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Step-up and step-down treatments for optimal asthma control in children and adolescents

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Abstract

Objective: To review therapeutic options for stepwise management of pediatric asthma in the context of this population's unique needs such as potential effects of asthma, treatments, or both on growth and psychosocial development, and caregiver involvement.

Data sources and study selection: We conducted PubMed searches to identify relevant articles then reviewed resultant articles, guidelines for asthma management in children, and articles from personal files.

Results: Stepwise management of asthma, similar to adults, is recommended for children in current global and US guidelines. Treatment may be stepped up or stepped down temporarily or long-term based on response over time. Inhaled corticosteroids remain the recommended treatment for persistent childhood asthma and any potential small effects on growth are considered relatively minor compared with their benefit. Controller medication options for patients <18 years old are limited, especially for Global Initiative for Asthma Steps 2–5. The long-acting antimuscarinic antagonist tiotropium (Steps 4/5, patients aged ≥ 12 years) and in certain circumstances (Step 5), anti-immunoglobulin E (aged ≥ 6 years) and interleukin-5

antibodies (aged ≥ 12 years) are newer treatment options. Tiotropium is indicated in the United States and Europe for patients ≥ 6 years old. Stepping down treatment, which is recommended but infrequently practiced, can maintain symptom control and minimize adverse events while substantially reducing costs. Patient education and better monitoring remain important for self-management and optimum outcomes.

Conclusion: A need exists to target individual treatment goals for children with asthma by using step-up and step-down approaches to maximize treatment benefits and minimize potential adverse effects.

Introduction

The prevalence of asthma in the pediatric population is high. In the United States, 9.6% of children (5–11 years old) and 10.0% of adolescents (12–17 years old) had asthma in 2015 [1]. Among infants and toddlers (0–4 years old), the prevalence was 4.7% [1].

Children with asthma require long-term treatment. The goals of asthma therapy are to maintain good symptom control, normal activity levels, and reduced exacerbation risk resulting in preventable emergency visits or hospitalizations. The minimally effective dose of therapy to reduce or prevent adverse effects should be used to prevent fixed airflow limitation and, particularly for children, to prevent reduced lung growth [2], [3]. Although pharmacological treatment is the mainstay of asthma management, non-pharmacological interventions such as pulmonary rehabilitation, breathing exercises, avoiding allergic triggers, and counseling adolescents about not smoking can also play integral roles [4]. Therefore, both pharmacological and appropriate non-pharmacological approaches should be included in each patient's asthma management plan. Minimizing adverse effects from medications is an important goal when treating chronic diseases such as asthma, particularly among children in whom long-term treatment may affect their physical, social, and psychological development. Preventing acute symptoms that interfere with daily activities and chronic effects that interfere with physical, mental, and social development are important treatment goals for patients, as well as their parents/caregivers. However, several of these goals may be conflicting (e.g., better control requires higher dose of medications, which may increase the type and number of adverse effects). Furthermore, besides individual goals, characteristics and preferences of patients (e.g., age, physical condition, psychosocial issues, and inhaler technique) and their parents/caregivers

(e.g., health literacy) [5] need be considered to achieve optimal concordant adherence to any medical regimen.

Since management of asthma is a cyclic process involving assessment, treatment adjustment, and reviewing treatment response [2], maintaining long-term treatment with the fewest adverse effects may be challenging. In this review, we discuss the therapeutic options for step-up and step-down treatment approaches for optimal asthma control in the pediatric population, potential obstacles with these treatments, and reasonable ways to overcome these obstacles.

Methods

We conducted multiple, targeted PubMed searches to identify relevant articles on various aspects of management of asthma in children, focusing on results from the last 5 years. We aimed to capture relevant articles on ‘Children/Adolescents/Pediatric population and Asthma’, through our searches. In addition to articles identified from these searches, we reviewed the relevant references cited in those articles; current guidelines for the management of asthma in children, most notably the Global Initiative for Asthma (GINA) 2018 report [2]; and articles from our personal files. Articles selected for inclusion in this review were based on author consensus. While reviewing the literature, we defined asthma as variable expiratory airflow limitation together with the history of respiratory symptoms such as wheeze, chest tightness, shortness of breath, and cough varying over time and in intensity. In most of the included articles, asthma severity was assessed based on the level of treatment required to control symptoms and exacerbations and, like in the GINA 2018 report [2], was deemed mild, moderate, or severe asthma based on the treatment received by patients.

Results

Treatment of children and adolescents requires unique considerations

Children and adolescents with asthma have increased nutritional requirements because of excess physiological work, and lack of nutrients may delay growth, puberty, and maturation of biological systems [6]. Delayed growth may also be attributable, in part, to treatment with inhaled corticosteroids (ICSs), though evidence exists both for and against this concept. Some evidence indicates that regular ICS use in pediatric patients with asthma negatively impacts growth [7], [8]; however, ICS use did not affect growth velocity and/or attainment of adult height in asthmatic children in other studies [9–11].

