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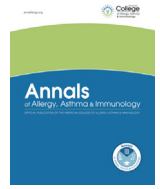
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## Special Article

## The pediatric asthma yardstick



## Practical recommendations for a sustained step-up in asthma therapy for children with inadequately controlled asthma

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## ABSTRACT

Current asthma guidelines recommend a control-based approach to management involving assessment of impairment and risk followed by implementation of treatment strategies individualized according to the patient's needs and preferences. However, for children with asthma, achieving control can be elusive. Although tools are available to help children (and families) track and manage day-to-day symptoms, when and how to implement a longer-term step-up in care is less clear. Furthermore, treatment is challenged by the 3 age groups of childhood–adolescence (12–18 years old), school age (6–11 years old), and young children (≤5 years old)—and what works for 1 age group might not be the best approach for another. The Pediatric Asthma Yardstick provides an in-depth assessment of when and how to step-up therapy for the child with not well or poorly controlled asthma. Development of this tool follows others in the Yardstick series, presenting patient profiles and step-up strategies based on current guidance documents, but modified according to newer data and the authors' combined clinical experience. The objective is to provide clinicians who treat children with asthma practical and clinically relevant recommendations for each step-up and each intervention, with the intent of helping practitioners better treat their pediatric patients with asthma, particularly those who do not always respond to recommended therapies.

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## Introduction

The Adult Asthma Yardstick, published in 2017, is a practical, yet comprehensive, update on how to conduct a sustained step-up in asthma therapy for the adult patient ( $\geq 18$  years of age) with inadequately controlled asthma.<sup>1</sup> Developed with asthma experts as an adjunct to guidelines and global strategies for the management of adults with asthma,<sup>2,3</sup> it provides a tool to help clinicians proactively address the loss of asthma control at all levels of severity. The content excluded children because they present special challenges in managing uncontrolled disease.

Asthma is one of the most common chronic diseases of childhood. The Centers for Disease Control and Prevention reported the overall prevalence of pediatric asthma in the United States in 2015 as 8.4% and among school-age children (6–19 years old) as approximately 10%.<sup>4,5</sup> For children, asthma is a primary cause of missed activities, including school<sup>2,5–8</sup>; it also is a cause of missed activities, including work, for their parents and caregivers.<sup>7,9</sup> Of long-term concern is that asthma can be associated with fixed airflow obstruction later in life. Approximately 75% of children with asthma have abnormal lung growth patterns.<sup>10</sup> Those with severe disease often show chronic airflow limitation—defined by a ratio of forced expiratory volume in 1 second (FEV<sub>1</sub>) to forced vital capacity lower than normal<sup>11</sup>—which, when identified at school age, commonly persists through adolescence and into adulthood.<sup>12–14</sup> Although age-dependent changes in respiratory system physiology are normal, in children with asthma, particularly those with severe disease, the impairment in lung function can affect assessment and response to therapy.<sup>10–26</sup> No current therapy, including inhaled corticosteroids (ICSs), leukotriene modifiers, or limited data with biological agents, has been shown to prevent or interrupt the enhanced age-dependent decline in FEV<sub>1</sub> that is a feature of childhood asthma. A full discussion of lung development in the child with asthma is beyond the scope of this article, but some changes in respiratory physiology that might affect response to treatment are presented in Table 1 and described in greater detail in eCommentary 1.

Although many children with asthma achieve symptom control with appropriate management, a substantial subset does not. From 2006 to 2010, more than 38% of children with current asthma had uncontrolled disease.<sup>5,27</sup> These children should undergo a step-up in care, but when and how to do that is not always straightforward.<sup>8,27–29</sup> The Pediatric Asthma Yardstick is a practical resource for starting or adjusting controller therapy based on the options that are currently available for children, from infants to 18 years of age. The recommendations, presented in Figure 1, are based on the therapeutic utility of current step-based strategies (Fig 2)<sup>2,3</sup> and presented around patient profiles, with commentary according to contemporary data and the authors' clinical experience.

Asthma control is defined according to the frequency and intensity of symptoms, functional limitations, and potential negative effects of treatment<sup>1–3,5</sup> (eTable 1). Left uncontrolled, asthma can have a significant cost to families and society.<sup>5,27</sup> Children with uncontrolled asthma are at increased risk for adverse events and morbidity, including life-threatening exacerbations and associated hospitalizations, emergency department (ED) visits, and urgent care visits, which significantly increase the economic burden.<sup>2,5,8,29,30</sup> Estimates indicate that children with poorly controlled asthma have double the annual costs for their disease compared with children with well-controlled asthma.<sup>31</sup> Children diagnosed with severe asthma, approximately 5% of pediatric patients with asthma, account for 50% of health care system costs related to the disease.<sup>28</sup>

Current strategies for managing asthma are based on the impairment and risk model (presented in eTable 1), with treatment guided by severity<sup>1–3</sup> (Fig 2). Different medications are included in each step to allow for individualizing treatment, although the choices are not necessarily of equal efficacy; preferred therapies are noted. The goals of management are 2-fold:

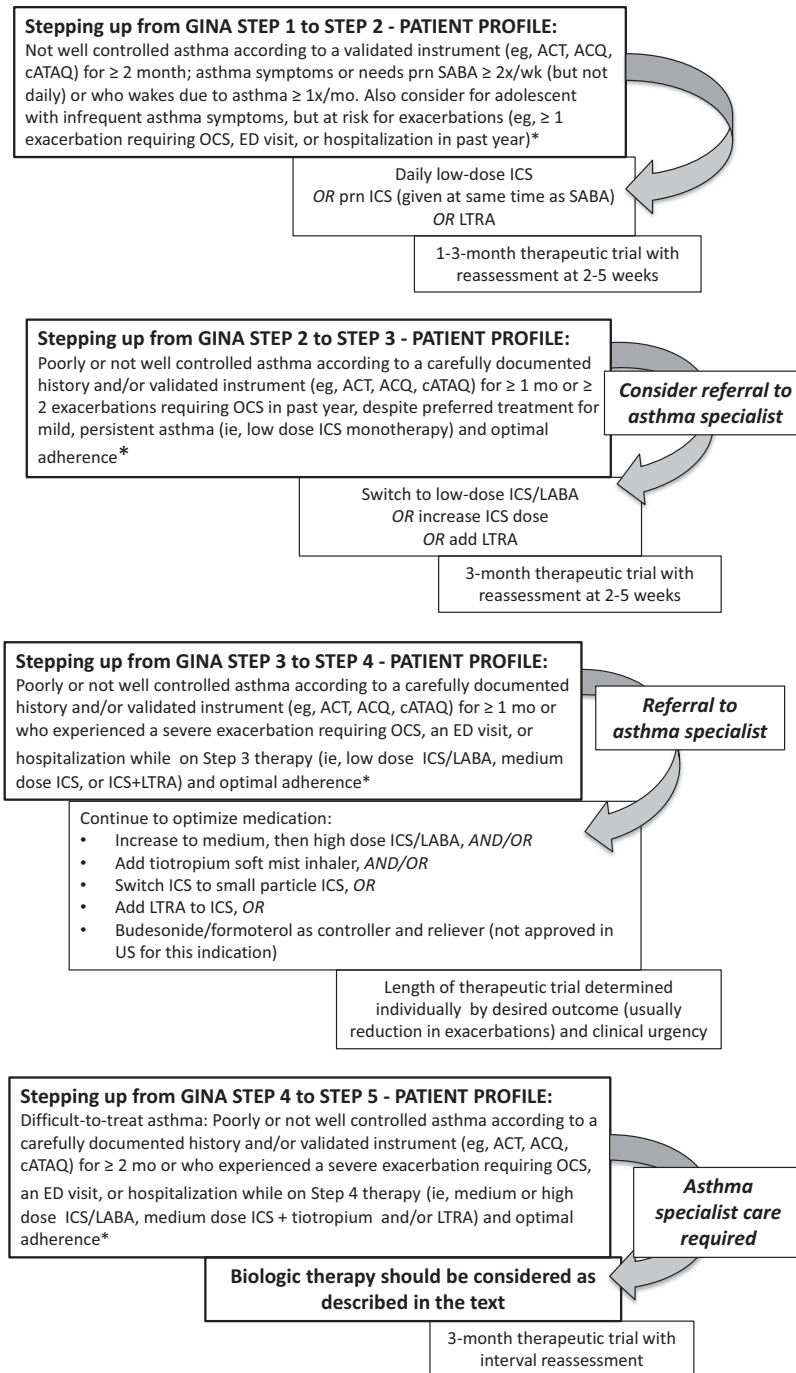
- To achieve good control of symptoms, which includes little or (ideally) no sleep disturbances from asthma and maintaining normal activity levels; and

**Table 1**  
Age-Dependent Factors in Respiratory Physiology That Can Affect Evaluation and Treatment of the Child With Asthma

Physiologic factor	Effect of age	Impact
Expired time-volume relations measured by spirometry <sup>10–12,15,16</sup>		
FEV <sub>1</sub>	increases up to young adulthood and then decreases	75% of children with asthma have abnormal decline patterns with age; at risk for persistent airflow limitation and COPD
FVC	decreases after young adulthood from decreased muscle strength and loss of tissue-supporting structures	can be low in asthma from increased secretions and mucus plugs
FEV <sub>1</sub> /FVC	pre-bronchodilator stable with age, whereas post-bronchodilator decreases with age	decrease in post-bronchodilator greater in severe vs nonsevere asthma with age
Airway lability <sup>11,25,26</sup>		
Bronchial hyperresponsiveness	decreases during school age	greater in asthma, decrease during puberty could account for remission in some young adults
Bronchodilator responsiveness	decreases	loss greater in severe asthma, a factor for progressive airflow limitation
Mechanical properties <sup>14,17–21</sup>		
Lung compliance	decreases; hence, elastic recoil pressure increases	airways close at a volume larger than FRC in preschool children; little change in adults
Chest wall compliance	decreases	rib cage distortion and unstable FRC in preschool children
Specific airway resistance corrected for FRC	increases	trajectory of increase greater in children with asthma
Peripheral airway resistance	decreases abruptly from preschool to school age	higher in asthma
Ventilation heterogeneity <sup>22–24</sup>		
Ventilation defects on inhaled hyperpolarized noble gas MRI	nonventilated regions increase with age	greater nonventilated regions in severe vs nonsevere asthma
Total resistance (R5) – proximal resistance (R20) by forced oscillometry	positive correlation with degree of peripheral ventilation heterogeneity	greater in children with poorly controlled asthma
Lung clearance index by multiple-breath nitrogen washout	increases with age	prolonged clearance in children with asthma despite normal FEV <sub>1</sub>

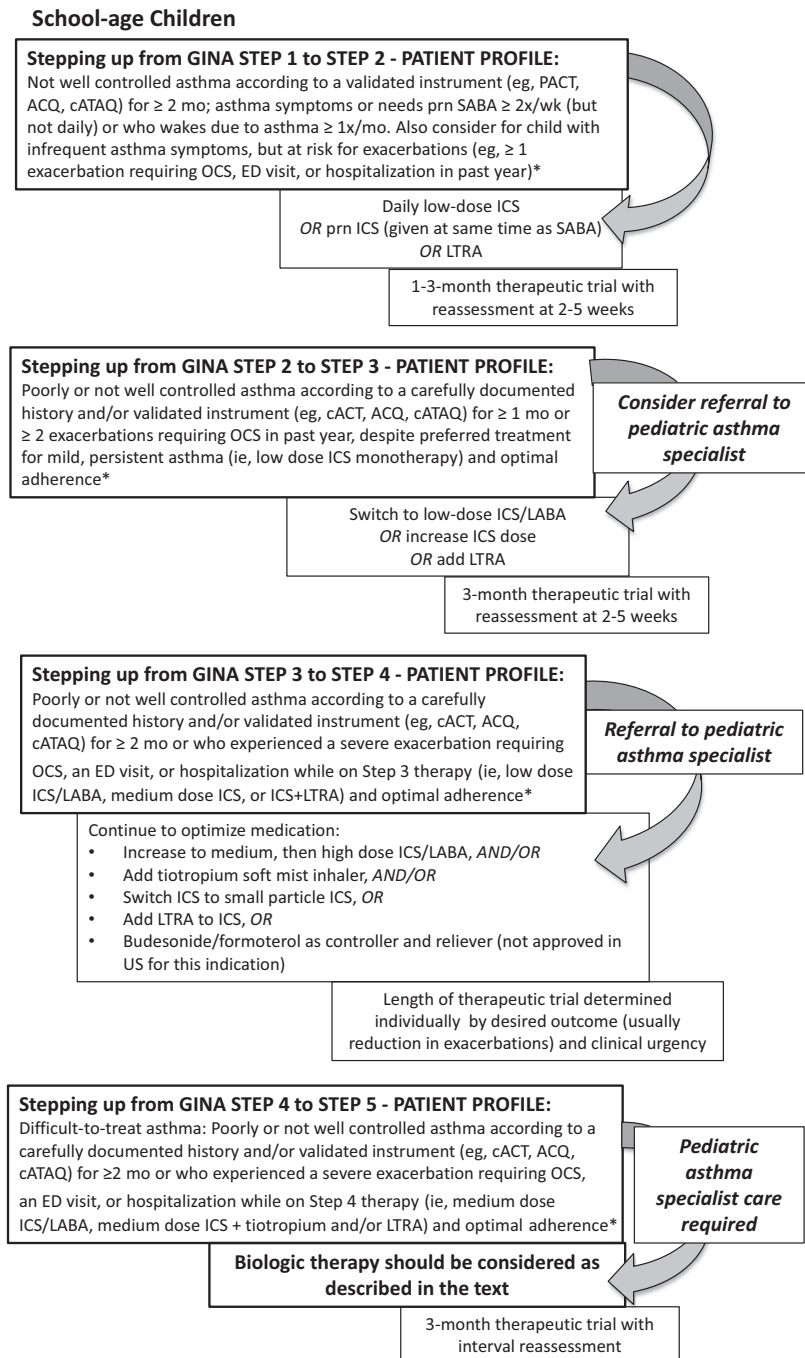
Abbreviations: COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 second; FRC, functional residual capacity; FVC, forced vital capacity; MRI, magnetic resonance imaging; R20, large airway resistance at 20 Hz; R5, total respiratory resistance measured at 5 Hz.

**Adolescents**



\*Prior to stepping up therapy, confirm that the increased level of symptoms is due to asthma. The patient should be assessed for non-adherence with the management plan, potential comorbidities, and other factors that might negatively impact response to therapy (see Table 3), including an age-appropriate understanding of asthma and the management plan as well as parent and/or caregiver knowledge.

**Figure 1.** The Pediatric Asthma Yardstick flowchart. Patient profiles and recommendations for treatment for the 3 age groups of childhood are shown: adolescence (12–18 years old), school age (6–11 years old), and preschool ( $\leq 5$  years old). Strategies are based on available guidelines, newer data, and the authors' clinical experience as described in the text. ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; cATAQ, Asthma Therapy Assessment Questionnaire for Children and Adolescents; ED, emergency department; FP, fluticasone propionate; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; PACT, Pediatric Asthma Control Test; SABA, short-acting  $\beta_2$ -agonist.



\*Prior to stepping up therapy, confirm that the increased level of symptoms is due to asthma. The patient should be assessed for non-adherence with the management plan, potential comorbidities, and other factors that might negatively impact response to therapy (see Table 3), including an age-appropriate understanding of asthma and the management plan as well as parent and/or caregiver knowledge.

Figure 1. (continued)

- To minimize the risk of asthma exacerbations, impaired lung function, and medication side effects

When and how to implement a step-up in therapy is not always clear. As shown in Figure 3, consideration for a sustained step-up is recommended when disease control is suboptimal during several months (eg, 1–3 months) of appropriate treatment.<sup>2</sup> Validated tools for self-assessing control and treatment response—such as the Asthma Control Test,<sup>31–33</sup> the Childhood Asthma Control

Test,<sup>34,35</sup> the Asthma Control Questionnaire (ACQ),<sup>36,37</sup> the Childhood Asthma Control Questionnaire,<sup>38</sup> the Asthma Therapy Assessment Questionnaire for Children and Adolescents,<sup>39</sup> the Test for Respiratory and Asthma Control in Kids (TRACK),<sup>40,41</sup> and the Composite Asthma Severity Index<sup>42,43</sup>—can be helpful. These are presented in eTable 2.

