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European Respiratory Society Statement on preschool wheezing disorders: updated definitions, knowledge gaps, and proposed future research directions

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Abstract

Since the publication of the European Respiratory Society (ERS) Task Force reports on the management of preschool wheezing in 2008 and 2014, a large body of evidence has accumulated suggesting the clinical phenotypes that were proposed, episodic (viral) wheezing and multiple-trigger wheezing, do not relate to underlying airway pathology and may not help determine response to treatment. Specifically, using clinical phenotypes alone may no longer be appropriate, and new approaches that can be used to inform clinical care are needed for future research. This ERS Task Force reviewed the literature published after 2008 related to preschool wheezing and has suggested the criteria used to define wheezing disorders in preschool children should include age of diagnosis (0 to <6 years), confirmation of wheezing on at least one occasion, and more than one episode of wheezing ever. Furthermore, diagnosis and management may be improved by identifying treatable traits, including inflammatory biomarkers (blood eosinophils, aeroallergen sensitization) associated with type-2 immunity and differential response to inhaled corticosteroids, lung function parameters, and airway infection. However, more comprehensive use of biomarkers/treatable traits in predicting the response to treatment requires prospective validation. There is evidence that specific genetic traits may help guide management, but these must be adequately tested. In addition, the Task Force identified an absence of caregiver-reported outcomes, caregiver/self-management options, and features that should prompt specialist referral for this age group. Priorities for future research include a focus on identifying i) mechanisms driving preschool wheezing, ii) biomarkers of treatable traits and efficacy of interventions in those without allergic sensitization/eosinophilia, iii) the need to include both objective outcomes and caregiver-reported outcomes in clinical trials, iv) the need for a suitable action plan for children with preschool wheezing and v) a definition of severe/difficult-to-treat preschool wheezing.
INTRODUCTION:
Wheezing disorders in children under 6 years are heterogeneous, incorporating several clinical phenotypes, with distinct underlying pathophysiological mechanisms that result in similar clinical manifestations.

The European Respiratory Society (ERS) published a Task Force report entitled “Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach” in 2008. [1] In 2014, this report was briefly updated. [2] Both documents proposed a pragmatic approach to classify and manage preschool wheezing based predominantly on the clinical history of symptom patterns. A body of evidence has accumulated since 2008, suggesting the distinction between the proposed phenotypes of “episodic (viral) wheezing” (EVW; children who wheeze intermittently and are well between episodes) and “multiple-trigger wheezing” (MTW; children who wheeze both during and outside discrete episodes) is not sufficient to predict the response to therapy. These phenotypes are often not stable over time [3-5] and do not reflect underlying airway pathology. [6] The use of these phenotypes based solely on the clinical history of symptom patterns to guide treatment decisions, without additional objective tests, may no longer be appropriate. Therefore, new approaches and research are needed to guide clinical practice.

SCOPE OF THE DOCUMENT:
This Task Force aimed to summarize new evidence and gaps in knowledge about the diagnosis and management of preschool wheezing disorders since the last (ERS) Task Force in 2008 (partially updated in 2014). Given the new evidence, the Task Force Committee: i) propose revised definitions for preschool wheezing disorders, ii) identify knowledge gaps, and iii) prioritize directions for future research to improve clinical management. This Task Force did not focus on factors predicting the progression of preschool wheezing to asthma, the aim was to highlight knowledge gaps in management to improve symptom control and prevent wheezing episodes.

METHODS:
The Task Force agreed on three overarching aims to be addressed (Table 1). Subsequently, specific questions were framed to aid the literature search and enable a thorough evaluation of the evidence for each aim. In some cases where very little evidence
was available, critical earlier studies were included as directed by the expertise of the Task Force members. A search of the published literature from the 01st of January 2008 until the 01st of December 2023 was performed via two databases – MEDLINE and the Cochrane Library by using Boolean algorithms described in detail in the Online Supplement. The screening and decision around the inclusion of relevant studies was performed by HM and VF under the supervision of senior Task Force members. All Task Force members declared that they have no conflicts of interest relevant to the subject matter or materials discussed in this document. The relevant methodology, details of databases, and composition of the Task Force are summarized in the Online Supplement.

**Task Force Aims and Questions:**

The search terms used are described in the Online supplement (Methods section).

The Task Force summarized the main findings from the literature review for each research question with concluding remarks for that question. Subsequently, based on an overall review of the available evidence, the Task Force agreed on Summary Statements and Recommendations for Future Research for each Aim.

**RESULTS:**

**Aim 1. Summarize current definitions for preschool wheezing in clinical guidelines and definitions used in preschool wheezing research studies**

**Question 1a: What is the age range used to define preschool wheezing?**

As described in the PRISMA Flowchart (Figure 1S), following the application of the search algorithm, 37 relevant studies were identified.

An agreed age range to define “preschool wheezing” is needed to enable consistency in diagnosis and uniform inclusion criteria for research studies. Studies have defined age cut-offs based on practicalities (e.g., convenience and feasibility), the study aims, planned investigations, and country-specific definitions of school entry age. Our literature search confirmed this heterogeneity in age definition in different countries and healthcare systems. [7] In summary, certain definitions, like that of the Centers for Disease Control (CDC), align with the “preschool age” category (i.e., the period between infancy and school age
corresponding roughly to 3 to 5 years old). [8] Other publications use the term “preschool” for all ages between birth to school age. The literature review revealed variable age ranges to define “preschool wheezing”, including 0-4 years [9-11], 1-4 years [12, 13], 0-5 years [14, 15], or 0-6 years [16, 17]. The ERS Task Force on preschool wheezing in 2008, and the current ERS Task Force defined the cut-off at <6 years. [1, 2] The Online supplement describes details of the age ranges used in different studies (Tables 1S and 3S). Importantly, to distinguish preschool wheezing from bronchiolitis, the current Task Force agreed more than one episode of wheezing was necessary in this age-range, and that the term “recurrent preschool wheezing” provided clarity.

**Question 1b. How is the presence of wheezing confirmed?**

As described in the PRISMA Flowchart (Figure 2S), following the application of the search algorithm, we identified 30 relevant studies.

Objective confirmation of wheezing can be difficult if the child is not wheezing during consultation. In research studies focusing on preschool wheezing prevalence, wheezing episodes are usually ascertained retrospectively from parental report. [18] However, parents do not always adequately distinguish wheezing from other respiratory sounds. [18-20] When interviewed about a validated video clip showing wheezing, stridor, snoring and normal breathing, only 38.5% of parents correctly identified wheezing, [21] and when questioned about their understanding of the term “wheezing”, only 31% recognized this condition. [22]

Approaches to determine the presence of wheezing differ according to the type of study. Intervventional trials which require wheezing confirmation frequently use “doctor diagnosed wheezing”, involving a record of objectively confirmed wheezing by a clinician. [23-25] In contrast, large observational studies, which require longitudinal assessments, usually rely predominantly on parental reports. However, one study suggested that up to one third of parentally-reported wheezing could not be objectively confirmed by the doctor, and that children with doctor-confirmed wheezing had poorer lung function compared to those with parentally-reported but unconfirmed wheezing. [20] The frequency of asking parents to report symptoms may also be important. [26] It is also of note that parental ability to recall
wheezing episodes is related to number of wheezing events during the period of recall, timing of the last episode and parental history of asthma. [27]

The prevalence of wheezing estimated from parental questionnaires tends to be higher compared to physician-confirmed wheezing, [28] and a combination of parental report and confirmation in medical records has also been used to investigate preschool wheezing. These differences in data sources have to be taken into account when making inference from observational studies to intervention trials and clinical practice. Finally, it may be important to consider other symptoms (e.g., cough, shortness of breath, chest tightness, chest congestion) and not wheezing alone, as the pattern of different co-existing symptoms may better reflect the presence of respiratory disease. [29]

Moving toward objective assessments of wheezing by caregivers, recent studies have described technologies that can be used to detect wheezing. Digital stethoscopes that use artificial intelligence, can identify normal breath sounds, crackles and wheezing in children [30, 31], even in a home setting. [32] Some studies have shown good concordance with clinician detection [33] and high sensitivity and specificity. [34, 35] However, larger studies validating use of electronic wheeze detection devices are needed, and very few to date have included change after interventions or longitudinal assessments in large cohorts.

Objective confirmation of wheezing symptoms is helpful for caregivers and clinicians who cannot always confirm the presence of wheezing during the consultation and often rely on parental reports. [36, 37] In the context of clinical decision-making, current evidence shows that evidence of objective confirmation of wheezing either during consultation, or from a recording, alongside parental reports can be useful. [37]

**Question 1c. Which risk factors are currently used in preschool wheezing definitions?**

As described in the PRISMA Flowchart (Figure 3S), following the application of the search algorithm, we identified 60 relevant studies.

As the impact of recurrent preschool wheezing on the healthcare system and caregivers and families is immense, identifying avoidable risk factors for preschool wheezing is important. [38] Some studies have identified risk factors for specific wheezing phenotypes (Table 3S). [39, 40] Broadly, these include behavioral (e.g., maternal smoking during
pregnancy, maternal nutrition), demographic (e.g., sex, ethnicity, socioeconomic factors),
environmental (e.g., air pollution, climatic variables, respiratory viral infections, allergens),
and genetic variables [41-48]. A concise overview of studies describing these risk factors is in
Table 2, and studies are depicted in detail in Tables 3S and 4S. Genetic risk factors are
discussed separately in section 2e.

Before considering any pharmacotherapy (discussed in Section 2f), evidence shows it is
important to address relevant risk factors and triggers for recurrent preschool wheezing.
For example, there is consistent evidence that passive exposure to tobacco smoke or vaping,
indoor and outdoor pollutants, and indoor allergens are associated with increased risk for
recurrent symptoms and exacerbations. [49-51] Consequently, families are usually advised
that exposure to air pollutants and allergens (when there is evidence of allergic sensitization
[52]) should be avoided where possible.

**Question 1d: What are the currently described phenotypes of preschool wheezing?**

As described in the PRISMA Flowchart (Figure 1S), following the application of the search
algorithm, we have identified 37 relevant studies.

Various features have been used to group preschool children with wheezing. [53] These
distinctions are mainly based on clinical observations, as described below:

1. **Temporal patterns** (such as transient early wheezing, disappearing around school-age,
or early-onset persistent wheezing, developing in early life and persisting into school-
age) [8, 54, 55].