High-dose ICSs have the potential for hypothalamic-pituitary-adrenal (HPA) axis suppression in adults and children. In adults with asthma, ICS use decreased bone mineral density and increased cataract risk, glaucoma risk, or both [12]. The risk of skin thinning and bruising increased with increased ICS dose, prolonged use, and female sex [12]. Furthermore, prolonged ICS therapy, even at low or medium doses, affected the growth trajectory of children in some studies [7], [8]. The authors of a systematic review and meta-analysis of 25 trials (8471 children) concluded that, compared with placebo or non-steroidal drugs, regular use of low or medium daily doses of ICS resulted in a significant mean reduction of 0.48 cm/year in linear growth velocity (based on 14 trials with 5717 children) and 0.61 cm in height (based on 15 trials with 3275 children) during 1 year of treatment of children with mild-to-moderate persistent asthma [7]. Maximum growth suppression occurred during the first year of therapy, and a significant difference in mean reduction of linear growth velocity was observed when six medications were compared with

placebo or non-steroidal drugs during a 1-year treatment period ($p < 0.001$). Specifically, treatment with chlorofluorocarbon (CFC)-beclomethasone 400 µg/d (3 trials [13–15] including 439 participants; mean difference: -0.91 cm/y, 95% confidence interval [CI]: -1.26 to -0.55), budesonide via dry powder inhaler (DPI [3 trials [16–18] including 2,790 participants; mean difference: -0.59 cm/y, 95% CI: -0.73 to -0.45]), and fluticasone propionate 100 to 200 µg/d (5 trials [19–23] including 1,405 participants; mean difference: -0.39 cm/y, 95% CI: -0.63 to -0.15) led to significant reductions in mean linear growth velocity during the 1-year treatment period. On the other hand, non-significant differences in mean linear growth velocity occurred with the use of hydrofluoroalkane (HFA)-flunisolide 400 µg/d (2 trials [14], [24] including 314 participants; mean difference: -0.22 cm/y, 95% CI: -0.63 to 0.18), HFA-ciclesonide 50 to 200 µg/d (1 trial [25] including 609 participants; mean difference: -0.08 cm/y, 95% CI: -0.27 to 0.11), and mometasone via DPI 100 to 200 µg/d (1 trial [26] including 184 participants; mean difference: -0.47 cm/y, 95% CI: -0.97 to 0.03). In another systematic review, analysis of 4 trials ($N=728$) in prepubescent children (school-aged children, <12 years old) with mild-to-moderate persistent asthma demonstrated that higher dose ICS use over a 1-year period produced a dose-dependent reduction in growth velocity compared to a lower dose ICS use [8]. In contrast, results of a systematic review of 23 studies and meta-analysis of 16 randomized controlled trials (RCTs) indicated ICS use for >1 year in asthmatic children did not have a major effect on annual growth velocity, leading to an approximate 1-cm (0.7%) reduction in final adult height compared with non-ICS users [27].

In addition to potential developmental delays, children and adolescents with asthma represent a particularly vulnerable population who may require lifestyle counseling in addition to self-

management instructions [28]. They are more likely to miss school and have poor performance [29], [30] because of their disease, treatment, or psychological problems [6]. Significantly more adolescents with asthma than healthy controls feel lonely, unhappy, or depressed and suffer from psychosomatic symptoms [28]. Furthermore, adolescents with asthma may indulge in risk-taking behavior (e.g., smoking, alcohol consumption) more than non-asthmatic adolescents [28]. Other factors unique to younger children with asthma include difficulty in communicating symptoms and understanding how and when to use inhalers, and lack of adherence when not monitored by parents/caregivers. Furthermore, in addition to parents or primary caregivers, day care personnel, schoolteachers, and nurses often play a unique role in the care of younger children with asthma [31].

Uncontrolled or poorly controlled asthma may, therefore, impact growth, limit physical activities, increase school presenteeism and absenteeism, limit socialization, and contribute to psychological/psychosomatic problems. These challenges, as well as poor adherence and risk-taking behavior, often lead to a vicious, negative cycle. Good control with appropriate changes in therapy as needed should obviate this negative cycle. Thus, a multidisciplinary and tailored approach is needed to manage asthma in children and adolescents (Fig 1).

Need for step-up or step-down treatment approaches in children

Asthma treatment in children may need to be stepped up on a day-to-day basis, for short periods of time, or on a sustained basis based on the patient's response to controller and reliever medications over time [2]. Before stepping up, care should be taken to ensure that modifiable patient factors (e.g., concomitant diseases, difficulty in using inhalers, improper inhaler

technique, environmental factors at home or school, and lack of adherence) are not contributing to loss of control. Age may also impact some patient factors: levels of parental/caregiver involvement may influence adherence in younger children, and adherence to treatment may be low in adolescents because of risk-taking behaviors [32].

Reasons for stepping up may be manifold. Exposure to exacerbation triggers such as allergens, irritants, and respiratory infections is common in childhood. Children and adolescents are usually very active. And, as mentioned, risk-taking behavior in adolescence, especially smoking, may lead to loss of control of asthma. Physicians must carefully judge whether or not exacerbations represent true loss of chronic asthma control. If events are singular and resolve after treatment, a change in medication may not be indicated. True loss of chronic asthma control requires stepping-up of maintenance therapy.

Multiple triggers for loss of control might make stepping down treatment difficult. Further, children and adolescents may not have stable disease without exacerbation for a long enough time to permit the opportunity for stepping down. Nevertheless, whenever possible, stepping down treatment is essential to minimize adverse effects and costs.

