a patient with acute bronchiolitis. Furthermore, it is difficult to differentiate asthma from bronchiolitis in children less than 2 y of age and hypertonic saline might precipitate bronchoconstriction in asthma children [35]. Hence, all preschool wheezers should be given salbutamol before hypertonic saline. For those who respond to salbutamol, this treatment can be continued regularly. Caution should be given on using nebulised hypertonic saline on asthma patients (*i.e.*, those who have more than one recurrence of salbutamol responsive wheeze episode) as it may induce bronchoconstriction [35]. Pre-treatment with salbutamol can be considered if nebulised hypertonic saline deemed necessary. It is also important to have trained staff to be by the side of patient, ready to provide suction of the oro- and hypopharynx as copious secretion may be coughed out after hypertonic saline (HS) nebulization.

Since removal of secretion from chest is important to prevent plugging and cough effort in pre-school child is usually not effective, the use of nebulized HS should be followed by vigorous chest physiotherapy.

Nebulized adrenaline is shown to provide short term improvement in acute bronchiolitis [36].

Short course systemic steroid could also be considered in moderate to severe case of asthmatic attack. However, neither inhaled nor systemic glucocorticoids are advised in the management of acute bronchiolitis [37, 38]. Antibiotics have not shown to be beneficial in the acute management of bronchiolitis and should not be prescribed in the absence of high CRP or neutrophilia suggestive of bacterial infection [39].

In the presence of significant respiratory distress, non-invasive pressure support measures by heated-humidified- high flow nasal cannula (HHHFNC) or continuous positive airway pressure (CPAP) ventilation is to be considered (Fig. 3 and Table 4).

Long-term Management

Daily Inhaled Corticosteroids (ICS)

A systemic review [4] of 29 trials of preschool children with recurrent wheezing or asthma showed a significant benefit with daily inhaled corticosteroids, which reduced the risk of exacerbations needing rescue oral corticosteroids by more than 40% compared to placebo (RR 0.57, 95% CI 0.4–0.8). Daily inhaled corticosteroids also increase asthma-free days as compared to placebo (Mean difference -5.52 ; 95% CI -8.81 to 2.22). Therapeutic trial of six to eight weeks is reasonable in preschoolers with recurrent or severe wheeze responsive to bronchodilator treatment [1]. Medications should be reviewed and discontinued if there is no benefit.

Pre-emptive High Dose ICS

Pre-emptive high dose ICS (budesonide 400 mcg QID for 3 d, then BD for 7 d [40]; budesonide 1 mg BD for 7 d [41]; fluticasone propionate 750mcg daily at first sign of illness until symptoms resolved for 48 h [42]) reduced the risk of exacerbations needing rescue oral corticosteroids by more than 30% as compared to placebo (RR 0.68; 95% CI 0.53–0.86) [4]. However pre-emptive high dose ICS has no effect on reducing asthma-free day. Further studies are required to clarify the dose, duration and safety in preschoolers.

Leukotriene Receptor Antagonists (LTRA)

Daily or pre-emptive LTRA are ineffective on reducing asthma-free days. Pre-emptive LTRA reduced use of rescue oral corticosteroids as compared to placebo or pre-emptive ICS. There are no studies on daily LTRA on use of rescue oral corticosteroids [4]. In contrast, a three way comparison between standard treatment, intermittent montelukast, and intermittent nebulized budesonide in 238 children aged 12–59 mo showed minor and equivalent benefits for the two active treatments compared with standard treatment [1, 43]. Benefits were greater in the subgroup with a modified asthma predictive index. In clinical setting, authors recommend starting treatment at the first sign of a viral cold and continue it for a minimum of a week or until symptoms disappear for 48 h [44].

Prevention

Palivizumab

Passive immunization by monoclonal antibody against RSV to babies born premature with bronchopulmonary dysplasia during the first year of life is effective to prevent RSV bronchiolitis [45].

