Asthma

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Practice Gap

Asthma is the most common chronic respiratory disease of childhood, a leading cause of emergency department visits, and 1 of the top 3 indications for hospitalization in children. Despite advances in the management of pediatric asthma, significant disparities in care and outcomes persist. To bridge these gaps, we must embrace the concept of asthma care across the continuum and extend our reach beyond the immediate patient-provider visit.

Objectives   After completing this article, readers should be able to:

1. Understand trends in prevalence, outcomes, and health disparities in pediatric asthma.

2. Describe advances in understanding the pathophysiology of asthma.

3. Translate an understanding of asthma to a differential diagnosis in a child with wheeze.

4. Practice guideline-based management with accurate assessment of asthma severity and control.

5. Apply recent evidence-based emerging trends in the treatment of asthma.

6. Identify community-based strategies and quality improvement projects in your practice setting to ensure asthma care across the continuum for vulnerable children.

ABBREVIATIONS

ARR	at-risk rate
CDC	Centers for Disease Control and Prevention
ED	emergency department
EILO	exercise-induced laryngeal obstruction
FeNO	fractional excretion of nitric oxide
FEV_1	forced expiratory volume in 1 second
ICS	inhaled corticosteroid
IgE	immunoglobulin E
IL	interleukin
LAIV	live attenuated influenza vaccine
LTRA	leukotriene receptor antagonist
NAEPP	National Asthma Education and Prevention Program
PBR	population-based rate
PEF	peak expiratory flow
PFT	pulmonary function testing
SABA	short-acting inhaled β_2-agonist

INTRODUCTION

Asthma is defined by episodic and reversible airway constriction and inflammation in response to infection, environmental allergens, and irritants. It is a complex, multifactorial, and immune-mediated process that presents with various clinical phenotypes.

Despite novel treatments and guideline-based care, asthma remains a significant public health problem. Medical care, missed school, and missed work related to asthma continue to burden our communities, costing more than $80 billion each year. (1) Furthermore, asthma disproportionately affects minorities and socioeconomically disadvantaged children. (2) Black children have the

highest asthma morbidity and mortality rates of any US group, with twice the emergency department (ED) visit/hospitalization rate and 9 times the mortality rate as white children. (3)(4)(5)

In 2012, the President's Task Force on Environmental Health Risks and Safety Risks to Children commissioned a cabinet-level, multiagency group to address overall asthma morbidity and its racial and ethnic disparities. (6) The group chose 4 integrated strategies.

- Remove barriers to guideline-based care.
- Improve the identification of at-risk children.
- Build capacity for integrated, community-based care.
- Support efforts to prevent asthma.

EPIDEMIOLOGY AND PREVALENCE

Asthma affects 1 in 12 US children aged 0 through 17 years. (3) After decades of increases, the prevalence of asthma in this group plateaued between 2010 and 2012, (2) decreased in 2013 from 9.3% in 2012 to 8.3%, and remained stable through 2016. (2)(3) In contrast, pediatric asthma prevalence in black children increased between 2001 and 2009, leveling off by 2013. (2) In 2016, asthma prevalence in black children rose sharply to 15.7% (a 2.3% increase from 2014 and 2015), twice that of white children. (3) This rate surpassed that of Puerto Rican children, who previously had the highest prevalence of asthma of all US children. (3) The prevalence of asthma in children in poverty did not decrease between 2001 and 2013 and remained high in 2016 (10.5%). (2)(3)

Outcomes

Asthma exacerbation is a leading cause of (ED) visits (7) and 1 of the top 3 indications for hospitalization in children. (8) Comparing asthma outcomes between subgroups, an at-risk rate (ARR) is preferred over the traditional population-based rate (PBR). (9) An ARR is the number of children with the outcome (eg, asthma hospitalization or death) divided by the total number of children at risk for that outcome (those with asthma). Conversely, a PBR is the number of children with the asthma outcome divided by the total population. PBRs measure the overall burden of disease in a particular population or subgroup, whereas an ARR accounts for differences in prevalence between subgroups to describe disparities.(4) Between 2001 and 2010, ARRs for black and white children revealed a decrease in racial disparities for ED visit and hospitalization rates and no change in death rate due to asthma. (4) It is important to note, however, that ARRs do not account for differences in underlying asthma severity. A 2013 analysis of hospitalizations for chronic conditions in the Pediatric Health Information System

database found that black children had the highest asthma readmission rate (21.4%) of any race or ethnicity. (10) Finally, because ARRs rely on prevalence estimates, any undercounting of "current asthma" in disadvantaged groups could result in an overestimation of risk.

Disparities in asthma outcomes and prevalence also exist based on geographic location. (11)(12) In Washington, DC, for example, 1 in 9 children, compared with 1 in 12 nationally, had asthma in 2014. (13) In addition, children in DC with the highest rates of ED visits and hospitalizations for asthma live in socioeconomically disadvantaged neighborhoods. Geographic variation in DC is likely due to a variety of factors, including but not limited to race and socioeconomic status. Population health using geospatial mapping, (2) disease-specific registries based on local electronic health records, and higher-level data analytics (machine learning, artificial intelligence, etc) (14) are promising tools to identify and decrease disparities in asthma outcomes. Collaborative efforts should target hot spots to address the causes of disparate outcomes. (15) Examples include the following:

- Map local asthma prevalence using geographic information systems software to identify hot spots of poor asthma control (ED visits, hospitalizations, readmissions, ICU admission, or death). Investigate neighborhood-specific factors (access to routine primary care, [16] housing conditions) through focus groups or needs assessments and initiate quality improvement projects to improve asthma control.
- Create an asthma registry using data from a health system's electronic health records to identify an at-risk subpopulation. Initiate a systemwide collaborative effort to address disparities in care (initiation of inhaled corticosteroid [ICS], [17] ensuring follow-up after hospitalization and emergency care, [18] management of comorbid conditions). Consider education or electronic decision support as interventions for a quality improvement project to reduce disparities in care.
- Use machine learning to analyze large data sets (eg, all ED visits, [19] asthma registry) to identify associations between risk factors and poor asthma outcomes previously not considered. Collaborate with local resources to mitigate risk (legal aid to assist with poor housing, care coordination to ensure medications prescribed are covered and there is subspecialty follow-up).

PATHOPHYSIOLOGY

Asthma is a highly complex, immune-mediated, inflammatory disease, with intermittent and reversible lower airway

obstruction due to smooth muscle constriction and airway narrowing in response to an environmental trigger, often in association with a viral upper airway infection. Numerous inflammatory pathways to airway swelling result in the many clinical phenotypes of pediatric asthma.

Longitudinal studies attempting to further understand the natural history of asthma have identified 3 distinct phenotypes: transient early wheezing, nonatopic wheezing, and atopy-associated wheezing. (20) Transient early wheezing is characterized by resolution of wheeze by 3 years of life, a lack of association with family history of asthma or early allergic sensitization as well as a positive association with prematurity, exposure to other children at child care, maternal smoking during pregnancy, and environmental tobacco smoke exposure during infancy. (20) Nonatopic wheezing is characterized by viral-induced wheeze during first the 2 to 3 years of life, with respiratory syncytial virus infection being associated with persistent wheeze later in life. (20) In contrast, atopic wheezing is characterized by a family history of atopy, early allergen sensitization, and a genetic predisposition for sensitization. (20) With any of these phenotypes, severe illness early in life is associated with progressive and persistent wheeze in later life. (20)

Five distinct clusters of asthma phenotypes (characterized by asthma and allergy severity, pulmonary physiology, allergy sensitization, total serum immunoglobulin E [IgE], and allergic inflammation) were recently described in a large urban longitudinal cohort from 9 cities in disadvantaged and largely minority children aged 6 to 17 years. (21) These phenotypes were distinguishable by the intensity of the allergic response. Similarly, a birth cohort study compared multiple groups with documented IgE antibody responses and found early exposure to multiple allergens predictive of asthma later in life. (22)