Composite Asthma Severity Index (CASI) is a validated instrument that quantifies asthma severity by considering impairment, risk, and amount of medication needed to maintain control [33]. The maximum CASI score is 20, based on day symptoms and albuterol use in the last 2 weeks, night symptoms and albuterol use in the last 2 weeks, lung function measures, controller treatment, and exacerbations. With the inclusion of lung function, controller treatment, and

exacerbations, CASI is a good composite instrument for measuring severity of asthma even in well-treated populations and can be used as a guide for stepwise management of asthma.

Therapeutic options for asthma treatment in children and adolescents

ICSs remain the recommended treatment for persistent childhood asthma [2], [3]. Overall, the small, short-term effect on growth potentially caused by ICS use can be considered relatively minor; effects are not long term, and the risk of ICS use is outweighed by the benefit [3].

Among children with asthma whose symptoms are not well controlled on ICS, step-up treatment approaches include increasing the dosage of ICSs or subsequently adding medications such as a leukotriene receptor antagonist (LTRA), long-acting beta-2-agonist (LABA), long-acting muscarinic antagonist (LAMA; i.e., tiotropium bromide [Spiriva[®] Respimat[®]; Boehringer Ingelheim, Ridgefield, CT]), anti-interleukin 5 (IL-5) antibodies (i.e., mepolizumab [Nucala[®]; GlaxoSmithKlein, Research Triangle Park, NC]), and benralizumab [Fasenra[®]; Astrazeneca Pharmaceuticals LP, Wilmington, DE]) and anti-immunoglobulin E (IgE) antibodies (i.e., omalizumab [Xolair[®]; Genentech USA, Inc., San Francisco, CA]) [2], [3]. However, the benefits and risks of each of these therapeutic options should be considered before use. As discussed, prolonged ICS therapy, even at low or medium doses, might affect the growth trajectory of children. Meanwhile, evidence regarding use of a LAMA or anti-IgE antibodies as potential add-on therapy in children is increasing. Also of note, as demonstrated in a RCT of step-up therapy with ICS or LABA or LTRAs for children with uncontrolled asthma receiving low-dose ICSs, response to each step-up therapy can vary [34]. Thus, asthma therapy in children should be regularly monitored and appropriately adjusted per response.

Step-up and step-down guideline recommendations

Guidelines for asthma management are available, and stepwise treatment for the management of asthma in children and adults is recommended in both the GINA 2018 report [2] and National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program (NHLBI/NAEPP) guidelines [3]. However, only the GINA report [2], published in 2018, is up to date. The last NHLBI/NAEPP guidelines [3] were published in 2007 and, therefore, do not include medications approved since that time. GINA 2018 recommendations are clear for adults (≥ 18 years old), with a various treatment options (Fig 2) [2]. In contrast, therapeutic options of controller medications are limited in children, especially for Steps 2 to 5 for those < 12 years old. We hereby describe the GINA 2018 steps, as well as supporting evidence, in detail for children and adolescents aged 6–17 years (Table 1).

Evidence supporting step-up treatment in children

LTRAs: LTRAs, which can be added at GINA Step 2 or higher [2], are more efficacious than placebo [35] but less efficacious than ICSs [2], [36]. However, heterogeneity of response must be noted given the fact that many children can have the best response to addition of LTRAs for step-up treatment [34].

Results of a systematic review and meta-analysis of 6 trials involving adults and adolescents with asthma showed that LTRA monotherapy improved asthma control compared with placebo and had a similar safety profile [35]. Furthermore, LTRAs significantly increased the forced expiratory volume in 1 second (FEV_1) when used as add-on to ICSs but did not have a

significant effect on FEV₁ % predicted or asthma exacerbations [35]. In another systematic review of 56 (19 pediatric) studies involving 10 005 adults and 3333 children, efficacy of ICSs was better than LTRAs as monotherapy in adults and children with persistent asthma, particularly in those with moderate airway obstruction, and safety profiles were comparable [36]. Furthermore, results of a systematic review of 4 trials representing 559 children and adolescents with mild-to-moderate asthma showed that LTRA+ICS did not reduce the need for rescue oral corticosteroids (OCS) or hospital admission compared to the same dose or an increased dose of ICSs. These findings, along with scarce data availability in pediatric population (e.g. absence of data in preschoolers, variability in design and outcomes from different trials) disallow recommending LTRAs as a reasonable add-on therapy to low-dose ICSs [37].

LTRAs have the advantage of being administered orally once or twice daily. And importantly, unlike long-term ICS use, they do not adversely affect growth or the adrenal axis [37]. However, LTRAs have been associated with other adverse drug reactions. For example, montelukast-induced adverse drug reactions include psychiatric and nervous system disorders like agitation, anxiety, depression, sleep disturbance, hallucinations, suicidal thinking and suicidality, tremor, dizziness, drowsiness, neuropathies, and seizures. Immune system involvement may lead to Churg-Strauss syndrome. Hypersensitivity reactions like anaphylaxis and eosinophilic infiltration may also occur with LTRA use [38].

Low-dose theophylline: At GINA Step 2 or higher, low-dose theophylline can be added to ICSs in children aged ≥ 12 years [2]. Authors of a recent meta-analysis of 8 RCTs, including 2 RCTs of children aged 5 to 14 years, concluded that add-on LTRA leads to moderate improvement in

lung function (morning peak expiratory flow [PEF] and FEV₁) versus add-on theophylline [39]. The safety profiles of these interventions were comparable.

