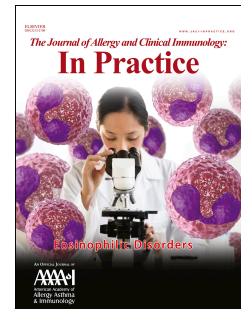


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Difficult-to-treat Asthma Management in School-Age Children**Prepared for the Journal of Allergy and Clinical Immunology: In Practice**

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Abbreviations:

BAL – bronchoalveolar lavage

FEV₁ – forced expiratory volume in 1 second

FVC – forced vital capacity

HIC – high income countries

ICS – inhaled corticosteroids

LABA – long acting β -adrenergic agonist

LAMA – long-acting muscarinic antagonist

LTRA – leukotriene receptor antagonist

NRAD - National Review of Asthma Deaths

SABA – short-acting β -2 agonist

STRA – severe therapy resistant asthma

TSLP – thymic stromal lymphopoietin

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Abstract

The World Health Organization divides severe asthma into three categories: untreated severe asthma, difficult-to-treat severe asthma, and severe, therapy resistant asthma. The apparent frequency of severe asthma in the general population of asthmatic children probably lies around 5%. Upon referral of these children, it is important to carefully evaluate the diagnosis of asthma before proceeding with modifying management along with applying a long-term monitoring plan. Identification of pathophysiological phenotypes using objective biomarkers is essential in our routine assessments of severe asthma. Although conventional pharmacologic approaches should be attempted first, there is a growing recognition that children with difficult-to-treat asthma may have unique clinical phenotypes that may necessitate alternative treatment approaches including asthma biologics. These new medications, especially those that have effects on multiple pathological features of asthma raise the hope that new treatment strategies could induce remission. Besides introducing new medications, the opportunity for closer monitoring is now feasible with advances in digital health. Therefore, we have the opportunity to improve response to medications, to individualize treatment and to monitor response along with potential steps to prevent severe asthma.

Introduction

Although many children with asthma experience an improvement in symptoms and airway inflammation with the initiation of asthma controller therapies, a subset of children remain symptomatic despite these therapeutic attempts. Not all of these symptomatic children have severe, therapy-resistant asthma (**STRA**), which is defined by the ERS/ATS [1] as asthma which requires treatment with high dose inhaled corticosteroids (**ICS**) plus a second controller medication to achieve asthma control. Instead, many of these children with asthma-like symptoms are *difficult-to-treat*. This is perhaps best conceptualized by the World Health Organization, which defines three categories of severe asthma [2]:

- Untreated severe asthma due to failure of diagnosis or lack of availability of treatment. This is common in low- and middle-income countries but there are pockets of poverty and deprivation in high income countries, especially where medications have to be purchased [3]. The solutions are largely political and include in some countries overcoming the stigma of an asthma diagnosis [4].
- Difficult-to-treat severe asthma, in which social and environmental factors and/or co-morbidities inhibit the response to treatment.
- Severe, therapy resistant asthma (**STRA**) which remains uncontrolled despite high level treatment with inhaled corticosteroids and other controllers, or alternatively, requires this high-level treatment to achieve control. The current ERS/ATS definition [1] is summarized in **Table 1**.

Therefore, difficult-to-treat asthma in children enters the differential diagnosis of the child referred with asthma-like symptoms which are not responding to standard therapies. An important consideration is to ensure another diagnosis is not being missed. As well as seeking clues to a different diagnosis, the positive evidence for a diagnosis of asthma should also be reviewed [5]. When considering apparently difficult-to-treat asthma, it is helpful always to think beyond airway pathology to extra-pulmonary co-morbidities such as obesity and breathing pattern disorders, and social and environmental factors, such as poor adherence and adverse environmental factors [6].

However, missing from most current definitions based on level of medication is the highly relevant assessment of level of risk, especially risk of a fatal or near fatal asthma attack. The UK National Review of Asthma deaths (**NRAD**) [7] and a recent meta-analysis [8] highlighted previous severe asthma attacks as a marker of risk. Other risk factors highlighted by NRAD in particular, but not most conventional definitions of severe asthma, include social/environmental factors such as over-use of short-acting β -2 agonists (**SABA**), under-use of ICS, recent discharge from the hospital, frequent emergency department visits with asthma and failure to attend routine checkups, and no provision or utilization of an asthma plan. Children with these risk factors are highly symptomatic and would be in the difficult-to-treat category. Unlike children with STRA, this difficult-to-treat group of children is also the one that asthma deaths are commonest.

The apparent frequency [9, 10] of severe asthma in the general population of asthmatic children will depend on resource availability, definition used and diagnostic work-up performed, but probably lies around 5%. There are some important general principles:

- Most children with asthma respond well to low dose ICS (100 mcg twice daily fluticasone) plus one other controller if administered regularly and correctly [11], and indeed few get any benefit from increasing the dose of ICS above this level. So if a child is not responding to low dose standard medications, the answer usually is not to prescribe more medications but look for extra-pulmonary co-morbidities and social/environmental factors to correct.
- At least half the children referred for 'beyond guidelines' therapy in fact become well controlled [12] after a detailed multi-disciplinary evaluation [13, 14], and indeed may be able to reduce the level of prescribed medication.
- STRA is rare in children. An important study was set up to determine whether children still symptomatic on ICS and long-acting β -2 agonists (**LABA**) responded better to the addition of azithromycin or a leukotriene receptor antagonist (**LTRA**) [15]. The study ended in futility because most children screened in fact did not have asthma at all or had difficult-to-treat asthma that needed addressing, and adequate recruitment could not be achieved.

It is clear that assessing these children requires time and the resources of a multi-disciplinary team. Information on management of severe asthma in children is limited, for example the number of studies with asthma biologics in children is small as compared to the number of medications and amount of information for adult asthmatics [16]. Many guidelines are very medication oriented, focusing on stepwise increase in therapy; this may be appropriate for adults, but for children there is no evidence that the highest steps are at all useful. Guidelines' writers must also be careful to avoid financial conflicts of interest [17]. However, the focus in the latest iteration of the Global Initiative for Asthma on looking for reasons for treatment failure

before prescribing more medications is very welcome [18]. There are reviews focusing on children specifically and the broader aspects of management which may help in assessment [19-21].

Attention in asthma guidelines needs to be directed to lung growth. Longitudinal studies show that for most, if not all children, lung function tracks from the pre-school years into the sixth decade at least [22-24]. Asthma of all severities, but particularly severe asthma, is associated with impaired childhood lung function and long term adverse respiratory outcomes such as adult chronic obstructive pulmonary disease; in the Melbourne study, early severe asthma was a bigger risk factor for chronic obstructive pulmonary disease than adult smoking [25]. Long term lung function worsens in those adults with multiple asthma attacks who do not use ICS [26]. Impaired lung function in young adults is also associated with premature and increased all cause morbidity and mortality, including cardiovascular and metabolic [27, 28]. There is also a strong transgenerational effect, with parental spirometry closely correlated with that of the offspring. As yet we have no strategies to stimulate impaired lung growth, but a focus on monitoring and protecting the child from adverse effects such as exposure to passive and active smoking and vaping, and indoor and outdoor pollution, is an essential part of management.

If co-morbidities and social/environmental factors are to be considered, the resources are unlikely to be found outside a specialist center. As well as respiratory pediatricians, the core multi-disciplinary team needs to comprise specialist nurses and physiotherapists, physiologists, pharmacists, clinical psychologists and social workers. There needs to be access to other specialists who understand the condition such as pediatric otorhinolaryngology, endocrinology and nutrition. Follow-up care by the center is also important. In the UK at least, the establishment of such centers for children lagged far behind that of adults, another example of how a real pediatric focus is lacking.

The purpose of this review is to discuss the management of school age children (age between 5 and 18 years) referred to a specialist clinic in a high-income country who have asthma apparently unresponsive to standard medications. This review focuses on mechanisms and phenotypes of severe asthma, current management approaches, opportunities to improve management, and unanswered questions.

Mechanisms and phenotypes of severe asthma

Identification of pathophysiological phenotypes using objective biomarkers is essential in our routine assessments of severe asthma. The aim of this section is to discuss biomarkers that are currently available, the strength of evidence for their utility in children and the gaps in knowledge. Key distinctions and similarities between adult and childhood phenotypes will be outlined.