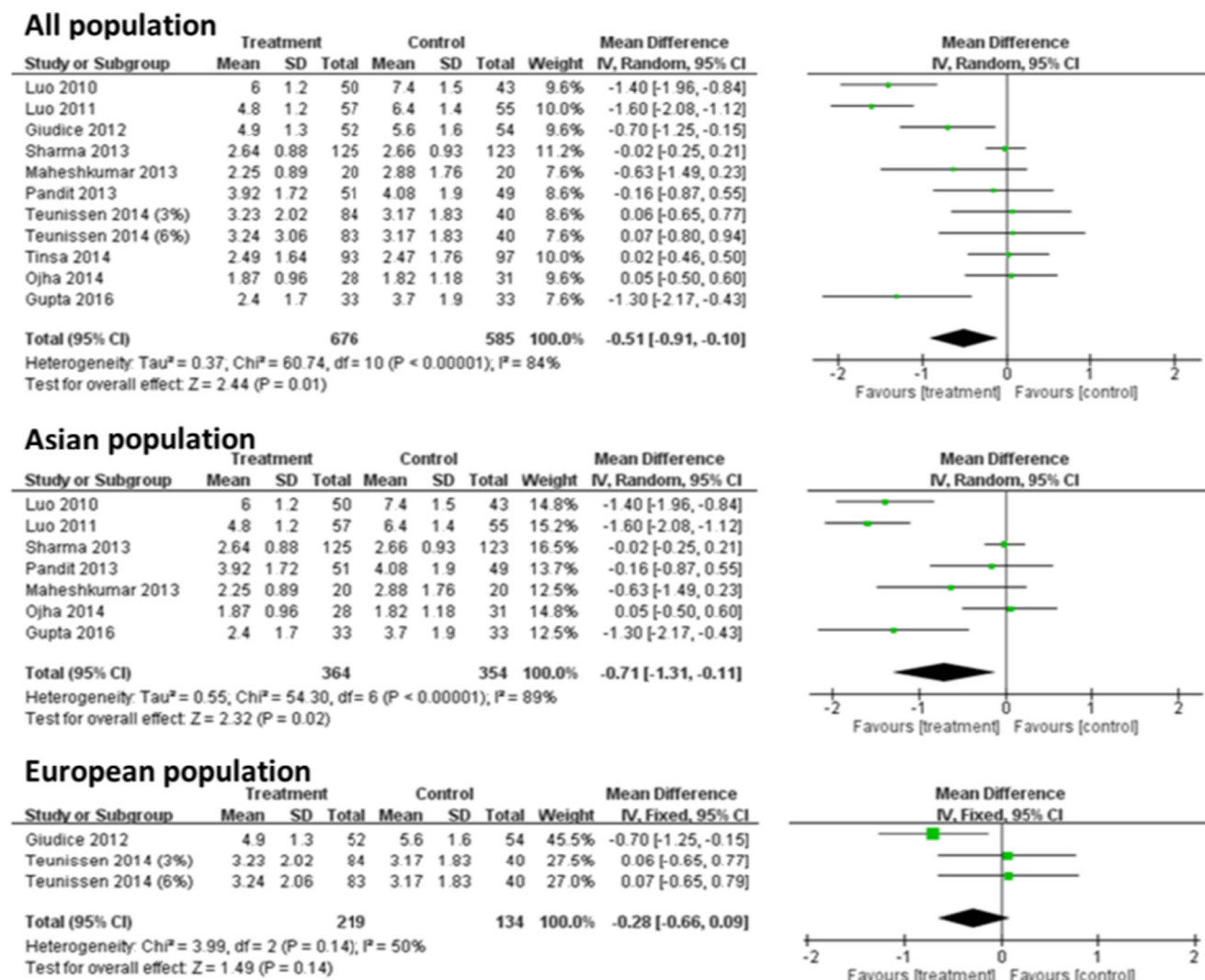


Fig. 2 Difference in length of stay comparing hypertonic saline group (treatment) and normal saline (control) group in all studies, vs. European studies (Revman version 5.3, The Cochrane Collaboration)

A double-blinded, randomized study of 429 infants born at 33–35 weeks' gestation showed that palivizumab reduced the number of days with wheeze in the first year of life by 61% and the proportion of infants with recurrent wheeze from 21% to 10% [46]. A recent prospective, multicenter, case-control, 6-y follow-up study involving Japanese preterm infants with a gestational age of 33–35 wk showed a significantly lower rate of recurrent wheeze until the age of 6 years in the treatment group than in the untreated group (15.3% vs. 31.6%) [47].

Tobacco Smoke Exposure Reduction

Smoking cessation among household members has shown to reduce wheezy attack in preschoolers as well as school aged-children in authors' unit. The benefit of smoking cessation should be promoted to parents during acute hospital admission and out-patient follow-ups.

