Childhood Asthma

13

Sy Duong-Quy and Krista Todoric

Contents

S. Duong-Quy (✉)
Respiratory and Lung Functional Exploration Department, Cochin Hospital, Paris Descartes University, Paris, France

Division of Pulmonary, Allergy and Critical Care Medicine, Penn State Health. Milton S. Hershey Medical Center and Pennsylvania State University College of Medicine, Hershey, PA, USA
e-mail: sduongquy.jfvp@gmail.com

K. Todoric
Division of Pulmonary, Allergy and Critical Care Medicine, Penn State Health. Milton S. Hershey Medical Center and Pennsylvania State University College of Medicine, Hershey, PA, USA

Penn State Hershey Allergy, Asthma and Immunology, Hershey, PA, USA
e-mail: ktodoric@pennstatehealth.psu.edu

M. Mahmoudi (ed.), *Allergy and Asthma*,
https://doi.org/10.1007/978-3-030-05147-1_14

Abstract

Asthma is the most common chronic respiratory disease in childhood. Although much progress has been made in the last decades in understanding the pathophysiology and management of asthma, the diagnosis and treatment of early childhood asthma remain great challenges. Due to the heterogeneity of asthma symptoms in childhood, it has been difficult to establish a clear and coherent definition of asthma in this population. Currently, in older children, the diagnosis of asthma is made similarly to that in adults and is based on chronic inflammation associated with airway hyperresponsiveness and reversible airflow limitation. However, the use of exhaled nitric oxide, bronchial challenge testing, and spirometry are often not feasible or reliable in younger children. In young children, the diagnosis of asthma is mostly based on symptom history, risk of allergic disease, and physical findings in the absence of respiratory tract infections. In all age groups, current asthma management guidelines focus on a stepwise approach to symptom and risk control while addressing comorbidities and other modifiable risk factors such as inhaler technique, treatment adherence, and environmental exposures. Asthma remains the leading cause of childhood morbidity from chronic disease as measured by rates of emergency department visits, length of hospitalization, and unscheduled school absences. Therefore, ongoing advances in the understanding of childhood asthma, the factors contributing to its development (both genetic and environmental), preventative strategies addressing these risks, and novel treatment options will continue to be crucial clinical considerations in the years to come.

Keywords

Asthma · Childhood asthma · Risk factors · Asthma treatment

13.1 Introduction

Asthma is the most common chronic respiratory disease in childhood and remains the leading cause of childhood morbidity from chronic disease as measured by rates of emergency department visits, length of hospitalization, and unscheduled school

absences. Although much progress has been made in the last decades in understanding the pathophysiology and management of asthma, the diagnosis and treatment of childhood asthma remain great challenges for pediatric physicians.

Due to the heterogeneity of asthma symptoms in childhood, especially in preschool children, it has been difficult to establish a clear and coherent definition of asthma in this population. Currently, the diagnosis of asthma in young children is mostly based on symptom history, risk of allergic disease, and physical findings in the absence of respiratory tract infections. In older children, the diagnosis of asthma is made similarly to that in adults and is based on chronic inflammation associated with airway hyper-responsiveness and reversible airflow limitation. While pulmonary assessments such as exhaled nitric oxide (F_ENO), bronchial challenge testing, and spirometry are useful in diagnosing asthma, these measures are difficult to obtain reliably in younger children.

It is well-accepted that asthma phenotypes result from a complex interplay of molecular mechanisms, epigenetic factors, and environmental exposures. However, there is a lack of consensus regarding asthma phenotypes in childhood, especially during infancy. While most childhood asthma is characterized by a T-helper type 2 (Th2) pathway, there is a growing body of evidence suggesting alternative mechanisms remain important in asthma development. Better understanding of childhood asthma phenotypes is needed and will be imperative for initiating asthma treatment, monitoring biomarkers, and targeting treatment strategies, especially as new therapies become available.

In addition, modifiable factors such as inhaler technique, treatment adherence, and harmful environmental exposures (e.g., tobacco smoke and pollution) persist as real challenges in disease control in children. These factors as well as the identification and treatment of comorbidities, such as atopic disease, sleep apnea, obesity, and gastroesophageal reflux, are critical in the evaluation of childhood asthma and in its treatment. Moreover, additional barriers to asthma care such as socioeconomic status, language proficiency, and literacy should be considered as part of a comprehensive asthma management program.

Finally, while the assessment and treatment of asthma are paramount for the pediatric physician, asthma prevention strategies must not be forgotten and should remain at the forefront of childhood asthma research.

13.2 Epidemiology

13.2.1 Prevalence of Childhood Asthma

Measure of asthma prevalence worldwide is challenging due to lack of consistent disease definition, difficulty with respiratory testing in some age groups, heterogeneous disease phenotypes, and socioeconomic impacts such as income, education, occupation, and area of residence. To date, the largest collaborative global cross-sectional survey of asthma prevalence in childhood has been the International Study of Asthma and Allergies in Childhood (ISAAC) (Asher et al. 1995). Phase I (1992–1996) included 721,601 pediatric participants from 156 centers in 56 countries. It used questionnaires to identify asthma-like symptoms in children (aged 6–7 years) and adolescents (aged 13–14 years). These results revealed a wide range of childhood wheezing prevalence worldwide, ranging from 4.1% to 32.1% in children (257,800 participants) and 2.1–32.2% in adolescents (463,801 participants). The highest prevalences of childhood wheeze were found in developed English-speaking countries (the United Kingdom, New Zealand, Australia, Canada, the United States) and some non-English-speaking Latin American countries (Asher and Weiland 1998); the lowest prevalences were found mostly in Asian countries (India, Taiwan, China, and Indonesia) (Asher et al. 1995).

ISAAC Phase III (2000–2003) was a repeat of the Phase I survey (with the inclusion of a new environmental questionnaire) occurring at least 5 years later with the intent to evaluate asthma trends. Phase III contained 193,404 children from 66 centers in 37 countries and 304,679 adolescents from 106 centers in 56 countries (Pearce et al. 2007). Results from Phase III revealed that asthma symptom prevalence mostly increased in

centers where it had previously been low and either stayed the same or decreased in centers where asthma symptom prevalence had previously been high (Pearce et al. 2007). However, almost all countries reported increases in lifetime asthma from Phase I to III irrespective of symptom prevalence (Pearce et al. 2007). These findings are consistent with other reports (Braun-Fahrländer et al. 2004; Kalyoncu et al. 1999; Mommers et al. 2005; Nowak et al. 2004; Ronchetti et al. 2001; Senthilselvan et al. 2003; Toelle et al. 2004).

13.2.2 Morbidity and Mortality

It is estimated that nearly 334 million individuals have asthma globally, and 14% of the world's children likely had asthma symptoms in the past year (Global Asthma Report 2014). Asthma morbidity is a major burden for children, their families, and healthcare systems. Asthma that is not well-controlled results in lifestyle disruption, reduced physical ability, school absences, and socioeconomic impacts resulting from lost work days, medication expenses, and healthcare costs associated with asthma care. In the United States alone, the total economic impact of asthma totals roughly $56 billion a year for the 25 million individuals with asthma (CDC 2011); more than half (53%) of individuals with asthma have an asthma attack per year, and, of those having an asthma attack, 59% of children and 33% of adults miss school or work, respectively (CDC 2011).

Overall, mortality from asthma is rare and comprises less than 1% of all deaths in most countries (Global Asthma Report 2014), likely due to better understanding of the underlying mechanisms of asthma and the availability of more effective treatments. In European countries, asthma mortality is highest among infants and preschool children, lower during school age, and increases again in adulthood (Wennergren and Strannegård 2002). In the United States, children with asthma have higher rates of primary care and emergency department visits but a lower death rate than adults (Akinbami et al. 2012); in 2007, in the United States, 185 children and 3262 adults died from asthma (CDC 2011).

13.3 Natural History of Asthma

Population studies assessing asthma remission or persistence/recurrence have differed in their results. Reported rates of childhood asthma remission range from 20% to 52% (Martin et al. 1980; Roorda et al. 1993; Vonk et al. 2004). Remission is associated with higher forced expiratory volume (FEV_1) in childhood and a higher increase in percent predicted FEV_1 through adulthood (Vonk et al. 2004), as well as earlier age of cessation of wheeze (Martin et al. 1980). Alternatively, analyses of population-based, childhood cohorts (starting age 7–9 years and followed through early adulthood) show asthma persistence rates ranging from 27% to 41% (Andersson et al. 2013; Sears et al. 2003). Factors that predicted persistence or relapse of asthma in these cohorts include sensitization to house dust mites, airway hyper-responsiveness, female sex, smoking at age 21 years, early age at onset (Sears et al. 2003), sensitization to furred animals, and more severe asthma (Andersson et al. 2013).

Further characterization of children experiencing remission versus persistence/relapse of asthma has been explored in the Tucson Children's Respiratory Study (TCRS). The TCRS, a birth cohort study of 1246 newborns followed through age 16 years, sought to identify the factors affecting wheezing before age 3 years and their relationship to wheezing and asthma through adolescence (Martinez et al. 1995; Morgan et al. 2005; Taussig et al. 2003). Participants were separated into three groups: (1) "transient infant wheezers," (2) "nonatopic wheezers," and (3) "atopic wheezers." The first group (transient infant wheezers) developed wheezing within the first 3 years of life. However, the majority (80%) of those with wheezing within the first year of life did not wheeze after age 3 years; this decreased to 60% and 40% with wheezing that persisted through years 2 and 3, respectively. These infants were not atopic, had diminished airway function at birth, and had either a mother who smoked during pregnancy or a younger mother; they did not have an increased risk of asthma later in life (Taussig et al. 2003). The second group (nonatopic wheezers) had lower respiratory infections

early in life (with strongest association noted with respiratory syncytial virus (RVS)) and continued to wheeze after age 3 years; it was felt that this group was more susceptible to acute airway obstruction following infection due to alterations in airway smooth muscle control, possibly virally induced or present at birth (Taussig et al. 2003). The third group (atopic wheezers) had wheezing that started both before and after age 3 years, but before age 6 years, most of these children had allergic sensitization noted by age 6 years, and most developed atopic asthma (Taussig et al. 2003).

Subsequently, the Isle of Wight Birth Cohort (IWBC) study, a whole population birth cohort, followed 1456 infants at 1 year, 2 years, 4 years, 10 years, and 18 years (Kurukulaaratchy et al. 2012). These participants were classified as "never asthma" (no asthma since birth), "adolescent-onset asthma" (asthma at age 18 years but not prior), "persistent-adolescent asthma" (asthma at both age 10 years and 18 years), and "recurrence of childhood asthma" (asthma in first 4 years of life, not at age 10 years, but again at age 18 years) (Kurukulaaratchy et al. 2012). Of asthmatics who had data available at both 10 years and 18 years, 63.1% had persistent-adolescent asthma, 28.3% had adolescent-onset asthma, and 8.6% had recurrence of earlier childhood asthma (Kurukulaaratchy et al. 2012). The IWBC study demonstrated that asthma remission was associated with mild disease before adolescence defined by few symptoms, low level of initial bronchial hyper-responsiveness (BHR), male sex, higher FEV_1 in boys, and low sputum eosinophil count (<3%) (Kurukulaaratchy et al. 2012).

The natural history of asthma in children might be schematically presented as in Fig. 1.

13.4 Risk Factors for Childhood Asthma

13.4.1 Genetic Risk Factors

Hereditary studies of families and twins indicate that genetics play a crucial role in development of childhood asthma (Willemsen et al. 2008). During the last decade, many studies have sought to delineate the role genetic factors play in the pathogenesis of asthma, especially childhood asthma, and whether these genes may correlate to airway inflammation, congenital BHR, and response to target treatment. Currently, by studying genome-wide linkage (GWL) or genome-wide association (GWA), more than 100 genes associated with asthma have been identified, and the number is growing.

The GABRIEL study a large meta-analysis of GWA studies in European populations genotyped 10,365 asthmatic patients and 16,110 control subjects to analyze the association between 582,892 single-nucleotide polymorphisms (SNPs) and asthma-identified genes on chromosomes 2 *(IL1RL1/IL18R1)*, 6 *(HLA-DQ)*, 9 *(IL33)*, 15 *(SMAD3)*, 17 *(ORMDL3/GSDMB)*, and 22 *(IL2RB)* (Moffatt et al. 2007). Especially, *ORMDL3* gene was associated with early-onset asthma in about 38% of all cases of childhood-onset asthma (Moffatt et al. 2007). A more recent meta-analysis evaluated >2 million SNPs in North American populations (European Americans, African Americans/African Caribbeans, and Latinos). This showed that SNPs near the 17q21 locus and the *IL1RL1*, *TSLP*, and *IL33* genes were associated with asthma risk in these ethnic groups, while the *PYHIN1* gene was associated with asthma in individuals of African descent (Torgerson et al. 2011).

Although GWA studies have discovered loci associated with childhood-onset asthma, the contribution of polygenic influences is more difficult to assess. The use of "genetic risk scores" may provide a useful tool to predict the link between genetic risks discovered in GWAS and the development or persistence of asthma in an individual.

13.4.2 Prenatal Risk Factors

13.4.2.1 Fetal Immune Response

Overall, maternal allergy impacts the development of allergic disease, presumably through alteration of the in utero environment and influence on prenatal immune development via placental transfer of immunoallergic factors (Lockett et al. 2015). Collectively, a multitude of studies

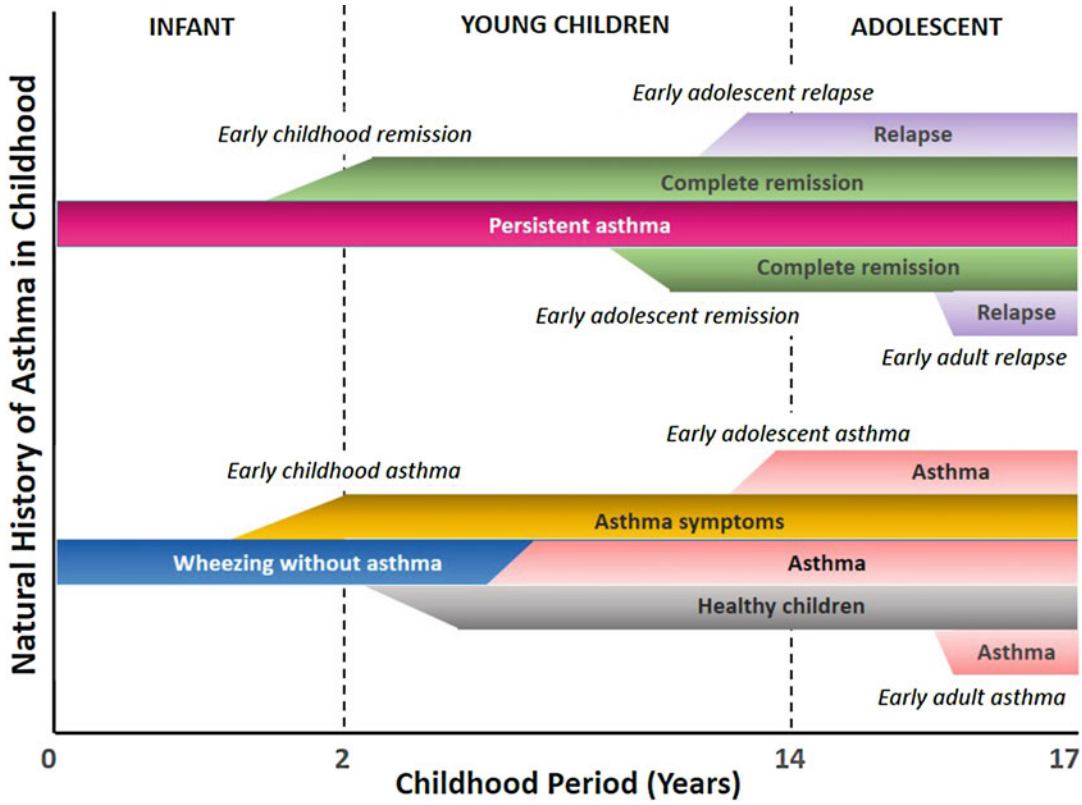


Fig. 1 Natural history of childhood asthma: persistent asthma in early childhood may have a complete remission in later childhood or remit and relapse later during childhood (top); early infants with wheezing without asthma may develop asthma symptoms/asthma or become healthy children without wheezing (bottom)

indicate that both innate and adaptive immune responses may be altered in utero in allergy-prone individuals through varied effects from immunoglobulin transfer, chemokine effects, toll-like receptor genotypes, Treg gene expression/development, Th2 cytokine levels, and methylation signals, among others (Bullens et al. 2015; Lockett et al. 2015; Fu et al. 2013; Liu et al. 2011; Martino et al. 2014). For example, in one study, maternal atopy status influenced Treg marker gene expression and Th2 cytokine levels in cord blood through interaction with toll-like receptor genotypes (Liu et al. 2011). In others, elevated cord blood levels of long-chain polyunsaturated fatty acids dose-dependently predicted the development of childhood respiratory allergies by age 13 years (Barman et al. 2013), and a cord blood CD4+ T cell DNA methylation signature at 96 CpGs sites predicted the development of food allergy by 12 months of age (Martino et al. 2014). The impact of such factors and other epigenetic changes induced by environmental exposures (de Planell-Saguer et al. 2014) on the development of asthma are still being explored.

13.4.2.2 Fetal Growth Restriction

There may be a causal link between fetal growth restriction and development of asthma, although the exact mechanism underlying this link is not well-demonstrated. Abnormalities in maternal-fetal circulation and development of the placenta, umbilical cord, and lung, as well as epigenetic alterations have all been suggested as pathways that explain fetal growth restriction during pregnancy (Martino and Prescott 2011).

The results of the Aberdeen birth cohort showed that for each millimeter increase in fetal crown-rump length (CRL), measured by ultrasound in

the first trimester, the odds of ever having wheezing decreased by 4%, and the odds of ever having asthma decreased by 5% (Turner et al. 2010). Additionally, this study revealed that reduced fetal size in the first trimester may be associated with reduced lung function and increased asthma symptoms at age five. Furthermore, the correlation between fetal dimension (by measuring CRL in the first trimester and biparietal diameter in the second trimester) and asthma remained at 10 years follow-up (Turner et al. 2011). The authors state that a continuous high fetal growth (high CRL at the first trimester and high biparietal diameter in the second trimester) may be a protective factor for future asthma development in childhood (odds ratio (OR) 2.8) (Turner et al. 2011).

13.4.2.3 Maternal Tobacco Smoke

Evidence-based data suggest that prenatal maternal smoking is associated with early childhood wheezing and reduced lung function in newborn infants compared to those of non-smoking mothers (Dezateux et al. 1999). Prenatal maternal smoking increases the risk of both asthma and impaired lung function throughout childhood as well as illness-related school absenteeism (Burke et al. 2012; Gilliland et al. 2003; Grabenhenrich et al. 2014); risk of childhood wheeze is increased with postnatal smoke exposure and is also noted with prenatal secondhand smoke exposure (Burke et al. 2012).

13.4.2.4 Maternal Drug Use

In the last decades, relationships between prenatal/infancy medication use and asthma in childhood have been reported. Longitudinal cohort studies and meta-analysis show that use of antibiotics during pregnancy increases risk of persistent wheeze and asthma in early childhood with a dose-response correlation between number of antibiotic courses and the risk of respiratory symptoms (wheeze or asthma) (Bisgaard et al. 2007; McKeever et al. 2002). In addition, this risk is further increased if the antibiotic is used during the last two trimesters of pregnancy (Jedrychowski et al. 2006). It has been hypothesized that an imbalance between pathogenic and beneficial bacteria due to antibiotic use plays a role in this asthma effect (Bisgaard et al. 2007).

Data assessing the association of prenatal and infancy use of paracetamol (acetaminophen) with increased risk of childhood asthma are mixed (Castro-Rodriguez et al. 2016; Hoeke et al. 2016; Migliore et al. 2015). A subsequent study involving 53,169 children at 3 years and 25,394 children at 7 years found a modest association between prenatal maternal paracetamol use and use of paracetamol in infancy with the development of asthma at both time points (Magnus et al. 2016). However, a systematic review and meta-analysis of 11 observational cohort studies found insufficient evidence to link paracetamol use to the development of childhood asthma due to confounding (Cheelo et al. 2015). Further studies are needed to better define the role that paracetamol may play in the development of asthma and to provide clarification of potential confounders.

13.4.2.5 Maternal Diet and Weight Gain

While no specific maternal dietary patterns have been associated with asthma in childhood, several ingestions during pregnancy seemingly reduce the risk of asthma or wheezing. These include "allergenic" foods (such as peanut, tree nuts, milk, and/or fish) (Bunyavanich et al. 2014; Maslova et al. 2012), long-chain fatty acid supplements (Bisgaard et al. 2016), and, in some studies, vitamin D and vitamin E (Nurmatov et al. 2011). Notably, results regarding vitamin D supplementation were not confirmed by randomized controlled trials (Chawes et al. 2016).

On the other hand, data currently suggest that maternal obesity and high gestational weight gain result in increased risk of development of wheezing or asthma (Forno et al. 2014; GINA 2017). However, unguided weight loss or dietary restriction in pregnancy is strongly not recommended due to concern for deleterious fetal and maternal effects.

13.4.2.6 Breastfeeding

Many studies report a beneficial effect of breastfeeding on asthma prevention and on reduction of wheezing in early life (Arbes

et al. 2007; Martinez et al. 1995). However, while breastfeeding should be encouraged, caution should be taken in advising families that breastfeeding will prevent asthma.

13.4.3 Childhood Risk factors

13.4.3.1 Aeroallergen Sensitization

Sensitization to allergens is one of the strongest determinants of subsequent development of asthma (Arbes et al. 2007; Martinez et al. 1995), and an increase in IgE level, a surrogate marker for allergen sensitivity, is associated with the incidence of childhood asthma (ISSAC 1998). Both the ISSAC study and the Childhood Asthma Management Program (CAMP) reveal that allergy-associated asthma is the most common asthma phenotype in children (CAMP Research Group et al. 2000; Strachan et al. 2015).

To date, studies focusing on single indoor allergen exposure (e.g., cat, dust mite, mold) and asthma development have been mixed, showing positive, negative, and no effect (Bufford and Gern 2007; Halonen et al. 1997; Lau et al. 2000; Lødrup Carlsen et al. 2012; Melén et al. 2001; Ownby et al. 2002; Quansah et al. 2012; Sporik et al. 1990; Takkouche et al. 2008). However, birth cohort studies suggest that a multifaceted allergen reduction strategy approach seems to reduce the incidence of asthma if applied in children, even up to age 18 years in some cases (MacDonald et al. 2007; van Schayck et al. 2007). Overall, evidence is insufficient to recommend increasing or decreasing exposure to common sensitizing allergens early in life as a means of primary prevention of asthma. Furthermore, the roles that a pro-allergic immune response in childhood, immature neonatal immune response, and innate system influences in atopic children play on the development of asthma require further clarification.