Although strategies provide specific recommendations for stepping up treatment,<sup>2,3</sup> suggested protocols for 1 age group might not be applicable to the others. For example:

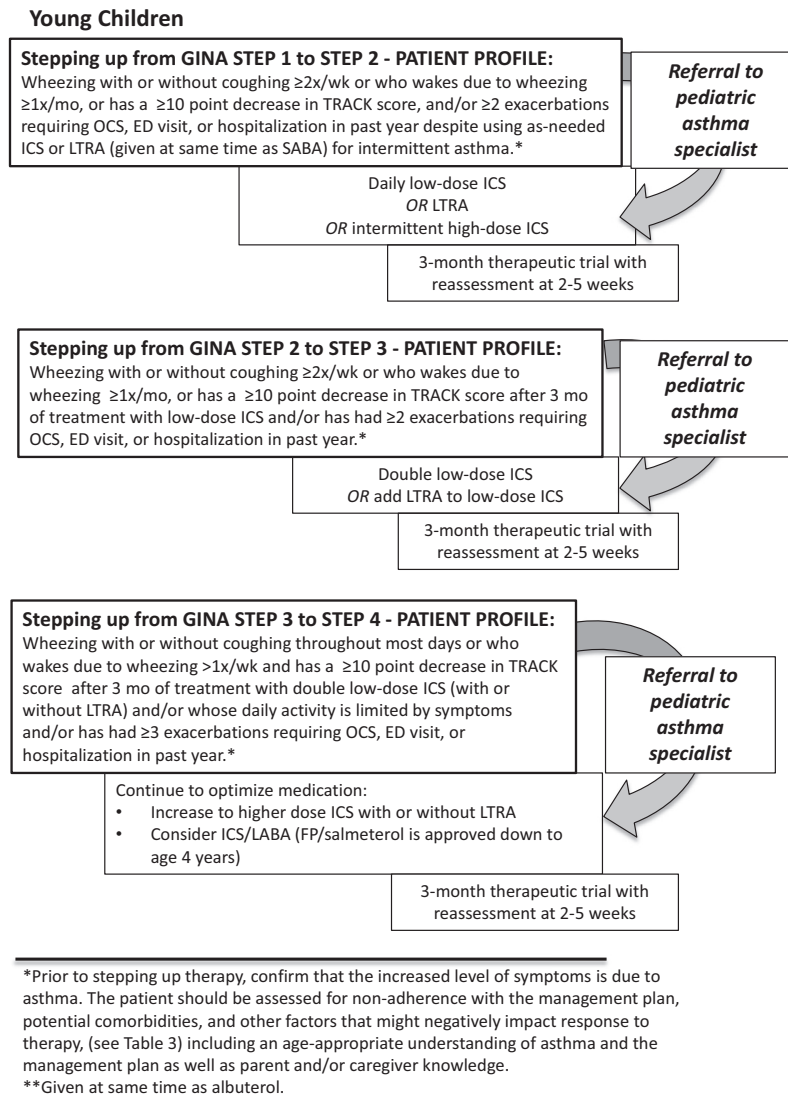
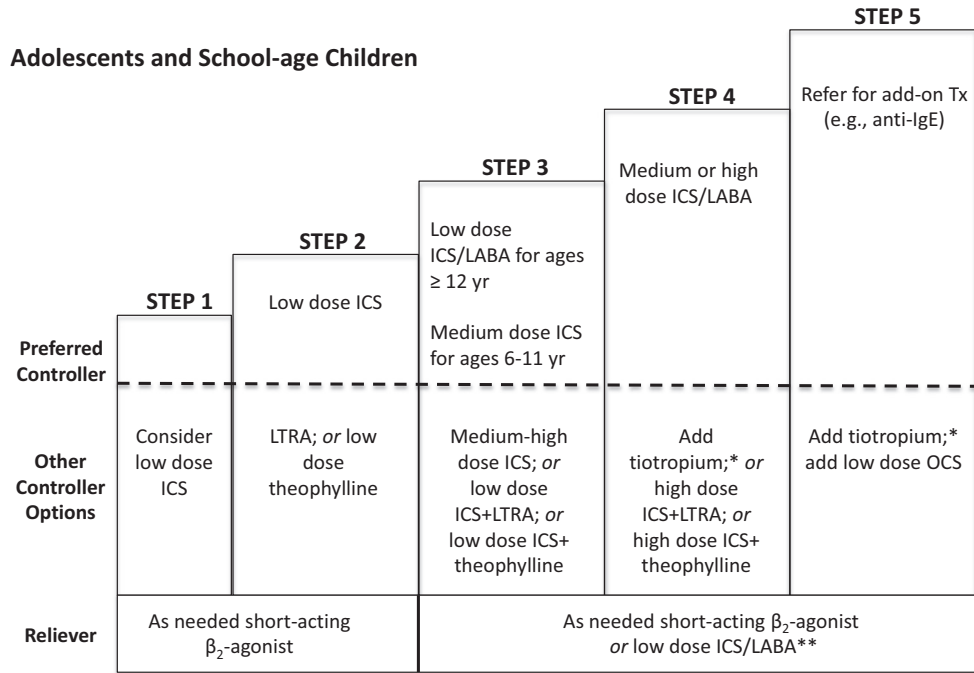


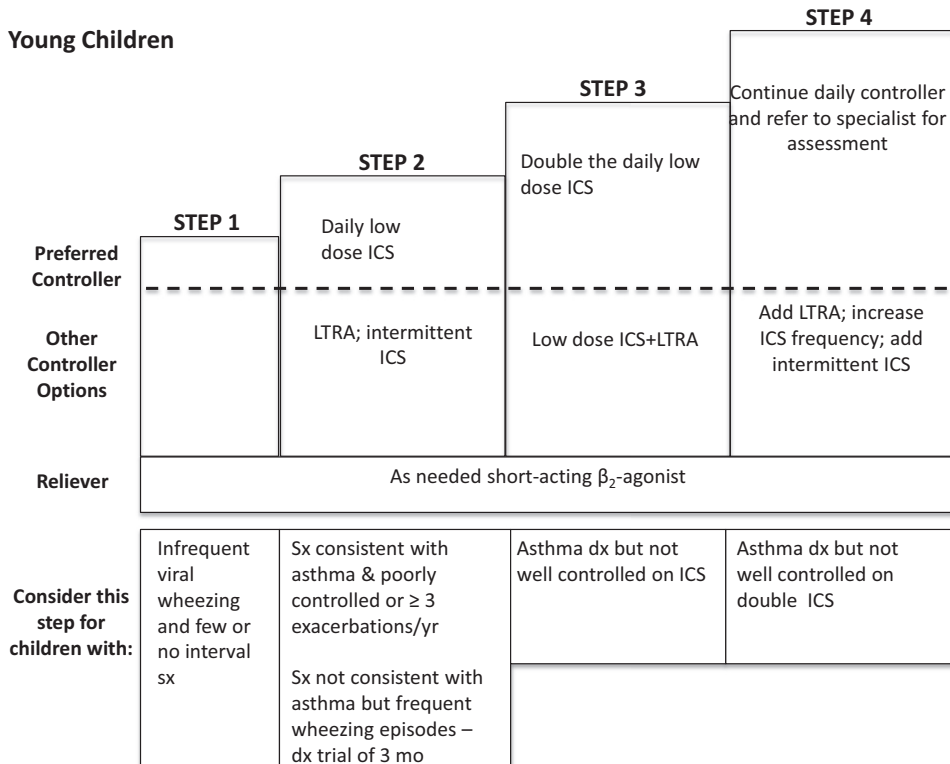
Figure 1. (continued)

- The diagnosis and management of asthma differ among the age groups, reflecting not only developmental issues but also challenges relating to daily activities (eg, information for caregivers, teachers, camp counselors, coaches about asthma and its treatment and permissions to administer treatment).<sup>2,3</sup>
- Although asthma often begins during early childhood, diagnosing asthma in the very young child is challenging because it is based largely on symptoms and is not easily supplemented by lung function because of difficulty in obtaining quality test results. The symptoms, notably wheezing and coughing, often are related to, or occur in the context of, common viral infections.<sup>2,3</sup> Recommendations guiding the diagnosis of asthma in young children are presented in Table 2. The National Asthma Education and Prevention Program (NAEPP) guidelines<sup>3</sup> and the Global Initiative for Asthma (GINA) management strategy provide more comprehensive recommendations.<sup>2</sup>
- The responsiveness of children to specific classes of medications can differ by age and from that observed in adults.<sup>29,44–47</sup> Inconsistencies in response to medications can reflect differences in pulmonary physiology, inflammatory pathology, and/or symptom presentation and persistence.<sup>29,44,45,48</sup> They also can reflect other factors such as comorbid conditions, suboptimal inhaled drug delivery, and nonadherence with treatment. Table 3 lists some common factors contributing to failure to achieve, or loss of, asthma control, aside from the pathophysiology itself. Before adjusting therapy, it is important to ensure that the child's change in symptoms is due to asthma and not to any of these factors that need to be addressed.
- The age of the child and the physiologic features of the developing respiratory system determine the optimal selection of delivery devices to administer inhaled medication. Deposition of inhaled particles including medications in the distal lung is affected by inspiratory flow velocity and particle size.<sup>49</sup> Preschool children are at a particular disadvantage because they might not be able to follow instructions to take a deep, slow breath so that relatively more medication affects the oropharynx. For this reason, jet nebulizers are commonly used in this age group, with the relative advantages of being effective with tidal breathing, not requiring a tight seal, and being used confidently in the face of respiratory distress.<sup>2</sup> More information on selection of delivery devices is provided in eCommentary 1.
- Pediatric data are limited owing to a paucity of robust randomized controlled clinical trials in children. The efficacy and safety of medications can differ from those for adults, particularly in younger children.<sup>29,46,48,50,51</sup>



\*Tiotropium by soft-mist inhaler is indicated as add-on treatment for patients with a history of exacerbations; it is not indicated in children <18 years

\*\*For patients prescribed beclomethasone/formoterol or budesonide/formoterol



**Figure 2.** Step therapy for children with asthma according to the Global Initiative for Asthma in 2017.<sup>2</sup> ED, emergency department; ICS, inhaled corticosteroid; IgE, immunoglobulin E; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SABA, short-acting β<sub>2</sub>-agonist.

The Pediatric Asthma Yardstick addresses these issues according to the 3 age ranges comprising childhood—adolescents (12–18 years old), school-age children (6–11 years old), and infants and young children (≤5 years old)—with severity classifications as subsections. The development of this document is described in eCommentary 2.

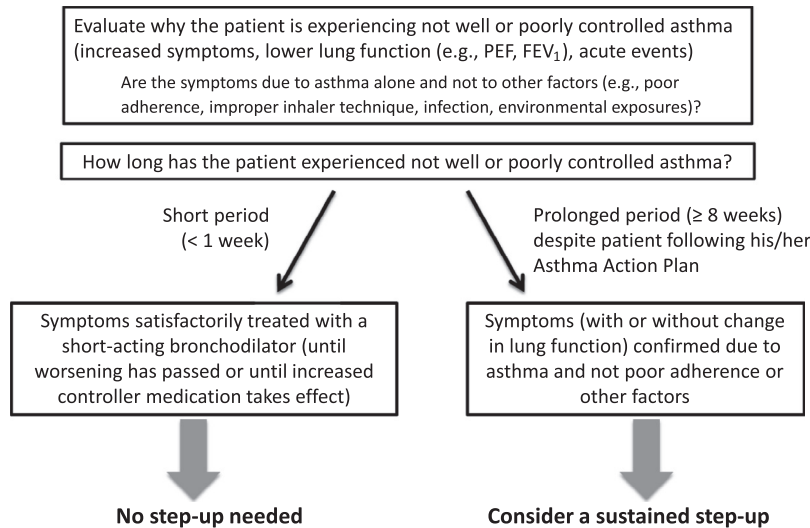
**Stepping Up Therapy**

*Step-Up Therapy for the Adolescent (12–18 Years Old) with Asthma*

*Step 1: intermittent asthma*

The diagnosis of asthma in adolescents, like adults, is based on a characteristic pattern of respiratory symptoms (eg, wheezing,





**Figure 3.** When should a sustained step-up in asthma therapy be considered?<sup>1,2</sup> FEV<sub>1</sub>, forced expiratory volume in 1 second; PEF, peak expiratory flow.

shortness of breath [dyspnea], chest tightness, and/or cough) and variable reversible expiratory airflow limitation. Differentiating asthma symptoms from other acute or chronic respiratory conditions (eg, hyperventilation, vocal cord dysfunction, deconditioning, etc) is important. Documenting the diagnosis of asthma is well covered by current guidelines.<sup>2,3</sup>

Treatment, too, is similar to that in adults, because many studies have included adolescents (≥12 years old). For adolescents with intermittent asthma, the most common treatment is an as-needed short-acting β<sub>2</sub>-agonist (SABA; Fig 2A), whereas low-dose ICS (Table 4) or intermittent ICS can be considered an option, possibly increasing the frequency of symptom-free days, decreasing exacerbations, and decreasing the potential decline in lung function over time.<sup>2,52</sup> A post hoc efficacy analysis of the Steroid Treatment as Regular Therapy (START) study that followed 7,138 patients (4–66 years old) with mild recent-onset (≤2 years) asthma treated for 3 years with low-dose budesonide (n = 3,577) or placebo (n = 3,561) did not support restricting ICS to patients with symptoms occurring more than 2 days a week<sup>53</sup> (eTable 3).

Step-up options are summarized below for mild persistent and moderate persistent asthma; the reader is directed to current guidelines and to the Adult Asthma Yardstick for a more comprehensive discussion.<sup>1–3</sup> Adolescents with severe and difficult-to-treat asthma present different challenges than adults with such asthma and those sections are addressed in greater detail.

*Step-up: intermittent asthma to mild persistent asthma (GINA step 1 to step 2)*

**Patient Profile**

This profile addresses the adolescent with asthma symptoms or as-needed SABA use at least 2 times a week, but not daily, or who wakes due to asthma at least once a month but less than twice weekly. A step-up in treatment also can be considered for the adolescent who has infrequent asthma symptoms but is at risk for exacerbations (eg, who has had ≥1 exacerbation requiring an oral corticosteroid [OCS], ED visit, or hospitalization in the past year). Infrequently, an adolescent might present with no symptoms but abnormal lung function and should be monitored, with any decision to treat based on a risk-benefit discussion among the physician, adolescent, and family.

For all adolescents with asthma, before stepping up therapy, it is important to confirm that the increased level of symptoms is due to asthma. The adolescent should be assessed for an age-appropriate understanding of asthma and the management plan in addition to parent and/or caregiver knowledge, nonadherence with the management plan, potential comorbidities, and other factors that might negatively affect response to therapy (Table 3).

**Table 2**  
Differential Diagnosis of Asthma in the Young Child<sup>2</sup>

Condition	Characteristics
Recurrent viral respiratory tract infections	recurrent cough; runny and congested nose (usually <10 days); mild wheeze with infection; there might be no symptoms between infections
Gastroesophageal reflux	cough when feeding; recurrent chest infections; vomits easily especially after a large feeding; poor response to trial of asthma medication
Foreign body aspirations	acute episode of abrupt severe cough or stridor during feeding or play; recurrent chest infections and cough; focal lung signs
Tracheomalacia	noisy breathing during crying, eating, and/or upper airway infections (noisy inspiration if extrathoracic, noisy expiration if intrathoracic); harsh cough; inspiratory or expiratory retraction; symptoms often present since birth; poor response to trial of asthma medication
Tuberculosis	persistent noisy respirations and cough; fever unresponsive to normal antibiotics; enlarged lymph nodes; contact with someone who has tuberculosis; poor response to trial of asthma medication
Congenital heart disease	cardiac murmur; cyanosis when eating; failure to thrive; tachycardia; tachypnea or hepatomegaly
Cystic fibrosis	cough starting shortly after birth; recurrent chest infections; failure to thrive (malabsorption); loose, greasy, bulky stools; poor response to trial of asthma medication
Primary ciliary dyskinesia	cough; recurrent mild chest infections; chronic ear infections and purulent nasal discharge; ~ 50% of children show situs inversus
Vascular ring	respirations often persistently noisy; poor response to trial of asthma medication
Bronchopulmonary dysplasia	premature birth; very low birthweight; needed prolonged mechanical ventilation or supplemental oxygen; difficulty breathing present since birth
Immune deficiency	recurrent fevers and infections (including nonrespiratory); failure to thrive

**Table 3**  
Some Common Factors Leading to Failure to Achieve or Loss of Asthma Control<sup>2,49</sup>

Environmental exposures (eg, allergens, irritants, viruses)
Comorbid conditions contributing to morbidity (eg, rhinosinusitis, obesity; respiratory infection, gastroesophageal reflux disease)
Difficulty using inhalers; improper technique
Poor adherence to the management plan, which could reflect
Fear of medication adverse effects
Poor understanding of treatment
Belief that the medication does not help (eg, in relation to patients reporting that they cannot feel an immediate effect)
Belief that even controller medication can be taken intermittently (eg, when symptoms become “noticeable”)
Inconvenience, including using multiple medications or inhalers and having to take medications several times a day
Dislike of provider; distrust of medical establishments
Just “not wanting” to have to take medication (particularly for adolescents)
Not recognizing symptoms or ignoring the need for using medication; belief that the medication is not necessary (particularly for adolescents)
Lack of parental support in following treatment plan
Family stress, emotional upsets; violence
Cost, including lack of insurance or medication not covered by insurance
Lack of access to health care

- The preferred step-up from step 1 to step 2 for adolescents is daily low-dose ICS<sup>2,3</sup> (Fig 2A; see Table 4 for ICS dosing). Lower pulmonary function and evidence of allergic inflammation (eg, immunoglobulin E [IgE], fractional exhaled nitric oxide [FeNO], blood eosinophils, eosinophil cationic protein) have been iden-

**Table 4**  
Inhaled Corticosteroid Dosing for Children<sup>2</sup>

Drug	Daily dose (μg)		
	Low dose <sup>a</sup>	Medium dose	High dose
<b>Adolescents (≥12 y old and adults)</b>			
Beclomethasone 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	400–1,000	>1,000–2,000	>2,000
<b>School-age children (6–11 y old)</b>			
Beclomethasone dipropionate (HFA)	50–100	>100–200	>200
Budesonide (DPI)	100–200	>200–400	>400
Budesonide (nebulas)	250–500	>500–1000	>1000
Ciclesonide (HFA)	80	>80–160	>160
Fluticasone furoate (DPI)	<sup>b</sup>	<sup>b</sup>	<sup>b</sup>
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	>800–1,200	>1,200
<b>Young children (≤5 y old)</b>			
Beclomethasone dipropionate (HFA)	100		
Budesonide (DPI)	<sup>b</sup>		
Budesonide pMDI + spacer	200		
Budesonide (nebulas)	500		
Ciclesonide (HFA)	160		
Fluticasone furoate (DPI)	<sup>b</sup>		
Fluticasone propionate (DPI)	<sup>b</sup>		
Fluticasone propionate (HFA)	100		
Mometasone furoate	<sup>b</sup>		
Triamcinolone acetonide	<sup>b</sup>		

Abbreviations: DPI, dry powder inhaler; HFA, hydrofluoroalkane; N/A, not applicable; pMDI, pressurized metered-dose inhaler.