Inflammatory phenotypes of severe asthma

Eosinophils underpinning disease and as biomarkers to guide therapy. Most children with severe asthma have allergic, eosinophilic disease associated with type 2 immune responses. When compared to non-asthmatic controls, children with severe asthma have evidence of both airway luminal and tissue eosinophilia [14]. However, the within group spread of data is wide, and more recent assessments of lower airway inflammation in broncho-alveolar lavage (**BAL**) from children with severe asthma confirm a heterogeneous profile of inflammation [29]. This is most likely explained by the influence of treatment with glucocorticoids, but also that only a cross-sectional assessment at a single time-point can be made. Pauci-granulocytic BAL (normal/absent eosinophils and neutrophils) was found in up to 52% of children with severe

asthma, while a mixed inflammatory profile (high neutrophils and eosinophils) was the next most common in 22%, 15% had neutrophilic BAL and 9.5% had eosinophilic BAL [30]. Only the mixed inflammatory phenotype with high BAL eosinophils and neutrophils demonstrated correlation between BAL and blood eosinophils.

The most direct non-invasive biomarker of lower airway inflammation is induced sputum [14]. Differential cell counts of eosinophils and neutrophils help to characterize the inflammatory phenotype and may be used to direct treatment [30]. However, induced sputum presents a challenge in clinical application because of the time taken for sample collection, processing and analysis. Sputum induction is also aerosol-generating and may not be safe to perform the COVID-19 pandemic. As a result, either blood eosinophils or exhaled nitric oxide are used as more pragmatic non-invasive inflammatory biomarkers. However, several studies in children have shown little direct correlation between blood and sputum or BAL eosinophils [30-32]. Despite this, blood eosinophils are assumed to be a surrogate for airway eosinophilic inflammation. Elevated blood eosinophils are required prior to prescription of biologics targeting eosinophilic inflammation. The concern is that the cut-off of 300 cells/mcl has been extrapolated from adult studies as a marker of efficacy [33]. But, in children, with such little evidence of an association between blood and airway eosinophilic inflammation, the optimal cut-off may be quite different and may impact efficacy. This discrepancy and extrapolation from adult studies highlights the need for childhood studies that assess both efficacy of anti-IL5 therapies and define pediatric specific biomarkers of response [34].

An important role of sputum eosinophils is in enabling a distinction between the clinical phenotypes of difficult-to-treat asthma and true STRA. A combined approach of clinical and sputum phenotyping has shown children with difficult-to-treat asthma may have elevated blood eosinophils, but have undetectable sputum eosinophils, while those with STRA have both blood and sputum eosinophilia [35]. This suggests difficult-to-treat asthma is a corticosteroid sensitive

phenotype, while STRA is characterized by a relatively corticosteroid resistant airway eosinophilia and highlights a pitfall of inappropriately considering that children with difficult-to-treat asthma need to be treated with biologicals if relying solely on blood eosinophils as a biomarker. Of course it may be that biologicals are appropriately prescribed in those intractably non-adherent as a rescue strategy to prevent asthma death.

Although induced sputum is the most reflective of lower airway inflammation, the practical difficulties in obtaining samples mean it is unlikely to be utilized frequently. However, there is currently no single non-invasive test or biomarker that identifies the presence of an airway eosinophilic inflammatory phenotype driven by type 2 mediators [36]. A composite-biomarker assessment which includes blood eosinophils, and indirect assessments of type 2 immunity, including total serum IgE and exhaled nitric oxide seems most appropriate and needs to be incorporated in future clinical trials (**Figure 2**). Alternatively, new biomarkers of type 2 immunity may also be needed. Adult data suggest none of the currently available biomarkers for airway eosinophilia, when used as an individual test, has ideal sensitivity or specificity to predict sputum eosinophilia [37]. A combined measure of these biomarkers may be more reliable but has yet to be established.

Neutrophils: a consequence of infection, corticosteroid treatment, or a marker of pathology?

In contrast to eosinophils, airway neutrophils are not increased in children with severe asthma when compared to non-asthma controls [38]. However, within severe asthma, there is a subgroup of children who have predominant lower airway neutrophilia. The most important point to consider in these patients is whether there is associated bacterial infection. The presence of bacterial pathogens is the most frequent explanation for a neutrophilic phenotype [29, 39]. However, even after excluding those with infection, there remains a group that have a

“neutrophil-high” phenotype [40]. A recent study divided children with severe asthma into BAL neutrophil-high (>5%) and low (<5%) and demonstrated increased neutrophil activation and degranulation and greater phagocytic capability in the neutrophil-high group, with the suggestion that treatments that target neutrophils may be important in this sub-group [40]. Although bacterial infection assessed by traditional culture was excluded, any associated alterations in the airway microbiome were not assessed. In addition, that was an assessment of airway luminal neutrophils, and in contrast, an assessment of intra-epithelial tissue neutrophils has shown the sub-group of children with high intra-epithelial neutrophils had better lung function, asthma control and were prescribed lower doses of ICS [38]. It is plausible that compartmental discrepancies may account for some of the differences in neutrophil-related findings in prior studies.

An unbiased analysis of BAL cytokines and their relation to an inflammatory phenotype in children with uncontrolled severe asthma has shown the highest cytokine levels were detected in children with a neutrophil predominant ($\geq 6\%$) BAL. Although the neutrophilic group had more bacterial and viral pathogens detected, higher cytokine levels were also present independent of infection. Of note, the neutrophilic group had a mixed cytokine response, characterized by Th1 (IL-12, TNF- α , IFN- γ), Th17 (IL-17, G-CSF) and Th2 (IL-4, IL-9) mediators [41]. It is hard to disentangle the impact of treatment with corticosteroids on numbers of airway neutrophils and the elevated cytokines, and the functional significance of both remains uncertain. The authors suggested persistent symptoms, despite corticosteroids and in the absence of eosinophils, means treatments that target type 2 immunity alone are unlikely to be successful in this group and alternatives are needed [41]. However, whether the cytokines are a consequence of infection, treatment with corticosteroids and the resulting neutrophilia, or are driving the disease cannot be determined without an interventional study. Interestingly, adult studies that have investigated efficacy of blocking IL-17 have not shown benefit [42], but airway neutrophilia was

not required for inclusion. Although azithromycin may be beneficial in a sub-group [43], whether the predominant benefit is from its anti-bacterial or anti-neutrophilic actions is unknown.

The data relating to neutrophils in childhood severe asthma highlight the importance of considering inflammation in context and emphasize that an isolated elevated neutrophil count is not sufficient for any meaningful clinical interpretation. The relevant compartment (peripheral, airway lumen, airway wall), presence or absence of infection, and ideally the functional characteristics of the neutrophils all need to be assessed before deciding whether the neutrophils are pathological or perhaps protective, or maybe bystanders [44]. In contrast to eosinophils, there is no relation between airway and blood neutrophil numbers [45]. Biomarkers or non-invasive tests that allow assessments of neutrophil function, not just their numbers, are therefore an important unmet need in the context of understanding their role in severe asthma.

Pauci-granulocytic inflammation: predominance of airway remodeling?

An important phenotype in children receiving high dose corticosteroids is pauci-granulocytic inflammation. A significant proportion, (approximately half [29]) of children with pauci-granulocytic inflammation remain symptomatic, with frequent exacerbations and poor lung function despite little evidence of airway inflammation. The most likely explanation for poor control in these patients is a predominance of structural airway changes, or remodeling. However, just as inflammation is heterogeneous, each feature of remodeling (increased reticular basement membrane thickness, airway smooth muscle, goblet cell hyperplasia, angiogenesis) is present to varying degrees in each child [29], making it important to consider phenotypes of remodeling [46] and highlighting the need for therapies that target individual structural changes. A significant unmet need is the current lack of non-invasive tests or biomarkers that reliably allow assessments of airway remodeling. Quantitative CT imaging techniques have been employed in adult studies [47], but direct relation to airway structural changes have not been

shown in children [48], and radiation exposure from repeated CT scans is hard to justify. However, there are data to suggest innate epithelial mediators, specifically IL-33, is associated with remodeling in childhood severe asthma [49]. Therefore, to facilitate remodeling biomarker discovery we must improve our understanding of the mechanisms underpinning structural changes in childhood disease.