13.4.3.2 Presence of Food Allergy

Having food allergy increases a child's risk of asthma fourfold (Liu et al. 2010) and has also been associated with increased rates of hospitalization, exacerbations necessitating mechanical ventilation, and corticosteroid use in asthmatics (Liu et al. 2010; Roberts et al. 2003; Simpson et al. 2007). One study suggests that asthma may present at a younger age in children with food allergies (Schroeder et al. 2009).

13.4.3.3 Presence of Atopic Dermatitis

In children with recurrent wheezing, the coexistence of atopic dermatitis (AD) increases the risk for developing asthma (Castro-Rodríguez et al. 2000). Severity and age of onset of AD may also play an informative role. In one study, only 26% of children with mild to moderate AD developed an allergic respiratory disease (mainly asthma) compared to 75% with severe AD (Patrizi et al. 2000). Early-onset AD (before age 2 years) is associated with increased risk of onset of asthma at an earlier age (at age 6 years), whereas late-onset AD (after age 2 years) is associated with increased risk of onset of asthma at a later age (at age 12 years) (Lowe et al. 2017).

13.4.3.4 Gender

Multiple studies support the finding that males have more wheeze and asthma in childhood, but females have more wheeze and asthma in adolescence and thereafter. Additionally, asthma after childhood is more severe in females than in males (Almqvist et al. 2008). In one study, childhood asthma hospitalization rates were highest for boys between 2 and 12 years of age (peak hospitalization rate at 4 years) but were higher for girls between 16 and 18 years of age (peak hospitalization rate at 17 years) (Debley et al. 2004). Although hormonal changes have been suggested as a possible explanation for this trend, one study could not link pubertal stages with gender shift in asthma prevalence (Vink et al. 2010). Furthermore, in adolescent girls, but not adolescent boys, development of wheeze was associated with current smoking or being overweight (Tollefsen et al. 2007), suggesting a multifaceted explanation for the reversal of gender predominance noted through adolescence. Further exploration of factors driving gender differences in childhood asthma is ongoing.

13.4.3.5 Postnatal Smoking Exposure and Outdoor Pollutants

Tobacco smoke exposure is strongly associated with wheezing (Akinbami et al. 2013), although postnatal maternal tobacco smoke exposure is most relevant in the development of asthma in older children (GINA 2017). Children with asthma exposed to tobacco smoke (passive smoking or second-hand smokers) are at higher risk for uncontrolled asthma, with more severe asthma symptoms, and asthma exacerbations (Burke et al. 2012; Wang et al. 2015). Likewise, exposure to outdoor pollutants, such as living near a main road, is also associated with increased risk of asthma in childhood, especially for those who are also exposed to tobacco smoke in infancy (Gasana et al. 2012).

13.4.3.6 Microbial Effects

Recently, results from studies on hygiene and microflora suggest that interactions with microbiota may be beneficial in preventing asthma in childhood. The prevalence of asthma is higher in children born by Caesarean section than those born vaginally, suggesting that exposure of an infant to the mother's vaginal microflora through vaginal delivery (Huang et al. 2015) or differences in the infant gut microbiota according to their mode of delivery (Azad et al. 2013) may also be important in prevention of asthma. Moreover, the risk of asthma is also reduced in children whose bedrooms have high levels of bacterial-derived lipopolysaccharide endotoxin (Karvonen et al. 2012), and children raised on farms with exposure to stables and consumption of raw farm milk have a lower risk of asthma than children of nonfarmers (Riedler et al. 2001).

13.4.3.7 Parental History of Asthma

Family history of asthma is a known risk factor for development of asthma. Children with parents reporting a history of asthma in childhood may have decreased lung function and increased respiratory symptoms such as wheezing in early infancy and in later childhood (Camilli et al. 1993). One study of 306 children found that the odds of having a child with asthma were threefold greater in families with one asthmatic parent and sixfold greater in families with two asthmatic parents than in families where only one parent had inhalant allergy without asthma (Litonjua et al. 1998). Additionally, in a larger study comprising 2552 children, children were almost twice as likely to have asthma if they had a parent with asthma and more than four times likely to develop asthma if both a parent and grandparent had asthma (Valerio et al. 2010). Interestingly, more recently, the Isle of Wight Cohort analysis, after stratification of child's sex, demonstrated that maternal asthma was associated with asthma in girls but not in boys, whereas paternal asthma was associated with asthma in boys but not in girls (Arshad et al. 2012). Parental asthma also increases the risk of aeroallergen sensitization, a strong association for asthma development in early childhood (Crestani et al. 2004).

13.4.3.8 Respiratory Tract Infections

The role of respiratory tract infections in early childhood asthma development has been the source of debate over the last decades. It is hypothesized that repeated lower respiratory tract infections in childhood induce airway injury and increase susceptibility to inhalant allergens and other environmental risk exposures for asthma or provide the stimulus needed for gene-by-environment interactions (Busse et al. 2010).

A study of 154,492 European children followed from birth through age 15 years showed that both upper and lower respiratory tract infection before age 5 years increase asthma risk later in childhood (van Meel 2017). Children with upper respiratory infections (sinusitis, laryngitis, tonsillitis, or pharyngitis) by age 5 years had a 1.5-fold increased risk of developing asthma later in life, while those who had lower respiratory tract infections (bronchitis, bronchiolitis, or pneumonia) experienced a two to fourfold increased risk of developing asthma later in life. Interestingly, young children with both aeroallergen sensitization and viral respiratory infection may have synergistic risk for development of asthma at age 6 years, increasing ninefold if both aeroallergen sensitivities and at least two viral infections with wheezing occurred compared to only twofold if only aeroallergen sensitivity developed (without

viral infection with wheezing) and fourfold if only viral infection with wheezing noted (without aeroallergen sensitivity) (Kusel et al. 2007).

The relationship between respiratory syncytial virus (RSV) infection and the development of asthma is documented (the ISSAC study; Sigurs et al. 2000; Wu et al. 2008; Kusel et al. 2007; Jackson et al. 2008), although not all studies support the connection between RSV and asthma later in life. Infants from the Avon Longitudinal Study of Parents and Children with a history of severe RSV bronchiolitis necessitating hospitalization were 2.5 times more likely than controls to develop asthma by age 7.5 years (Henderson et al. 2005). The TCRS found that RSV infection before age 3 years was associated with wheezing and asthma in early childhood but not after age 11 years (Stein et al. 1999). Another study of twins suggested that RSV does not cause asthma but that genetic factors coupled with RSV infection are responsible for the development of asthma (Thomsen et al. 2009).

Studies assessing the impact of RSV prophylaxis or treatment on the development of asthma suggest an impact on the development of asthma but are limited in number and design. A retrospective investigation of 13 children treated with RSV immunoprophylaxis showed improved spirometry (FEV_1/FVC) and less atopy and were less likely to have an asthma attack 7–10 years after receiving immunoprophylaxis compared to those who did not receive immunoprophylaxis (Wenzel et al. 2002). An open-label compassionate-use RSV immunoprophylaxis (using palivizumab) study in a European cohort of 191 preterm infants suggested decreased wheeze at 19–43 months follow-up in those receiving prophylaxis (Simoes et al. 2007). One open-label study showed a reduction in the risk of asthma and allergic sensitization at 6 years of age among children less than 2 years old who were hospitalized and received ribavirin for RSV bronchiolitis (Chen et al. 2008).

The role of rhinovirus (RV) infection in predicting future asthma and severe asthma exacerbation has only been reported in more recent years. In the Childhood Origins of Asthma (COAST) birth cohort study, 90% of children with RV-associated wheezing episodes at age 3 years had asthma at age 6 years (Jackson et al. 2008). In this study, there was a 2.6 odds ratio (OR) for asthma by age 6 years if RSV infection occurred by age 3 years; this increased to a 9.8 OR if the infection was RV (Jackson et al. 2008). Additionally, similar to a prior study, Jackson et al. found that infants with both aeroallergen sensitization and RV wheezing had the highest incidence of asthma at age 6 years compared to populations with only RV wheezing or aeroallergen sensitization (Jackson et al. 2008).

13.4.3.9 Miscellaneous Risk Factors

Studies are ongoing regarding the aforementioned childhood asthma risk factors. Generally, it is not easy to identify the cause-effect of each risk factor for asthma development in childhood because children are usually exposed to multiple risk factors in early life that interfere with the control of gene-by-environment interactions (epigenetic factors) (Subbarao et al. 2009). Furthermore, the relationship between asthma in childhood and risk factors may change over time due to changes in living environment and/or modification of susceptibility. To date, the roles of maternal stress during pregnancy, mode of delivery, or breastfeeding on the risk of childhood asthma remain controversial. Other risk factors such as family socioeconomic status, air pollution, or microbiome remain to be clarified.

13.5 Asthma Phenotypes in Childhood

13.5.1 Background

Asthma in childhood is a heterogeneous disease with clinical manifestations varying from early infancy through later childhood. The phenotypes of asthma in childhood depend on molecular mechanism characteristics, or endotypes, epigenetic factors, and environmental exposures. The main molecular mechanism of childhood asthma is chronic inflammation resulting from inhalant

allergen-induced inflammation driven by the T-helper type 2 (Th2) pathway and mediated by the related cytokines IL-4, IL-5, and IL-13. These cytokines stimulate inflammatory cells such as eosinophils, basophils, and mast cells as well as injure epithelial and smooth muscle cells, thus contributing to the pathophysiology of asthma (Wenzel 2012). Asthma phenotyping in childhood related to Th2 pathophysiology mainly includes allergic asthma (early-onset asthma). However, there is a large body of evidence showing that non-Th2, or Th2-low, pathways may trigger asthma by alternative means such as neutrophilic, Toll-like receptor (TLR), Th1, and Th17 related-mechanisms. Examination of cellular components and biomarkers of airway inflammation are helpful in delineating Th2-high (eosinophilic) or Th2-low (non-eosinophilic) and for informing treatment. Better understanding of such phenotypes is imperative for initiating asthma treatment, monitoring of compatible biomarkers, and targeting treatment strategies.

13.5.2 Asthma Phenotypes in Childhood

13.5.2.1 Asthma Phenotypes in Infancy

Asthma in infancy is mostly Th2-related disease characterized by early-onset asthma. The diagnosis of asthma in infancy and in preschool age is based on wheezing as the main presenting clinical symptom. However, some children have wheezing early in life but do not have asthma, contributing to the challenge of diagnosing asthma in early childhood. Therefore, both pre- and postnatal risk factors should be considered in addition to wheezing in the classification of asthma phenotypes in this population. Of note, most infants with asthma also display other atopic diseases, such as atopic dermatitis and aeroallergen sensitization (Burgess et al. 2008; Guilbert et al. 2004; Shaaban et al. 2008). Currently, there is no consensus on classification of asthma phenotypes in early childhood (early infancy through preschool age), although several clusters have been proposed (Table 1).

Table 1 Asthma phenotypes in early infant (early childhood)

Phenotypes	Features
Phenotype 1: Recurrent wheezing with risk factor	
	Atopy: allergic dermatitis, allergic rhinitis, or skin prick test (+) Recurrent wheezing: unrelated to airway infection Pre- or postnatal risk factors of asthma: see Sect. 4
Phenotype 2: Persistent wheezing with risk factor	
	Atopy: allergic dermatitis, allergic rhinitis, or skin prick test (+) Persistent wheezing: unrelated to airway infection Pre- or postnatal risk factors of asthma: see Sect. 4
Phenotype 3: Recurrent or persistent wheezing with high rate of hospitalization	
	Atopy: allergic dermatitis, allergic rhinitis, or skin prick test (+) Recurrent or persistent wheezing High rate of annual hospitalization: ≥4 times/years
Phenotype 4: Recurrent or persistent wheezing with risk factor and high rate of hospitalization	
	Atopy: allergic dermatitis, allergic rhinitis, or skin prick test (+) Recurrent or persistent wheezing High rate of annual hospitalization: ≥ 4 times/years Pre- or postnatal risk factors of asthma: see Sect. 4

13.5.2.2 Asthma Phenotypes After Infancy

In children 5 years of age or older, clinical manifestations of asthma are often more diverse and follow the trends of diagnosis similar to adult patients. Furthermore, in these older children, the interaction between genetic factors and environmental factors may modify the clinical presentation of asthma. The Childhood Asthma Management Program (CAMP) study, evaluating 1041 children aged 5–12 years over 48 months, suggested 5 asthma phenotypes based on 3 main features: allergy status, degree of airway obstruction, and history of exacerbations (Howrylak et al. 2014); these are summarized in Table 2. These clusters were consistent with those identified in

Table 2 Asthma phenotypes in children according to Howrylak et al. (2014)

Phenotypes	Features
Phenotype 1: Mild asthma with low atopy, obstruction, and exacerbation rate	
	Largest subgroup of patients (28.8%) No history of allergic disease, lowest prevalence of hay fever or skin prick test reactivity, lowest IgE levels Preserved lung function (highest FEV_1/FVC ratio) Lowest bronchodilator response, intermediate airway hyper-responsiveness No prior hospitalization for asthma and lowest reported prevalence of emergency department visits Lowest risk of exacerbation[a]
Phenotype 2: Atopic asthma with low levels of obstruction and medium rates of exacerbation	
	Universally report allergic disease, high prevalence of allergic rhinitis, and skin test reactivity Preserved lung function (highest FEV_1) Intermediate bronchodilator response and airways hyper-responsiveness No prior hospitalization, low rates of prior emergency department visits Low-to-intermediate risk of exacerbations[a]
Phenotype 3: Atopic asthma with high levels of obstruction and medium rates of exacerbation	
	Rarely self-report allergic disease (in contrast to cluster 2) but have the highest prevalence of allergic rhinitis and skin test reactivity Most reduced lung function (lowest FEV_1 and FEV_1/FVC ratio) High bronchodilator response and most severe airways hyper-responsiveness Few prior hospitalizations but intermediate rates of prior emergency department visits (similar to cluster 4) Intermediate risk of exacerbations[a]
Phenotype 4: Moderately atopic asthma with high levels of obstruction and high exacerbation rates	
	No history of allergic disease, intermediate prevalence of hay fever (52.9%), lower IgE levels Reduced lung function (low FEV_1/FVC ratio, similar to cluster 5) High bronchodilator response and high airways hyper-responsiveness Most reports of prior hospitalization but intermediate rates of prior emergency department visits but intermediate rates of prior emergency department visits Intermediate-to-high risk of exacerbation[a]
Phenotype 5: Highly atopic asthma with high levels of obstruction and high exacerbation rates	
	Smallest subgroup of patients (9.3%) Nearly universal allergic disease, highest prevalence of skin test reactivity, highest IgE levels, highest eosinophilia, intermediate prevalence of allergic rhinitis Reduced lung function (low FEV_1/FVC ratio, similar to cluster 4) Highest bronchodilator response and severe airways hyper-responsiveness Most reports of prior hospitalization and highest rate of emergency department visits Highest risk of exacerbation[a]

[a]Poor long-term asthma exacerbation risk is defined from prospective survival analysis of time to first course of oral prednisone. This variable was derived by using the defined cluster groupings and was therefore not considered in spectral cluster analyses used to define the clusters (Howrylak et al. 2014)

the Severe Asthma Research Program (SARP) study (Fitzpatrick et al. 2011).

The SARP study also sought to better characterize the phenotypes of severe childhood asthma in children and identified 4 clusters in 161 severe asthmatic children greater than 5 years old based on symptom frequency, medication usage, lung function abnormalities, and comorbidities such as atopy (Fitzpatrick et al. 2011): (1) relatively normal lung function and less atopy; (2) slightly lower lung function, more atopy, and increased symptoms/medication usage; (3) greater comorbidity, increased bronchial responsiveness, and lower lung function; and (4) lowest lung function and the greatest symptoms/medication usage. The most severe phenotype in SARP study (phenotype 4) is consistent with the severe "Th2-high" phenotype in adults, characterized by IL-13-induced epithelial gene expression (high levels of periostin), immunoallergic airways inflammation

(increased eosinophil counts), and high risk of exacerbation (Woodruff et al. 2009).

13.6 Diagnosis of Asthma in Childhood

13.6.1 Clinical Manifestations of Childhood Asthma

Recurrent wheezing is the main symptom of asthma in children ≤5 years old, although not all wheezing in this age group indicates asthma (see Sect. 6.2 below). Parent or family report of symptoms may include recurrent or persistent nonproductive coughing accompanied with wheezing episodes and/or breathing difficulties, cough without cold symptoms, and recurrent breathlessness described as "difficult breathing," "heavy breathing," or "shortness of breath" during exercise. Atypical symptoms such as unwillingness to walk and play, irritability, tiredness, and mood changes may also be present and signal uncontrolled asthma in young children. Hence, review of a child's wheezing, daily activities, and behavior are important keys when assessing children with asthma.

Asthmatic children older than 5 years usually report shortness of breath, chest congestion or tightness, and sometimes non-focal chest pain that may be triggered by viral infection, inhaled allergens, and/or exercise. Respiratory symptoms may be worse at night, causing sleep disturbance and increased incidence of obstructive sleep apnea (OSA). Daytime respiratory symptoms are often linked with physical activities, especially in children with exercise-induced asthma. Other nonspecific asthma symptoms in school-age children may include school absence, decreased quality of learning, and general fatigue.

Physical examination in children is most informative during an acute asthma exacerbation. Expiratory wheezing, prolonged expiratory phase, and rhonchi may be auscultated. Additionally, physical examination may reveal labored breathing, respiratory distress, suprasternal and intercostal retractions, nasal flaring, and accessory respiratory muscle use. In the case of severe exacerbation, physical exam may be falsely reassuring when severe airflow limitation results in a "silent chest." A normal lung examination without acute asthma exacerbation does not rule out the diagnosis of asthma in childhood. Just as family history of asthma and atopic diseases such as eczema, atopic dermatitis, allergic rhinitis, or food allergy are useful for supporting the diagnosis of asthma, so are the concomitant findings of nasal polyposis, atopic dermatitis, and rhinitis.

Lung function testing or bronchial responsiveness testing (see below) are useful in defining impaired lung function or reversible obstruction consistent with asthma. These measures, coupled with history and physical exam, aid in the diagnosis of asthma in childhood.

13.6.2 Differential Diagnoses of Childhood Asthma

Many conditions in childhood have respiratory symptoms and signs similar to those of asthma. In early life, chronic coughing and wheezing might suggest gastroesophageal reflux (GER), rhinosinusitis, recurrent aspiration, laryngotracheobronchomalacia, airway anatomic abnormality (e.g., vascular ring), foreign body aspiration, cystic fibrosis, or bronchopulmonary dysplasia. Suspected asthma with chronic cough and recurrent upper and lower airways infections should be differentiated from primary cilliary dyskinesia, bronchiolitis obliterans, Churg-Strauss vasculitis (eosinophilic granulomatosis with polyangiitis), and immunodeficiency.

13.6.3 Laboratory Tests

13.6.3.1 Pulmonary Function Testing

Forced Oscillation Technique

Forced oscillation technique (FOT), also referred as the impulse oscillometry (IOS), is a useful tool for diagnosing young children with asthma (<5 years) because it requires only passive tidal breathing. FOT measures respiratory system resistance and reactance at several frequencies. It involves the application of a miniature loudspeaker

placed proximal to the device's flow sensor and produces forced oscillations of flow with a range of frequencies into the airway via a mouthpiece. Technically, children will be asked to breathe normally (tidal breathing) through a mouthpiece over a 30-s interval during which 10 stable respiratory rhythms are obtained (Fig. 2). Children must sit still with a mouthpiece in mouth and nose clips in place. The technician's or parent's hands should support the child's cheeks and floor of the mouth. The tongue cannot move around or obstruct the mouthpiece. In children with asthma, FOT can be used to measure bronchodilator response and perform methacholine challenges. Due to its relative ease of use, FOT is a reproducible and suitable method of lung function testing in younger children and especially in children who cannot perform spirometry (Delacourt et al. 2001).

Interrupter Technique (Rint)

The interrupter technique (Rint) is an alternative method that measures airway resistance (Raw) in very young asthma children. Similar to FOT, it also involves passive tidal breathing through a mouthpiece in a seated child wearing a nose clip (Beydon et al. 2007). Technically, the mouthpiece has to be held between the teeth, and the lips must be sealed around its circumference. The child's neck should be slightly extended with the cheeks supported by the operator's hands to decrease upper airway compliance. With passive breathing, the respiratory cycle is automatically "interrupted" multiple times (no more than 100 ms at a time) at a preset trigger to allow equilibration of alveolar and mouth pressure. "Rint" is defined as this pressure divided by the airflow measured immediately before interruption. Rint measurements may be obtained during either inspiratory or expiratory cycle with no significant difference between values obtained in either phase (Beydon et al. 2007). Rint measurements are useful to evaluate bronchodilator response and may be helpful in methacholine challenge, although Rint sensitivity in diagnosing bronchial hyper-responsiveness is lower than that of other more conventional methods such as methacholine challenge or histamine challenge (Beydon et al. 2007). To date, this technique is used extensively in Europe but remains primarily a research technique in the United States.