LABAs: LABAs are recommended as add-on therapy at GINA Step 3 and higher for patients aged ≥ 12 years [2]. In an historical cohort study conducted using the Clinical Practice Research Datalink (CPRD) and Optimum Patient Care Research Database (OPCRD) between 1999 and 2011, one-third of initial step-up episodes in children involved adding LABAs to ICS therapy [40]. Based on a systematic review of 33 trials involving 6381 children with persistent asthma, authors concluded that add-on LABA did not result in a significant reduction in the rate of asthma exacerbations requiring OCS but led to improvement of lung function compared with the same or higher doses of ICSs [41]. Adverse effects were generally comparable, except for better growth with the use of lower dose ICS+LABA compared with a higher dose ICS. The risk of hospital admissions was higher, but not significantly, with add-on LABA [41]. Further, in a sub-analysis of data on children in a systematic review, children taking regular formoterol (n=843) had a higher risk of serious adverse events (SAEs) than those taking placebo (n=492; Peto odds ratio 2.48; 95% CI: 1.27 to 4.83) [42]. As mentioned, SAEs, including hospitalization and death in small numbers of patients, were reported with the use of LABAs; however, the evidence is mostly non-conclusive and stems from studies in adults [43–45]. In 2017, the US Food and Drug Administration (FDA) removed the ‘black box’ warning for asthma-related deaths from the drug labels of medicines that contain both an ICS and LABA [46].

Newer alternatives for step-up treatment

Long-acting muscarinic antagonists: Results of clinical trials of tiotropium in children and adolescents suggest that anticholinergics can be used as bronchodilators in the treatment of asthma [47–51]. Tiotropium is FDA approved for the long-term, once-daily, prescription maintenance treatment of asthma in patients ≥ 6 years old (February 2017) [52] and is the recommended treatment at GINA Steps 4 and 5 for patients ≥ 12 years old [2]. Of note, though tiotropium also is indicated for children ≥ 6 years old in Europe (March 2018), this expanded indication has not yet been incorporated into GINA recommendations.

Besides evidence generated in clinical trials in adults, results of phase II/III clinical trials [47–51], [53] demonstrated the efficacy and safety of tiotropium as an add-on to at least ICS $\pm$ ≥ 1 controller in children (6–11 years) [50], [51] and adolescents (12–17 years) [47–49] with moderate-to-severe asthma (Table 2). For example, in one phase II study (N=301), tiotropium added to medium-dose ICSs, with or without a LTRA, was efficacious in pediatric patients with symptomatic asthma despite the ICS, and had safety and tolerability comparable to placebo [50]. And, in a systematic review of 3 clinical trials involving 895 adolescents, tiotropium was well tolerated and efficacious as an addition to ICS or ICS+LABA [54]. Further, emerging evidence also supports safety and efficacy of tiotropium in younger children (1–5 years [55] and 6–11 years [56]) with persistent asthmatic symptoms.

Omalizumab: Omalizumab, an anti-IgE monoclonal antibody, is FDA approved for treating moderate-to-severe persistent asthma in children 6–11 years old (also approved for patients ≥ 12 years old) who have had a positive skin test or in vitro reactivity to an airborne allergen and with symptoms that are inadequately controlled with ICSs (July 2016) [57]. The efficacy and safety of

omalizumab in children has been evaluated in several clinical trials (Table 3) [58–64], and it is recommended at GINA Step 5 [2]. Results of a systematic review of 3 RCTs demonstrated the efficacy and safety of omalizumab in children and adolescents (N=1381) with moderate-to-severe allergic asthma uncontrolled with ICS treatment [64]. Omalizumab treatment resulted in fewer patients with ≥ 1 significant asthma exacerbation during stable disease. During the steroid-reduction phase, omalizumab reduced the number of patients with ≥ 1 exacerbation and the mean number of asthma exacerbations per patient. Moreover, omalizumab had an acceptable safety profile.

Mepolizumab: Mepolizumab, a humanized monoclonal antibody against IL-5, is FDA approved as add-on maintenance treatment for patients ≥ 12 years old with severe eosinophilic asthma (November 2015) [65] and is also a recommended option for treatment at GINA Step 5 [2]. Results of studies conducted in patients aged ≥ 12 years with recurrent severe asthma exacerbations and signs of eosinophilic inflammation suggest that mepolizumab is well tolerated, inhibits eosinophilic inflammation, and significantly reduces risk of acute asthma exacerbations, in addition to reducing the blood eosinophil count [66–67].

Evidence supporting step-down treatment in children

Guidance on step-down treatment that can be applied to children and adolescents are provided in the GINA 2018 report [2]: “Consider stepping down when asthma symptoms have been well controlled and lung function has been stable for 3 or more months. If the patient has risk factors for exacerbations or fixed airflow limitation, it is recommended that step down should only be conducted under close supervision by a health care provider. Choose an appropriate time to step

down when the patient is not having a respiratory infection, not travelling or pregnant. Approach each step as a therapeutic trial. Engage the patient in the process; document their asthma status (symptom control, lung function and risk factors); provide clear instructions; provide a written asthma action plan and ensure that the patient has sufficient medication to resume their previous dose if necessary; monitor symptoms and/or PEF; and schedule a follow-up visit. Stepping down ICS doses by 25–50% at 3-month intervals is feasible and safe for most patients.”