Longitudinal inflammatory patterns – “phenotype stability”

Almost all studies that have reported airway inflammatory phenotypes in childhood severe asthma have the limitation of being cross-sectional, thus presenting only a single snap-shot picture. The limited data available suggest little inflammatory phenotype stability over time, and there is no data reporting change after interventions [50, 51]. In contrast, studies in adult severe asthma are increasingly focusing on identifying longitudinally stable phenotypes. Four phenotypes that were stable over time were identified and validated in two independent severe asthma cohorts, ADEPT and U-BIOPRED, these included disease severity, lung function, sputum inflammation, blood eosinophils and exhaled nitric oxide [52]. Sputum granulocyte variability over time has been assessed in the adult Severe Asthma Research Program (SARP) III cohort, with predominantly eosinophilic, predominantly low eosinophils and highly variable groups, and similar categories for neutrophils. The highly variable eosinophil group had more asthma exacerbations, while the group with both persistently high eosinophils and neutrophils had the worst lung function [53]. The importance of assessing blood eosinophils over time, is highlighted by changes in adults that received placebo in trials of benralizumab [54]. Two-thirds of patients had a change in blood eosinophils over 6 months, and 59% in the low eosinophil group had changed to high eosinophils after 4 weeks. A single blood eosinophil count is therefore insufficient when phenotyping severe asthma, emphasizing the need for repeated measures and a composite biomarker approach (**Figure 1**).

Evaluation of difficult-to-treat asthma

In children with difficult-to-treat asthma, it important to consider whether the child truly has asthma or a condition that mimics asthma. Therefore, the physician should perform a thorough evaluation of comorbid conditions that can make asthma difficult to manage. In this section, the tests useful in evaluating difficult-to-treat asthma will be discussed, followed by a brief summary of available medications and then a summary of a practical approach to the assessment and management of difficult-to-treat asthma in children.

Laboratory tests

Laboratory tests such as blood eosinophil counts and allergen specific IgE testing may be useful for ascertaining asthma phenotype, but are not diagnostic for asthma itself.

Spirometry

Forced expiratory airflow measures from spirometry can help with confirmation of the asthma diagnosis and are also useful for the evaluation of asthma control and response to therapy over time. Spirometry provides an objective measure of airflow limitation and is particularly advantageous in children who have a poor perception of respiratory symptoms or in children who are at risk for asthma exacerbations. However, valid spirometry results require that children properly perform a prolonged and forceful expiratory maneuver. Children with asthma typically have reduced airflow with forced exhalation, manifested by an abnormally low FEV₁ or FEV₁/FVC, or by an improvement in FEV₁ $\geq$ 12% after an inhaled SABA (e.g., albuterol). However, spirometric measures are not sensitive for asthma, since approximately half of children with asthma will have normal spirometric values when otherwise healthy. Abnormalities of the shape of the flow volume curve may give a clue to an alternative diagnosis, such as large airway obstruction.

Bronchoprovocation and exercise challenges

Bronchoprovocation challenges with inhaled methacholine, mannitol, and cold or dry air can also be helpful with the diagnosis of asthma since the degree of airway hyperresponsiveness to these exposures tends to correlate with the degree of asthma severity and airways inflammation. However, these tests are most often used to rule out asthma or to confirm asthma in children with normal spirometry and are rarely practical outside of an investigational setting. Exercise challenges, which involve aerobic exertion on a treadmill, can also identify exercise-induced bronchospasm and airflow obstruction. However, exercise challenges in the clinical setting may not reproduce the level of exertion and can miss asthma that is induced from vigorous exertion associated with many sports.

Exhaled nitric oxide testing

Exhaled nitric oxide is a noninvasive measure of airway inflammation obtained from the exhaled breath. Exhaled nitric oxide may support a diagnosis of asthma in children for whom the diagnosis is uncertain, although the sensitivity and specificity of the measure is dependent on the clinical situation. Elevated exhaled nitric oxide values can also be seen in children with allergic rhinitis without asthma and are therefore not diagnostic of asthma when considered alone. Values more than 50 ppb (or 35 ppb in children 5-12 years of age) are consistent with type 2, eosinophilic-mediated inflammation and may indicate a greater likelihood of response to corticosteroid treatment [55]. A normal exhaled nitric oxide value in a highly symptomatic, treatment-naïve child casts strong doubt on the diagnosis of allergic asthma as the cause of symptoms.

Radiology

Chest radiographs are often normal in children with asthma but may show nonspecific findings of hyperinflammation (with flattening of the diaphragm) and peribronchial thickening. Chest radiographs are recommended during the initial evaluation of the children with difficult-to-treat asthma and are useful for ruling out other differential diagnoses. High-resolution, thin-section chest computed tomography may also be considered to rule out other lung abnormalities, such as bronchiectasis, which are difficult to appreciate on a chest radiograph.

Bronchoscopy

Bronchoscopy is often indicated to rule out other conditions such as or endobronchial obstruction or pulmonary aspiration. Indications for bronchoscopy include persistent stridor, persistent wheezing unresponsive to therapy, and recurrent atelectasis or pneumonia. Central airway biopsies may show changes to the reticular basement membrane and submucosal inflammatory cells. However, the distribution of the pathology in the bronchial tree is heterogeneous, so the representativeness of small biopsy samples could be limited. BAL for differential inflammatory cell counts may also be of limited value unless profound eosinophilia or neutrophilia is present, although cultures of the BAL fluid may be useful for the identification of any pathogens present.

Treatment of difficult-to-treat asthma

First-line controller therapy

The cornerstone of pharmacologic therapy for children with difficult-to-treat asthma is higher-dose ICS combined with other secondary controller therapies. These should only be used after ensuring that management has been optimized, including checking technique with inhaler devices and ensuring adherence. This recommendation is based on evidence from children with mild-to-moderate asthma which demonstrates a reduction in symptoms, a lesser risk of exacerbations, and improved quality of life in children treated with ICS compared to those

411 treated with placebo [56]. Although there are few randomized studies of high-dose ICS in
412 children with asthma, there is some evidence that oral corticosteroid doses can be lowered if
413 children are treated with higher ICS dosages [57]. Careful monitoring of children treated with
414 continuous, high-dose ICS is warranted, since these medications can result in suppression of
415 growth and adrenal function and altered skin and bone metabolism. In children who achieve
416 sustained asthma control over 3 or more months, corticosteroid doses should be gradually
417 tapered to the lowest possible dose that maintains control.

418
419 A few children may require continuous oral corticosteroids to keep their asthma under control.
420 Use of oral corticosteroids increases the risk of systemic side effects such as growth
421 retardation, adrenal suppression, and altered skin and bone metabolism. These medications
422 should therefore be used cautiously. If used, the dose should be gradually tapered to the lowest
423 dose that maintains symptom control. In general, the use of oral corticosteroids has been
424 superseded with the advent of the biologicals (below).

426 ***Secondary controller therapies***

427 Other recommended secondary controller medications for children with severe asthma include
428 LABAs and LTRAs. LABAs are the preferred secondary treatment and are superior to LTRA for
429 the prevention of exacerbations and for the improvement of lung function and symptoms in
430 adults inadequately controlled on low doses of ICS [58]. In children, the addition of a LABA to an
431 ICS does not significantly reduce exacerbations or healthcare utilization for asthma but does
432 significantly improve lung function compared to doubling of the ICS dose [59]. LABA add-on
433 therapy is also associated with better asthma symptom control and lung function than LTRA
434 add-on therapy in children [11], although treatment responses can vary.

While questions have been raised regarding the safety profile of LABA, namely the risk of severe asthma exacerbations in patients of African ancestry [60], a large Phase 4 study found that LABA in a fixed-dose ICS combination inhaler did not result in a higher rate of serious asthma-related events in adults [61] or children [62]. Nonetheless, providers and parents may remain hesitant about the use of LABA medications in children [63]. In those cases, the addition of an LTRA or a long-acting antimuscarinic antagonist (**LAMA**) to higher dose ICS therapy may be warranted.

