



Small Airway Disease in Pediatric Asthma: the Who, What, When, Where, Why, and How to Remediate. A Review and Commentary

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Abstract

Asthma affects all portions of the airways. Small airways, however, comprise a substantial component of the conducting lung air flow. In asthma, inflammatory processes can affect the whole respiratory tract, from central to peripheral/small airways. The emphasis in adult and pediatric respiratory disease clinics is to focus on large airway obstruction and reversibility. This information, although valuable, underemphasizes a large portion of the conduction airway of asthmatics. Standard descriptions of asthma management focus on a multiple medication approaches. We particularly focused on the management of asthma in the international guidelines for the Global Initiative for Asthma (GINA). Overall, however, minimal attention is placed on the small airway pool in asthma medical management. We took the opportunity to thoroughly review and present specific data from the adult asthma literature which supported the concept that small airway abnormalities may play a role in the pathogenesis and clinical expression of asthma. Based on the conclusions of the adult asthma literature, we here present a thorough review of the literature as it relates to small airway disease in children with asthma. We used, collectively, individual data sources of data to expand the information available from standard diagnostic techniques, especially spirometry, in the evaluation of small airway disease. As the pharmacological approaches to moderate to severe asthma are advancing rapidly into the realm of biologics, we sought to present potential pharmacological options for small airway dysfunction in pediatrics prior to biological modifier intervention.

Keywords Asthma · Small airway · Small airway disease · Pediatrics · Children

Abbreviations

SAD	Small airway disease (dysfunction)
GINA	Global Initiative for Asthma
FeNO	Fractional expired nitric oxide
IOS	Impulse oscillometry
FVC	Forced vital capacity
FEV ₁	Forced expiratory flow at 1 sec
FEF ₂₅₋₇₅	Forced expiratory flow at 25–75 of forced vital capacity
FEF ₅₀	Forced expiratory flow at 50% of forced vital capacity
R5-R20	Measurement of respiratory resistance between R5 and R20

AX	Area of reactance. X5: Represents the reactance throughout the respiratory system
RV	Residual volume
TLC	Total lung capacity
ICS	Inhaled corticosteroid
(CalvNO)	Calculated alveolar nitric oxide
FEV _z	Z score for FEV ₁
sRaw _z	Z score for specific airway conductance
MMEF _z	Z score for mid-maximal expiratory flow
AIT	Allergy immunotherapy
LABA	Long-acting beta-agonist
LAMA	Long-acting muscarinic antagonist
ACT	Asthma control test scores
CASI	Composite asthma severity index

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Introduction

Airway flow through the approximately twenty-seven divisions from the trachea into the alveoli moves from large airways into small airways less than 2 mm in diameter, which start about the 7–8th generation of airway division [1].

Relative resistance to airflow is higher in the early generation airways, falling slowly until generation 5, with a relative increase again, and then a rapid reduction in airflow resistance until the alveoli (Fig. 1) [1]. The rapidly increasing numbers of parallel airways beyond the 8th generation reduce the overall resistance by an increase in the total airway cross-sectional area (Fig. 1) [1].

This extensive array of small airways adds potential resistance of airflow when acutely or chronically involved [2]. Airflow obstruction in the small airways likely accompanies a significant portion of children with chronic lung disease, even when larger airway patency is optimal [3–16]. In the case of chronic asthma, airflow can be obstructed by segmental or broad-based inflammatory changes in the airway walls and mucous [17, 18]. The measurement of small airway airflow obstruction has perplexed both physiologists and clinicians [19–22] and the discussion of the “best” test for measuring small airway disease in children dates from the 1970s [14, 16]. Unfortunately, the ability to effectively treat this compartment of the total lung airway pathway has remained an orphan even in recent asthma therapeutic decisions trees [23] (GINA guidelines). The concept of a dissociation between the size of larger and small airways is termed dysanapsis [24, 25] (Smith, Forno).

A comprehensive review of small airway dysfunction (SAD) in asthma was published in 2013 [7], updated by Usmani in 2016 for adults [26] and by Carr et al. in 2017 for severe asthma [27]. We do not intend a systematic update to these previous reviews but rather to take a pragmatic view to small airway disease in children with asthma, providing a review of clinical observations and commentary on the more recent updates of small airway disease in pediatric asthma. We also provide perspective on

treatment options for small airway dysfunction within the 2020 GINA strategies schematic [23].

What Is Pediatric Asthma?

The definition of asthma has undergone major changes. Asthma is characterized as having phenotype differences including high type 2 and low type 2, that is further delineated as lavage mixed granulocytic or neutrophilic dominant [28, 29]. Pediatric asthma has followed, in large part, the same classifications as in the adult literature, but the predominate phenotype is high type 2 [30, 31]. Phenotypic pediatric asthma is presented in Table 1. Furthermore, a small airway disease phenotype has been suggested [32].

Has Small Airway Disease Been Generally Considered in the Pediatric Asthma Continuum?

