Published in final edited form as:

Paediatr Respir Rev. 2019 February ; 29: 25–30. doi:10.1016/j.prrv.2018.10.003.

Question 3: Can we diagnose asthma in children under the age of 5 years?

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Abstract

The diagnosis of asthma in children under five years has been controversial due to changing concepts of what true asthma is in this age group. Previous diagnostic algorithms that used clinical indices to predict the persistence of asthma symptoms or phenotypes based on asthma triggers do not predict which children will benefit from asthma medication. A pragmatic approach to asthma diagnosis in this age group is based on identifying signs and symptoms of reversible airflow obstruction and documenting their response to asthma medication. Hopefully, this approach will provide clearer guidance to clinicians and improve asthma morbidity in these young children.

Keywords

Asthma; Child; Infant; Diagnosis; Viral wheeze

INTRODUCTION

Asthma is the most common chronic disease of childhood [1] and is characterized by the presence of reversible airflow obstruction and airways inflammation in the setting of compatible clinical symptoms [2–4]. In older children and adults, diagnosis centers around identifying asthma symptoms and confirming variable airflow obstruction. The ability to diagnose asthma in preschool children, typically defined as those under age 5 [3,5,6] or 6 [2,4] years is controversial. Several issues contribute to the debate including difficulty in differentiating bronchiolitis from asthma [7], reticence in assigning a chronic disease label at an early age [8], belief that asthma medications do not work in this age group [9], and the impression among some physicians that pulmonary function testing [PFT] is required to make a diagnosis of asthma given the inaccuracy of a clinical diagnosis in older children and adults [10,11]. Moreover, a larger debate is whether symptoms or a common pathophysiology defines asthma. This was highlighted in a recent Lancet Commission which suggested that the term asthma be used to describe a constellation of symptoms with no

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assumptions of underlying pathophysiology and that treatable traits such as inflammation or airflow limitation be identified and treated [12]. This review will discuss the controversies, frameworks, and current state of testing for the diagnosis of asthma in children under 5 years of age.

BURDEN OF ASTHMA IN PRESCHOOLERS

The prevalence of asthma among children ranges from 8.3% to 12.3% in westernized countries [13–16] with 80% of pediatric asthma patients manifesting symptoms before the age of 6 years [17]. Preschool aged children experience the highest rate of morbidity with a 4-fold higher prevalence of emergency room visits [18], and up to a 10-fold higher rate of hospitalizations [19] than older age groups.

Long term cohort studies have found that lung function trajectory is established in childhood [20,21] and that children with asthma are at risk for irreversible airways obstruction in adulthood with pathologic findings of airways remodeling developing between 12 months and 3 years of age [22,23]. Therefore, the pre-school years are a critical time for intervention [24]. While there is some degree of over-diagnosis of asthma [25,26], much of the morbidity associated with preschool asthma relates to underdiagnosis [1] and concomitant lack of initiation or adherence to preventative therapies. As such, recognition and accurate diagnosis of asthma in preschool aged children may help the child and caregivers understand symptoms, improve treatment adherence [8], and adjust life-style to minimize exposure to potential triggers.

PARADIGMS FOR THE DIAGNOSIS OF ASTHMA IN PRESCHOOL CHILDREN

Symptoms that persist into childhood = true asthma

The Tucson Children's Respiratory Study allowed the separation of 3 groups of wheezing children: (i) transient early wheezers, (ii) persistent wheezers and (iii) late onset wheezers, based on whether wheeze was present at 3 and 6 years of age [27]. Markers of atopy were significantly but weakly associated with persistent wheezing and it was this group that was classified as having "true asthma". Using these data, the Asthma Predictive Index (API) [28] and later the Modified Asthma Predictive Index were developed [29]. The API has a sensitivity of 57% and specificity of 81% for predicting asthma at age 6; with a population prevalence of 10% this equates to a positive predictive value of 26% and negative predictive value of 94% [28]. In the last two decades, a variety of asthma predictive algorithms have been developed and include factors such as age at wheeze onset [30], frequency and timing of wheeze episodes, presence of personal or family history of atopy, skin prick tests [31] and markers of allergic inflammation in blood [32], exhaled breath [33,34] and sputum [35–38] to forecast persistence of asthma symptoms. Unfortunately, the low predictive power of these indices makes them unreliable for individual patients and as they were derived from population based samples, they do not reflect the patients that are seen in the clinical setting.