Spirometry Testing

Spirometry is the most common pulmonary function testing performed in school-age children and may be utilized in some younger children who are able to meet technical criteria. However, children

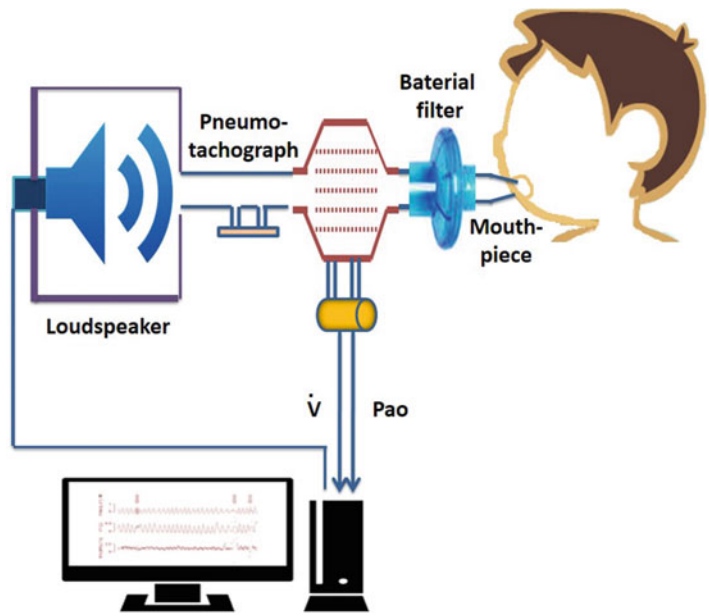


Fig. 2 Model of forced oscillation technique system (FOT)

of all ages may have difficulty meeting quality-control criteria outlined by the American Thoracic Society (ATS) and European Respiratory Society (ERS) (Miller et al. 2005); hence, as is true in all patients, attention to test performance is crucial in interpreting results. Most asthmatic children can perform spirometry with adequate technique and repeatability by age 5 years. Technically, spirometry is performed with the child in a standing or seated upright position wearing nose clips. The child's lips must be sealed around the mouthpiece, and the maneuver should begin with minimal hesitation. As recommended, a minimum of three maneuvers should be recorded (Beydon et al. 2007). For some children, if technique is improving with successive maneuvers, then more attempts may be helpful, although results should note number of technically satisfactory maneuvers and the repeatability of results.

Measures of spirometry include forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, and peak expiratory flow (PEF). In children with asthma, the goals of performing spirometry are to identify the presence of airflow limitation (obstructive defect) based on FEV_1/FVC ratio $<80\%$, to quantify the severity of airflow limitation based on FEV_1 (mild, FEV1 $>80\%$; moderate, $60\% \leq FEV_1 \leq 80\%$; and severe, $FEV_1 <60\%$ of predicted values), and to measure the response to bronchodilator (with short acting β_2-agonist) or a bronchial provocation test (with methacholine or histamine) by comparing the change of FEV_1 pre- and posttests. Spirometry is especially useful in children who are poor perceivers of airflow obstruction or when physical signs or symptoms of asthma do not occur until airflow obstruction becomes severe.

13.6.3.2 Bronchial Responsiveness Tests

Bronchodilator Reversibility Testing

Measure of bronchodilator responsiveness, also called reversibility testing (BRT), aims to determine evidence of reversible airflow limitation by comparing baseline spirometry with that obtained after short-acting bronchodilator administration. To perform BRT, children should avoid short-acting β_2–agonists (SABA) for 4 h prior to testing and long-acting β_2-agonists (LABA), slow release β_2-agonists, or oral therapy with aminophylline at least 12 h prior to testing (Miller et al. 2005). After obtaining baseline spirometry (as per above), two inhaled doses of 100 mcg of albuterol/salbutamol, separated by 30 s, through a spacer device are administered. Each dose should be followed by holding the breath for 5–10 s, and post-bronchodilator spirometry should be performed 10–15 min after the second dose. The improvement of FEV1 $\geq 12\%$ or >200 mL is consistent with asthma in children (Miller et al. 2005).

Bronchial Challenge Testing (BCT)

Bronchial challenge testing (BCT) utilizes pharmacological therapy or other challenge mediums to determine bronchial hyper-responsiveness in children with nonspecific respiratory symptoms who have normal pulmonary function testing, including response to bronchodilators. BCT can be performed with methacholine, histamine, carbachol, adenosine 5′-monophosphate (AMP), cold air, dry air, or exercise (Beydon et al. 2007).

In asthmatic children, children eligible for BCT are those free of respiratory infections for at least 3 weeks, free of wheezing, with normal oxygen saturation ($>95\%$), and with near-normal pulmonary function parameters in the setting of doubtful asthma (Crapo et al. 2000). Current guidelines recommend against use in preschool-age children (Crapo et al. 2000). Medications known to influence bronchial responsiveness should be withheld before the test (β_2-agonists, leukotriene modifiers, cromolyn sodium, and nedocromil).

The five-breath dosimeter method is generally used to deliver methacholine (or histamine) in BCT for children. The minimal inspiratory time required to inhale a dosimeter-delivered dose of solution is at least 3–5 s (deep inhalation) with a maximal nebulization time of 0.6 s. The interval between two inhalations should be 5 min (American Thoracic Society 2000). The provocative concentration (PC) or provocative dose (PD) is the accumulated inhaled concentration necessary to obtain a given pulmonary function test change from baseline. The dose that provokes a 20% baseline decrease of FEV_1 (or $PtcO_2$) is referred

as PD20-FEV_1 (or PD20-$PtcO_2$, transcutaneous partial pressure of oxygen), and the concentration that induces a 40% baseline increase in Rrs (total resistance of the respiratory system) is PC40-Rrs. Exercise induced-BCT is positive when FEV_1 decreases during or after exercise by >15%.

At the end of BCT, bronchodilators (β_2-agonist) should be administered even if the child does not demonstrate significant bronchoconstriction (wheezing or dyspnea), and the child should be monitored until the FEV_1 has returned to baseline. Oxygen, resuscitation equipment, and bronchodilators should be readily available throughout the provocation challenge.

13.6.3.3 Measure of Exhaled Nitric Oxide in Childhood Asthma

Role of Exhaled Nitric Oxide in Childhood Asthma

In the human respiratory system, nitric oxide (NO) is a biological mediator produced by the airways and lung (Dinh-Xuan et al. 2015). NO is present in the exhaled breath and implicated in the pathophysiology of lung diseases, including asthma. Currently, NO is considered a biomarker of Th2 or T2 airway inflammation and is synthesized by inducible nitric oxide synthase (iNOS) in epithelial cells, macrophages, neutrophils, eosinophils, and mononucleated cells (Prado et al. 2011). The levels of NO in exhaled air (fractional exhaled nitric oxide: F_ENO) is significantly increased in the majority of asthma phenotypes and can be detected with portable devices by using a chemical electrolytic technique. The measurement of F_ENO is a noninvasive, easy to perform, and safe technique for assessing airway inflammation in asthma. Since the early 1990s when F_ENO was first measured, many studies show close correlations between F_ENO levels and eosinophil counts in peripheral blood, sputum, bronchoalveolar lavage fluid, and in biopsied lung tissue. Therefore, F_ENO can be used as a relevant biomarker of airway inflammation in management of adult as well as childhood asthma. The measure of F_ENO also helps to predict asthma exacerbations, ICS response (decreases with ICS), and compliance to ICS (Dweik et al. 2011). Recently, F_ENO measurement has been recommended by GINA in monitoring patients with asthma (GINA 2017). Moreover, as recommended by the ATS, F_ENO predicts the likelihood of response to ICS more consistently than spirometry, bronchodilator response, peak flow variation, or airway BCT to methacholine (Dweik et al. 2011). Thus, high levels of F_ENO in children with asthma are a reliable marker for T2 or Th2 airway inflammation mediated by eosinophils and suggest a robust response to ICS.

Technical Issues Related to Measurement of Exhaled Nitric Oxide

Fractional exhaled nitric oxide (F_ENO), as measured in parts per billion (ppb), can be obtained by chemiluminescence or an electrochemical method. The technique using an electrochemical method has been developed recently for ambulatory use with portable devices. In children <12 years old, F_ENO should be obtained at a single flow rate of 50 mL/s for a duration of exhalation lasting at least 4 s (with 3 s at a plateau curve) (Dweik et al. 2011). The use of a nose clip to avoid the risk of contamination from NO produced in the nasal and sinus cavities is not necessary in children (Dinh-Xuan et al. 2015). It is recommended that F_ENO measurements be obtained before performing forced expiratory maneuvers for spirometry and at least 30 min after sustained exercise, as these may impact F_ENO results. In children, F_ENO may also be affected by age. However, it is suggested that in children (<18 years), F_ENO <20 ppb indicates non-eosinophilic inflammation with less likely responsiveness to ICS, and F_ENO >35 ppb is suggestive of eosinophilic inflammation to which ICS responsiveness is more likely. The values of F_ENO between 20 ppb and 35 ppb in children should be interpreted cautiously and with reference to clinical context. Moreover, when using F_ENO in monitoring airway inflammation in children with asthma, variation of F_ENO of 20% (if F_ENO >50 ppb at baseline) or 10 ppb (if F_ENO <50 ppb at baseline) may be considered significant (Dweik et al. 2011).

13.6.3.4 Other Laboratory Test in Childhood Asthma

Allergy Tests

Allergy tests are necessary examinations in childhood asthma. The presence of allergic status (atopy) increases the probability of asthma in children with respiratory symptoms. Children with atopic status can be identified by skin prick testing (SPT) or by measuring the level of specific immunoglobulin E (sIgE) in serum. SPT with standard environmental allergens is easily performed in children, is inexpensive, and has high sensitivity. Measurement of sIgE is more expensive than SPT and may be preferred for uncooperative patients, those with widespread skin disease, or if history suggests a risk of anaphylaxis to aeroallergens (GINA 2017). However, the presence of a positive SPT or sIgE does not mean that the allergen is responsible for respiratory symptoms, and the relevance of allergen exposure and its relationship to symptoms must be confirmed by the patient's history.

Radiology

Chest radiographs are not often indicated in childhood asthma except for eliminating different diagnoses such as foreign-body aspiration, abnormal airway structure, or parenchymal diseases. Chest radiographs (posteroanterior and lateral views) can help identify abnormalities that are hallmarks of asthma masqueraders (aspiration pneumonitis or bronchiolitis obliterans) and complications during acute asthma exacerbations (atelectasis or pneumothorax). The abnormalities in chest radiographs can be better analyzed with high-resolution (HR), thin-section, and low-dose CT scans. HR-CT scans may suggest the diagnosis of bronchiectasis, cystic fibrosis, or allergic bronchopulmonary aspergillosis.

13.7 Assessment of Asthma in Childhood

13.7.1 Assessment of Asthma Severity

Assessment of asthma severity informs treatment strategies and provides information regarding potential future risk. Asthma severity has traditionally been divided into intermittent or persistent categories with the latter being further subdivided into mild, moderate, and severe asthma, based on guidelines from the National Asthma Education and Prevention Program (NAEPP): Expert Panel Report 3 (NAEPP 2007). These guidelines have distinct criteria for three groups of childhood asthma (4 years, 5–11 years, and $\geq$12 years). In assessing asthma severity, data concerning daytime and nighttime symptoms, short-acting beta$_2$-agonist (SABA) usage for quick relief, ability to engage in daily activities, airflow limitation evaluated by spirometry in children 5 years of age and older, and risk of severe asthma exacerbations is recorded. Recommendations for initial treatment(s) follow this characterization of asthma severity (NAEPP 2007). The reader is referred to the NAEPP-Expert Panel Report 3 (NAEPP 2007), or its associated asthma care quick reference (NHLBI 2017), for further detail.

While assessment of asthma severity continues to play a role in the provision of asthma care, emphasis has more recently been placed on assessment of asthma control.

13.7.2 Assessment of Asthma Control

Asthma control is defined as the reduction or removal of respiratory manifestations of asthma symptoms with or without treatment (Reddel et al. 2009). In children, for whom pulmonary function testing may not be a reliable method for monitoring changes in FEV_1, asthma control refers to minimal symptoms, lung function impairment, and risk of adverse events while obtaining goals of treatments (Reddel et al. 2009). Assessment of asthma control includes two components: a child's asthma status (symptom control and lung function if measurable) and future risk of adverse events (loss of control, acute exacerbation, accelerated decline of lung function, and adverse effects of treatment). According to the National Heart, Lung, and Blood Institute (NHLBI) guidelines, it is recommended that symptom control, lung function if measurable, and risk be monitored regularly to allow for the characterization

of asthma as well controlled, not well controlled, or very poorly controlled and to inform strategies for adjusting therapy and reducing asthma morbidity (NHLBI 2011).

In children, symptoms such as wheeze, chest tightness, shortness of breath, and cough usually vary in frequency and intensity throughout time. However, poor asthma symptom control is strongly associated with an increased risk of asthma exacerbations (Reddel et al. 2009). Assessment of symptoms in children varies by age. In younger children, symptoms are most often reported by caregivers. However, caregivers may under- or overestimate asthma symptoms in the child or may fail to recognize symptoms. Of importance, a child's daily activities, including sports, play, and social life, should be carefully reviewed as some children with poorly controlled asthma avoid strenuous exercise; as such, their asthma may appear well controlled when it really is not. In addition, other potential symptoms related to uncontrolled asthma in children, such as irritability, tiredness, and changes in mood, should be queried and monitored.

The second component of asthma control is assessment of asthma risk. Here the goal is to identify whether the child is at risk of adverse asthma outcomes, particularly exacerbations, fixed airflow limitation, and side effects of medications. While the relationship between symptom control and future risk of adverse outcomes such as exacerbations has not been sufficiently studied in young children (GINA 2017), the risk is greater if current symptom control is poor (Meltzer et al. 2011). Furthermore, acute asthma exacerbations may occur after months of apparently good symptom control, may have different causes, and may require different treatment options. Therefore, it is imperative that the asthma provider remain attune to changes in symptoms and potential triggers and take steps to counter these changes. In young children with asthma, especially in infancy, "fixed" airflow limitation is very difficult to evaluate. In children >5 years of age who can perform spirometry, a persistent and accelerated decline in lung function (mainly FEV_1) associated with airflow limitation (FEV_1/FVC <75% in children) that is not fully reversible is a relevant functional marker of fixed airflow obstruction. Medication side effects are also considered risks for adverse outcomes due to systemic and local effects (e.g., changes in growth rate or facial rash due to inhaled corticosteroid use); thus, medication choices must strive to balance these types of risks with the benefit of impacting asthma control.

13.7.2.1 Current Guidelines for Assessment of Asthma Control

The 2017 Global Initiative for Asthma (GINA) guidelines have suggested a schema for assessing asthma control in children ≤5 years old (Table 3) and in those 6–11 years old (Table 4) (GINA 2017). In addition, the NHLBI guidelines also have distinct criteria for three childhood age groups (0–4 years, 5–11 years, and ≥12 years) for the assessment of asthma control (NAEPP 2007). These guidelines have integrated lung function and validated numeric scales to classify the control of asthma. The reader is referred to the NAEPP-Expert Panel Report 3 (NAEPP 2007), or its associated asthma care quick reference (NHLBI 2017), for further detail.

13.7.2.2 Asthma Control Assessment Tools for Children

In addition to the guidelines reported above, a variety of validated scoring tools have been developed to aid physicians in assessing asthma control in children. These numeric tools are useful for monitoring patient progress and are more sensitive to change in symptom control than categorical tools (O'Byrne et al. 2010). While these tools usually correlate significantly with each other, results are not identical (O'Byrne et al. 2010). Additionally, respiratory symptoms in children with asthma may be non-specific; therefore, when assessing changes in symptom control, it is important to clarify whether these symptoms are due to asthma or other diseases/comorbidities.

These tools include the Childhood Asthma Control Test (c-ACT), the Asthma Control Test (ACT), the Asthma Control Questionnaire (ACQ), the Test for Respiratory and Asthma Control in Kids (TRACK), the Composite Asthma Severity Index (CASI), and the Asthma Therapy

Table 3 Assessment of asthma control in children under 5 years (GINA 2017). (Reprinted with permission)

A. Asthma symptom control			**Level of asthma control**		
In the past 4 weeks, has the child had	**Yes**	**No**	**Well controlled**	**Partly controlled**	**Uncontrolled**
Daytime asthma symptoms for more than a few minutes, more than once a week?	c	c	None of these	1–2 of these	3–4 of these
Any activity limitation due to asthma? (Runs/plays less than other children, tires easily during walks/playing?)	c	c			
Reliever medication needed[a] more than once a week?	c	c			
Any night waking or night coughing due to asthma?	c	c			
B. Future risk for poor asthma outcomes					
Risk factors for asthma exacerbations within the next few months Uncontrolled asthma symptoms One or more severe exacerbation in previous year The start of the child's usual "flare-up" season (especially if autumn/fall) Exposures: tobacco smoke; indoor or outdoor air pollution; indoor allergens (e.g., house dust mite, cockroach, pets, mold), especially in combination with viral infection Major psychological or socioeconomic problems for child or family Poor adherence with controller medication or incorrect inhaler technique					
Risk factors for fixed airflow limitation Severe asthma with several hospitalizations History of bronchiolitis					
Risk factors for medication side effects Systemic: Frequent courses of OCS; high-dose and/or potent ICS Local: Moderate/high-dose or potent ICS; incorrect inhaler technique; failure to protect the skin or eyes when using ICS by nebulizer or spacer with face mask					

ICS inhaled corticosteroids, *OCS* oral corticosteroids
[a]Excludes reliever taken before exercise

Assessment Questionnaire (ATAQ). Comparison of these tools, including recommended ages, scoring scale, assessment interval, and score noting well-controlled asthma, is highlighted below in Table 5.

13.8 Treatment of Asthma in Childhood

13.8.1 Goals of Asthma Treatment in Childhood

Overall, the goals of asthma treatment include symptom control, maintaining normal daily activities, and minimizing exacerbations, fixed lung impairment, and treatment side effects (GINA 2017). Asthma management should include a cycle of assessment (diagnosis, symptom control, risk factors, inhaler technique, adherence, parent preference), treatment adjustment (medications, non-pharmacological strategies, and modification of risk factors), and review of response (including medication effectiveness and adverse effects) (GINA 2017). This is carried out in combination with education of parents/caregivers and child (depending on the child's age), skills training for effective use of inhaler devices, treatment adherence encouragement, monitoring of symptoms by parents/caregivers, cost considerations, and a written asthma action plan (GINA 2017).

13.8.2 Choosing Medications for Childhood Asthma

Asthma control requires a multimodal approach. In most cases, pharmacological treatment aids in achieving control, even in infancy, and should be established after partnership between parents/caregivers and healthcare providers. The GINA guidelines recommend that both general and individual questions should be utilized when recommending treatment (GINA 2017): (1) What is the "preferred" medication option at each

Table 4 Assessment of asthma control in children 6–11 years and adolescents (GINA 2017). (Reprinted with permission)

A. Asthma symptom control			**Level of asthma control**		
In the past 4 weeks, has the children had	**Yes**	**No**	**Well controlled**	**Partly controlled**	**Uncontrolled**
Daytime asthma symptoms more than twice a week?	c	c	None of these	1–2 of these	3–4 of these
Any night waking due to asthma?	c	c			
Reliever medication needed for symptoms[a] more than twice a week?	c	c			
Any activity limitation due to asthma?	c	c			
B. Future risk for poor asthma outcomes					
Assess risk factors at diagnosis and periodically, particularly for patients experiencing exacerbations Measure FEV_1 at start of treatment, after 3–6 months of controller treatment to record the patient's personal best lung function, then periodically for ongoing risk assessment					
Potentially modifiable independent risk factors for flare-ups (exacerbations) Uncontrolled asthma symptoms High SABA use (with increased mortality if >1 × 200-dose canister/month) Inadequate ICS: not prescribed ICS; poor adherence; incorrect inhaler technique Low FEV_1, especially if <60% predicted Major psychological or socioeconomic problems Exposures: smoking; allergen exposure if sensitized Comorbidities: obesity; rhinosinusitis; confirmed food allergy Sputum or blood eosinophilia *Other major independent risk factors for flare-ups (exacerbations)* Ever intubated or in intensive care unit for asthma. ≥1 severe exacerbation in last 12 months					**Having one or more of these risk factors increases the risk of exacerbations even if symptoms are well controlled**
Risk factors for developing fixed airflow limitation Lack of ICS treatment Exposures: tobacco smoke;93 noxious chemicals; occupational exposures Low initial FEV1;94 chronic mucus hypersecretion; sputum or blood eosinophilia					
Risk factors for medication side effects Systemic: Frequent courses of OCS; long-term, high-dose, and/or potent ICS; also taking P450 inhibitors[b] Local: high-dose or potent ICS; poor inhaler technique					

ICS inhaled corticosteroids, *OCS* oral corticosteroids, *SABA* short-acting $beta_2$-agonist
[a]Excludes reliever taken before exercise
[b]P450 inhibitors: cytochrome P450 inhibitors such as ritonavir, ketoconazole, and itraconazole

treatment step to control asthma symptoms and minimize future risk? These decisions are based on data for efficacy, effectiveness, and safety from clinical trials and on observational data; (2) How does this particular child differ from the "average" child with asthma, in terms of response to previous treatment, parental preference (goals, beliefs, and concerns about medications), and practical issues (cost, inhaler technique, and adherence)? Additionally, all clinical, functional, and biological characteristics or phenotypes that predict the child's response to treatment should be evaluated carefully.

GINA guidelines (see below) recommend a stepwise treatment approach, inclusive of reliever medications for as-needed symptom relief and daily use of controller medications or other add-on therapies, if needed, to keep asthma well controlled. In children with asthma, daily controller treatment initiated after the diagnosis of asthma is made affords the best results (GINA 2017). Previous studies, including a more recent Cochrane review of 1211 patients (Chauhan et al. 2013), have shown that early initiation of low-dose ICS in asthma patients leads to a greater improvement in lung function when compared to later treatment initiation using higher doses of ICS (Busse et al. 2008; Selroos 2008; Chauhan et al. 2013). However, the Childhood Asthma Management Program (CAMP), following 1041 children aged 5–12 years for a total of

Table 5 Asthma control assessment tools

Asthma control assessment tools				
	Ages validated	Scoring range	Score for well controlled	Assessment interval
Childhood Asthma Control Test (ACT-c)	4–11 years	0–27	>19	Month
Asthma Control Test (ACT)	≥12 years	5–25	>19	Month
Asthma Control Questionnaire (ACQ 5/6[a]/7[b])	≥11 years[c]	0–6	<0.75	Week
Test for Respiratory and Asthma Control in Kids (TRACK)	1–5 years	0–100	≥80	Month-year
Composite Asthma Severity Index (CASI)	6–17 years	0–20	Not defined[d]	2 weeks, symptoms; 2 months, exacerbations
Asthma Therapy Assessment Questionnaire (ATAQ)	5–17 years	"Other" 0–5; "control" 0–7	<1	Month

[a]ACQ-6 comprises all questions from ACQ-5 and adds a question about inhaler use
[b]ACQ-7 comprises all questions from ACQ-6 and includes spirometry in the score
[c]Has been used down to age 6 years if questionnaire administered by a trained interviewer (Juniper et al. 2010)
[d]Used to follow an individual's asthma. Lower score is better controlled

4–6 years, showed that, while inhaled corticosteroids reduce the risk of exacerbation, improve symptoms, and improve baseline lung function overall, these effects disappear after therapy is stopped (Covar et al. 2012). Furthermore, CAMP results suggest that ICS therapy does not prevent reduction in lung function nor does it seem to affect the natural history of childhood asthma (Covar et al. 2012).

