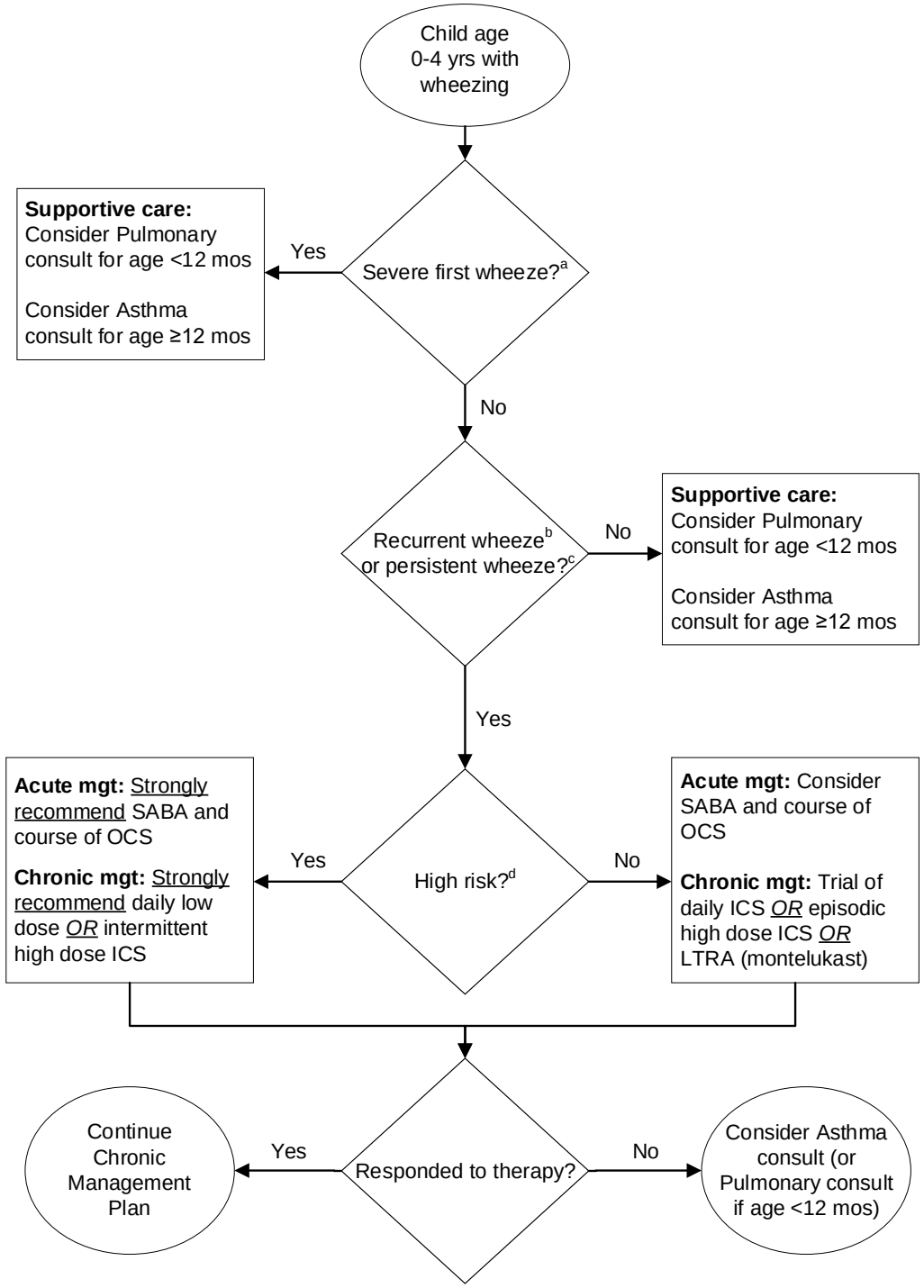
Evidence-Based Care Guideline
Publication Date: January 24, 2024

Management of Preschool Wheezing – Severe First Episode or Recurrent Wheezing

Algorithm for 0–4-year-old child with recurrent wheezing *(or a severe first episode of wheezing)*



Target Population

Inclusion Criteria

Children ages 0 – 4 years who have had within the past year:

- *3 or more* (≥ 3) wheezing episodes lasting longer than 24 hours,
- ≥ 1 episode of wheezing requiring admission to the ICU, or
- ≥ 2 admissions for wheezing.

Exclusion Criteria

Children 0 - 4 years of age with other lung disease including, but not limited to: cystic fibrosis, bronchiolitis obliterans, or interstitial lung disease.

Children with other chronic disease such as congenital cardiac disease or airway abnormalities.

Children ≥ 5 years old.

Abbreviations

SABA:	short–acting beta–agonists
OCS:	oral corticosteroids
ICS:	inhaled corticosteroids
LTRA:	leukotriene receptor antagonist
yrs:	years
mos:	months
mgt:	management
mAPI:	Modified Asthma Predictive Index
PARS:	Pediatric Asthma Risk Score

Definitions

Guilbert et al. 2006 [2a], Expert Panel 2007 [5a]

[a] *Severe first wheeze:* patient requires PICU admission or continuous albuterol
[b] *Recurrent wheeze:* > 3 episodes of wheezing in past year
[c] *Persistent wheeze:* Wheeze, cough or breathlessness with activity or sleep occurring > 2 days per week or > 2 nights per month
[d] *High risk:* +mAPI, *OR* high-risk PARS score, *OR* > 1+ specific IgE to aeroallergen or skin prick test, *OR* serum absolute eosinophils > 300

Evidence-Based Care Recommendations

Preschool Children with First Episode of Wheezing

1. ***It is recommended that clinicians provide supportive care to children ages 0 to 4 years with first episode of wheezing*** *(Local Consensus 2023 [5])*. *(Evidence–Consensus)*

Recommendation Strength ***Consensus***

2. ***It is recommended that clinicians consider referring children ages 0 to 4 years for either a Pulmonary Consult*** *(<12 months of age)* ***or an Asthma Consult*** *(≥12 months of age)* ***for the following reasons:***
   - ***does not improve as expected with supportive care***
   - ***has multiple risk factors***
   - ***presents with severe first episode of wheezing*** *(requiring PICU admission and/or continuous albuterol)*.