Although this approach was adopted by asthma guidelines in the past [3], the limitation of retrograde extrapolation to diagnose asthma in preschool aged children is the lack of

sensitivity of existing asthma predictive indices at the individual patient level [38,39]. Relying on such predictive indices would result in the underdiagnosis of asthma in non-atopic wheezers. As non-atopic children comprise 60–75% of children with asthma in this age group [40,41], this would result in significant untreated morbidity. This paradigm also assumes that individuals who eventually outgrow their symptoms do not have a response to asthma medications in their preschool years, which has not been shown in clinical trials [40].

Multi-trigger wheeze = true asthma

A second paradigm differentiates multi-trigger wheeze from episodic viral wheeze. A 2008 ERS Task Report [5] recommended that those with multi-trigger wheeze be treated with inhaled steroids and that those with episodic viral wheeze be treated with leukotriene receptor antagonists. Although not stated, it was popularized that episodic viral wheeze was a benign condition that did not respond to inhaled steroids and that it was synonymous with transient wheezing. A 2014 update of this statement downplayed the distinction between multi-trigger and episodic viral wheeze [42] however this terminology continues to be popular [43].

The key limitations to this approach are that phenotypes are not stable in individuals over time and those with episodic viral wheezing do not necessarily outgrow their symptoms [44,45]. Additionally, the *frequency* and *severity* of viral-triggered episodes was not a factor when deciding on a therapeutic plan and these factors have been shown to predict response to inhaled corticosteroids [46].

Asthma symptoms that respond to asthma medication = asthma

To address the morbidity burden in preschoolers, current asthma consensus statements advocate for a pragmatic approach and a trial of asthma therapy (bronchodilators and daily inhaled corticosteroids or a short burst of systemic corticosteroids) in all children with clinical evidence of significant persistent or recurrent episodic reversible airflow obstruction [2,4,6] (Fig. 1). For those children who improve, a diagnosis of asthma can be made. Given that 50–60% of patients with wheezing outgrow their symptoms by school age [27], the diagnosis and treatment must be reassessed periodically [2].

The reason to diagnose asthma in younger children is to initiate treatment that will decrease short term asthma-related morbidity given that inhaled steroids do not have a disease modifying effect in this age group [47–49]. Although there are fewer clinical trials of asthma medications in this age group, there is growing evidence that supports the benefit of asthma medication in young children. Systematic reviews of inhaled steroids show that compared to placebo they decrease the symptoms of wheezing and asthma exacerbations with a relative risk of 0.59 and a number needed to treat of 7 [50]. Leukotriene receptor antagonists have been largely studied in children with episodic viral wheeze, without evidence of benefit in a recent systematic review [51] although further studies showing benefit have been published since that review [40]. There have been contradicting studies examining the usefulness of systemic steroids in this age group for acute exacerbations in the emergency room setting, which may be related to the severity of presentation in these studies [52,53]. Improvement with oral steroids in patients with bronchiolitis and a personal or family history of atopy

suggests overlap between these two disease or syndromes and points to the need for identification of treatable traits in all airways diseases [54].

This pragmatic approach is limited by the subjective nature of treatment effectiveness and the fact that symptoms such as cough may spontaneously resolve without treatment, leading to an over diagnosis of asthma. These limitations are balanced by a decrease in short-term morbidity.

SUMMARIZING BOX: HOW TO MAKE A DIAGNOSIS OF ASTHMA IN A CHILD UNDER 5 YEARS [2,4,6]

In a child presenting with acute symptoms of airflow obstruction (wheeze, signs of increased work of breathing), a trial of short acting beta agonists $\pm$ oral steroids should be given to assess response. If there is clear improvement and the child has had similar episodes previously, a diagnosis of asthma can be made.

In a child that has a history of recurrent asthma symptoms (wheeze, work of breathing, cough) but is not acutely symptomatic the frequency and severity of the reported symptoms should be considered. If the child has a history of severe exacerbations (requiring oral steroids, emergency room visits, hospitalization) or frequent symptoms, a trial of daily inhaled corticosteroids should be undertaken to determine response. If the frequency and/or severity of symptoms improves, a diagnosis of asthma can be made. If the symptoms are infrequent and mild, the child can be assessed when symptomatic to better determine the nature of the symptoms and their acute response to treatment (Fig. 1).