The majority of step-down clinical trials have been conducted in adults or children ≥ 12 years old [68–71]. Clear evidence on discontinuation of LABAs, which is likely to lead to asthma-associated impairment [72], in the pediatric population is lacking [73]. However, evidence does suggest that stepping down asthma medication in children is frequently successful but is infrequently done in everyday clinical practice [74], [75] despite the fact that a step-down treatment approach can reduce costs while preserving asthma control. For example, in a study including 4235 patients with stable asthma for ≥ 1 year, stepping down and maintaining chronic asthma medications resulted in similar clinical outcomes [76]. Of the patients who stepped down, 89.4% had preserved asthma control (versus 83.5% of those who did not step-down despite being eligible). Furthermore, stepping down treatment was associated with a significant asthma-related cost saving (\$34.02/month; 95% CI: \$5.42–61.24/month) and did not lead to an increase in emergency department visits, hospital visits, outpatient visits, or missed work/school days [76]. These findings demonstrated that controlling symptoms and preventing exacerbations with the least amount of medication is indeed possible. Further, in a retrospective observational study, Price et al analyzed primary care clinical data from the General Practice Research Database and the OPCRd [77]. Patients with asthma aged 4–80 years on ICS twice daily (n=26834) or

ICS/LABA (n=20 814) for ≥ 1 year before $\geq 50\%$ step-down in ICS dose were evaluated. The proportion of patients with no exacerbation significantly increased from the baseline year to the year after step-down ($p < 0.001$ for all groups). Adherence also improved significantly after stepping down treatment [77]. In general, data on stepping down treatment in children and adolescents is limited, and more studies are warranted to bridge gaps in knowledge.

Discussion

Step-up and step-down treatment approaches are recommended in children and adolescents when appropriate; however, goals of treatment and individual needs of patients and parents/caregivers must be considered before taking such a course of action. And, these approaches have gained traction, though modestly, in clinical practice. In a UK-based study using data from the CPRD and OPCR [40], the incidence of initial step-up episodes among 10 793 children aged 5–12 years with asthma was evaluated: ICS dose was increased in 58% of the children, add-on LABA was initiated in 32%, and an LTRA was added in 10%. However, results of a recent survey of 200 Australian physicians suggest familiarity with and adherence to childhood asthma management guidelines, particularly for step-down therapy, could be improved [75].

Additionally, gaps exist between what is recommended for stepwise management and what is being implemented in clinical practice. In a prospective study, data were collected from 924 patients recruited by general practitioners and 455 patients recruited by chest physicians in France over a follow-up period of 2 years [78]. Overall, asthma control was acceptable in 24% of patients at baseline and in 33.6% at the end of the study. ICS dose was maintained throughout the follow-up period for 56.3% of patients, and controller therapy was stepped-up only in 12.2% of patients with unacceptable asthma control at baseline [78].

This review draws its strengths from our extensive review of the recent literature and our clinical experience in management of asthma in the pediatric population. As a narrative review, our aim was not to focus on a specific research question—as in a systematic review—but rather to provide a broad, practical summary of evidence supporting step-up and step-down treatment approaches in the management of pediatric asthma.

Conclusions

Physicians need to consider multiple factors when treating children and adolescents with asthma. Treatment options have expanded with the approval of newer drugs. In line with available guidelines, optimized treatment needs to include both step-up and step-down approaches in this patient population. Implementing such approaches will maximize benefits and minimize associated adverse effects while attempting to meet individual patient goals. Patient education and monitoring asthma control both at home and in clinical practice settings are essential for successful changes in chronic asthma therapy.

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Declaration of Interest

LM has no conflict of interest relevant to this review. JB has worked as a principal investigator for Boehringer Ingelheim; sub-principal investigator for GlaxoSmithKline; principal investigator, speaker, and consultant for AstraZeneca; principal investigator, speaker, and consultant for Novartis; principal investigator and consultant for Sanofi/Regeneron; and editor-in-chief for *Journal of Asthma*. JB and LM have received no payment for authorship of this review.