   (Local Consensus 2023 [5]) *(Evidence–Consensus)*

Recommendation Strength ***Consensus***

Note: Patients less than 12 months of age are at higher risk of anatomic airway abnormalities; thus, consultation with a pediatric subspecialist with expertise in preschool wheezing, lung disease and airway abnormalities, such as a pediatric pulmonologist, is recommended for an infant with first time wheezing severe enough to require the ICU or continuous albuterol *(Bacharier et al. 2009 [2a], Local Consensus 2023 [5])*.

Identification of the Child with Recurrent Wheezing at Risk for Asthma

3. ***It is strongly recommended that clinicians use a validated risk score to guide management of recurrent wheezing in preschool children*** *(Cloutier et al. 2020 [5a], Guilbert et al. 2004 [5a], Guilbert et al. 2006 [2a], Expert Panel Report-3 2007 [5a], GINA 2023 [5a], Biagini Myers et al. 2018 [4a], Smit et al. 2015 [1a], Castro-Rodriquez 2019 [5a], Bacharier et al. 2009 [2a])*.
   (Appendix and Evidence Synthesis)

Recommendation Strength ***Strong***

Note 1: Several scores have been developed for preschool age children with at least one episode of wheezing to predict risk of asthma symptoms at 6–12 years *(Cloutier et al. 2020 [5a], Guilbert et al. 2004 [5a], Guilbert et al. 2006 [2a], Expert Panel Report-3 2007 [5a], GINA 2023 [5a], Biagini Myers et al. 2018 [4a], Smit et al. 2015 [1a], Castro-Rodriquez 2019 [5a], Bacharier et al. 2009 [2a], Local Consensus 2023 [5a])*.

Note 2: Children with positive or high risk scores have an atopic phenotype, are at increased risk of persistent asthma symptoms by the time they reach school age, and are likely to respond well to inhaled corticosteroids *(Bacharier et al. 2009 [2a], Local Consensus 2023 [5a])*.

Management of Wheezing

4. ***It is strongly recommended that preschoolers with an atopic phenotype*** *(positive mAPI, high risk PARS, evidence of aeroallergen sensitization and/or blood eosinophil levels of at least 300/μL)* **and** ***recurrent wheezing be started on a trial of daily low dose inhaled corticosteroids*** *(ICS)* ***as first line therapy*** *(Castro-Rodriguez et al. 2000 [2a], Guilbert et al. 2004 [5a], Castro-Rodriquez 2019 [5a])*. *(Evidence Synthesis)*

Recommendation Strength ***Strong***

Note 1: Daily ICS has been shown to be an effective therapy among preschoolers with a positive mAPI.

Note 2: Children with intermittent wheezing that is severe and have a positive mAPI have been shown to benefit from treatment with *intermittent high dose* ICS *(Fitzpatrick et al. 2016 [2a])* started at the first sign of symptoms.

Note 3: Use of ICS has been shown to reduce exacerbations in children with a positive mAPI, allergic sensitization or eosinophilia when used either daily at low dose or intermittently at high dose during respiratory tract infections *(Guilbert et al. 2004 [5a], Castro-Rodriguez et al. 2019 [5a], Bacharier et al. 2009 [2a], Fitzpatrick et al. 2016 [2a], Bacharier et al. 2008 [2a], Zeiger et al. 2001 [2a], Kaiser et al. 2016 [1a], Ducharme et al. 2009 [2b])*.

Note 4: Even among children with a positive mAPI, there is differential response to medications *(Castro-Rodriguez et al. 2019 [5a], Bacharier et al. 2009 [2a])*.

5. ***It is recommended that, for children with recurrent wheezing and a negative or low risk assessment score*** *(negative mAPI or low risk PARS)****, clinicians consider acute management of wheezing episodes with a short-acting beta-agonist and a course of oral corticosteroids*** *(Tal et al. 1990 [2b], Csonka et al. 2003 [2a], Jartti et al. 2015 [2b], Ducharme et al. 2016 [3a], Panickar et al. 2009 [2a], Foster et al. 2018 [2a], Zorc et al. 2018 [5a], Beigelman et al. 2016 [5a], Beigelman et al. 2013 [4a], Oommen et al. 2003 [2b])* (Evidence Synthesis)***.***

Recommendation Strength ***Moderate***

6. ***It is recommended that, for children with recurrent wheezing and low risk assessment score*** *(low risk PARS and positive mAPI)****, clinicians consider chronic management of wheezing episodes with one of three approaches for:***
   - **daily low dose ICS,**
   - **intermittent high dose ICS given in response to symptoms, or**
   - **daily LTRA**

   (McKean and Ducharme 2000 [1a], Fitzpatrick et al. 2016 [2a], GINA 2023 [5a], Cloutier et al. 2007 [5a]) (Evidence Synthesis)***.***

   Note 1: Any of the three strategies—daily low dose ICS, intermittent, symptom driven high dose ICS, or daily LTRA—could be considered for long term management of the nonatopic preschool child with recurrent wheezing *(Local Consensus 2023 [5])*.

   Note 2: In clinical studies**,** children with low risk of developing asthma have responded well to each of the three strategies, and there were no factors identified to predict the best therapy for any child *(Local Consensus 2023 [5])*.