ASTHMA PHENOTYPES

A variety of different pathophysiologic processes may result in airways inflammation and reversible airway obstruction. “Lumping” all of these pathways under the diagnosis of asthma is likely to be an oversimplification [12]. Nonetheless, numerous attempts to “split” asthma into different phenotypes based on age of onset (early, persistent or late onset wheeze [27]) and types of triggers (multi-trigger vs episodic viral wheeze [5]), have so far failed to demonstrate clinical usefulness in this age group [55].

Theoretically, phenotyping provides an opportunity for predicting treatment response and prognosis, but this is limited in preschoolers due to the narrow range of available asthma medications in this age group and instability of phenotypic classification over time [44]. Studies in this age group have found characteristics or biomarkers that predict improvement with inhaled or systemic corticosteroids including markers of Th2 inflammation such as serum eosinophils over 300 cells/ul, aeroallergen sensitization or elevated serum eosinophilic cationic protein [40], demographic characteristics such as being male or Caucasian and having more severe disease identified by an Emergency Room [ER] visit or hospitalization for asthma in the past year, and being more symptomatic at baseline [46].

Research to identify genetic or metabolomic biomarkers that classify children into asthma phenotypes is ongoing. Such research is critical for promoting our understanding of the

causal pathways in asthma and to allow development and use of targeted therapies in this age group in future. However, the importance of such research should not overshadow the current need to diagnose, treat and thereby reduce morbidity in children under 5 years with asthma.

ASSESSING AIRWAY FUNCTION

The objective assessment of reversible airflow obstruction or hyperresponsiveness to bronchoprovocation challenge is a key supporting element in the diagnosis of asthma [3]. The American Thoracic Society (ATS) Report on lung function testing in young children found several assessments to be safe and feasible, including infant raised-volume rapid thoracic compression and plethysmography (i.e. infant PFTs), preschool spirometry, specific airway resistance, the interrupter technique, the forced oscillation technique, and multiple breath washout [56]. However, aside from infant PFTs, few data exist in children under 5 years. While infant PFTs may have some value in monitoring drug response in infants with recurrent wheeze [57,58] it does not reliably differentiate infants who ultimately develop persistent asthma [59] even with the use of bronchoprovocation challenge [60]. The reliance on specialized equipment, staffing, and sedation, as well as, lack of normative data and demonstrable value in diagnosing asthma limits its clinical applicability. Spirometry, the gold standard for diagnosing obstructive lung disease in children and adults, may be achievable with loosened testing criteria for preschool-aged children [61], however successful production of a forced expiratory flow manoeuvre is age dependent [62].

Effort-independent tests in infants and toddlers show promise [63], with forced oscillation technique (FOT) seeming closest to clinical utility. FOT [64] detects airways resistance and reactance from oscillatory waveforms of energy at distinct frequencies. Several studies in older children have demonstrated FOT to have clinical utility in diagnosis [65] and management of asthma [66–68]. Some studies suggest that young children may have more success with oscillometry than with spirometry [69], particularly when ill [70], however this also diminishes with younger children [71]. Recently, FOT techniques have proven feasible without sedation in newborns [72] and infants, with adaptation of standard equipment [73,74]. The optimal parameters for diagnostic utility, response to therapy, and device-specific normative values [56], need to be determined in the youngest age [75].

Multiple breath washout has been studied across age ranges as young as infants [76], however reliable data collection in the toddler age has required the use of sedatives in some studies [77]. Despite success in detecting early CF lung disease, the differences between preschool wheezers and control children has been less pronounced, even after administration of bronchodilators [78].

ASSESSING INFLAMMATION

Airway inflammation is considered a key feature in asthma although its assessment is not part of current diagnostic criteria in any age group. There are various ways to measure airway inflammation ranging from endobronchial biopsy, alveolar lavage or induced sputum cell counts to indirect measures of airway inflammation such as serum eosinophil counts and

fractional exhaled nitric oxide (FeNO). All of these tests measure inflammation in different lung compartments and it is not known which measurement best predicts response to treatment or prognosis. Induced sputum samples for cellular analysis are difficult in this age group with only 32% of samples being of adequate quality to be assessed in one study [79]. On the other hand, exhaled nitric oxide using a tidal breathing method has been successful even in young children [80].