<sup>a</sup>This is not a table of equivalence. A low daily dose in young children is defined as the dose not associated with clinically adverse effects in trials that included measures of safety. Increasing the dose in this age group usually is a doubling of the “low dose” as described in the text.

<sup>b</sup>Not studied in this age group.

tified as predictors of favorable response to ICS over other therapies.<sup>54–58</sup>

- Leukotriene receptor antagonists (LTRAs), although less effective than ICSs for most patients, are an option for adolescents who cannot, or prefer to not, use an ICS.<sup>2,45,59,60</sup> A high urinary leukotriene E<sub>4</sub> level (which might not be readily available) and/or low (or no) levels of indicators of allergic inflammation might help predict a favorable response.<sup>54</sup>
- Symptom reduction is the preferred outcome, and a 1- to 3-month therapeutic trial should be sufficient. Interval reassessment is recommended.
- A challenge when addressing inadequate disease control in adolescents is the need for the adolescent to recognize symptoms and agree that better control is desired.<sup>61</sup> Regular reassessment is particularly important, working with the adolescent to adjust therapy as needed to maintain disease control while at the same time accommodating their changing needs and preferences. Adolescence also is a period during which stress can significantly affect disease outcomes.<sup>62,63</sup> Suggestions for encouraging adolescents to participate in their care can be found in guidance documents and the published literature.<sup>3,64,65</sup>

*Step-up: mild persistent asthma to moderate persistent asthma (GINA step 2 to step 3)*

#### Patient Profile

This profile concerns the adolescent with poorly or not wellcontrolled asthma according to a carefully documented history and/or a validated instrument (eTable 2) for at least 1 month or who had at least 2 exacerbations requiring OCS in the past year, despite preferred treatment (low-dose ICS monotherapy) for mild persistent asthma.

Before stepping up therapy, it is important to confirm that the increased level of symptoms is due to asthma, as described in the profile for the initial step-up, GINA step 1 to step 2.

- The preferred step-up for adolescents with persistent symptoms despite using recommended therapy for mild persistent asthma is a low-dose combination of an ICS and a long-acting β<sub>2</sub>-agonist (LABA).<sup>1,2</sup> Studies in adults and adolescents and pediatric trials including adolescents have shown the combination to provide equivalent or better asthma control to ICS monotherapy, as evidenced by less need for rescue medication, fewer nights with disturbed sleep, and more symptom-free days, with no difference in the risk of serious adverse events<sup>66–70</sup> (eTable 3). Whether adding LABA can yield equivalent asthma control at a lower ICS dose—a goal for treatment and suggested by 1 26-week study in children (6–16 years old)<sup>71</sup>—requires confirmation.
- Alternative strategies include increasing the dose of ICS monotherapy or adding a LTRA to an ICS.<sup>2,69</sup> These strategies were examined in the Best Add-On Giving Effective Response (BADGER) study, a crossover comparison of these 3 commonly used step-up protocols—adding LABA, increasing the dose of ICS monotherapy 2.5-fold, and adding LTRA—for children with uncontrolled asthma despite guideline-based treatment for mild persistent asthma (ie, low-dose ICS: 100 μg of fluticasone propionate [FP] twice daily)<sup>69</sup> (eTable 3). Although the best response occurred most frequently with the LABA step-up, some children responded better to increasing ICS monotherapy or to adding LTRA. Which therapy was best for which patient could not be predicted by a priori baseline characteristics, but subsequent post hoc analyses indicated some potential baseline factors that might be predictive, including race and ethnicity, eczema, urinary

leukotriene E<sub>4</sub>, and, possibly, lung function.<sup>47,71</sup> These are presented in eTable 3.

- Replacing a conventional ICS with a small-particle ICS formulation might be another option,<sup>72</sup> but safety concerns remain regarding the potential for greater systemic absorption.<sup>73</sup> More data are needed.
- Low-dose budesonide plus formoterol as maintenance and reliever medication might decrease the risk of exacerbations compared with budesonide alone,<sup>2,74</sup> but this approach has not received Food and Drug Administration (FDA) approval. Similar data for other ICS and LABA combinations are limited, and an as-needed SABA should be used as reliever medication with those agents as directed by current guidelines.<sup>2,3</sup>
- The addition of dust mite sublingual immunotherapy could be a step-up option for some adolescents with asthma and dust mite allergy.<sup>75</sup> In the United States sublingual dust mite immunotherapy is indicated for patients older than 18 years with allergic rhinitis.<sup>76</sup>
- A 3-month trial with interval reassessment based on impairment and risk should be sufficient to evaluate the success of treatment.

*Step-up: moderate persistent asthma to severe persistent asthma (GINA step 3 to step 4)*

#### Patient Profile

This profile concerns the adolescent with poorly or not well-controlled asthma according to a carefully documented history and/or a validated instrument (eTable 2) for at least 2 months or who experienced a severe asthma exacerbation in the past year requiring OCS or an ED visit or hospitalization while on step 3 therapy (ie, low-dose ICS plus LABA; medium-dose ICS monotherapy; low-dose ICS plus LTRA).

Before stepping up therapy it is important to confirm that the increased level of symptoms is due to asthma, as described in the profile for the initial step-up, GINA step 1 to step 2.

The clinical burden is great in adolescents with severe and/or difficult-to-treat asthma, many of whom have symptoms despite GINA step 3 or higher-level asthma therapy.<sup>2,77</sup> This level of severity is often associated with very poorly controlled asthma symptoms despite the use of multiple controller medications; frequent exacerbations requiring urgent care and even hospitalizations; impaired lung function; impaired quality of life including negative effects on sleep, daily activities, and emotions; and high direct and indirect costs.<sup>73,78</sup> Identifying and then improving the care and outcomes of these severe and/or difficult-to-treat adolescents (and children) remain major clinical challenges. Most importantly, and different from adults, physicians must address the potential risks associated with more intensive treatment including (1) the potential adverse effects associated with higher ICS dosages (eg, growth effects, suppression of the hypothalamic-pituitary-adrenal axis, weight gain), (2) the stigma associated with being labeled as having “severe” asthma, and (3) challenges with the need for greater surveillance of control.<sup>2</sup>

The National Institute of Allergy and Infectious Disease Inner City Asthma Consortium (ICAC) has identified characteristics differentiating easy-to-control asthma (defined as controlled with  $\leq 100$   $\mu\text{g}/\text{d}$  of FP) from difficult-to-control asthma (defined as requiring daily therapy with  $\geq 500$   $\mu\text{g}$  of FP  $\pm$  LABA) in these patients based on a year-long prospective study of 619 urban children (6–17 years old) who had been receiving guideline-based care<sup>79</sup> (eTable 3). At baseline 40.9% ( $n = 253$ ) of the children were identified as having difficult-to-control disease, and 37.5% ( $n = 232$ ) had easy-to-control disease;

the remainder did not match the criteria for either group. Over the course of the year, controller use decreased significantly in the easy-to-control group; but despite optimal treatment and good adherence, children with difficult-to-control asthma showed little improvement in symptoms, exacerbations, and pulmonary function.<sup>79</sup> A sub-analysis evaluated baseline variables that might distinguish difficult-to-control from easy-to-control subgroups. FEV<sub>1</sub> and bronchodilator responsiveness were key factors; others included Childhood Asthma Control Test score, evidence of allergen sensitization, severity of rhinitis, and body mass index percentile.<sup>79</sup>

Referral to an asthma specialist (allergist/pulmonologist) is strongly recommended before stepping up from GINA step 3 therapy. Asthma specialists have the expertise and time to manage more severe asthma, and better outcomes for these patients compared with non-asthma specialists have been documented.<sup>2,80–83</sup>

Current strategies recommend medium-dose ICS plus LABA in fixed combination as the preferred step 4 step-up treatment for adolescents, based on studies conducted with adults and adolescents.<sup>1–3,67,68</sup> Fewer adolescents treated with FP plus salmeterol (42 of 613, 6.9%) experienced severe asthma exacerbations vs FP monotherapy at equivalent ICS dosage (64 of 615, 10.4%; hazard ratio [HR] 0.65, 95% confidence interval [CI] 0.44–0.95,  $P = .03$ ).<sup>67</sup> Low, medium, and high doses of ICS were used in this study, but determination of effect by dose was not possible because efficacy was reported according to the combined data for all strengths. Likewise, although no difference in the time to the first asthma exacerbation was reported for adolescents treated with budesonide plus formoterol (52 of 632, 8.2%) compared with budesonide monotherapy (51 of 636, 8.0%) at equivalent ICS dosage (HR 1.04, 95% CI 0.71–1.54,  $P = .83$ ), the risk of an exacerbation was 16.5% lower with the combination based on analysis of all subjects (adults and adolescents: HR 0.84, 95% CI 0.74–0.94,  $P = .002$ ).<sup>68</sup> The combination also was statistically superior to monotherapy for parameters of asthma control (ie, ACQ6 score, symptom-free days, night-time awakenings, use of rescue medication). However, for these patients with more severe disease, decreasing the number of exacerbations could be at least an equally important determinant of control.

#### Other Options

Adding the long-acting muscarinic agent, tiotropium bromide, by soft mist inhaler is an alternative option for maintenance therapy in adolescents with poorly controlled asthma and a prior recent history of asthma exacerbations, and the data in adolescents are consistent with findings in adults.<sup>1,2,84–87</sup>

Studies in adolescents (12–17 years old) with uncontrolled asthma (ACQ score  $\geq 1.5$ ) have evaluated tiotropium administered by soft mist inhaler once daily as add-on therapy to ICS with or without LTRA.<sup>84,86</sup> In these studies, doses of 5 and 2.5  $\mu\text{g}$  significantly improved the primary outcome, evening peak FEV<sub>1</sub> response 3 hours after dosing compared with baseline, and secondary spirometric outcomes (eg, FEV<sub>1</sub> area under the curve, peak expiratory flow), with safety and tolerability comparable to placebo. The 5- $\mu\text{g}$  dose is not FDA approved for the treatment of asthma. The studies are presented in eTable 3.

Adding a LTRA to an ICS is another option, albeit with lower efficacy compared with other step-up strategies. For more information, the reader is directed to current guidelines and the Adult Asthma Yardstick.<sup>1–3</sup>

Using budesonide plus formoterol as maintenance and reliever medication could be an option,<sup>2</sup> although this approach has not received FDA approval. For more information, the reader is directed to current guidelines and the Adult Asthma Yardstick.<sup>1,2</sup>

The duration of the therapeutic trial is determined by the desired outcomes, which for adolescents with severe asthma is a decrease

in exacerbations in addition to control of impairment. Three to 6 months might be needed to appropriately evaluate success.

*Step-up: severe persistent asthma to severe difficult-to-treat asthma (GINA step 4 to step 5)*

#### Patient Profile

This profile concerns the adolescent with poorly or not well-controlled persistent asthma according to a carefully documented history and/or a validated instrument (eTable 2) for at least 2 months or who experienced at least 1 severe asthma exacerbation requiring an OCS or an ED visit or hospitalization while on step 4 therapy in the past year (ie, medium-dose ICS plus LABA; medium-dose ICS plus tiotropium or plus LTRA). Before stepping up therapy it is important to confirm that the increased level of symptoms is due to asthma, as described in the profile for the initial step-up, GINA step 1 to step 2.

A subgroup of patients with severe asthma continue to experience exacerbations, poor symptom control, and/or diminished lung function despite optimal adherence with anti-inflammatory and bronchodilator medications, proper inhaler technique, and treatment of coexisting conditions, and can be categorized as having severe difficult-to-control (or difficult-to-treat) asthma.<sup>1,88–90</sup> Data are limited for adolescents (and children). In the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study, which included school-age children (6–12 years old, n = 770), adolescents (13–17 years old, n = 497), and adults (≥18 years old, n = 3,489), more than 55% of all patients, regardless of age, were symptomatic despite using at least 3 asthma maintenance medications (eg, ICS, LABA, and LTRA)<sup>77,91</sup> (eTable 3). Approximately 40% of adolescents (and 50% of children) reported OCS courses and unscheduled visits despite their regular medications. In the ICAC study identifying characteristics of difficult-to-control asthma in school-age children and adolescents (described in the previous section), approximately 25% of the difficult-to-control subgroup still had asthma that was not controlled at the end of the study year despite good adherence with treatment.<sup>79</sup>

Adolescents who remain symptomatic after a therapeutic trial of step 4 care should be referred to an asthma specialist (if they have not previously been) for evaluation and appropriate treatment.

Continued trials with increasing doses of medication—such as high-dose ICS plus LABA—have been the usual therapeutic paradigm for these adolescents, in similar manner to adults.<sup>1,2</sup> Alternate approaches to high-dose ICS plus LABA include adding tiotropium or switching to (or adding) a small-particle ICS and/or increasing the dose of ICS monotherapy with or without added LTRA, although the latter might not be as successful as high-dose combination treatment,<sup>92</sup> and for some adolescents, switching to a different delivery device might be helpful after assessing technique (Table 3).

For adolescents with severe difficult-to-control asthma, a therapeutic trial of at least 6 months with interval assessment for impairment might be needed. Monitoring potential adverse effects is important when higher doses of ICS are used.

#### Targeted Therapy: Biologics

When asthma remains uncontrolled despite a strategy of multiple medications or if the adolescent is sensitive to increasing the ICS dose, the next step might be to attempt to target treatment according to the underlying pathologic mechanisms.<sup>1,88,89</sup> Identifying the asthma phenotype and then implementing treatment that targets the cellular inflammation in the airway has been shown to provide

clinical benefit for some adults and adolescents with severe difficult-to-control asthma.<sup>1,88,89</sup> This is an area of ongoing research with a number of agents currently being reviewed at the FDA, including for pediatric use.<sup>90–93</sup>

Referral to an appropriate asthma specialist who can evaluate the adolescent for targeted therapy is important.

#### Targeting IgE: omalizumab

#### Patient Profile

This profile concerns the adolescent with moderate-to-severe allergic asthma who has a total serum IgE level of 30 to 700 IU/mL and demonstrates IgE-mediated hypersensitivity by cutaneous or in vitro testing to a perennial allergen (eg, house dust mite, animal dander, cockroach, mold) and who is still symptomatic (eg, poorly or not well-controlled asthma according to a validated instrument; eTable 2) or experiencing exacerbations while taking high doses of anti-inflammatory and reliever medications or who might be sensitive to the adverse effects of higher doses of ICS.

Before stepping up therapy it is important to confirm that the increased level of symptoms is due to asthma, as described in the profile for the initial step-up, GINA step 1 to step 2.

Omalizumab is a humanized monoclonal anti-IgE antibody that inhibits binding of IgE to mast cells and decreases serum levels of free IgE.<sup>94,95</sup> It is FDA approved for children at least 6 years of age with moderate-to-severe asthma. The dose and dosing frequency are determined according to the total serum IgE level (international units per milliliter) determined before starting treatment and bodyweight (kilograms).<sup>94</sup>

A therapeutic trial with omalizumab is recommended for patients with moderate-to-severe allergic asthma for whom other add-on therapies provide inconsistent or incomplete control, particularly those with recurrent severe exacerbations.<sup>1,2,89</sup> It also can be helpful for patients with a history of poor asthma control and poor adherence to ICS and conventional therapies.<sup>96</sup> In studies in adolescents (and children), omalizumab has lowered the frequency of asthma exacerbations, ED visits, hospitalizations, and decreased the need for rescue medications.<sup>97–103</sup> Omalizumab has been studied as part of the ICAC initiative<sup>103</sup>: the Inner-City Anti-IgE Therapy for Asthma (ICATA) study<sup>98</sup> and the subsequent Preventative Omalizumab or Step-up Therapy for Fall Exacerbations (PROSE) study,<sup>104</sup> which are presented in eTable 3.

The PROSE study was conducted to evaluate the association between omalizumab treatment and decrease in seasonal peaks of asthma exacerbations observed in the ICATA data.<sup>98,104</sup> This potential preventive effect of omalizumab was assessed in comparison with regular guideline-based care or increased ICS monotherapy. The study treatments were initiated 4 to 6 weeks before the start of school and continued for 90 days. The fall seasonal exacerbation rate was significantly lower with omalizumab vs placebo, particularly in children with more severe asthma—those who required 500 mg of fluticasone equivalent twice daily (National Heart, Lung, and Blood Institute step 5 therapy or GINA step 4) during run-in and/or those who had at least 1 exacerbation during the same period.<sup>104</sup> Increased peripheral blood eosinophil counts and FeNO levels were associated with exacerbations during run-in, suggesting that these children had higher levels of inflammation despite appropriate guideline-directed treatment.<sup>104,105</sup>

As with all biologics, omalizumab is expensive, and research into specific biomarkers (eg, blood eosinophils, FeNO) and risk factors (eg, rhinovirus infections) is ongoing to better identify patients who

will obtain the greatest benefit from treatment. More information is provided in eCommentary 3.

Long-term studies of up to 3 years in adults,<sup>106,107</sup> adolescents,<sup>98,104,107</sup> and children<sup>98,99,108</sup> have shown omalizumab to be well tolerated, and the improvement in symptoms and lung function to be maintained.

#### Targeting eosinophils: anti–interleukin-5

##### Patient Profile

This profile concerns adolescents who are still symptomatic with poorly or not well-controlled severe asthma according to a carefully documented history and/or a validated instrument (eTable 2) despite treatment with high-dose ICS plus LABA and/or other anti-inflammatory and reliever medications and who have evidence of peripheral blood eosinophilia and frequent exacerbations requiring OCSs.