   Note 3: The *Asthma Shared Decision Making Tool for Families* can guide clinicians in decision making for the best strategy/therapy for management of chronic wheezing, taking into consideration the provider and/or patient preferences *(Local Consensus 2023 [5])*.

Recommendation Strength ***Moderate***

7. ***It is recommended that clinicians request an Asthma Consult*** *(≥12 months of age)* ***or Pediatric Pulmonary Consult*** *(<12 months of age)* ***for children with poor response to therapy, whether atopic or nonatopic*** *(GINA 2023 [5a], Local Consensus 2023 [5])****.*** *(Evidence–Consensus)*

Recommendation Strength ***Consensus***

Background

Most children have bronchiolitis in the first year of life given the exposure to daycare and siblings. However, not all children with wheezing early in life will continue to have recurrent or persistent symptoms. A significant proportion of wheezing in this age group is virally induced regardless of whether the child has asthma. Some viral infections such as rhinovirus and respiratory syncytial virus are associated with recurrent wheezing. Determining when preschool wheezing represents clinical presentation of asthma can be difficult. Management of recurrent wheezing in preschool children can be guided by assessment of a child's risk of developing asthma or having persistent asthma symptoms by the age of 6 years old.

In general, a child is more likely to have or develop asthma if:

a. Wheezing occurs in response to triggers other than respiratory tract infection (e.g. exercise, laughing, or crying, tobacco smoke exposure).
b. There is a family history of asthma or atopy (allergic rhinitis, eczema, allergic sensitization) in a first degree relative.
c. Symptoms improve with 2-3 months of controller therapy.

Other considerations may include:

- Asthma in the preschool age group consists of heterogeneous phenotypes, which may exhibit differential responses to treatment approaches.
- Morbidity is high as health care utilization for asthma during childhood is greatest among the 0-4 year old group *(Akinbami et al. 2009 [5a])*.
- Children 1 year of age or older admitted to CCHMC with history of multiple wheezing episodes are often discharged without treatment. This represents an opportunity to improve care of these children and prevent readmission.
- There is recent evidence to guide treatment of preschool-aged children with recurrent wheezing.

Clinical Question

In children ages 0 to 4 years old with recurrent wheezing or a severe first episode of wheezing,

- What are best practices for conducting an asthma risk assessment to guide management decisions?
- What are effective first line therapies for management of chronic wheezing based on risk assessment?

Target Users for the Recommendations

Inpatient providers who care for children with preschool wheezing *(Hospital Medicine, Pulmonary, Pediatric Intensive Care Unit),* Outpatient providers who care for preschool children with wheezing *(General Pediatrics, Pulmonary, Allergy, Emergency Department),* Primary Care Providers, Residents, Community Physicians, Advanced Practice Clinicians, Patient Care Staff

Evidence Syntheses

Consensus for all recommendations was achieved through the institutional standardization of asthma committee with representation from residents, nurses, respiratory therapy, home care, hospital medicine, PICU, ED, pulmonary, allergy, and general pediatrics. Recommendations/Documents were shared with members of the committee. Comments were obtained during meetings and via email. Consensus was obtained following review of all comments.

Preschool Children with First Episode of Wheezing: *Care Recommendations 1 & 2*

Although this document is focused on management of the child with recurrent wheezing, special mention is required for a preschool child whose first episode of wheezing is severe, particularly when severe enough to require admission to the pediatric intensive care unit or continuous albuterol *(Local Consensus 2023 [5])*. Evidence from the NAEPP *(Cloutier et al. 2020 [5a])* and GINA guidelines *(GINA 2023 [5a])* recommend that children with a history of recurrent wheezing particularly those with severe episodes should be considered for treatment. Consensus for treatment of children presenting with a first-time episode of severe wheezing was achieved through the standardization of asthma committee.

Identification of the Child at Risk: *Care Recommendation 3*

Evidence supports management of recurrent wheezing in preschool children based on results of risk assessment using a validated risk score. These risk scores predict likelihood of continuing to have asthma symptoms at the age of 6–7 years old. Children with a positive or high risk score on either the mAPI or the PARS are considered to have an allergic (or atopic) phenotype and are at increased risk of having persistent asthma symptoms by the time they are school age. Additionally, they are likely to have a good response to therapy with ICS *(Cloutier et al. 2020 [5a], Guilbert et al. 2004 [5a], Castro-Rodriguez et al. 2019 [5a])*. However, it is important to note that even among children with a positive mAPI, there is a differential response to medications *(Castro-Rodriguez et al. 2019 [5a], Bacharier et al. 2009 [2a])*, which is discussed in more detail in the Appendix.

Management of Children with Positive Risk Assessment: *Care Recommendation 4* *(positive mAPI or high risk PARS)*

If a child has a positive mAPI *(see Appendix)*, the preferred initial treatment option is a daily inhaled corticosteroid (ICS), which has been shown to be an effective therapy especially among preschoolers in this group *(Castro-Rodriguez et al. 2000 [2a], Cloutier et al. 2020 [5a], Guilbert et al. 2004 [5a], Castro-Rodriguez et al. 2019 [5a])*. Furthermore, even children with intermittent wheezing that is severe and have a positive mAPI have been shown to benefit from treatment with intermittent high dose ICS *(Fitzpatrick et al. 2016 [2a])*. There is evidence supporting the use of ICS in children with an atopic phenotype and recurrent wheezing *(See Appendix)*.

Treatment of at risk children will beneficially result in reduced need for hospitalizations and oral steroids, with a small risk of height growth delay, if inhaled steroids are used.