There are very few studies comparing different tests of inflammation in this age group. When comparing induced sputum and alveolar lavage samples, sputum was found to be more neutrophilic and less eosinophilic than alveolar lavage samples [79]. Serum eosinophilia, and not sputum eosinophilia, was found to correlate better with alveolar lavage eosinophils [79].

Although eosinophilic airway inflammation is well described in older children and adults with asthma, airway neutrophilia and mixed inflammation has also been described in adults during exacerbations and older children with severe asthma [81–83]. Induced sputum samples in wheezy preschool children did not show eosinophilia, although paired alveolar lavage samples did show an increased eosinophil percentage compared to non-wheezers [79]. In comparison to older children with asthma, infants with recurrent viral wheezing were less likely to have alveolar eosinophils (27% of infants compared to 64% of older asthmatics) and more likely to have alveolar neutrophilia over 10% (1/2 of infants compared to 1/3 of asthmatics) and this was particularly the case in infants with positive bacterial cultures [84].

These studies of airway inflammatory markers highlight the heterogeneity of inflammation in the wheezy young child and the difficulty in obtaining these samples precludes their widespread use in diagnostic algorithms.

DIRECTIONS FOR FUTURE RESEARCH

If asthma is considered a constellation of signs and symptoms with no assumptions on underlying pathophysiology [12], the diagnosis of asthma in children under 5 years is less controversial. The challenge then becomes identifying the different components of airway disease in this age group. The focus can then shift to assessing how patterns of symptoms, airway inflammation and obstruction can be treated to prevent exacerbations and long term airway remodeling.

Future needs for diagnostic testing in the wheezy infant and toddler will add greatest value by providing objective measures of airway structure and function and patterns of inflammation. These tests can then be used to find associations with the risk for repeat exacerbations of airways disease, chronic respiratory impairment, or irreversible airway obstruction. Ultimately, the lessons learned from preschool children about the pathobiology of viral induced exacerbations and mechanisms of airway remodeling will have applications and implications into adulthood.

Until we have improved diagnostic methods in this age group, the diagnosis of asthma in preschool children will continue to be based on a history of the frequency and severity of symptoms and the response of these symptoms to asthma medications.

ACKNOWLEDGEMENT

Dr. Gaffin has received funding for his research from NIH grant K23AI106945.

References

- [1]. Asthma Key facts 2017; <http://www.who.int/news-room/fact-sheets/detail/asthma>. [accessed July 11, 2018, 2018].
- [2]. Ducharme FM, Dell SD, Radhakrishnan D, et al. Diagnosis and management of asthma in preschoolers: A Canadian Thoracic Society and Canadian Paediatric Society position paper. *Canadian Respir J: J Canadian Thoracic Soc* 2015;22 (3):135–43.
- [3]. National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma US Department of Health and Human Services, national Institutes of Health; 2007.
- [4]. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention Available from: www.ginasthma.org; 2018.
- [5]. Brand PL, Baraldi E, Bisgaard H, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J* 2008;32(4):1096–110. [PubMed: 18827155]
- [6]. National Institute for Health and Care Excellence NICE. Asthma: diagnosis, monitoring and chronic asthma management (NG80), 2017; 2018 [accessed July 27, 2018].
- [7]. Hancock DG, Charles-Britton B, Dixon DL, Forsyth KD. The heterogeneity of viral bronchiolitis: a lack of universal consensus definitions. *Pediatr Pulmonol* 2017;52(9):1234–40. [PubMed: 28672069]
- [8]. Klok T, Kaptein AA, Duiverman E, Oldenhof FS, Brand PL. General practitioners' prescribing behaviour as a determinant of poor persistence with inhaled corticosteroids in children with respiratory symptoms: mixed methods study. *BMJ Open* 2013;3(4).
- [9]. Bush A Practice imperfect—treatment for wheezing in preschoolers. *N Engl J Med* 2009;360(4): 409–10. [PubMed: 19164192]
- [10]. Aaron SD, Vandemheen KL, Boulet LP, et al. Overdiagnosis of asthma in obese and nonobese adults. *CMAJ* 2008;179(11):1121–31. [PubMed: 19015563]
- [11]. Yang CL, Simons E, Foty RG, Subbarao P, To T, Dell SD. Misdiagnosis of asthma in schoolchildren. *Pediatr Pulmonol* 2017;52(3):293–302. [PubMed: 27505297]
- [12]. Pavord ID, Beasley R, Agusti A, et al. After asthma: redefining airways diseases. *Lancet* 2018;391(10118):350–400. [PubMed: 28911920]
- [13]. Most Recent Asthma Data. 2018; https://www.cdc.gov/asthma/most_recent_data.htm; 2018 [accessed July 11, 2018].
- [14]. Asthma, by age group. 2018; <https://www150.statcan.gc.ca/t1/tb11/en/tv.action?pid=1310009608>; 2018 [accessed July 11, 2018].
- [15]. AIHW. Asthma 2017; <https://www.aihw.gov.au/reports/asthma-other-chronic-respiratory-conditions/asthma/data>; 2018 [accessed July 11, 2018].
- [16]. Thomas EM. Recent trends in upper respiratory infections, ear infections and asthma among young Canadian children. *Health Rep* 2010;21(4):47–52.
- [17]. Hafkamp-de Groen E, Lingsma HF, Caudri D, et al. Predicting asthma in preschool children with asthma-like symptoms: validating and updating the PIAMA risk score. *J Allergy Clin Immunol* 2013;132(6):1303–10. [PubMed: 23987795]
- [18]. Oasis: Data Tables health Services Use 2016; <http://lab.research.sickkids.ca/oasis/data-tables/>; 2018 [accessed July 11, 2018].