2. **Severity** (such as mild or severe preschool wheezing); with severity having been
defined variably either as severe (potentially life-threatening) attacks resulting in
hospitalization, oxygen need, or intensive care unit (ICU) use (independent of their
frequency); or alternatively, as frequency of attacks; [1, 39, 56].

3. **Trigger factors**, distinguishing children who wheeze only when they have an infection
(viral or virus-induced wheezing, or wheezy bronchitis), from children who also wheeze
between infections (multiple trigger wheezing, chronic wheezing); [53].

4. **Atopy**, distinguishing atopic wheezing, and non-atopic wheezing; [54, 57, 58].
Over the last 15 years, data-driven techniques that group individuals using unbiased approaches have been increasingly used to uncover the temporal patterns of wheezing (recently reviewed in [59]). Approaches have included latent class analysis (LCA) [54, 60-62], cluster analysis [63], latent trajectory analysis, etc. The classes/clusters identified in such analyses are not observable but latent (i.e., hidden), and should ideally not be referred to as “phenotypes”. Such approaches are hypothesis-generating, and the results to some extent remain dependent on the study designs, sample size, frequency and timing of data collection [26], methods and choice of indicator variables used for modelling, and model selection. Nevertheless, most cohorts have reported similar “phenotypes”, including never wheezing, early-onset remitting (transient), late-onset wheezing and persistent wheezing [26]. Ultimately, the important question is whether different wheezing “phenotypes” derived by data-driven methods are underpinned by different mechanisms. The largest study of this type to date, which used LCA to investigate development of wheezing from birth to adolescence in >15,000 participants in five birth cohorts, recently suggested that genetic associates of different wheeze phenotypes are indeed phenotype-unique [48], highlighting the potential value of using data-driven analyses for deep phenotyping to disaggregate childhood wheezing, with follow-up genetic/mechanistic studies probing underlying mechanisms of discovered classes/clusters. [59]

Irrespective of the uncertainties related to data-driven methods, one important finding must be emphasized: All clusters/phenotypes of preschool wheezing (including the transient) are associated with impaired lung function trajectories from childhood through early adulthood. Since diminished lung function at physiological peak is associated with adverse health outcomes through the life-course, including higher risk of COPD, cardiovascular/cerebrovascular events, and premature death of all causes, [66] we have to pursue research to understand mechanisms of all preschool wheeze phenotypes.

Rather than using only the information on presence/absence of wheezing, some studies have used several symptoms assessed cross-sectionally or longitudinally, including measurable traits (such as allergic sensitization, reversible airways obstruction, bronchial reactivity). [67] There are also studies linking biological variables (i.e., genetic variation) to derived phenotypes. [47, 48, 68]
There are ongoing reports describing preschool wheezing phenotypes and their associations with school-age asthma and various risk factors. However, assessments of their utility for predicting response to treatment (phenotype-based management) has not been reported, highlighting an unmet need of clinical community.

Studies related to Aim 1d are tabulated in Table 1S. For clinical practice, in the short-term, it may be more useful to describe preschool wheezing illness using treatable traits that reflect underlying disease processes (such as allergy, airway obstruction, inflammation and infection, or frequency of attacks) rather than trying to classify patients into discrete groups (distinct phenotypes) of uncertain etiology.

There are ongoing reports describing preschool wheezing phenotypes and their associations with school-age asthma and various risk factors. However, assessments of their utility for predicting response to treatment (phenotype-based management) has not been reported, highlighting an unmet need of clinical community.

**Question 1e. Which objective biomarkers are used to phenotype patients?**

As described in the PRISMA Flowcharts (Figures 4S, 5S, and 6S), following the application of three search algorithms, we have identified 51 relevant studies. This section discusses recent findings to understand the potential utility of objective biomarkers in patient classification.

**Biomarkers for recurrent wheezing**

Studies have identified biomarkers that may better address the heterogeneity of preschool wheezing, including i. peripheral blood eosinophilia, ii. aeroallergen sensitization, iii. fractional exhaled nitric oxide (FeNO), and iv. volatile organic compounds (VOCs). It should be noted that currently described biomarkers only help to identify children who are more likely to have type-2 preschool wheezing. Studies describing these biomarkers and their links to preschool wheezing are summarized in Table 3 and are described in detail in
Tables 3S and 4S. Basic characteristics linking these biomarkers to preschool wheezing are described below and in Figure 1.

i) **Peripheral blood eosinophilia:**

Although peripheral blood eosinophilia ≥4% has been used as a minor criterion in the asthma predictive index [73], cut-offs for normal/elevated blood eosinophils are likely different between preschool and school-age children, and the optimal cut-off for elevated blood eosinophils remains uncertain in preschool wheezing. [74] In addition, data relating blood eosinophils to the number of wheezing episodes and clinical, symptom-based wheezing phenotypes remain inconclusive. For example, elevated blood eosinophil levels have been associated with increased odds of exacerbations in preschoolers with recurrent wheezing, but when stratifying treatment based on peripheral blood eosinophil count, there was no association between eosinophil count and reduction in exacerbations in children with either episodic viral wheeze or multiple-trigger wheeze. [75] Changes over time and the impact of atopic comorbidities such as eczema on blood eosinophilia as a biomarker for recurrent wheezing are also unknown.

The current evidence suggests blood eosinophils are most helpful as a biomarker of response to treatment, whereby elevated eosinophils identify those recurrent preschool wheezers most likely to respond to maintenance inhaled corticosteroids (ICS). This is discussed in more detail in Question 2f.

ii) **Aeroallergen sensitization**

Early-life sensitization to aeroallergens such as pollen, dust mites, and mold spores has been associated with an increased risk of preschool recurrent wheezing. [16, 76, 77] In addition, aeroallergen sensitization has been identified as a possible biomarker of wheezing persistence and response to treatment. For example, in children enrolled in the Childhood Origins of Asthma study (COAST), early-life aeroallergen sensitization and an elevated blood eosinophil count were robust predictors of the development of persistent wheezing. [78] However, recent data suggest that although early-life sensitization increases the risk of wheezing persistence, >50% of children with infantile-onset-atopic wheezing did not develop asthma 10 years later, while up to 40% of those with infantile wheezing and recurrent infections did have asthma at age 10 years. [69]
Like blood eosinophils, data suggest that aeroallergen sensitization in preschool recurrent wheezing may help to identify children most likely to respond to maintenance ICS (see Question 2f).

iii) FeNO

Various methods have been used to measure FeNO in preschool children. Due to the lack of subject cooperation, standardization is limited in this age group and there is high variability in the cut-offs for FeNO in preschool children. In most studies the offline method was used. [79, 80] An online tidal breathing method, the single breath method, allows measurements in natural sleep [81, 82] and is performed by forced exhalation in addition to sedated sleep. The standard method with exhalation flows at 50ml/sec is only successful in older preschoolers aged 4-6 years. [83, 84]

Studies describing associations between elevated FeNO, and preschool wheezing incidence and phenotypes are depicted in Table 3 and 4S at the Online supplement.

iv) Volatile organic compounds (VOCs)

Analysis of exhaled breath condensate (EBC) to measure volatile organic compounds (VOCs) is feasible and reproducible in young children. [85-87] It has been shown that a prediction model combining information about inflammatory gene expression, VOCs, and airway resistance has increased predictive value for childhood asthma development. [88] However, limited data to date (Table 4S) do not allow firm conclusions about using specific VOCs in preschoolers with recurrent wheezing for diagnosis or to distinguish phenotypes.

SUMMARY STATEMENTS Aim 1 (See Future Directions Figure 2 and Figure 5):

Definition of preschool wheezing:

This Task Force proposes the following clinical definition for preschool wheezing based on current evidence. The definition incorporates age, wheezing confirmation, and wheezing recurrence as follows:

1. Children aged below 6 years
2. Current/prior documented objective confirmation of wheezing
3. More than one episode of wheezing

Proposed preschool wheezing phenotyping incorporating objective biomarkers:

1. There is preliminary evidence to suggest that assessment of blood eosinophils
and/or aeroallergen sensitization identifies children who will preferentially respond to maintenance ICS in preschool recurrent wheezing.

2. Based on current evidence for the clinical utility of FeNO or VOCs in preschool children, it is not possible to justify their use in a diagnostic definition. Utility of lung function is discussed in Aim 2a.

3. Although different symptom patterns can be described, such as “infection-induced episodes” or “wheezing during and between episodes”, additional objective tests to define allergic status, eosinophil phenotype, lung function (Question 2a) and airway infection (Question 2d) may be helpful.

**Aim 2: Identify current evidence defining the physiology, pathology and mechanisms underpinning preschool wheezing.**

**Question 2a. Which lung function tests can be used in preschool children and which tests have been used to define preschool wheeze phenotypes?**

As described in the PRISMA Flowchart (Figure 7S, Online Supplement), following the application of the search algorithm, we have identified 99 relevant studies which have been summarized in Tables 5S, 6S, and 7S.

**Lung function techniques**

A diverse range of lung function tests have been reported in preschool children with wheezing (Tables 5S, 6S, and 7S). The commonest techniques used are impulse oscillometry (IOS) and spirometry. For impulse oscillometry (IOS), several parameters have been measured in preschool children including resistance and reactance. [89] IOS measures have been used to record changes with exercise [90], or to measure bronchodilator response [91] and bronchial provocation tests [92]. Studies have also reported the use of IOS to assess response to inhaled corticosteroids, as well as lung function trajectory over time. [89, 93]

Other tests are the forced oscillometry technique (FOT) [94], resistance interrupter technique (Rint) [95], multiple breath washout (MBW) [96], plethysmography [96], raised volume rapid thoracoabdominal compression technique (RVRTC) [97], tidal breathing flow and dynamics, impedance pneumology [98] and thoraco-abdominal synchrony.
Compared to healthy children, preschool children with persistent wheezing have reportedly lower infant flow measures such as maximum flow measured at functional residual capacity (Vmax FRC) [99], higher specific airway resistance (sRaw) by plethysmography [100], reduced FEV\textsubscript{0.5} z-score and forced mid-expiratory flow (FEF)\textsubscript{25-75} using forced flow techniques (RVRTC manoeuvre) [101], higher baseline resistance measured by FOT [102], higher R5-R20 [103], higher respiratory resistance at the end of expiration [104] and lower spirometry values. [105] Higher values of LCI (Lung Clearance Index) [106] and Scond (conducting zone ventilation inhomogeneity) [96] have been found in studies conducted in preschool children with persistent or multiple trigger wheezing. LCI, [107] plethysmography [108], spirometry [107], airway resistance measured by IOS [109] and specific airway resistance (sRaw) [108] are significantly distinct among children with preschool wheezing experiencing exacerbations compared to healthy children.