Small airway dysfunction in obstructive lung disease was hallmarked in the 1960–1970s [21, 22], but details were limited to existing invasive studies [19, 20], and documentation of resistance changes after early childhood [22] with statements of the “lungs quiet zone” in the mid-last century [13–16, 20–22]. A re-emergence of the concept of SAD occurred in the past decade, when a comprehensive review and a treatment perspective from the Netherlands were published. Each concluding evidence was available to support the concept of “addressing” the small airway compartment [7, 33].

Two recent important publications have included significant recommendations for the future of asthma care [34, 35]. Neither, however, include any direct considerations for monitoring the small airway compartment. In addition, the 2020 GINA guidelines update asthma strategies but with limited recommendations for addressing small airway dysfunction [23]. The lack of well-recognized tests and therapy for small airway disease limits evidence-based recommendation.

What Is the Current Status of the Pediatric Small Airway Disease Understanding?

The conceptualization of small airway disease in pediatric asthma has been to consider it a longitudinal process, worsening or expressing itself with time [36–39]. When the “start” of small airway disease occurs has remained a critical question, and would detecting it “earlier” be advantageous? [37] (Lanz). Assessing early lung function

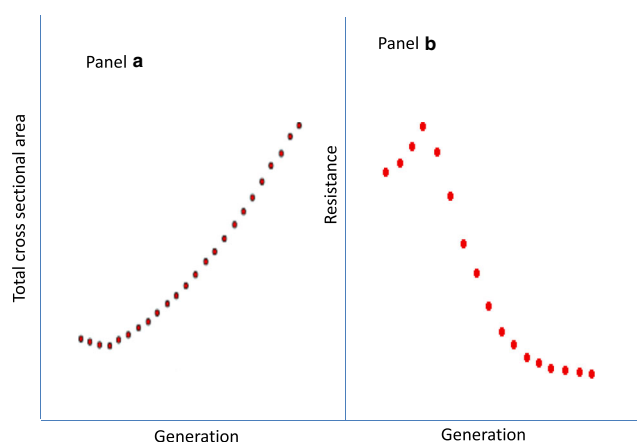


Fig. 1 Panel A depicts the total cross-sectional area of the conducting airways. Airways 2 mm and smaller add the most cross sectional area. Panel B depicts the resistance to airflow down the conducting airways to the alveoli. There are approximately 27 generations from trachea to the alveoli

Table 1 Characteristics of pediatric asthma

	High type 2	Low type 2
Reversibility	12% FEV1	12% FEV1
Peripheral Eosinophilia	Moderate to high	Low to moderate
IgE (total)	Elevated	Low
Another allergic disease	Usually	Never
Allergic skin tests or ImmunoCAP RAST specific IgE	Positive	Negative
FeNO	Off inhaled steroids: Elevated	Off inhaled steroids: Normal
Lavage Eosinophils	Off inhaled steroids: Present	Off Inhaled steroids: Presumably present

FEV1 forced expiratory flow at 1 sec; *FeNo* fraction of exhaled nitric oxide

disability may be the next wave of asthma care for children [40] (Subbarao).

Why Should we Care About Small Airway Disease in Asthma?

The insightful recommendations outlined by Szefer in 2018 provide a roadmap for the “cradle to rocker” approach to asthma care [35]. Prominently mentioned in that manuscript was the concern (based on previous reports of McGeachie [38, 39] that non-optimization of FEV1 might have significant long-term consequences, with the lung growth trajectory being of prime concern for reducing adult-based COPD development [38, 39]. Further evidence for the disconnect between larger and small airways (dysanapsis) was recently published using a longitudinal community-based population. [24].

Recent articles have also emphasized the role of small airway disease in asthma [4, 5, 26, 27, 41]. Usami explicitly states “the small airways have been neglected for many years” [26]; Zinuella states “small airways were historically considered to be almost irrelevant” [41]. Carr et al. provide the argument that small airway disease is relevant, and especially in more severe disease, or in those with frequent exacerbations, and that there are tests that are reasonable to perform, and that small airway dysfunction deserves targeted therapy [27]. Cottini et al. argues for optimizing “peripheral airway dysfunction” and not doing so results in poor asthma control [5].

Where Is Small Airway Disease?

The publication of Carr provides a concise statement of the targeted area of small airway disease [27]. The defined conducting airways are 2 mm or smaller, starting at the 7th generation, and accounting for >95% of the airway cross section [1, 27]. Their lack of cartilage in these small airways provides concern for collapse and has raised the validity of

less invasive tests of airflow due to test variability. The understanding that disease exists in the smaller conducting airways is becoming less controversial than is the consensus how to measure small airway obstruction. Epithelial wall thickening, mucous gland hypertrophy, sub-mucosal cellular infiltration, and other changes can increase resistance at all levels of airways, and likely more so in those of smaller diameter [42]. What is surprising is that some children with asthma do not have any (measurable) obstructed small airways. If “normal” small airway caliber is accepted, then why is obstructed small airway less accepted? The skepticism assumes that conventional small airway measures are intrinsically unreliable.

How Do we Effectively Measure Small Airway Disease in Asthma?

This is the million-dollar question. We endeavor to present data to support routinely evaluating the small airway in all pediatric asthmatics and to take the position that we can provide recommendations for small airway disease. Using this approach, clinicians, clinical protocols, and population studies in chronic pediatric asthma can track changes related to the implementation of small airway therapies following outcomes such as hospitalization and exacerbation rates based on the presence of baseline small airway dysfunction.