Management of Children with Recurrent Wheezing and a Negative or Low Risk Assessment: *Care Recommendations 5 & 6 (negative mAPI or low risk PARS; positive mAPI and low risk PARS)*

For children without evidence or risk of atopy, viral lower respiratory tract illnesses (LRTI) can still result in significant wheezing. However, in very young children (< 12 months) and those with low risk scores, other causes of recurrent wheezing such as structural airway abnormalities, chronic aspiration or rare lung diseases should be considered. If these alternative etiologies are unlikely or have been excluded, treatment with a short-acting beta-agonist and a course of oral corticosteroids should be considered for acute management of wheezing episodes *(McKean et al. 2000 [1a], Cloutier et al. 2020 [5a], Tal et al. 1990 [2b], Csonka et al. 2003 [2a], Jartti et al. 2015 [2b], Ducharme et al. 2016 [3a], Panickar et al. 2009 [2a], Foster et al. 2018 [2a], Zorc et al. 2018 [5a], Beigelman et al. 2016 [5a])*. Atopy or high risk score is associated with response to ICS but in the INFANT trial, daily ICS was still the best therapy for some children who did not have risk of atopy or developing asthma.

There was a significant proportion of patients who responded equally well to daily low dose ICS, intermittent high dose ICS and LTRA as indicated by low exacerbation rates during treatment. Additionally, among those that did not respond to daily ICS, there were equal percentages who responded best to intermittent ICS or LTRA. No factors were identified that predicted the best therapy for these children.

Thus, any of the three strategies—daily low dose ICS, intermittent, symptom driven high dose ICS, or daily LTRA—could be considered for long term management of the nonatopic preschool child with recurrent wheezing. The decision regarding which therapy to trial should take into consideration provider and/or parent preferences.

Management of Children with a Poor Response to Therapy: *Care Recommendation 7*

For children with poor response to therapy, regardless of asthma risk, an Asthma Consult is recommended.
If the child is less than 12 months old and has a poor response to therapy, consultation with a pediatric pulmonologist is recommended, because of increased risk of structural airway abnormalities in this age range.

Dimensions for Judging the Strength of the Recommendations

Care Recommendation 1

1. Safety versus Harm	☒ Safety > Harm	☐ Balanced Safety & Harm	☐ Safety < Harm	
2. Clinically Effective / Benefits Patient	☒ Beneficial/Effective	☐ Neutral Effect or Benefit	☐ Ineffective/No Benefit	
3. Adherence *(Burden for staff/patient/family; Access to care)*	☒ Low Burden	☐ Moderate/Neutral Burden	☐ High Burden	
4. Cost *(Cost for organization and/or patient/family)*	☒ Cost–Effective	☐ Cost–Neutral	☐ Cost–Prohibitive	
5. Impact on quality of life, morbidity, or mortality	☒ Positive Impact	☐ Moderate/Neutral Impact	☐ Negative Impact	
6. Directness of Evidence	☐ Directly Related	☐ Somewhat Directly Related	☒ Indirectly Related	
7. Grade of the Body of Evidence	☐ High ⊕⊕⊕⊕	☐ Moderate ⊕⊕⊕◯	☐ Low ⊕⊕◯◯	☐ Very Low ⊕◯◯◯	☒ No BOE ◯◯◯◯
Overall Strength of the Recommendation:	☐ ***Strong***	☐ ***Moderate***	☐ ***Weak***	☒ ***Consensus***

Care Recommendation 2

1. Safety versus Harm	☒ Safety > Harm	☐ Balanced Safety & Harm	☐ Safety < Harm	
2. Clinically Effective / Benefits Patient	☒ Beneficial/Effective	☐ Neutral Effect or Benefit	☐ Ineffective/No Benefit	
3. Adherence *(Burden for staff/patient/family; Access to care)*	☒ Low Burden	☐ Moderate/Neutral Burden	☐ High Burden	
4. Cost *(Cost for organization and/or patient/family)*	☒ Cost–Effective	☐ Cost–Neutral	☐ Cost–Prohibitive	
5. Impact on quality of life, morbidity, or mortality	☒ Positive Impact	☐ Moderate/Neutral Impact	☐ Negative Impact	
6. Directness of Evidence	☐ Directly Related	☐ Somewhat Directly Related	☒ Indirectly Related	
7. Grade of the Body of Evidence	☐ High ⊕⊕⊕⊕	☐ Moderate ⊕⊕⊕◯	☐ Low ⊕⊕◯◯	☐ Very Low ⊕◯◯◯	☒ No BOE ◯◯◯◯
Overall Strength of the Recommendation:	☐ ***Strong***	☐ ***Moderate***	☐ ***Weak***	☒ ***Consensus***

Care Recommendation 3

1. Safety versus Harm	☒ Safety > Harm		☐ Balanced Safety & Harm		☐ Safety < Harm
2. Clinically Effective / Benefits Patient	☒ Beneficial/Effective		☐ Neutral Effect or Benefit		☐ Ineffective/No Benefit
3. Adherence *(Burden for staff/patient/family; Access to care)*	☒ Low Burden		☐ Moderate/Neutral Burden		☐ High Burden
4. Cost *(Cost for organization and/or patient/family)*	☒ Cost–Effective		☐ Cost–Neutral		☐ Cost–Prohibitive
5. Impact on quality of life, morbidity, or mortality	☒ Positive Impact		☐ Moderate/Neutral Impact		☐ Negative Impact
6. Directness of Evidence	☒ Directly Related		☐ Somewhat Directly Related		☐ Indirectly Related
7. Grade of the Body of Evidence	☒ High ⊕⊕⊕⊕	☐ Moderate ⊕⊕⊕◯	☐ Low ⊕⊕◯◯	☐ Very Low ⊕◯◯◯	☐ No BOE ◯◯◯◯
Overall Strength of the Recommendation:	☒ ***Strong***	☐ ***Moderate***	☐ ***Weak***	☐ ***Consensus***	