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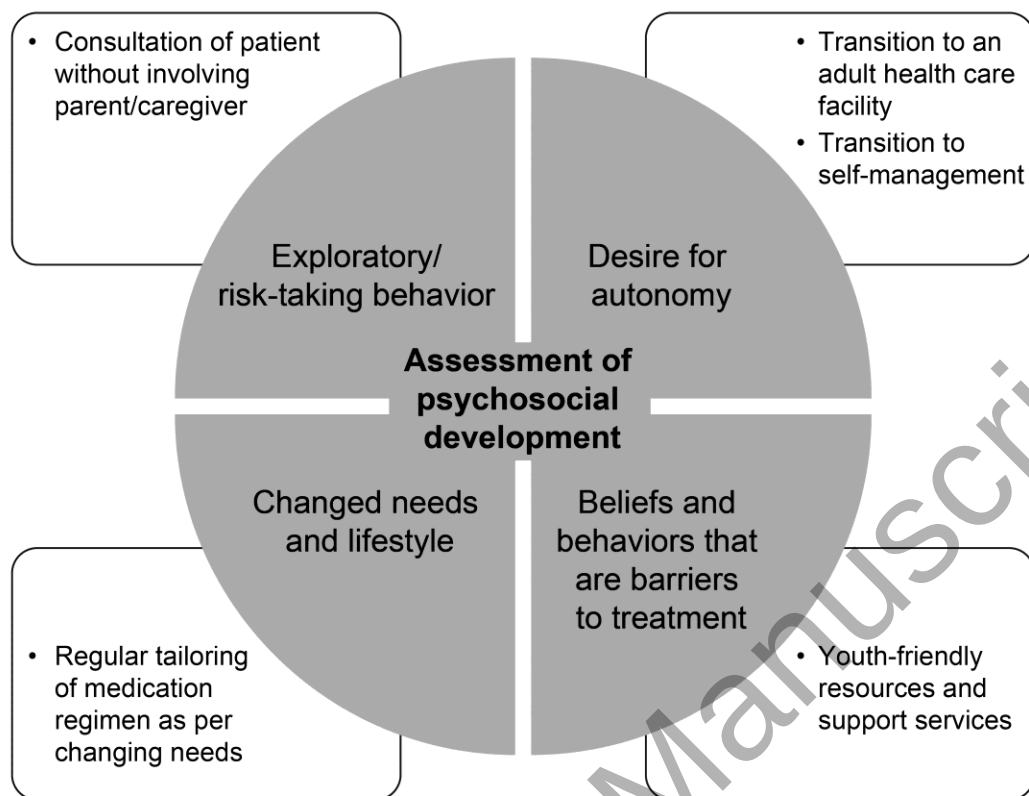
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Strategies for asthma management in adolescents

FIG 1. Strategies for asthma management in children and adolescents

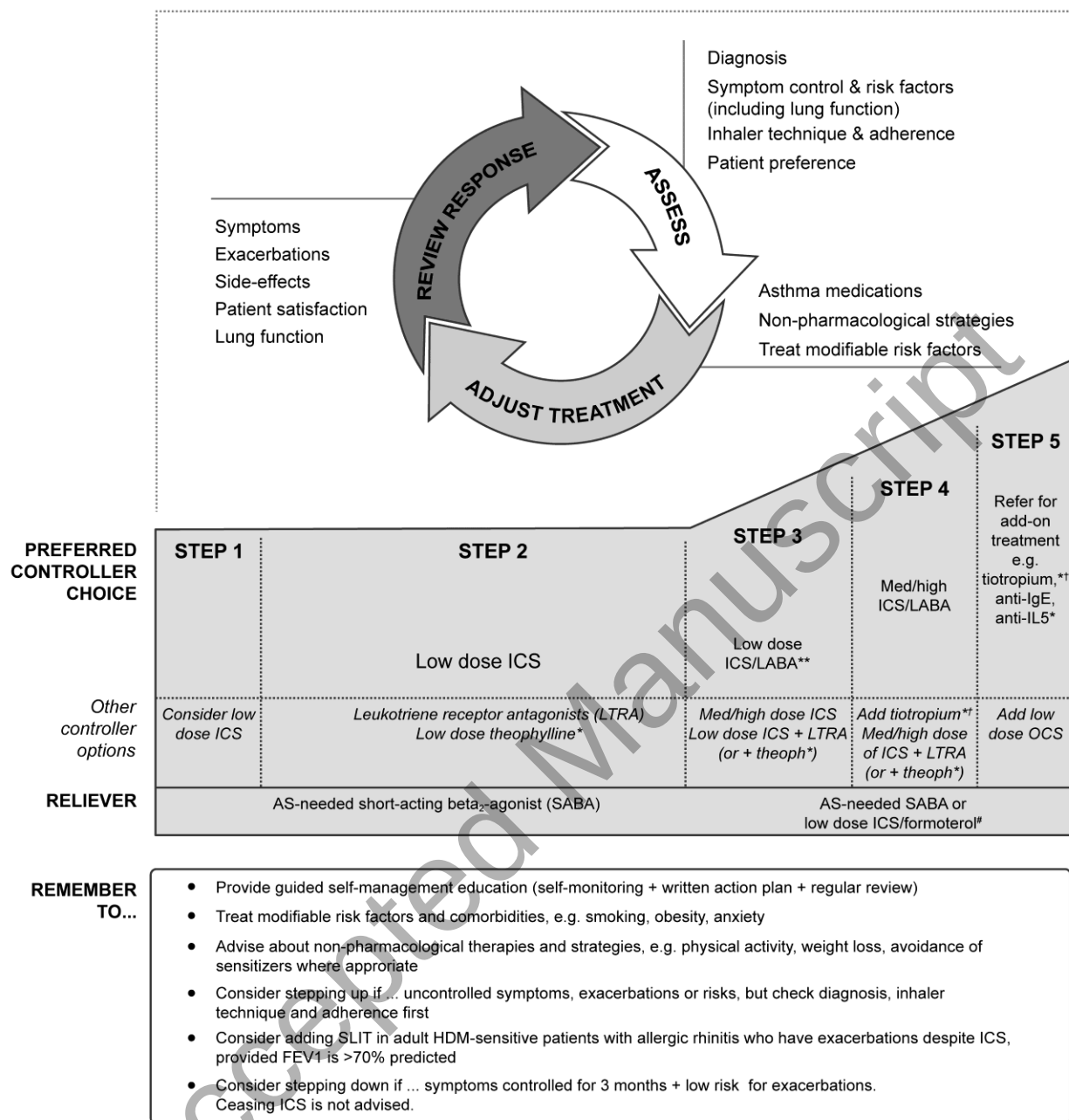


FIG 2. GINA stepwise management of asthma [2]