Several studies suggest practical approaches for assessing small airway dysfunction at any asthma visit in children. The first study was reported in 2019 and compares the “actual” presence of a small airway dysfunction using multiple techniques in adolescents/adults 18–65 years of age with asthma [43]. Using standard spirometry, impulse oscillometry, and body plethysmography, the investigators could detect an abnormality of small airway flow most effectively, as compared to the computerized tomography (CT) defined small airway obstruction, using two very available methodologies. The rank order of study utility reported in the publication is presented in Table 2 and based on the data of [43].

Table 2 Suggested small airways tests

Test	Likelihood for detection of small airway dysfunction	Test method
Low FVC	Very good	Spirometry
FEF25-75	Good	Spirometry
FEF50	Good	Spirometry
R5-R20	Fair	Oscillometry
AX	Fair	Oscillometry
X5	Fair	Oscillometry
Residual volume	Fair	Plethysmography

FVC forced vital capacity, *FEV1* forced expiratory flow at 1 sec, *FEF25-75* forced expiratory flow at 25–75 of forced vital capacity, *FEF50* forced expiratory flow at 50% of forced vital capacity, *R5-R20* measurement of respiratory resistance between R5 and R20, *AX* area of reactance, *X5* represents the reactance throughout the respiratory system

The second study was specifically in children and explored the use of a percent change in FVC (forced vital capacity) and the baseline FVC z score to infer air trapping due to obstruction, a parameter of lung function historically measured using body plethysmography. In short, a baseline FVC z score of -1.64 or an increase in FVC of 10% or greater after bronchodilators correlated with more severe asthma [44]. The predictability of low FVC in the report of Potsma [43] and the low FVC in the report of Sorkness provides good confidence for FVC improvement in detecting small airway disease [43, 44].

The third publication (Simon), also in children, demonstrated that a low FEF25-75 ($< 65\%$ predicted) was very predictive of larger airway dysfunction, and using a low FEF25-75 or a FEV1 that increased $> 20\%$ after albuterol reflected a “whole” (larger and small) airway concern [45].

Using the results of these three studies [43–45], a “composite” of standard spirometry measures could be used to stratify clinic or research patients and provide scoring systems or study outcomes, as was the focus of the adult protocol. [43] (Table 3).

Standard spirometry in a pediatric respiratory specialty clinic can detect airway obstruction at various airway diameters [46]. Oscillometry adds additional information.

In practical terms, spirometry and oscillometry cannot be billed on the same clinic day. An ICD-10 code for “other disorders of the lungs” (J98.4) can be used to track small airway disease in clinical practice for asthma management and clinical research.

Other measures of small airway disease have been studied and are listed here for completeness (Table 4). Applicability and availability and advantages or disadvantages to asthma specialists are included [16, 47].

These other tests to measure small airway obstruction are not cost-effective, easily reproducible, or widely available, even in specialty pediatric asthma clinics [9, 41, 47–49].

How Do Asthma Guidelines Approach Small Airway Disease in Asthmatics?

A review of 5 major asthma guidelines showed minimal comment or approach to small airway dysfunction in adults or children [23, 35, 50–52]. This included the Pediatric Asthma Yardstick published in 2018 [50]; a Lancet Commission of Asthma in 2018 [51]; the 2020 GINA global strategy for asthma management [23]; the working group for EPR-4 guidelines [52]; and a set of recommendations from Szefer [35].

The 2018 Pediatric Asthma Yardstick mentions measuring the small airway using impulse oscillometry and discusses small particle ICS products in a broader schema [50]. A comment small airway dysfunction was included as a rationale for adding a long-acting muscarinic antagonist.

The 2018 Lancet Commission published a comprehensive overview of asthma, redefining airways diseases [51]. Severe asthma was defined by 5 characteristics, without direct mention of a small airway. It included spirometry “persistently” being low and having “variable airflow obstruction” as

Table 3 Suggested combinations of tests that demonstrate small airway disease

Test or combination	Likelihood for small air dysfunction	Test needed
FVC < -1.64 z score and FEF25-75 $< 65\%$ predicted	High	Spirometry
FVC < -1.64 z score, FVC 10% improvement	High	Spirometry
FVC < -1.64 z score, or FVC 10% improvement and FEF25-75 $< 65\%$ predicted	Very high	Spirometry
FVC < -1.64 z score, FVC 10% improvement and FEF25-75 $< 65\%$ predicted and low R5-R20 with $> 35\%$ reversibility	Extremely high	Spirometry and Oscillometry

FVC forced vital capacity, *FEV1* forced expiratory flow at 1 sec, *FEF25-75* forced expiratory flow at 25–75 of forced vital capacity