- [19]. Asthma hospital stays by children and youth 2018; <https://www.cihi.ca/en/asthma-hospital-stays-by-children-and-youth>; 2018 [accessed July 11, 2018].
- [20]. Sears MR, Greene JM, Willan AR, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003;349 (15):1414–22. [PubMed: 14534334]
- [21]. McGeachie MJ, Yates KP, Zhou X, et al. Patterns of growth and decline in lung function in persistent childhood asthma. *N Engl J Med* 2016;374(19):1842–52. [PubMed: 27168434]
- [22]. Saglani S, Payne DN, Zhu J, et al. Early detection of airway wall remodeling and eosinophilic inflammation in preschool wheezers. *Am J Respir Crit Care Med* 2007;176(9):858–64. [PubMed: 17702968]
- [23]. Saglani S, Malmström K, Pelkonen AS, et al. Airway remodeling and inflammation in symptomatic infants with reversible airflow obstruction. *Am J Respir Crit Care Med* 2005;171(7):722–7. [PubMed: 15657459]
- [24]. Yoshihara S Early intervention for infantile and childhood asthma. *Expert Rev Clin Immunol* 2010;6(2):247–55. [PubMed: 20402387]
- [25]. Looijmans-van den Akker I, van Luijn K, Verheij T. Overdiagnosis of asthma in children in primary care: a retrospective analysis. *Br J Gen Pract* 2016;66(644): e152–7. [PubMed: 26917656]
- [26]. Bush A, Fleming L. Is asthma overdiagnosed? *Arch Dis Child* 2016;101 (8):688–9. [PubMed: 27049005]
- [27]. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;332(3):133–8. [PubMed: 7800004]
- [28]. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162(4 Pt 1): 1403–6. [PubMed: 11029352]
- [29]. Chang TS, Lemanske RF, Jr, Guilbert TW, et al. Evaluation of the modified asthma predictive index in high-risk preschool children. *J Allergy Clin Immunol Pract* 2013;1(2):152–6. [PubMed: 24187656]
- [30]. Spycher BD, Silverman M, Brooke AM, Minder CE, Kuehni CE. Distinguishing phenotypes of childhood wheeze and cough using latent class analysis. *Eur Respir J* 2008;31(5):974–81. [PubMed: 18216047]
- [31]. Henderson J, Granell R, Heron J, et al. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax* 2008;63(11):974–80. [PubMed: 18678704]
- [32]. Simpson A, Tan VY, Winn J, et al. Beyond atopy: multiple patterns of sensitization in relation to asthma in a birth cohort study. *Am J Respir Crit Care Med* 2010;181(11):1200–6. [PubMed: 20167852]
- [33]. Singer F, Luchsinger I, Inci D, et al. Exhaled nitric oxide in symptomatic children at preschool age predicts later asthma. *Allergy* 2013;68(4):531–8. [PubMed: 23414302]
- [34]. Wandalsen GF, Solé D, Bacharier LB. Identification of infants and preschool children at risk for asthma: predictive scores and biomarkers. *Curr Opin Allergy Clin Immunol* 2016;16(2):120–6. [PubMed: 26807784]
- [35]. Bao Y, Chen Z, Liu E, Xiang L, Zhao D, Hong J. Risk factors in preschool children for predicting asthma during the preschool age and the early school age: a systematic review and meta-analysis. *Curr Allergy Asthma Rep* 2017;17 (12):85. [PubMed: 29151195]
- [36]. Savenije OE, Kerkhof M, Koppelman GH, Postma DS. Predicting who will have asthma at school age among preschool children. *J Allergy Clin Immunol* 2012;130(2):325–31. [PubMed: 22704537]
- [37]. Sears MR. Predicting asthma outcomes. *J Allergy Clin Immunol* 2015;136 (4):829–36. quiz 837. [PubMed: 26449797]
- [38]. Luo G, Nkoy FL, Stone BL, Schmick D, Johnson MD. A systematic review of predictive models for asthma development in children. *BMC Med Inform Decis Mak* 2015;15:99. [PubMed: 26615519]