Before stepping up therapy it is important to confirm that the increased level of symptoms is due to asthma, as described in the profile for the initial step-up, GINA step 1 to step 2.

Treating the eosinophilic asthma phenotype has targeted molecules involved in the activation and recruitment of eosinophils, such as the cytokine interleukin-5 (IL-5). This is described in greater detail in the Adult Asthma Yardstick, including use of the 2 FDA-approved IL-5 antagonist monoclonal antibodies to treat patients with severe asthma, mepolizumab and reslizumab.<sup>109,110</sup> Since publication of the Adult Asthma Yardstick, the anti-IL-5 receptor  $\alpha$  monoclonal antibody, benralizumab, has been approved by the FDA as add-on maintenance therapy for patients with severe eosinophilic asthma.<sup>111</sup> Benralizumab and mepolizumab are approved for adolescent patients as young as 12 years.<sup>109,111</sup>

Mepolizumab is a humanized monoclonal antibody against IL-5, which has been shown to decrease sputum and blood eosinophil counts, usually within 1 month; clinical improvement can take longer.<sup>112–114</sup> It is administered by subcutaneous injection at a standard dose of 100 mg every 4 weeks.<sup>109</sup> Current prescribing parameters require a blood eosinophil threshold of at least 150 cells/ $\mu$ L at treatment initiation or at least 300 cells/ $\mu$ L in the 12 months before treatment initiation. Patients also must have uncontrolled asthma despite receiving maximal standard therapy with a high-dose ICS and at least 1 additional controller medication.<sup>109</sup> Treatment effectiveness is strongly associated with the exacerbation history of the patient and peripheral eosinophil counts. Patients most likely to experience a decrease in exacerbations are those with eosinophil counts of at least 300 cells/ $\mu$ L and at least 2 exacerbations in the past year. Patients who have experienced more exacerbations might respond despite eosinophil levels as low as 150 cells/ $\mu$ L.<sup>109,112–114</sup> For most patients, fewer exacerbations and health care use are indicators of successful treatment. Additional data are warranted because of the limited number of adolescents in the studies; long-term use of mepolizumab in adolescents also is the subject of ongoing clinical trials.

Benralizumab is a humanized, afucosylated anti-IL-5 receptor  $\alpha$  monoclonal antibody that binds to the IL-5 receptor  $\alpha$  on eosinophils, thereby inhibiting their proliferation and activation.<sup>110</sup> Afucosylation of the oligosaccharide core of the antibody enhances binding to the Fc $\gamma$ RIII  $\alpha$  receptor on natural killer cells, macrophages, and neutrophils, which increases antibody-dependent cell-mediated cytotoxicity.<sup>115,116</sup> Indicated for patients with a blood eosinophil level of at least 300 cells/ $\mu$ L, it is administered by subcutaneous injection as a standard 30-mg dose given every 4 weeks for 3 doses and every 8 weeks thereafter.<sup>110</sup> Studies have shown improvements in pulmonary function and quality of life and decreases

in exacerbations.<sup>117,118</sup> However, only a limited number of adolescent subjects were included; additional data are anticipated for this age group.

#### Oral Corticosteroids

The over-prescription of OCSs for asthma is a concern, particularly for adolescents.<sup>119</sup> A short-term course of daily or alternate-day OCSs can be helpful for some adolescents with difficult-to-treat severe asthma, to help gain control while initiating other therapies, including biological therapies, more so than for adults with difficult-to-control asthma.<sup>16</sup> If OCSs are used, the adolescent should be monitored for adverse events (eg, adrenal function, growth, bone density) regularly and switched to other therapies as soon as control is achieved.<sup>2</sup> If an adolescent is receiving OCS as maintenance therapy, the dose should be titrated to the lowest dose that maintains adequate control to prevent asthma exacerbations.

#### Step-Up Therapy for the School-Age Child (6–11 Years Old) with Asthma

##### Step 1: intermittent asthma

Intermittent asthma in school-age children is diagnosed and treated similarly to that in adolescents, as described in that section. Diagnosis is based on the pattern of respiratory symptoms and evaluation of expiratory airflow limitation. Ensuring that the symptoms are due to asthma is important (Table 3). Classification of asthma control for this age group is presented in Table 1B. Validated tools can be helpful; eTable 2 presents those specific for children 4 to 11 years old.<sup>34,35</sup>

The usual treatment for intermittent asthma in school-age children is an as-needed SABA with or without low-dose daily or intermittent ICS<sup>2</sup> (Fig 2A; see Table 4 for ICS dosing).

##### Step-up: intermittent asthma to mild persistent asthma (GINA step 1 to step 2)

##### Patient Profile

This profile concerns the child (6–11 years old) with asthma symptoms or as-needed SABA use more than 2 times a week, but not daily, or who wakes due to asthma more than twice monthly but less than twice weekly. A step-up in treatment can be considered for the child who has infrequent asthma symptoms but is at risk for exacerbations (eg, has had an exacerbation requiring an OCS, ED visit, or hospitalization in the past year). Infrequently, a child can present with no symptoms but abnormal lung function and should be monitored, with any decision to treat based on a risk-benefit discussion among the physician, child, and family.

Before stepping up therapy, it is important to confirm that the increased level of symptoms is due to asthma. The child should be assessed for an age-appropriate understanding of asthma and the management plan in addition to parent and/or caregiver knowledge, nonadherence with the management plan, potential comorbidities, and other factors that might negatively affect the response to therapy (Table 3).

For the 6- to 11-year-old child with persistent but mild symptoms, the preferred controller medication is daily low-dose ICS<sup>2,3</sup> (Fig 2A; Table 4). If the child is already using a low-dose daily ICS or intermittent ICS, increasing the dose or stepping up from intermittent to daily dosing can be considered.<sup>2</sup> Regular use of ICS has been shown to decrease asthma symptoms, improve quality of life, and decrease the risk of exacerbations for most school-age

children with mild persistent asthma.<sup>2</sup> Predictors of a favorable response to ICS include evidence of allergic inflammation (eg, IgE, FeNO, eosinophil cationic protein, personal or family history) and, in some cases, lower pulmonary function.<sup>54–56</sup>

Parents who might be averse to their child using an ICS should be encouraged to ask questions and be educated to the clinical benefits and risk-benefit ratio of using low-dose ICSs. Steroid phobia needs to be addressed early.

### Other Options

The LTRAs are often less effective than an ICS<sup>2,59,120</sup> but can be chosen as initial controller therapy for children who cannot use or prefer to not use an ICS. LTRAs can be helpful for children with concomitant allergic rhinitis, particularly those with high urinary leukotriene E<sub>4</sub> levels, although measurement might not be readily available.<sup>2,54</sup>

A therapeutic trial of 1 to 3 months with interval reassessment of symptoms, daily activities, exacerbations, and lung function is recommended.

*Step-up: mild persistent asthma to moderate persistent asthma (GINA step 2 to step 3)*

#### Patient Profile

This profile concerns the 6- to 11-year-old child with poorly or not well-controlled asthma according to a carefully documented history and/or a validated instrument (eTable 2) for at least 1 month or who experienced at least 2 exacerbations requiring OCS in the past year, despite preferred treatment (low-dose ICS monotherapy) for mild persistent asthma.

Before stepping up therapy it is important to confirm that the increased level of symptoms is due to asthma, as described in the profile for the initial step-up, GINA step 1 to step 2

It is suggested that children 6 to 11 years old be referred to an asthma specialist for assessment and to review other potential problems affecting management before stepping up therapy from step 2 to step 3.<sup>2</sup>

The preferred step-up option for GINA step 2 to step 3 in children 6 to 11 years old is a moderate-dose ICS<sup>2</sup> (Fig 2A; Table 4). However, based on the authors' clinical experience and the efficacy and safety studies described below, low-dose ICS plus LABA can be considered.

Using low-dose ICS plus LABA in this age group is supported by the BADGER study described earlier, which compared adding LABA, LTRA, or more ICS to the therapy of children still symptomatic on low-dose ICS<sup>69</sup> (eTable 3). Overall, more children had a best response to the LABA step-up than to adding a LTRA (52% vs 34%,  $P = .02$ ) or increasing the dose of ICS (52% vs 32%,  $P = .004$ ). Age did not predict response to treatment,<sup>69</sup> although, as described earlier, post hoc analyses (described in eTable 3) suggested that baseline FEV<sub>1</sub>, race and ethnicity, and history of eczema might help predict which therapy to use.<sup>46,69</sup> Additional data are needed to confirm the findings.

A more recent prospective evaluation compared 26 weeks of twice-daily treatment with FP plus salmeterol (100 plus 50 µg twice daily or 250 plus 50 µg) or FP alone (100 or 250 µg) in children 4 to 11 years old who were using daily asthma medications and had a history of exacerbations in the previous year.<sup>66</sup> No between-treatment differences were determined for the primary end point, serious asthma-related adverse events, or secondary end points of asthma control. The findings are similar to the previous study comparing FP plus salmeterol (100 plus 50 µg twice daily) with FP

monotherapy (200 µg twice daily) in children 6 to 16 years of age<sup>71</sup> (eTable 3). In that study, the outcomes were similar between treatments, but efficacy was achieved with a lower dose of FP in the combination arm. No between-treatment differences in growth were observed for the 26-week studies comparing FP plus salmeterol with doubling the FP dose.<sup>66,71</sup>

The results of the BADGER study, which used FP and salmeterol as the ICS and LABA, were similar to a year-long study in school-age children (N = 341, 4–11 years old) that compared budesonide monotherapy (320 µg) with the fixed-dose combination of budesonide and formoterol (80 and 4.5 µg) as maintenance therapy<sup>121</sup> (eTable 3). A third treatment group received the fixed-dose ICS plus LABA as maintenance therapy and as reliever therapy, an approach not approved by the FDA. Using the budesonide plus formoterol combination as maintenance and reliever therapy significantly decreased exacerbations and increased the time to first exacerbation compared with the other treatments. The adjusted mean growth rate was significantly greater (by approximately 1 cm) for children in the ICS plus LABA group compared with the higher-dose budesonide group.<sup>121</sup> In contrast, in children (5–11 years old) with mild-to-moderate persistent asthma using ICS daily, quintupling the dose of ICS at the earliest signs of loss of asthma control did not lower the severe exacerbation rate or improve symptoms and could be associated with decreased linear growth.<sup>122</sup>

The differences in results from these trials warrant longer-term study. However, the outcomes underscore the need for regular and careful monitoring and appropriately adjusting therapy to the child (eTable 3).

### Other Options

The utility of adding a LTRA to the ICS treatment of some children as a step-up was demonstrated in the BADGER trial.<sup>69</sup> Although the switch to ICS plus LABA produced the greatest clinical benefit for the largest proportion of children in the study, some children did best with LTRA added to low-dose ICS, as described in the previous section for adolescents and included in eTable 3.<sup>47,70</sup>

Matched retrospective cohort analyses of school-age children (5–11 years old) from large primary care databases have shown that switching to a small-particle ICS (eg, beclomethasone, mass median aerodynamic diameter 1.1 µm) has potential for clinical benefit based on risk domain measures and exacerbation rates.<sup>50</sup> Compared with doubling the ICS dose of a standard-particle formulation (eg, fluticasone, mass median aerodynamic diameter 2.4–3.2 µm), the odds of the step-up improving asthma control measures were significantly greater for children using the small-particle ICS and comparable to those using a fixed-dose ICS plus LABA combination. This approach has not produced comparable results in adolescents and adults,<sup>72</sup> and safety concerns related to the potential for greater systemic absorption with the smaller particle<sup>73</sup> need to be addressed.

Another option for a step-up in school-age children is to add tiotropium to a low-dose ICS. This strategy was tested in a dose-ranging study of once-daily tiotropium (1.25, 2.5, 5 µg) by soft mist inhaler added to the therapy of children (6–11 years old) who were symptomatic despite treatment with low-dose ICS.<sup>123</sup> All doses significantly improved measures of lung function compared with placebo, and adverse events were similar between treatment groups. Only the 2.5-µg dose is currently FDA approved for asthma in this age group.

A therapeutic trial of up to 3 months with interval reassessment of symptoms, daily activities, exacerbations, and impairment is recommended.

*Step-up: moderate persistent asthma to severe asthma (GINA step 3 to step 4)*

#### Patient Profile

This profile concerns the 6- to 11-year-old child with poorly or not well-controlled asthma according to a carefully documented history and/or a validated instrument (eTable 2) for at least 2 months or who experienced a severe asthma exacerbation requiring OCS or an ED visit or hospitalization in the past year while on step 3 therapy (ie, low-dose ICS plus LABA; medium-dose ICS monotherapy; low-dose ICS plus LTRA). Before stepping up therapy it is important to confirm that the increased level of symptoms is due to asthma, as described in the profile for the initial step-up, GINA step 1 to step 2.

It is recommended that children 6 to 11 years old be referred to an asthma specialist for expert assessment and advice before stepping up therapy from step 3 to step 4.<sup>2</sup>

Medium- to high-dose ICS plus LABA fixed combination, with the ICS dose adjusted to age, is the preferred step-up therapy according to GINA<sup>2</sup> (Fig 2A, Table 4). The recommendation is based on the limited data available for using LABA as add-on treatment to ICS in children 6 to 11 years old and the clinical benefit of combination treatment observed in adolescents (and adults) and described in previous sections. This recommendation differs from NAEP Expert Panel Report 3 guidelines, which date back to 2007 and predate most of the clinical trial results cited earlier, which recommend increasing the ICS dose as the preferred option.<sup>2,3</sup>

The safety of ICS plus LABA was evaluated in children 4 to 11 years of age using a fixed combination of fluticasone plus salmeterol compared with fluticasone monotherapy<sup>66</sup> (eTable 3). No differences were determined for the time to the first severe asthma exacerbation (HR 0.85, 95% CI 0.73–1.01); overall, 265 of 3,107 children (8.5%) in the combination group had a severe exacerbation compared with 309 of 3,101 children (10.0%) treated with fluticasone monotherapy. Similar findings were determined when the data were analyzed separately for the 4- to 6- and 7- to 11-year-old groups.<sup>66</sup> An efficacy subgroup analysis based on treatment and asthma control status at the start of the study showed a lower HR for time to first asthma exacerbation for the ICS plus LABA combination compared with fluticasone monotherapy (HR 0.75, 95% CI 0.57–0.98).<sup>66</sup>

Recently, a FDA review of 4 large clinical safety trials reported that treating asthma with an ICS plus LABA combination did not result in significantly more serious asthma-related side effects than ICS alone; and on December 20, 2017 the FDA removed the boxed warning about asthma-related death from the drug labels of medicines containing an ICS and a LABA.<sup>124</sup> Based on the efficacy and safety data presented, the authors conclude that, given the reassuring data of ICS plus LABA safety in adults, adolescents<sup>67,68</sup> and children,<sup>66</sup> current treatment protocols should be reassessed in future guideline updates. For now, attention to individualizing treatment in patients 6 to 11 years old using the findings of GINA step 4 data in adolescents and adults and GINA step 3 data in children is recommended.

#### Other Options

Children 6 to 11 years of age with uncontrolled asthma (ACQ score  $\geq 1.5$ ) were included in the dose-ranging study of tiotropium (1.25, 2.5, 5  $\mu\text{g}$ ) as add-on therapy to ICS with or without LTRA, described in the previous section (step 2 to step 3).<sup>123</sup> The adjusted mean peak FEV<sub>1</sub> responses with all doses of tiotropium (1.25  $\mu\text{g}$ ;

261 mL; 2.5  $\mu\text{g}$ : 290 mL; 5  $\mu\text{g}$ : 272 mL) were significantly greater than with placebo (185 mL;  $P \leq .001$  for all comparisons) with no differences in adverse effects. A recent study conducted in 400 children 6 to 11 years old with severe symptomatic asthma showed clinical benefit with the addition of once-daily tiotropium added to ICS and at least 1 controller medication.<sup>125</sup> Compared with placebo, significant improvements were observed in peak and trough FEV<sub>1</sub> ( $P < .001$ ,  $P = .01$ , respectively) with the 5- $\mu\text{g}$  dose at 3-hours after dosing, with no between-treatment differences for safety outcomes, although at this time the 5- $\mu\text{g}$  dose is not FDA approved for this age group. These studies are presented in eTable 3.

High-dose ICS plus LTRA is an alternative treatment in school-age children.<sup>2</sup> Using budesonide plus formoterol combination as maintenance and reliever medication at moderate to high ICS dose also can be an option, but this approach has not received FDA approval in the United States.

The desired outcome for school-age children with severe asthma is a decrease in exacerbations and resumption of normal activities. At least 6 months might be needed for a therapeutic trial when exacerbations are the major reason for lack of control.

*Step-up: severe persistent asthma to severe difficult-to-treat asthma (GINA step 4 to step 5)*

#### Patient Profile

This profile concerns the 6- to 11-year-old child with poorly or not well-controlled asthma according to a carefully documented history and/or a validated instrument (eTable 2) for at least 2 months or who experienced a severe asthma exacerbation requiring OCS or an ED visit or hospitalization in the past year while on step 4 therapy (ie, medium-dose ICS plus LABA; medium-dose ICS plus tiotropium with or without LTRA). Before stepping up therapy it is important to confirm that the increased level of symptoms is due to asthma, as described in the profile for the initial step-up, GINA step 1 to step 2.