Table 4 Alternative tests for demonstrating small airway dysfunction

Test	Availability	Applicability and comment
Body plethysmography	Specialty PFT laboratories	Time honored test for RV and TLC. Cost is a limitation for longitudinal testing
Methacholine challenge	Specialty PFT laboratories	Tests critical component of asthma, not necessarily SAD only
Inert gas washout	Specialty PFT laboratories	Cost and repeatability after therapy are limiting factors
High-resolution CT, MRI, gamma scintigraphy, positron emission tomography, single photon emission tomography	Radiology availability	Cost and repeatability after therapy and radiation exposure are limiting factors
Exhaled nitric oxide	Specialty PFT laboratories	Correlates with ICS use. Whether persisting elevated levels correlate with SAD is unknown. Can be repeated longitudinally for evidence of control
Alveolar nitric oxide (CalvNO)	Research laboratories	Measured nitric oxide concentration at different flow rates using a mathematical model. Discriminates between bronchial alveolar nitric oxide

PFT pulmonary function test. RV residual volume. TLC total lung capacity. SAD small airway dysfunction. ICS inhaled corticosteroid. (CalvNO) calculated alveolar nitric oxide

metrics. It made a comment that “small airway” size will diminish as child age [51].

The 2020 GINA guidelines did not mention small airway disease directly, although in contrast to small airway obstruction in children central airway obstruction was used in reference to adult asthma [23].

The working group for the National Heart, Lung and Blood Institute EPR-4, established in 2018, has 5 core areas, including indoor allergen management, FENO measurement, immunotherapy, and muscarinic antagonists, all of which are potential targets for small airway disease management, but are not specifically mentioned as such.[52].

The excellent recommendations of Szefer in 2018 did not address the small airway dimension in chronic asthma care [35].

The future EPR-4 has several topics of importance for therapeutic interventions and will be discussed in the following section. However, specific discussion of small airway disease management has not been part of the EPR-4 update [52].

A very recent review of systematic approaches to difficult to treat asthma in four international asthma centers agrees that care extends beyond pharmacotherapy [53]. Approaches to lower airway structure were discussed in a section on asthma diagnosis, including oscillometry, CT imaging, FeNO measures, volatile exhaled compounds, and 3D ventilation imaging [53]. Suggestions for difficult pediatric asthma were also reviewed [53].

How Common Is Small Airway Disease (SAD) in Pediatric Asthma?

Included here are summaries of studies or reviews of SAD in adults and children. Several pertinent adult studies are presented to provide reference in adults and to provide perspective for the limited number of pediatric studies.

A 2016 systematic review by Usami et al. reported 15 studies using multiple techniques for identifying small airway disease in adult asthmatics [26]. Across a range of asthma severity, upward of 60% of adult asthmatics had accompanying small airway disease (Ref- Usami) [26].

A recent study of adult asthmatics suggested that a low FVC or FEF25-75 was the most helpful (Postma: Atlantis) [43].

Impaired oscillometry of the peripheral airway was seen in 25% of approximately 100 encounters of “controlled asthmatics, 4–18 years, in a report by Tirakitsoontron et al. The FEV1 on the same day of the oscillometry suggested stability [13].

Using nitrogen washout technique, an abnormality of acinar ventilation was seen in about 1/3 of 31 children with mild asthma (Singer) [11]. Oscillometry and FEF25-75 were lower in children with frequent wheeze compared to control children [8].

Using standard spirometry, Francisco et al. evaluated over 2000 tests on 821 asthmatic children [46]. The FEV1/FVC

ratio was used as defining mild or more severe obstruction. In the range of FEV1/FVC ratios of 81–85%, the FEF25-75 was the most sensitive indicator. A ratio of < 80%, the FEF25-75 was again the most sensitive. Overall, the tests in the small airway range proved more valuable. The asthma severity (FEV1 value) was directly determined using spirometry (not symptoms) [46].

Pulmonary function tests in severe childhood are not well-represented in the characterization of the incidence small airway disease. It is likely overrepresented as compared to mild asthma. If a FEV1 less than 80% is used as an indicator of the moderate-severe asthma state, it is almost certain that a small airway measure can be found that will be concomitantly abnormal. A report from 2007 suggested that high-resolution CT could be helpful in severe pediatric asthma [48].

A logical companion question is: does small airway dysfunction happen so early it cannot be affected by any therapy, or if present, is it amendable to intervention? A potential answer to these questions comes from seminal reports from the COPSAC2000 study [54, 55].

A pediatric longitudinal asthma study provides partial answers to the question as to when SAD occurs and how long it has been present prior to detection clinically [54, 55]. Children of 411 asthmatic mothers were enrolled and studied with infant and routine pulmonary function. Ninety-seven children developed asthma by 13 years. Asthmatics were defined as having frequent exacerbations or not. Pulmonary testing included airway resistance measures, forced expiratory volume (FEV1), and maximal mid-expiratory flow (MMEF) and methacholine responsiveness.

The end-point analysis occurred at age 13 in the subjects [54, 55]. The data was presented as z scores. FEVz score was not significantly different in the children with asthma with or without exacerbations. The sRawz score measured at years 3–13 was significantly increased in children with asthma with exacerbations versus without exacerbations. MMEFz score measured from early life until 13 years was always lower in the asthma exacerbation group. Methacholine responsiveness was equally reactive in the two asthma groups. The methacholine responsiveness was equal in both groups (ages 7–13 was measured solely by FEV1 change). The authors concluded that the asthma exacerbation group had long-standing small airway disease (at birth?) that tracked throughout childhood and did not worsen with more exacerbations [54, 55]. An accompanying editorial (Gold) provides perspective on the report from Hallas but raised an extensive range of questions regarding this study [3]. A critical concern was the potential future risk of adult COPD in children with significant early small airway dysfunction [3, 38, 39].