- [39]. Smit HA, Pinart M, Anto JM, et al. Childhood asthma prediction models: a systematic review. *Lancet Respir Med* 2015;3(12):973–84. [PubMed: 26597131]
- [40]. Fitzpatrick AM, Jackson DJ, Mauger DT, et al. Individualized therapy for persistent asthma in young children. *J Allergy Clin Immunol* 2016;138(6). 1608–1618.e1612. [PubMed: 27777180]
- [41]. Herr M, Just J, Nikasinovic L, et al. Risk factors and characteristics of respiratory and allergic phenotypes in early childhood. *J Allergy Clin Immunol* 2012;130 (2). 389–396.e384. [PubMed: 22846748]
- [42]. Brand PL, Caudri D, Eber E, et al. Classification and pharmacological treatment of preschool wheezing: changes since 2008. *Eur Respir J* 2014;43(4):1172–7. [PubMed: 24525447]
- [43]. Harding TW, Driscoll C, Hensey CC. Strategies for treatment of pre-schoolers with episodic viral wheeze. *J Paediatr Child Health* 2017;53(12):1241. [PubMed: 29205654]
- [44]. Schultz A, Devadason SG, Savenije OE, Sly PD, Le Souëf PN, Brand PL. The transient value of classifying preschool wheeze into episodic viral wheeze and multiple trigger wheeze. *Acta Paediatr* 2010;99(1):56–60. [PubMed: 19764920]
- [45]. Kappelle L, Brand PL. Severe episodic viral wheeze in preschool children: high risk of asthma at age 5–10 years. *Eur J Pediatr* 2012;171(6):947–54. [PubMed: 22234479]
- [46]. Bacharier LB, Guilbert TW, Zeiger RS, et al. Patient characteristics associated with improved outcomes with use of an inhaled corticosteroid in preschool children at risk for asthma. *J Allergy Clin Immunol* 2009;123(5):1077–82. 1082.e1071–1075. [PubMed: 19230959]
- [47]. Bisgaard H, Hermansen MN, Loland L, Halkjaer LB, Buchvald F. Intermittent inhaled corticosteroids in infants with episodic wheezing. *N Engl J Med* 2006;354(19):1998–2005. [PubMed: 16687712]
- [48]. Guilbert TW, Morgan WJ, Zeiger RS, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;354 (19):1985–97. [PubMed: 16687711]
- [49]. Murray CS, Woodcock A, Langley SJ, Morris J, Custovic A, team Is. Secondary prevention of asthma by the use of Inhaled Fluticasone propionate in Wheezy Infants (IFWIN): double-blind, randomised, controlled study. *Lancet* 2006;368 (9537):754–62. [PubMed: 16935686]
- [50]. Castro-Rodriguez JA, Rodrigo GJ. A systematic review of long-acting b2-agonists versus higher doses of inhaled corticosteroids in asthma. *Pediatrics* 2012;130(3):e650–657. [PubMed: 22926172]
- [51]. Brodlić M, Gupta A, Rodriguez-Martinez CE, Castro-Rodriguez JA, Ducharme FM, McKean MC. Leukotriene receptor antagonists as maintenance and intermittent therapy for episodic viral wheeze in children. *Cochrane Database Syst Rev* 2015;10:CD008202.
- [52]. Panickar J, Lakhanpaul M, Lambert PC, et al. Oral prednisolone for preschool children with acute virus-induced wheezing. *N Engl J Med* 2009;360 (4):329–38. [PubMed: 19164186]
- [53]. Foster SJ, Cooper MN, Oosterhof S, Borland ML. Oral prednisolone in preschool children with virus-associated wheeze: a prospective, randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2018;6(2):97–106. [PubMed: 29373235]
- [54]. Alansari K, Sakran M, Davidson BL, Ibrahim K, Alrefai M, Zakaria I. Oral dexamethasone for bronchiolitis: a randomized trial. *Pediatrics* 2013;132(4): e810–816. [PubMed: 24043283]
- [55]. Schultz A, Brand PL. Episodic viral wheeze and multiple trigger wheeze in preschool children: a useful distinction for clinicians? *Paediatr Respir Rev* 2011;12(3):160–4. [PubMed: 21722843]
- [56]. Rosenfeld M, Allen J, Arets BH, et al. An official American Thoracic Society workshop report: optimal lung function tests for monitoring cystic fibrosis, bronchopulmonary dysplasia, and recurrent wheezing in children less than 6 years of age. *Ann Am Thorac Soc* 2013;10(2):S1–S11. [PubMed: 23607855]
- [57]. Kraemer R, Graf Bigler U, Casaulta Aebischer C, Weder M, Birrer P. Clinical and physiological improvement after inhalation of low-dose beclomethasone dipropionate and salbutamol in wheezy infants. *Respiration* 1997;64 (5):342–9. [PubMed: 9311050]
- [58]. Straub DA, Moeller A, Minocchieri S, et al. The effect of montelukast on lung function and exhaled nitric oxide in infants with early childhood asthma. *Eur Respir J* 2005;25(2):289–94. [PubMed: 15684293]