The significance of variation in early exposures to allergens versus microbes in children with asthma has been an area of speculation for some time. Ecologic data are suggestive of the "hygiene hypothesis" whereby countries with higher rates of early microbial exposure have decreased prevalence of asthma, and, conversely, countries with less exposure during childhood have higher rates of asthma. (23) Current understanding of cellular and molecular immunology suggests that exposures very early in life shape the development of a child's immune system to favor either a Th1 (nonallergic) or Th2 (allergic) lymphocyte predominance. (24) Theoretically, if a child is exposed to various microbes early in life, the immune system will favor a nonallergic, infection-fighting, ie, healthy, response. On the other hand, if a child is not exposed to many microbes and is instead exposed to certain allergens (eg, dust, mold,

animal dander) the immune system will favor an allergic, inflammatory, ie, unhealthy, response. Studies support that children exposed to microbes early in life (living on farms, with older siblings or pets) have a lower risk of developing persistent wheeze later in life. Thus, the microbiome may be the intermediary step between the genetic risk of the host and clinical phenotype in asthma, and perhaps the key to primary prevention of asthma. (25)

Furthermore, allergen exposure and viral infections act synergistically in the development of asthma. (26) Children with asthma, or at risk for asthma, sensitized and exposed to perennial allergens (ie, dust, mold, mouse, rat, or cockroach), often experience airway inflammation when infected with rhinovirus. (27) Rhinovirus (subtype C) has specifically been implicated in connection with development of asthma and asthma exacerbation. (27)(28)

Cytokine-mediated inflammation in allergic asthma is the most important recent discovery in asthma pathogenesis. The airways of a sensitized child with asthma release mediators, damaging the epithelium. Th2 lymphocytes trigger the release of cytokines (interleukin [IL]-4, IL-5, IL-9, IL-13, among others), which upregulate or downregulate other cytokine receptors. (29)(30) Cytokines stimulate IgE production, mast cells, basophils, and eosinophils, which mediate inflammation via histamine, prostaglandins, and leukotrienes. (30) Newer therapies interrupt the inflammatory pathway by inhibiting the actions of specific mediators (IgE and IL-5).

Mechanistic analysis at an individual's cellular level could help guide targeted therapy. A precision medicine approach could reduce morbidity in disproportionately affected subgroups. (31) A recent study identified pro-inflammatory monocytes and type 2 cytokine activity to be more commonly associated with poorly controlled asthma in socioeconomically disadvantaged children than children with a higher socioeconomic status after controlling for potential confounders (age, sex, racial group, BMI, asthma severity, and medication use). These children also had reduced expression of genes that coded for interferon. (32) Lower levels of interferon have previously been associated with increased viral-induced exacerbations. (33)(34)(35)

TRIGGERS

Respiratory viral infections are the most common triggers of asthma exacerbation in children. (36)(37) Annual fall increases in asthma exacerbation, or the *September epidemic,* occur when many children returning to school have asthma exacerbations triggered by rhinovirus infection. (38)(39) Specific viral infections have also been found to be

associated with increased exacerbation severity (rhinovirus [subtype C] [27] and influenza A [H1N1] [40]) and treatment failure (respiratory syncytial virus, influenza, and parainfluenza). (41) A study of influenza-related pediatric deaths between 2000 and 2016 found that 12% had asthma. (42) Annual influenza vaccination for children with asthma is considered best practice and is recommended for patients with asthma. (43) The 2018-2019 recommendations from the Advisory Committee on Immunization Practices recommend against use of the live attenuated influenza vaccine (LAIV) in children aged 2 through 4 years who have a diagnosis of asthma or have had a wheezing illness in the preceding 12 months due to a concern that the LAIV could induce exacerbation. (44) Although the 2018-2019 LAIV guidelines have not been changed, new evidence from a large trial showed improved protection and no increased risk of exacerbation with the LAIV in children with asthma. (45) Of note, the 2017-2018 and 2018-2019 American Academy of Pediatrics guidelines did not recommend the LAIV as the primary choice of influenza vaccination for all children 6 months and older owing to concerns of decreased effectiveness of the LAIV against influenza A/H1N1 in past seasons and uncertainty regarding its effectiveness this season. (46) Recently published 2019-2020 American Academy of Pediatrics guidelines, consistent with Centers for Disease Control and Prevention (CDC) recommendations, advise patients to get the LAIV. To be clear, however, details regarding recommendations for patients with asthma have not been released.

Other triggers can be organized into several categories. First, irritants bother any airway and can induce bronchospasm when a child with asthma is exposed. These include environmental tobacco smoke (47)(48)(49) and other burnt substances (candles, incense, marijuana, and electronic cigarettes); air pollution, particulate matter (fractions of particles with an aerodynamic diameter smaller than 2.5 and 10 μm), and ozone (50); chemicals in certain cleaning products; particles in the air (construction sites, perfumes, paints, soaps); and wood or charcoal fires. Allergens are specific to the child and trigger asthma in children with atopy, sometimes referred to as *allergic asthma*. These are divided into perennial allergens (mold spores, cockroaches, rats, mice, dust mites, and pet dander) and seasonal allergens (tree, weed, and grass pollens).

Weather (rapid changes or extreme cold/hot air) and strong emotions (laughter, crying, or anger) are other common triggers of bronchospasm in children with asthma. Also, medications such as β-blockers, aspirin, and nonsteroidal anti-inflammatory drugs are associated with inducing asthma exacerbations in a subset of the population.

Last, exercise and other strenuous activity are frequent triggers. Exercise-induced symptoms are more common with poorly controlled asthma. (43) Preexercise preventive short-acting inhaled β_2-agonist (SABA) with or without a step-up in asthma control is standard management. (43) Exercise-induced asthma is a rare, often overdiagnosed phenotype, where a child wheezes or coughs only after a short period of vigorous activity and symptoms improve 20 to 30 minutes after cessation of activity. Other comorbid conditions, such as severe uncontrolled allergic rhinitis, obesity, and vocal cord dysfunction, should be considered when evaluating exercised-induced symptoms. Vocal cord dysfunction, or paradoxical vocal cord motion on inspiration, typically presents with the following distinguishing features: rapid onset and offset, usually minutes to seconds; dyspnea reported on inspiration (or inspiration and expiration); patient localization of the throat and not the chest as the source of discomfort; SABA or rescue inhaler usually reported as not helping; symptoms induced by stress, anxiety, aerobic exercise, or irritants; and a flow-volume loop with a classic appearance, ie, a truncated inspiratory flow loop with a normal expiratory loop.

Another entity often confused with asthma is exercise-induced laryngeal obstruction (EILO). Any concern for vocal cord dysfunction and EILO should prompt referral to otolaryngology for further testing. Continuous laryngoscopy during exercise is the gold standard for diagnosis of EILO.

Families should be counseled on trigger identification and avoidance at routine visits for asthma care. Efforts should be made to mitigate exposure to perennial allergens (mold spores, dust mites, animal dander, cockroaches, rats, and mice) for patients with asthma with evidence by clinical history (symptoms with exposure) and allergen sensitization on skin prick testing or from serum specific IgE measurements. The following is a list of recommendations by allergen:

- Dust mites—provide mattress and pillow encasements, (51) vacuum twice a week, consider removal of carpet in the bedroom if there are significant nighttime symptoms, remove any stuffed animals from the child's bed or recommend machine washing of stuffed animals in hot water
- Mold spores—avoid humidifier use; remediate any water damage/mold in the home
- Pests—keep food out of the bedroom and in closed trash containers, exterminate if needed (preference of traps over sprays)
- Animal dander—consider removal of animal if that is an option or recommend special hypoallergenic breeds

Environmental triggers are a major contributor to health disparities in pediatric asthma. (6) Removal of allergens in homes of children younger than 6 years with associated asthma could reduce asthma risk by 40%. (52) In addition, poor mental health is associated with poor asthma control. (53)(54) A thorough approach to potential exposures includes care coordination of appropriate referrals (allergist, nutritionist, gastroenterologist, otolaryngologist, mental health consultant), connection to community partners (local organizations that conduct home visits, provide vacuums or mattress and pillow encasements; local housing authority; 1-800-QUITLINE or other smoking cessation assistance), legal advocacy (legal aid to assist the family in advocating for housing remediation if the landlord is not being compliant with housing regulations, local law schools may also have free legal services), social work, and close follow-up for at-risk children. Tailored, comprehensive interventions reduce asthma morbidity rates in at-risk children. (15)(18)(55)(56)

CLINICAL ASPECTS

Diagnosis

Asthma in children remains largely a clinical diagnosis. A child with a family history of asthma presenting with episodic and recurring chest tightness, cough, difficulty breathing, or wheeze in response to common triggers who also demonstrates improvement with a SABA likely has asthma. In older children, demonstration of reversible bronchospasm on pulmonary function testing (PFT) is diagnostic for asthma.