Children requiring steps 4 and 5 care should be co-managed by a pediatric asthma specialist.<sup>80–82</sup> The initial strategy for stepping up therapy is the same as for adolescents, described earlier—namely adding and/or increasing the doses of medications. This includes:

- A therapeutic trial of higher doses of ICS plus LABA (preferred approach)<sup>2,92</sup>
- Increasing the dose of ICS monotherapy
- Higher doses of the combination of ICS and LTRA
- Adding tiotropium
- Using a small-particle ICS
- Addition of a biologic therapy based on patient characteristics

These approaches have been discussed in the adolescent section.

For these children with severe difficult-to-control asthma, a therapeutic trial of at least 3 to 6 months with interval assessment for impairment might be needed.

#### Targeted Therapy: Biologics

Targeted therapies for severe difficult-to-control asthma have largely been studied in adults and, to some extent, in adolescents as previously described. The monoclonal IgE antibody omalizumab received FDA approval for use in school-age children (6–11 years old) with allergic asthma in July 2016. Referral to an appropriate asthma specialist is important. Other targeted therapies have not yet been approved for use in this age group but are currently under study.

Targeting IgE: Omalizumab

**Patient Profile**

This profile concerns children 6 to 11 years old with moderate-to-severe allergic asthma who have a total serum IgE level of 30 to 1,300 IU/mL and demonstrated IgE-mediated hypersensitivity by cutaneous or in vitro testing to a perennial allergen (eg, house dust mite, animal dander, cockroach, mold) and who are still symptomatic (eg, poorly or not well-controlled asthma according to a validated instrument; eTable 2) or experiencing exacerbations while taking high doses of anti-inflammatory and reliever medications or who might be sensitive to the adverse effects of higher doses of ICS. Before stepping up therapy it is important to confirm that the increased level of symptoms is due to asthma, as described in the profile for the initial step-up GINA, step 1 to step 2.

Initial studies of omalizumab in school-age children showed a corticosteroid-sparing effect concomitant with a decrease in asthma exacerbations. These studies were conducted in children with moderate-to-severe allergic asthma that was well controlled on ICS (168–429 µg/d of beclomethasone dipropionate).<sup>126,127</sup> Approximately 55% of omalizumab-treated children could completely withdraw from their ICS during a 12-week steroid-reduction phase compared with 39% of placebo-treated patients ( $P = .004$ ). The decrease in ICS use was maintained during a 24-week open-label extension phase in which the placebo-treated patients were given omalizumab; during this phase, 81.4% of all patients used no concomitant asthma medication, and 90.8% of patients who had used omalizumab in the initial study and had stopped ICS remained ICS free.<sup>126,127</sup> Follow-up analyses showed improvement in asthma-related quality of life<sup>128</sup> and decreases in IgE and FeNO levels<sup>105,126,127</sup> (eTable 3).

Similar results were subsequently reported for double-blinded, placebo-controlled, prospective studies of school-age children with

allergic asthma uncontrolled on medium-high dose ICS with or without other controller medications.<sup>102,129</sup> Compared with placebo, exacerbations decreased by more than 30% at week 24, with continued improvement throughout the year of treatment.

Sixty percent of children in the ICATA study (described in the adolescent section and eTable 3) were 6 to 12 years old. In these children, as in the adolescents, omalizumab improved asthma control compared with placebo, evident as fewer symptom days and less exacerbations and concomitant with an overall decrease in use of controller medications, including ICS.<sup>98,103</sup> In the PROSE study, described earlier (eTable 3), omalizumab started shortly before the fall return to school produced a decrease in fall seasonal exacerbations, particularly in children receiving higher step controller therapy.<sup>104</sup>

Omalizumab has had pediatric approval in the European Union for more than 7 years, and clinical experience from those countries supports the study data.<sup>99</sup> Adding omalizumab to the treatment of children with severe persistent allergic asthma can diminish the burden of disease by improving asthma control, enhancing quality of life, and decreasing corticosteroid use.<sup>97,108,130</sup> Safety data from studies and real-world experience show omalizumab treatment to be well tolerated in school-age children with allergic asthma.<sup>99,131</sup>

*Step-Up Therapy for the Young Child (≤5 Years Old) with Asthma*

Up to 50% of children experience at least 1 acute episode of wheezing before 6 years of age.<sup>45,132–135</sup> Of these, approximately 30% to 40% have recurrent wheezing<sup>132,134</sup>; and it is estimated that up to 15% will develop asthma, continuing to wheeze beyond 6 years of age.<sup>136,137</sup> Therefore, evaluating wheezing in the young child (Fig 4; Table 2) is very important. Regardless of asthma predictive status, wheezing episodes in young children are associated with increased morbidity and use of health care compared with school-age children.<sup>16</sup> Factors for identifying those children who are most likely to develop asthma remain the subject of current study.

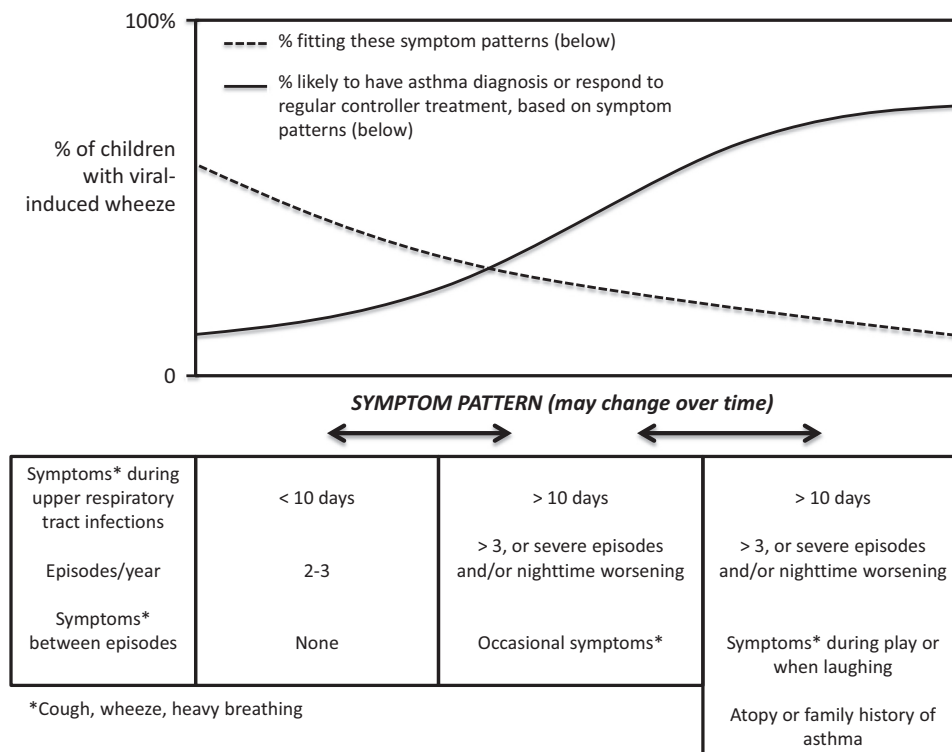


Figure 4. Patterns of symptoms when diagnosing asthma in the young child.<sup>2</sup>



### Step 1: intermittent asthma

Diagnosing asthma in the young child can be challenging, requiring careful observation and monitoring on the part of the clinician and the family. Because routine assessment of airflow limitation is not generally available in this age group, the diagnosis of asthma is largely based on a probability analysis of symptom patterns (Fig 4) and review of family medical history and physical findings<sup>2</sup> (Table 2). The key symptom for diagnosing asthma in this age group is recurrent wheezing (with or without cough), and occurrence during and between respiratory infections and in relation to other triggers should be reviewed. Recurrent wheezing is common in young children, often in relation to upper respiratory tract infections, which in this age group can be frequent—at least 6 to 8 times per year—and with some viral infections occurring throughout childhood (eg, rhinovirus, respiratory syncytial virus); other conditions also produce wheeze and can masquerade as asthma in this age group<sup>2</sup> (Table 2). A careful differential assessment of cause for these episodic symptoms is important. A positive family history of allergic disease or the presence of atopic dermatitis or allergic sensitization can be predictive, because early allergic sensitization to multiple allergens increases the likelihood that a wheezing child will develop persistent asthma.<sup>2,3,133,138,139</sup> The Asthma Predictive Index (API) and modified API (mAPI) are validated measures that have shown good correlation with likelihood of developing asthma in the young child; positive scores have been associated with risk of persistent wheeze<sup>140–142</sup> (see eCommentary 4 for more description). Recent analyses of multiple cohorts have highlighted the role of timing of sensitization and other risk factors, and ongoing efforts are focused on how best to target risk and potentially prevent the progression from intermittent wheeze to persistent asthma.<sup>137,143–147</sup>

Respiratory symptoms during early childhood often change, so when asthma is suspected or diagnosed, regular reassessment of symptoms (eg, every 2–3 months) is important.

For diagnosis, younger children present additional challenges for treatment. Although the goals of managing asthma in young children are similar to those for older children and adults, maintaining normal activity and play levels is particularly important for social and physical development. Recognizing and incorporating the goals of parents and caregiver also is important.<sup>2</sup>

Young children might require different considerations as to what medications to use and how to deliver them. There are no studies that directly compare different drug delivery systems in this age group. The following recommendations are based on published current guidance and the authors' expert opinion.

First, the initial treatment of any wheezing episode is an inhaled SABA, administered every 4–6 hours as needed for at least 1 day until symptoms disappear. This treatment should be administered regardless of whether the diagnosis of asthma has been made<sup>2</sup> (Fig 2B).

Second, choices for preschool children with intermittent asthma symptoms or episodic virus-induced wheezing and a positive mAPI score include pre-emptive high-dose episodic ICS or LTRA. These approaches can lessen intermittent symptoms of asthma and decrease cumulative corticosteroid exposure.<sup>45,135</sup> Intermittent ICS also can lessen the risk of severe exacerbations.<sup>29</sup>

Seven days of budesonide inhalation suspension (1 mg twice daily) or montelukast (4 mg daily) given in addition to albuterol at the first sign of symptoms associated with respiratory tract illness significantly improved indicators of severe acute illness (eg, trouble breathing, decrease in activities) compared with conventional therapy in young children (1–5 years old) with moderate-to-severe intermittent wheezing.<sup>148</sup> Positive response to treatment was associated with a history of an asthma exacerbation requiring OCS in the prior year and/or a positive mAPI score.<sup>58</sup> Neither treat-

ment affected other outcome measures (eg, OCS rescue, urgent care visits, ED visits, hospitalizations).

The effect of intermittent vs conventional daily treatment with budesonide inhalation suspension was subsequently studied in 278 children (12–53 months old) with recurrent wheezing, positive mAPI score, and at least 1 asthma or wheezing exacerbation in the prior year and infrequent impairment.<sup>149</sup> The children received treatment over the course of a year: intermittent treatment, 1 mg of budesonide nebulization twice daily for 7 days, starting early during a predefined respiratory tract illness, vs daily budesonide nebulization treatment using 0.5 mg nightly throughout the year. The treatments were comparable in decreasing the frequency and severity of exacerbations, but the intermittent protocol decreased total exposure to budesonide by approximately 100 mg over the 1-year period.<sup>149</sup>

Third, the findings of differential clinical benefit to treatment in young children have contributed to the recent emphasis on a phenotype-based approach to managing preschool children with recurrent wheezing. (Fig 5).<sup>45,135</sup> In addition to mAPI status and wheezing severity, parental history of asthma and eczema can be assessed to identify potential involvement of a T2 inflammatory pathway and help with decision making.<sup>29,140,150</sup>

For children with a positive mAPI score and uncontrolled respiratory symptoms or frequent wheezing episodes ( $\geq 3$ /season) or those with a family or personal history of atopy and/or aeroallergen sensitization, a trial of daily low-dose ICS is recommended (Fig 5; see Table 4 for ICS dosing), with evaluation of response to therapy after 2 to 3 months or sooner if necessary.<sup>2,29,45,135</sup>

Fourth, for preschool children who have recurrent severe wheezing with lower respiratory tract illnesses, a therapeutic trial of azithromycin early in the course of the illness could be helpful to prevent symptom progression to the level requiring OCS<sup>45,135,151</sup> (Fig 5). It is notable that this therapy was comparably effective in children with positive and negative mAPI scores. If wheezing is decreased with a trial of azithromycin, then this approach is reasonable and can be considered for subsequent illnesses in these children.<sup>2,45</sup>

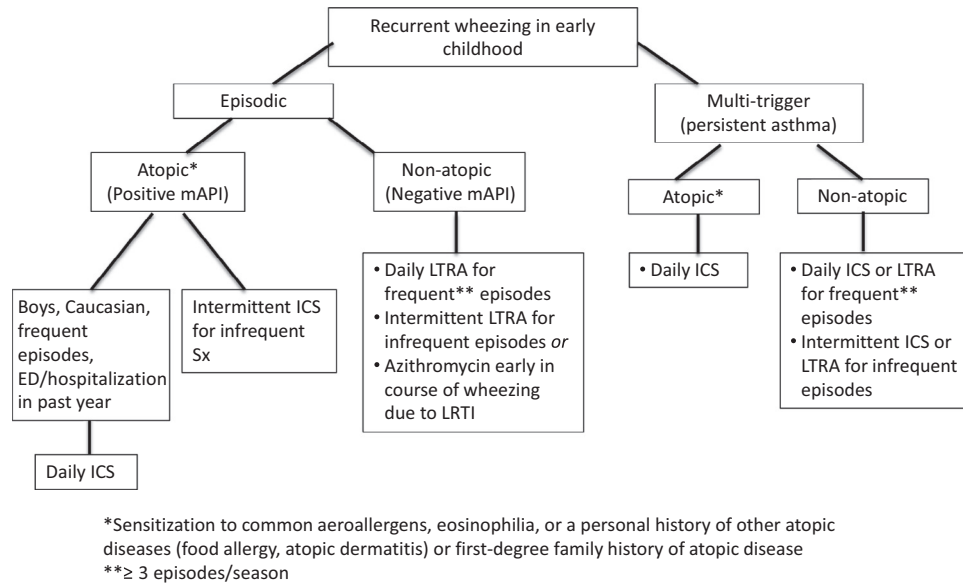
Fifth, choosing an inhalation device to deliver ICSs with or without bronchodilators should be based on the child's age, capability, and family preference. There are advantages and disadvantages with nebulizers and pressurized metered-dose inhalers and valved holding chambers with facemask for children younger than 4 years and mouthpiece for those who are older<sup>49</sup> (Table 5). Nebulizer and metered-dose inhaler delivery have been used in clinical trials demonstrating efficacy of ICS in young children.

Sixth, frequent reassessment (1–3 months) is necessary because asthma-like symptoms remit in some young children. Recommendations are lacking for the frequency of reassessing management, but hospitalizations, urgent care visits, and need for short courses of OCSs should prompt an early follow-up. The 5-item TRACK questionnaire can help parents evaluate the level of control of respiratory symptoms in their young child<sup>40,41</sup> (eTable 2). A change in score of at least 10 points suggests the need to re-evaluate the child's treatment.

Seventh, the parents and caregiver should be included in treatment decisions; their involvement is critical for management success. They need to understand the relative benefits and risks of the treatments and the importance of maintaining normal sleep and activity levels for their child's physical and social development.<sup>2,3</sup>

Parents can have concerns about the effects of ICS on growth and should be reassured that the benefits of treatment outweigh the risks. Poorly controlled asthma adversely affects growth and adult height. For more information, the reader is directed to current guidelines.<sup>2,3</sup>

Referral to a pediatric asthma specialist is suggested at the lower steps and strongly recommended at the higher steps before adjusting therapy.



**Figure 5.** Strategies to evaluate and treat recurrent wheezing in young children.<sup>45,135</sup> ED, emergency department; ICS, inhaled corticosteroid; LRTI, lower respiratory tract infection; LTRA, leukotriene receptor antagonist; mAPI, modified Asthma Predictive Index; OCS, oral corticosteroid; Sx, symptoms.

**Table 5**  
 Considerations When Using Aerosol Delivery Devices in Children

	Nebulizer	pMDI + spacer	DPI
General considerations <sup>47</sup>			
Advantages	<ul style="list-style-type: none"> <li>patient coordination not required</li> <li>effective with tidal breathing</li> <li>potential to administer multiple medications</li> <li>dose modification possible</li> </ul>	<ul style="list-style-type: none"> <li>portable and compact</li> <li>can be used quickly</li> <li>possible lower cost</li> <li>no drug preparation</li> <li>MDI with breath-actuated mouthpiece requires less patient coordination</li> </ul>	<ul style="list-style-type: none"> <li>portable and compact</li> <li>can be used quickly</li> <li>no drug preparation</li> <li>breath actuated, requires less patient coordination</li> <li>no need for propellant</li> </ul>
Disadvantages	<ul style="list-style-type: none"> <li>lack of portability</li> <li>lengthy treatment times</li> <li>some medications might not be available in appropriate formulation</li> <li>variability of performance</li> <li>efficiency</li> <li>facemask must fit properly—unless the nebulizer mist is entrained, the therapeutic effect might not be adequate</li> <li>less efficient</li> <li>more expensive</li> </ul>	<ul style="list-style-type: none"> <li>need to coordinate actuation and inhalation</li> <li>potential for high pharyngeal deposition</li> </ul>	<ul style="list-style-type: none"> <li>loss of dose if patient exhales back into device</li> <li>potential for high pharyngeal deposition</li> </ul>
Recommendations for children and infants (courtesy Anne M. Fitzpatrick, PhD)			
Infants (<2 y old)	most reliable, easy to use	masks required, unpredictable	never appropriate
Preschool (2–5 y old)	effective and efficient with breath-enhanced mouthpiece	can work, requires practice	not appropriate
School age (>5 y old)	effective and efficient with breath-enhanced mouthpiece	results less predictable	easy to use
		effective, requires practice	deposition varies by device
		could be less predictable	

Abbreviations: DPI, dry powder inhaler; pMDI, pressurized metered-dose inhaler.