Air-Pollutants Control

Air pollution has shown to increase vulnerability to preschool wheeze in a birth cohort [48]. Environmental policies should be made to reduce pollution. Children should also be kept indoor when the pollution index is high.

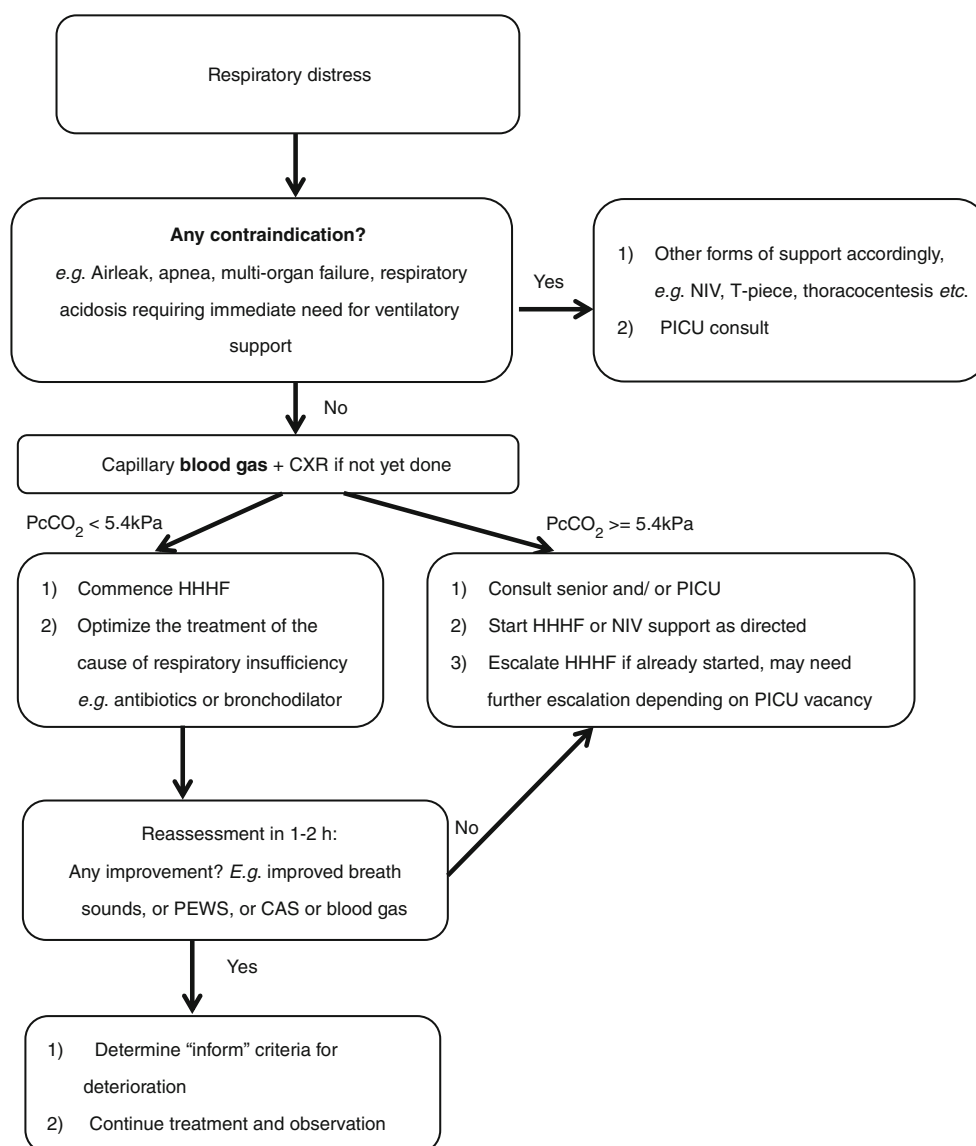
Allergen Avoidance

Parents should be educated on control of common indoors allergens e.g., house-dust mite in children with atopic pre-school asthma.