Bronchodilator response has been demonstrated in preschool children with wheezing [110]. Children with uncontrolled symptoms show less reversibility compared to children with totally/partly controlled symptoms, mainly explained by the fact that young children with severe symptoms require a high dose of salbutamol to obtain/demonstrate airway bronchodilator response. [111] Although it is still unclear, demonstration of bronchodilator response may be helpful in selecting which wheezy preschool children are likely to benefit from inhaled steroids.

Importantly, it is noted that tests reported are diverse, the populations and ages of those studied differ, the context of the assessments (acute wheezing versus baseline versus bronchial challenge etc.) and even the measurements reported from studies using the same tests are not consistent.
Longitudinal studies (Tables 5S, 6S, and 7S) from infancy to school age demonstrate that reduced lung function identified in infancy often remains at school age. Consequently, preschool children with recurrent wheezing will be expected to show similar trajectories. Studies in preschool children have demonstrated that poor lung function may correlate with wheezing (acute or reported recurrence), deteriorate over time with exacerbations [112], and predict a diagnosis of persistent asthma. [113]

2b. What is known about inflammation (airway and peripheral) and allergic sensitization in preschool wheezing?

As described in the PRISMA Flowchart (Figure 8S), following the application of the search algorithm, we have identified 21 relevant studies.

Difficulties obtaining lower airway samples from preschool children mean very few direct assessments of inflammation are made. Blood sampling is used as an indirect assessment. Nasal epithelial cell brushing or lavage, and other non-invasive sampling such as exhaled breath and exhaled breath condensate analysis are limited at present to research settings.

Studies investigating lower airway inflammation are limited to preschool children with severe recurrent wheezing episodes. [114, 115] In a subgroup of these children, eosinophils contribute to pathogenesis. For example, increased numbers of eosinophils are present in the airway submucosa of children with severe recurrent wheezing episodes compared to control patients [116], irrespective of their atopic status. [117, 118] However, the site and compartment may affect their relative abundance.

In addition to eosinophils, neutrophils likely play a role in the inflammatory process underlying recurrent preschool wheezing, and certain markers indicate their activation and involvement. For instance, the shedding of L-selectin from the neutrophil cell surface, suggesting that neutrophils become activated and move towards sites of inflammation, and the upregulation of macrophage-1 (Mac-1) expression, have been linked to the underlying pathology in preschool wheezing. [119] In another study including 350 children with moderate to severe preschool wheezing, distinct clusters of children based on peripheral blood and BAL eosinophils, neutrophils, and other clinical symptoms (e.g., gastroesophageal reflux) have been identified. [120] The cluster with the highest BAL neutrophil count was distinct and linked to a steroid-refractory phenotype with an increased incidence of
pneumonia and gastroesophageal reflux, while aeroallergen sensitization was associated with a separate cluster whose symptoms were controlled on high-dose inhaled corticosteroids. [120]

Other inflammatory mediators that have been identified by using upper airway samples (e.g., nasopharyngeal aspirates) and serve as surrogates of increased inflammation and remodelling include the epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and transforming growth factor beta 1 (TGF-β) mediators. [121] Assessment of inflammation using other non-invasive samples such as nasal epithelial lining fluid has shown immune mediator levels of interferon-gamma (IFN-γ), tumor necrosis factor (TNF)-alpha, interleukin (IL)-1beta, and IL-10 from children aged 0-3 years with “asthma-like episodes” have been significantly higher during episodes than during stable disease, in a post-hoc analysis. [122] Data on exhaled breath condensate and VOCs point towards different inflammatory mediators and are depicted in Table 4S (Online supplement).

The current data suggest important roles for both lower airway eosinophils and neutrophils in recurrent preschool wheezing. However, reliable inflammatory biomarkers easily measured and applied in the clinic are missing.

**Question 2c. What is known about airway remodelling in recurrent preschool wheeze?**

As described in the PRISMA Flowchart (Figure 9S, Online Supplement), following the application of the search algorithm, we have identified 17 relevant studies.

Studies published prior to 2008 show evidence of increased reticular basement membrane thickness in severe preschool wheezing compared to non-wheezing patients, independent of atopic status. [118, 123] Defective bronchial epithelial cell repair has also been described in recurrent preschool wheezing similar to school-age asthma. [124] Primary bronchial epithelial cells from children with preschool wheezing secrete high levels of pro-inflammatory cytokines (IFN-γ, IL-6, and IL-13), and show reduced proliferation capacity thereby delaying wound healing and restoration of barrier function. [125] In addition, submucosal interleukin-33 (IL-33)-positive cells are increased in non-treatment responsive preschool children with wheezing. This is also the case for ST2, the receptor of IL-33. [126] Latent class analysis of several remodelling parameters (epithelial integrity, reticular basement membrane thickness, mucus glands, smooth muscle, and vessels) show distinct
remodelling patterns that are associated with more frequent and severe preschool wheezing exacerbations. [126] In summary, there is evidence supporting early airway remodelling in recurrent preschool wheezing, but there are currently no therapeutic targets to modulate these changes, and critically, there are no non-invasive tests to quantify remodelling.

**Question 2d. What is known about infection in recurrent preschool wheezing?**

As described in the PRISMA Flowchart (Figure 10S), following the application of the search algorithm, we have identified 43 relevant studies.

**a. Infections during acute preschool wheezing episodes**

Several observational studies have identified respiratory viral infections as the main triggers of preschool wheezing episodes. [127, 128] Respiratory viruses are isolated from nasal airway secretions in 80-90% of children presenting with acute wheezing. [129] RSV and human rhinovirus are the most detected viral pathogens and account for more than half of all detected viruses within the first three years of life. [130]

The COPSAC study is among the first to investigate the role of both respiratory viruses and bacteria in acute wheezing. [131] Children with *Haemophilus influenzae* and *Moraxella catarrhalis*, when detected in high abundance in hypopharyngeal aspirates, have three times higher odds for an acute wheezing episode than those with no bacteria detected. [131] The emerging understanding is that both respiratory viruses and bacteria are implicated in acute preschool wheezing pathogenesis. In preschool wheezing, airways are not sterile from bacteria during stable disease, and it is unclear whether airway microbial dysbiosis is associated with an increased risk for future wheezing attacks. Understanding whether respiratory viruses or bacteria are the triggering pathogens, or whether microbial dysbiosis represents an underlying dysfunctional innate immune system requires interventional study designs and mechanistic studies to improve our understanding of whether infections are a cause or trigger of recurrent wheezing.

Severe bronchiolitis cohort studies have shown that rhinovirus-induced bronchiolitis is associated with an increased risk for future recurrent wheezing, particularly in infants with
allergic sensitization. [132] In addition, interactions between respiratory viruses and bacteria detected in nasal airway samples from infants with severe bronchiolitis are linked to endotypes at high risk for recurrent wheezing development. [133] These data require validation but suggest nasal airway pathogens present during acute wheezing episodes could be used as biomarkers to identify children at risk of subsequent recurrent wheezing.

b. The role of viral and bacterial infection in recurrent preschool wheezing

There is evidence from several longitudinal studies that rhinovirus in nasopharyngeal samples acquired during acute wheezing episodes is associated with an increased risk of recurrent wheezing episodes. [124, 132] Equally, 20% of children have asymptomatic rhinovirus in upper airway samples and this has also been associated with an increased risk of school-age asthma. [134, 135]

In stable diseases, there are variable rates of respiratory viruses detected. [136] *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae* are also cultured from lower airway samples in up to 50% of these children. [6, 136] Moreover, there appears to be an association between specific bacterial species and allergic sensitization. *Moraxella catarrhalis* is the most commonly cultured pathogen (30% of children) in BAL from children with preschool wheezing and aeroallergen sensitization and is linked to co-existing lower airway neutrophilia. [6, 137]

In summary, airway infection, both viral and bacterial, is associated with recurrent preschool wheezing. However, we need reliable non-invasive techniques to identify airway infections, to understand whether infections play a causal role in recurrent wheezing episodes, and whether treatments targeting infection can improve outcomes in preschool wheezing. Interventional trials with targeted antibiotics, antivirals, bacterial lysates, or vaccines may enable us to understand this better.

**Question 2e. What is the role of genetic susceptibility in recurrent preschool wheeze?**

Our search strategy aimed to identify research studies focusing on genetic determinants of preschool wheezing incidence and severity. We identified 31 publications with relevant information (Figure 11S).

The studies investigating genetic susceptibility and recurrent preschool wheezing have been summarized in Table 4. Overall, these studies focus on the investigation of gene (i.e.,
GSDMB, ORMDL3, IL33, IL1R1, ILRL1, RAD50, IL13, CDHR3, FUT2, MAMSTR, IL10, IL4RA, IL9R, VDR, GSTP1, TLR2, TNFRSF13B, ANXA1)-gene or gene-environment interactions in preschool children with recurrent wheezing. Strongest genetic effects were seen for more severe disease. As different genes are likely to represent specific underlying mechanisms, genetics might in theory help guiding treatment, but the role of these genetic markers in stratifying patients in clinical trials and defining responsiveness to treatment approaches has not been investigated.

**Question 2f. What is the evidence for treatments for preschool wheezing being determined by and impacting pathophysiology and mechanisms?**

As described in the PRISMA Flowchart (Figures 12S and 13S), following the application of the search algorithm, we have identified 41 relevant studies. 20/41 studies are randomized controlled trials (RCTs). A summary of these studies is depicted in Table 5 and Table 12S. In addition, the studies investigating the impact of treatments on biomarkers, lung function, and clinical symptoms are summarized in Table 6. Key novel data relating to the efficacy of ICS and the use of mixed bacterial lysates in recurrent preschool wheezing without allergen sensitization are highlighted below.