The diagnosis of asthma in younger children remains challenging. Children younger than 5 years are unable to provide the effort required to reliably obtain PFT results. The Asthma Predictive Index is a clinical tool sometimes applied to children 3 years and younger with wheezing to assist with treatment and prediction of asthma. A combination of major criteria (doctor-diagnosed parental asthma or eczema) and minor criteria (doctor-diagnosed allergic rhinitis, wheezing without viral upper respiratory tract infections, or peripheral eosinophilia ≥4%) help determine risk. (57) In the original cohort, a child with wheezing and either 1 major or 2 minor criteria was 2 to 5 times more likely to have active asthma at age 6 to 13 years and 4 to 9 times more likely if they had both 1 minor and 2 major criteria. (57) A recent study developed a new clinical tool, the Pediatric Asthma Risk Score, which performed better than the Asthma Predictive Index to predict mild to moderate asthma. (58) The tool is available online for clinicians to use at https://pars.research.cchmc.org/.

In addition, measuring airway inflammation using fractional excretion of nitric oxide (FeNO) may help evaluate asthma in children who have eosinophil-mediated lung inflammation. (59) However, FeNO testing is not always covered by insurance, the equipment is seldom available in the primary care office, and guidelines do not recommend routine use. (43)(60) The 2018 Global Initiative for Asthma guidelines did report on benefits in certain situations, (60) and the update for the next National Asthma Education and Prevention Program (NAEPP) guidelines has listed FeNO as 1 of 5 areas for intensive future review. (61)

Wheezing is the characteristic finding on lung auscultation in a child experiencing asthma exacerbation, but it is not specific to asthma. Wheezing results from airflow obstruction in the lower airways and is present in many other conditions. Broad differential diagnoses of wheezing should be considered for any child with an initial episode of wheeze or difficult-to-control asthma or if there is report of little or no relief of symptoms with SABA rescue. When considering an alternative diagnosis, it is important to remember that a child could still have concomitant asthma. Table 1 lists alternative diagnoses in a child with wheeze, starting with more common entities, by age, typical findings, and testing recommendations. Another approach would be to consider alternative diagnoses by system (infectious, cardiac, pulmonary, hematologic) or mechanical obstruction causing wheeze. The latter approach is helpful when eliciting a review of systems and completing a focused physical examination in a child with first-time wheeze or difficult-to-control previously diagnosed asthma. Finally, several key historical features are important to elicit to assess severity: family history of asthma/atopy or other illness, age at onset of symptoms, episodic versus persistent disease, potential triggers or exposures, responsiveness to SABA, positionality of symptoms, and systemic signs of illness (poor weight gain, fevers, fatigue, or pallor) (Fig 1). Occasionally, a dry chronic cough is the only presenting symptom of asthma in children. These children warrant a detailed history and examination, spirometry, and a trial of bronchodilators if asthma is suspected. However, cough variant asthma is rare in children, and failure to improve with bronchodilator use should prompt further investigation.

Children with poor access to primary care often use urgent or emergency care for wheezing episodes; the chronic and recurrent nature of symptoms may lead to a delayed or missed asthma diagnosis. (63)

Diagnostic Testing/Adjuncts in Asthma

Peak Flows. Measurement of peak expiratory flow (PEF) is portable and relatively inexpensive and provides families of children older than 5 years with objective data to initiate rescue medications. A child should determine his or her personal best (the best of 3 measurements performed daily

## TABLE 1. Differential Diagnosis of Asthma by Age and Characteristic Findings

DIAGNOSIS	AGE	FINDINGS THAT DIFFERENTIATE FROM ASTHMA	DIAGNOSTIC TESTS
Bronchiolitis	<24 mo	No atopy, typically not responsive to SABA, context of fever and viral respiratory tract infection	Clinical diagnosis
Viral-induced wheeze	Any age (<4 y more common)	Wheezing only with viral respiratory tract infections, less atopy; usually resolves by age 4 y (62)	PFT if frequent or severe
Bronchopulmonary dysplasia	<24 mo	Symptoms since birth in premature infant	Clinical diagnosis
Chronic aspiration/GERD	Any	Chronic cough especially after meals, gastrointestinal symptoms	Gastroenterology referral, endoscopy, pH probe
Tracheomalacia/bronchomalacia	<24 mo	Symptoms since birth, constant (as opposed to intermittent or triggered); stridor present with tracheomalacia	Laryngoscopy
Bronchiectasis	Any	Symptoms since birth, wet chronic cough, recurrent wheeze with focal lung findings, recurrent pneumonia in same location on CXR, sometimes with hemoptysis	Chest CT, bronchoscopy
Food allergy	Any	First-time wheeze in context of new food exposure and other signs of food allergy (lip swelling, vomiting, hives, hypotension)	Allergy testing, PFT
Anxiety/panic attack	School age or older	No wheezing, no improvement with SABA	Clinical diagnosis, PFT results normal
Vocal cord dysfunction	Adolescent +	Acute onset of symptoms within minutes of exercise or exposure to an irritant, symptoms quickly resolve and do not respond to SABA, sensation of airway closing, throat tightness, no symptoms during sleep; occasionally will hear inspiratory stridor on examination; hoarse voice	PFT shows classic pattern of dynamic airflow obstruction: laryngoscopy
Heart failure	Any	Fever (viral myocarditis), missed congenital heart disease, failure to thrive, symptoms worsen with feeding in young infant or with laying down; murmur, poor central pulses, hepatomegaly, crackles	Echocardiography, electrocardiography, CXR
Foreign body aspiration	<4 y (could be any age)	Acute onset of symptoms, unilateral findings, history of choking spell	Anteroposterior/posteroanterior or bilateral decubitus CXR; bronchoscopy
Mass effect (from vascular anomaly or tumor)	Any	Unilateral wheeze or stridor (may be positional, if due to a mass, ring, or sling around upper airways), symptoms worse with laying down; weight loss and other systemic signs if oncologic	Chest CT, bronchoscopy
Underlying immunodeficiency	Any	Recurrent bacterial pneumonia	CXR, immunology evaluation
Allergic bronchopulmonary aspergillosis	Any	Difficult-to-control asthma symptoms, chronic cough and intermittent fevers	Sputum, *Aspergillus* IgE and IgG, CXR
Cystic fibrosis	Any	Failure to thrive (may still have a normal newborn screen)	Sweat chloride testing, genetic testing

CT=computed tomography, CXR=chest radiography, GERD=gastroesophageal reflux disease, IgE=immunoglobulin E, IgG=immunoglobulin G, PFT=pulmonary function testing. SABA=short-acting inhaled β_2-agonist.

for 2 weeks) and use this number to guide acute management. (43) If the PEF falls below 80% of the child's personal best, the child or caregiver should initiate rescue medications per the asthma action plan. Generally, 70% to 80% of personal best is equivalent to yellow zone management of asthma, and 40% to 70% is equivalent to red zone management (Tables 2 and 3, Fig 2). (43) In practice, specialists who have access to in-office spirometry sometimes correlate a patient's PFT to PEF and use that to guide the determination of a child's personal best. If a child does not know his or her personal best, charts based on age and height can be used to provide general ranges. Symptoms (cough, shortness of breath, exercise intolerance) correlate with PEF and should be used to guide acute management, especially in younger children who are not able to reliably measure their PEF. When teaching patients how to use a peak flow meter, it is important to demonstrate and ask that a tight seal is made with the lips around the mouthpiece. After forcefully inhaling in, the child forcefully exhales with 1 quick breath to measure his or her PEF. Limitations of PEF include poor reliability between devices, high dependence on patient effort, and inability to detect small airway obstruction. Therefore, patients should use the same peak flow meter each time, and technique should be reviewed frequently.