Care Recommendation 4

1. Safety versus Harm	☒ Safety > Harm		☐ Balanced Safety & Harm		☐ Safety < Harm
2. Clinically Effective / Benefits Patient	☒ Beneficial/Effective		☐ Neutral Effect or Benefit		☐ Ineffective/No Benefit
3. Adherence *(Burden for staff/patient/family; Access to care)*	☒ Low Burden		☐ Moderate/Neutral Burden		☐ High Burden
4. Cost *(Cost for organization and/or patient/family)*	☒ Cost–Effective		☐ Cost–Neutral		☐ Cost–Prohibitive
5. Impact on quality of life, morbidity, or mortality	☒ Positive Impact		☐ Moderate/Neutral Impact		☐ Negative Impact
6. Directness of Evidence	☒ Directly Related		☐ Somewhat Directly Related		☐ Indirectly Related
7. Grade of the Body of Evidence	☒ High ⊕⊕⊕⊕	☐ Moderate ⊕⊕⊕◯	☐ Low ⊕⊕◯◯	☐ Very Low ⊕◯◯◯	☐ No BOE ◯◯◯◯
Overall Strength of the Recommendation:	☒ ***Strong***	☐ ***Moderate***	☐ ***Weak***	☐ ***Consensus***	

Care Recommendation 5

1. Safety versus Harm	☒ Safety > Harm		☐ Balanced Safety & Harm		☐ Safety < Harm
2. Clinically Effective / Benefits Patient	☒ Beneficial/Effective		☐ Neutral Effect or Benefit		☐ Ineffective/No Benefit
3. Adherence *(Burden for staff/patient/family; Access to care)*	☒ Low Burden		☐ Moderate/Neutral Burden		☐ High Burden
4. Cost *(Cost for organization and/or patient/family)*	☒ Cost–Effective		☐ Cost–Neutral		☐ Cost–Prohibitive
5. Impact on quality of life, morbidity, or mortality	☒ Positive Impact		☐ Moderate/Neutral Impact		☐ Negative Impact
6. Directness of Evidence	☒ Directly Related		☐ Somewhat Directly Related		☐ Indirectly Related
7. Grade of the Body of Evidence	☐ High ⊕⊕⊕⊕	☒ Moderate ⊕⊕⊕◯	☐ Low ⊕⊕◯◯	☐ Very Low ⊕◯◯◯	☐ No BOE ◯◯◯◯
Overall Strength of the Recommendation:	☐ ***Strong***	☒ ***Moderate***	☐ ***Weak***	☐ ***Consensus***	

Care Recommendation 6

1. Safety versus Harm	☒ Safety > Harm		☐ Balanced Safety & Harm		☐ Safety < Harm
2. Clinically Effective / Benefits Patient	☒ Beneficial/Effective		☐ Neutral Effect or Benefit		☐ Ineffective/No Benefit
3. Adherence *(Burden for staff/patient/family; Access to care)*	☒ Low Burden		☐ Moderate/Neutral Burden		☐ High Burden
4. Cost *(Cost for organization and/or patient/family)*	☒ Cost–Effective		☐ Cost–Neutral		☐ Cost–Prohibitive
5. Impact on quality of life, morbidity, or mortality	☒ Positive Impact		☐ Moderate/Neutral Impact		☐ Negative Impact
6. Directness of Evidence	☒ Directly Related		☐ Somewhat Directly Related		☐ Indirectly Related
7. Grade of the Body of Evidence	☐ High ⊕⊕⊕⊕	☒ Moderate ⊕⊕⊕◯	☐ Low ⊕⊕◯◯	☐ Very Low ⊕◯◯◯	☐ No BOE ◯◯◯◯
Overall Strength of the Recommendation:	☐ ***Strong***	☒ ***Moderate***	☐ ***Weak***	☐ ***Consensus***	

Care Recommendation 7

1. Safety versus Harm	☒ Safety > Harm	☐ Balanced Safety & Harm	☐ Safety < Harm
2. Clinically Effective / Benefits Patient	☒ Beneficial/Effective	☐ Neutral Effect or Benefit	☐ Ineffective/No Benefit
3. Adherence *(Burden for staff/patient/family; Access to care)*	☒ Low Burden	☐ Moderate/Neutral Burden	☐ High Burden
4. Cost *(Cost for organization and/or patient/family)*	☒ Cost–Effective	☐ Cost–Neutral	☐ Cost–Prohibitive
5. Impact on quality of life, morbidity, or mortality	☒ Positive Impact	☐ Moderate/Neutral Impact	☐ Negative Impact
6. Directness of Evidence	☐ Directly Related	☐ Somewhat Directly Related	☒ Indirectly Related

7. Grade of the Body of Evidence	☐ High ⊕⊕⊕⊕	☐ Moderate ⊕⊕⊕◯	☐ Low ⊕⊕◯◯	☐ Very Low ⊕◯◯◯	☒ No BOE ◯◯◯◯
Overall Strength of the Recommendation:	☐ ***Strong***	☐ ***Moderate***	☐ ***Weak***	☒ ***Consensus***	

Implementation Plan

Outcome

Reduce recurrent healthcare utilization for preschool children at Cincinnati Children's Hospital (CCHMC) with recurrent wheezing-related ED visits and admissions

Outcome Measures

- Hospitalizations for children 0-4 years old with recurrent wheezing
- Emergency Department visits for recurrent wheezing in children 0-4 years old
- Reduction in need for oral steroids for severe wheezing exacerbations

Process Measures

- Use of preschool wheezing order set once developed
- Use of risk assessment tools (link to PARS website or .pdf of mAPI) to determine treatment regimen

Search Strategies & Results

Search Strategy

To select evidence for critical appraisal for this Evidence Summary, the databases below were searched using search terms, limits, filters, and date parameters to generate an unrefined, "combined evidence" database. This search strategy focused on answering the clinical questions addressed in this document and employing a combination of Boolean searching on human-indexed thesaurus terms (e.g., MeSH) as well as "natural language" searching on words in the title, abstract, and indexing terms.