13.8.3 Choice of Inhaler Device

The use of inhaled treatment constitutes a cornerstone of asthma therapy in children. A pressurized metered dose inhaler (pMDI) with a valved spacer (or chamber) is preferred; in children ≤3 years old, a low-volume spacer (<350 mL) should be used. A face mask should be added to the spacer for patients up to 3 years of age. The pMDI with spacer should be used during tidal breathing with approximately 5–10 breaths per actuation or enough to empty the spacer.

13.8.4 Reviewing Response and Adjusting Treatment

In children with asthma, symptom control, risk factors for exacerbation, and adverse treatment effects should be monitored at every visit. For those treated with ICS, especially with moderate to high doses, height should be measured regularly. Importantly, the ability to step-down therapy and even the need for long-term therapy with controller treatment should be evaluated every 3 months as some children have remission of asthma. The clinical benefit from ICS may be seen at low doses, and the evidence of dose-response relationships is controversial (Busse et al. 2008; Selroos 2008). Therefore, once asthma control is achieved, the ICS dose should be carefully titrated to the minimum dose (Table 6). If therapy is discontinued, children should be followed within 1–3 months, and, if asthma symptoms recur, asthma treatment should be reinstated.

13.8.4.1 Treatment of Asthma in Children 5 Years of Age or Younger

The stepwise approach to asthma treatment recommended by GINA for children ≤5 years old comprises four steps (Fig. 3).

Step 1 includes a short-acting beta-agonist (SABA) which should be prescribed to all children with wheezing; SABA should be used every 4–6 h as needed for one or more days until symptoms disappear. If wheezing episodes are frequent or severe, symptoms are not controlled, inhaled

Table 6 Low, medium, and high daily doses of inhaled corticosteroids (GINA 2017). (Reprinted with permission)

Drug	Daily dose (mcg)		
	Low	Medium	High
Children 12 years and older			
Beclometasone dipropionate (CFC)[a]	200–500	>500–1000	>1000
Beclometasone dipropionate (HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (HFA)	80–160	>160–320	>320
Fluticasone furoate (DPI)	100	n.a.	200
Fluticasone propionate (DPI)	100–250	>250–500	>500
Fluticasone propionate (HFA)	100–250	>250–500	>500
Mometasone furoate	110–220	>220–440	>440
Triamcinolone acetonide	400–1000	>1000–2000	>2000
Children 6–11 years			
Beclometasone dipropionate (CFC)[a]	100–200	>200–400	>400
Beclometasone dipropionate (HFA)	50–100	>100–200	>200
Budesonide (DPI)	100–200	>200–400	>400
Budesonide (nebules)	250–500	>500–1000	>1000
Ciclesonide	80	>80–160	>160
Fluticasone furoate (DPI)	n.a.	n.a.	n.a.
Fluticasone propionate (DPI)	100–200	>200–400	>400
Fluticasone propionate (HFA)	100–200	>200–500	>500
Mometasone furoate	110	≥220- < 440	≥440
Triamcinolone acetonide	400–800	>800–1200	>1200

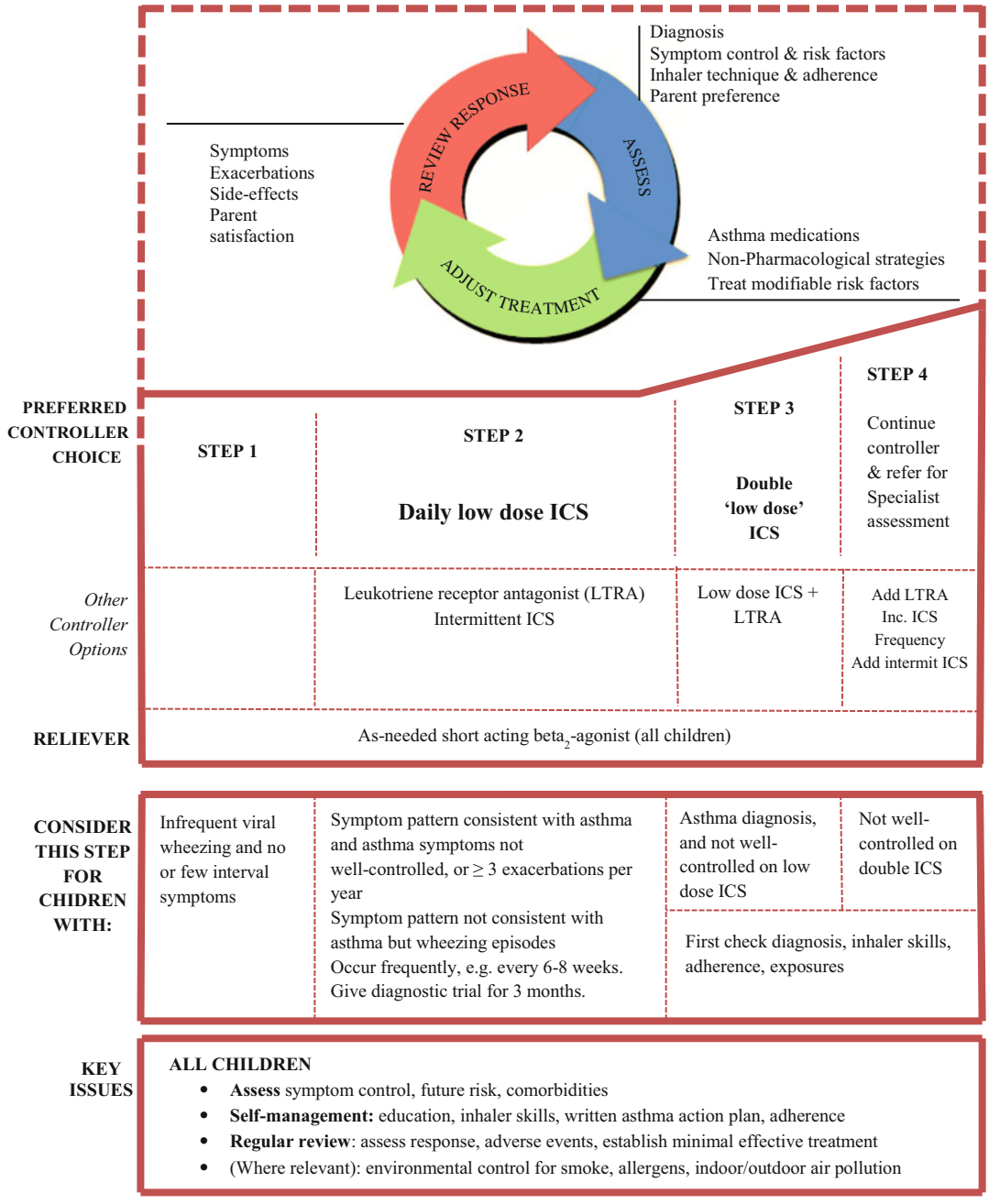
CFC chlorofluorocarbon propellant, *DPI* dry powder inhaler, *HFA* hydrofluoroalkane propellant, *n.a.* not applicable
[a]Beclometasone dipropionate CFC is included for comparison with older literature

SABA therapy needs to be repeated more than every 6–8 weeks, or wheezing episodes associated with viral infection are severe, escalation of therapy to Step 2 should be considered.

Step 2 includes use of a daily controller medication (inhaled corticosteroid, ICS, or leukotriene receptor antagonist, LTRA) as well as continued use of SABA as needed. Use of regular daily low-dose ICS (see Table 7) is recommended as the preferred initial treatment and should be administered for at least 3 months to establish efficacy. In young children with persistent asthma, regular treatment with LTRA modestly reduces symptoms and need for oral corticosteroids compared with placebo. In young children with recurrent virally induced wheezing, regular LTRA use improves some asthma outcomes compared with placebo but does not reduce the frequency of hospitalizations, courses of prednisone, or number of symptom-free days (Bisgaard et al. 2005). For preschool children with frequent virally induced wheezing and interval asthma symptoms existing in-between viral infection, as-needed episodic ICS may be considered, but a trial of regular ICS should be undertaken first. However, in one meta-analysis, while there was no statistically significant difference in the rate of asthma exacerbations between these types of patients using daily versus intermittent ICS, those using daily ICS had significantly more asthma-free days (Rodrigo and Castro-Rodríguez 2013).

When asthma symptoms or exacerbations are not controlled after 3 months on Step 2 therapies, Step 3 strategies are recommended, starting with review of modifiable factors (inhaler technique, treatment adherence, and environmental/allergen exposures). It is also important to confirm that symptoms are due to asthma rather than a concomitant or alternative condition; if the diagnosis of asthma is in doubt, there should be a low threshold to refer for expert assessment. Once these topics are reviewed and addressed, doubling the low-dose ICS (to medium dose) for another 3 months is preferred, although an acceptable alternative is to add a LTRA to the initial low-dose ICS.

If Step 3 strategies fail to achieve and maintain asthma control or side effects of treatment are



ICS: inhaled corticosteroid; intermit; intermittent; LTRA: leukotriene receptor antagonist.

Fig. 3 Stepwise treatment recommended by GINA 2017 for children 5 years and younger (GINA 2017). (Reprinted with permission)

Table 7 Low daily doses of inhaled corticosteroids for children 5 years and younger (GINA 2017). (Reprinted with permission)

Drug	Low daily dose (mcg)
Beclomethasone dipropionate (HFA)	100 200
Budesonide pMDI + spacer	500
Budesonide nebulized	100
Fluticasone propionate (HFA)	160
Ciclesonide	Not studied below age 4 years
Mometasone furoate	Not studied in this age group
Triamcinolone acetonide	

This is not a table of clinical equivalence. A low daily dose is defined as the dose that has not been associated with clinically adverse effects in trials that included measures of safety

HFA hydrofluoralkane propellant, *pMDI* pressurized metered dose inhaler

observed, the child should be referred for expert assessment. Step 4 options include further increase in ICS dose (perhaps combined with more frequent dosing) for a few weeks until asthma improves; addition of LTRA (if not already employed), theophylline, or low-dose oral corticosteroid (for a limited time only); and/or addition of intermittent high-dose ICS to the regular daily ICS if exacerbations are the main problem. The need for additional controller treatment should be re-evaluated at each visit and maintained for as short a period as possible, taking into account potential risks and benefits. Treatment goals and their feasibility should be reconsidered and discussed with the child's family/caregiver; it may become necessary to accept a degree of persisting asthma symptoms to avoid excessive and harmful medication doses. While there has been prior debate regarding use of LABA in a pediatric population and GINA guidelines do not include use of LABA, more recent studies and meta-analysis demonstrate that the addition of LABA to baseline ICS can reduce exacerbations when compared to ICS use alone without significantly increased adverse effects (Nelson et al. 2006; Rodrigo et al. 2009; Tal et al. 2002). The use of LABA in young remains an issue of debate (Malone et al. 2005).

13.8.4.2 Treatment of Asthma in Children 6 Years and Older

The stepwise approach to asthma treatment recommended by GINA for children >5 years old comprises five steps (Fig. 4) (GINA 2017). These guidelines recommend an approach similar to that used in adults.

Step 1, as in younger children, includes use of SABA as needed. However, in special circumstances, it is appropriate to immediately start an ICS; these cases include children with more frequent symptoms, FEV_1 <80% predicted or personal best, or an exacerbation within the past 12 months (GINA 2017). When asthma remains uncontrolled with Step 1 therapies, escalation to Step 2 is warranted.

Step 2 preferred option consists of adding a low-dose ICS to the as-needed SABA. In some (those unable/unwilling to use ICS, with intolerable side effects to ICS, or with concomitant allergic rhinitis), LTRA may be appropriate initial Step 2 therapy, although LTRAs are less effective than ICS (GINA 2017). Likewise, while low-dose ICS/LABA could be considered in controller-naive patients, these combinations are generally more expensive and do not further reduce the risk of exacerbations compared to ICS alone (GINA 2017). Additionally, for patients with purely seasonal allergic asthma and no interval asthma symptoms, ICS should be started immediately when symptoms commence and continued for 4 weeks after the relevant pollen season ends.

As in children <5 years old, when symptoms persist, the first recommendation for Step 3 treatment includes review of modifiable factors (inhaler technique, treatment adherence, and environmental/allergen exposures), and confirmation of asthma rather than alternative conditions are again recommended. If evaluation continues to suggest uncontrolled asthma, the Step 3 preferred option differs by age and includes one to two controller medications plus an as-needed reliever medication. For children 6–11 years, identical to those ≤5 years, the preferred option is to increase ICS to medium dose as this is similar to or more effective than adding a LABA. However, in adolescents (children >11 years), adding LABA to

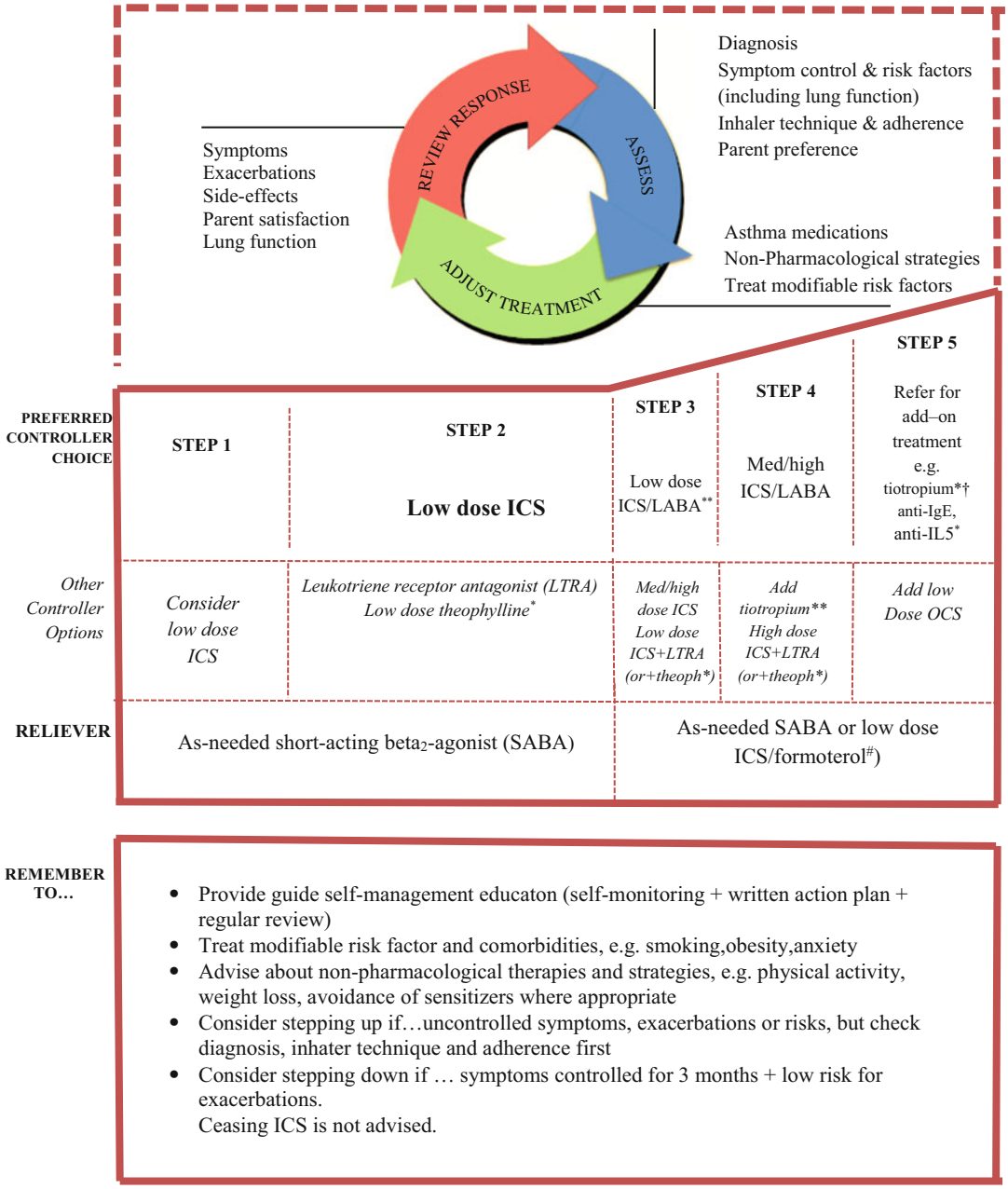


Fig. 4 Stepwise treatment recommended by GINA 2017 for children 6 years and older (GINA 2017). *ICS,* inhaled corticosteroids, *LABA* long-acting beta2-agonist, *med* medium dose, *OCS* oral corticosteroids. *Not for children <12 years. **For children 6–11 years, the preferred Step 3 treatment is medium-dose ICS. # Low-dose ICS/formoterol is the reliever medication for patients prescribed low-dose budesonide/formoterol or low-dose beclometasone/formoterol maintenance and reliever therapy. † Tiotropium by mist inhaler is an add-on treatment for patients with a history of exacerbations; it is not indicated in children <12 years. (Reprinted with permission)

the same dose ICS improves symptoms and lung function, reduces risk of exacerbations, and is more effective than increasing to medium-dose ICS (GINA 2017). One strategy using a single ICS/LABA inhaler for both maintenance and reliever treatment (using an overall lower-dose ICS/LABA as maintenance since additional corticosteroid will be administered with rescue doses using the same inhaler) has been employed. This strategy has been shown to increase time to first asthma exacerbation (Papi et al. 2013); result in fewer exacerbations requiring oral corticosteroids, ED visit, or hospitalization compared to higher fixed-dose combination inhaler (Kew et al. 2013); and reduce risk of exacerbation requiring oral corticosteroids compared to fixed higher dose of ICS (Cates and Karner 2013). Therefore, the preferred option in this age group is low-dose ICS/LABA (suggested as beclomethasone or budesonide with formoterol due to onset of action of formoterol similar to albuterol) as both maintenance and reliever treatment or low-dose ICS/LABA as maintenance with SABA as needed. Alternative controller options for adolescents include increase to medium-dose ICS, low-dose ICS plus LTRA, or low-dose ICS plus low-dose, sustained-release theophylline; however, all these are again less efficacious than ICS/LABA combination in this age group.

The selection of Step 4 treatment depends on the prior selection at Step 3 but generally consists of review of the modifiable factors mentioned in Step 3 (see above) and the preferred use of two controller medications plus as needed reliever medication. In children aged 6–11, it is recommended to refer for expert assessment and advice at Step 4. For adolescents on low-dose ICS/LABA with as needed SABA in Step 3, treatment may be increased to medium-dose ICS/LABA with as needed SABA or may be altered to low-dose ICS/LABA as maintenance and reliever with consideration for additional add-on therapy. In those with more than one asthma exacerbation in the past year, low-dose ICS/LABA as maintenance and reliever medication has been shown to be more effective in reducing exacerbations than the same dose of maintenance ICS/LABA or higher doses of ICS (GINA 2017).

Alternative add-on options in children include LTRA and in adolescents include LTRA, tiotropium (long-acting muscarinic antagonist or LAMA), high-dose ICS/LABA (although increase in ICS generally provides little additional benefit and increases risk of side-effects), and low-dose sustained-release theophylline. High-dose ICS is only recommended for a 3–6-month trial basis when asthma remains uncontrolled on medium-dose ICS/LABA and/or third controller such as LTRA.

Step 5 treatment options should be directed by a specialist with expertise in management of severe asthma. These add-on treatments include omalizumab (Xolair™; anti-immunoglobulin E) in children $\geq$6 years and tiotropium (Spiriva™; anticholinergic) and mepolizumab (Nucala™; anti-interleukin-5) in children $\geq$12 years. Another anti-IL-5 agent, reslizumab (Cinqair™), has not been approved for use in children $<$18 years. Omalizumab is a subcutaneous injection for those with moderate to severe asthma not well controlled on conventional therapies; currently dosing recommendations stratify individuals based on IgE level and weight to receive 75, 150, 225, 300, or 375 mg at every 2- or 4-week dosing intervals (Xolair™ Prescribing Information 2017). Mepolizumab is utilized in severe eosinophilic asthma and is given as a 100 mg injection every 4 weeks (Nucala™ Prescribing Information 2017).

13.9 Treatment of Acute Exacerbation Asthma in Childhood

13.9.1 Treatment of Acute Asthma Exacerbation in Children 5 years and Younger

13.9.1.1 Diagnosis of Acute Asthma Exacerbations in Children 5 Years and Younger

Acute asthma exacerbation (AAE) in children $\leq$5 years old is defined as an acute deterioration in symptom control that may cause respiratory

distress and death in some severe cases (Swern et al. 2008). Young children with AAE must be evaluated by a healthcare provider to determine the severity of exacerbation and to modify treatment, including starting systemic corticosteroids, if needed. Early symptoms of an AAE may include increased wheezing, worsened shortness of breathing, increased coughing (especially while the child is asleep), and poor response to reliever medication. While no single symptom is predictive of exacerbation in children aged 2–5 years, the combination of increased daytime cough or wheeze and nighttime beta$_2$-agonist use is a strong predictor for exacerbation (Swern et al. 2008). Frequently, viral respiratory tract infection precedes the onset of an asthma exacerbation in young children.

13.9.1.2 Assessment of Acute Asthma Exacerbation Severity in Children 5 Years and Younger

In children ≤5 years old, the presence of any of the following features may suggest a severe acute exacerbation requiring urgent treatment and immediate transfer to the hospital: altered consciousness (agitation, confusion, or drowsiness), desaturation (oximetry on presentation <92%), tachycardia (pulse rate >200 beats/minute for infant 0–3 years or >180 beats/minute for children 4–5 years), central cyanosis, or "quiet chest" on auscultation. Several clinical scoring systems such as PRAM (Preschool Respiratory Assessment Measure) and PASS (Pediatric Asthma Severity Score) are available for assessing the severity of acute asthma exacerbations in children (Gouin et al. 2010). PRAM scores are used in children aged 1–17 years and include pulse oximetry, substernal muscle retraction, scalene muscle retraction, air entry, and wheezing; scores range from 0 to 12 with "severe" at 8–12 and "mild" as 0–3 (Chalut et al. 2000; Ducharme et al. 2008). PASS scores are used in children aged 1–18 years and include respiratory rate, pulse oximetry, auscultation, retractions, and dyspnea; scores range from 5 to 15 with "severe" at ≥12 and "mild" at ≤7 (Maue et al. 2017).