LAMAs such as tiotropium were recently approved for use in patients with asthma and have been shown to improve lung function in adults with poorly controlled asthma despite ICS therapy [64]. Tiotropium also reduces the likelihood of exacerbations requiring systemic corticosteroids in adults treated with ICS monotherapy [65]. Studies in children have yielded similar results. In two Phase 3 studies of children 6-11 years of age with severe asthma and adolescents 12-17 years with moderate persistent asthma, tiotropium also improved lung function as an add-on therapy to ICS [66, 67]. Therefore, for patients 12 years and older with uncontrolled persistent asthma for whom a LABA is not used, current guidelines recommend addition of LAMA to the ICS as a step-up approach [55]. Adding a LAMA is not more efficacious than adding a LABA, so LAMAs should not be selected over a LABA unless necessary. LAMAs also have a less favorable benefit-harm profile and should not be used in patients with a risk of urinary retention or glaucoma.¹ LAMAs can also be added to ICS/LABA combination therapy if the patient remains symptomatic [55].

Current guidelines do not recommend the routine use of methylxanthines such as theophylline in children given the potential for side effects [6]. However, sustained-release low-dose theophylline may be considered in adolescents who remain uncontrolled despite other therapy attempts. The addition of theophylline to low-to-medium dose ICS improves lung function

measures in a manner similar to doubling the dose of the ICS [68]. Studies on the efficacy of theophylline compared to LABA add-on therapy are lacking.

Immunosuppressants such as cyclosporine A, methotrexate or azathioprine have a limited evidence base and are not recommended due to low quality of available evidence and a high risk of side effects [6]. Guidelines indicate that if methotrexate is to be used, it should be administered by specialized centers only in patients with daily systemic corticosteroid use. Chest radiography, complete blood counts with differential and platelets, liver function tests, serum creatinine and diffusion capacity are recommended before treatment is initiated and during the treatment period. As with oral corticosteroids, these strategies have been superseded by the biologicals (below),

Allergen immunotherapy

Many children with difficult-to-treat asthma have type 2 inflammation with aeroallergen sensitization. Current guidelines recommend the use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in patients whose asthma can be adequately controlled at the initiation, build up, and maintenance phase of immunotherapy. These individuals may benefit from improvements in allergic rhinitis and conjunctivitis which could positively impact quality of life. The efficacy of subcutaneous immunotherapy with regard to medication use and exacerbations is not clear. Subcutaneous immunotherapy is also not recommended in patients with severe asthma given the potential for systemic reactions of potentially great severity. Children with severe asthma also tend to have sensitization to multiple versus single aeroallergens [69] which may complicate the delivery of therapy [70]. Sublingual immunotherapy is not currently recommended based on available data.

Biologic therapy

Although conventional pharmacologic approaches should be attempted first, there is a growing recognition that children with STRA may have unique clinical phenotypes (each of which corresponds to a unique biological endotype) that may necessitate alternative treatment approaches. Biologics may be selected for these children when conventional therapy fails. There are currently five approved biologics for the treatment of asthma in the United States and only omalizumab and mepolizumab for children in the UK at present (**Table 3**). However, it is important to note that although the pivotal Phase 3 studies for several of these biologics included adolescents 12-17 years of age, adolescents were not largely represented in these studies [71-75]. These biologics also exclusively target patients with type 2-mediated inflammation. Yet despite careful selection of eligible patients for biologic initiation, patients have different responses to these interventions in real-world clinical settings. In one study, responses ranged from super response (14% of patients), partial response (69% of patients), and non-response (11% of patients) [76]. In that same study, asthma remained poorly controlled in 48% of patients after 2 years of treatment, while 32% of patients remained on chronic oral corticosteroids [76]. There is also no consensus about which biologic to select first and no evidence for the use of multiple biologics simultaneously. If biologics are to be used, patients should be carefully selected before initiation. Given the high cost of these agents, treatment response should be globally assessed, with discontinuation if there is no response within four months of administration [6].

Anti-IgE therapy (omalizumab). Omalizumab is an injectable recombinant humanized IgG1 monoclonal anti- antibody that prevents IgE from binding to its receptor on mast cells and basophils. It is given every 2-4 weeks in patients 6 years and older with persistent allergic asthma with at least one positive skin test (or an elevated specific IgE level) to an aeroallergen and an elevated serum IgE level with a restricted range. In a meta-analysis of 25 trials of adults and children, omalizumab reduced asthma exacerbations and hospitalizations when administered as an adjunct to ICS [77]. In children aged 6–12 years, two randomized, placebo-

controlled studies with moderate-to-severe asthma showed omalizumab reduced ICS doses and the number of exacerbations [78, 79]. In another study, omalizumab significantly reduced the rate of clinically significant asthma exacerbations, severe exacerbations, and emergency department visits in adolescents and adults with poorly controlled severe persistent asthma [80]. Omalizumab may be most effective in children with allergic sensitization and asthma who require high doses of ICS and experience frequent exacerbations. In inner-city children and young-adults with asthma, treatment with omalizumab added to a regimen of guidelines-based therapy further improved asthma control, nearly eliminated seasonal peaks in exacerbations, and reduced the need for additional medications to control asthma [81]. However, variability in clinical responses to omalizumab defined by asthma control, asthma-related quality of life, and lung function over 4 years of therapy, have been noted and cannot be easily predicted [85]. In one study, response to omalizumab was significantly poorer in patients with a longer duration of asthma, a history of a near-fatal asthma episode, or a hospitalization for asthma in the year before therapy [82]. Hypersensitivity reactions (including anaphylaxis) have also been reported following approximately 0.1% of injections.

Anti-IL-5 therapy (mepolizumab, reslizumab, benralizumab). Mepolizumab (the only licensed anti-IL5 monoclonal in the UK for children) is an anti-IL-5 antibody that binds to the IL-5 ligand and prevents IL-5 from binding to its receptor. This blocks IL5-mediated eosinophil production. Mepolizumab is administered subcutaneously every 4 weeks in patients 6 years and older with severe eosinophilic asthma with a suggested absolute blood eosinophil count of at least 150 cells per microliter (300 in the UK) and at least 4 exacerbations necessitating systemic corticosteroids in the previous year. Like omalizumab, mepolizumab reduces annual exacerbation rates and improves quality of life as compared to placebo in adults with eosinophilic asthma [83]. It rarely causes hypersensitivity reactions. A lack of clinical response to omalizumab does not necessarily predict a lack of clinical response to mepolizumab [84].

Reslizumab is also an anti-IL-5 antibody that binds to the IL-5 ligand and prevents IL-5 from binding to its receptor. Reslizumab is administered intravenously and is approved for patients ≥ 18 years with severe asthma. It is suggested for patients with an absolute blood eosinophil count of at least 400 cells per microliter, with weight-based dosing every three weeks. Reslizumab is not currently approved for use in children. In two large Phase 3 clinical studies, reslizumab also improved lung function, asthma control and asthma symptom in adults with elevated blood eosinophils who were inadequately controlled with ICS [85, 86].

Benralizumab is also an anti-IL-5 antibody, that unlike mepolizumab and reslizumab, binds to the IL-5 receptor alpha subunit, resulting in apoptosis of eosinophils and basophils. Benralizumab is approved for patients 12 years and older with severe eosinophilic asthma with a suggested absolute blood eosinophil count of at least 300 cells per microliter. Benralizumab is administered subcutaneously every 2 weeks and has been shown to reduce asthma exacerbations compared to placebo [87, 88]. The reduction in exacerbations was greatest in patients with higher blood eosinophils and a more frequent exacerbation history [89]. Two-year follow-up data also demonstrate sustained improvements in asthma exacerbations, as well as modest improvements in health-related quality of life and lung function [90]. Improvements in quality of life and lung function are more prominent in patients with higher baseline eosinophils [91].

Anti-IL-4 receptor antibody therapy (dupilumab). Dupilumab is an anti-IL-4 receptor antibody that binds to the IL-4 receptor alpha subunit and blocks signaling of both IL-4 and IL-13. Dupilumab is administered subcutaneously every 2 weeks in patients 6 years and older with severe eosinophilic asthma. It is suggested that patients have an absolute eosinophil count of at least 150 cells per microliter or an exhaled nitric oxide level of at least 25 ppb. In meta-analysis,

dupilumab was associated with significant reductions of the annualized rate of severe asthma exacerbations and oral corticosteroid use and a statistical increase in the absolute FEV₁ [92]. Other studies have shown improvements in asthma control, quality of life and rescue medication use, although these improvements did not meet the minimal important clinical difference [93]. Long-term safety data are lacking.