**a. Inhaled corticosteroids (ICS)**

Management with maintenance ICS remains the first line of treatment for preschool wheezing according to GINA guidelines. [138] A meta-analysis of studies comparing the effectiveness of daily versus intermittent treatment with ICS in preschool children shows no significant difference in the number of wheezing exacerbations between treatment groups. [139] Evidence from three RCTs shows that there is no effect of ICS on long-term respiratory sequelae (i.e., asthma development). [23-25] When choosing between ICS or leukotriene receptor antagonists (LTRAs) as the first line of management, the Individualized Therapy for Asthma in Toddlers (INFANT) trial [140] did not identify markers of differential responders to LTRA. However, the trial did demonstrate that by using two easily detectable biomarkers (elevated blood eosinophils [>300 cells/mcl] and/or aeroallergen sensitization) differential responders to daily ICS treatment could be identified. [140] Further prospective validation of this approach is needed, therefore, using blood eosinophils as a biomarker in preschool
children is currently not an evidence-based recommended clinical approach. [74] The cut-off levels for elevated blood eosinophils recommended in the INFANT trial were within the normal range for children and, evidently, children with co-existing allergic diseases (i.e., eczema) are expected to have higher blood eosinophils regardless of their recurrent wheezing diagnosis. [74] Differential treatment responses in the INFANT trial have provided evidence for the heterogeneity of recurrent preschool wheezing. An LCA of 5 clinical trials, incorporating 1,708 children with recurrent preschool wheezing also showed aeroallergen sensitization identified children most likely to respond to maintenance ICS. [141] The role of alternative biomarkers that may identify ICS responders, such as FeNO, still remains unknown. Results from both interventional and observational studies in preschool wheezing identifying characteristics of ICS responders are depicted in Tables 5 and 6.

b. Macrolides

Macrolides, most commonly azithromycin, have only been investigated for treatment of acute preschool wheezing episodes. [142] Data show that if macrolides are started within six days of onset of “asthma like episodes” in 1–3-year-old children, duration of symptoms is reduced by 83%, but with unclear mechanism of action, and in the absence of bacterial detection. [142] In contrast, there is no benefit of azithromycin in 1–5-year-old children presenting with acute wheezing in the emergency room either on the duration of the episode or time to re-occurrence of an episode. [143] In a third RCT testing the impact of azithromycin on progression to severe lower respiratory tract infection (LRTI) requiring oral corticosteroid prescription, azithromycin, when started at the onset of upper respiratory tract infection, was associated with a significantly reduced risk of progression to severe LRTI. [144] However, induction of azithromycin-resistant organisms was observed. [144] A systematic review of the three trials concluded limited evidence for efficacy of macrolides in acute preschool wheezing based on available data. [145] Importantly, no trials have assessed the efficacy of longer-term prophylactic azithromycin as a maintenance therapy to prevent recurrent preschool wheeze attacks.

c. Mixed bacterial lysates

There have been several clinical trials to determine the efficacy of mixed bacterial lysates as a treatment to prevent preschool wheezing episodes. [146] Bacterial lysates are orally or sublingually delivered inactivated bacterial extracts from a mix of pathogenic respiratory
bacteria and are proposed to work by exhibiting immunomodulatory activity. [147] The mixed bacteria in the compounds include the three that have been most commonly cultured from lower airways in severe recurrent preschool wheezing (Moraxella catarrhalis, Haemophilus influenzae, Streptococcus pneumoniae). [148] The immunomodulatory activity is proposed to occur via nuclear factor-kappa B and mitogen-activated protein kinase pathways that activate dendritic cells. This activation is proposed to stimulate an antiviral response by its effect on the production of antiviral cytokines, including interferons, Th1 cytokines, and (local) immunoglobulins. [149] Their greatest benefit is thought to be in the group of children who have virus-induced episodes and are non-allergic. An initial double-blind randomised controlled trial of 75 children aged 1-6 years showed a significant reduction in rate and duration of wheezing attacks associated with acute respiratory infections. [150] Subsequently, a phase-3 double-blind randomised placebo-controlled trial which included 120 children under 3 years old with at least three wheeze attacks in the previous year, showed 6-months treatment with the bacterial lysates MV130 resulted in fewer wheeze attacks at 1 year (even though the intervention was for only 6 months). [151] A cost-utility analysis showed the use of bacterial lysates as add-on to standard care of preschool children with recurrent wheezing was an efficient treatment intervention that reduced the clinical and economic burden. [152]

Impact of currently available pharmacological interventions on wheezing pathophysiology

Impact of treatments on lung function

Discordant results have been reported on the effect of ICS or montelukast on lung function in children with preschool wheeze. These results have been summarised in Table 7.

Impact of treatments on type2 biomarkers

There are two studies from the same group suggesting systemic corticosteroids might impact eosinophil activation, especially in rhinovirus-induced episodes. Other than these studies, there is no evidence of impact of currently available treatments on blood biomarkers. The studies are summarised in Table 6.

In addition to blood biomarkers, studies have assessed the impact of ICS or montelukast on FeNO with conflicting results (Table 6).

SUMMARY STATEMENTS – Aim 2 (See Future Directions Figure 3 and Figure 5)
1. Lung function is feasible in specialist centres in preschool children and provides measures of bronchodilator response, response to treatment, and can be tracked from preschool to school-age.

2. There is emerging evidence that blood eosinophils and aeroallergen sensitisation may help to define the group of preschool children with recurrent wheezing who have a predominant lower airway type 2, eosinophilic inflammatory phenotype and who will have a differential response to ICS.

3. The current understanding of the role of inflammation in preschool wheezing mainly derives from studies utilizing lower airway samples from children with severe wheezing episodes. These studies show both airway eosinophils and neutrophils in preschool wheezing. However, understanding the relationships between blood, upper airway, and lower airway inflammation, and in children with different wheezing severity remains limited.

4. The current evidence does not clearly identify specific markers of reduced responsiveness to treatment with inhaled corticosteroids (Table 6). However, absence of both blood eosinophilia and aeroallergen sensitization can indicate reduced steroid responsiveness.

5. Respiratory viruses are involved in preschool wheezing pathogenesis. Based on current evidence, rhinoviruses are commonly detected in the upper and lower airways both during acute attacks and during stable disease.

6. Three bacterial species are most identified in upper and lower airways using traditional culture and culture independent techniques in preschool wheezing: *Moraxella catarrhalis, Haemophilus influenzae* and *Streptococcus pneumoniae*.

7. Whether infections play a role in driving recurrent preschool wheezing, or simply uncover underlying susceptibility is unknown.

8. There is emerging evidence that oral mixed bacterial lysates reduce number and duration of preschool wheezing attacks, especially in children without aeroallergen sensitisation.

9. Airway remodelling is present in severe recurrent preschool wheezing, however, there are no non-invasive biomarkers and presence of remodelling in low severity preschool wheezing is unknown.
10. The most robust gene signals relate to ORMDL3, GSDMB, and IL33 genes. However, the role of these genetic markers in stratifying patients in clinical trials and defining responsiveness to treatment approaches is unknown.

**Aim 3: Important outcomes for patients, caregivers and clinicians following diagnosis and/or management of preschool wheezing.**

To help highlight some priorities for parents and caregivers, we interviewed parents of preschool children with wheezing in the UK and the Netherlands who highlighted several important issues which are summarized in Table 8. These patient and public involvement (PPI) colleagues were recruited via the European Lung Foundation in collaboration with the PPI platform of the Asthma UK Centre for Applied Research.

**Question 3a. What is known about important outcomes for patients/parents/caregivers following diagnosis and management of recurrent preschool wheeze?**

Our search strategy aimed to identify research studies focusing on important outcomes for patients/caregivers. Our search has identified 34 relevant publications (Figure 14S, Online Supplement).

**Important outcomes for patients and caregivers**

**Improved understanding about recurrent preschool wheezing among caregivers**

Educational programs, including training about management and parental coaching for a wide age range of children have shown improvements in knowledge [153], symptom-free days [154-157], need for emergency consultation [154, 155, 158], and reduction in oral steroid courses [155]. Below we discuss the impact of educational programs on important outcomes for caregivers of preschool children with recurrent wheezing.

**Support with administering daily medications**

Managing daily treatments can be a major issue for parents. Smart inhalers reveal that only half of children with preschool wheezing use ICS optimally, [159] and adherence is influenced by parental beliefs regarding benefit and harms of daily ICS treatment. [160, 161] Administering inhaler devices to their young children can be a source of distress for parents who describe feeling poorly prepared for the task. [162] A feedback mechanism attached to a spacer provided reassurance of correct inhalation technique. [163] Families reporting
better overall management of wheezing had fewer oral corticosteroid courses and higher caregiver asthma-related quality of life. [164]

**Managing acute wheeze attacks**

Acute wheeze attacks and the need for emergency care are relatively frequent in preschool children compared to older children [165] and most parents report that their decisions to attend an emergency department (ED) are driven by perceptions of urgency [166], with a third citing difficulty accessing timely advice from primary care. [166] When interviewed during emergency care (in the ED or primary care) about wheeze attacks, parents reported the need for a better understanding of their child’s condition, need for more support from clinicians in terms of medication use, and supportive communication. [38]

This information could be provided during discharge from a hospital setting. For example, a study showed that video discharge instructions following a wheeze attack rather than written instructions improved caregivers’ understanding of their child’s diagnosis, treatment, and follow-up care. [167] A written wheeze plan given to parents in the emergency department to explain the discharge medication improves adherence to medication. [168]

**Achieving a better family quality of life**

Children with severe wheezing have reportedly lower quality of life. [169-171] Poor disease control impacts on caregivers. [172] This impact, that can be measured with a validated (Effects of a Young Child’s Asthma Flare-up on the Parents) ECAP questionnaire [173] may be reflected in domains of sleep/activity disruption; emotions; concerns about medication and acute care; concerns about losing control; and concerns about leaving the child with another caregiver.

**Question 3b. Does supported self-management improve outcomes for children with preschool wheezing and what components of support are effective?**

Our first objective was to establish the evidence for the effectiveness of supported self-management interventions. Our primary interests were clinical outcomes of acute attacks and symptom control, but also the impact on caregiver quality-of-life. Process and intermediate outcomes were noted as evidence of feasibility, fidelity, or potential for
improving outcomes (improved adherence, self-efficacy). Our second objective was to explore evidence for specific components of supported self-management to inform future development of interventions.