A recent report from a center with long-standing experience in asthma epidemiology has reported that structural

changes in asthma with adults can be tracked to abnormal infant lung function [56].

The implication of these studies is that any attempt to modify small airway dysfunction in selected asthmatics needs to occur early and that exacerbation-prone children are more likely to have small airway dysfunction. Also, it is obvious that FEV1, the cornerstone guide for care decisions, appears to be of less relevance to predicting exacerbation-prone children, or by the time FEV1 can be measured reliably, lung function (larger and small airways) may be only partially reversible. Maximizing the large and medium airway caliber, using FEV1 measurement is critical, but not simultaneously defining small airway dysfunction could subvert effective therapy.

How should the clinician (or researcher) approach the assessment of the small airway as amendable to therapeutic intervention?

The time-honored use of a significant FEV1 change after albuterol has served diagnostically and clinically to determine if the symptomatic child has asthma. This measure has had a long track record, and the history of the measurement in pediatrics has been recently systematically reviewed [57]. We have provided ample evidence that small airway dysfunction is readily measurable and can be assessed using the same albuterol response when testing larger airway caliber. A suggestion for single variable testing is included here. Additive variables are previously outlined in Table 3. The hierarchy used in an adult study is emphasized (Table 5) [43].

FVC: Forced vital capacity. FEV1: Forced expiratory flow at one second. FEF25-75: Forced expiratory flow at 25–75% of forced vital capacity. FEF50: Forced expiratory flow at 50% of forced vital capacity. MMEF: maximum mid-expiratory flow R5-R20: Measurement of respiratory resistance between R5 and R20. AX: Area of reactance. X5: Represents the reactance throughout the respiratory system. FeNO: Forced expiratory nitric oxide.

Table 5 Reference values for detecting significant small airway improvement

TEST	Suggested value	Reference
FVC (PFT)	10%	[44]
FEF75 (PFT)	35%	[46]
FEF25-75 (PFT)	35%	[46]
FEF50 (PFT)	35%	[54, 55]
MMEF (PFT)	35%	[54]
R5-R20 (oscillometry)	25%	[9, 47, 49, 58]
R5 (oscillometry)	25%	[9, 47, 49, 58]
AX (oscillometry)	25%	[9, 47, 49, 58]
FeNO	> 25 ppb	[59]

How Can Small Airway Disease Be Approached Therapeutically?

The approach to addressing the whole airway in an asthmatic presumes the known measurements, and medications have broad abilities to detect and to affect the airway from the 1st generation to far distal airways [60]. Numerous reports of small airway dysfunction suggest that this assumption is not necessarily true [3–16, 26, 61]. This paper takes a pragmatic approach, suggesting a series of specific concepts, with supportive data when available, to provide a framework to approaching small airway dysfunction in clinical practice, clinical studies, or population surveys. The information is presented to be thought-provoking, and not necessarily a definitive answer to resolving dysfunction in an airway region of “relative silence”.

Table 6 outlines potential approaches to directly or systematically affect the extensive small airway field in chronic asthma. In large part, the discussed therapies have applicability for asthma but with minimal or no direct evidence as therapy for small airway disease.

Adult asthma can be phenotyped into several relevant clinical entities, with reasonable pediatric crossover [28, 29]. A high type 2 phenotype is most identified pathophysiology in pediatrics, while a low type 2 is less common [30]. The role of obesity adds inflammatory complexity to both phenotypes [62, 63]. A neutrophilic phenotype may rarely occur (Teague) but is associated with severe pediatric asthma [64], and severe asthma in children provides its own therapeutic challenges [65]. Using sophisticated lung computed tomography modeling, small airway narrowing has been improved using type 2 directed biological modifiers [66]. It is not totally clear that all phenotypes are equally responsive to both larger and/or small airway remediation. High type 2 asthma has a larger repertoire of potential therapeutic options as compared to type 2 low asthma [28, 29].

Environmental Control

A nearly obligatory statement is that pediatric asthmatics require effective environmental control to help minimize exacerbations and improve pulmonary function and asthma control [52, 65, 67–69]. The actual data is surprisingly sparse, and the

potential indoor and outdoor modifications suggested appear to be daunting. Obvious allergen exposures (pets, mold, cockroach, dust mites, and rodents) may lead to some success [70, 71], while indoor smoke exposure has decreased in most nations where pediatric asthma is common. However, the number of outdoor allergens and the lengthy list of pollutants are likely too many to be effectively controlled [72]. The future EPR-4 includes a section on environmental control and points out the limitations (through 2018) of the data and lack of pulmonary function assessment [52]. A 2020 manuscript of adherence to asthma management in children lists “detecting and removing environmental triggers” as a critical component [73]. The ability to longitudinally affect pulmonary function, in both larger and small airways, might be limited when an egregious allergen is present, such as a pet. Based on time spent in their bedroom, reasonable efforts to improve the sleeping environment for children have the most time and cost-effective benefit.