Opportunities to improve management of difficult to treat asthma

Advances in asthma care

Times have significantly changed in the management of severe asthma for children. Back in the 1980s, children were often referred to specialty centers for management or suffered the consequences of frequent courses or even daily systemic corticosteroids and theophylline therapy [94]. In the 1980s there were residential facilities, such as National Jewish Center for Immunology and Respiratory Medicine (now National Jewish Health) in Denver, Colorado, and Pilgrim's School in the UK that sought to gain better control by providing an escape from environmental factors and supervised medication administration.

Fortunately, the 1990s ushered in better treatments, such as inhaled medication administration to take the place of orally administered medications and the application of asthma guidelines. Medications, such as ICS with greater potency, especially when combined with LABA, had a significant impact on reducing the need for oral corticosteroids and theophylline. That medication strategy of an anti-inflammatory with a potent bronchodilator combined with the introduction of asthma biologics in the 2000s, resulted in theophylline largely disappearing as maintenance therapy and limited use of systemic corticosteroids, except for significant asthma exacerbations.

The development of new medications, as well as the focused attention of government agencies, such as the National Institutes of Health on developing asthma guidelines, investment in conducting research to address emerging questions and conducting research to identify biomarkers associated with favorable medication response have elevated overall care in general. The ongoing revision of asthma guidelines, including global strategies, specifically the Global Initiative for Asthma, as well as increased number of trained asthma specialists have improved access to state-of-the art asthma care and eliminated the need for asthma residential facilities.

Asthma biologics – recent developments

The introduction of asthma biologics has made a significant impact on reducing exacerbations in severe asthma. This was initiated by the introduction of anti-IgE in the early 2000s, followed by recent approvals of anti-IL5 and anti-IL4/13 therapies with approvals in adolescents and some having approval down to six years of age. As previously summarized, the available asthma biologics tend to work better in those patients having characteristics of allergic airway inflammation or high TH2 features. New medications are on the horizon, such as anti-TSLP, that may have a greater chance of improving asthma control not only in high T2 individuals but also in low T2 patients [95-97]. This medication not only reduces exacerbations but also has a significant effect on improving pulmonary function and reducing biomarkers of inflammation [97]. These new medications, especially those that have an effect on multiple pathological features of asthma raise the hope that new treatment strategies could induce remission.

The concept of asthma remission

Remission has been observed in other chronic diseases, but to date, no asthma medication has been capable of inducing asthma remission. Remission can occur spontaneously in some patients, usually those with good pulmonary function, low airway hyperresponsiveness and low

IgE and blood eosinophils [98]. Menzies-Gow and colleagues sought to define asthma remission as induced by medications and they followed this discussion with a review of medications that had the potential to induce remission [99, 100]. Clinical remission is characterized by the elimination of asthma symptoms for at least one year while off medication. Complete remission would occur where there is reduction in underlying features of the disease, such as reduction in biomarkers. It remains to be seen whether any of the current biologics are capable of inducing remission, or alternatively, are capable of improving asthma control to the point that asthma medications are not required while on the biologic therapy. Longer term studies and experience will be needed to make these observations. One of the caveats is that reduced airway caliber that happens antenatally or longstanding severe asthma that results in airway remodeling may be irreversible and thus unresponsive to treatment [101].

Even now, the current potential for asthma biologics has prompted questions on whether early intervention in the appropriate population may be useful in altering the natural history of asthma and preventing airway structural changes associated with severe asthma. Meanwhile, asthma biologics can be selected for children based on the age of regulatory approval, potential for alleviating other co-morbid conditions, such as atopic dermatitis, urticaria and nasal polyps, as well as the feasibility for home administration [102].

Application of technology to improve communication

Our introduction to electronic communication came with the development of electronic medical records. In the United States, this was introduced as a form to validate billing for services. However, the systematic collection of information, provides the opportunity to communicate more effectively across health care locations. In addition, modifications of these records now presents the opportunity to summarize information over the life course of a patient. One obvious

application would be to look at pulmonary function over time to evaluate progression of the disease as indicated by loss of pulmonary function [22, 103].

Beyond electronic medical records, advances have been made in electronic medication monitoring. While these instruments have not necessarily improved asthma control, they do provide the opportunity to assess patient and parent behavior around controller and rescue medication use on a day-by-day basis as compared to only monitoring medication refills [104, 105]. In addition, various companies are working on non-invasive methodology to assess pulmonary function, vital signs and symptoms on hand-held devices and thus facilitate home monitoring [106]. The non-intrusiveness of these innovations is particularly appealing, since the intrusiveness of older technology has hindered the field. It is therefore feasible, that the clinician could have easy access to multiple forms of information at their fingertips including that obtained at a visit, that obtained from home monitoring and laboratory and climate information. Indeed, that would provide a full picture of asthma control between visits as compared to brief and focused evaluations at periodic patient visits [107]. Home monitoring could become useful in identifying early signs of loss of control and impending asthma exacerbations. To date, a reliable marker of an impending asthma exacerbation with high specificity and high sensitivity has not been identified, however, the area of telehealth has been jump-started by the COVID pandemic.

We now have characteristics to assess the likelihood of an asthma exacerbation in the coming year. The best predictor is an exacerbation in the prior year and low pulmonary function. However, biomarkers, such as blood eosinophils, serum IgE and the number of allergen skin tests can be used to predict seasonal exacerbations [108, 109]). Also, composite asthma scores, such as CASI and ASSESS, have been developed that allow the clinician to look at asthma burden over time and evaluate response to various interventions including asthma

biologics [110, 111]. The growing information about asthma phenotypes and endotypes developed from long-term studies of severe asthma and clustering techniques, allows us to characterize patients and establish pathways that can be alleviated for response to medications [112].

Approach to the School-Aged Child with Difficult-to-Treat and Severe Treatment Resistant Asthma

The authors would like to propose an approach to children with difficult-to-treat and STRA incorporating the previously discussed management and phenotyping strategies into clinical practice (**Figures 2, 3, and 4**). An algorithmic approach for other conditions, such as that used in chronic pediatric cough, results in an expedited diagnosis, reduced unnecessary interventions, and improved quality of life [113]. Asthma physicians should recognize that a one-size-fits-all approach to difficult-to-treat and STRA populations may ignore patient-specific factors, including phenotypes, biomarkers, previous therapies, and psychosocial barriers. As such, this approach should be tailored as needed.

Diagnosing Difficult-to-Treat Asthma

Distinguishing asthma, as opposed to a disease mimicker or a co-morbidity, as the cause of the patient's symptoms should initially be based upon history, physical examination, and spirometry (**Figure 2**). Alternative diagnosis to asthma should be considered if the history reveals symptoms resistant to albuterol, systemic steroids, escalating controller therapy, or removal of triggering exposures [114].

In children, many respiratory conditions can present with signs and symptoms that are similar to those of asthma. These are detailed in **Table 1** and include upper respiratory tract conditions such as rhinitis and sinusitis, middle respiratory tract conditions such as vocal cord

dysfunction and airway anomalies, and lower respiratory tract conditions such as bronchiolitis and pneumonia. Gastroesophageal reflux and rhinosinusitis are common causes of chronic or intermittent cough yet can be challenging to diagnose in children. For example, gastroesophageal reflux tends to be clinically silent and children with chronic sinusitis often do not report sinus-specific symptoms such as sinus pressure and tenderness. Gastroesophageal reflux and rhinosinusitis are also frequently comorbid with childhood asthma and can make asthma difficult to control. Vocal cord dysfunction can also co-exist with asthma and manifests as intermittent wheezing, coughing and shortness of breath (sometimes in the setting of exercise or psychological stress) due to involuntary adduction of the vocal cords. Treatment of the causes of vocal cord irritability, which include high gastroesophageal reflux/aspiration, allergic rhinitis, rhinosinusitis, and asthma, can improve vocal cord dysfunction in affected children.