*Step-up: intermittent asthma to mild persistent asthma (GINA step 1 to step 2)***Patient Profile**

This profile concerns the child no older than 5 years with wheezing (with or without coughing) more than twice a week or who wakes up due to wheezing at least once a month and/or has a TRACK score at least 10 points lower than previously determined (eTable 2) or at least 2 exacerbations requiring OCS, urgent care, or hospitalizations in the past year despite using as-needed (intermittent) ICS or LTRA (given at same time as as-needed SABA).

The child should be assessed for nonadherence with the management plan, potential comorbidities, and other factors that might negatively affect response to therapy including parent and/or caregiver understanding of asthma and its management (Table 3).

Daily low-dose ICS is the preferred initial treatment for persistent asthma in most young children (<5 years old) with asthma symptoms and recurrent wheezing episodes for whom step 2 treatment is warranted.<sup>2,3</sup> However, there is considerable phenotypic heterogeneity in symptoms and response to treatment in this age group, and some children might respond well to regular treatment with a LTRA or to as-needed treatment with an ICS (given at the same time as as-needed albuterol).<sup>45,135</sup> This was demonstrated in the Individualized Therapy for Asthma in Toddlers (INFANT) study (eTable 3), which evaluated these 3 approaches in preschool children (12–59 months old) using a crossover design of 16 weeks for each.<sup>29</sup> Outcomes were assessed in relation to OCS use in the previous year, sex, and evidence of aeroallergen sensitivity at baseline. Overall, daily ICS was associated with more asthma control days and less risk of exacerbation than the other 2 therapies, and the likelihood of positive outcomes for this approach increased with indicators of T2 type inflammation (aeroallergen sensitization and/or blood eosinophil level  $\geq 300 \mu\text{L}$ ). However, other children had a best response to LTRA or to as-needed ICS.<sup>29,45</sup> Reviews of the use of ICS in young children with recurrent wheezing support the role of atopy and family history of atopy as predictors of a favorable response.<sup>45,58,135,147</sup>

Treatment was further differentiated according to the nature of the child's wheezing episodes—intermittent ICS (given at the same time as as-needed SABA) provided clinical benefit for some children with episodic wheeze, whereas children with multi-trigger wheeze were more likely to do well on daily ICS.<sup>29</sup>

The selection of medication and how it is administered in this age group should be carefully reviewed and monitored. There is no universal approach. More data are needed on treatment decision making in relation to phenotypic characteristics and likelihood of benefit.

**Other Options**

Young children with frequent viral-induced wheezing but who have asthma symptoms between infections might be able to use the episodic high-dose ICS approach described in the previous section (step 1) to prevent exacerbations.<sup>2,58,148</sup> High-dose budesonide (1 mg twice daily) given for 7 days starting at the outset of a pre-defined respiratory tract illness showed similar efficacy to daily low-dose budesonide (0.5 mg given once daily in the evening) in decreasing the frequency of exacerbations requiring OCS, but over time decreased corticosteroid exposure.<sup>149</sup>

The use of daily ICS could be particularly important for young children to lower risk, because it is clear that:

1. Chronic airway inflammation exists even in patients with infrequent symptoms and in newly diagnosed patients.<sup>2</sup>
2. Treatment with regular low-dose ICS can lessen asthma-related exacerbations, including severe events requiring hospitalization.<sup>2</sup>

How much ICS is necessary to counter the adverse effects of ongoing respiratory inflammation is not clear. Although the efficacy of using episodic ICS was demonstrated in 2 1-year clinical trials, that treatment was given specifically in response to the onset of a respiratory tract illness, and not year-round on a regular basis.<sup>148,149</sup> Treatment of the young child should be individualized according to presentation with regard to the frequency and severity of symptoms and parental perception. Long-term regular and consistent follow-up is critical in this age group. Early, frequent, and severe symptoms should be a red flag for closer supervision and follow-up.

*Step-up: mild persistent asthma to moderate persistent asthma (GINA step 2 to step 3)***Patient Profile**

This profile concerns the child no older than 5 years who remains symptomatic (eg, wheezing with or without coughing more than twice a week or who wakes up from wheezing  $\geq 1$  time a month) after 3 months of treatment with a daily low-dose ICS, who has a TRACK score that has decreased at least 10 points (eTable 2), and/or has experienced at least 2 exacerbations requiring OCS or ED visit or hospitalization in the past year.

Before stepping up therapy, the young child should be assessed for nonadherence, potential comorbidities, and other factors that might negatively affect response to therapy, as described in the profile for the initial step-up, GINA step 1 to step 2.

The preferred option for the young child needing a step-up from mild persistent to moderate asthma is to double the initial low-dose ICS<sup>2</sup> (Table 4).

Although data are very limited, the option of increasing the ICS dose in a young child (or infant) is supported by a few older studies that have shown small improvements in some outcomes for some patients by increasing the dose of FP delivered by the BabyHALER Spacer Device (GlaxoSmithKline, Mississauga, Ontario, Canada)<sup>152</sup> or budesonide inhalation suspension<sup>153</sup>; other studies have not shown similar incremental increases in efficacy with dose.<sup>154</sup> The differences in achieving symptom control in these studies suggest that dose requirements for young children should be individually and carefully titrated. Further comparisons are difficult because of different age groups and study design.

**Other Options**

The addition of LTRA to low-dose ICS is an alternative to increasing the dose of ICS.<sup>2,3</sup> There are no published data supporting this approach in this age group; its consideration is based on the approval of LTRA for this age group and extrapolation from studies, including the BADGER study in older children<sup>69</sup> (eTable 3).

Low-dose ICS plus LABA is not recommended as step 3 therapy for children younger than 5 years.<sup>2,3</sup> However, the prospective evaluation of adding salmeterol to FP in children with asthma (described earlier; also see eTable 3) included some patients as young as 4 years.<sup>66</sup> A sub-analysis of the 4- to 6-year-old group, like the data overall, showed no between-treatment differences.

Step-up: moderate persistent asthma to severe asthma (GINA step 3 to step 4)

#### Patient Profile

This profile concerns the young child who is symptomatic (eg, wheezing with or without coughing throughout most days or who wakes up due to wheezing  $\geq 1$  time a week) and/or who has a decrease in TRACK score of at least 10 points (eTable 2) after 3 months of treatment for moderate persistent asthma (ie, double low-dose ICS with or without LTRA) and/or whose daily activity is limited by symptoms and/or who has experienced at least 3 exacerbations requiring OCS or ED visit or hospitalization in the past year.

Before stepping up therapy, the patient should be assessed for nonadherence, potential comorbidities, and other factors that might negatively affect response to therapy, as described in the profile for the initial step-up, GINA step 1 to step 2.

Treating preschool children with uncontrolled moderate-to-severe asthma presents clinical challenges. These children frequently present with more severe intermittent and episodic disease than with continuous or persistent severe illness.<sup>8</sup> Furthermore, GINA step 4 care has not been studied in clinical trials in young children with asthma. The absence of credible data to support specific GINA step 4 treatment in preschool children presents a major clinical challenge. As such, recommendations are extrapolated from those used for children 6 to 11 years of age, while recognizing the limitation.

Many illnesses masquerade as asthma in the young child with recurrent wheezing and respiratory symptoms (Table 2), so it is paramount that great effort is extended to ensure that asthma is not misdiagnosed in this age group, which is further complicated by the difficulty of obtaining useful lung function in young children in the clinical setting.

Increasing the ICS dose for at least 3 months could help to gain better asthma control in the young child.<sup>2</sup> For children using a metered-dose inhaler with spacer and facemask, a trial of nebulized budesonide might be considered.<sup>152</sup> Once control is gained, it might be possible to lower the ICS dose with or without adding other treatment options (eg, LTRA). Optimizing ICS use is essential to ensure that the lowest dose is used (Table 4) and that inappropriate dosing is avoided; adverse steroid effects can be particularly detrimental at this age.<sup>48,155</sup>

The addition of a LTRA to medium-dose ICS could be helpful. The LTRA montelukast is indicated for children with asthma as young as 12 months.<sup>156</sup> A trial of montelukast with medium-dose ICS might be an option for some patients.

Although FP plus salmeterol (100  $\mu\text{g}$  plus 50  $\mu\text{g}$ ) dry powder is approved for 4 years of age,<sup>157</sup> other doses and ICS plus LABA combination agents are not approved for use in this age group. FP plus salmeterol in fixed combination (with FP daily doses of 200 and 500  $\mu\text{g}$  divided twice daily) compared with FP monotherapy has been studied in children 4 to 11 years old ( $N = 6,208$ ) as described earlier.<sup>66</sup> (eTable 3). Approximately one-third of children were 4 to 6 years of age. The risk of serious asthma-related events was comparable for the combination therapy and the monotherapy, with incidences of 0.9% and 0.7%, respectively, and no asthma-related deaths or intubations in any group.<sup>66</sup> The safety results are similar to data reported for adults and adolescents<sup>67</sup> and provide some reassurance of the safety of LABAs used in fixed combination with ICS in the treatment of persistent asthma in children as young as 4 years. Using a fixed-dose combination might provide some added flexibility for young children with difficult-to-control disease (step 4 and beyond). Prospective studies are needed to confirm the clinical value of this approach in younger children.

## Discussion

Children and adolescents have different needs than adults when it comes to identifying and managing poorly controlled asthma. The patient profiles presented in the Pediatric Asthma Yardstick (and summarized in Fig 1) are based on current guidelines and clinical experience, but gaps exist.

- Managing asthma in children is evolving in relation to heterogeneity of response. Treating by phenotype is becoming the new care model.

Although monotherapy with low-dose ICS remains the initial recommendation for a sustained step-up for most children diagnosed with mild persistent asthma in the United States, intermittent use of ICS has been suggested as an alternative for some.<sup>2</sup> Similarly, although the preferred step-up from mild persistent asthma to moderate persistent asthma is adding a LABA to an ICS, some children do better with increasing the dose of ICS or adding a LTRA.<sup>2</sup> Predictors of a positive response to either step-up likely reflect an interplay among genetic background, immunopathology, and early environmental exposures.<sup>16,29,47,58,69,70,135</sup> Studies are ongoing to better understand the differences for determining potential “best” treatments.

However, it should not be inferred that a particular therapy will be ineffective if the child does not meet specific characteristic(s); rather, if 1 treatment within a given step is not effective, another therapy within the step should be tried before stepping up to a higher level.<sup>29,44,54,69,70,120,149</sup>

By limiting therapies to those who are more likely to respond, treating by phenotype should allow better personalization of care, leading to improved clinical outcomes, fewer adverse effects, and, possibly, lower costs.

- For children with persistent asthma who can perform spirometry, monitoring lung function on at least a yearly basis is recommended to identify those at risk for adverse adult outcomes, including chronic irreversible loss in pulmonary function.

Most children with asthma show abnormal patterns of lung growth and have evidence of diminished lung growth by early adulthood.<sup>10,14</sup> More data are needed regarding whether earlier identification of the child with asthma and more aggressive and targeted intervention, including after spirometry as early as possible and then over the long-term as part of risk assessment, might help slow the decline in lung function and deterioration into fixed airway obstruction. More detail is provided in eCommentary 1.

- Strategies to assist in identifying the child with a loss of, or ongoing poor, asthma control are needed. Electronic monitoring could be helpful.

Continued symptoms, night-time sleep disturbance, and exacerbations despite optimal medication use suggest a need to re-evaluate the child’s treatment plan. Most strategies rely to some extent on self-reporting using different tools available for patients, with various degrees of accuracy. Despite increasing symptoms, the patient (or caregiver) might not recognize the need for attention. Electronic monitoring of SABA rescue has been proposed as another way to obtain real-time feedback for intervention, possibly helping to identify the onset of uncontrolled asthma, even when the child (or parent or caregiver) does not recognize the increase in symptoms.<sup>158–161</sup>

What is meant by good asthma control and how to achieve it require regular discussion and agreement among the child patient, family, and clinician. The Pediatric Asthma Yardstick provides a prac-

tical resource to help manage these patients who bear a significant burden of the disease and whose care challenges current understanding of asthma because of its variable presentation within individuals and within the population of children affected. Improving asthma management for children can lead to better outcomes as they become adults.

### Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.anai.2018.04.002>.

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## Supplementary Data

### eCommentary 1

#### *Lung Health with Age and Impact on Asthma Therapy in Children*

The physiologic characteristics of the healthy human lung change with age, and these changes significantly affect the phenotypic features of asthma and response to treatment. Lung function volume indicators measured by spirometric change during normal development (summarized in Table 1). The FEV<sub>1</sub> and forced vital capacity increase during childhood, peak by 20 to 25 years of age, and then decrease during adulthood.<sup>e1</sup> However, 75% of children with asthma have abnormal lung growth patterns.<sup>e2</sup> With severe disease, chronic airflow limitation is common and is defined by a ratio of FEV<sub>1</sub> to forced vital capacity lower than normal.<sup>e3</sup> Airflow limitation, when identified at school age, commonly persists through adolescence and into adulthood.<sup>e4,e5</sup> Although most children with asthma have normal lung function between exacerbations, in children with severe asthma and airflow limitation, even treatment with a systemic corticosteroid might not improve FEV<sub>1</sub> when given at a time of disease stability.<sup>e6</sup> No current therapy, including anti-leukotrienes, corticosteroids, or biological agents, has been shown to prevent or interrupt the enhanced age-dependent decrease in FEV<sub>1</sub> that is a feature of childhood asthma.

Forced expiratory flow between 25% and 75% has been suggested as a possibly more sensitive predictor of lack of asthma control compared with FEV<sub>1</sub>. However, although it is a measure associated with symptoms, its utility as a predictor of loss of control or improved control is limited.<sup>e7</sup>

Bronchial hyperresponsiveness (BHR), the tendency of the airways to constrict in response to a range of provocative stimuli, is a cardinal feature of asthma. BHR decreases with age in healthy children.<sup>e8</sup> In children with asthma, BHR likewise decreases significantly across puberty, more so in boys than in girls.<sup>e9</sup> Increased bronchodilator responsiveness (BDR), the change in FEV<sub>1</sub> from baseline after albuterol, is an important feature of asthma. Although a 12% increase in FEV<sub>1</sub> is generally considered a positive test result, many children, particularly those with normal pre-albuterol FEV<sub>1</sub>, do not demonstrate BDR. BDR decreases with age, is greater in severe than in nonsevere asthma, and loss of BDR with maturation strongly correlates with the development of chronic airflow limitation.<sup>e3</sup>

Other age-dependent changes in respiratory system physiology can affect response to asthma treatment and should be considered before a long-term treatment change. Static lung compliance, measured in the absence of flow, is relatively stable with age.<sup>e10</sup> In contrast, chest wall compliance is relatively high in preschool children and decreases significantly with maturation.<sup>e11</sup> The fact that lung compliance is lower than chest wall compliance in young children contributes to chest wall distortion manifested by retractions with episodes of wheeze. Dynamic lung compliance, measured during tidal breathing, decreases when measured at rapid breathing frequencies and is a valid test of small airway obstruction in patients with asthma.<sup>e12</sup> Specific respiratory resistance, airway resistance during tidal breathing normalized for functional residual capacity, increases with age, and the trajectory of this increase is greater in school-age children with asthma compared with healthy children.<sup>e13</sup> Although resistance of the peripheral airways contributes relatively little to the overall flow resistance of the lung, the peripheral airways account for a large surface area involved in respiratory gas exchange. Peripheral airway resistance decreases from preschool to school age<sup>e14</sup> and is increased in adults with asthma.<sup>e15</sup>

The distribution of ventilation in the developing lung is governed in part by flow resistance of the branching airways and regional elastic recoil forces. In asthma the distribution of flow resistance in the respiratory tree is heterogeneous and promotes maldistribution of ventilation. Large nonventilated lung regions are

visible as ventilation defects on inhaled hyperpolarized helium-3 magnetic resonance images and are common in asthma.<sup>e16</sup> Children with severe asthma have greater nonventilated and poorly ventilated lung volume compartments compared with children with nonsevere asthma. Ventilation heterogeneity in the peripheral airways also can be measured with forced oscillometry as the difference in total respiratory resistance measured at 5 Hz minus large airway resistance at 20 Hz. Children with asthma and poor symptom control have greater ventilation heterogeneity measured with this technique compared with children with controlled asthma.<sup>e17</sup> Multiple breath nitrogen washout is a third method that can be used to measure ventilation heterogeneity using the lung clearance index, a metric that is abnormally high in children with asthma even with normal lung function and few symptoms.<sup>e18</sup>

*Age-dependent considerations for medication delivery devices* The physiologic features of the developing respiratory system determine the optimal selection of delivery devices to administer inhaled medication. Deposition of inhaled particles including medications in the distal lung is affected by inspiratory flow velocity and particle size.<sup>e19</sup> Young preschool children are at a particular disadvantage because they might not be able to follow instructions to take a deep, slow breath so that relatively more medication affects the oropharynx.<sup>e20</sup> For this reason jet nebulizers are commonly used in this age group, with the relative advantages of being effective with tidal breathing, not requiring a tight seal, and being used confidently in the face of respiratory distress.<sup>e19,e20</sup> Disadvantages of nebulized medications include lack of portability, prolonged administration time, and generation of relatively large medication droplets by standard nebulizers for home use, thereby decreasing deposition in the peripheral lung zones.<sup>e19</sup>

Metered-dose inhalers with hydrofluoroalkane propellant are widely used to administer corticosteroids in suspension or in solution. A significant advantage of solution formulations is the ultrafine particle size with enhanced penetrability compared with ICS in suspension. In the latter, the particle size is relatively coarse, resulting in greater deposition in the oropharynx.<sup>e19</sup> However, currently there are no comparative clinical trials that conclusively show greater benefit of fine-particle vs coarse-particle ICS in attaining asthma control in children. Another important factor when selecting therapy is the biological potency of the corticosteroid molecule, which varies considerably among available products. Table 4 presents relative dosing thresholds for children at different age levels, which are based not on biological potency but on reported adverse effects profiles for consideration.