The Utilization of Air Filtration

There is good evidence that both indoor and outdoor allergens/pollutants can act as inflammatory inducers in the airway [67]. Children with asthma are routinely allergy tested to help identify phenotypic characteristics (high type 2) which then provides a rationale for specific allergen control measures. Interestingly, only recently has a randomized double-blind crossover study shown pulmonary-based improvement using a bedroom placed air filtration system [74]. Pulmonary function over a 2-week period of active filtration showed small airway function improvement using oscillometry [74].

The EPR-4 working group summarized the limited data up to 2018 and provided further support for particulate filtration [52].

Strong Emphasis on Proper Inhaler Technique

The therapeutic foundation for (almost) all children with persistent asthma is a continuous use of an inhaled medication, specifically corticosteroid, with, or without, long-acting bronchodilators. A review of inhaler technique provides perspective on this important cornerstone of asthma care [75]. In addition, a recent review of childhood asthma therapy adherence states inhaler technique as a key component [73], which was also recently emphasized by the American Academy of Pediatrics [76].

If inhaled albuterol improves larger and especially small airway function in the clinical laboratory, it provides proof that the inhalation of medication, especially long-acting beta-agonists and inhaled corticosteroids, should penetrate to the small airway. Documented bronchodilation response in the

Table 6 Outline of recommendations for small airway disease remediation

- | |
|--|
| <ul style="list-style-type: none"> • Non-medication approaches • Immunomodulatory approaches • Existing medication approaches • Future medication approaches • Biological modifier approaches |
|--|

clinical setting with reinforcement of optimal inhalation technique is the foundation for successful daily controller therapy [73].

Dietary Modifications

At least two potential dietary modifications have reached epidemiological and/or basic science investigation and are reasonable to be included. The optimization of vitamin D levels has some asthma and larger health benefits, while a high soluble fiber diet has general health benefits and a potential as an anti-inflammatory approach to asthma management.

The majority of the Vitamin D studies has been cross-sectional, and systematic reviews have suggested larger intervention protocols [77–82]. A small prospective study with thirty pediatric asthmatics used daily vitamin D or placebo [83]. Lessons derived from the study showed a large population with long-term use of therapy, and higher doses of vitamin D (> 1000 IU/day) will be necessary to detect benefit [83]. Larger airways were not improved in the active drug group, and small airway function was not measured.

A recent study of vitamin D3 supplementation did not prove successful in reducing time to first severe asthma exacerbation, viral triggered exacerbations, or ability to reduce inhaled corticosteroids in active vitamin D3 supplemented vs control asthmatic children [84].

A high-fiber diet has positive findings in animal models of asthma [85]. A review of pertinent studies in animals is available [86]. The basis of asthma benefit potentially derives from modifications in the gut microbiome and subsequent interaction on lung inflammation [87, 88]. There is a single human open-label study of high-fiber diet as single-dose, 4-h, treatment in asthma which showed decrease FeNO and increased FEV1 [89]. Overall health benefits likely derive from such a diet and could be part of a holistic “approach” to small airway disease directed care. A recent manuscript shows that asthma is decreased in adults with higher fiber diets [90].

Neither the addition of vitamin D supplementation or high-fiber diet together or as independent variables has reached clinical certainty for asthma or small airway benefit, but either or both have general health implications which could promote unexpected benefits for children with asthma [91, 92].

Weight Management

Asthma and obesity in children have had an associative link for two decades [62, 93–99]. The benefits of weight management and weight loss in asthma control could derive from improved forced vital capacity and air flow dynamics [25, 99] and/or a decrease in systemic inflammatory influence [63, 91, 100–102].

Laboratory Testing

A rationale for considering other laboratory tests is provided when a difficult pediatric asthmatic requires step-up in care plan, and small airway direct care is being considered (Table 7). These overlap with recent international centers that have difficulty to treat asthmatics clinics [53].

Immunotherapy

Recent reviews have concluded there is a beneficial role of allergy immunotherapy (AIT) in asthma [52, 106–109]. AIT in severe asthma has risks, although the concomitant use of omalizumab may be helpful [110]. Compelling evidence for pulmonary function improvement, either in larger airways or small airway measures, is, however, limited. The decision to start AIT in the larger context of improving asthma control has merit, but the time and cost can prove challenging. The ideal endpoint of improving small airway measures using medication or life style/environmental modifications over months rather than years is appealing. Therefore, the goal of tamping down immunological drivers of the allergy, (type 2 high phenotype) [28] using AIT deserve strong consideration in many pediatric asthmatics.

Conventional Asthma Medication Therapy

Inhaled corticosteroids are a required step using GINA or Pediatric Asthma Yardstick guidelines for many mild and all moderate to severe pediatric asthmatics [23, 50]. The question remains, what to do for a personalized approach to the small airway disease burdened pediatric asthmatic? [37] The standard of treatment is to up-dose the same ICS (with a LABA) [23, 50]. An experiential approach could include adding a LABA and a long-acting muscarinic (LAMA) to a lower dose of ICS to maximize bronchodilatation and ICS distal delivery; adding small particle beclomethasone dipropionate HFA to a low dose ICS-LABA ($\pm$ LAMA); and considering a switch to a different ICS-LABA combination. The less studied options have insurance coverage restrictions, ICS particle size considerations, and minimal guidelines direction. But individual clinical outcome and serial pulmonary function changes can provide support for their inclusion.