Exam and spirometry are not without their limitations. An obstructive pattern on spirometry can be seen in other pediatric lung disorders in the differential diagnosis for asthma, including cystic fibrosis. In the difficult-to-treat or uncontrolled asthmatic, clinicians should always confirm a bronchodilator response and have a low threshold for obtaining lung volumes.

Supporting testing including FeNO, peripheral blood eosinophils, serum IgE, and allergy skin prick or blood testing, may support a diagnosis of asthma given the common atopic nature of pediatric asthma, with non-atopic asthma or TH2 low asthma potentially portending poor response to standard therapies [115]. These biomarkers can also guide selection of the best step-up controller therapy to improve asthma control [116], thereby minimizing exposures to less beneficial or potentially harmful therapies. Environmental aeroallergy testing can direct the use of allergen immunotherapy; however, it should be noted that NHLBI guidelines indicate that allergen immunotherapy should only be considered in patients with mild-to-moderate asthma, not uncontrolled severe persistent asthma [55].

Throughout this approach, asthma control should be reassessed, as utilization of evidence-based guidelines therapy may be sufficient alone to enable asthma control. The definition of control should not be limited to guidelines-based definitions alone but also include fatal or near fatal asthma, CASI and ASSESS scores, and patient and family goals of care. Patient-centered goals can increase patient and family “buy-in” into asthma management, ultimately leading to improved asthma control [117].

Monitoring over time

For children with well-controlled or mild asthma, two to four checkups per year are recommended for reassessing and maintaining asthma control. However, more frequent evaluations are needed for children with difficult-to-treat asthma. For these children, a structured approach to evaluation is beneficial. This includes a careful search for co-morbidities and triggers and a review of exacerbations and healthcare utilization for asthma (such as hospitalizations and Emergency Department visits). Routine spirometry and exhaled nitric oxide monitoring may also be useful for assessing the response to pharmacologic therapy, predicting loss of control with ICS tapering, and predicting future asthma exacerbation. Psychological screenings may be also worthwhile since psychosocial factors such as anxiety and depression are important risk factors for frequent asthma-related healthcare utilization. Encouraging adoption of a healthy lifestyle with programs that address poor diet, inactivity, and sedentary lifestyles of the child with asthma can also be important for achieving adequate asthma control. At each visit, adherence to the prescribed treatment regimen should also be evaluated. Education on how to use asthma medications and how to follow an asthma action plan should be provided and reinforced at each visit. Home visits are also useful to evaluate exposures in the home, access to prescribed therapies, psychosocial factors and other risk factors such as social vulnerability to poorer asthma outcomes. However, it is recognized that real-world practicality of home visits is limited given issues of labor and time costs. Also, CoVID may limit

the ability to do such visits, but perhaps in the future virtual visits using facetime or a similar platform may be useful.

If corticosteroid responsiveness is in question, this could be evaluated after a high dose of oral corticosteroids or an injectable dose of depot triamcinolone acetonide. Responsiveness is typically assessed 2-3 weeks after these interventions with a battery of measures. A multi-domain approach to assessment of corticosteroid responses is recommended since there is currently no gold standard for this purpose and there are no reliable single predictors of response pattern [30]. For example, in one report, only 11% of children with severe refractory asthma had a “complete” response to systemic corticosteroids, evidenced by improvements in symptoms, FEV₁, FEV₁ bronchodilator reversibility and exhaled nitric oxide concentrations [118]. Separate studies of children with difficult-to-treat asthma have further highlighted discordance between asthma symptoms, lung function parameters, exhaled nitric oxide concentrations and blood and sputum eosinophil counts after corticosteroid administration [119, 120].

Domains in the Management of Difficult to Treat Asthma

Additional testing: More invasive testing may be indicated based on a patient’s response, or lack thereof, to therapy, physical exam, or history features (**Figure 3**). The benefits of this additional testing must be weighed against the risks, including anesthesia with bronchoscopy, radiation with CT scan, or the possibility of a false negative in an exercise challenge. *In vivo* corticosteroid responsiveness evaluations are not standardized, leading to potential false negatives or adverse effects pending on the duration and dose of steroid used. Intramuscular triamcinolone injections have been associated with subcutaneous atrophy at the injection site [121] but have the merit of assuring adherence. Alternatively, direct observation in a hospital setting can be utilized to ensure adherence and assess steroid responsiveness [122].

Corticosteroid responsiveness can be explored through *in vitro* testing of PBMCs, where available [123].

Treatment of co-morbid conditions: The benefit of a multidisciplinary team is highlighted when co-morbidities are identified, including inducible laryngeal obstruction, obstructive sleep apnea, tonsillar and/or adenoid hypertrophy, and obesity. Multidisciplinary care has been used successfully in the management of chronic pediatric conditions across other fields with similar benefits observed for asthma as well [124]. Speech language pathology can be beneficial both in the diagnosis and management of inducible laryngeal obstruction and in-clinic swallow evaluations for dysphagia or aspiration. A dietitian can counsel a patient on weight loss strategies or vitamin D and calcium supplementation in the setting of chronic steroid use. Rheumatology can assist in the diagnosis of early onset eosinophilic granulomatosis with polyangiitis, if suspected.

Evaluation of the home and school environment: The 2020 focused NHLBI expert panel guideline update highlighted the role of a multicomponent aeroallergen mitigation strategy to assist in asthma management [55]. While the COVID-19 pandemic may lead to barriers to traditional home evaluations, the increase utilization of video web platforms for telehealth visits allows increased opportunities to assess the home, including the presence of animals, secondhand tobacco exposure, or accessibility to controller therapies. Similarly, evaluation of the school environment can provide insight into school-based triggers, including sports and physical education associated symptoms [19].

Psychosocial barriers to care: Depression and anxiety with asthma is associated with increased emergency room visits, hospitalizations, and poorer medication adherence [125, 126], emphasizing the importance of routine screening for these conditions in difficult to treat asthma.

Providers may be hesitant to explore anxiety and depression in their patients, either secondary to time constraints or lack of resources should they identify any mental health disorders, especially suicidal ideation. Screening questionnaires exist for anxiety and depression that do not specifically address suicidal ideation [127], thereby overcoming this hurdle. The treatment of anxiety and depression in patients with asthma has been associated with improved asthma control questionnaire scores and less prednisone for exacerbations [128]. Partnership with social work or psychology can assist in the diagnosis and management of these conditions, including engagement of community and school resources, such as development of school support plans.

Adherence and technique evaluation: Adherence monitoring strategy choice of either more historical routes, including prescription refill history, insurance claims, or dose counters, or newer technology-based options, such as electronic medication monitors or home-based spirometry, must be weighed between the limitations and required resources of each strategy. Electronic medication monitoring provides real-time, passive, date- and time-stamped insight into a patient's medication use, but does require both human, technology, and time resources. Electronic medication monitoring technology can provide insights beyond just reminders, allowing providers to address adherence phenotypes, correlation with ACT scores, and administration technique [129-131]. Actuations measured on electronic medication monitoring devices does not ensure the medication was administered or with correct technique. Inhaler devices that incorporate inspiratory flow sensing help address these hurdles [132]. Regardless of approach, once non-adherence is identified, providers should explore the underlying cause of the poor adherence, whether intentional or unintentional, to develop a patient-centered, tailored treatment plan [133].

Managing Severe Treatment Resistant Asthma

Following evaluation of difficult to treat asthma, if the asthma remains uncontrolled after addressing modifiable factors it is classified as STRA. In STRA, an escalation of controller therapies, most notably biologics are considered (**Figure 4**). If not previously or recently obtained, a composite biomarker approach should be taken to phenotype the patient and forecast potential response to treatment. The decision on which biologic to choose should be a shared decision making process with the patient and family focused on anticipated outcomes, side effects, administration strategies, and time and financial costs. A consideration could be made to utilizing biologics earlier in the process, especially in the non-adherent patient; however, the cost-effectiveness of such an approach should be considered when balancing the potential risk for exacerbations, especially if life-endangering, versus the use of a more expensive medication [134]. Response to a biologic should be reassessed every 3-6 months. Ultimately, if a patient fails to respond to biologic therapy a switch to an alternative biologic can still lead to improved asthma control [135] or potentially the outlined algorithm should be re-started.