FEV₁, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; HDM, house dust mite; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL, interleukin; LABA, long-acting beta-2-agonist; LTRA, leukotriene receptor antagonist; med, medium dose; OCS, oral corticosteroids; SABA, short-acting beta-2-agonist; SLIT, sublingual immunotherapy

* Not for children <12 years old

** For children 6–11 years old, the preferred Step 3 treatment is medium dose ICS

Low dose ICS/formoterol is the reliever medication for patients prescribed low dose budesonide/formoterol or low dose beclometasone/formoterol maintenance and reliever therapy

† Tiotropium by mist inhaler is an add-on treatment for patients with a history of exacerbations; it is not indicated in children <12 years old

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TABLE 1: Stepwise management of asthma in children and adolescents as per GINA 2018 guidelines [2]

GINA	Adolescents: ≥ 12 to 17 years old	Children: 6 to <11 years old
Step 1 <i>As-needed reliever inhaler (SABA)</i>	No controller treatment Alternatively, consider low dose ICS	No controller treatment Alternatively, consider low dose ICS
Step 2 <i>Low dose controller medication plus as-needed reliever medication (SABA)</i>	Start low dose ICS if not already started Alternatively, consider LTRA or low dose theophylline	Start low dose ICS if not already started Alternatively, consider LTRA
Step 3 <i>One or two controllers plus as-needed reliever medication (SABA or low dose ICS/formoterol)</i>	Add LABA to low dose ICS Alternatively, - Consider low dose ICS+LTRA (or theophylline) in adolescents who have still not completed growth OR - Consider medium/high dose ICS^a in adolescents who have completed growth	Increase dose of ICS and start medium dose ICS^a Alternatively, consider low dose ICS+LTRA
Step 4 <i>Two or more controllers plus as-needed reliever medication (SABA or low dose ICS/formoterol)</i>	Refer to asthma specialist Increase ICS dose to medium/high dose ICS^a with LABA Alternatively, Start tiotropium add-on treatment for patients with a history of exacerbations OR	Refer to asthma specialist Increase ICS dose to medium/high dose ICS^a with LABA Alternatively, consider high dose ICS^a+LTRA

	Consider high dose ICS+LTRA (or theophylline)	
Step 5 Higher level care and/or add-on treatment (SABA or low dose ICS/formoterol)	Asthma specialist care is required Add tiotropium, omalizumab, mepolizumab, or benralizumab to high dose ICS ^a Alternatively, low dose OCS may be considered in adolescents who have completed growth	Asthma specialist care is required Add omalizumab to high dose ICS ^a Alternatively, low dose OCS may be considered ^a

^aAt any time in treatment, if medium/high dose ICS or low dose OCS is started in adolescents who have not completed growth, monitor growth regularly and consider changing to other alternatives or stepping down at the earliest possible time

For children aged 6–11 years, increasing the ICS dose is preferred over combination ICS/LABA.

For adolescents with exacerbations despite other therapies, the risk of exacerbations is reduced with combination low dose ICS/formoterol (with beclomethasone or budesonide) as both maintenance and reliever, compared with maintenance controller treatment plus as-needed SABA.

For patients with persistent symptoms and/or exacerbations despite 2–3 months of controller treatment, consider step-up after ruling out common problems such as wrong inhaler technique, poor adherence, persistent allergen exposure, comorbidities, and incorrect diagnosis

Consider step-down once good asthma control has been achieved and maintained for about 3 months, to determine the patient's lowest treatment that controls both symptoms and exacerbations

GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LABA, long-acting beta-2-agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; SABA, short-acting beta-2-agonist

TABLE 2: Efficacy and safety of tiotropium in children and adolescents in pivotal clinical trials

Referen ce	Szefer 2017 [51] NCT01634 152/Viva	Hamelmann 2016 [47] NCT0125723 0/ Ruba	Hamelmann 2017 [48] NCT01277523 / Pensie	Huang 2016 [53]	Vogelberg 2015 [50] NCT01383 499	Vogelberg 2014 [49] NCT01122 680
N, treated patients	400	397	392	80	101	105
Asthma severity	Severe	Moderate	Severe	Moderate	Not mentioned	Moderate
Study populati on	Children: 6 to 11 years	Adolescents: 12 to 17 years	Adolescents: 12 to 17 years	Children/ Adolesce nts; 6 to 14 years	Children: 6 to 11 years	Adolescents : 12 to 17 years
Study phase	III	III	III	Not mentione d	II	II
Treatme nt arms	TioR 2.5 µg QD, TioR 5 µg QD, PboR QD	TioR 2.5 µg QD, TioR 5 µg QD, PboR QD	TioR 2.5 µg QD, TioR 5 µg QD, PboR QD	Fluticaso ne propionat e aerosol, Fluticaso ne propionat e aerosol+ti otropium	TioR 1.25 µg QD, TioR 2.5 µg QD, TioR 5 µg QD, PboR QD	TioR 1.25 µg QD, TioR 2.5 µg QD, TioR 5 µg QD, PboR QD
Mainten	High-dose	ICS	High-dose		Medium-	Medium-