Adding a leukotriene receptor antagonist (LTRA) to any steps 2–5 pediatric asthmatic has minimal downside as asthma therapy. A systemic approach to the downregulation of leukotriene activity (in small airways) has attractiveness and has been shown to decrease air trapping [111]. The current black box warning for behavioral changes may, however, add pause. The benefit in small airway dysfunction has been reviewed,

Table 7 Suggested clinical test for problematic pediatric asthmatics

Test	Rationale or comment
CBC with differential	Absolute eosinophil quantification for biologic therapy. Avoid oral steroids × 1 month
IgE (total)	Consideration of biologic therapy
Urinary cotinine	Evidence of active or passive smoke exposure
Vitamin D3	Prior to initiation of Vitamin D, preferably in summer for maximum natural level. Recent study calls this into question [84]
Cholesterol, triglycerides hemoglobin A1c FeNO	Part of a weight management program
High-sensitivity CRP	Elevated levels strongly support airway inflammation and can be followed longitudinally for compliance and ICS success [59, 103]
Plasma complement C3	Has been shown as a marker for small airway disease [104]
	Elevated levels (> 1.20 g/L) are an asthma exacerbation risk [105]

CBC complete blood count, *FeNo* fractional exhaled nitric oxide, *CRP* C-reactive protein

with no superiority over ICS therapy was seen [112]. Individual clinical benefit and serial PFT can provide support.

Less Conventional Medications

The following commentary discusses several available medications that do not have widespread pediatric indication and are unlikely to have step guideline inclusion or placebo-controlled trials. They are added here for the purposes of completeness in the approach to attack small airway dysfunction and provide potential clinical benefit prior to the step 5 addition of biological modifiers.

Theophylline

Theophylline at low doses has an anti-inflammatory effect [113]. Its addition in adolescents with chronic severe asthma is mentioned in 2020 GINA strategies, but only in step 5 and for short periods of time, its use was discouraged in children. It is unlikely to have utility even in the picture of chronic sub-optimal small airway function.

Leukotriene Synthesis Inhibitors

Although not included by class, leukotriene modifiers were mentioned once in the 2020 GINA guidelines [23] and in the Pediatric Asthma Yardstick [50] only as leukotriene receptor antagonists. In several regards, a leukotriene synthesis inhibitor has advantages over a receptor antagonist. The signaling of prostaglandin D2 (PGD2) through a G protein-coupled receptor (GPCR) CTRH2 is a major pathway in TH2 inflammation and raises the question of anti-prostaglandin therapy in asthma management [42, 114–116]. The drug has an

impressive pharmacological profile [115] (Rossi). Its approval predates the understanding of the role of PGD2 on mast cell activity. [116] Prostaglandin D2 receptor antagonists may eventually play a role in asthma management. [116, 117].

Zileuton is the only arachidonate 5-lipoxygenase inhibitor available in the USA. It is approved for asthma for ages 12 and older. A single study with zileuton as an add-on to ICS-LABA for 1 month was not supportive of its effect on nitric oxide or on larger airways PFT [118] (Gelb).

Macrolide Antibiotics

A macrolide antibiotic is an infrequently used with-in step suggestion in pediatric asthma. The evidence is limited but supported in a review [119] and in type 2 low asthma [29, 30, 120]. Interesting, type 2 low asthma in children gains little attention but was recently discussed in some detail [29]. Some of the therapeutic options reviewed here have better applicability to the type 2 high phenotype pediatric asthmatic, but macrolides use may match better for low type 2 asthma [29, 121].

Small and Ultra-Small Particle ICS Inhalers

Small particle ICS and when available ultra-small particle ICS have a theoretical role as targeted therapy for both larger and small airway disease. The evidence is abundant, and pertinent questions were answered directly in a systematic review by Laverni et al. in 2017 [122]. Their potential benefit for small airway disease was reviewed in 2013 [60]. A complex but real-life protocol in children 5–11 years with first-line small particle, standard ICS particle with or without LABA was published in 2015 [123]. Small particle was favorable as

first-line therapy and was comparable to ICS-LABA and superior to standard size particle [123].

The current US market in the small particle ICS is breath-actuated (beclomethasone), and the meter-dosed (ciclesonide) has unfavorable insurance coverage.

A strategy to add a smaller particle ICS could also include its add-on to ICS-LABA instead a step-up to standard dose medium- or high-dose ICS-LABA. The 2020 GINA management protocol does not mention small particle as a step care product or add-on.