13.9.1.3 Emergency Treatment and Initial Pharmacotherapy for Children 5 Years and Younger

The initial management of acute asthma exacerbations (AAE) in children 5 years and younger recommended by GINA 2017 is presented in Table 8 below and summarized here:

Oxygen

In young children with AAE and hypoxemia (SpO_2 <92%), urgent treatment with oxygen

Table 8 Initial management of asthma exacerbations in children 5 years and younger recommended by GINA (GINA 2017). (Reprinted with permission)

Therapy	Dose and administration
Supplemental oxygen	24% delivered by face mask (usually 1 L/minute) to maintain oxygen saturation 94–98%
Short-acting beta$_2$-agonist (SABA)	2–6 puffs of salbutamol by spacer or 2.5 mg of salbutamol by nebulizer, every 20 min for first hour[a], and then reassess severity. If symptoms persist or recur, give an additional 2–3 puffs per hour. Admit to hospital if >10 puffs required in 3–4 h
Systemic corticosteroids	Give initial dose of oral prednisolone (1–2 mg/kg up to a maximum 20 mg for children <2 years old; 30 mg for children 2–5 years) or intravenous methylprednisolone 1 mg/kg 6-hourly on day 1
Additional options in the first hour of treatment	
Ipratropium bromide	For children with moderate-severe exacerbations, 2 puffs of ipratropium bromide 80 mcg (or 250 mcg by nebulizer) every 20 min for 1 h only
Magnesium sulfate	Consider nebulized isotonic magnesium sulfate (150 mg) 3 doses in the first hour of treatment for children aged ≥2 years with severe exacerbation

[a]If inhalation is not possible, an intravenous bolus of terbutaline 2 mcg/kg may be given over 5 min, followed by continuous infusion of 5 mcg/kg/h. The child should be closely monitored, and the dose should be adjusted according to clinical improvement and side effects

by face mask is warranted to maintain oxygen saturation 94–98%. To avoid hypoxemia during changes in treatment, children who are acutely distressed should be treated immediately with oxygen and SABA delivered by an oxygen-driven nebulizer.

Bronchodilator Therapy

The initial dose of SABA may be given by a pMDI with spacer and mask/mouthpiece, an air-driven nebulizer, or, if oxygen saturation is low, an oxygen-driven nebulizer. For most children, pMDI plus spacer is favored as it is more efficient than a nebulizer for bronchodilator delivery. In acute severe asthma, 6 puffs of salbutamol (100 mcg per puff) or equivalent should be given. If a nebulizer is used, a dose of 2.5 mg salbutamol or albuterol solution is recommended. The frequency of dosing depends on the response observed over 1–2 h. For children with moderate-severe exacerbation and a poor response to initial SABA, ipratropium bromide may be given as 2 puffs (80 mcg per puff) or nebulizer treatment (250 mcg) every 20 min for 1 h only (Griffiths and Ducharme 2013a).

Magnesium Sulfate

There are few studies evaluating the role of magnesium sulfate in children <5 years old. However, nebulized isotonic magnesium sulfate may be considered as an adjuvant to standard treatment with nebulized salbutamol/albuterol and ipratropium in the first hour of treatment for children ≥2 years old with acute severe asthma, particularly those with symptoms lasting <6 h (Powell et al. 2013). One study enrolled 62 patients aged 5–17 years presenting to the emergency room with mild-to-moderate asthma exacerbation to receive either nebulized albuterol 2.5 mg mixed with 2.5 mL of normal saline or nebulized albuterol 2.5 mg mixed with 2.5 mL of isotonic magnesium supplied as 6.3% solution of magnesium heptahydrate (Mahajan et al. 2004). Patients randomized to receive albuterol mixed with magnesium had statistically improved FEV1 at 10 min, but not at 20 min, compared to the group that received albuterol mixed with normal saline, suggesting that nebulized magnesium may have short-term, but not necessarily long-term, benefit in the treatment of acute exacerbation (Mahajan et al. 2004). Further review of five trials in 2009 suggested IV magnesium (25–75 mg/kg) resulted in improved pulmonary function (FEV1, FVC, PEFR), clinical asthma score, and decreased hospitalization, although another trial found no evidence to support use of IV magnesium in addition to B2-agonist therapy in treatment of moderate to severe childhood asthma exacerbations (Bichara and Goldman 2009). Additional study suggests that a single dose of 40–50 mg/kg (maximum 2 g) by slow infusion (20–60 min) may be beneficial (Powell et al. 2013).

Oral Corticosteroids

For children with severe AAE, the sooner therapy is started in relation to the onset of symptoms, the more likely the impending exacerbation may be clinically attenuated or prevented (Rowe et al. 2001). A 3–5-day course of oral corticosteroids (OCS) equivalent to prednisolone 1–2 mg/kg/day (to a maximum of 20 mg/day for children <2 years and 30 mg/day for children 2–5 years) is recommended and can be stopped abruptly (Rowe et al. 2001).

13.9.1.4 Assessment of Treatment Response and Follow-up for Acute Asthma Exacerbation Severity in Children 5 Years and Younger

As recommended by GINA guidelines, children with a severe AAE must be observed for at least 1 h after initiation of treatment, at which time further treatment can be planned depending on the following scenarios:

1. If symptoms persist after initial bronchodilator, 2–6 additional puffs (depending on severity) of salbutamol/albuterol may be given 20 min after the first dose and repeated at 20-min intervals for an hour. Failure to respond at 1 h, or earlier deterioration, should prompt urgent admission to hospital and a short course of oral corticosteroids.
2. If symptoms have improved by 1 h but recur within 3–4 h, the child may be given more frequent doses of bronchodilator (2–3 puffs each hour), and oral corticosteroids should be

given. The child may need to remain in the emergency room, or, if at home, should be observed by the family/caregiver and have ready access to emergency care. Children who fail to respond to 10 puffs of inhaled SABA within a 3–4 h period should be referred to the hospital.

3. If symptoms resolve rapidly after initial bronchodilator and do not recur for 1–2 h, no further treatment may be required. Further SABA may be given every 3–4 h (up to a total of 10 puffs/24 h), and, if symptoms persist beyond 1 day, other treatments including inhaled or oral corticosteroids are indicated, as outlined below. Before being allowed to go home, the child's condition must be stable.

Children who have had an AAE within the past 3 months are at risk of further episodes and require close follow-up. Prior to being allowed to go home from the emergency department or hospital, family/caregivers should receive the following advice and information: instruction on recognition of signs of recurrence and worsening of asthma and the factors that precipitated the AAE; a written, individualized action plan, including details of accessible emergency services; careful review of inhaler technique; a supply of SABA and, where applicable, the remainder of the course of oral corticosteroid, ICS, or LTRA; and a follow-up appointment within 2–7 days and another within 1–2 months, depending on the clinical, social, and practical context of the exacerbation.

The summary of primary care management of acute asthma exacerbation in children 5 years and younger is summarized in Fig. 5.

13.9.2 Treatment of Acute Asthma Exacerbation in Children 6 Years and Older

13.9.2.1 Diagnosis of Acute Asthma Exacerbations in Children 6 Years and Older

In children 6 years and older, AAE represents a change in symptoms and lung function from a stable status with suddenly decreasing peak expiratory flow (PEF) or FEV_1 compared with previous lung function or predicted values. In these children, the frequency of symptoms may be a more sensitive measure of the onset of an exacerbation than PEF; however, in some children, the change in symptoms may not be perceived or reported, and change should be measured by lung function testing, especially in children with a history of near-fatal asthma. Similar to younger children, AAE in children >5 years is potentially life threatening, and treatment requires prompt medical evaluation with careful assessment and close monitoring.

13.9.2.2 Assessment of Acute Asthma Exacerbation Severity in Children 6 Years and Older

A brief focused history and relevant physical examination should be conducted concurrently with the prompt initiation of therapy. Medical history should include timing of onset and cause of the present exacerbation, severity of asthma symptoms including any exercise limitation or sleep disturbance, symptoms of anaphylaxis, current reliever and controller medications (including current doses, recent changes to dosing, and devices used), adherence pattern, and risk factors for asthma-related death. Risks for asthma-related death include hospitalization or emergency care visit for asthma in the past year, not currently using ICS, SABA use of more than one canister (200 actuations) per month, or a history of near-fatal asthma requiring intubation and mechanical ventilation.

Physical examination should assess signs of exacerbation severity (temperature, blood pressure, pulse oximetry (SpO2), PEF, pulse rate, respiratory rate, level of consciousness, ability to complete sentences, use of accessory muscles, wheeze), complicating factors (anaphylaxis, pneumonia, pneumothorax), and alternative conditions that could explain acute breathlessness (upper airway dysfunction or inhaled foreign body). In children with AAE, SpO_2 <92% is a predictor of the need for hospitalization, and <90% signals the need for aggressive therapy. Arterial blood gas (ABG) measurements and

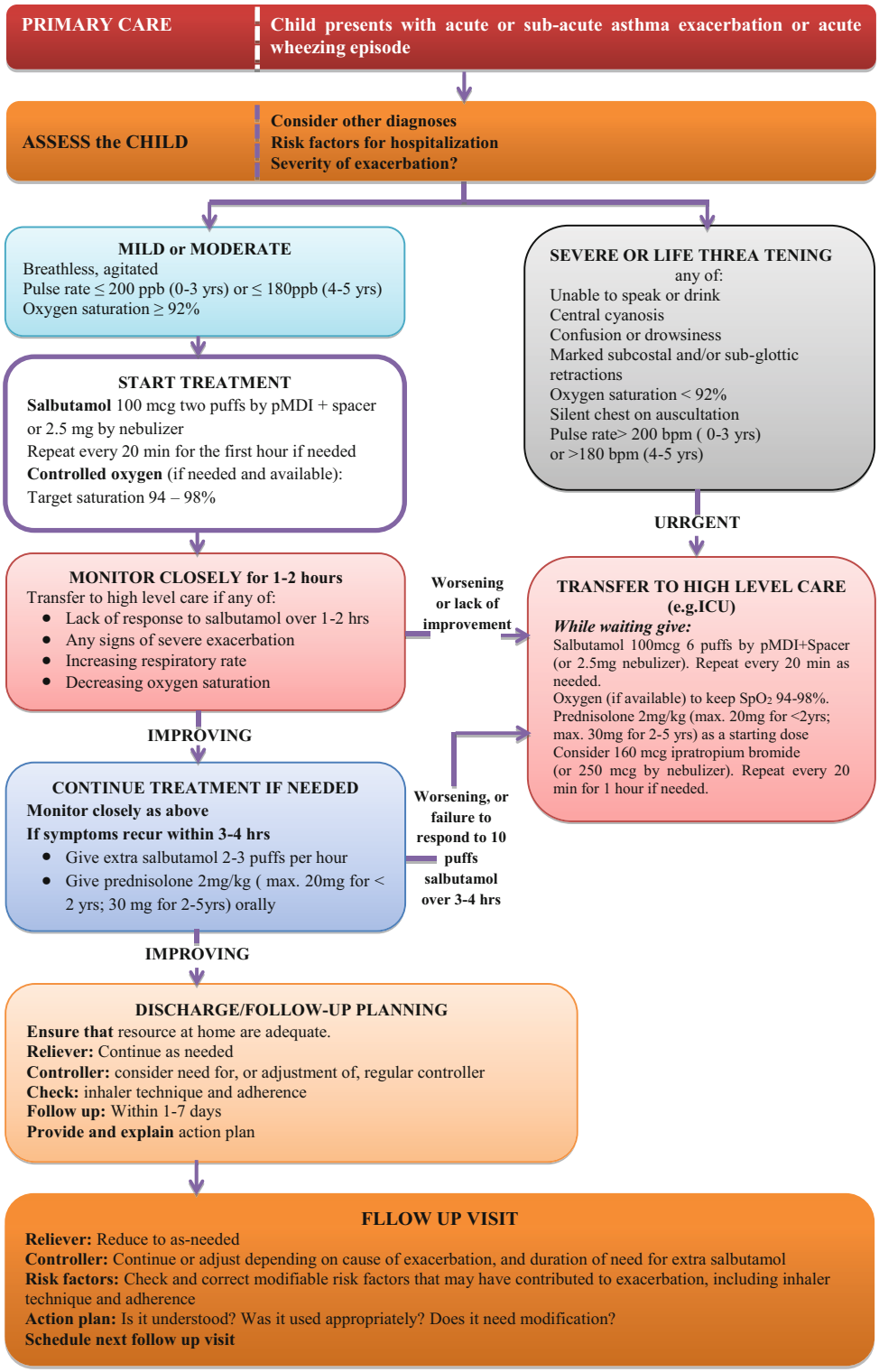


Fig. 5 Primary care management of acute asthma exacerbation in children 5 years and younger (GINA 2017). (Reprinted with permission)

chest radiographs are not routinely required in children with AAE except in the cases of severe AAE when PEF or FEV1 is <50% predicted or when a complicating or alternative diagnosis is suspected such as pneumothorax, parenchymal disease, or an inhaled foreign body, respectively (GINA 2017).

If the patient shows signs of a severe or life-threatening exacerbation, treatment with SABA, controlled oxygen (to maintain SpO_2 between 94% and 98% in asthmatic children), and systemic corticosteroids should be initiated while arranging for the patient's urgent transfer to an acute care facility or for hospital admission. Milder exacerbations can usually be treated in a primary care setting, depending on resources and expertise.

PRAM and PASS scoring tools are also used in children up to age 17 and 18, respectively (see Sect. 9.1.2).

13.9.2.3 Management of Acute Asthma Exacerbation in Children 6 Years and Older

The initial therapies in an AAE for children 6 years of age and older are similar to those in younger children, although dosing strategies differ slightly. GINA provides an algorithmic approach for both ambulatory (Fig. 6) and emergency care settings (Fig. 7), summarized here. The basic approach includes repetitive administration of SABA, early introduction of systemic corticosteroids, and oxygen supplementation. The aims of treatment include rapid relief of airflow obstruction and hypoxemia, addressing the underlying inflammatory pathophysiology, and preventing relapse.

Oxygen Therapy

Oxygen therapy should be titrated against pulse oximetry to maintain oxygen saturation at 94–98% for children 6–11 years and younger. Controlled or titrated oxygen therapy gives better clinical outcomes than high-flow 100% oxygen therapy (Perrin et al. 2011). Oxygen should not be withheld if oximetry is not available, but children should be monitored for deterioration, somnolence, or fatigue.

Inhaled Short-Acting $Beta_2$-agonists

For mild to moderate exacerbations, repeated administration of inhaled SABA (up to 4–10 puffs every 20 min for the first hour) is usually the most effective and efficient way to achieve rapid reversal of airflow limitation. After the first hour, the dose of SABA required varies from 4 to 10 puffs every 3–4 h up to 6–10 puffs every 1–2 h or more often. No additional SABA is needed if there is a good response to initial treatment (PEF >60–80% of predicted values). Delivery of SABA via pMDI and spacer or a DPI leads to a similar improvement in lung function as delivery via nebulizer (Selroos 2014). Currently, there is no evidence to support the use of intravenous $beta_2$-agonists in children with severe AAE (GINA 2017).

Systemic Corticosteroids

Systemic corticosteroids may improve exacerbations and prevent relapse; they should be utilized in mild-to-moderate exacerbations in children 6–11 years (Edmonds et al. 2012). Where possible, systemic corticosteroids should be administered promptly with the preferred route being oral, especially using liquid formulations in children. Intravenous corticosteroids can be administered when patients are too dyspneic to swallow, are vomiting, or are requiring noninvasive ventilation. The use of systemic corticosteroids is particularly important when initial SABA treatment fails to achieve lasting improvement in symptoms, exacerbation developed while the patient was taking OCS, or there is a history of previous exacerbations requiring OCS (GINA 2017). In children with AAE, an OCS dose of 1–2 mg/kg/day up to a maximum of 40 mg/day for 3–5 days is adequate; GINA guidelines recommend once-daily dosing. A duration of 3–5 days is usually considered sufficient, although longer duration (5–7 days) is recommended if the patient is being treated in the ambulatory setting (GINA 2017).

Ipratropium Bromide

For children with moderate-severe exacerbations, treatment in the emergency department with both SABA and ipratropium, a short-acting anticholinergic, was associated with fewer hospitalizations

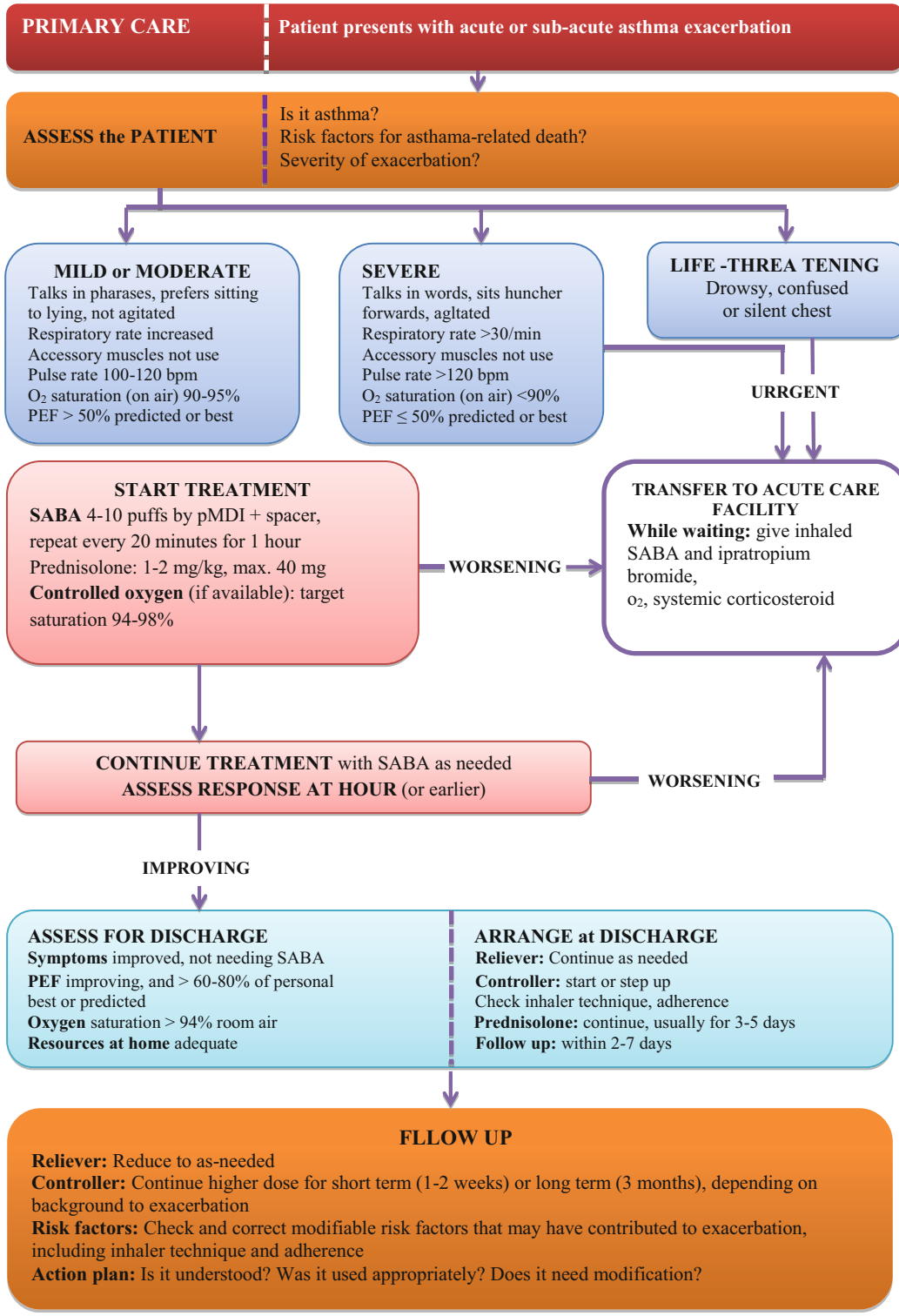


Fig. 6 Management of asthma exacerbations in primary care for children 6–11 years and adolescents (GINA 2017). *O_2* oxygen, *PEF* peak expiratory flow, *SABA* short-acting beta2-agonist (doses are for salbutamol). (Reprinted with permission)

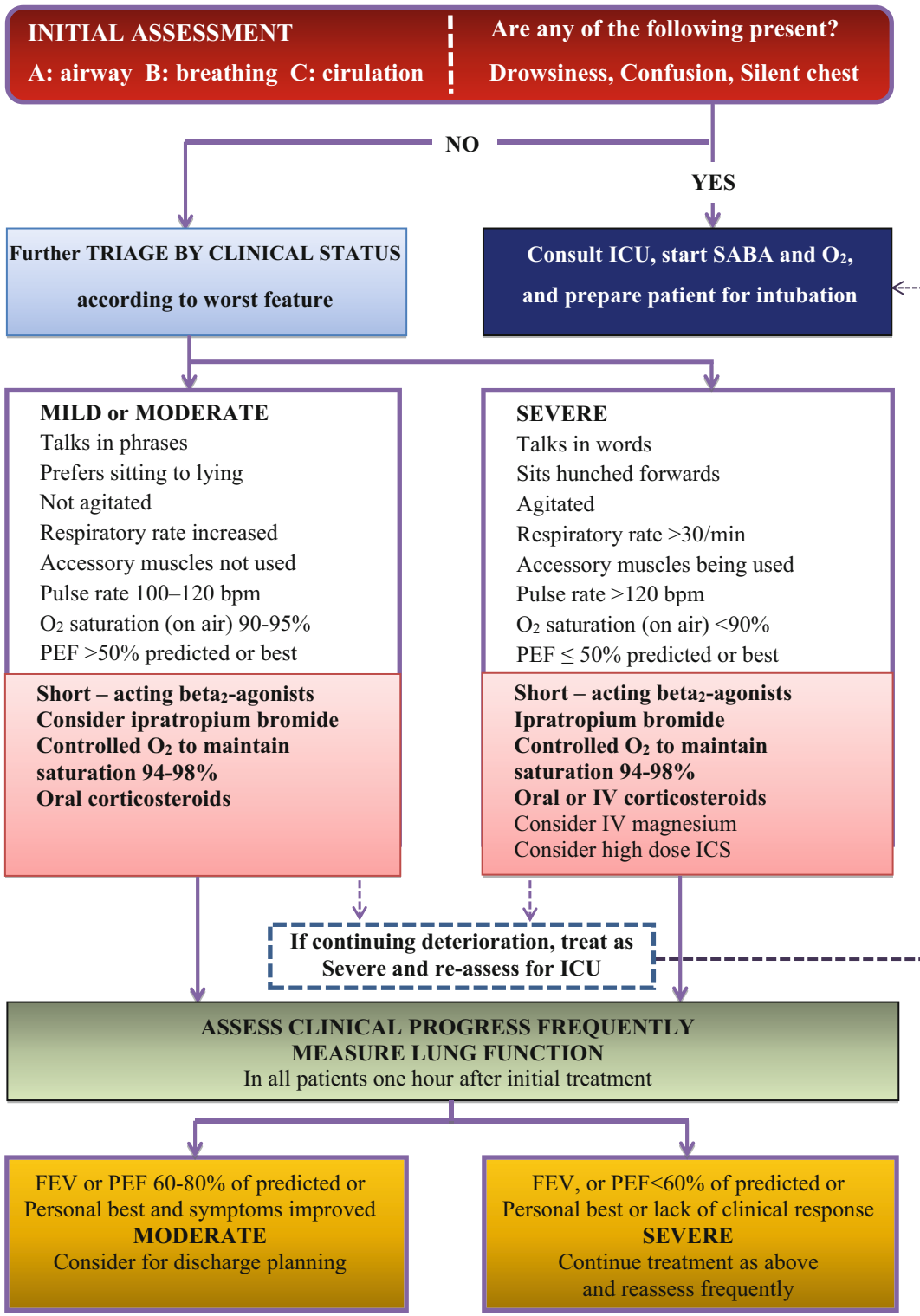


Fig. 7 Management of asthma exacerbations in emergency department for children 6 years and older (GINA 2017). *ICS* inhaled corticosteroids, *ICU* intensive care unit, *IV* intravenous, O_2 oxygen, *PEF* peak expiratory flow, *FEV1* forced expiratory volume in 1 s. (Reprinted with permission)

and greater improvement in PEF and FEV_1 compared with SABA alone (Griffiths and Ducharme 2013b). However, in children hospitalized for acute asthma, no benefits were seen from adding ipratropium to SABA, including no reduction in length of stay (Vézina et al. 2014).