Databases Searched	Search Terms		Limits, Filters, and Search Dates & Parameters
• MedLine • CINAHL • Cochrane Database for Systematic Reviews • Footnote Crawling, Reference List and/or Hand Searching	• Preschool • Wheezing • Recurrent wheezing • Persistent wheezing • Preschool wheezing management	• Asthma • Asthma risk • Asthma prediction • Risk factors for asthma • Childhood asthma • Sensitization	Date of Most Recent Search • 04/19/2022 Publication Dates Searched • Search dates not restricted Age Groups in Evidence • Pediatric Evidence Only English Language Other Criteria • *None*

Search Results

The searches *(electronic search engines, manual searches of citations/references)* for evidence identified 4,529 articles. 3,619 articles were discarded, as they were duplicates or not related to the clinical question of interest based on title and abstract review. The final 28 articles chosen for extensive and critical review are listed in the references below.

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Conflicts of Interest were declared for each team member and:

No financial or intellectual conflicts of interest were found.
Conflict of interest declaration information is maintained in Cincinnati Children's HRS/Huron COI system.

External Funding

No external funding was received for development of this guideline.
Recommendations were developed through hospital funding via salaries.

Evidence-Based Clinical Care Recommendation Development Process

Recommendation statements were developed in accordance with Cincinnati Children's Evidence-Based Care Guideline Development Process *(for more details, contact EBDMinfo@cchmc.org)*. The recommendations contained in this guideline were formulated by a multidisciplinary working group based on best-available and peer-reviewed evidence, patient and family values, clinical expertise, and stakeholder consensus. The team performed a systematic search and critical appraisal of the literature using the LEGEND Evidence Evaluation System *(see next section below)*. During formulation of these recommendations, the team members have remained cognizant of controversies and disagreements over the management of these patients. Controversial issues were resolved by stakeholder and team member consensus where possible *(using a pre-defined consensus process)* and, when not possible, were offered optional approaches to care in the form of information that includes best supporting evidence of efficacy for alternative choices.

LEGEND Evidence Evaluation System (Let Evidence Guide Every New Decision)

Evidence Levels of Individual Studies by Domain, Study Design, & Quality *(Link to Full Table)*

Individual studies are appraised for reliability, validity, and applicability, using standardized appraisal forms, to determine the Quality Level or Evidence Level (**a** vs **b**)†.

Quality Level	Definition
1**a**† or 1**b**†	Systematic review, meta-analysis, or meta-synthesis of multiple studies
2a or 2b	Best study design for domain
3a or 3b	Fair study design for domain
4a or 4b	Weak study design for domain
5a or 5b	General review, expert opinion, case report, consensus report, or guideline
5	Local Consensus

†***a*** *= good quality study OR* ***b*** *= lesser quality study*

Grade for the Body of Evidence *(Link to Full Table)*

The Body of Evidence *(BOE)* is evaluated for quantity, quality, and consistency to determine the grade of the BOE and what the impact of the BOE is on our confidence in the precision of the answer to the clinical question (and its associated recommendation statement).

Grade	Definition
High	Good quality, High-level studies with consistent results
Moderate	Good quality, Lower-level OR Lesser quality, Higher-level studies with consistent* results
Low	Good or lesser quality, Lower-level with results that may be inconsistent
Very Low	Few Good or Lesser quality, Lower-level studies that may have inconsistent results
Grade Not Assignable	Local Consensus

Dimensions for Judging the Strength of the Recommendation *(Link to Full Table)*

1. Safety versus Harm
2. Clinically Effective / Benefits Patient
3. Adherence
4. Cost
5. Impact of Quality of Life, Morbidity, or Mortality
6. Directness of the Evidence
7. Grade of the Body of Evidence

Language and Definitions for Recommendation Strength *(Link to Full Table)*

Language for Strength	Definition
It is strongly recommended that… It is strongly recommended that… not…	When the dimensions for judging the strength of the recommendation are applied *(including safety/harm, effectiveness/benefit, body of evidence, etc.)*, there is high support that benefits clearly outweigh risks and burdens. *(or visa-versa for negative recommendations)*
It is recommended that… It is recommended that… not…	When the dimensions for judging the strength of the evidence are applied, there is moderate support that benefits are closely balanced with risks and burdens.
It is suggested that… It is suggested that… not…	When the dimensions for judging the strength of the evidence are applied, there is weak support that benefits are closely balanced with risks and burdens.
There is insufficient evidence to make a recommendation…	

Review Process

All feedback received from internal and external reviewers was appropriately discussed and addressed by the development team.

Internal Review

This guideline has been reviewed against quality criteria by independent peer reviewers from Cincinnati Children's including, but not limited to, evidence methodologists, relevant subject matter experts, or other stakeholders who were not involved in the development process.

External Review

The guideline was also externally appraised by independent peer reviewers not involved in the development process using the **AGREE II instrument** *(Appraisal of Guidelines for REsearch and Evaluation II)*.

Revision Process

The guideline will be removed from the Cincinnati Children's website if content has not been revised within five years from the most recent publication date. A revision of the guideline may be initiated at any point within the five year period that evidence indicates a critical change is needed. Team members reconvene to explore the continued validity and need of the guideline.

Review History

Date	*Event*	*Outcome*
	Original Publication	New guideline developed and published

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For more information

About this guideline, its companion documents, or the Cincinnati Children's Evidence-Based Care Recommendation Development process, contact the Cincinnati Children's Evidence-Based Decision Making Team at EBDMinfo@cchmc.org.

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In lieu of an evidence table, please contact the Preschool Wheezing Guideline Development Team with any specific questions related to included studies.