Long-Acting Muscarinic Antagonists (LAMA)

Tiotropium has a role as an add-on therapy for early sequences of asthma management [124–126]. Their single day use and added bronchodilator benefit are clear-cut. It may have a role in reducing intrinsic bronchial reactivity [127]. Its support includes the EPR-4 working group, GINA guidelines, and a review of type 2 low asthma [23, 50, 52]. It has recently been shown as a valuable add-on therapy instead of step-up therapy in a real-world protocol in subjects > 12 years [128] (Chippis). Its primary difficulty in children is the device methodology. Adding it to an ICS-LABA in a single device, as in COPD, seems reasonable as a future option.

Immunomodulatory Approaches

Currently in step 5 in the GINA pathway, the biological modifiers have the theoretical ability to offer a systemic option to the many type 2 high immunological influences in moderate to severe asthmatics [129]. The agents are moving closer to preschool availability. The evidence for a distal airway affect is the measurement of exhaled alveolar nitric oxide [103, 130]. Some studies have shown pulmonary function improvement [131–134]. A more practical approach, when biologics are considered in asthmatic children, is to use conventional metrics, and add a small airway parameter as a 3rd or 4th metric: (exacerbations, oral corticosteroid requirement, larger airway function improvement, small airway function improvement). Its valuable for the long-term use of biologics to have multiple metrics that can guide each child's personalized asthma plan. An approach of this type has been done in adults [133] (Sposato). A recent guideline for biological modifiers in severe asthma has been recently published [134].

It is conceivable that the long-term use of a systemic biological modifier may reduce distal airway inflammation and allow for an eventual reduction in small airway airflow obstruction. At present there is no research data in children to support this possibility.

What additional with-step considerations may allow stabilization of uncontrolled asthma and potentially improve larger and small airways prior to do a step-up of GINA strategies?

At the time of an asthma diagnosis or at any follow-up visit, the step care plan could have with-in therapies be initiated, as outlined below (Table 8), to stabilize control, especially when larger and small airway reversibility are present and before a step-up in GINA strategies is implemented.

As with standard step-up care decisions, repeat pulmonary function or oscillometry, asthma control test scores (ACT), composite asthma severity index (CASI) scores, and nitric oxide measure or CRP can demonstrate if with-in step suggestions prove beneficial, especially if a sustained improvement of small airway function can be documented [51]. The listed metrics are components of the comprehensive monitoring of pediatric asthma [135–137] (Brand, Pijnenburg, Wildfire).

Two pediatric asthma studies performed in 2006 and 2009 used a measure of small airway function to successfully document benefit in a step-up care plan [138, 139]. This include a 16-week cross-over study of fluticasone vs montelukast [138] and a 48-week study of an ICS vs combination therapy or a leukotriene receptor antagonist [139]. Both studies used oscillometry. Selected improvement in small airway dysfunction was discerned (depending on drug). Unfortunately, the use of small airway measures has not been a regular component of subsequent asthma protocols since these reports. However, their use in these two studies supports the co-benefit of measuring small airway functions during follow-up of in-step additions (see Table 8). In clinical practice, the baseline pulmonary function testing can include a post-albuterol evaluation. Then, the benefit on small airway change (post albuterol) seen at an earlier visit can be used as compared at subsequent visits after therapy has been initiated. It should be noted that standard pulmonary function and oscillometry cannot be billed on the same day for insurance reimbursement.

Conclusion

There is mounting evidence to include small airway measures, easily performed doing standard spirometry and/or oscillometry, in routine asthma testing. Additional tests (e.g., CT scans) add cost and radiation and do not add significant additional information nor are they easily performed serially. Identifying significant improvement in small airway caliber at the initial clinic visit bronchodilator study adds support for addressing a “maintenance” of all levels of airway caliber with serial clinical and spirometric evaluation. The need for additional step-up therapy reinforces following the small airway disease at the earliest stage of detection.

Table 8 GINA management steps and suggested additions#

2020 GINA Step	With-in step care suggestions to stabilize asthma control and to possibly improve larger and small airway function without a step-up in care strategies as outlined in GINA 2020	2020 GINA step
Step 1	Base suggestions Optimal inhaler technique Environmental control (based on allergy testing) Air filtration in bedroom with HEPA filtration Selective laboratory Weight management Vitamin D supplementation High-fiber diet Immunotherapy	Step 2
Step 2	Add additional with-in-step base suggestions Add LTRA to ICS	Step 3
Step 3	Switch to small particle ICS Add additional with-in step base suggestions Switch to a different ICS-LABA combo Add LAMA	Step 4
Step 4	Add low dose small particle ICS Add additional with-in step Base suggestions Laboratory to access best biological therapy Switch to a leukotriene synthesis inhibitor Add LAMA Add low dose small particle ICS to ICS-LABA combo Add low dose theophylline in adolescents	Step 5
Step 5	Extended macrolide therapy Prior to starting biologics consider: Additional alternatives from above	

ICS inhaled corticosteroid. LABA long-acting bronchodilator

Current national guidelines direct (appropriate) attention to larger caliber airways and asthma symptoms. Up-step therapy alone under-emphasizes a wide potential of additional efforts that might be employed for SAD. Until these intermediate step approaches have widespread support based on clinical studies, small airway dysfunction in pediatric asthma seems to continue to be a “relative quiet zone” and not much different from the 50-year-old perspective of Mead. [15].

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Compliance with Ethical Standards

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