Future directions

As a result of COVID, we have seen the accelerated application of telemedicine to both clinical practice and research. Patients can now conduct visits from home and thus for children, it can reduce the need for school absence for frequent visits. This strategy combined with digital technology should also facilitate access to care for children living in rural communities to receive regular care without traveling long distances for evaluation. Therefore, we have seen many changes in asthma management that provide the opportunity to improve response to medications, to individualize treatment and to monitor response.

While there are remarkable advances in medication development and digital health in recent years, there are still some underlying scientific questions that must be addressed to improve the overall management of asthma and especially severe asthma in children including the following:

1. What is the stability of asthma phenotypes?
2. What is the mechanism of asthma related to non- or low-type 2 endotypes and what management strategies may be effective?
3. What biomarkers can distinguish inflammatory endotypes?
4. What determines the variability in response to medications?
5. What medications are effective?
6. How do we choose from the various asthma biologics available with varying mechanisms of effect?
7. What biomarkers can be used to predict response and detect early treatment response to asthma biologics?
8. With medications, such as benralizumab, that reduce eosinophils is there a lower limit of safety for eosinophil reduction?
9. What is the role of infection in severe asthma?
10. What is the interaction of immunomodulation and respiratory infection?
11. Do ICS, especially at high doses predispose to respiratory infections?

Work is in progress in national and international asthma networks, such as the National Heart, Lung and Blood Institute Precision Medicine in Severe and Exacerbation Prone Asthma (PrecISE) Network, looking at medications that may be effective in the low or non-T2 pathway [136]. In addition, early intervention studies are being conducted in young children with emerging asthma that might individuate whether medications, such as omalizumab [137] or a bacterial lysate ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/NCT02148796) registration: <https://clinicaltrials.gov/ct2/show/NCT02148796>)

872 might alter the natural history of asthma and even prevent severe asthma in children. As we
873 gain more information from these studies, we will continue to refine our approach not only to the
874 management of severe asthma but also to its prevention.

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Figure legends

Figure 1. Components of a composite biomarker of childhood severe asthma; should be measured longitudinally to determine phenotype stability.

Figure 2. Approach to a child with untreated asthma and diagnosis of difficult to treat asthma.

Figure 3. Evaluation of difficult to treat asthma in a pediatric patient.

Figure 4. Management of severe treatment resistant asthma.

Table 1 ATS/ERS criteria for severe asthma.

Treatment with high-dose inhaled corticosteroids (ICS): For children 6-12 years: > 800 mcg of beclomethasone equivalent/day For children 12 years and older: > 2000 mcg of beclomethasone equivalent/day	
PLUS	
Using, or having had a failed trial of, long-acting β -2 agonists (LABA), a leukotriene receptor antagonist (LTRA), and sometimes low dose (anti-inflammatory) theophylline	
AND ALSO: Uncontrolled asthma, defined as one or more of-	
Poor symptom control (Asthma Control Questionnaire (ACQ) consistently ≥ 1.5 or Asthma Control Test (ACT) < 20 .	
Frequent severe asthma attacks, defined as ≥ 2 courses of systemic corticosteroids (≥ 3 days each) in the previous year	
≥ 1 serious attacks, namely least one hospitalization, intensive care unit stay or mechanical ventilation in the previous year	
Airflow limitation defined as a forced expiratory volume in 1 s (FEV_1) $< 80\%$ predicted (in the presence of reduced FEV_1 /forced vital capacity (FVC) ratio defined as less than the lower limit of normal) following a withhold of both short- and long-acting bronchodilators	
An additional criterion used in paediatrics is persistent airflow limitation (PAL), defined as failure to improve spirometry to within the normal range despite a course of systemic corticosteroids and acute administration of short-acting β -2 agonist (SABA).	

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1309 **Table 2. Differential diagnosis of difficult-to-treat asthma**
 1310

• Laryngotracheobronchomalacia • Laryngotracheobronchitis • Laryngeal web, cyst or stenosis • Exercise-induced laryngeal obstruction • Vocal cord dysfunction • Vocal cord paralysis • Tracheoesophageal fistula • Vascular ring, sling, or external mass compressing the airway • Endobronchial tumor • Foreign body aspiration • Chronic bronchitis from environmental tobacco smoke exposure • Repaired tracheoesophageal fistula • Toxic inhalations	• Bronchopulmonary dysplasia (chronic lung disease of prematurity) • Viral bronchiolitis • Gastroesophageal reflux • Causes of bronchiectasis (cystic fibrosis, immunodeficiency, allergic bronchopulmonary mycoses, chronic aspiration) • Primary ciliary dyskinesia • Bronchiolitis obliterans • Interstitial lung diseases • Hypersensitivity pneumonitis • Eosinophilic granulomatosis with angiitis • Eosinophilic pneumonia • Pulmonary hemosiderosis • Tuberculosis • Pneumonia • Pulmonary edema (e.g., congestive heart failure) • Vasculitis • Sarcoidosis • Medications associated with chronic cough (acetylcholinesterase inhibitors, β-adrenergic antagonists, angiotensin-converting enzyme inhibitors)
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1311 **Table 3. Biologics for the treatment of difficult-to-treat asthma**

1312

Name	Mechanism of action	Age indicated	Other indications	Administration
Omalizumab	Prevents IgE from binding to its receptor	≥ 6 years	Moderate-to-severe persistent asthma with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms inadequately controlled with inhaled corticosteroid	Subcutaneous, 150 to 375 mg every 2-4 weeks. Dose determined by total IgE level and body weight
Mepolizumab	Binds to IL-5 ligand	≥ 6 years	Severe eosinophilic asthma, with baseline blood eosinophil count ≥150 cells/microliter and at least two asthma exacerbations in the previous year	Subcutaneous, 40 mg for children 6-11 years and 100 mg for age 12 and older every 4 weeks
Reslizumab	Binds to IL-5 ligand	≥ 18 years	Severe eosinophilic asthma, with baseline blood eosinophil count of ≥400 cells/microliter, at least one asthma exacerbation in the previous year, and reduced lung function with FEV ₁ <80% predicted	Intravenous, 3 mg/kg every 4 weeks
Benralizumab	Binds to IL-5 receptor	≥ 12 years	Severe asthma with an eosinophilic phenotype (suggested blood eosinophil count of ≥300 cells/microliter and at least two asthma exacerbations in the previous year)	Subcutaneous, 30 mg every 4 weeks for three doses, then 30 mg every 8 weeks
Dupilumab	Binds to IL-4 receptor alpha	≥ 6 years	Uncontrolled moderate-to-severe eosinophilic or oral corticosteroid dependent asthma (suggested blood eosinophil count ≥150 cells/microliter and exhaled nitric oxide ≥25 ppb)	Subcutaneous, 200 mg (after loading dose of 400 mg) or 300 mg (after loading dose of 600 mg) every 2 weeks

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Table 2. Differential diagnosis of difficult-to-treat asthma