PFT/Spirometry. PFT is recommended in children older than 5 years for routine management of asthma and when the diagnosis is in question. PFT is more accurate than PEF. The 2 readings important in the diagnosis and evaluation of asthma are forced expiratory volume in 1 second (FEV_1) and the ratio of FEV_1 to forced vital capacity or $FEV_{1\%}$. $FEV_{1\%}$ is the proportion of forced vital capacity a child is able to expire in 1 second. The goal of PFT in asthma is to document expiratory flow limitation or obstruction with reversibility. An $FEV_{1\%}$ of less than 0.80 is diagnostic for airflow obstruction, and reversibility with administration of a bronchodilator is diagnostic for asthma. If a child is able to fully cooperate, an $FEV_{1\%}$ greater than 0.8 is normal. The classic flow-volume curve for asthma shows a dampening and scooping out of the expiratory curve. Periodic spirometry measurements can also be helpful to measure lung function because a primary goal of asthma is to maintain healthy lung function.
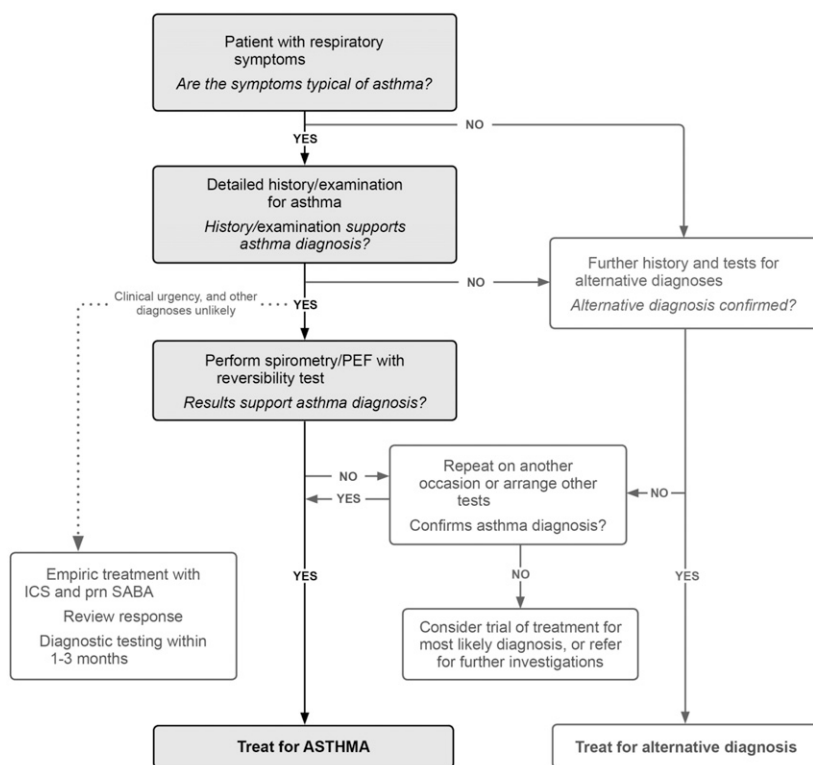
ICS: inhaled corticosteroids; PEF: peak expiratory flow (highest of three readings). When measuring PEF, use the same meter each time as the value may vary by up to 20% between different meters; prn: as-needed; SABA: short-acting beta₂-agonist.
Bronchodilator reversibility may be lost during severe exacerbations or viral infections, and in long-standing asthma. If bronchodilator reversibility is not found at initial presentation, the next step depends on the availability of tests and the clinical urgency of need for treatment.

Figure 1. Diagnosis of asthma: basic approach to a child with respiratory symptoms consistent with asthma. ©2019 Global Initiative for Asthma, available from www.ginasthma.org [ginasthma.org], reprinted with permission.

TABLE 2. Asthma Medications (Quick Relief) (43)

MEDICATION	DOSING RECOMMENDATION	NOTES
INH Short-Acting β_2-Agonists (to relax the smooth muscles; activates β_2 adrenergic receptors in the lungs, resulting in bronchodilation)		
Albuterol MDI (90 μg/puff; 200 puffs/canister)	Preexercise dosing: 2 puffs INH 15 min before exercise For single dose (yellow zone management on AAP): 2–4 puffs INH every 4–6 h as needed for symptoms For acute exacerbation (red zone management on AAP): 4–8 puffs every 20 min × 3 doses: ≥5 to <10 kg: 4 puffs INH every 20 min for 3 doses ≥10 to <30 kg: 6 puffs INH every 20 min for 3 doses ≥30 kg: 8 puffs INH every 20 min for 3 doses	Indicated for quick relief of bronchospasm or to prevent bronchospasm related to exercise Adverse effects include tachycardia and tachypnea
Albuterol inhalation solution (0.63 mg/3 mL, 1.25 mg/3 mL, 2.5 mg/3 mL, or 5 mg/mL)	≥5 to <30 kg: 2.5-mg neb INH for single dose OR 7.5-mg neb INH for 1 h ≥30 kg: 5-mg neb INH for single dose OR 15-mg neb INH for 1 h If still wheezing and in distress after 2 h of short-acting β_2-agonist, consider continuous neb treatment (0.6 mg/kg per hour): ≥5 to <10 kg: 5-mg/h neb INH every 1 h ≥10 to <20 kg: 10-mg/h neb INH every 1 h ≥20 to <30 kg: 15-mg/h neb INH every 1 h ≥30 kg: 20-mg/h neb INH every 1 h	
Anticholinergics (antimuscarinic agent [blocks action of acetylcholine], which results in decreased contractility of smooth muscle resulting in bronchodilation)		
Ipratropium bromide inhalation solution (0.25 mg/mL)	0.25–0.5 mg neb INH every 20 min for 3 doses ≥5 to <30 kg: 0.5 mg neb INH once 30 kg: 1 mg neb INH once	Indicated in the ED setting for moderate to severe exacerbation Can cause transient dilation of the pupil(s) and blurry vision if neb formulation is blown into the eyes for a prolonged period
Ipatropium bromide MDI (18 μg/puff)	4–8 puffs every 20 min INH for 3 doses	
Systemic Corticosteroids (anti-inflammatory; reverses B2-receptor downregulation)		
Dexamethasone	Short course (burst): ≥7 to <10 kg: 6 mg PO once with repeat dose in 24 h ≥10 to <20 kg: 10 mg PO once with repeat dose in 24 h ≥30 kg: 16 mg PO once with repeat dose in 24 h OR 0.6 mg/kg IV or IM (max, 16 mg) in children not tolerating oral medications	Indicated for treatment of moderate to severe exacerbations
Prednisone (1-, 2.5-, 5-, 10-, 20-, and 50-mg tablets)	Short course (burst): 1–2 mg/kg per day PO (max, 60 mg) for 3–10 d divided twice daily	Consider comorbidities, eg, studies show patients with sickle cell disease and asthma have rebound acute chest syndrome with systemic corticosteroids and, hence, should be avoided (64)
Prednisolone (5 mg/5 mL or 15 mg/5 mL)	Short course (burst): 1–2 mg/kg per day PO (max, 60 mg) for 3–10 d divided twice daily	Will raise serum glucose so use with caution in diabetes
Methylprednisolone	Short course (burst): 1–2 mg/kg per day IV (max, 60 mg) for 3–10 d divided every 6–12 h	
Adjunct acute asthma medications		
Magnesium sulfate	50 mg/kg per dose (max, 2,000 mg/dose) IV once over 20 min	Consider after 1 h of short-acting β_2-agonists and after systemic corticosteroids if still with respiratory distress and wheezing

Continued

TABLE 2. (Continued)

MEDICATION	DOSING RECOMMENDATION	NOTES
Epinephrine (1:1,000) (1 mg/mL)	0.01 mg/kg per dose (max, 0.5 mg/dose) IM once	Consider in severe, life-threatening asthma

AAP=asthma action plan, ED=emergency department, h=hour, INH=inhaled, IM=intramuscular, IV=intravenous, max=maximum, MDI=metered-dose inhaler, neb=nebulized, PO='per os' or by mouth.