**Objective 1: Effectiveness of supported self-management interventions in children with preschool wheezing**

Eight RCTs assessed effectiveness of a supported self-management intervention; Five studies were conducted more than 10 years ago [158, 174-176] and thus do not reflect current understanding of heterogeneity of preschool wheezing. A diagnosis of “asthma” (as opposed to wheeze/asthma) was an eligibility criterion for six of the studies. [156, 174-178]

Interventions ranged in duration from two 20-minute hospital-based educational sessions [179] to eight 90-minute home visits. [174] One programme was delivered in preschool classes,[156] and one was a tailored computer programme. [247] Most were led by respiratory-trained paediatric nurses [156, 174, 175, 178, 179] or GPs [176], but one was delivered by a paediatrician, nurse and psychologist team. [158] Education was a core component of all the interventions, but one included a psychological component [158], one targeted self-efficacy,[177] and two addressed the social challenges of the low-income African American communities. [174, 178] One observational study reporting data on preschool children referred to a Diagnostic Therapeutic Educational Pathway. [180]

There is considerable heterogeneity of study design: individually RCTs [174, 175, 177-179] two cluster RCTs [156, 158] and follow-on from a RCT. [176] The most common outcome was acute attacks, but there was great diversity in how this was measured (any unscheduled care, ED/admission either combined, or separately [158, 176, 179] and reported (proportion with the outcome [156, 158], number of attacks per participant [178, 179], total number of attacks from routine data. [176] A range of patient reported outcomes were used such as knowledge around preschool asthma, self-efficacy feeling. A validated questionnaire for caregiver quality-of-life was used by four trials [174, 177-179] two used non-validated questionnaires. [174, 175]

**Impact on clinical outcomes**

The four trials that used emergency care visits as their primary outcome reported no significant between-group difference. [156, 174, 178, 179] Emergency healthcare
consultations [156, 158] and hospitalisations [158] were similar in the psychoeducational intervention (P²AET) and control groups. There was no difference in mean number of GP consultations, ED attendances or admissions experienced by participants in the intervention group compared to controls and no reduction in wheeze attacks. [174, 179] The only trial to demonstrate a reduction in ‘emergency and non-emergency visits’ was a cluster RCT from 1994 that used routine data to assess the impact of training general practitioners. [176]

A reduction in ED visits and hospitalisations was seen in preschool children before and after enrolment in the Diagnostic Therapeutic Educational Pathway [177], with a reduction in outpatient visits and oral steroid courses in children aged 3-5 years. [177] Three studies using unvalidated questions reported a reduction in asthma symptoms [156, 174, 175], but another three studies which used validated questionnaires reported no between-group difference in asthma control. [158, 178, 179]

**Impact on caregivers’ quality-of-life**

The home-delivered Wee Wheezers programme improved caregivers’ quality-of-life in the sub-group of 0–3-year-olds, but not overall. [174] In contrast, neither the multi-faceted HeadStart programme [178], nor a less intensive educational intervention [179], or a computer-based educational programme [177] showed a beneficial effect.

**Knowledge, self-efficacy and adherence**

Improving knowledge was a key aim of seven of the interventions, and four reported improvement in knowledge [158], self-management skills [175, 176], inhaler technique [156], and self-efficacy [176, 177] as well as an improvement in confidence among preschool staff. [177]

One of two Wee Wheezer trials reported improvement in adherence to preventer medication [177] but there was a large between-group difference at baseline; the other reported no effect. [174] The preschool-based intervention reported an increase in the number of children using inhaled corticosteroids. [156]

**Objective 2: Effectiveness of components of supported self-management**

We identified four RCTs which evaluated components of supported self-management; one each from France [181], USA [182], Hong Kong [183], and Australia. [184] In addition,
we included a ‘before and after’ feasibility study from Germany [32], and developmental work using routine data from Australia. [185] Although the earlier studies specified a diagnosis of ‘asthma’ as an eligibility criterion [182, 184] two of the more recent studies explicitly included recurrent wheeze as well as asthma. [32, 183, 185] The five studies investigated a range of potential components (e.g., carefully designed asthma education resources, web-based asthma education programmes, use of “wheezing detectors” to support parental confidence) described in Table 9.

Question 3c. Which strategies should clinicians use to highlight need for further investigation and referral from primary care or general paediatrician – to secondary and tertiary care?

The results of the search for this question did not reveal any original research manuscripts. Only review articles which included authors’ opinions / consensus were available (Online Supplement, Discussion and Figure 15S).

SUMMARY STATEMENTS – Aim 3: (See Future Directions Figure 4 and Figure 5)

The need for additional research in the area of patient and caregiver related outcomes has been highlighted.

1. There is currently insufficient evidence about supported self-management interventions that are effective for parents/caregivers of preschool children who wheeze, and a suitable action plan for preschool wheezers is urgently needed.
2. The impact of self-management interventions should be assessed using outcomes that reflect acute attacks (such as unscheduled healthcare), symptom control and impact on the child, the caregiver, and their family quality of life (using control or quality of life questionnaires validated in this age group)
3. There is a need for evidence to underpin clear guidance about when preschool children with recurrent wheeze should be referred for further investigations and specialist tests.

Conclusions and future directions

This ERS Task Force reviewed the literature related to recurrent preschool wheezing (Figure 5). We suggest three criteria should be fulfilled to define wheezing disorders in preschool children: 1. age (0-6 years), 2. confirmation of wheezing on at least one
occasion, 3. more than one episode of wheezing. Although children with recurrent preschool wheezing may have similar clinical manifestations including acute episodes with/without interval symptoms, the underlying pathophysiology and causal mechanisms are heterogeneous. Therefore, in a similar manner to the approach proposed for school-age asthma, diagnosis and management may be improved by identifying treatable traits, which include inflammatory markers and lung function parameters. The current evidence suggests certain biomarkers may be helpful to define the wheeze phenotype and to identify children likely to respond to inhaled corticosteroids. [70] These include elevated blood eosinophils and aeroallergen sensitisation. They require validation in prospective, longitudinal interventional studies to understand their role in daily clinical practice. However, a big gap at present is biomarkers that may help to identify children unlikely to respond to inhaled corticosteroids, and those who may have a “type-2 low” phenotype. There is evidence that airway infection (bacterial and viral) may play a role in recurrent preschool wheezing, however, nothing is known about the cause-effect relationship, impact of anti-infection treatment strategies, and biomarkers of treatment response. There is also increasing evidence that testing genetic traits that have been identified by GWAS studies may be helpful to identify phenotypes and guide management but has not yet been tested. Importantly, the efficacy of any intervention should be assessed with both objective outcomes (e.g., reduction in the number of acute episodes and healthcare visits) and caregiver-reported outcomes. However, currently, there is little / no evidence from trials that have incorporated caregiver reported outcomes or quality of life measures. In summary, to effectively manage recurrent preschool wheeze, we need to accept the need to objectively identify observable traits, treat this based on measurable traits, and efficiently follow this through based on observable, measured, and caregiver-reported traits.
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<tr>
<th><strong>Aim 1. Summarise current definitions for preschool wheezing in clinical guidelines and definitions used in preschool wheeze research studies</strong></th>
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<td>a. What is the age range used to define “preschool” wheeze?</td>
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<td>b. How is the presence of wheeze confirmed?</td>
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<tr>
<td>c. Which risk factors are used in preschool wheeze definitions?</td>
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<tr>
<td>d. What are the currently proposed phenotypes of preschool wheeze?</td>
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<tr>
<td>e. Which objective biomarkers are used to phenotype patients?</td>
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<tr>
<th><strong>Aim 2. Identify the current evidence available for the physiology, pathology, and mechanisms underpinning preschool wheeze</strong></th>
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<tr>
<td>a. Which lung function tests can be used in preschool children and which tests have been used to define preschool wheeze phenotypes?</td>
</tr>
<tr>
<td>b. What is known about inflammation (airway and peripheral) and allergic sensitisation in recurrent preschool wheeze?</td>
</tr>
<tr>
<td>c. What is known about airway remodelling in recurrent preschool wheeze?</td>
</tr>
<tr>
<td>d. What is known about infection in recurrent preschool wheeze?</td>
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<tr>
<td>e. What is known about genetic susceptibility in recurrent preschool wheeze?</td>
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<td>f. What is the evidence for treatments for recurrent preschool wheezing being determined by and impacting pathophysiology and mechanisms?</td>
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<td>c. Which strategies should clinicians use to highlight need for further investigation and referral from primary care or general paediatrician – to secondary and tertiary care?</td>
</tr>
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</table>
### Table 2. Summary of studies investigating risk factors for preschool wheezing