Magnesium Sulfate

Intravenous magnesium sulfate is not recommended for routine use in asthma exacerbations in children. However, when administered as a single 2 g infusion over 20 min, it reduces hospital admissions in some children who fail to respond to initial treatment, who have persistent hypoxemia, or whose FEV_1 fails to reach 60% predicted after 1 h of care. Moreover, nebulized salbutamol/albuterol can also be administered in isotonic magnesium sulfate (Powell et al. 2012). While the overall efficacy of this practice is unclear, pooled data from three trials suggest possible improved pulmonary function in those with severe asthma exacerbations (FEV_1 <50% predicted). However, the efficacy of combined treatment of magnesium by both nebulized and IV route in children with AAE remains controversial.

Epinephrine

Intramuscular (IM) epinephrine (adrenaline) is indicated in addition to standard therapy only in cases for which AAE is associated with anaphylaxis or angioedema. IM dose of epinephrine 1:1000 at 0.01 mg/kg (with a maximum dose of 0.5 mg) should be administered (Chipps et al. 2005). Parenteral epinephrine is a consideration when other more expensive therapies are not available. IV epinephrine must be given very cautiously and slowly. Add 1 mg of epinephrine (1 mg in 1 cc, 1:1000 dilution) to an IV bag of saline or D5W, and run this drip through a microdrip chamber at 15 microdrops per minute (Chipps et al. 2005).

Inhaled Corticosteroids

High-dose ICS given within the first hour after presentation to an emergency room reduces hospitalizations in patients not receiving systemic corticosteroids (GINA 2017). The evidence for the impact of ICS in addition to systemic corticosteroids during this early evaluation and treatment is conflicting (GINA 2017). Patients already prescribed ICS should be provided with advice about increasing the dose for the next 2–4 weeks. Patients not currently taking controller medication should usually be commenced on regular ICS-containing therapy, as an exacerbation requiring medical care indicates that the patient is at increased risk of future exacerbations.

13.9.2.4 Assessment of Treatment Response and Follow-up for Acute Asthma Exacerbation in Children 6 Years and Older

During treatment of AAE, children should be carefully monitored and treatment adapted according to their response. Children with AAE who present to the ambulatory setting with severe or life-threatening symptoms, who fail to respond to pharmacotherapy, or who continue to deteriorate should be transferred immediately to an acute care facility. Children with weak response to SABA treatment should be closely monitored and evaluated. Lung function, including FEV_1 if the child can perform spirometry and it is available, should be monitored before and at regular intervals starting at 1 h after SABA therapy. Moreover, additional treatment should continue until PEF or FEV_1 reaches a best value or returns to previously stable values.

When children with AAE are discharged after having favorable treatment response, medications should include as-needed reliever medication, usually OCS and, for most patients, regular controller treatment. Inhaler technique and adherence should be reviewed before discharge. GINA guidelines recommend a follow-up appointment in 2–7 days depending on the clinical and social-familial situation. At the follow-up visit, the healthcare provider should assess the patient's level of symptom control and risk factors, explore the potential cause of the exacerbation, and review the written asthma action plan. Previous maintenance controller regimens can generally be resumed at 2–4 weeks after the exacerbation unless the exacerbation was preceded by symptoms suggestive of chronically poorly controlled asthma. In this situation, provided inhaler technique and adherence have been checked, a step up in treatment is indicated.

13.10 Severe Therapy-Resistant Asthma in Childhood

13.10.1 Background

Severe asthma, also called severe therapy-resistant (STRA) or refractory asthma, accounts for less than 5% of all childhood asthma (Lang et al. 2008) and has become less common over time, possibly due to the effectiveness of asthma guideline implementation worldwide and the use of controller medications. STRA in childhood constitutes a poorly controlled asthma group and represents a significant challenge for healthcare due to associated morbidity and mortality as well as high utilization of healthcare resources. In addition, STRA in childhood has long-term negative impact on adult lung function, and an association with chronic obstructive pulmonary disease (COPD) in later life has emerged (McGeachie et al. 2016).

13.10.2 Nomenclature and Definition

There is a lack of international consensus regarding the definition of severe and resistant (or refractory) asthma. Severe treatment-resistant asthma (STRA) in childhood refers to children having three main criteria (Reddy et al. 2014): (1) chronic uncontrolled symptoms, defined as the use of SABAs on at least 3 days/week for at least 3 months, combined with high-dose ICS and in association with LABAs, LTRAs, and/or low-dose theophylline; (2) severe acute exacerbation in the previous year, defined as one admission to pediatric intensive care with the need for more than two intravenous treatments or the use of two or more high doses of OCS; (3) fixed or persistent airflow limitation, defined as FEV_1 (or PEF) of $<80\%$ after SABA withhold or an FEV_1 (or PEF) of $<80\%$ despite a trial of OCS and acute administration of SABA.

STRA must be differentiated from difficult-to-treat asthma, as the former is a candidate for immunosuppressive or other anti-inflammatory modalities. Difficult-to-treat asthma is characterized by poor asthma control due to nonadherence, persistent triggers, inadequate inhalation, and other comorbidities (Bush et al. 2008; Martin Alonso et al. 2017). Unlike difficult asthma, severe asthma patients remain symptomatic after these factors are addressed.

13.10.3 Approach to the Childhood with Severe Therapy-Resistant Asthma

13.10.3.1 Confirm Diagnosis of Severe Therapy-Resistant Asthma

Before labeling a child as having STRA, the first step is to confirm the diagnosis of asthma with a full history, physical examination, and directed testing. Once the diagnosis of asthma is confirmed, comorbidities and modifiable factors should be identified and addressed. Additional testing may then be undertaken as directed by prior findings.

13.10.3.2 Identify Comorbidities

Comorbidities may contribute directly to the severity of asthma, may complicate the assessment of asthma, or may be a coincidental finding. These include atopic diseases, obesity, gastroesophageal reflux (GER), and obstructive sleep apnea (OSA). Other potential comorbidities such as dysfunctional breathing, vocal cord dysfunction, and mental health disorders such as anxiety and depression have not been well studied in children.

Inadequate treatment of common atopic diseases such as allergic rhinitis, food allergy, and atopic dermatitis is usually associated with worse asthma control (Bush et al. 2008; Martin Alonso et al. 2017). However, more data are needed to more fully evaluate the relationship between these atopic conditions and asthma severity and to determine whether their treatment improves asthma control.

In children, obesity may cause breathlessness and "wheeze" without evidence of asthma, leading to the wrong diagnosis and inappropriate treatment. However, although some studies have found no difference (Brenner et al. 2001; Schachter et al. 2003; Story 2007), the majority of studies demonstrate an increased prevalence of asthma in overweight children (Castro-Rodríguez

et al. 2000; Ogden et al. 2002; Schaub and von Mutius 2005; Scholtens et al. 2010). In addition, according to one meta-analysis, obesity is a minor risk factor for asthma exacerbation and, as such, should also be addressed in the child with severe asthma (Ahmadizar et al. 2016).

GER is typically considered a comorbid condition in asthma patients; however, it is not clear if treatment for GER improves asthma control (Writing Committee for the American Lung Association Asthma Clinical Research Centers et al. 2012). One study showed improvement in asthma exacerbations on protein pump inhibitor (PPI) while another showed decreased nighttime symptoms while taking ranitidine (Gustafsson et al. 1992; Khoshoo and Haydel 2007). However, a double-blind study from the American Lung Association showed that, in children without GERD symptoms, treatment with PPI made no difference in asthma control even if pH studies showed GER (Holbrook et al. 2012). Hence, the impact of GER treatment on asthma control and severity remains controversial.

Obstructive sleep apnea (OSA) is an additional comorbid condition that contributes to bronchial hyperreactivity/inflammation (Janson et al. 1996; Lewis 2001) and is associated with increased likelihood of uncontrolled asthma (Teodorescu et al. 2010) and more severe asthma (Julien et al. 2009). These effects may be due to increased GER, leptin dysregulation (in obese subjects), and pro-inflammatory cytokine milieu in asthmatic patients with OSA (Salles et al. 2013). It is estimated that nearly 60% of children with severe asthma have OSA (Kheirandish-Gozal et al. 2011). Some argue that the ICS treatments used in more severe asthma contribute to OSA rather than OSA contributing to severe asthma (DelGaudio 2002; Teodorescu et al. 2010; Williams et al. 1983). The relationship of OSA and asthma is explored in more detail in the review by Salles et al. (2013).

13.10.3.3 Review Modifiable factors

After identifying and addressing potential comorbidities, modifiable factors such as incorrect inhaler technique, poor treatment adherence, or harmful environmental exposures should be reviewed and improved. In childhood asthma, correct inhaler technique is a cornerstone to assure treatment success, and the majority of children make mistakes when inhaler technique is assessed (Alexander et al. 2016). Direct assessment of inhaler technique with the use of appropriate spacer devices (nasal mask or mouthpiece) in young children should be reviewed carefully by a specialist nurse or physician in the presence of child's family/caregiver.

In addition, treatment adherence also should be reviewed systematically in childhood with STRA as the impact of poor adherence on asthma-related morbidity is also well-described (Levy 2015; Lindsay and Heaney 2013).

Among harmful environmental exposures, passive (second-hand) and active smoking in children should be identified and eliminated prior to diagnosis of STRA. Passive tobacco smoke exposure is common in children with asthma and usually associated with corticosteroid resistance (Kobayashi et al. 2014). Therefore, exposure to tobacco smoke must be eliminated before the diagnosis of refractory asthma can be made. Besides tobacco smoke exposure, persistent exposure to indoor and outdoor allergens in a sensitized child with STRA should also be identified and addressed if possible. A home visit by a specialist nurse may help to identify objective evidence of allergen exposure before confirming the diagnosis of STRA.

13.10.3.4 Perform Laboratory and Pulmonary Testing

Finally, in children with a clinical diagnosis of STRA, laboratory testing results should be reviewed to re-evaluate the concordance between skin prick tests, fungal sensitization, total and specific IgE concentrations, blood (or sputum) eosinophil counts, and F_ENO. Spirometry should be done to confirm fixed airway limitation (obstruction) with bronchodilator responsiveness testing. While bronchial challenge testing (BCT) is not routinely performed in children with a clinical diagnosis of STRA due to typically poor baseline spirometry with low FEV_1 and/or an extreme bronchial hyper-responsiveness, BCT may be helpful in cases with suspected STRA

with reported chronic severe symptoms but normal spirometry. Other sophisticated examinations such as Th2-related cytokine level and gene expression studies may be performed in some severe acute exacerbations or resistant asthma in childhood (Nguyen-Thi-Dieu et al. 2017). Low-dose high-resolution computed tomography (HRCT) scanning is rarely done in childhood asthma except for those with suspected bronchiectasis or for analyzing bronchial remodeling or distal airway structures in special cases (Jain et al. 2005; Tillie-Leblond et al. 2008). Invasive investigation such as bronchoscopy with possible bronchoalveolar lavage and endobronchial biopsy or brushing may be indicated and performed in select cases (Bossley et al. 2012).

13.10.4 Treatment of Severe Therapy-Resistant Asthma in Childhood

Currently, there is a lack of high-quality evidence and international consensus for treating childhood STRA. Therefore, children with STRA need add-on "beyond guidelines" therapies because of poor control despite maximal conventional treatments and optimization of basic asthma management (Bush et al. 2011).

13.10.4.1 Optimization of Conventional Medications

High Dose of Corticosteroids

Before starting add-on "beyond guidelines" therapies for children with STRA, standard therapies should be optimized. Bush et al. suggest a sequence for consideration of therapy for severe corticosteroid-resistant asthma in childhood (Bush et al. 2011). Children with STRA may be treated with increasing dose of ICS (up to 1000–2000 mcg/day for fluticasone propionate or equivalent). A small percentage of children with STRA may benefit from increasing the dose to as high as 2000 μg/day. If asthma symptoms and frequency of asthma exacerbation improve, ICS dose should be gradually reduced to the lowest dose which maintains significant benefits. If there is no response to ICS dose escalation, it is recommended that maximal dose ICS be promptly stepped down to a lower dose. If no benefit is seen with maximal high dose of ICS, systemic oral corticosteroids, starting at prednisolone 0.5 mg/kg, should be tried preferentially to extra fine particle ICS in most patients (except in those with proven distal airway inflammation by transbronchial biopsy or high level of alveolar nitric oxide) (Bush et al. 2011). If significant clinical benefit is seen with oral corticosteroid, this must be stepped down to the lowest dose (or alternate day dosing) needed to control disease; importantly, potential adverse side effects of systemic long-term treatment must be assessed and appropriately treated if possible.

Anti-IgE Antibody

Omalizumab reduces the frequency of asthma exacerbation (Busse et al. 2011; Deschildre et al. 2013; Kulus et al. 2010; Lanier et al. 2009; Milgrom et al. 2001) and ICS dose (Milgrom et al. 2001) as well as increases symptom-free days (Busse et al. 2011; Deschildre et al. 2013) in children with severe allergic asthma. Long-term (>1 year) safety and efficacy data are not available in children. At this time, omalizumab is included in GINA guidelines as a possible step 5 add-on therapy in children ≥6 years old who are not controlled on step 4 therapies (GINA 2017). However, while omalizumab is primarily indicated for allergic asthma, it may also be administered in rare cases of nonatopic STRA when IgE is in range for described omalizumab dosing (Milgrom et al. 2001).

Anti-interleukin-5

Mepolizumab has been studied in individuals aged 12 years and older with severe eosinophilic asthma (Castro et al. 2015; Haldar et al. 2009; Pavord et al. 2012). GINA guidelines recommend mepolizumab as a possible Step 5 add-on therapy if criteria (absolute eosinophil count) threshold is met (GINA 2017).

Other Therapies

Other treatments have been used in childhood with STRA, but their efficacy is still controversial. These include use of the SMART regimen (symbicort™ maintenance and reliever therapy)

by using budesonide/formoterol as maintenance and reliever dry powder inhaler device or a trial of low-dose theophylline (Bush et al. 2011).

13.10.4.2 Trials with Unconventional Medications

Antibiotic and Antifungal Therapy

Macrolides, such as azithromycin and clarithromycin, with immunomodulatory properties may be indicated for children with STRA, especially for those with suspected atypical bacterial infection (Brusselle and Joos 2014). Recently, the diagnosis of severe asthma with fungal sensitization (SAFS) has been described; this is defined as severe asthma combined with sensitization to at least one fungus as evidenced by skin prick test (SPT) or IgE testing (Denning et al. 2009). If a diagnosis of SAFS is being considered in childhood with STRA, treatment with oral itraconazole or voriconazole may be considered in association with reducing fungal exposures in the environment. The side effects of antifungal drugs (including loss of appetite, vomiting, diarrhea, headache, muscle and joint pain, and anemia) should be monitored regularly, particularly since these therapies interfere with corticosteroid metabolism.

Immunosuppressant and Immunoglobulin Therapy

There is a lack of randomized, controlled trials or strong evidence for the benefits of cytotoxic or immunosuppressive drugs in childhood STRA. Immunosuppressants have been used in children with oral corticosteroid (OCS)-dependent asthma on the basis of small case series (Aaron et al. 1998; Marin 1997). A trial with methotrexate or cyclosporine may be considered in children with eosinophilic STRA with persistent inflammation despite OCS therapy or in those who require very high dose of OCS (>2 mg/kg or 60 mg/day of prednisone) to maintain control of asthma (Bush et al. 2011). The use of nebulized cyclosporine, an attractive and alternative way of drug delivering the immunosuppressant to avoid systemic toxicity, may be a consideration in children with STRA, but data from randomized controlled studies are still needed. Finally, after attempts with previously described therapies, immunoglobulin administration could be considered in children with OCS-dependent STRA, although there is no adequately powered pediatric trial to support its use (Bush et al. 2011).

13.11 Prevention of Asthma in Childhood

Studying the natural history of asthma in childhood may assist in the development of a vision and strategy for prevention of the disease (primary prevention). Asthma is a heterogeneous disease with the inception and persistence driven by gene-environment interactions. While these interactions may occur in early life and even in utero, a "window of opportunity" may exist during childhood for influencing asthma development (GINA 2017). Asthma prevention focuses on addressing the risk factors for asthma development both in utero and throughout childhood (see above). While this knowledge base continues to increase, clear recommendations are guarded at this time, due to the complexity of gene-environment interplay. Preventative strategies should remain at the forefront of future childhood asthma research.

13.12 Conclusion

Asthma is the most common chronic respiratory disease in childhood and is the leading cause of childhood morbidity from chronic disease. While much progress has been made over the past years in the understanding of childhood asthma, clearly there remains work to be done. The factors contributing to asthma development (both genetic and environmental), preventative strategies addressing these risks, and novel treatment options will be crucial clinical considerations in the years to come. Not only will these pursuits strengthen our understanding of a complex disease process, but they will also inform the manner in which the lives of millions of children with asthma worldwide are impacted. It is no small goal but one certainly worthy of the effort.

References

Aaron SD, Dales RE, Pham B. Management of steroid-dependent asthma with methotrexate: a meta-analysis of randomized clinical trials. Respir Med. 1998;92(8): 1059–65.

Ahmadizar F, Vijverberg SJ, Arets HG, de Boer A, Lang JE, Kattan M, Palmer CN, Mukhopadhyay S, Turner S, Maitland-van der Zee AH. Childhood obesity in relation to poor asthma control and exacerbation: a meta-analysis. Eur Respir J. 2016;48(4):1063–73.

Akinbami LJ, Moorman JE, Bailey C, Zahran HS, King M, Johnson CA, Liu X. Trends in asthma prevalence, health care use, and mortality in the United States, 2001–2010. NCHS Data Brief. 2012;(94):1–8.

Akinbami LJ, Kit BK, Simon AE. Impact of environmental tobacco smoke on children with asthma, United States, 2003–2010. Acad Pediatr. 2013;13:508–16.

Almqvist C, Worm M, Leynaert B, working group of GA2LEN WP 2.5 Gender. Impact of gender on asthma in childhood and adolescence: a GA2LEN review. Allergy. 2008;63:47–57.

Alexander DS, Geryk L, Arrindell C, DeWalt DA, Weaver MA, Sleath B, Carpenter DM. Are children with asthma overconfident that they are using their inhalers correctly? J Asthma. 2016;53(1):107–12.

American Thoracic Society. Guidelines for methacholine and exercise challenge testing—1999. Am J Respir Crit Care Med. 2000;161:309–29.

Andersson M, Hedman L, Bjerg A, Forsberg B, Lundbäck B, Rönmark E. Remission and persistence of asthma followed from 7 to 19 years of age. Pediatrics. 2013;132:e435–42.

Arbes SJ, Gergen PJ, Vaughn B, Zeldin DC. Asthma cases attributable to atopy: results from the Third National Health and Nutrition Examination Survey. J Allergy Clin Immunol. 2007;120:1139–45.

Arshad SH, Karmaus W, Raza A, Kurukulaaratchy RJ, Matthews SM, Holloway JW, Sadeghnejad A, Zhang H, Roberts G, Ewart SL. The effect of parental allergy on childhood allergic diseases depends on the sex of the child. J Allergy Clin Immunol. 2012;130:427–434.e6.

Asher MI, Weiland SK. The International Study of Asthma and Allergies in Childhood (ISAAC). ISAAC Steering Committee. Clin Exp Allergy. 1998;28(Suppl 5): 52–66; discussion 90–91

Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, Mitchell EA, Pearce N, Sibbald B, Stewart AW. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. Eur Respir J. 1995;8:483–91.

Azad MB, Konya T, Maughan H, Guttman DS, Field CJ, Chari RS, Sears MR, Becker AB, Scott JA, Kozyrskyj AL, CHILD Study Investigators. Gut microbiota of healthy Canadian infants: profiles by mode of delivery and infant diet at 4 months. CMAJ. 2013;185:385–94.

Barman M, Johansson S, Hesselmar B, Wold AE, Sandberg AS, Sandin A. High levels of both n-3 and n-6 long-chain polyunsaturated fatty acids in cord serum phospholipids predict allergy development. 2013;8(7):e67920.

Beydon N, Davis SD, Lombardi E, Allen JL, Arets HGM, Aurora P, Bisgaard H, Davis GM, Ducharme FM, Eigen H, Gappa M, Gaultier C, Gustafsson PM, Hall GL, Hantos Z, Healy MJR, Jones MH, Klug B, Lødrup Carlsen KC, McKenzie SA, Marchal F, Mayer OH, Merkus PJFM, Morris MG, Oostveen E, Pillow JJ, Seddon PC, Silverman M, Sly PD, Stocks J, Tepper RS, Vilozni D, Wilson NM, American Thoracic Society/European Respiratory Society Working Group on Infant and Young Children Pulmonary Function Testing. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. Am J Respir Crit Care Med. 2007;175:1304–45.