The use of a mask and spacers or spacers alone (also termed valved holding chambers) to enhance the delivery of ICS is strongly advised in most treatment guidelines for children.<sup>e20,e21</sup> The selection of a mask with a spacer or a spacer with a mouthpiece is based on the age of the child, developmental level, and confidence of the parent. Newer formulations including dry powder inhalers to deliver ICS and reliever therapies are available for use in children. The advantage of these systems is ease of use and portability, but clinicians should be aware that the particle deposition from these devices is dependent on a relatively higher inspiratory flow velocity.<sup>e19</sup> Thus, they might not be suitable for young children who cannot generate the necessary inspiratory flow or for children who have difficulty following instructions. In addition, and especially for younger children, parent and caregiver understanding of the inhalation device and how it should be used is important for successful treatment.<sup>e20</sup>

### eCommentary 2

#### *Methods*

The authors reviewed the current evidence for various FDA-approved treatment options identified by the most recent



guidelines<sup>e20,e21</sup> according to age (adolescence, 12–18 years old; school age, 5–11 years old; young, <5 years old) and the type of step-up (mild persistent asthma to moderate persistent asthma, GINA step 2 to step 3; moderate persistent asthma to severe persistent asthma, GINA step 3 to steps 4 and 5). Newer data and potential treatment options not yet described in the guidelines also were evaluated when appropriate. The evidence was not graded, except as graded for the guidance documents. For the initial draft, the authors worked on sections as follows: GINA step 1 to step 2: Dr Szefer and Dr Bacharier; GINA step 2 to step 3: Dr Murphy and Dr Jackson; children with severe and difficult-to-treat disease: Dr Zeiger and Dr Phipatanakul; and lung development and implications for drug delivery: Dr Teague. Patient profiles were created as practical points of reference for the reader, and the associated flow diagrams (Fig 1) provide the authors' concept for a "best practice summary" of the available strategies for increasing and/or modifying therapy according to the child's asthma severity and level of disease control. All authors reviewed and provided appropriate revisions to the manuscript in development, and all gave written approval to the final document. It is anticipated that, like the guidelines, the Pediatric Asthma Yardstick will be updated on a regular basis according to new research findings.

### eCommentary 3

#### Identifying Biomarkers for Omalizumab Success

The EXTRA trial, a prospective, multicenter, randomized, double-blinded, placebo-controlled study that included adolescents and adults with uncontrolled severe persistent asthma, reported significant decreases in exacerbation rates with omalizumab treatment compared with placebo (incidence rate: omalizumab 0.66; placebo 0.88).<sup>e22</sup> Post hoc analyses divided the 850 enrolled subjects into groups with high and low T<sub>H</sub>2, with the latter further defined by the baseline levels of several biomarkers associated with T<sub>H</sub>2-driven inflammation, including blood eosinophil count of at least 260/ $\mu$ L and FeNO of at least 24 ppb.<sup>e23</sup> After 48 weeks of treatment, the high T<sub>H</sub>2 group demonstrated significant decreases of exacerbations compared with the low T<sub>H</sub>2 group (FeNO 53% vs 16%; eosinophils 32% vs 9%), supporting the use of these biomarkers for predicting response.

Other attempts to delineate potential patient characteristics for successful outcomes with omalizumab included studies of comorbid conditions that can exacerbate allergic asthma, such as concomitant rhinosinusitis and nasal polyyps. Rhinovirus (RV) and serum IgE are associated with acute asthma exacerbation severity in children,<sup>e24</sup> and treatment with omalizumab has been shown to lessen the severity of RV-induced exacerbations<sup>e25</sup> and to decrease the duration of RV infections, viral shedding, and risk of RV illnesses.<sup>e26</sup> Ex vivo analysis of peripheral blood mononuclear cells from a subset of children in the pre-seasonal omalizumab study<sup>e27</sup> showed that omalizumab enhanced the interferon- $\alpha$  response to RV. Children treated with omalizumab who had greater increases in interferon- $\alpha$  levels had fewer exacerbations (odds ratio 0.14; 95% CI 0.01–0.88). Additional studies are needed to confirm the findings.

### eCommentary 4

#### The Asthma Predictive Index and Modified Asthma Predictive Index

The API and the mAPI are tools to help clinicians identify young children at high risk for developing asthma.<sup>e28</sup> The primary criteria for the indices reflect wheezing episodes in the young child; the secondary criteria include diagnosis or likelihood of allergic disease.

Index	Primary criteria	Secondary criteria	
		Major ( $\geq 1$ )	Minor ( $\geq 2$ )
API	early frequent "wheezing" (parent classification $\geq 3$ on 1–5 scale)	parental history of asthma physician-diagnosed atopic dermatitis	physician-diagnosed allergic rhinitis wheezing unrelated to colds blood eosinophils $\geq 4\%$
mAPI	$\geq 4$ wheezing episodes/y	parental history of asthma physician-diagnosed atopic dermatitis allergic sensitization to $\geq 1$ aeroallergen	allergic sensitization to milk, egg, or peanuts wheezing unrelated to colds blood eosinophils $\geq 4\%$

Abbreviations: API, Asthma Predictive Index; mAPI, modified Asthma Predictive Index.

The API was first used in the Tucson Children's Respiratory Study, which evaluated the characteristics of a general cohort of 1,246 infants in an attempt to "predict" the occurrence of asthma at 6, 8, 11, and 13 years of age, based on questionnaire data from toddlers (2–3 years old).<sup>e29–e31</sup> The positive likelihood ratio and negative likelihood ratio for asthma diagnosis at 6 years were 7.4 and 0.75, respectively. Following the children showed a strong correlation between a positive ratio and probability of future asthma at school age and persisting beyond school age; the correlation between a negative score and decreased probability of future asthma expression was not as substantial.<sup>e29,e30</sup>

The mAPI uses more objective criteria than the API. For example, wheezing episodes are quantified by number rather than subjective scoring, and allergen sensitization is determined by IgE levels or skin prick testing.<sup>e32</sup> The diagnostic utility of the mAPI was prospectively demonstrated in a high-risk asthma cohort of toddlers (1–3 years old) for asthma diagnosis at 6, 8, and 11 years of age.<sup>e28</sup> A positive mAPI score was associated with an increased probability of future asthma risk, whereas a negative score was associated with a small decrease in future asthma probability.

The API and mAPI are easily applied in the clinical setting.<sup>e28,e32,e33</sup> A separate index developed from the mAPI, the m<sup>2</sup>API, requires 2 instead of 4 wheezing episodes in the course of a year for a positive test result, thereby shortening the wait before clinical decision making.<sup>e28</sup> However, the m<sup>2</sup>API has shown less correlation with future asthma risk than the mAPI.

Regardless of instrument and outcome, subsequent clinical decision making should involve further monitoring alone or with the addition, or modification, of therapy, as described in the text.

**eTable 1**  
Assessing Asthma Control by Impairment and Risk (Adapted From National Asthma Education and Prevention Program, 2007)<sup>e21</sup>

Components of control		Classification of asthma control		
		Well controlled	Not well controlled	Very poorly controlled
<b>A. Children ≥12 y old (and adults)</b>				
Impairment	symptoms	≤2 d/wk	>2 d/wk	throughout day
	night-time awakenings	≤2 × /mo	1–3 × /wk	≥4 × /wk
Risk	interference with normal activities	none	some limitation	extremely limited
	using SABA for symptoms (not prevention of EIB)	≤2 d/wk	>2 d/wk	several times daily
	FEV <sub>1</sub> or PEF	>80% predicted or personal best	60–80% predicted or personal best	<60% predicted or personal best
	validated questionnaires			
	ACT	≥20	16–19	≤15
	ACQ	≤0.75	≥1.5	N/A
	ATAQ	0	1–2	3–4
	exacerbations requiring OCS	≤1/y	≥2/y	
	progressive loss of lung function	long-term follow-up required		
	treatment-related adverse effects	can vary from none to troublesome or worrisome; intensity does not correlate with level of control but should be considered in overall assessment of risk		
<b>B. Children 5–11 y old</b>				
Impairment	symptoms	≤2 d/wk and not >1 × /d on those days	>2 d/wk or multiple times on ≤2 d/wk	throughout day
	Night-time awakenings	≤1 × /mo	≥2 × /mo	≥2 × /wk
Risk	interference with normal activities	none	some limitation	extremely limited
	using SABA for symptoms (not prevention of EIB)	≤2 d/wk	>2 d/wk	several times daily
	FEV <sub>1</sub> or PEF	>80% predicted or personal best	60–80% predicted or personal best	<60% predicted or personal best
	FEV <sub>1</sub> /FVC	>80%	75–80%	<75%
	Validated questionnaires			
	cACT	≥20	13–19	≤12
	exacerbations requiring OCS	≤1/y	≥2/y	
	progressive loss of lung function	long-term follow-up required		
	treatment-related adverse effects	can vary from none to troublesome or worrisome; intensity does not correlate with level of control but should be considered in overall assessment of risk		
<b>Children 0–4 y old</b>				
Impairment	symptoms	≤2 d/wk	>2 d/wk	throughout day
	nighttime awakenings	≤1 × /mo	≥1 × /mo	≥1 × /wk
Risk	interference with normal activities	none	some limitation	extremely limited
	using SABA for symptoms (not prevention of EIB)	≤2 d/wk	>2 d/wk	several times daily
	validated questionnaires			
	TRACK	score of 80–100	a change in TRACK score ≥10 points indicates clinically meaningful change in respiratory or asthma control; for children with symptoms consistent with asthma, this should alert the health care provider to review the child's asthma treatment plan	
	exacerbations requiring OCS	≤1/y	2–3/y	>3/y
	treatment-related adverse effects	can vary from none to troublesome or worrisome; intensity does not correlate with level of control but should be considered in overall assessment of risk		

Abbreviations: ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; ATAQ, Asthma Therapy Assessment Questionnaire for Children and Adolescents; cACT, Childhood Asthma Control Test; EIB, exercise-induced bronchoconstriction; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; N/A, not applicable; OCS, oral corticosteroid; PEF, peak expiratory flow; SABA, short-acting β<sub>2</sub>-agonist; TRACK, Test for Respiratory and Asthma Control in Kids.

**eTable 2**  
Validated Asthma Control Questionnaires<sup>e34,e35</sup>

Questionnaire	Description	Included in questionnaire					Other comments
		Symptom frequency	Rescue therapy use	Sleep disturbance	Activity limitation	Exacerbations	
Asthma Control Test(ACT) <sup>e36,e37</sup>	≥12 y old 5 questions answered monthly	X	X	X	X	no	overall self-rating of control included; each item scored from 1 to 5 maximum score 25 score <19 suggests asthma not controlled MID 3 survey license request required for use
Childhood ACT (cACT) <sup>e38,e39</sup>	4–11 y old 7 questions answered monthly (by parent and/or child)	X	no	X	X	no	overall parent and child ratings of control included: 4 questions to child, maximum score for each question is 3; 3 questions for parent, maximum score for each question is 5 combined maximum score 27 score <19 suggests asthma not controlled; score <12 suggests asthma poorly controlled MID 2
Pediatric Asthma Therapy Assessment Questionnaire for Children and Adolescents (pATAQ) <sup>e40</sup>	5–17 y old 7 questions answered monthly (by parent or caregiver)	X	X	X	X	no	overall parent rating of control domain scored from 0 (no asthma control problems) to 7 (very high rates of asthma-related health-care use) no MID
Asthma Control Questionnaire (ACQ) <sup>e41–e44</sup> and for children (cACQ)	6–16 y old (and adults) 7 questions including FEV <sub>1</sub> completed weekly; shorter versions with symptoms only (5 questions) or symptoms + rescue medication (6 questions) or symptoms + FEV <sub>1</sub> (6 questions) validated in patients ≥6 y old trained interviewer required for children 6–10 y old	X	X	X	X	no	items measured on scale of 0–6; score is averaged score ≥1.5 suggests asthma is uncontrolled; score <0.75 suggests asthma is well controlled
Test for Respiratory and Asthma Control in Kids (TRACK) <sup>e45,e46</sup>	≤5 y old 5 questions answered by parents or caregivers: 3 on monthly symptoms, 1 on 3-mo rescue medication use, 1 on exacerbations in past year	X	X	X	X	X	MID 0.5 permission needed from author to use <sup>e41,e42</sup> each item scored from 0 to 20 maximum score 100 score <80 suggests possible poor control of child's breathing problems; ≥10-point change in score suggests need to re-evaluate child's treatment MID 10
Composite Asthma Severity Index <sup>e47,e48</sup>	6–17 y old 5 domains: daytime symptoms and albuterol use (past 2 wk); nights with symptoms and albuterol use (past 2 wk); lung function (current); controller treatment (current); exacerbations (past 2 mo)	X	X	X	no	X	maximum score 20 ≥1-point change suggests change in asthma severity; for defining asthma risk levels, CASI score ≤3 identifies mild asthma (although an increase in CASI score represents increased severity above and below cutoff point) predominantly a research tool CASI is free to use; sample forms, calculator, and other resources are publicly available at <a href="http://www.asthmaseverity.org">www.asthmaseverity.org</a>

Abbreviations: CASI, Composite Asthma Severity Index; FEV<sub>1</sub>, forced expiratory volume in 1 second; MID, minimal important difference.

**eTable 3**  
Key Asthma Studies in Children and Adolescents

Study	Description	Subjects	Outcomes	Comments
Defining difficult-to-control asthma Chipps et al, 2012 <sup>e49</sup> ; Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study	3-y observational multi-cohort study to characterize natural history of difficult-to-treat asthma data were collected every 6 mo, including demographics, medical history, comorbidities, asthma control, asthma-related health care use, medication use, lung function, IgE levels, self-reported asthma triggers, and asthma-related QoL	N = 1,267 children 6–17 y old (497 adolescents, 13–17 y; 770 school-age children, 6–12 y) study also included 3,489 adults (≥18 y)	Burden of illness 3 mo before BL: hospitalizations/ED visits: 10%/17% for adolescents, 9%/22% for children ≥3 asthma controller medications used by >55% of adolescents + adults and children OCS courses (despite using ≥3 asthma controller meds) were 44% in adolescents, 53% in children ED visits (despite using ≥3 asthma controller medications) by 19% of adolescents, 25% of children ED visits + hospitalizations were significantly and clinically meaningfully higher (≈2–3-fold) in children vs adolescents + adults regardless of BL lung function, but at 24 mo, OCS courses were significantly higher in children with FEV <sub>1</sub> ≤80% predicted  Risk factors for future severe exacerbation: recent severe exacerbation was associated with risk for future severe asthma exacerbation at 6 mo (OR 3.08, 95% CI 2.21–4.28) for children and at 18 mo for adolescents + adults (OR 6.33; 95% CI 4.57–8.76) for children, other risk factors were having 3–4 allergic triggers (OR 2.05, 95% CI 1.31–3.20), race or ethnicity (OR 1.77, 95% CI 1.25–2.51), and having VPC asthma (OR 1.59, 95% CI 1.14–2.23) children who continued to have VPC asthma over 24 mo of study had 6-fold increased risk of hospitalization, ED visit, or OCS burst (OR 6.4, 95% CI 1.2–34.5)	regardless of age, patients with severe or difficult-to-treat asthma showed frequent asthma exacerbations, high rates of health care use, and substantial asthma burden despite multiple long-term controller medications and good adherence FEV <sub>1</sub> ≤80% predicted could indicate more severe disease for children than for adults continued VPC asthma despite appropriate treatment and adherence was predictive of clinically significant burden of disease subgroup cross-sectional analysis of school-age children (6–12 y) assessed asthma control in relation to economic burden: greater impairment was associated with increased direct and indirect costs; at 12 and 24 mo, total costs decreased for children whose asthma control improved vs those whose asthma remained VPC; indirect costs accounted for ~50% of VPC costs at 12 mo and >50% at 24 mo <sup>e50</sup>
Pongracic et al, 2016 <sup>e51</sup> ; Asthma Phenotypes in the Inner City (APIC)	1-y prospective longitudinal study of children with asthma living in 9 urban areas at BL, children were classified as having difficult-to-control and easy-to-control asthma based on daily therapy (FP ≥500 µg FP ± LABA vs ≤100 µg) assigned at ≥4 visits asthma and rhinitis were managed using guideline-derived treatment algorithms with assessment and medication adjustments every 2 mo for 1 y 44 BL variables were used to compare groups to identify the most relevant features of difficult-to-control asthma	N = 619 (6–17 y) children with asthma receiving guideline-based care (≥1 y) at BL, 40.9% met criteria for difficult-to-control asthma; 37.5% met criteria for easy-to-control asthma; 21.6% did not meet criteria for either	FEV <sub>1</sub> bronchodilator responsiveness was most distinguishing characteristic identifying children with difficult-to-control asthma; others included asthma control (using ACT or cACT), spirometry, markers of atopy, and rhinitis children with difficult-to-control asthma showed no trend toward improvement with guideline-based care, despite comparable adherence to treatment between groups	findings support those of TENOR and suggest a need for early identification and more aggressive treatment of children with difficult-to-control asthma

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**eTable 3** (continued)