Methacholine Challenge. Bronchoprovocation tests, such as the methacholine challenge, are not a common practice in pediatrics and are usually performed only by specialists. In addition, methacholine challenge testing has high negative predictive power and, hence, performs well in establishing the lack of asthma, or ruling out disease. (66)

Impulse Oscillometry. Impulse oscillometry is a newer PFT that allows for passive measurement of lung function. It is useful for children as young as 3 years and other children who have difficulty with traditional PFT because minimal effort is required by the child. (67) However, impulse oscillometry is only available in a pulmonologist's office.

Chest Radiography. Chest radiographs are low yield in the acute setting and rarely change management. However, obtaining a radiograph should be considered when a child presents with hypoxia and high fever and is not improving on albuterol and systemic corticosteroids. (68)

Furthermore, a chest radiograph may be indicated at the first presentation of wheeze or when considering alternative diagnoses other than asthma (Table 1).

Management

The overall goal in managing asthma in children is to reduce impairment (maintaining a good quality of life, allowing for normal activities without limitation, and reducing missed school days) and to reduce risk (keeping children off systemic corticosteroids, out of the hospital and ED, and maintaining healthy lung function to prevent airway remodeling that is associated with chronic inflammation).

Severity Classification

The NAEPP guidelines, last revised in 2007, set age-based criteria to standardize the classification and management of asthma. The guidelines for classification are based on the magnitude of a child's risk (occurrence of acute severe exacerbations in the past 12 months) and impairment (day-to-day symptoms over the past 4 weeks). Based on risk and impairment, asthma is classified into intermittent, mild persistent, moderate persistent, and severe persistent.

Control, using similar assessments of risk and impairment, should be assessed every 3 months at routine asthma visits and is classified as well controlled, not well controlled, or very poorly controlled. Figure 2 details the current approach to initial assessment of disease severity and ongoing assessment of control. Classification and control designation of asthma guides should be made at each visit per NAEPP guidelines.

Longitudinal Care

Once asthma severity and level of control have been determined, the guidelines specify initial therapy or change of therapy in a stepwise manner. (43) The mainstay of asthma therapy consists of bronchodilators (ie, SABA) for rescue therapy to relax the smooth muscles surrounding the airway (bronchodilation) and corticosteroids to help reduce inflammation inside the airway. A routine asthma visit should be scheduled every 3 to 6 months. Barriers to asthma control, adherence, and demonstration of proper medication administration should be assessed and addressed at each visit. Treatment decisions should be based on recommended step level only after adherence has been assessed and triggers have been identified in conjunction with a plan for trigger modification/avoidance (Fig 2). (69)

Management of chronic asthma can be confusing for children and families. Education should be provided using lay terminology. Visual aids to illustrate narrowed airways and explain which medications reverse bronchospasm and offer quick relief (SABAs) versus reduce and control inflammation (corticosteroids or leukotriene receptor antagonists [LTRAs]) are helpful. A misunderstanding in the difference between quick-relief medications and daily controller medications is a common barrier to adherence (Tables 2 and 3). The instructions should be clear, communicated verbally and in writing (with a detailed asthma action plan), and reinforced at each visit. A typical asthma action plan is divided into 3 sections. The green zone provides instructions on routine medications (ICSs, LTRAs, preexercise SABAs, allergy medications). The yellow zone provides instructions about home management of acute, mild

TABLE 3. Asthma Medications (Maintenance or Controller Medications) (65)

MEDICATION	DAILY DOSE, BY AGE			ADVERSE EFFECTS
	0–4 Y	5–11 Y	≥12 Y	
Leukotriene modifiers				
Montelukast (leukotriene receptor antagonist) 4- or 5-mg chewable tablet 4-mg granules or 10-mg tablet	(1–5 y): 4 mg by mouth once before bedtime (6–14 y): 5 mg by mouth once before bedtime (>14 y): 10 mg by mouth once before bedtime			
Immunomodulators				
Omalizumab (anti-IgE) SC injection, 150 mg/1.2 mL, after reconstitution with 1.4 mL of sterile saline	NA	≥6 y: 150–375 mg SC every 2–4 wk (depends on bodyweight and pretreatment serum IgE levels)	150–375 mg SC every 2–4 wk (depends on bodyweight and pretreatment serum IgE levels)	Pain and bruising at injection sites Risk of anaphylaxis (0.2%)
Long-acting muscarinic antagonist				
Tiotropium bromide*2.5 µg (2 actuations; 1.25 µg/actuation)	NA	≥6 y: 2 actuations inhaled daily	2 Actuations inhaled daily	Caution with use if creatinine clearance <60 ml/min
Inhaled corticosteroids				
Beclomethasone HFA: 40 or 80 µg/puff	NA	(L): 80–160 µg (M): >160–320 µg (H): >320 µg	(L): 80–240 µg (M): >240–480 µg (H): >480 µg	Must rinse mouth after each use to prevent oral thrush and systemic absorption
Budesonide DPI: 90 or 180 µg/inhalation	NA	(L): 180–360 µg (M): 360–720 µg (H): >720 µg	(L): 180–540 µg (M): 540–1080 µg (H): >1,080 µg	
Budesonide nebules: 0.25, 0.5, or 1 mg	(L): 0.25–0.5 mg (M): >0.5–1 mg (H): >1 mg	(L): 0.5 mg (M): 1 mg (H): 2 mg		
Flunisolide HFA: 80 µg/puff	NA	(L): 160 µg (M): 320–480 mg (H): >480 µg	(L): 320 µg (M): >320–640 µg (H): >640 µg	
Fluticasone HFA/MDI: 44, 110, 220 µg/puff	(L): 176 µg (M): >176–352 µg (H): >352 µg	(L): 88–176 µg (M): >176–352 µg (H): >352 µg	(L): 88–264 µg (M): >264–440 µg (H): >440 µg	
Fluticasone DPI: 50, 100, or 250 µg/inhalation	NA	(L): 100–200 µg (M): >200–400 µg (H): >400 µg	(L): 100–300 µg (M): >300–500 µg (H): >500 µg	
Mometasone DPI: 110 µg, 220 µg/inhalation HFA: 100 µg, 200 µg/puff	NA	(L): 110 µg (M):>220–440 µg (H): >440 µg	(L): 100–220 µg (M): >200–440 µg (H): >440 µg	

Continued

TABLE 3. (Continued)

MEDICATION	DAILY DOSE, BY AGE			ADVERSE EFFECTS
	0–4 Y	5–11 Y	≥12 Y	
Inhaled corticosteroid + long-acting B₂-agonist (combination medications)				
Fluticasone/salmeterol DPI: 100 mcg/50 µg, 250 mcg/50 µg, or 500 mcg/50 µg HFA: 45 mcg/21 µg, 115 mcg/21 µg, 230 mcg/21 µg	NA	1 Inhalation BID Not well controlled and on low- to medium-dose ICS: 100/50 DPI or 45/21 HFA Not well controlled and on medium- to high-dose ICS: 250/50 DPI or 115/21 HFA		Must rinse mouth after each use to prevent oral thrush
Budesonide/formoterol HFA MDI: 80 mcg/4.5 µg, 160 mcg/4.5 µg	NA	Not well controlled and on low- to medium-dose ICS: 80/4.5 Not well controlled and on medium- to high-dose ICS: 160/4.5		
Mometasone/formoterol MDI: 100 µg/5 mcg	NA	NA	2 Inhalations BID (depends on asthma severity)	

Doses are per National Asthma Education and Prevention Program update in September 2012 except for (*). Source: National Heart, Lung, and Blood Institute; National Institutes of Health; US Department of Health and Human Services. BID=twice a day, DPI=dry powder inhaler, (H)=high daily dose, HFA=hydrofluoroalkane, ICS=inhaled corticosteroid, IgE=immunoglobulin E, (L)=low daily dose, (M)=medium daily dose, MDI=metered-dose inhaler, NA=not available (not approved, no data available, or safety and efficacy not established in this age group), SC=subcutaneous.

exacerbations with escalation to red zone management while seeking emergency medical care. Children with persistent asthma should be seen every 3 months to assess ongoing control and to adjust controller medications. Providing tools (smartphone alarms, mobile applications, or simply placing the daily inhaler and spacer next to the toothbrush) may improve adherence. (70)

Adherence to medication is also affected by improper delivery. Spacer use with a demonstration of appropriate technique should be assessed at each visit. All patients, regardless of age, should use a spacer when using a metered-dose inhaler rescue or controller medication. The spacer ensures delivery of the medication to the lungs and reduces medication that deposits inside of the mouth with subsequent systemic absorption. Both mask and mouthpiece spacer should be appropriate, and the choice is mostly based on age and ability to demonstrate proper technique. Exceptions for spacer use include new devices that either have a built-in spacer and devices with specific instructions to not use a spacer (this should be included in the package insert). All children taking controller ICSs should rinse their mouth after use to prevent oral thrush and to minimize systemic absorption. A video demonstrating proper spacer technique is available online (https://vimeo.com/channels/impactdc).