Appendix: Identification of the Child at Risk

Several scores have been developed to predict risk of asthma symptoms at ≥ 6 years for children with at least one episode of wheezing in early childhood. Most of the risk factors included in these scores are easily determined from the patient history and physical exam. Two such scores are discussed below.

Modified Asthma Predictive Index (mAPI)

One of the risk scores that has been most widely studied is the asthma predictive index *(API)* Castro-Rodriguez et al. 2000 [2a] which has been modified to include allergic sensitization to foods and aeroallergens Guilbert et al. 2004 [2a] *(Table 1)*. If a child has a positive modified API *(mAPI)*, the preferred initial treatment option for recurrent wheezing is daily inhaled corticosteroid *(ICS)*, which has been shown to be an effective therapy in the preschool age group in general, but particularly among those with a positive mAPI Guilbert et al. 2006 [2a]. The mAPI has been adopted by the NAEPP 2007 Expert Panel Report 2007 [5a] and the API by both NAEPP and GINA GINA 2023 [5a] guidelines.

Table 1: Original and modified asthma predictive indexes

	Asthma predictive index (API)	Modified asthma predictive index (mAPI)
Positive index requirements: Wheezing PLUS at least 1 major or 2 minor criteria	Wheezing during first 3 years of life *Loose:* Any wheezing *Stringent:* early frequent wheezing	At least 4 wheezing episodes per year
Major criteria:	1. MD-diagnosed asthma in a parent 2. MD-diagnosed eczema	1. MD-diagnosed asthma in a parent 2. MD-diagnosed eczema 3. Allergic sensitization to ≥ one aeroallergen
Minor criteria:	1. MD-diagnosed allergic rhinitis 2. Wheezing apart from URI 3. Eosinophilia (≥4%)	1. Allergic sensitization to milk, eggs, or peanut 2. Wheezing apart from URI 3. Eosinophilia (≥4%)

The Pediatric Asthma Risk Score (PARS)

Demographic and clinical data from 762 children from a birth cohort enrolled in the Cincinnati Childhood Allergy and Air Pollution Study were used to identify factors that predicted asthma development *(Table 2)*. From these factors a Pediatric Asthma Risk Score *(PARS)* was created. PARS predicted asthma development for children in the Cincinnati Childhood Allergy and Air Pollution Study with a sensitivity of 0.68 and a specificity of 0.77. Variables in PARS that predicted asthma were similar to those in the mAPI and included parental asthma, eczema, wheezing apart from colds, early wheezing, sensitization to 2 or more food allergens and/or aeroallergens, and African American race. The PARS was then replicated in the Isle of Wight birth cohort with similar sensitivity and specificity as in the original population *(sensitivity = 0.67, specificity = 0.79)* Biagini Myers et al. 2018 [4a].

Table 2: Pediatric Asthma Risk Score

Pediatric Asthma Risk Score (PARS) Scoring Sheet

	Possible Scores		
	No	Yes	Child's Score
1. Parental Asthma	0	2	
2. Eczema before age 3 years	0	2	
3. Wheezing apart from colds	0	3	
4. Wheezing before age 3 years	0	3	
5. African-American Race	0	2	
6. SPT positive to ≥ 2 aero and/or food allergens	0	2	
Child's PARS (add lines 1-6 above):			

Patient Score Interpretation

Score	Risk of Asthma by age 7 years	Interpretation
0	3%	LOW RISK: Children with these scores have a 1 in 33 [score of 0] to a 1 in 9 [score of 4] risk of developing asthma by age 7 years
2	6%	
3	8%	
4	11%	
5	15%	MODERATE RISK: Children with these scores have a 1 in 7 risk [Score of 5] to a 1 in 3 [Score of 8] risk of developing asthma by age 7 years
6	19%	
7	25%	
8	32%	
9	40%	HIGH RISK: Children with these scores have a 2 in 5 [Score of 9] to a 4 in 5 [Score of 14] risk of developing asthma by age 7 years
10	49%	
11	58%	
12	66%	
14	79%	

A systematic review of 12 childhood asthma prediction tools was published in 2015 Smit et al. 2015 [1a]. Tools assessed children up to 4 years of age with either symptoms and/or high risk of asthma and predicted subsequent development of asthma at school-age. A more recent analysis of clinical prediction scores for asthma discussed the development, validation, impact and implementation of seven published prognostic scores for the occurrence of asthma Castro-Rodriguez et al. 2019 [5a]. There was variability among the paradigms of which factors were noted to predict asthma, and included demographic factors, respiratory symptoms, number of respiratory tract infections or wheezing episodes and hospitalizations, family history of allergy or asthma, other comorbid allergic conditions, eosinophilia, total IgE, specific IgE and allergen skin prick testing to both food and aeroallergens, FeNO levels, preterm or post term delivery.

Synopsis of Key Studies in Preschool Wheezing

a. The **Prevention of Early Asthma in Kids (PEAK) trial** enrolled 285 children 2-3 years of age with a positive mAPI Guilbert et al. 2004 [5a]. Those with persistent symptoms during a run-in period were excluded. Participants were randomized to active treatment with either inhaled low dose fluticasone propionate 88 mcg twice daily or placebo for 2 years. Monitoring of outcomes continued for an additional 12 months after discontinuing treatment. In this trial, daily ICS use was associated with a greater number of symptom-free days and fewer exacerbations during the 2 years of active therapy compared to placebo for children with increased

risk of developing asthma *(e.g. positive mAPI)*. Furthermore, in a post hoc subgroup analysis, ICS use in those with a positive mAPI was associated with more symptom-free days and fewer exacerbations if the participants were male, Caucasian, had an asthma-related emergency department *(ED)* visit or hospitalization within the past year, or had sensitization to an aeroallergen Bacharier et al. 2008 [2a]. Thus, even within the positive mAPI group, there is substantial heterogeneity in ICS treatment response.