Bichara MD, Goldman Ran D. Magnesium for treatment of asthma in children. Can Fam Physician. 2009;55(9): 887–9.

Bisgaard H, Zielen S, Garcia-Garcia ML, Johnston SL, Gilles L, Menten J, Tozzi CA, Polos P. Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. Am J Respir Crit Care Med. 2005;171:315–22.

Bisgaard H, Hermansen MN, Buchvald F, Loland L, Halkjaer LB, Bønnelykke K, Brasholt M, Heltberg A, Vissing NH, Thorsen SV, Stage M, Pipper CB. Childhood asthma after bacterial colonization of the airway in neonates. N Engl J Med. 2007;357:1487–95.

Bisgaard H, Stokholm J, Chawes BL, Vissing NH, Bjarnadóttir E, Schoos A-MM, Wolsk HM, Pedersen TM, Vinding RK, Thorsteinsdóttir S, Følsgaard NV, Fink NR, Thorsen J, Pedersen AG, Waage J, Rasmussen MA, Stark KD, Olsen SF, Bønnelykke K. Fish oil-derived fatty acids in pregnancy and wheeze and asthma in offspring. N Engl J Med. 2016;375:2530–9.

Bossley CJ, Fleming L, Gupta A, Regamey N, Frith J, Oates T, Tsartsali L, Lloyd CM, Bush A, Saglani S. Pediatric severe asthma is characterized by eosinophilia and remodeling without T(H)2 cytokines. J Allergy Clin Immunol. 2012;129(4):974–82.e13.

Braun-Fahrländer C, Gassner M, Grize L, Takken-Sahli K, Neu U, Stricker T, Varonier HS, Wüthrich B, Sennhauser FH, Swiss Study on Childhood Allergy and Respiratory symptoms, Air Pollution (SCARPOL) team. No further increase in asthma, hay fever and atopic sensitisation in adolescents living in Switzerland. Eur Respir J. 2004;23:407–13.

Brenner JS, Kelly CS, Wenger AD, Brich SM, Morrow AL. Asthma and obesity in adolescents: is there an association? J Asthma. 2001;38(6):509–15.

Brusselle GG, Joos G. Is there a role for macrolides in severe asthma? Curr Opin Pulm Med. 2014;20(1):95–102.

Bufford JD, Gern JE. Early exposure to pets: good or bad? Curr Allergy Asthma Rep. 2007;7:375–82.

Bullens DMA, Seys S, Kasran A, Dilissen E, Dupont LJ, Ceuppens JL. Low cord blood Foxp3/CD3γ mRNA

ratios: a marker of increased risk for allergy development. Clin Exp Allergy. 2015;45:232–7.
Bunyavanich S, Rifas-Shiman SL, Platts-Mills TA, Workman L, Sordillo JE, Camargo CA, Gillman MW, Gold DR, Litonjua AA. Peanut, milk, and wheat intake during pregnancy is associated with reduced allergy and asthma in children. J Allergy Clin Immunol. 2014;133:1373–82.
Burgess JA, Dharmage SC, Byrnes GB, Matheson MC, Gurrin LC, Wharton CL, Johns DP, Abramson MJ, Hopper JL, Walters EH. Childhood eczema and asthma incidence and persistence: a cohort study from childhood to middle age. J Allergy Clin Immunol. 2008;122:280–5.
Burke H, Leonardi-Bee J, Hashim A, Pine-Abata H, Chen Y, Cook DG, Britton JR, McKeever TM. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. Pediatrics. 2012;129:735–44.
Bush A, Fleming L. Phenotypes of refractory/severe asthma. Paediatr Respir Rev. 2011;12(3):177–81.
Bush A, Hedlin G, Carlsen KH, de Benedictis F, Lodrup-Carlsen K, Wilson N. Severe childhood asthma: a common international approach? Lancet. 2008;372(9643):1019–21.
Busse WW, Pedersen S, Pauwels RA, Tan WC, Chen Y-Z, Lamm CJ, O'Byrne PM, START Investigators Group. The Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study 5-year follow-up: effectiveness of early intervention with budesonide in mild persistent asthma. J Allergy Clin Immunol. 2008;121:1167–74.
Busse WW, Lemanske RF, Gern JE. Role of viral respiratory infections in asthma and asthma exacerbations. Lancet. 2010;376:826–34.
Camilli AE, Holberg CJ, Wright AL, Taussig LM. Parental childhood respiratory illness and respiratory illness in their infants. Pediatr Pulmonol. 1993;16:275–80.
Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, Murphy K, Maspero JF, O'Brien C, Korn S. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med. 2015;3:355–66.
Castro-Rodríguez 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;162:1403–6.
Castro-Rodriguez JA, Forno E, Rodriguez-Martinez CE, Celedón JC. Risk and protective factors for childhood asthma: what is the evidence? J Allergy Clin Immunol Pract. 2016;4:1111–22.
Cates CJ, Karner C. Combination formoterol and budesonide as maintenance and reliever therapy versus current best practice (including inhaled steroid maintenance), for chronic asthma in adults and children. Cochrane Database Syst Rev. 2013;(4):CD007313.
Centers for Disease Control and Prevention. Asthma in the US Vital Signs. 2011. https://www.cdc.gov/vitalsigns/asthma/index.html. Accessed 30 Oct 2017.
Chauhan BF, Ben Salah R, Ducharme FM. Addition of anti-leukotriene agents to inhaled corticosteroids in children with persistent asthma. Cochrane Database Syst Rev. 2013;(10):CD009585.
Chalut DS, Ducharme FM, Davis GM. The Preschool Respiratory Assessment Measure (PRAM): a responsive index of acute asthma severity. J Pediatr. 2000;137:762–8.
Chawes BL, Bønnelykke K, Stokholm J, Vissing NH, Bjarnadóttir E, Schoos A-MM, Wolsk HM, Pedersen TM, Vinding RK, Thorsteinsdóttir S, Arianto L, Hallas HW, Heickendorff L, Brix S, Rasmussen MA, Bisgaard H. Effect of vitamin D_3 supplementation during pregnancy on risk of persistent wheeze in the offspring: a randomized clinical trial. JAMA. 2016;315:353.
Cheelo M, Lodge CJ, Dharmage SC, Simpson JA, Matheson M, Heinrich J, Lowe AJ. Paracetamol exposure in pregnancy and early childhood and development of childhood asthma: a systematic review and meta-analysis. Arch Dis Child. 2015;100:81–9.
Chen CH, Lin YT, Yang YH, Wang LC, Lee JH, Kao CL, Chiang BL. Ribavirin for respiratory syncytial virus bronchiolitis reduced the risk of asthma and allergen sensitization. Pediatr Allergy Immunol. 2008;19:166–72.
Childhood Asthma Management Program Research Group, Szefler S, Weiss S, Tonascia J, Adkinson NF, Bender B, Cherniack R, Donithan M, Kelly HW, Reisman J, Shapiro GG, Sternberg AL, Strunk R, Taggart V, Van Natta M, Wise R, Wu M, Zeiger R. Long-term effects of budesonide or nedocromil in children with asthma. N Engl J Med. 2000;343:1054–63.
Chipps BE, Murphy KR. Assessment and treatment of acute asthma in children. J Pediatr. 2005;147(3):288–94.
Covar RA, Fuhlbrigge AL, Williams P, Kelly HW, the Childhood Asthma Management Program Research Group. The Childhood Asthma Management Program (CAMP): contributions to the understanding of therapy and the natural history of childhood asthma. Curr Respir Care Rep. 2012;1(4):243–250.
Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, MacIntyre NR, McKay RT, Wanger JS, Anderson SD, Cockcroft DW, Fish JE, Sterk PJ. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. Am J Respir Crit Care Med. 2000;161:309–29.
Crestani E, Guerra S, Wright AL, Halonen M, Martinez FD. Parental asthma as a risk factor for the development of early skin test sensitization in children. J Allergy Clin Immunol. 2004;113:284–90.
de Planell-Saguer M, Lovinsky-Desir S, Miller RL. Epigenetic regulation: the interface between prenatal and early-life exposure and asthma susceptibility. Environ Mol Mutagen. 2014;55:231–43.
Debley JS, Redding GJ, Critchlow CW. Impact of adolescence and gender on asthma hospitalization: a population-

based birth cohort study. Pediatr Pulmonol. 2004;38: 443–50.
Delacourt C, Lorino H, Fuhrman C, Herve-Guillot M, Reinert P, Harf A, Housset B. Comparison of the forced oscillation technique and the interrupter technique for assessing airway obstruction and its reversibility in children. Am J Respir Crit Care Med. 2001;164:965–72.
DelGaudio JM. Steroid inhaler laryngitis: dysphonia caused by inhaled fluticasone therapy. Arch Otolaryngol Head Neck Surg. 2002;128(6):677–81.
Denning DW, O'Driscoll BR, Powell G, Chew F, Atherton GT, Vyas A, Miles J, Morris J, Niven RM. Randomized controlled trial of oral antifungal treatment for severe asthma with fungal sensitization: The Fungal Asthma Sensitization Trial (FAST) study. Am J Respir Crit Care Med. 2009;179(1):11–8.
Deschildre A, Marguet C, Salleron J, Pin I, Rittié JL, Derelle J, Taam RA, Fayon M, Brouard J, Dubus JC, Siret D, Weiss L, Pouessel G, Beghin L, Just J. Add-on omalizumab in children with severe allergic asthma: a 1-year real life survey. Eur Respir J. 2013;42 (5):1224–33.
Dezateux C, Stocks J, Dundas I, Fletcher ME. Impaired airway function and wheezing in infancy: the influence of maternal smoking and a genetic predisposition to asthma. Am J Respir Crit Care Med. 1999;159:403–10.
Dinh-Xuan AT, Annesi-Maesano I, Berger P, Chambellan A, Chanez P, Chinet T, Degano B, Delclaux C, Demange V, Didier A, Garcia G, Magnan A, Mahut B, Roche N, French Speaking Respiratory Society. Contribution of exhaled nitric oxide measurement in airway inflammation assessment in asthma. A position paper from the French Speaking Respiratory Society. Rev Mal Respir. 2015;32: 193–215.
Ducharme FM, Chalut D, Plotnick L, Savdie C, Kudirka D, Zhang X, Meng L, McGillivray D. The pediatric respiratory assessment measure: a valid clinical score for assessing acute asthma severity from toddlers to teenagers. J Pediatr. 2008;152:476–480, 480.e1.
Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, Olin A-C, Plummer AL, Taylor DR, American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med. 2011;184:602–15.
Edmonds ML, Milan SJ, Camargo CA, Pollack CV, Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute asthma. Cochrane Database Syst Rev. 2012;12:CD002308.
Fitzpatrick AM, Teague WG, Meyers DA, Peters SP, Li X, Li H, Wenzel SE, Aujla S, Castro M, Bacharier LB. Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. J Allergy Clin Immunol. 2011;127:382–389.e13.
Forno E, Young OM, Kumar R, Simhan H, Celedón JC. Maternal obesity in pregnancy, gestational weight gain, and risk of childhood asthma. Pediatrics. 2014;134: e535–46.
Fu Y, Lou H, Wang C, Lou W, Wang Y, Zheng T, Zhang L. T cell subsets in cord blood are influenced by maternal allergy and associated with atopic dermatitis. Pediatr Allergy Immunol. 2013;24:178.
Gasana J, Dillikar D, Mendy A, Forno E, Ramos Vieira E. Motor vehicle air pollution and asthma in children: a meta-analysis. Environ Res. 2012;117:36–45.
Gilliland FD, Berhane K, Li Y-F, Rappaport EB, Peters JM. Effects of early onset asthma and in utero exposure to maternal smoking on childhood lung function. Am J Respir Crit Care Med. 2003;167:917–24. https://doi.org/10.1164/rccm.200206-616OC.
Global Asthma Report 2014. 2014. http://www.globalasthmareport.org/resources/Global_Asthma_Report_2014.pdf. Accessed 15 Sept 2017.
Global Initiative for Asthma (GINA). 2017. http://ginasthma.org/archived-reports/. Accessed 25 July 2017.
Gouin S, Robidas I, Gravel J, Guimont C, Chalut D, Amre D. Prospective evaluation of two clinical scores for acute asthma in children 18 months to 7 years of age. Acad Emerg Med. 2010;17:598–603.
Grabenhenrich LB, Gough H, Reich A, Eckers N, Zepp F, Nitsche O, Forster J, Schuster A, Schramm D, Bauer C-P, Hoffmann U, Beschorner J, Wagner P, Bergmann R, Bergmann K, Matricardi PM, Wahn U, Lau S, Keil T. Early-life determinants of asthma from birth to age 20 years: a German birth cohort study. J Allergy Clin Immunol. 2014;133:979–88.
Griffiths B, Ducharme FM. Combined inhaled anticholinergics and short-acting beta2-agonists for initial treatment of acute asthma in children. Cochrane Database Syst Rev. 2013a;8:CD000060.
Griffiths B, Ducharme FM. Combined inhaled anticholinergics and short-acting beta2-agonists for initial treatment of acute asthma in children. Paediatr Respir Rev. 2013b;14:234–5.
Guilbert TW, Morgan WJ, Zeiger RS, Bacharier LB, Boehmer SJ, Krawiec M, Larsen G, Lemanske RF, Liu A, Mauger DT, Sorkness C, Szefler SJ, Strunk RC, Taussig LM, Martinez FD. Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. J Allergy Clin Immunol. 2004;114:1282–7.
Gustafsson PM, Kjellman NI, Tibbling L. A trial of ranitidine in asthmatic children and adolescents with or without pathological gastro-oesophageal reflux. Eur Respir J. 1992;5(2):201–6.
Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, Marshall RP, Bradding P, Green RH, Wardlaw AJ, Pavord ID. Mepolizumab and exacerbations of refractory eosinophilic asthma. N Engl J Med. 2009;360:973–84.
Halonen M, Stern DA, Wright AL, Taussig LM, Martinez FD. Alternaria as a major allergen for asthma

in children raised in a desert environment. Am J Respir Crit Care Med. 1997;155:1356–61.

Henderson J, Hilliard TN, Sherriff A, Stalker D, Al Shammari N, Thomas HM. Hospitalization for RSV bronchiolitis before 12 months of age and subsequent asthma, atopy and wheeze: a longitudinal birth cohort study. Pediatr Allergy Immunol. 2005;16:386–92.

Hoeke H, Roeder S, Mueller A, Bertsche T, Borte M, Rolle-Kampczyk U, von Bergen M, Wissenbach DK. Biomonitoring of prenatal analgesic intake and correlation with infantile anti-aeroallergens IgE. Allergy. 2016;71:901–6.

Howrylak JA, Fuhlbrigge AL, Strunk RC, Zeiger RS, Weiss ST, Raby BA, Childhood Asthma Management Program Research Group. Classification of childhood asthma phenotypes and long-term clinical responses to inhaled anti-inflammatory medications. J Allergy Clin Immunol. 2014;133:1289–1300.e1–12.

Huang L, Chen Q, Zhao Y, Wang W, Fang F, Bao Y. Is elective cesarean section associated with a higher risk of asthma? A meta-analysis. J Asthma. 2015;52:16–25.

Jackson DJ, Gangnon RE, Evans MD, Roberg KA, Anderson EL, Pappas TE, Printz MC, Lee W-M, Shult PA, Reisdorf E, Carlson-Dakes KT, Salazar LP, DaSilva DF, Tisler CJ, Gern JE, Lemanske RF. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. Am J Respir Crit Care Med. 2008;178:667–72.

Jain N, Covar RA, Gleason MC, Newell JD Jr, Gelfand EW, Spahn JD. Quantitative computed tomography detects peripheral airway disease in asthmatic children. Pediatr Pulmonol. 2005;40(3):211–8.

Janson C, De Backer W, Gislason T, Plaschke P, Björnsson E, Hetta J, Kristbjarnarson H, Vermeire P, Boman G. Increased prevalence of sleep disturbances and daytime sleepiness in subjects with bronchial asthma: a population study of young adults in three European countries. Eur Respir J. 1996;9(10):2132–8.

Jedrychowski W, Gałaś A, Whyatt R, Perera F. The prenatal use of antibiotics and the development of allergic disease in one year old infants. A preliminary study. Int J Occup Med Environ Health. 2006;19:70–6.

Julien JY, Martin JG, Ernst P, Olivenstein R, Hamid Q, Lemière C, Pepe C, Naor N, Olha A, Kimoff RJ. Prevalence of obstructive sleep apnea-hypopnea in severe versus moderate asthma. J Allergy Clin Immunol. 2009;124(2):371–6.

Juniper EF, Gruffydd-Jones K, Ward S, Svensson K. Asthma Control Questionnaire in children: validation, measurement properties, interpretation. Eur Respir J. 2010;36:1410–6.

Kalyoncu AF, Selçuk ZT, Enünlü T, Demir AU, Cöplü L, Sahin AA, Artvinli M. Prevalence of asthma and allergic diseases in primary school children in Ankara, Turkey: two cross-sectional studies, five years apart. Pediatr Allergy Immunol. 1999;10:261–5.

Karvonen AM, Hyvärinen A, Gehring U, Korppi M, Doekes G, Riedler J, Braun-Fahrländer C, Bitter S, Schmid S, Keski-Nisula L, Roponen M, Kaulek V, Dalphin J-C, Pfefferle PI, Renz H, Büchele G, von Mutius E, Pekkanen J, PASTURE Study Group. Exposure to microbial agents in house dust and wheezing, atopic dermatitis and atopic sensitization in early childhood: a birth cohort study in rural areas. Clin Exp Allergy. 2012;42:1246–56.

Kew KM, et al. Combination formoterol and budesonide as maintenance and reliever therapy versus combination inhaler maintenance for chronic asthma in adults and children. Cochrane Database Syst Rev. 2013;(12): CD009019.

Kheirandish-Gozal L, Dayyat EA, Eid NS, Morton RL, Gozal D. Obstructive sleep apnea in poorly controlled asthmatic children: effect of adenotonsillectomy. Pediatr Pulmonol. 2011;46(9):913–8.

Khoshoo V, Haydel R Jr. Effect of antireflux treatment on asthma exacerbations in nonatopic children. J Pediatr Gastroenterol Nutr. 2007;44(3):331–5.

Kobayashi Y, Bossley C, Gupta A, Akashi K, Tsartsali L, Mercado N, Barnes PJ, Bush A, Ito K. Passive smoking impairs histone deacetylase-2 in children with severe asthma. Chest. 2014;145(2):305–12.

Kulus M, Hébert J, Garcia E, Fowler Taylor A, Fernandez Vidaurre C, Blogg M. Omalizumab in children with inadequately controlled severe allergic (IgE-mediated) asthma. Curr Med Res Opin. 2010;26(6):1285–93.

Kurukulaaratchy RJ, Raza A, Scott M, Williams P, Ewart S, Matthews S, Roberts G, Hasan Arshad S. Characterisation of asthma that develops during adolescence; findings from the Isle of Wight Birth Cohort. Respir Med. 2012;106:329–37.

Kusel MMH, de Klerk NH, Kebadze T, Vohma V, Holt PG, Johnston SL, Sly PD. Early-life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. J Allergy Clin Immunol. 2007;119:1105–10.

Lang A, Carlsen KH, Haaland G, Devulapalli CS, Munthe-Kaas M, Mowinckel P, Carlsen K. Severe asthma in childhood: assessed in 10 year olds in a birth cohort study. Allergy. 2008;63:1054–60.

Lanier B, Bridges T, Kulus M, Taylor AF, Berhane I, Vidaurre CF. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. J Allergy Clin Immunol. 2009;124(6):1210–6.

Lau S, Illi S, Sommerfeld C, Niggemann B, Bergmann R, von Mutius E, Wahn U. Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. Multicentre Allergy Study Group. Lancet. 2000;356:1392–7.

Levy ML. The national review of asthma deaths: what did we learn and what needs.

Lewis SA, Weiss ST, Britton JR. Airway responsiveness and peak flow variability in the diagnosis of asthma for epidemiological studies. Eur Respir J. 2001;18 (6):921–7.

Lindsay JT, Heaney LG. Non-adherence in difficult asthma and advances in detection. Expert Rev Respir Med. 2013;7(6):607–14.

Litonjua AA, Carey VJ, Burge HA, Weiss ST, Gold DR. Parental history and the risk for childhood asthma. Does mother confer more risk than father? Am J Respir Crit Care Med. 1998;158:176–81.

Liu AH, Jaramillo R, Sicherer SH, et al. National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005–2006. J Allergy Clin Immunol. 2010;126:798–806.e13.

Liu J, Rädler D, Illi S, Klucker E, Turan E, von Mutius E, Kabesch M, Schaub B. TLR2 polymorphisms influence neonatal regulatory T cells depending on maternal atopy. Allergy. 2011;66:1020–9.

Lockett GA, Huoman J, Holloway JW. Does allergy begin in utero? Pediatr Allergy Immunol. 2015;26:394–402.

Lødrup Carlsen KC, Roll S, Carlsen K-H, Mowinckel P, Wijga AH, Brunekreef B, Torrent M, Roberts G, Arshad SH, Kull I, Krämer U, von Berg A, Eller E, Høst A, Kuehni C, Spycher B, Sunyer J, Chen C-M, Reich A, Asarnoj A, Puig C, Herbarth O, Mahachie John JM, Van Steen K, Willich SN, Wahn U, Lau S, Keil T, GALEN WP 1.5 'Birth Cohorts' working group. Does pet ownership in infancy lead to asthma or allergy at school age? Pooled analysis of individual participant data from 11 European birth cohorts. PLoS One. 2012;7:e43214.

Lowe AJ, Angelica B, Su J, Lodge CJ, Hill DJ, Erbas B, Bennett CM, Gurrin LC, Axelrad C, Abramson MJ, Allen KJ, Dharmage SC. Age at onset and persistence of eczema are related to subsequent risk of asthma and hay fever from birth to 18 years of age. Pediatr Allergy Immunol. 2017;28:384–90.

MacDonald C, Sternberg A, Hunter PR. A systematic review and meta-analysis of interventions used to reduce exposure to house dust and their effect on the development and severity of asthma. Environ Health Perspect. 2007;115:1691–5.

Magnus MC, Karlstad Ø, Håberg SE, Nafstad P, Davey Smith G, Nystad W. Prenatal and infant paracetamol exposure and development of asthma: the Norwegian Mother and Child Cohort Study. Int J Epidemiol. 2016;45:512–22.

Mahajan P, et al. Comparison of nebulized magnesium sulfate plus albuterol to nebulized albuterol plus saline in children with acute exacerbations of mild to moderate asthma. J Emerg Med. 2004;27(1):21–5.