Frequent introductions of new delivery systems for asthma medications are common with changes in insurance formularies and the availability of new devices on the market. Providers must be vigilant to ensure insurance coverage of prescribed medications and should check manufacturer websites for online videos to familiarize themselves with proper technique of new devices to teach their patients.

Finally, it is crucial to assess parent and adolescent "buy-in" to chronic medication use. For a parent, it helps to explain the process inside the lungs in the context of therapeutic effect and potential for airway remodeling (71) if chronic uncontrolled asthma persists. For an adolescent, the consequences have to be more immediate, ie, the ability to perform better at their specific sport or extracurricular activity with regular use of controller medications.

Persistent asthma requires a thorough and ongoing assessment of potential comorbid conditions. Addressing potentially treatable comorbidities commonly seen with childhood asthma (obesity, [72] obstructive sleep apnea, allergic rhinitis, gastroesophageal reflux, and stress or depression) could avoid unnecessary escalation of asthma therapy. A complete review of symptoms should reveal these diagnoses.

Finally, when prescribing controller medications, the provider should ensure patient access to medications. In addition to assessing insurance coverage of the ICS brand, a

Figure 2. Asthma control, severity classification, and treatment flow diagram for children 5 years and older. (43)(69)

1. Assess Severity (4 weeks prior)	IMPAIRMENT	Daytime symptom Frequency	≤ 2 days per week	> 2 days per week but not daily	daily	throughout the day
		Nighttime awakenings	≤ 2 nights per month	3-4 nights per month	> 1 night per week	every night
		SABA rescue (not counting pre-exercise)	≤ 2days per week	> 2 days per week (not daily)	daily	several times per day
		Activity Limitation[a]	none	minor	some	extreme
	RISK	Exacerbations requiring systemic corticosteroids	0-1 per year	≥ 2 exacerbations in 12 months requiring systemic steroids or more severe exacerbations (intensive care, etc.)		

If already on a controller (assess CONTROL):

NO ← Maintain current therapy STEP AND address barriers to adherence[b] — **Is controller being taken appropriately?** — YES → Increase by 1 STEP unless well-controlled (all answers in GREEN column above)

2. Assign Severity	Assign based on WORST symptom column above	INTERMITTENT	MILD PERSISTENT	MODERATE PERSISTENT	SEVERE PERSISTENT	
3. Treatment recommendation by NHLBI Step (age-based doses available in NAEPP Guidelines)	**5-11 years old**	Step 1 — SABA as needed	Step 2 — low-dose ICS or LTRA[b]	Step 3 — low-dose ICS + LABA/LTRA[b]	Step 3 — medium-dose ICS	Step 4/5 — Step 4: medium-dose ICS + LABA/LTRA[b]; Step 5: high-dose ICS + LABA/LTRA[b]
	≥ 12 years old	Step 1 — SABA as needed	Step 2 — low-dose ICS or LTRA[b]	Step 3 — low-dose ICS + LABA/LTRA[b] or medium-dose ICS	Step 4 — medium-dose ICS+ LABA/LTRA[b]	Step 5 — high-dose ICS + LABA/LTRA[b]
	Other considerations (if poorly controlled)		Allergy immunotherapy — Short course of oral steroids, referral to specialist — Immunomodulators			

4. Ensure access	• Remember to prescribe spacer and rescue inhaler for home, school and second place of residence if child splits time between family members • Check insurance coverage
5. Address environmental triggers	• Refer to 1800-QUIT LINE if amenable to smoking cessation • Refer to local services that offer in home trigger assessment • Advocate for better housing through landlord letters or pro-bono lawyers (mold, dust, ventilation)
6. Complete *Asthma Action Plan* and schedule follow-up visits	• Provide multiple copies of asthma action plan for school, home and providers • Schedule follow-up care every (2-6 weeks while gaining control, 1-6 months to monitor control, 3 months if step down therapy is anticipated) • Assess and address any side effects, comorbid conditions (obesity, depression, allergic rhinitis, gastroesophageal reflux, obstructive sleep apnea) • Ensure routine influenza vaccination • Review technique and adherence at each visit

[a] Activity limitation is more often a symptom of poor control and not exercise induced asthma
[b] LTRA considered alternative therapy, if on an alternative therapy and patient needs STEP UP consider preferred regimen before STEP UP; LTRA helpful in patients with allergies or exercise induced symptoms
Abbreviations: **ICS** – Inhaled Corticosteroid **SABA**- Short-acting inhaled β₂-agonist **LABA**- Long-acting inhaled β₂-agonist **LTRA**- Leukotriene receptor antagonist

family's ability to pay or afford the co-pay should be considered. Privately insured families with limited additional funds may qualify for coupons available on the manufacturer's website. Also, if possible, one should obtain prior authorizations for additional spacers and rescue inhalers for school and multiple residences because a child may live in multiple households. Routine follow-up appointments should be scheduled at the time of visits, and the importance of these visits with plans for step-up or step-down therapy should be communicated to families. Addressing barriers, (73) coordinating care, (15) and ensuring adherence to guideline-based care (74) are imperative for reducing disparities in asthma care.

Allergy testing for indoor allergens (certain molds, animal dander, house dust mites, and cockroach) is recommended for patients with persistent asthma and reported exposure to allergens. (43)(60) Guidelines recommend targeted skin prick testing because it is low cost and accurate, and targeted serum specific IgE if a child is uncooperative. (60) In practice, it is important to obtain a clinical history of allergen exposure because any report of asthma symptoms in reference to an exposure supersedes allergy testing

results, and allergen avoidance should continue to be recommended.

In addition, children with severe allergic rhinitis may benefit from subspecialist referral to an allergist for consideration of specific and targeted immunotherapy. Current evidence supports in-office subcutaneous immunotherapy for single allergens in children with persistent asthma and a clear relationship between symptoms and exposure to a specific allergen to which the patient has documented sensitivity. Guidelines support immunotherapy for 3 specific allergens: dust mites, animal dander, and pollen. (43) Patients who receive immunotherapy are at risk for anaphylaxis and should be closely monitored. The update for the 2007 NAEEP guidelines lists immunotherapy as 1 of the 5 specific areas of future in-depth review. (61)

Severe Asthma

Immunomodulatory medications, or biological agents, are emerging treatments in children with moderate to severe asthma. If a child is taking medium- to high-dose ICS and long-acting inhaled β₂-agonist and demonstrates poor control despite proper technique and good adherence (frequent