Prognosis

Parents of preschool recurrent wheezers often ask whether their children will develop asthma later. Almost 60% of

Fig. 3 Initiation of heated humidified high-flow (HHHF). CAS Modified Wood-Downes Clinical Asthma Score; NIV Non-invasive ventilation; PEWS Pediatric early warning score; PICU Pediatric intensive care unit



children who wheezed before the age of 3 y, stopped wheezing by the age of 6 y as suggested in the Tucson Children's Respiratory Study [2]. Two other birth cohorts, namely the

ALSPAC and PIAMA studies also showed that most cases of preschool wheeze were transient early wheeze (wheeze before 3 y of age but not thereafter) [4]. A retrospective study

Table 4 Titration of HHHF

	Neonate (up to 1 mo)	Infant (1 to 12 mo)	Pre-school (1–4 y)	School-aged (5 y or above)
Initial settings	• 6 L/min • PRN oxygen to keep $\text{SpO}_2 \geq 92\%$	• 8 L/min • PRN oxygen to keep $\text{SpO}_2 \geq 92\%$	• 10 L/min • PRN oxygen to keep $\text{SpO}_2 \geq 92\%$	• 12 L/min • PRN oxygen to keep $\text{SpO}_2 \geq 92\%$
First escalation	• 8 L/min • PRN oxygen to keep $\text{SpO}_2 \geq 92\%$	• 10 L/min • PRN oxygen to keep $\text{SpO}_2 \geq 92\%$	• 12 L/min • PRN oxygen to keep $\text{SpO}_2 \geq 92\%$	• 16 L/min • PRN oxygen to keep $\text{SpO}_2 \geq 92\%$
Second escalation	• N/A	• N/A	• 15 L/min • PRN oxygen to keep $\text{SpO}_2 \geq 92\%$	• 20 L/min • PRN oxygen to keep $\text{SpO}_2 \geq 92\%$

HHHF Heated-humidified high flow

of 463 children in the authors' department in Hong Kong from January 1999 to December 2011 showed that only 41% who wheeze before age of 2 y were transient [18]. This difference could be accounted by the fact that a significant portion of the subjects in index cohort were recruited from preschool wheezers who were hospitalized or attending outpatient clinics of authors' department. This might capture the group with wheeze severe enough to seek physician advice in hospital. In addition, ethnic difference could also explain the phenomenon as 94% of index study population was Chinese [49], as compared to Hispanic and non-hispanic white in Tucson study. Previous studies on prevalence of wheeze and related health-service use in south Asian and white preschool children in the United Kingdom suggested that south Asians have higher odd ratios (2.21; 95% CI 1.19–4.09) for viral wheeze and multiple wheeze (wheeze with other triggers) as compared to white children (1.43; 95% CI 0.77–2.65), after controlling for socio-economic conditions, environmental exposures and family history [50]. South Asian children aged 2 to 4-y were more likely to be admitted to hospital for wheeze or asthma [50]. A meta-analysis of ethnic variations in UK asthma frequency and health-service use also showed that south Asian children had increased risk of asthma admission, as compared to white and black children (OR 1.5; 95 CI 1.2–1.9) [51]. The difference could be related to ethnic variations in asthma severity, differences in health-seeking behavior, or difficulties in accessing high-quality primary care services [51]. Thus ethnic difference should be taken into account on prognosis of each individual. Concerning about lung function, several birth cohorts have shown that preschool children with wheeze had permanent deficits in lung function at 6 y of age [52]. These deficits were probably established by 4 y of age or younger, suggesting early airway remodeling like reticular membrane thickening [4].

Children with transient early wheezing and persistent early wheezing had decreased lung function compared to children with wheeze onset after 6 y of age and those who never wheeze [53]. In addition, those with recurrent and severe symptoms seem to have a high probability of continuing symptoms with impaired lung function in adult life [54]. These findings highlight the importance of age at onset and severity of preschool wheeze for long-term asthma morbidity in adulthood [4].

Conclusions

Preschool wheeze is a common condition for both general pediatrician and pediatric respiratory specialist. Demonstration of airway hyperresponsiveness to bronchodilator is critical for early diagnosis of asthma as it allows application of the asthma protocol. Recurrent moderate to severe preschool wheeze that is non-

bronchodilator responsive should be referred for expert management.

Contributions All authors have participated in the concept and design; analysis and interpretation of data; drafting or revising of the manuscript, and that they have approved the manuscript as submitted.

Compliance with Ethical Standards

Conflict of Interest None.

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