<table>
<thead>
<tr>
<th>Categories</th>
<th>Risk factors</th>
<th>Associations with recurrent wheeze incidence or severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral</td>
<td>Maternal smoking during pregnancy</td>
<td>Maternal smoking during pregnancy is associated with increased odds of recurrent wheezing up to age 3 years (adjusted OR: 1.39 to 3.8; p-values&lt;0.05) [186-189] with significant interaction with premature birth [186, 188]</td>
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<td></td>
<td>Maternal passive smoking during pregnancy</td>
<td>Maternal passive smoking during pregnancy is associated with increased odds of recurrent wheezing incidence up to age 3 years (adjusted OR: 1.29 to 3.8; p-values&lt;0.05) [41, 190]</td>
</tr>
<tr>
<td></td>
<td>Maternal vitamin D status during pregnancy</td>
<td>Low vitamin D levels during pregnancy are borderline associated with reduced odds of recurrent wheezing during the first three years of life (adjusted OR: 0.66 to 0.77; p-values&gt;0.05) [191, 192] In addition, supplementation with vitamin D during pregnancy is not associated with a significantly reduced odds of recurrent wheezing [42, 193, 194]</td>
</tr>
<tr>
<td></td>
<td>Maternal vitamin E intake during pregnancy</td>
<td>Maternal intake of vitamin E during pregnancy is associated with reduced odds of recurrent wheezing during the second year of life (OR: 0.67; p-value&lt;0.01) [195]</td>
</tr>
<tr>
<td></td>
<td>Maternal psychological stress and depression</td>
<td>Prenatal maternal psychological stress is associated with increased odds of recurrent wheezing during the first three years of life (adjusted OR: 1.56 to 1.87; p-values&lt;0.05) [196, 197]</td>
</tr>
<tr>
<td>Demographic</td>
<td>Male gender</td>
<td>The male gender is associated with increased odds of recurrent wheezing during the first three years of life (adjusted OR: 2.9 to 3.2; p-values&lt;0.05) [198-200]</td>
</tr>
<tr>
<td></td>
<td>Race and ethnicity</td>
<td>Maternal and children of black race are at higher risk for recurrent wheezing during the first three years of life (adjusted HR: 1.2 to 2.9; p-values&lt;0.05) [201, 202]. Children of Hispanic and African American ethnicities have a significantly higher risk for recurrent wheezing development in comparison to other ethnicities [43].</td>
</tr>
<tr>
<td></td>
<td>Socioeconomic factors</td>
<td>Children at a low socioeconomic status, as defined by neighbourhood-level socioeconomic indicators (US census tract) are at a higher risk for recurrent wheezing within the first three years of life (adjusted HR: 1.47 to 2.9; p-values&lt;0.05) [43, 203]</td>
</tr>
<tr>
<td><strong>Environmental</strong></td>
<td><strong>Viruses/bacteria</strong></td>
<td>Severe rhinovirus-induced lower respiratory tract infections in infancy (including severe bronchiolitis) are associated with increased risk of recurrent wheezing during the first three years of life (adjusted OR: 1.67 to 3.5, all p-values&lt;0.05) [76, 204-206]. Respiratory syncytial virus and <em>Staphylococcus aureus</em> or <em>Klebsiella pneumoniae</em> combined infection is associated with an increased risk of recurrent wheezing during the first three years of life [207, 208].</td>
</tr>
<tr>
<td><strong>Allergens</strong></td>
<td>First-year exposure to cockroach, mouse, and cat allergens is negatively associated with recurrent wheezing incidence (OR: 0.60 to 0.75, all p-values&lt;0.05) [208]. However, cumulative allergen exposure over the first 3 years is associated with allergic sensitization, and sensitization at age 3 years is related to recurrent wheezing [208].</td>
<td></td>
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<tr>
<td><strong>Air pollution exposure</strong></td>
<td>Children exposed to high levels of air pollutants between birth and hospitalization with severe bronchiolitis or from birth to toddler years (adjusted OR: 1.5; p-value&lt;0.05) [209] have a higher risk of recurrent wheezing incidence during the first three years of life (adjusted HR: 1.59; p-value&lt;0.05) [210].</td>
<td></td>
</tr>
<tr>
<td><strong>Climatic variables</strong></td>
<td>Hospitalization with severe wheezing illnesses is more frequent during winter periods (i.e., low temperatures) [44] and high air pollutant levels may interact with this association [211].</td>
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<tr>
<td><strong>Exposure to residential greenness</strong></td>
<td>Residential proximity to green spaces or exposure since birth to increased residential greenness [212] is associated with a decreased risk of recurrent wheezing incidence during the first three years of life [213].</td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Summary of studies investigating biomarkers for preschool wheezing

<table>
<thead>
<tr>
<th>Sample source</th>
<th>Biomarkers</th>
<th>Prediction of recurrent wheeze incidence or severity</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Peripheral blood</em></td>
<td>Peripheral blood eosinophils</td>
<td>Peripheral blood eosinophilia (≥400/mm3) consists of a dimension (multiple component factorial analysis with serum IgE levels as another factor) identified as being associated with persistent wheezing at age 6 years (lambda=0.15),[214] and consists of one item at the Asthma Predictive Index (API). [215]                                                                aled by an improved response to the initiation of daily inhaled corticosteroids in exploratory analyses. [216]</td>
</tr>
<tr>
<td></td>
<td>Sensitization to aeroallergens</td>
<td>The addition of a second biomarker of type 2 inflammation (peripheral blood IgE levels) improves exacerbation of preschool wheezing detection and is further associated with an improved response to the initiation of daily inhaled corticosteroids in exploratory analyses. [216]</td>
</tr>
<tr>
<td></td>
<td>Periostin</td>
<td>Rhinovirus C infection with IgE sensitization is associated with significantly higher risks of recurrent wheezing with subsequent development of asthma at age 4 years (HR, 4.06; 95% CI, 1.17-14.1). [76]</td>
</tr>
<tr>
<td></td>
<td>Vitamin D</td>
<td>Children with recurrent episodes of preschool wheezing group (n = 80) have a greater median serum periostin level (1,122.32 pg/mL [&lt;10-6,978.93]) than that of the healthy control group (n = 40) (&lt;10 pg/mL [&lt;10-2,116.69]), p-value = 0.006. [217]</td>
</tr>
<tr>
<td></td>
<td>Eosinophilic cationic protein (ECP)</td>
<td>Mean 25OHD levels are lower in patients with recurrent wheezing than in healthy controls (r: -0.238; p: 0.012). The duration of illness and the number of wheezing episodes are correlated with vitamin D levels. [218]</td>
</tr>
<tr>
<td>Exhaled breath</td>
<td>FeNO</td>
<td>Elevated serum ECP levels have been associated with recurrent wheezing in 4- to 6-year-old children (OR: 3.2, p-value&lt;0.05). [219]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FeNO levels above 15 ppb are predictive of preschool wheezing of reduced control (positive predictive value = 65%, negative predictive value = 90%). [220]</td>
</tr>
</tbody>
</table>
Exhaled breath condensate (EBC)

Volatile organic compounds (VOCs)

Per 5 ppb FeNO increase, the odds ratio (95% CI) for asthma increases by 2.44 (1.61-3.70) without changing when adjusting for confounders. [79]

Children with frequent episodes of recurrent wheezing showed significantly higher median (interquartile range) fractional exhaled NO (FeNO) levels (11.7 [11.85]) compared to children with recurrent cough but no wheezing (6.5 [5.5]; p-value < 0.001) and 2 (6.4 [6.5]; p-value < 0.001). [80]

Preschool children with recurrent wheezing, with or without a positive allergy test, had significantly lower EBC pH compared to healthy controls (7.91 (6.95-8.37), p-value = 0.007 and 7.82 (7.32-8.39), p-value = 0.005, respectively). [85]

Exhaled VOCs could discriminate preschool children with recurrent wheezing of different severity. [86]

A prediction model combining VOCs, gene expression and API in preschool children with recurrent wheezing was predictive of asthma at age 6 years. [88]

**Table 4. Summation of genetic association studies in preschool wheezing**

<table>
<thead>
<tr>
<th>Locus</th>
<th>Biological pathways</th>
<th>Associations with recurrent wheeze/preschool asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>17q12-21</td>
<td>ORMDL3</td>
<td>Rhinovirus-induced wheezing illnesses age 0-3 yrs, and asthma by age 6 yrs in children with both rhinovirus-induced wheezing and 17q (rs7216389) risk variants. (M. Çalışkan et al. [221]) Recurrent wheeze hospitalizations age 2-6 yrs in GWAS (rs2305480, OR=2.3, p=1.3x10^{-48}), with the highest effect estimate in children with &gt;= 6 hospitalizations (OR=2.7, p=3.5x10^{-27}). (K. Bønnelykke et al. [222])</td>
</tr>
<tr>
<td>GSDMB</td>
<td>Regulation of sphingolipid biosynthesis and innate inflammatory responses</td>
<td></td>
</tr>
<tr>
<td>ORMDL3</td>
<td>GSDMB</td>
<td></td>
</tr>
<tr>
<td>Region</td>
<td>Gene(s)</td>
<td>Function</td>
</tr>
<tr>
<td>--------</td>
<td>---------</td>
<td>----------</td>
</tr>
<tr>
<td>9p24 IL33</td>
<td>Regulation of airway immune responses and allergic airway diseases</td>
<td>Recurrent asthma hospitalizations age 2-6 yrs in GWAS (rs928413, OR:1.5, p=4.2x10^{-13}) with the highest effect estimate in children with &gt;= 6 hospitalizations (OR:1.9, p=6.2x10^{-14}). (K. Bønnelykke et al. [222])</td>
</tr>
<tr>
<td>2q12 IL1R1 IL1RL1</td>
<td>Activation of cell effector mechanisms in the context of an inflammatory response</td>
<td>Recurrent asthma hospitalizations age 2-6 yrs in GWAS (rs1558664, OR:1.6, p=4.2x10^{-9}) with the highest effect estimate in children with &gt;= 6 hospitalizations (OR:2.2, p=3.2x10^{-8}). (K. Bønnelykke et al. [222])</td>
</tr>
<tr>
<td>5q31 RAD50 IL13</td>
<td></td>
<td>Recurrent asthma hospitalizations age 2-6 yrs in GWAS (rs6871536, OR:1.4, p=1.8x10^{-8}) with highest effect estimate in children with &gt;= 6 hospitalizations. (OR:1.6, p=1.3x10^{-6}). (K. Bønnelykke et al. [222])</td>
</tr>
<tr>
<td>Chromosome</td>
<td>Gene</td>
<td>Function and Effect</td>
</tr>
<tr>
<td>------------</td>
<td>------</td>
<td>---------------------</td>
</tr>
<tr>
<td>7q22</td>
<td>CDHR3</td>
<td>Recurrent asthma hospitalizations age 2-6 yrs in GWAS (rs6967330, OR:1.5, p=1.4x10^{-8}) with highest effect estimate in children with = 6 hospitalizations (OR:1.6, p=1.6x10^{-8}). (K. Bønnelykke et al. [222]) Association of rs6967330 with any asthma hospitalization and asthma onset from the first 2 years of life. (A.U. Eliasen et al. [228]) Association of rs6967330 with Intermittent and persistent temporal wheeze phenotypes. (Haider S. et al. [47])</td>
</tr>
<tr>
<td>19q13.3</td>
<td>FUT2/MAMSTR</td>
<td>SNPs near FUT2/MAMSTR associated with asthma hospitalizations age 0-6 yrs in GWAS (rs281379, OR=1.2, p=2.6 × 10^{-9}). (T.S. Ahluwalia et al. [230])</td>
</tr>
<tr>
<td>1q32</td>
<td>IL10</td>
<td>IL10 deletion rs79309463 or the SNP rs3024498 (block 4) as a risk factor for wheeze (71% of patients at block 4 having the SNP, p=0.02). (D. Raedler et al.[231])</td>
</tr>
<tr>
<td>16p12.1</td>
<td>IL4RA/IL9R</td>
<td>VDR variant (rs2228570) associated with number of hospital admissions age 0-5 yrs with respiratory (p=0.011) and wheezing (p=0.021) illnesses. (K. Leiter et al.[233])</td>
</tr>
<tr>
<td>12q13.11</td>
<td>VDR</td>
<td>GSTPI variants associated with risk for recurrent wheezing (&lt;11 yrs) (OR: 2.59; p&lt;0.05). (J. Wu et al. [234])</td>
</tr>
<tr>
<td>4q23</td>
<td>GSTPI</td>
<td></td>
</tr>
</tbody>
</table>
Antioxidant defences in response to indoor and outdoor pollutants