TABLE 4. Recent Evidence for Emerging Trends in the Treatment of Asthma

PRACTICE CONSIDERATION	EVIDENCE POPULATION, NO.	DESIGN	FINDINGS (LIMITATIONS)	RECOMMENDATION
School-based asthma therapy				
Halterman et al (2011) (82)	Children aged 3–10 y with asthma and Medicaid insurance (n = 530)	Prospective RCT comparing home versus school administration of ICS	School administration of ICS effectively improves adherence (performed in conjunction with dose adjustment as needed and tobacco smoke reduction program) (single site)	Recommend partnership with local school to see whether school-based asthma therapy is a feasible alternative to home-based therapy, especially for those patients with poor adherence. Consider direct delivery of medications to the school.
Fall montelukast				
Johnston et al (2007) (83)	Children aged 2–14 y with asthma (n = 194)	RCT, double-blind, placebo-controlled trial comparing a group started on age-appropriate nightly dose of montelukast from September 1 for 45 d	53% Decrease in "worse asthma symptoms" and 78% reduction in unscheduled asthma visits; boys 2–5 y and girls 10–14 y with most benefit (no minimum asthma severity for inclusion; pragmatic trial with poor adherence to ICS in study population)	Mixed results; could consider Fall montelukast in a persistent asthma population with poor ICS adherence (especially males aged 2–5 y and females aged 10–14 y)
Weiss et al (2010) (84)	Children aged 6–14 y with asthma (n = 1162)	RCT, multicenter, double blind, placebo controlled, comparing 5-mg montelukast night before day 1 of school for 8 wk; evaluated percent days with worse asthma	No difference between placebo and montelukast groups (no minimum asthma severity for inclusion)	
Preseasonal treatment with omalizumab				
Teach et al (2015) (85)	Inner-city asthmatic children aged 6–17 y with ≥1 recent exacerbations (n = 727)	3-arm RCT, double blind, double placebo controlled, multicenter	Compared to placebo, omalizumab had a significantly lower rate of fall exacerbations, and omalizumab boosted interferon levels with a decrease in rhinovirus infection in the omalizumab group	Consider the addition of omalizumab to guidelines-based therapy for inner city children, aged 6-17 y, before the fall season, especially if they have a recent history of exacerbation
Intermittent, extreme high-dose ICS dose for acute asthma				
Jackson et al (2018) (86)	Children aged 5–11 y with mild to moderate persistent asthma, with 1 course of systemic corticosteroids in previous year (n = 254)	Double-blind RCT comparing low-dose ICS with quintupled-dose ICS for 7 d at early signs of loss of asthma control	No difference between the groups in degree of asthma control	Good evidence to recommend against intermittent escalation in ICS for yellow zone management in children; however, seasonal increase may be supported in an urban setting (87)(88)

Continued

TABLE 4. (Continued)

PRACTICE CONSIDERATION	EVIDENCE POPULATION, NO.	DESIGN	FINDINGS (LIMITATIONS)	RECOMMENDATION
McKeever et al (2018) (89)	≥16 y on any dose of ICS with ≥1 exacerbation in previous 12 mo requiring systemic corticosteroids (n = 1,922)	Pragmatic, randomized, unblinded trial comparing self-increase in ICS to 4 times the dose with those that did not increase baseline ICS dose for yellow zone management × 14 d or peak flow normal	Fewer severe exacerbations in high-dose ICS group (no children in low-dose ICS group; subject to bias and found only 19% reduction in increased ICS group) (87)(88)	* This contradicts current GINA recommendations. (60)
Decision support for guideline-based care				
Bell et al (2010) (17)	Urban primary care clinics (n = 12)	Cluster RCT trial of clinical decision support in the electronic health record	Improved primary care provider compliance with NAEPP guideline–based care (17)	Strong recommendation to consider implementation if feasible
Oral prednisolone in preschoolers with wheeze				
Panickar et al (2009) (90)	Children aged 10–24 mo hospitalized for viral-induced wheeze (n = 700)	RCT, double-blind, placebo-controlled, 5-d course of oral prednisolone	No difference in LOS of hospitalization	Good evidence to suggest against use of OCS in viral-induced wheeze
Foster et al (2018) (91)	Children aged 24–72 mo presenting to ED with viral-induced wheeze (n = 605)	RCT, double-blind, placebo-controlled, noninferiority trial, single dose of oral prednisolone to reduce ED LOS	Placebo group with longer LOS (540 min) versus prednisone group (370 min), single center, baseline very long LOS, unclear whether generalizable to different settings, unclear whether meaningful outcome studied)	
Dupilumab (anti–interleukin-4 receptor α monoclonal antibody) for moderate to severe uncontrolled asthma				
Castro et al (2018) (92)	Children aged ≥12 y, uncontrolled asthma (n = 1902)	Randomized to 4 arms to receive add on dupilumab every 2 weeks versus placebo for 1 y at 2:2:1:1 ratio	Lower rates of severe exacerbation and better lung function; results better in children with higher baseline eosinophilia	Promising results, good evidence for use of dupilumab in severe uncontrolled asthma (93)
Rabe et al (2018) (80)	Children age ≥12 y; OCS-dependent severe asthma (n = 210)	Random assignment of add-on dupilumab every 2 wk versus placebo for 24 wk in an attempt to reduce OCS dose	Improved lung function, decreased OCS dose, and fewer exacerbations in treatment group (small study)	

ED=emergency department, GINA=Global Initiative for Asthma, ICS=inhaled corticosteroid, LOS=length of stay, NAEPP=National Asthma Education and Prevention Program, OCS=oral corticosteroid, RCT=randomized controlled trial.

TABLE 5. Evidence-Based Management of Acute Asthma

PRACTICE	RECOMMENDATION
Systemic corticosteroids	Supports early administration of systemic corticosteroids in moderate to severe asthma exacerbations with reduction in need for hospitalization if given within 1 h of ED presentation. (100) Oral route is preferred route, and effects are considered equivalent. (43) Short course (1–2 d) of dexamethasone equivalent to 3- to 5-d burst of prednisolone in acute asthma exacerbation. (101) Equivocal data on single versus 2 doses of dexamethasone. (102)
Bronchodilator administration	MDI with spacer equally effective as nebulized bronchodilator therapy in the ED. (103)(104) Additional benefits include cost-savings (105) and decreased ED length of stay. (106) Equivocal studies on continuous versus intermittent bronchodilator nebulization for severe asthma, GINA guidelines recommend initial continuous therapy with spacing to intermittent in severe asthma. (60)
Inhaled ipratropium bromide	Supports use in moderate to severe exacerbations with SABA in preventing need for hospitalization, (107) no additional benefit during hospitalization. (108) Not routinely recommended in mild exacerbations. (43)(60)
Intravenous magnesium sulfate	No clear support for routine use due to paucity of data; however, administration of intravenous magnesium sulfate in moderate to severe asthma exacerbations if not improving after 1 h of bronchodilator and systemic corticosteroid treatment may reduce need for admission. (43)(109) A recent trial showed potential benefit for patients with severe asthma and pulse oximetry <92%. (95) More data needed.
Epinephrine	Insufficient evidence; however, guidelines support administration for children with very poor effort unable to adequately inhale nebulized bronchodilators or possibility of anaphylaxis and in life-threatening situations. Although no significant detrimental effects either. (43)(60)
Noninvasive respiratory support	Bilevel positive airway pressure has been studied more than HFNC in the management of severe asthma exacerbation, however still with limited evidence to support or recommend against its use. (110) Insufficient data in support of HFNC in setting of asthma to recommend use. Small pilot study using HFNC for severe asthma compared it with nasal cannula oxygen with promising results. (111) Often used in ICU settings to avoid intubation.
Heliox	Consensus-based recommendation for severe exacerbations in conjunction with standard therapy, but caution to not delay intubation if needed. (43)(60) Maximum oxygen content of heliox is 30% FiO_2 and, therefore, is not recommended in patients requiring higher % FiO^2.
Terbutaline	Insufficient evidence to support use. (112) Sometimes given to children with very poor effort unable to adequately inhale nebulized bronchodilators, similar to epinephrine indicated in life-threatening situations; however, has more adverse effects than epinephrine. (43)(60)
Ketamine	Insufficient evidence for ventilated or nonventilated patients. (113)
Intravenous aminophylline	Evidence recommends against use due to poor safety profile in children. (43)(60)(112)
Volatile anesthetics	Used in ICU settings in ventilated patients, not mentioned in guidelines, with insufficient evidence for routine use; no difference in outcomes in a large pediatric retrospective review. (114)
Chest radiography	Low yield in the ED and rarely changes management, consider with hypoxia and high fever if not improving on albuterol and systemic corticosteroids. (68)
ICS prescription at time of discharge from ED or admission	ICS should be initiated before ED discharge. (115) Regular use of low-dose ICS is associated with decreased risk of death from asthma. (116)

ED=emergency department, FiO₂=fraction of inspired oxygen, GINA=Global Initiative for Asthma, HFNC=high-flow nasal cannula, ICS=inhaled corticosteroid, MDI= metered-dose inhaler, SABA=short-acting inhaled β₂-agonist.

exacerbations requiring systemic corticosteroids, intensive care, or intubation), (43)(60) he or she should be referred to a specialist for treatment of severe asthma. The specialist should evaluate for other diagnoses that mimic asthma (Table 1) before consideration of asthma treatment with biological agents (anti-IgE, anti–IL-5, or anti–IL-5α).