Study	Description	Subjects	Outcomes	Comments
ICS + LABA Lemanske et al, 2010 <sup>e52</sup> ; Best Add-on Therapy Giving Effective Response (BADGER)	48-wk R, DB, 3-treatment, 3-period, crossover study: FP 250 µg 2 × /d (ICS step-up); FP 100 µg + LABA 50 µg 2 × /d (LABA step-up); FP 100 µg 2 × /d + LTRA 5 or 10 mg 1 × /d (LTRA step-up) each treatment was given for 16 wk without washout	N = 182 (6–17 y) who had uncontrolled asthma while receiving FP 100 µg 2 × /d	161 of 165 children evaluated had differential response to treatment ( $P < .001$ ) LABA step-up was most likely to be the best response vs LTRA step-up (relative probability 1.6, 95% CI 1.1–2.3, $P = .004$ ) vs ICS step-up (relative probability 1.7, 95% CI 1.2–2.4, $P = .002$ )	not all children showed best response with LABA step-up; some did better with ICS or LTRA results indicate it is important to regularly monitor and adjust each child's asthma therapy possible BL predictors of response: better asthma control and white race showed likelihood of best response to LABA; black race showed weaker response to LTRA potential predictors were assessed further in post hoc analyses, which suggested associations between lower lung function and better response to LABA step-up and increased LTE <sub>4</sub> and marginally better response to LTRA step-up <sup>e53</sup> ; although children without eczema appeared to respond best to LABA step-up, step-up for those with eczema could reflect race <sup>e54</sup>
Vaessen-Verbene et al, 2010 <sup>e55</sup>	26-wk R, PC, DB study of FP 100 µg + Sal 50 µg vs doubling FP monotherapy (200 µg); both given 2 × /d	N = 158 (6–16 y) symptomatic on FP 100 µg 2 × /d FP + Sal (n = 78) FP double (n = 80)	percentage of symptom-free days: no difference between treatments with ≈25% increase in the 2 groups ( $P < .001$ vs BL) percentage of days with rescue albuterol: no difference between treatments and decreased with both (FP/Sal, from 38% to 22%; FP, from 35% to 20%) lung function: no difference between treatments and no significant changes from BL mean statural growth: no difference between treatments	combination provided similar clinical efficacy at half steroid dose
Stempel et al, 2016 <sup>e56</sup>	26-wk, R, DB, active comparator study evaluating safety of FP + Sal vs FP monotherapy	N = 6208 (4–11 y) who required daily asthma meds and had history of asthma exacerbation(s) in years before study; FP + Sal (n = 3,107), FP (n = 3,101)	primary (safety): time to first serious asthma-related event: no difference between treatments (HR 1.28, (CI 0.73–2.27, $P = .006$ ) secondary (efficacy): mean percentage of rescue therapy-free days: FP + Sal 83.0%; FP 81.9% ( $P = NS$ ) mean percentage of days with asthma controlled: FP + Sal 74.8%; FP 73.4% ( $P = NS$ )	evidenced safety of LABA when used in combination with ICS in same inhaler (ICS + LABA) with findings similar to studies in adults and adolescents <sup>e57,e58</sup>

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eTable 3 (continued)

Study	Description	Subjects	Outcomes	Comments
Bisgaard et al, 2006 <sup>e59</sup> ; Symbicort Maintenance and Relief Therapy (SMART)	12-mo, R, DB study of Bud 80 µg + Form 4.5 µg 1 × /d + additional inhalations if needed for symptom relief (SMART), Bud 80 µg + Form 4.5 µg 1 × /d (fixed combination), Bud 320 µg 1 × /d (fixed-dose Bud)	N = 341 (4–11 y) with asthma history ≥6 mo and ≥1 exacerbation in prior year and who were using ICS at a constant dose for ≥3 mo (200–500 µg/d) SMART (n = 118) fixed combination (n = 117) fixed-dose Bud (n = 106)	percentage of children with exacerbation: SMART 14% vs fixed combination 38% ( $P < .001$ ) vs fixed-dose Bud 26% ( $P = NS$ ) children using SMART had fewer OCS days vs children in other 2 groups SMART significantly prolonged time to first exacerbation vs fixed combination ( $P < .001$ ) and vs fixed-dose Bud ( $P < .02$ ) both combination treatments improved lung function and decreased NT symptoms vs fixed-dose Bud; other asthma control variables (eg, control days, symptom-free days) were comparable between groups growth rate over the year for children in the 2 combination treatment groups was ~1 cm greater than children using fixed-dose Bud	pediatric asthma associated with higher incidence of exacerbations data suggest that the SMART approach (not approved by the FDA) might benefit some children
Tiotropium Vogelberg et al, 2014 <sup>e60</sup>	12-wk phase II, DB, PC, incomplete crossover (3 4-wk treatment periods), dose-ranging study of once-daily Tio Respimat (5, 2.5, and 1.25 µg) given in evening and added to medium-dose ICS (Bud 200–400 µg or equivalent) ± LTRA	N = 101 (6–11 y) with asthma history ≥6 mo Tio 5 µg (n = 76); Tio 2.5 µg (n = 74); Tio 1.25 µg (n = 75); PI (n = 76)	peak FEV <sub>1</sub> (0–3 h) response after 4 wk (primary end point, adjusted mean differences from PI): Tio 5 µg, 87 mL ( $P = .0002$ ); Tio 2.5 µg, 104 mL ( $P < .0001$ ); Tio 1.25 µg, 75 mL ( $P = .0011$ ) with no dose-dependent response secondary and additional efficacy end points also improved with Tio, including trough FEV <sub>1</sub> , FEV <sub>1</sub> AUC (0–3 h), FEV <sub>1</sub> over 3 h after dosing, and AM and PM PEF all treatments were well tolerated with no between-treatment differences in AEs	this was the first study of the Tio Respimat in children with symptomatic asthma focus of this phase II trial was lung function rather than full assessment of symptom control and exacerbations
Hamelmann et al, 2016 <sup>e61</sup>	48-wk DB, PC, PG study of once-daily Tio Respimat (5 or 2.5 µg) given in evening and added to medium-dose ICS (Bud 200–400 µg or equivalent) ± LTRA	N = 398 (12–17 y) with asthma history ≥3 mo and were symptomatic at screening Tio 5 µg (n = 134); Tio 2.5 µg (n = 125); PI (n = 138)	peak FEV <sub>1</sub> (0–3 h) response after 24 wk (primary end point, adjusted mean differences from PI): Tio 5 µg, 174 mL (95% CI 76–272, $P < .001$ ); Tio 2.5 µg, 134 mL (95% CI 34–234, $P < .01$ ) secondary end points at 24 wk (adjusted mean differences from PI): Trough FEV <sub>1</sub> : Tio 5 µg, 117 mL (95% CI 10–223, $P = .03$ ); Tio 2.5 µg, 84 mL (95% CI –25 to 194, $P = NS$ ) FEV <sub>1</sub> AUC (0–3 h): Tio 5 µg, 181 mL (95% CI 88–275, $P < .001$ ); Tio 2.5 µg, 130 mL (95% CI 34–225, $P = .008$ ) trends for improvement in asthma control and health-related QoL over 48-wk treatment period were observed all treatments were well tolerated with no between-treatment differences in AEs	
Szeffler et al, 2017 <sup>e62</sup>	12-wk DB, PC, PG study of once-daily Tio Respimat (5 or 2.5 µg) given in evening as add-on to background therapy (high-dose ICS (Bud >400 µg or equivalent) + ≥1 controller med (eg, LABA ± LTRA); or medium-dose ICS (Bud 200–400 µg or equivalent) + ≥2 controller meds (eg, LABA ± LTRA ± SRT))	N = 401 (4–11 y) with severe asthma, an asthma history ≥6 mo, and who were symptomatic at screening Tio 5 µg (n = 130); Tio 2.5 µg (n = 136); PI (n = 134)	Peak FEV <sub>1</sub> (0–3h) response after 12 wk (primary end point, adjusted mean differences from PI): Tio 5 µg, 139 mL (95% CI 75–203 mL), $P < 0.0001$ ; Tio 2.5 µg, 34 mL (95% CI 28–99 mL), $P = NS$ secondary end point at 12 wk: trough FEV <sub>1</sub> (adjusted mean differences from PI): Tio 5 µg, 87 mL (95% CI 19–154, $P = .01$ ); Tio 2.5 µg, 18 mL (95% CI –48 to 85, $P = NS$ ) other secondary end points were similar between treatment groups risk of severe asthma exacerbations and episodes of asthma worsening was lower with Tio vs PI (HR < 1); however, this difference was significant only for episodes of asthma worsening with Tio 2.5 µg vs PI ( $P = .006$ ) all treatments were well tolerated with no between-treatment differences in AEs	

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**eTable 3** (continued)

Study	Description	Subjects	Outcomes	Comments
Omalizumab Milgrom et al, 2001 <sup>e63</sup>	28-wk R, DB, PC study of safety, steroid-sparing effects, efficacy for exacerbations of omalizumab omalizumab dose based on bodyweight and initial serum IgE: 0.016 mg/kg per IgE level (IU/mL) treatment was added to stable BDP dose (initial range 168–420 g/d) for 16 wk (stable-steroid phase), decreased over 8 wk to minimum effective dose (steroid-decrease phase), and maintained constant for final 4 wk	N = 334 (6–12 y) with moderate-to-severe allergic asthma requiring ICS omalizumab (n = 225); PI (n = 109)	median decrease in BDP dose from BL: omalizumab 100%, PI 66.7% ( $P = .001$ ) percentage of patients completely stopping BDP: omalizumab 55%, PI 39% ( $P = .004$ ) percentage of patients with exacerbation requiring doubling BDP dose or OCS during steroid-decrease phase: omalizumab 18.2%, PI 38.5% ( $P < .001$ ) mean number exacerbations per patient: omalizumab 0.42, PI 2.72 ( $P < .001$ ) no serious treatment-related AEs; 5 PI-treated patients required hospitalization for asthma exacerbation	no significant between-treatment differences for asthma symptom scores, lung function measures (AM PEFr, FEV <sub>1</sub> , FVC, FEF <sub>25–75</sub> ), but other secondary measures suggest improved asthma control with omalizumab percentage of patients requiring urgent, unscheduled physician visit: omalizumab 12.9%, PI 30.3% ( $P = .001$ ) percentage of patients with $\geq 20\%$ decrease in AM PEFr on 2 or 3 successive days: omalizumab 6.7%, PI 17.4% ( $P = .002$ ) percentage of patients with awakenings requiring rescue medications on 2 or 3 successive nights: omalizumab 11.6%, PI 21.1% ( $P = .002$ ) subsequent 24-wk OL study in which all subjects received omalizumab + their other asthma medications showed trends similar to core study <sup>e64</sup>
Lanier et al, 2009 <sup>e65</sup>	52-wk R, DB, PC study of omalizumab (75–375 mg SC q2 or q4) including 24-wk fixed-steroid phase followed by 28-wk adjustable-steroid phase	N = 627 (6– < 12 y) with perennial allergen sensitivity and history of asthma exacerbations and symptoms despite at least medium-dose ICS omalizumab (n = 421); PI (n = 206)	rate of clinically significant exacerbations (ie, worsening symptoms requiring doubling BL ICS dose and/or OCS) over fixed-steroid phase: omalizumab 0.45, PI 0.64 ( $P = .007$ ; rate ratio 0.69) over 52 wk, exacerbation rate with omalizumab was decreased by 43% vs PI ( $P < .001$ ) and significantly decreased severe exacerbations no between-treatment differences in overall incidence of AEs	
Kulus et al, 2010 <sup>e66</sup>	52-wk R, DB, PC study of omalizumab (75–375 mg SC q2 or q4) including 24-wk fixed-steroid phase followed by 28-wk adjustable-steroid phase	N = 246 (6– < 12 y) with perennial allergen sensitivity and history of asthma exacerbations and symptoms despite using ICS (FP $\geq 500$ $\mu\text{g}/\text{d}$ or equivalent) + LABA; omalizumab (n = 166); PI (n = 80)	rate of clinically significant exacerbations (ie, worsening symptoms requiring doubling BL ICS dose and/or OCS) over fixed-steroid phase: omalizumab 0.42, PI 0.63 ( $P = .047$ ; rate ratio 0.662) over 52 wk, exacerbation rate with omalizumab was decreased by 50% vs PI ( $P < .001$ ) no between-treatment differences in overall incidence of AEs	
Busse et al, 2011 <sup>e67</sup> ; Inner City Anti-IgE Therapy for Asthma (ICATA) study	60-wk R, DB, PC, PG study of omalizumab (75–375 mg SC q2 or q4)	N = 419 inner city children and adolescents or young adults (6–20 y) with persistent allergic asthma; subjects using controller medications required to have evidence of persistent symptoms or evidence of uncontrolled asthma in prior year, those not receiving controller meds were required to have persistent symptoms and evidence of uncontrolled disease omalizumab (n = 208), PI (n = 211)	omalizumab decreased symptom days per 2-wk interval (primary end point) of 1.04 (95% CI 0.46–1.62) and decreased percentage of subjects with exacerbations (from 10.2% to 6.1%)	effects of omalizumab were evident in seasonal patterns of asthma symptoms and exacerbations exacerbations during fall and spring vs summer (respectively): PI 9.0% and 8.1%, vs 4.6% ( $P < .001$ ); omalizumab 4.3% and 4.2% vs 3.3% ( $P = \text{NS}$ ); difference between treatments was significant ( $P < .001$ )

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**eTable 3** (continued)

Study	Description	Subjects	Outcomes	Comments
Teach et al, 2015 <sup>e27</sup> ; The Preventive Omalizumab or Step-up Therapy for Fall Exacerbations (PROSE) study	3-arm, R, DB, DPC study of effect of omalizumab vs PI and vs ICS boost (doubling ICS dose) on fall asthma exacerbations rates when treatment was initiated 4–6 wk before return to school	N = 513 inner city children (6–17 y) with allergic asthma, asthma symptoms for ≥1 y, using FP ≥200 µg/d (or equivalent), and ≥1 recent exacerbation for 318 children using FP 200– < 500 µg/d: omalizumab (n = 133), ICS boost (n = 138), PI (n = 47) for 195 children using FP ≥500 µg/d: omalizumab (n = 145), PI (n = 50)	fall exacerbation rate was significantly lower for omalizumab vs PI (11.3% vs 21.0%; OR 0.48, 95% CI 0.25–0.92), but not for omalizumab vs ICS boost (8.4% vs 11.1%; OR 0.73, 95% CI 0.33–1.64) exacerbation rate was significantly lower for omalizumab vs PI and vs ICS boost in subgroup analysis of children who had exacerbation during run-in: omalizumab vs PI 6.4% vs 36.3% (OR 0.12, 95% CI 0.02–0.64); omalizumab vs ICS boost 2.0% vs 27.8% (OR 0.05, 95% CI 0.002–0.98) omalizumab significantly decreased asthma symptoms days in 2-wk intervals vs PI but not vs ICS boost omalizumab was associated with a trend toward lower odds of respiratory virus-associated exacerbation (OR 0.52, 95% CI 0.24–1.13), which was statistically significant for children with more severe asthma (OR 0.35, 95% CI 0.15–0.85) omalizumab improved IFN-α responses to rhinovirus, and within the omalizumab group, greater IFN-α increases were associated with fewer exacerbations (OR 0.14, 95% CI 0.01–0.88)	targeted seasonal treatment could help in management of high-risk children; the cost would be lower than a full year of treatment if appropriate patients could be identified; more data are needed for confirmation
Young children Fitzpatrick et al, 2016 <sup>e68</sup> ; The Individualized Therapy for Asthma in Toddlers (INFANT) study	R, DB, DD, crossover study of 3 16-wk treatment periods: daily ICS, daily LTRA, and as-needed ICS coadministered with albuterol	N = 300 (12–59 mo) with asthma requiring daily controller medication (step 2 care)	74% of children with analyzable data (170 of 230) had a differential response to treatment, with the probability of best response highest for daily ICS response to daily ICS was predicted by aeroallergen sensitization but not by exacerbation history or sex; in children with aeroallergen sensitization and blood eosinophil count ≥300/mL (suggesting T2 phenotype), daily ICS use was associated with more asthma control days and fewer exacerbations vs other treatments	results suggest (1) daily low-dose ICS is the most effective treatment for most young children with asthma symptoms and recurrent wheezing episodes who require controller medication; (2) there is potential for phenotype-directed asthma care for younger children, but more study is warranted to better identify predictors; (3) evidence of a T2 phenotype is associated with children who do best with daily ICS

Abbreviations: ACT, Asthma Control Test; AE, adverse event; AUC, area under the curve; BDP, ??; BL, baseline; Bud, budesonide; cACT, Childhood Asthma Control Test; CI, confidence interval; DB, double-blinded; DPC, double placebo-controlled; ED, emergency department; FDA, Food and Drug Administration; FEF<sub>25–75</sub>, forced expiratory flow between 25% and 75%; FEV<sub>1</sub>, forced expiratory volume in 1 second; Form, formoterol; FP, fluticasone propionate; HR, hazard ratio; Hx, history; ICS, inhaled corticosteroid; IFN-α, interferon-α; IgE, immunoglobulin E; LABA, long-acting β-agonist; LTE4, leukotriene E<sub>4</sub>; LTRA, leukotriene receptor antagonist; med, medication; NS, not significant; NT, night-time; OCS, oral corticosteroid; OL, ??; OR, odds ratio; PC, placebo-controlled; PEFR, peak expiratory flow rate; PG, parallel group; PI, placebo; q2, every 2 weeks; q4, every 4 weeks; QoL, quality of life; R, randomized; Sal, salmeterol; SC, subcutaneously; SRT, sustained release theophylline; Sx, symptoms; Tio, tiotropium; Tx, treatment; VPC, very poorly controlled.



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