- [59]. Morgan WJ, Stern DA, Sherrill DL, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med* 2005;172(10):1253–8. [PubMed: 16109980]
- [60]. Turner SW, Young S, Goldblatt J, Landau LI, Le Souef PN. Childhood asthma and increased airway responsiveness: a relationship that begins in infancy. *Am J Respir Crit Care Med* 2009;179(2):98–104. [PubMed: 18990677]
- [61]. Eigen H, Bieler H, Grant D, et al. Spirometric pulmonary function in healthy preschool children. *Am J Respir Crit Care Med* 2001;163(3 Pt 1):619–23. [PubMed: 11254514]
- [62]. Kanengiser S, Dozor AJ. Forced expiratory maneuvers in children aged 3 to 5 years. *Pediatr Pulmonol* 1994;18(3):144–9. [PubMed: 7800430]
- [63]. Nielsen KG, Bisgaard H. Discriminative capacity of bronchodilator response measured with three different lung function techniques in asthmatic and healthy children aged 2 to 5 years. *Am J Respir Crit Care Med* 2001;164 (4):554–9. [PubMed: 11520714]
- [64]. Skylogianni E, Douros K, Anthracopoulos MB, Fouzas S. The forced oscillation technique in paediatric respiratory practice. *Paediatr Respir Rev* 2016;18:46–51. [PubMed: 26777151]
- [65]. Shin YH, Jang SJ, Yoon JW, et al. Oscillometric and spirometric bronchodilator response in preschool children with and without asthma. *Can Respir J* 2012;19 (4):273–7. [PubMed: 22891189]
- [66]. Marotta A, Klinnert MD, Price MR, Larsen GL, Liu AH. Impulse oscillometry provides an effective measure of lung dysfunction in 4-year-old children at risk for persistent asthma. *J Allergy Clin Immunol* 2003;112(2):317–22. [PubMed: 12897737]
- [67]. Shi Y, Aledia AS, Galant SP, George SC. Peripheral airway impairment measured by oscillometry predicts loss of asthma control in children. *J Allergy Clin Immunol* 2013;131(3): 718–23. [PubMed: 23146376]
- [68]. Shi Y, Aledia AS, Tatavoosian AV, Vijayalakshmi S, Galant SP, George SC. Relating small airways to asthma control by using impulse oscillometry in children. *J Allergy Clin Immunol* 2012;129(3):671–8. [PubMed: 22178635]
- [69]. Lebecque P, Desmond K, Swartebroekx Y, Dubois P, Lulling J, Coates A. Measurement of respiratory system resistance by forced oscillation in normal children: a comparison with spirometric values. *Pediatr Pulmonol* 1991;10 (2):117–22. [PubMed: 2030920]
- [70]. Ducharme FM, Davis GM. Respiratory resistance in the emergency department: a reproducible and responsive measure of asthma severity. *Chest* 1998;113(6):1566–72. [PubMed: 9631795]
- [71]. Alblooshi A, Alkalbani A, Albadi G, Narchi H, Hall G. Is forced oscillation technique the next respiratory function test of choice in childhood asthma. *World J Methodol* 2017;7(4):129–38. [PubMed: 29354485]
- [72]. Hantos Z, Czovek D, Gyurkovits Z, et al. Assessment of respiratory mechanics with forced oscillations in healthy newborns. *Pediatr Pulmonol* 2015;50 (4):344–52. [PubMed: 25154334]
- [73]. Gray D, Czovek D, Smith E, et al. Respiratory impedance in healthy unsedated South African infants: effects of maternal smoking. *Respirology (Carlton, Vic)* 2015;20(3):467–73.
- [74]. Gray D, Willemsse L, Visagie A, et al. Determinants of early-life lung function in African infants. *Thorax* 2017;72(5):445–50. [PubMed: 27856821]
- [75]. Frei J, Jutla J, Kramer G, Hatzakis GE, Ducharme FM, Davis GM. Impulse oscillometry: reference values in children 100 to 150 cm in height and 3 to 10 years of age. *Chest* 2005;128(3): 1266–73. [PubMed: 16162717]
- [76]. Horsley A Lung clearance index in the assessment of airways disease. *Respir Med* 2009;103(6): 793–9. [PubMed: 19246184]
- [77]. Stahl M, Wielputz MO, Graeber SY, et al. Comparison of lung clearance index and magnetic resonance imaging for assessment of lung disease in children with cystic fibrosis. *Am J Respir Crit Care Med* 2017;195(3):349–59. [PubMed: 27575911]
- [78]. Sonnappa S, Bastardo CM, Wade A, Bush A, Stocks J, Aurora P. Repeatability and bronchodilator reversibility of lung function in young children. *Eur Respir J* 2013;42(1):116–24. [PubMed: 23222876]