b. The effect of daily low dose ICS was compared with intermittent high dose ICS therapy for preschool children with a severe intermittent disease pattern and positive mAPI in the **Maintenance and Intermittent Inhaled Corticosteroids in Wheezing Toddlers (MIST)** study Zeiger et al. 2011 [2a]. Episodic high dose ICS were started for 7 days at the earliest recognized onset of respiratory tract symptoms, prior to onset or progression of wheezing. The daily low dose ICS and episodic high dose ICS strategies were comparable with no significant differences in asthma exacerbations or other indicators of asthma activity, control, and growth. Overall corticosteroid exposure was lower in the episodic ICS group.

c. A 2016 meta-analysis of 5 studies and 422 participants found that episodic high-dose ICS was associated with a 35% decrease in wheezing exacerbations Kaiser et al. 2016 [1a]. The number needed to treat was 6 children to prevent 1 exacerbation. This episodic ICS strategy has also been shown to decrease the use of rescue oral corticosteroids *(OCS)* Ducharme et al. 2009 [2b], McKean et al. 2000 [1a]. Based on these findings, treatment for children with severe intermittent wheezing, particularly those with a positive mAPI, could be either preemptive high dose episodic ICS during respiratory episodes or daily low dose ICS.

d. The ***Individualized Therapy for Asthma in Toddlers (INFANT)*** study featured a crossover design. Children aged 12-59 months of age who were candidates for Step 2 *(i.e. daily controller)* therapy were enrolled to assess differential response to daily ICS, intermittent ICS whenever a short acting beta-agonist was used, and daily leukotriene receptor antagonist *(LTRA)* Bacharier et al. 2009 [2a]. All participants were treated with 16 weeks of each therapy in a randomized order. Asthma control was most likely to be best during the daily ICS treatment periods, and this was further increased in the patients with aeroallergen sensitization or blood eosinophil counts of at least 300/μL *(i.e. those with an atopic phenotype)*, again supporting daily ICS for management of preschool wheezing in children with a positive mAPI. Of note, 26% of the participants did not demonstrate a preference for any of the three therapies and were called non-differential responders. After incorporating this subgroup into the analysis, the probability of a best response to ICS was below 40% for the entire cohort, suggesting that there is a significant subgroup of patients for whom daily ICS is not the most likely to be effective, and comparable proportions of these patients responded best to either montelukast or intermittent ICS. While atopic markers predicted best response to daily low dose ICS, the investigators were unable to identify predictors of best response to LTRA or intermittent ICS.

For children with a positive mAPI and a severe intermittent pattern of wheezing, the use of episodic high dose ICS at the onset of respiratory tract symptoms is an acceptable alternative strategy which resulted in overall lower steroid exposure but no difference in growth or asthma outcomes compared to daily low dose ICS.

Asthma Shared Decision Making Tool for Families:

Management of Children with Recurrent Wheezing and Low Asthma Risk*

Treatment	Daily low dose ICS (Inhaled Corticosteroids)	Intermittent, symptom driven high dose ICS (Inhaled Corticosteroids)	Daily LTRA (Leukotriene Receptor Antagonist)
Medication Examples	Beclomethasone (Qvar) Budesonide (Pulmicort) Fluticasone (Flovent™) Mometasone (Asmanex™)	Beclomethasone (Qvar™) Budesonide (Pulmicort™) Fluticasone (Flovent™) Mometasone (Asmanex™)	**Montelukast (Singulair™)**
How the Medicine Works	▪ Most medication is taken through metered-dose inhaler (MDI) or nebulizer ▪ Reduces swelling which opens airways in the lungs allowing you to breathe better ▪ Maintains reduced swelling ▪ Take daily even when there are no symptoms	▪ Most medication is taken through metered-dose inhaler (MDI) however one is available through nebulizer ▪ Reduces swelling which opens airways in the lungs allowing you to breathe better ▪ Reduces swelling only while symptoms present ▪ Take only when symptoms are present	▪ Medication is a chewable tablet or packet of granules ▪ Reduces swelling which opens airways in the lungs allowing you to breathe better ▪ Not as effective as inhaled steroids ▪ Take daily even when there are no symptoms
Benefits	▪ Most effective therapy for preschoolers with high asthma risk ▪ May be an option for preschoolers with frequent or severe asthma symptoms ▪ More symptom-free days and fewer exacerbations ▪ Effective for some preschoolers who do not respond to other therapies	▪ Option other than daily inhaled steroids for preschoolers with increased asthma risk who have intermittent but severe asthma symptoms ▪ May be an option for preschoolers with less frequent asthma symptoms ▪ More symptom-free days and fewer exacerbations ▪ Effective for some preschoolers who do not respond to LRTA	▪ Option for some preschoolers with daily asthma symptoms who are at low risk for ongoing asthma symptoms as they get older ▪ More symptom-free days and fewer exacerbations
Potential Side Effects	▪ Hoarseness ▪ Oral thrush (risk is decreased when a spacer is used) ▪ Slowing of height growth (high doses only)	▪ Hoarseness ▪ Oral thrush (risk is decreased when a spacer is used) ▪ Slowing of height growth (high doses only)	▪ Headache ▪ Rash ▪ Mood swings ▪ Irritability

* Each of these three strategies has demonstrated effectiveness in children with recurrent wheezing who are at low risk of having continued asthma symptoms as they get older.

- The evidence does not support any one of the three as being best for children who do not have eosinophilia or allergic sensitization.
- No factors were identified which predicted the most effective therapy for any particular child with low asthma risk.
- For children with high asthma risk, the evidence supports the use of daily low dose inhaled steroids as the most effective therapy.