**Gene-environment interaction**
Significant interaction between GSTP1 variants and maternal smoking on recurrent wheezing. (J. Wu et al. [234])

**4q31 TLR2**
Recognition of microbial components and activation of innate immune responses

**Gene-environment interaction**
No significant overall associations between SNPs in TLR2 and recurrent wheezing (<5 yrs), but the effect of day care attendance on recurrent wheezing differed among children with different TLR2 variants. (A. Custovic et al. [235])

**17p12 TNFRSF13B**
T cell-independent B cell antibody responses

**Gene-environment interaction**
TNFRSF13B rare variants associated with increased risk of wheezing at 2 and 4 years (OR=1.9 and OR=2.4, p<0.05). (M. Janzi et al. [236])

### Table 5. Summary of studies describing current treatments in preschool wheezing

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Treatment plan</th>
<th>Treatment outcomes (recurrent wheeze outcomes)</th>
</tr>
</thead>
</table>
| Short-acting inhaled β-2-agonists | **Salbutamol (200 mcg)** three times per day for four or six weeks via a Babyhaler and mask [237]  
Two doses of **nebulized salbutamol at a dose of 0.15 mg/kg** [238]  
A single **nebulized dose of salbutamol at 2.5 mg** [239]  
**Salbutamol (600 mcg)** by inhaler and spacer [240] | **Symptom scores**  
Improvement in symptom score (e.g., wheeze, accessory muscle score, and respiratory rate) but not associated with a reduction in admission rate [237, 241]  
**Oxygenation**  
No significant change in saturation between attendance in the emergency room and discharge or admission [241]  
**Lung function**  
No change in functional residual capacity following salbutamol inhalation with protection against metacholine challenge [237, 242]  
**Parent-reported response**  
Parents report no significant change in symptoms as perceived by them [243] |
| Long-acting beta 2 agonists | **Formoterol** 9 mcg via Turbohaler [244]  
**Salmeterol** a single dose of 25 and 100 mcg [245] | **Formoterol** offers sustained and stable bronchodilation for at least 8 hours [244]  
**Salmeterol** has a dose-dependent effect on methacholine-induced wheeze, and this is significantly different from placebo at 50 and 100 mcg [245] |
<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergics</td>
<td>Once-daily <strong>tiotropium bromide</strong> 5 mcg for 7 to 14 days during respiratory tract infections [246]</td>
<td>The proportion of episode-free days is higher in those receiving <strong>intermittent tiotropium bromide</strong> (median 97% [interquartile range, 93% to 99%]) than in those receiving intermittent <strong>fluticasone propionate</strong> (87% [78% to 93%], <em>p</em>-value = 0.002) [246]</td>
</tr>
</tbody>
</table>
| Inhaled corticosteroids | **Fluticasone propionate** at a dose of 100 mcg twice daily reduced every 3 months to the minimum [23]  
**Beclomethasone dipropionate** 200 mcg twice daily via a metered dose inhaler for 4 months [75]  
**Inhaled budesonide 0.5 mg** daily [247] | Treatment with **fluticasone propionate** does not impact on physician-diagnosed asthma or use of asthma medication, lung function, or airway reactivity (percentage change in FEV1, adjusted mean for placebo 5.5% [95% CI: -2.5 to 13.4]) vs for treatment 5.0% [-2.2 to 12.2], *p*=0.87) [23]  
**16 out of 30 children** receiving beclomethasone dipropionate presents with unplanned healthcare visits over 4 months of follow-up, whilst **15 out of 30 children** in the control group presented with unplanned healthcare visits over 4 months of follow-up [75]  
Statistically significant differences are observed in favour of **budesonide over montelukast** in the percentage of patients requiring oral steroids at 52 weeks (21.9% vs 37.1%; *p*-value = 0.022), the rate (number/patient/year) of additional courses of medication (1.35 vs 2.30; *p*-value = 0.003), the rate of additional oral steroid therapy (0.44 vs 0.88; *p*-value = 0.008), and caregivers’ ability to manage the patient’s symptoms (*p*-value =0.026) [247] |
| Montelukast | 7 days trial with **4 mg montelukast** [248] | During RTIs, budesonide and **7-days montelukast therapy** led to modest reductions in trouble breathing (38% [p-value = 0.003] and 37% [p = 0.003], respectively) and interference with activity scores (32% [p-value = 0.01] and 40% [p-value = 0.001], respectively) that were most evident in those with positive asthma predictive indices [248] The **intermittent treatment with montelukast** is associated with a non-significant reduction in specialist attendances and hospitalizations, duration of episode, and beta-agonist and prednisolone use, but with significantly less days off from school or childcare by 37% and parent time off from work by 33% (p-value < 0.0001 for both) [249, 250] |
| Macrolides | **3-day course of oral solution of azithromycin 10 mg/kg per day** for any episode with acute asthma symptoms lasting for more than 3 days [142] **5-day course of oral solution of azithromycin 10 mg/kg per day** following an emergency department presentation with wheezing [143] | Azithromycin causes a **significant shortening of the episode of 63-3% (95% CI 56-0-69-3; p-value<0.0001)**. The effect size increases with early initiation of treatment, showing a reduction in episode duration of 83% if treatment is initiated before day 6 of the episode compared with 36% if initiated on or after day 6 (p-value<0.0001) [142] Azithromycin **neither reduces duration of respiratory symptoms nor time to respiratory exacerbation** in the following six months after treatment among wheezing preschool children presenting to an emergency department. Participants who received azithromycin had a 0.91 hazard ratio for time to six-month exacerbation compared to placebo (95% CI 0.61, 1.36, p = 0.65) [143] |
| Bacterial lysates | **OM-85 BV one capsule per day for 10 days each month for 3 consecutive months in total** [251] **Sublingual active treatment with MV130 once daily for 6 consecutive months** [151] | **Subjects given OM-85 BV** had a lower rate of wheezing attacks. The cumulative difference in wheezing attacks between the 2 groups was 2.18 wheezing attacks per patient in 12 months; there was a 37.9% reduction in the group given OM-85 BV compared with the group given placebo (p-value<0.001) [251] **Sublingual active treatment with MV130** once daily for 6 consecutive months is associated with a reduction of 40% in the number of wheeze attacks in the treatment vs the placebo group (p-value<0.001) [151] |

**Table 6.** Summary of studies describing impact of treatments in preschool wheezing on symptom score, biomarkers, and lung function
<table>
<thead>
<tr>
<th>Type of treatment</th>
<th>Treatment plan</th>
<th>Impact of treatment on outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Corticosteroids</strong></td>
<td><strong>Ciclesonide</strong> 40, 80, 160 μg once daily for 24 weeks [252]</td>
<td><strong>Symptom score</strong>&lt;br&gt;No effects of ciclesonide on symptom scores and rescue medication use were found. <strong>Lung function</strong>&lt;br&gt;Improvements in FEV1 and FEF(25-75) (measured in 284 4-6-year-old children) were larger in the ciclesonide than in the placebo group (p-value &lt; 0.05).</td>
</tr>
<tr>
<td><strong>Fluticasone propionate</strong> 75 μg per day, beginning at the onset of an upper respiratory tract infection and continuing for a maximum of 10 days [253-255]</td>
<td><strong>Symptom score</strong>&lt;br&gt;No significant differences between those treated and non-treated in symptom <strong>Biomarkers</strong>&lt;br&gt;No significant differences between those treated and non-treated in biomarkers, such as scores in basal cortisol level, bone mineral density <strong>Lung function</strong>&lt;br&gt;No significant differences in lung function parameters were noted between treated and non-treated groups</td>
<td></td>
</tr>
<tr>
<td><strong>Fluticasone propionate</strong> (two inhalations, 44 μg each, twice daily)&lt;br&gt;<strong>As-needed inhaled corticosteroid</strong> treatment co-administered with albuterol sulfate, two inhalations, 90 μg each for a <strong>16-week treatment</strong> [140, 256]</td>
<td><strong>Symptom score</strong>&lt;br&gt;Daily inhaled corticosteroid treatment was associated with more asthma control days and fewer exacerbations compared to the other treatments (i.e., improved symptom score) [140, 256] <strong>Lung function</strong>&lt;br&gt;There were no significant changes in bronchodilation test (median −21% versus −21% versus −16%, p=0.12) or baseline lung function defined as resistance at 5 Hz (median 0.06sd versus −0.55sd versus −0.69sd, p=0.054)[256]</td>
<td></td>
</tr>
<tr>
<td><strong>Budesonide</strong> 0.5 mg once daily for 12 weeks [257]</td>
<td><strong>Symptom score</strong>&lt;br&gt;Asthma control days increased significantly in the budesonide treatment group (p-value &lt; 0.05) over the 12-week study period. <strong>Biomarkers</strong>&lt;br&gt;There was no significant change in serum eosinophil-derived neurotoxin in the budesonide treatment group (p-value &lt; 0.05).</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Symptom score</td>
<td>Biomarkers</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Beclomethasone</strong> 200 μg daily for eight weeks in 175 children (2-4 years old) with recurrent wheeze [258, 259]</td>
<td>Symptoms slightly improved to those who received beclomethasone and had atopic profile</td>
<td>No significant differences between those treated and non-treated in biomarkers</td>
</tr>
<tr>
<td><strong>Nebulized flunisolide</strong> 40 mcg/kg twice daily for 7 days and then 20 mcg/kg twice daily for 14 days, or with nebulized budesonide 0.5 mg twice daily for 7 days, then 0.25 mg twice daily for 15 days [260]</td>
<td>Symptom scores decreased in both groups; however, the decrease was greater in patients treated with nebulized flunisolide (p&lt; 0.05)</td>
<td>No significant differences in FeNO were noted between treated and non-treated groups</td>
</tr>
<tr>
<td><strong>Corticosteroids with long-acting bronchodilators</strong></td>
<td>Symptom score No treatment differences were found concerning respiratory symptoms or median rescue use.</td>
<td>No significant differences were found concerning respiratory symptoms or median rescue use.</td>
</tr>
<tr>
<td>Inhaled salmeterol and fluticasone propionate combination, 50/100 μg twice daily, with fluticasone propionate, 100 μg twice daily, or salmeterol, 50 μg twice daily for 8 weeks [89]</td>
<td></td>
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</tr>
</tbody>
</table>
| Montelukast | **Montelukast** once daily intermittently (i.e., after each wheezing episode for 12 weeks) [249]  
*Montelukast* 4 mg or placebo | **Symptom score**  
No differences on symptoms scores were noted between those who were treated and those who were not treated [249, 261]  
**Lung function**  
Significant improvements in mean+/SD FEV0.5 (189.0+/−37.8 and 214.4+/−44.9 mL before and after treatment, respectively), FeNO (29.8+/−10.0 and 19.0+/−8.5 ppb) were noted following treatment with montelukast [261] |
|---|---|---|
| Azithromycin | **Azithromycin** 10 mg/kg once daily for 3 days at the beginning of the episode [262] | **Symptom score**  
**Azithromycin** treatment reduced the episode duration by 43% (95% CI, 15.9–61.6%; p-value = 0.005). |
Table 7. Summary of studies describing characteristics of patients with preschool wheezing who respond to inhaled corticosteroid (ICS) treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Age group</th>
<th>Definition of preschool wheeze</th>
<th>Randomized controlled trial or cohort study</th>
<th>Definition of intervention vs control arms</th>
<th>Characteristics of ICS non-responders</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Saglani S. et al. [75] | 1-5 yo    | Moderate to severe wheeze (two short courses of oral steroids for an acute wheeze attack in the last 6 months) | Randomized controlled trial                 | Intervention: Beclomethasone dipropionate 200 mcg twice daily via a metered dose inhaler for 4 months and salbutamol inhaler as required +/- antibiotics  
Control: Plan followed by their pediatrician +/- antibiotics | Children who had unplanned healthcare visits did not differ significantly from children who did not have unplanned healthcare visits in regard to atopic status and eosinophil count  
(p>0.05) | 67% of children were prescribed ICS in each group  
16 out of 30 children in the intervention group presented with unplanned healthcare visits over 4 months of follow-up  
15 out of 30 children in the control group presented with unplanned healthcare visits over 4 months of follow-up |
| Teague WG. et al. [263] | Under 6 yo | Persistent wheeze refractory to ICS                                | Cohort study                                | N/A                                       | All recruited patients are non-responders to ICS  
Variables used at clustering are serum IgE levels, peripheral blood eosinophilia, BAL respiratory virus loads, BAL cytology, BAL lipid-laden macrophages | 4 clusters were identified based on the most prevalent variables:  
airway malacia, gastroesophageal reflux, indolent human rhinovirus bronchoalveolitis, and type-2 high inflammation |