Malone R, LaForce C, Nimmagadda S, Schoaf L, House K, Ellsworth A, Dorinsky P. The safety of twice-daily treatment with fluticasone propionate and salmeterol in pediatric patients with persistent asthma. Ann Allergy Asthma Immunol. 2005;95:66–71.

Marin MG. Low-dose methotrexate spares steroid usage in steroid-dependent asthmatic patients: a meta-analysis. Chest. 1997;112(1):29–33.

Martin AJ, McLennan LA, Landau LI, Phelan PD. The natural history of childhood asthma to adult life. Br Med J. 1980;280:1397–400.

Martin Alonso A, Fainardi V, Saglani S. Severe therapy resistant asthma in children: translational approaches to uncover sub-phenotypes. Expert Rev Respir Med. 2017;11(11):867–74.

Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. N Engl J Med. 1995;332:133–8.

Martino D, Prescott S. Epigenetics and prenatal influences on asthma and allergic airways disease. Chest. 2011; 139:640–7. https://doi.org/10.1378/chest.10-1800.

Martino D, Joo JE, Sexton-Oates A, Dang T, Allen K, Saffery R, Prescott S. Epigenome-wide association study reveals longitudinally stable DNA methylation differences in CD4+ T cells from children with IgE-mediated food allergy. Epigenetics. 2014;9:998–1006.

Maslova E, Granström C, Hansen S, Petersen SB, Strøm M, Willett WC, Olsen SF. Peanut and tree nut consumption during pregnancy and allergic disease in children-should mothers decrease their intake? Longitudinal evidence from the Danish National Birth Cohort. J Allergy Clin Immunol. 2012;130:724–32.

Maue DK, Krupp N, Rowan CM. Pediatric asthma severity score is associated with critical care interventions. World J Clin Pediatr. 2017;6:34.

McGeachie MJ, Yates KP, Zhou X, Guo F, Sternberg AL, Van Natta ML, Wise RA, Szefler SJ, Sharma S, Kho AT, Cho MH, Croteau-Chonka DC, Castaldi PJ, Jain G, Sanyal A, Zhan Y, Lajoie BR, Dekker J, Stamatoyannopoulos J, Covar RA, Zeiger RS, Adkinson NF, Williams PV, Kelly HW, Grasemann H, Vonk JM, Koppelman GH, Postma DS, Raby BA, Houston I, Lu Q, Fuhlbrigge AL, Tantisira KG, Silverman EK, Tonascia J, Weiss ST, Strunk RC. Patterns of growth and decline in lung function in persistent childhood asthma. N Engl J Med. 2016;374:1842–52.

McKeever TM, Lewis SA, Smith C, Hubbard R. The importance of prenatal exposures on the development of allergic disease: a birth cohort study using the West Midlands General Practice Database. Am J Respir Crit Care Med. 2002;166:827–32.

Melén E, Wickman M, Nordvall SL, van Hage-Hamsten M, Lindfors A. Influence of early and current environmental exposure factors on sensitization and outcome of asthma in pre-school children. Allergy. 2001;56: 646–52.

Meltzer EO, Busse WW, Wenzel SE, Belozeroff V, Weng HH, Feng J, Chon Y, Chiou C-F, Globe D, Lin S-L. Use of the asthma control questionnaire to predict future risk of asthma exacerbation. J Allergy Clin Immunol. 2011;127:167–72.

Migliore E, Zugna D, Galassi C, Merletti F, Gagliardi L, Rasero L, Trevisan M, Rusconi F, Richiardi L. Prenatal paracetamol exposure and wheezing in childhood: causation or confounding? PLoS One. 2015;10:e0135775.

Milgrom H, Berger W, Nayak A, Gupta N, Pollard S, McAlary M, Taylor AF, Rohane P. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). Pediatrics. 2001;108(2):E36.

Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der

Grinten CPM, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J. 2005;26:319–38.

Moffatt MF, Kabesch M, Liang L, Dixon AL, Strachan D, Heath S, Depner M, von Berg A, Bufe A, Rietschel E, Heinzmann A, Simma B, Frischer T, Willis-Owen SAG, Wong KCC, Illig T, Vogelberg C, Weiland SK, von Mutius E, Abecasis GR, Farrall M, Gut IG, Lathrop GM, Cookson WOC. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. Nature. 2007;448:470–3.

Mommers M, Gielkens-Sijstermans C, Swaen GMH, van Schayck CP. Trends in the prevalence of respiratory symptoms and treatment in Dutch children over a 12 year period: results of the fourth consecutive survey. Thorax. 2005;60:97–9.

Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW, Taussig LM, Wright AL, Martinez FD. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. Am J Respir Crit Care Med. 2005;172:1253–8.

National Asthma Education and Prevention Program. Expert Panel Report. III Guidelines for the Diagnosis Management Asthma. Bethesda: National Heart Lung Blood Institute; 2007.

National Heart, Lung, and Blood Institute. National Institutes of Health. U.S. Department of Health and Human Services. Asthma care quick reference: diagnosing and managing asthma. 2011. https://www.nhlbi.nih.gov/files/docs/guidelines/asthma_qrg.pdf. Accessed 30 Oct 2017.

Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM, SMART Study Group. The Salmeterol Multicenter Asthma Research trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest. 2006;129:15–26.

Nguyen-Thi-Dieu T, Le-Thi-Thu H, Duong-Quy S. The profile of leucocytes, CD3+, CD4+, and CD8+ T cells, and cytokine concentrations in peripheral blood of children with acute asthma exacerbation. J Int Med Res. 2017;45(6):1658–69.

Nowak D, Suppli Ulrik C, von Mutius E. Asthma and atopy: has peak prevalence been reached? Eur Respir J. 2004;23:359–60.

Nucala [Prescribing Information]. GlaxoSmithKline LLC, Philadelphia. 2017. https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL.PDF. Accessed 1 Nov 2017.

Nurmatov U, Devereux G, Sheikh A. Nutrients and foods for the primary prevention of asthma and allergy: systematic review and meta-analysis. J Allergy Clin Immunol. 2011;127:724–733.e1–30.

O'Byrne PM, Reddel HK, Eriksson G, Ostlund O, Peterson S, Sears MR, Jenkins C, Humbert M, Buhl R, Harrison TW, Quirce S, Bateman ED. Measuring asthma control: a comparison of three classification systems. Eur Respir J. 2010;36:269–76.

Ogden CL, Flegal KM, Carroll MD, Johnson CL. Prevalence and trends in overweight among US children and adolescents, 1999–2000. JAMA. 2002;288(14):1728–32.

Ownby DR, Johnson CC, Peterson EL. Exposure to dogs and cats in the first year of life and risk of allergic sensitization at 6 to 7 years of age. JAMA. 2002;288:963–72.

Papi A, et al. Beclometasone-formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial. Lancet Respir Med. 2013;1(1):23–31. https://doi.org/10.1016/S2213-2600(13)70012-2.

Patrizi A, Guerrini V, Ricci G, Neri I, Specchia F, Masi M. The natural history of sensitizations to food and aeroallergens in atopic dermatitis: a 4-year follow-up. Pediatr Dermatol. 2000;17:261–5.

Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, Ortega H, Chanez P. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet. 2012;380:651–9.

Pearce N, Ait-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, Robertson C, the ISAAC Phase Three Study Group. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax. 2007;62:758–66.

Perrin K, Wijesinghe M, Healy B, Wadsworth K, Bowditch R, Bibby S, Baker T, Weatherall M, Beasley R. Randomised controlled trial of high concentration versus titrated oxygen therapy in severe exacerbations of asthma. Thorax. 2011;66:937–41.

Powell C, Dwan K, Milan SJ, Beasley R, Hughes R, Knopp-Sihota JA, Rowe BH. Inhaled magnesium sulfate in the treatment of acute asthma. Cochrane Database Syst Rev. 2012;12:CD003898.

Powell C, Kolamunnage-Dona R, Lowe J, Boland A, Petrou S, Doull I, Hood K, Williamson P, MAGNETIC study group. Magnesium sulphate in acute severe asthma in children (MAGNETIC): a randomised, placebo-controlled trial. Lancet Respir Med. 2013;1:301–8.

Prado CM, Martins MA, Tibério IF. Nitric oxide in asthma physiopathology. ISRN Allergy. 2011;2011:832560. https://doi.org/10.5402/2011/832560.

Quansah R, Jaakkola MS, Hugg TT, Heikkinen SAM, Jaakkola JJK. Residential dampness and molds and the risk of developing asthma: a systematic review and meta-analysis. PLoS One. 2012;7:e47526.

Reddel HK, Taylor DR, Bateman ED, Boulet L-P, Boushey HA, Busse WW, Casale TB, Chanez P, Enright PL, Gibson PG, de Jongste JC, Kerstjens HAM, Lazarus SC, Levy ML, O'Byrne PM, Partridge MR, Pavord ID, Sears MR, Sterk PJ, Stoloff SW, Sullivan SD, Szefler SJ, Thomas MD, Wenzel SE, American Thoracic Society/European Respiratory Society Task Force on Asthma Control and Exacerbations. An official American Thoracic Society/European Respiratory Society statement:

asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med. 2009;180:59–99.

Reddy MB, Doshi J, Covar R, Spahn JD. The changing face of severe childhood asthma: a comparison of two cohorts of children evaluated at National Jewish Health over the past 20 years. Allergy Asthma Proc. 2014;35:119–25.

Riedler J, Braun-Fahrländer C, Eder W, Schreuer M, Waser M, Maisch S, Carr D, Schierl R, Nowak D, von Mutius E, ALEX Study Team. Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. Lancet. 2001;358:1129–33.

Roberts G, Patel N, Levi-Schaffer F, Habibi P, Lack G. Food allergy as a risk factor for life-threatening asthma in childhood: a case-controlled study. J Allergy Clin Immunol. 2003;112(1):168–74.

Rodrigo GJ, Castro-Rodríguez JA. Daily vs. intermittent inhaled corticosteroids for recurrent wheezing and mild persistent asthma: a systematic review with meta-analysis. Respir Med. 2013;107:1133–40.

Rodrigo GJ, Moral VP, Marcos LG, Castro-Rodriguez JA. Safety of regular use of long-acting beta agonists as monotherapy or added to inhaled corticosteroids in asthma. A systematic review. Pulm Pharmacol Ther. 2009;22:9–19.

Ronchetti R, Villa MP, Barreto M, Rota R, Pagani J, Martella S, Falasca C, Paggi B, Guglielmi F, Ciofetta G. Is the increase in childhood asthma coming to an end? Findings from three surveys of schoolchildren in Rome, Italy. Eur Respir J. 2001;17:881–6.

Roorda RJ, Gerritsen J, Van Aalderen WM, Schouten JP, Veltman JC, Weiss ST, Knol K. Risk factors for the persistence of respiratory symptoms in childhood asthma. Am Rev Respir Dis. 1993;148:1490–5.

Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW. Early emergency department treatment of acute asthma with systemic corticosteroids. Cochrane Database Syst Rev. 2001;(1):CD002178.

Salles C, Terse-Ramos R, Souza-Machado A, Cruz ÁA. Obstructive sleep apnea and asthma. J Bras Pneumol. 2013;39(5):604–12.

Schachter LM, Peat JK, Salome CM. Asthma and atopy in overweight children. Thorax. 2003;58(12):1031–5.

Schaub B, von Mutius E. Obesity and asthma, what are the links? Curr Opin Allergy Clin Immunol. 2005;5(2):185–93.

Scholtens S, Wijga AH, Brunekreef B, Kerkhof M, Postma DS, Oldenwening M, de Jongste JC, Smit HA. Maternal overweight before pregnancy and asthma in offspring followed for 8 years. Int J Obes (Lond). 2010;34(4):606–13.

Schroeder A, Kumar R, Pongracic JA, Sullivan CL, Caruso DM, Costello J, Meyer KE, Vucic Y, Gupta R, Kim JS, Fuleihan R, Wang X. Food allergy is associated with an increased risk of asthma. Clin Exp Allergy. 2009;39(2):261–70.

Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, Cowan JO, Herbison GP, Silva PA, Poulton R. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. N Engl J Med. 2003;349:1414–22.

Selroos O. Effect of disease duration on dose-response of inhaled budesonide in asthma. Respir Med. 2008;102:1065–72.

Selroos O. Dry-powder inhalers in acute asthma. Ther Deliv. 2014;5:69–81.

Senthilselvan A, Lawson J, Rennie DC, Dosman JA. Stabilization of an increasing trend in physician-diagnosed asthma prevalence in Saskatchewan, 1991 to 1998. Chest. 2003;124:438–48.

Shaaban R, Zureik M, Soussan D, Neukirch C, Heinrich J, Sunyer J, Wjst M, Cerveri I, Pin I, Bousquet J, Jarvis D, Burney PG, Neukirch F, Leynaert B. Rhinitis and onset of asthma: a longitudinal population-based study. Lancet. 2008;372:1049–57.

Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. Am J Respir Crit Care Med. 2000;161:1501–7.

Simoes EA, Groothuis JR, Carbonell-Estrany X, Rieger CH, Mitchell I, Fredrick LM, Kimpen JL, Palivizumab Long-Term Respiratory Outcomes Study Group. Palivizumab prophylaxis, respiratory syncytial virus, and subsequent recurrent wheezing. J Pediatr. 2007;151:34–42.

Simpson AB, Glutting J, Yousef E. Food allergy and asthma morbidity in children. Pediatr Pulmonol. 2007;42:489–95.

Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ. Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood. A prospective study. N Engl J Med. 1990;323:502–7.

Stein RT, Sherrill D, Morgan WJ, Holberg CJ, Halonen M, Taussig LM, Wright AL, Martinez FD. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. Lancet. 1999;354:541–5.

Strachan DP, Aït-Khaled N, Foliaki S, Mallol J, Odhiambo J, Pearce N, Williams HC, the ISAAC Phase Three Study Group. Siblings, asthma, rhinoconjunctivitis and eczema: a worldwide perspective from the International Study of Asthma and Allergies in Childhood. Clin Exp Allergy. 2015;45:126–36.

Story RE. Asthma and obesity in children. Curr Opin Pediatr. 2007;19(6):680–4.

Subbarao P, Mandhane PJ, Sears MR. Asthma: epidemiology, etiology and risk factors. CMAJ. 2009;181:E181–90.

Swern AS, Tozzi CA, Knorr B, Bisgaard H. Predicting an asthma exacerbation in children 2 to 5 years of age. Ann Allergy Asthma Immunol. 2008;101:626–30.

Takkouche B, González-Barcala F-J, Etminan M, Fitzgerald M. Exposure to furry pets and the risk of asthma and allergic rhinitis: a meta-analysis. Allergy. 2008;63:857–64.

Tal A, Simon G, Vermeulen JH, Petru V, Cobos N, Everard ML, de Boeck K. Budesonide/formoterol in a single inhaler versus inhaled corticosteroids alone

in the treatment of asthma. Pediatr Pulmonol. 2002;34: 342–50.

Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. Tucson Children's Respiratory Study: 1980 to present. J Allergy Clin Immunol. 2003;111:661–75; quiz 676

Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Lancet. 1998;351:1225–32.

Teodorescu M, Polomis DA, Hall SV, Teodorescu MC, Gangnon RE, Peterson AG, Xie A, Sorkness CA, Jarjour NN. Association of obstructive sleep apnea risk with asthma control in adults. Chest. 2010;138(3): 543–50.

Thomsen SF, van der Sluis S, Stensballe LG, Posthuma D, Skytthe A, Kyvik KO, Duffy DL, Backer V, Bisgaard H. Exploring the association between severe respiratory syncytial virus infection and asthma: a registry-based twin study. Am J Respir Crit Care Med. 2009;179:1091–7.

Tillie-Leblond I, de Blic J, Jaubert F, Wallaert B, Scheinmann P, Gosset P. Airway remodeling is correlated with obstruction in children with severe asthma. Allergy. 2008;63(5):533–41.

Toelle BG, Ng K, Belousova E, Salome CM, Peat JK, Marks GB. Prevalence of asthma and allergy in schoolchildren in Belmont, Australia: three cross sectional surveys over 20 years. BMJ. 2004;328:386–7.

Tollefsen E, Langhammer A, Romundstad P, Bjermer L, Johnsen R, Holmen TL. Female gender is associated with higher incidence and more stable respiratory symptoms during adolescence. Respir Med. 2007; 101:896–902.

Torgerson DG, Ampleford EJ, Chiu GY, Gauderman WJ, Gignoux CR, Graves PE, Himes BE, Levin AM, Mathias RA, Hancock DB, Baurley JW, Eng C, Stern DA, Celedón JC, Rafaels N, Capurso D, Conti DV, Roth LA, Soto-Quiros M, Togias A, Li X, Myers RA, Romieu I, Van Den Berg DJ, Hu D, Hansel NN, Hernandez RD, Israel E, Salam MT, Galanter J, Avila PC, Avila L, Rodriquez-Santana JR, Chapela R, Rodriguez-Cintron W, Diette GB, Adkinson NF, Abel RA, Ross KD, Shi M, Faruque MU, Dunston GM, Watson HR, Mantese VJ, Ezurum SC, Liang L, Ruczinski I, Ford JG, Huntsman S, Chung KF, Vora H, Li X, Calhoun WJ, Castro M, Sienra-Monge JJ, del Rio-Navarro B, Deichmann KA, Heinzmann A, Wenzel SE, Busse WW, Gern JE, Lemanske RF, Beaty TH, Bleecker ER, Raby BA, Meyers DA, London SJ, Mexico City Childhood Asthma Study (MCAAS), Gilliland FD, Children's Health Study (CHS) and HARBORS study, Burchard EG, Genetics of Asthma in Latino Americans (GALA) Study, Study of Genes-Environment and Admixture in Latino Americans (GALA2) and Study of African Americans, Asthma, Genes & Environments (SAGE), Martinez FD, Childhood Asthma Research and Education (CARE) Network, Weiss ST, Childhood Asthma Management Program (CAMP), Williams LK, Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-Ethnicity (SAPPHIRE), Barnes KC, Genetic Research on Asthma in African Diaspora (GRAAD) Study, Ober C, Nicolae DL. Meta-analysis of genome-wide association studies of asthma in ethnically diverse North American populations. Nat Genet. 2011;43: 887–92.

Turner SW, Campbell D, Smith N, Craig LCA, McNeill G, Forbes SH, Harbour PJ, Seaton A, Helms PJ, Devereux GS. Associations between fetal size, maternal {alpha}-tocopherol and childhood asthma. Thorax. 2010;65:391–7.

Turner S, Prabhu N, Danielan P, McNeill G, Craig L, Allan K, Cutts R, Helms P, Seaton A, Devereux G. First- and second-trimester fetal size and asthma outcomes at age 10 years. Am J Respir Crit Care Med. 2011;184:407–13.

Valerio MA, Andreski PM, Schoeni RF, McGonagle KA. Examining the association between childhood asthma and parent and grandparent asthma status: implications for practice. Clin Pediatr (Phila). 2010;49:535–41.

van Meel ER, Dekker HD, Ahluwalia TS, Annesi-Maesano I, Arshad SH, Baïz N et al. Early-life respiratory tract infections and the risk of lower lung function and asthma: a meta-analysis of 154,492 children. 2017.

van Schayck OCP, Maas T, Kaper J, Knottnerus AJA, Sheikh A. Is there any role for allergen avoidance in the primary prevention of childhood asthma? J Allergy Clin Immunol. 2007;119:1323–8.

Vézina K, Chauhan BF, Ducharme FM. Inhaled anticholinergics and short-acting beta(2)-agonists versus short-acting beta2-agonists alone for children with acute asthma in hospital. Cochrane Database Syst Rev. 2014;(7):CD010283.

Vink NM, Postma DS, Schouten JP, Rosmalen JGM, Boezen HM. Gender differences in asthma development and remission during transition through puberty: the TRacking Adolescents' Individual Lives Survey (TRAILS) study. J Allergy Clin Immunol. 2010;126: 498–504.e1–6.

Vonk JM, Postma DS, Boezen HM, Grol MH, Schouten JP, Koëter GH, Gerritsen J. Childhood factors associated with asthma remission after 30 year follow up. Thorax. 2004;59:925–9.

Wang Z, May SM, Charoenlap S, Pyle R, Ott NL, Mohammed K, Joshi AY. Effects of secondhand smoke exposure on asthma morbidity and health care utilization in children: a systematic review and meta-analysis. Ann Allergy Asthma Immunol. 2015;115: 396–401.e2.

Wennergren G, Strannegård IL. Asthma hospitalizations continue to decrease in schoolchildren but hospitalization rates for wheezing illnesses remain high in young children. Acta Paediatr. 2002;1992(91):1239–45.

Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. Nat Med. 2012;18:716–25.

Wenzel SE, Gibbs RL, Lehr MV, Simoes EA. Respiratory outcomes in high-risk children 7 to 10 years after prophylaxis with respiratory syncytial virus immune globulin. Am J Med. 2002;112:627–33.

Willemsen G, van Beijsterveldt TCEM, van Baal CGCM, Postma D, Boomsma DI. Heritability of self-reported asthma and allergy: a study in adult Dutch twins, siblings and parents. Twin Res Hum Genet. 2008;11:132–42.

Williams AJ, Baghat MS, Stableforth DE, Cayton RM, Shenoi PM, Skinner C. Dysphonia caused by inhaled steroids: recognition of a characteristic laryngeal abnormality. Thorax. 1983;38(11):813–21.

Woodruff PG, Modrek B, Choy DF, Jia G, Abbas AR, Ellwanger A, Koth LL, Arron JR, Fahy JV. T-helper type 2-driven inflammation defines major subphenotypes of asthma. Am J Respir Crit Care Med. 2009;180:388–95.

Writing Committee for the American Lung Association Asthma Clinical Research Centers, Holbrook JT, Wise RA, Gold BD, Blake K, Brown ED, Castro M, Dozor AJ, Lima JJ, Mastronarde JG, Sockrider MM, Teague WG. Lansoprazole for children with poorly controlled asthma: a randomized controlled trial. JAMA. 2012;307(4):373–81.

Wu P, Dupont WD, Griffin MR, Carroll KN, Mitchel EF, Gebretsadik T, Hartert TV. Evidence of a causal role of winter virus infection during infancy in early childhood asthma. Am J Respir Crit Care Med. 2008;178:1123–9.

Xolair [Prescribing Information]. Genentech, Inc/Novartis Pharmaceuticals Corporation, San Francisco/East Hanover. 2017. https://www.gene.com/download/pdf/xolair_prescribing.pdf. Accessed 1 Nov 2017.