ance treatme nt	ICS+1 or more controller therapies (e.g., LABA or LTRA) or medium- dose ICS+2 or more controller therapies (e.g., LABA and/or LTRA and/or sustained- release theophyllin e)	background therapy, with or without LTRA; LABA therapy was not permitted during the study	ICS+1 or more controller therapies (e.g., LABA or LTRA) or medium-dose ICS+2 or more controller therapies (e.g., LABA and/or LTRA and/or sustained- release theophylline)		dose ICS background therapy, with or without LTRA; LABA therapy was not permitted during the study	dose ICS background therapy with or without LTRA; LABA therapy was not permitted during the study
Study duration	12 weeks	48 weeks ^a	12 weeks	12 weeks	Three 4- week treatment periods (Total 12 weeks)	Three 4- week treatment periods (Total 12 weeks)
Efficacy	Compared with placebo,	Improvement in peak FEV ₁ within 3 hours	The primary end point of efficacy	Tiotropiu m significan	For the primary efficacy	Peak FEV _{1(0-3h)} (the

	tiotropium 5 µg add-on therapy improved the primary end point, peak FEV₁, within 3 hours after dosing	after dosing at 24 weeks (primary endpoint) was statistically significant with both tiotropium doses compared with placebo. Significant improvements in trough FEV₁ at week 24 (a secondary endpoint) were observed with the 5-µg dose only	(change from baseline in FEV_{1(0-3h)}) was not met, although positive trends for improvement in lung function and asthma control were observed	tly improved lung function, reduced the use of SABAs, and improved sleep	endpoint, statistically significant differences in peak FEV_{1(0-3h)} response after 4 weeks of treatment were observed for each TioR dose group versus PboR. There was no dose-dependent response observed in patients treated with TioR. Compared to placebo, TioR also improved secondary and	primary endpoint), trough FEV₁, and FEV₁ AUC_(0-3h) responses for TioR 5 µg were superior to those for PboR and were greater than those observed with the 2.5-µg or 1.25-µg doses of TioR. Morning PEF response for all 3 TioR and evening PEF response in the TioR 5 µg and 2.5 µg groups
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					additional efficacy endpoints, including trough FEV ₁ response, FEV ₁ AUC _(0-3h) response, and FEV ₁ response over 3 hours post-dosing	were significantly higher than in the PboR group
Safety	Well-tolerated	Once-daily tiotropium was safe and well tolerated	Well-tolerated	Few adverse reactions with tiotropium	Well-tolerated across all three doses	Well-tolerated across all three doses

^aPrimary pulmonary function endpoint was assessed after 24 weeks of treatment

AUC, area under curve; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting beta-2-agonist; LTRA, leukotriene receptor antagonist; PboR, tiotropium Respimat[®]; PEF, peak expiratory flow; QD, once daily; SABA, short-acting beta-2-agonist; TioR, tiotropium Respimat[®]

TABLE 3: Efficacy and safety of omalizumab in children and adolescents in pivotal clinical trials

Reference	Busse 2011 [58] NCT00377572	Lanier 2009 [59] NCT00079937	Milgrom 2001 [60]
N, treated patients	419	627	334
Asthma severity	Allergic asthma of all levels of severity, 73% moderate-to-severe asthma	Moderate-to-severe, inadequately controlled allergic asthma	Moderate-to-severe allergic asthma requiring treatment with ICS
Study population	Children, adolescents, and young adults: 6 to 20 years	Children: 6 to 12 years	Males and premenarchal females: 6 to 12 years
Study phase	IV	III	Not available
Treatment arms	Omalizumab and Placebo	Omalizumab and Placebo	Omalizumab and Placebo
Maintenance treatment	Not clearly mentioned, LABA, ICS	The first 24 weeks of the treatment period was a fixed steroid phase, where the steroid dose was maintained constant; in the following 28 weeks the steroid dose was adjustable, depending on the patient's condition.	Beclomethasone dipropionate: The dose (initial range 168–420 mg/d) was kept stable for 16 weeks (stable-steroid phase), reduced over 8 weeks to the minimum effective dose (steroid-reduction phase), and maintained constant for the final 4 weeks.
Study	60 weeks	52 weeks	28 weeks

duration			
Efficacy	Omalizumab (versus placebo) significantly reduced the number of days with asthma symptoms and the proportion of participants who had ≥ 1 exacerbations	Over the 24-week and 52-week periods, omalizumab reduced the rates of clinically significant asthma exacerbations and the exacerbation rate, respectively, compared with placebo	More participants in the omalizumab (versus placebo) group decreased their beclomethasone dipropionate dose, with greater mean reductions in dose. Omalizumab reduced the requirement for rescue medication, incidence and frequency of clinically significant asthma exacerbations, asthma exacerbations requiring hospitalization, school absenteeism, and serum free IgE levels.
Safety	Comparable safety profiles	Comparable safety profiles	Comparable safety profiles

ICS, inhaled corticosteroid; IgE, immunoglobulin E; LABA, long-acting beta-2-agonist