<table>
<thead>
<tr>
<th>Study</th>
<th>Age Range</th>
<th>Study Population</th>
<th>Study Design</th>
<th>Control Group</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guiddir T. et al. [120]</td>
<td>Under 6 yo</td>
<td>Children presenting at ED with recurrent wheezing episodes</td>
<td>Cohort study</td>
<td>N/A</td>
<td>Variables identified at a higher percentage of children with recurrent wheeze refractory to inhaled corticosteroids treatment included allergic rhinitis, atopic dermatitis, food allergies, blood eosinophil count, BAL eosinophils</td>
</tr>
<tr>
<td>Fitzpatrick A.M. et al. [140]</td>
<td>Under 6 yo</td>
<td>Children under 6 yo who required daily controller treatment</td>
<td>Randomized controlled trial</td>
<td>Daily inhaled corticosteroids vs as needed inhaled corticosteroids vs daily montelukast only</td>
<td>A significantly higher number of children with aeroallergen sensitization and blood eosinophils ≥300/μL responded better to inhaled corticosteroids in comparison to other children</td>
</tr>
<tr>
<td>Szefer S.J. et al. [247]</td>
<td>2-4 yo</td>
<td>Children with preschool asthma</td>
<td>Randomized controlled trial</td>
<td>Daily inhaled budesonide vs daily inhaled montelukast</td>
<td>Race/ethnicity, the ability of caregivers to administer inhaled budesonide (proxy for caregiver education and socioeconomic status)</td>
</tr>
<tr>
<td>Papi A. et al. [264]</td>
<td>1-4 yo</td>
<td>Children with frequent wheezing (i.e., at least 3 episodes of wheezing over the previous 6 months)</td>
<td>Randomized controlled trial</td>
<td>400 μg inhaled corticosteroids vs 800 μg inhaled corticosteroids vs no treatment</td>
<td>Variables such as gender, having already risk factors for asthma, morning cortisol levels were investigated in the non-responders</td>
</tr>
<tr>
<td>Campusano L. et al., [265]</td>
<td>Under 2 yo</td>
<td>Children with recurrent wheezing (i.e., more than 3)</td>
<td>Randomized controlled trial</td>
<td>Atopics (eosinophils in peripheral blood more than 4%) and non-atopics</td>
<td>Variables such as paternal and grand paternal asthma, rhinitis, and eczema were investigated in non-responders to inhaled corticosteroids</td>
</tr>
</tbody>
</table>

108 children with uncontrolled recurrent wheezing despite high-dose ICS (76%, p < 0.001) had more allergic rhinitis, atopic dermatitis, and food allergies (82%, 40%, 31%, p < 0.001, respectively)

170 out of 249 children with aeroallergen sensitization and blood eosinophils ≥300/μL presented no exacerbations at follow-up when treated with inhaled corticosteroids

No significant difference in preschool asthma control between the two treatment arms (p>0.05)

Regular inhaled corticosteroids were the most effective treatment in preschool children with asthma in regard to the number of exacerbations.

Regular inhaled budesonide therapy decreased the episodes of wheezing in preschool children with recurrent wheezing.
| episodes of wheezing during the last year | (eosinophils in peripheral blood less than 4%) treated with inhaled budesonide for 3 months | corticosteroids too but there was no significant difference | recurrent wheezing, independently of atopy |
Table 8. Priorities suggested by Patient and Public Involvement colleagues

<table>
<thead>
<tr>
<th>Theme</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis, treatment, and prognosis</strong></td>
<td>While parents/carers of children with preschool wheezing understood and appreciated the difficulty of making a precise diagnosis, current uncertainties surrounding the diagnosis of preschool wheezing left parents ‘in limbo’ and unclear how to manage their child’s symptoms.</td>
</tr>
<tr>
<td><strong>Information</strong></td>
<td>Key areas where more information is needed from healthcare professionals are long-term prognosis and day-to-day management. Online information can be “alarming”.</td>
</tr>
<tr>
<td><strong>Action plans</strong></td>
<td>Parents/carers need clarity on how to recognize symptoms and how and when to administer emergency treatment (including when to seek help in an attack of wheezing).</td>
</tr>
<tr>
<td><strong>Proactive support</strong></td>
<td>Professional support for carers was helpful but needed to be consistent and accessible.</td>
</tr>
<tr>
<td><strong>Research gaps</strong></td>
<td>In addition to the above (long-term prognosis, clarity on day-to-day management), the parents/carers identified important knowledge gaps related to understanding the impact on social life (for example, needing to plan holidays to be near medical services) and the effect on early years education</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention and findings</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Fremont et al. 2018 [181] Pilot crossover RCT</td>
<td>This study showed that delivery of inhaled treatment to young children can be “dramatically improved” by the use of animated cartoons played on the parent’s mobile phone clipped on their spacer just in front of the pMDI. The distraction of watching the animated cartoons increased the child’s cooperation up to 97% (55-100%; p=0.008).</td>
</tr>
<tr>
<td>Hussein-Rizvi et al. 2009.[182] RCT</td>
<td>Compared to a physician-delivered nebulisation, supervising (Latino/Black American) parents to deliver rescue medication via a pMDI+spacer during an ED visit improved parental skills of delivering inhaled therapy to their preschool child</td>
</tr>
<tr>
<td>Holzheimer et al. 1998. [184] 4-arm RCT</td>
<td>Carefully designed asthma education resources were useful for providing children as young as 2-years with information about asthma and its management. Both book and video formats increased knowledge and reduced healthcare contacts.</td>
</tr>
<tr>
<td>Ng et al. 2021.[183] RCT</td>
<td>A web-based education programme improved parent’s knowledge, attitude and practice, and reduced the number of unscheduled asthma visits and admissions but had no effect on asthma control.</td>
</tr>
<tr>
<td>Dramburg et al. 2021. [183] Feasibility study</td>
<td>Using a ‘wheeze detector’ to support parental confidence in monitoring the status of pre-school child was feasible and identified wheeze in 20% of measurements compared to 3% of events detected by parents</td>
</tr>
<tr>
<td>O’Leary et al. 2016. [185]</td>
<td>Children discharged from the ED with a diagnosis of “wheeze” were less likely to be given an action plan compared to children diagnosed with</td>
</tr>
<tr>
<td>Cross-sectional study</td>
<td>“asthma” (63% vs. 86%). This study describes adaptations to the electronic asthma action plan for wheezy pre-school children (e.g., removing reference to preventer ICS and oral steroid for attacks). Effectiveness of this plan has not yet been evaluated</td>
</tr>
</tbody>
</table>
References


149. Lu Y, Li Y, Xu L, Xia M, Cao L. Bacterial lysate increases the percentage of natural killer T cells in peripheral blood and alleviates asthma in children. *Pharmacology* 2015: 95(3-4): 139-144.


Corticosteroids.


Allergy interleukin


Immunol

influence

AG, Bisgaard H, Bønnelykke K. FUT2

Mors

Kr


Figure 1.

**Figure note:** Biological pathways in peripheral blood (left) and nasopharyngeal airway (right) linked to biomarkers (i.e., eosinophils, immunoglobulin E, type 2 cytokines and FeNO) in preschool wheezing

**Abbreviations:** IFN, interferon; IL, interleukin; IgE, immunoglobulin E; IRF, interferon regulatory factor; NF-κB, nuclear factor kappa beta; NO, nitric oxide; Th0, T helper 0; Th2, T helper 2; TLR, toll-like receptor

**Figure 2.** Future directions for Aim 1

**Figure 3.** Future directions for Aim 2

**Figure 4.** Future directions for Aim 3

**Figure 5.** Summary statements