(43)(60) Omalizumab, a monoclonal antibody that binds to IgE, is recommended for difficult-to-control moderate to severe persistent asthma in children 6 years and older with elevated IgE counts. (75) In a cohort of inner-city youth aged 6 to 20 years with uncontrolled persistent asthma and elevated IgE levels, omalizumab significantly decreased fall

exacerbations and improved overall control of asthma. (76) Mepolizumab (anti–IL-5), (77) benralizumab (anti–IL-5α), (78)(79) and dupilumab (anti–IL-4α) (80) are options for children with eosinophilia (eosinophil count >150 and 300/μL [0.15 and 0.30×10^9/L], respectively) who are 12 years and older. Early initiation of biological agents in poorly controlled moderate to severe asthma is associated with reduced hospitalizations and ED visits for asthma. (81) Newer biological agents that target different mediators of the inflammatory pathway and other emerging trends are discussed in Table 4.

Acute Asthma

The management of acute asthma includes early and repeated administration of SABA per the individual asthma action plan (usually 2–4 puffs inhaled with spacer every 4 hours in the yellow zone) at the first symptoms of bronchospasm for mild exacerbations. For moderate to severe exacerbations (red zone on the asthma action plan), the typical asthma action plan usually recommends 4 to 8 puffs inhaled with spacer every 15 minutes for 3 doses while on the way to the ED. High-dose ICS for yellow zone management of acute asthma is not effective and should not generally be recommended. (86)(89) Specific guidelines for prescribing a home supply of emergency oral corticosteroids with specific instructions for use with or without a telephone consultation with a physician do not exist. However, a small study did show decreased ED use in children with moderate to severe asthma who had a home supply of emergency oral corticosteroids. (94)

ED management of acute asthma includes prompt systemic corticosteroids and higher doses of SABA mixed with 2 to 3 doses of ipratropium bromide for moderate to severe exacerbations. It is important to assess response to therapy after 1 hour of treatment and if there is no significant improvement to consider intravenous magnesium sulfate because this has been shown to reduce risk of hospitalization. (95) SABA should be continued until there is clinical evidence of reversal of obstruction (decreased respiratory effort and rate, improved oxygenation and ventilation) (Tables 2 and 3). In addition to reversing bronchoconstriction, supportive therapies, including supplemental oxygen,

intravenous fluids, or ventilatory support, should be initiated as needed. A lethargic or agitated child with asthma exacerbation may have acidosis from hypercarbia secondary to poor ventilation and would benefit from noninvasive positive pressure support or intubation. In addition, transient hypoxia secondary to ventilation-perfusion mismatch is not uncommon after treatment with bronchodilator therapy.

ED management of asthma often relies on clinical pathways using asthma severity scores to expedite initiation of treatment. (96) Multiple pediatric asthma severity scores exist, with wide variation in rigor of validation and ability to predict response to treatment. (97)(98)(99) Evidence-based management of acute asthma is discussed in Table 5.

Pharmacogenetics and Race/Ethnicity. As mentioned previously, Puerto Rican children had the highest asthma prevalence of any group until 2016, when the prevalence in black children increased to 15.7%. (3) Although it is likely multifactorial, there is some evidence of impaired response to SABAs in Puerto Rican children secondary to factors involving the β_2-adrenergic receptor genes. (117) In addition, a small cross-sectional study of children with persistent asthma compared response to SABA in Mexican American and Puerto Rican children and found improved responsiveness in Puerto Rican children when an LTRA was added. (118) Further investigation of asthma pharmacogenetics comparing children from different ethnic groups may help address health disparities in asthma.

CONCLUSION

Management of many other chronic diseases has benefited from a coordinated approach extending beyond the clinic and into the community. Quality improvement efforts should focus on improving outcomes for vulnerable children by ensuring adherence to guideline-based therapy, correct assessment of severity and control, and a coordinated approach to care. Population health approaches and novel therapies showing effectiveness in specific phenotypes present an opportunity to identify at-risk children with asthma and to begin to decrease the health disparities in childhood asthma.

Summary

- Based on observation, health disparities in pediatric asthma exist. (4) Based on expert opinion, providers should design and implement quality improvement projects to help bridge the gap. (15)

- Based on observation, environmental triggers are a major contributor to health disparities in pediatric asthma. Working to reduce exposure to individual triggers will improve asthma control. (52)(55)

- Based on observation, complex interactions between a child's genetic risk, environment (allergen sensitization, exposure to viral infections), (26) and changes to the airway at the cellular level help predict disease and target therapy. (31)

- Based on expert opinion, always consider alternative or concomitant diagnoses in a child with new wheeze or difficult-to-control asthma. (43)(60)

- Based on moderate recommendation, guideline-based care is associated with improved outcomes in asthma. (74)

- Based on moderate recommendation, children with moderate to severe asthma often benefit from treatment with seasonal escalation of inhaled corticosteroid dose (although not higher than recommended by the National Asthma Education and Prevention Program guidelines), (43)(85) leukotriene receptor antagonist (83) or novel immunomodulatory medications (85) to reduce fall exacerbations. There seems to be no benefit from high-dose inhaled corticosteroid use for yellow zone management of acute asthma. (86)(89)

PIR Quiz

1. You have been appointed as the president of a large pediatric health system. In looking at the system's readmission data, it was clear that asthma readmissions have one of the highest rates compared with national benchmarks. You design a strategic plan aimed at improving prevention strategies for childhood asthma in the population you serve with the goal to decrease readmissions. Although your plan should target all children admitted with asthma, in which of the following groups of children will prevention strategies have the highest impact due to their highest rates of readmission?

    A. Asian.
    B. Black.
    C. White.
    D. Hispanic.
    E. Native American.

2. A 15-month-old girl is seen in the clinic with a 2-day history of upper respiratory tract infection symptoms, including clear rhinorrhea and cough. The patient was born at 30 weeks' gestation and was in the nursery for 6 weeks, where she received supplemental oxygen. Physical examination is significant for low-grade fever and scattered wheezes heard diffusely over both lungs. The remaining examination findings are normal. There is no family history of asthma or atopy. The patient is an only child and stays at home with mom. There are no sick contacts, and there are no pets or smokers in the house. Which of the following is the most likely natural history of wheezing in this patient?

    A. Atopic wheezing.
    B. Exercise-induced wheezing.
    C. Nonatopic wheezing.
    D. The patient will most likely be an asthmatic adult.
    E. Transient early wheezing.

3. You are developing asthma education materials aimed at parents and school personnel. In discussing asthma triggers, which of the following is the most common trigger of asthma exacerbation in children?

    A. Bacterial pneumonia.
    B. Dust mite antigen.
    C. Pet dander.
    D. Perfumes.
    E. Viral respiratory infections.

4. A 6-year-old boy is brought to the emergency department by his parents because he woke up from sleep with acute onset of coughing, increased work of breathing, and chest pain. The family is visiting with the grandparents, who have a dog. The grandfather smokes outside. There is no history of fever or upper respiratory tract infection symptoms. Family history is positive for allergic rhinitis in the mother. On physical examination the child is alert and awake and in moderate respiratory distress. He is coughing and seems short of breath. His pulse oximetry is 89% on room air. Lung examination shows decreased air entry diffusely with scattered wheezes bilaterally. There is no history of similar symptoms, and the family has no pets. In the emergency department he was given 3 albuterol aerosols, resulting in significant improvement. His chest radiograph is normal except for hyperinflation. Which of the following is the most appropriate test to confirm the diagnosis in this patient?

    A. Fractional excretion of nitric oxide.
    B. Impulse oscillometry.
    C. Methacholine challenge test.
    D. Response to bronchodilators on pulmonary function testing.
    E. Skin testing.

5. An 8-year-old girl is being evaluated by her primary care physician with pulmonary function testing before and after bronchodilator administration for a suspected diagnosis of asthma. Which of the following parameters is most important in the diagnosis and evaluation of asthma?

    A. Closing capacity.
    B. Ratio of closing capacity to residual volume.
    C. Ratio of forced expiratory volume in 1 second to forced vital capacity.
    D. Residual volume.
    E. Total lung capacity.

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