- [79]. Jochmann A, Artusio L, Robson K, et al. Infection and inflammation in induced sputum from preschool children with chronic airways diseases. *Pediatr Pulmonol* 2016;51(8):778–86. [PubMed: 26678320]
- [80]. Gouvis-Echraghi R, Saint-Pierre P, Besharaty AA, Bernard A, Just J. Exhaled nitric oxide measurement confirms 2 severe wheeze phenotypes in young children from the Trousseau Asthma Program. *J Allergy Clin Immunol* 2012;130(4):1005–1007.e1001. [PubMed: 22920491]
- [81]. Ullmann N, Bossley CJ, Fleming L, Silvestri M, Bush A, Saglani S. Blood eosinophil counts rarely reflect airway eosinophilia in children with severe asthma. *Allergy* 2013;68(3):402–6. [PubMed: 23347007]
- [82]. O'Brien CE, Tsirilakis K, Santiago MT, Goldman DL, Vicencio AG. Heterogeneity of lower airway inflammation in children with severe-persistent asthma. *Pediatr Pulmonol* 2015;50(12):1200–4. [PubMed: 25739748]
- [83]. Fahy JV, Kim KW, Liu J, Boushey HA. Prominent neutrophilic inflammation in sputum from subjects with asthma exacerbation. *J Allergy Clin Immunol* 1995;95(4):843–52. [PubMed: 7722165]
- [84]. Marguet C, Jouen-Boedes F, Dean TP, Warner JO. Bronchoalveolar cell profiles in children with asthma, infantile wheeze, chronic cough, or cystic fibrosis. *Am J Respir Crit Care Med* 1999;159(5 Pt 1):1533–40. [PubMed: 10228122]

Educational aims

The reader will appreciate that children under 5 years of age:

- Can be diagnosed with asthma on the basis of having symptoms of reversible airway obstruction that respond to asthma medication.
- Have the highest rates of emergency room visits and hospitalizations for asthma compared to older children.
- Have improved symptom control and fewer asthma exacerbations with use of inhaled corticosteroids.

Fig. 1.
 From the diagnosis and management of asthma in preschoolers: A Canadian Thoracic Society and Canadian Pediatric Society position paper.