• Laryngotracheobronchomalacia • Laryngotracheobronchitis • Laryngeal web, cyst or stenosis • Exercise-induced laryngeal obstruction • Vocal cord dysfunction • Vocal cord paralysis • Tracheoesophageal fistula • Vascular ring, sling, or external mass compressing the airway • Endobronchial tumor • Foreign body aspiration • Chronic bronchitis from environmental tobacco smoke exposure • Repaired tracheoesophageal fistula • Toxic inhalations	• Bronchopulmonary dysplasia (chronic lung disease of prematurity) • Viral bronchiolitis • Gastroesophageal reflux • Causes of bronchiectasis (cystic fibrosis, immunodeficiency, allergic bronchopulmonary mycoses, chronic aspiration) • Primary ciliary dyskinesia • Bronchiolitis obliterans • Interstitial lung diseases • Hypersensitivity pneumonitis • Eosinophilic granulomatosis with angiitis • Eosinophilic pneumonia • Pulmonary hemosiderosis • Tuberculosis • Pneumonia • Pulmonary edema (e.g., congestive heart failure) • Vasculitis • Sarcoidosis • Medications associated with chronic cough (acetylcholinesterase inhibitors, β-adrenergic antagonists, angiotensin-converting enzyme inhibitors)
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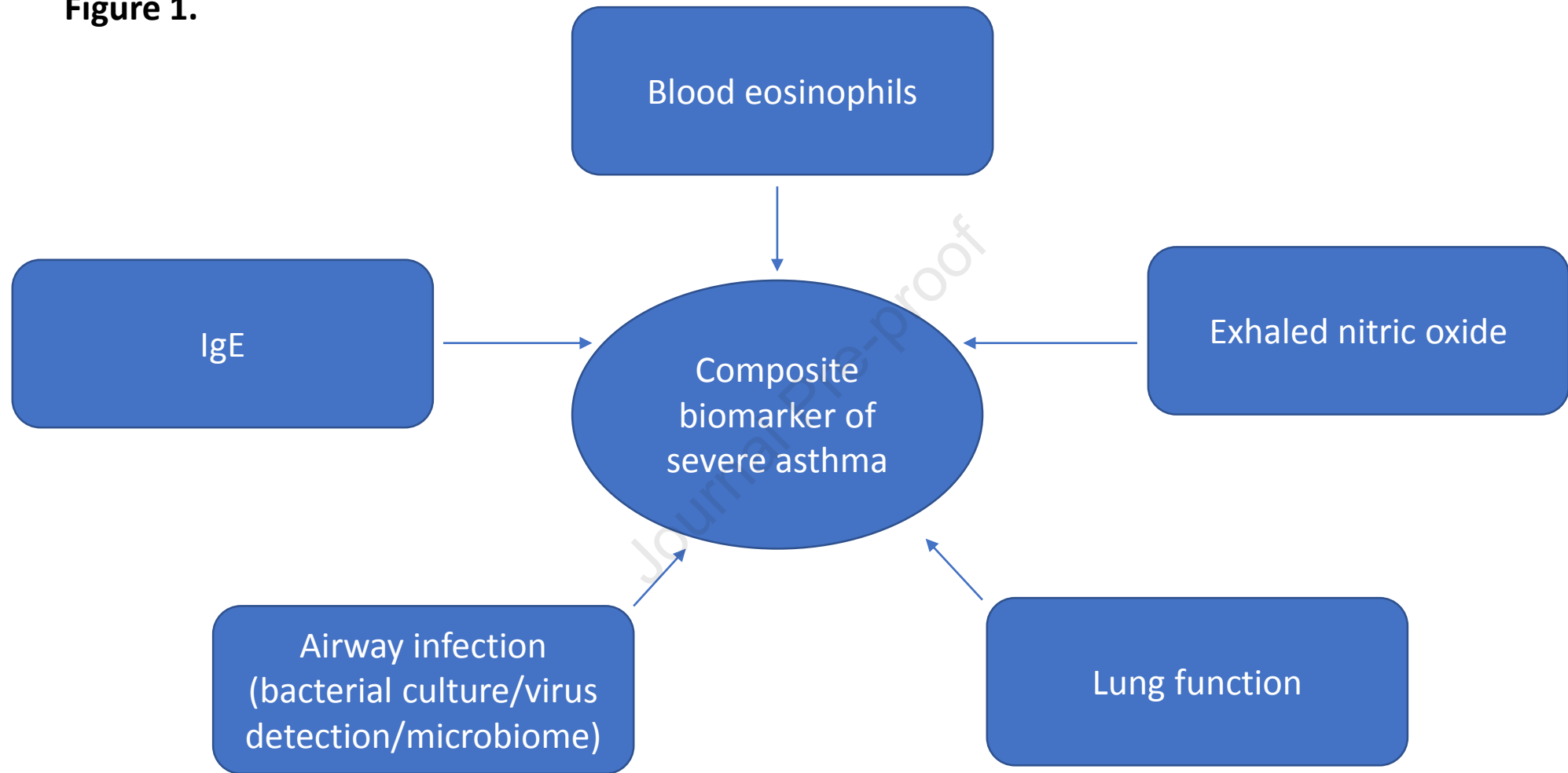
Table 3. Biologics for the treatment of difficult-to-treat asthma

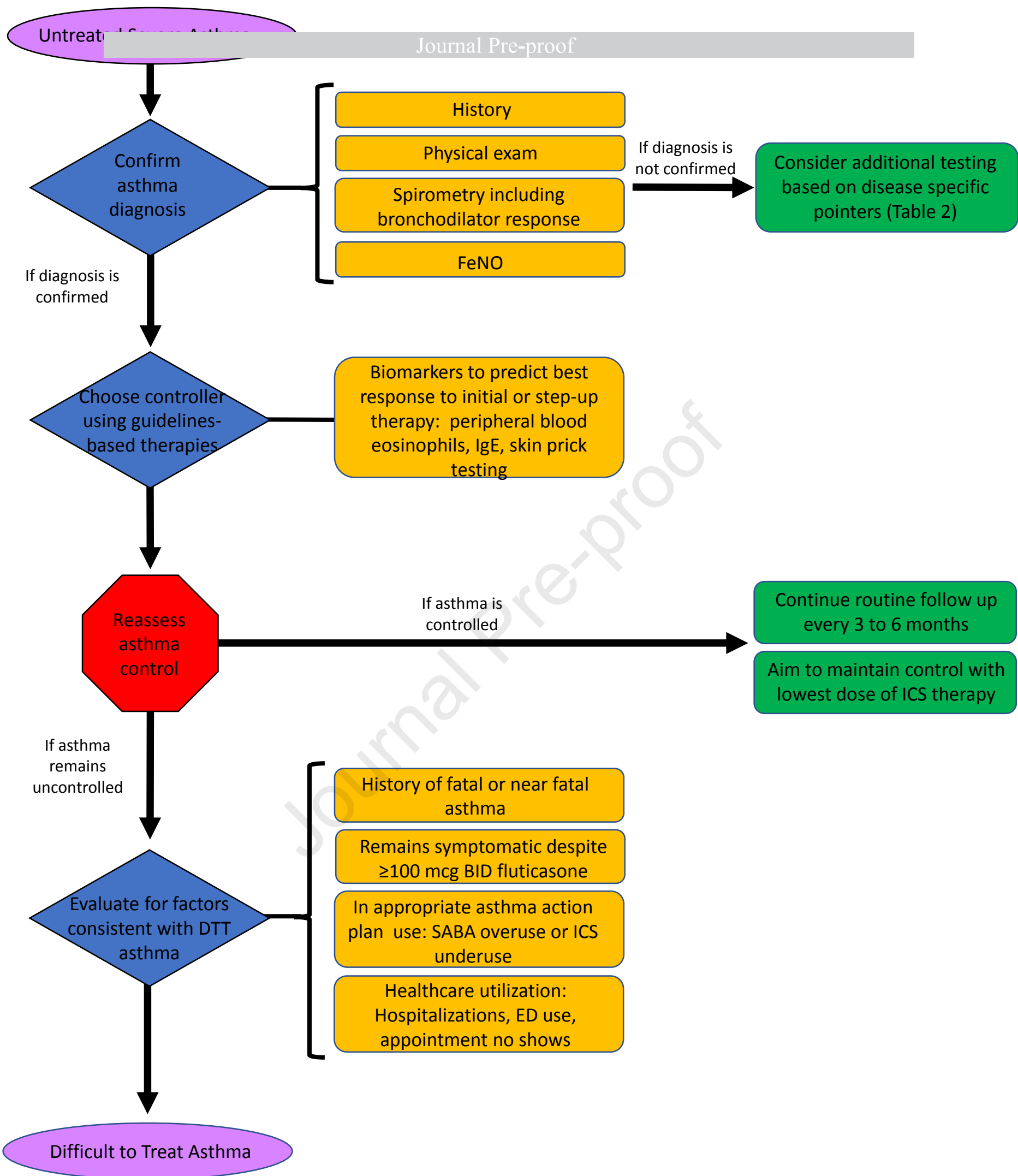
Name	Mechanism of action	Age indicated	Other indications	Administration
Omalizumab	Prevents IgE from binding to its receptor	≥ 6 years	Moderate-to-severe persistent asthma with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms inadequately controlled with inhaled corticosteroid	Subcutaneous, 150 to 375 mg every 2-4 weeks. Dose determined by total IgE level and body weight
Mepolizumab	Binds to IL-5 ligand	≥ 6 years	Severe eosinophilic asthma, with baseline blood eosinophil count ≥150 cells/microliter and at least two asthma exacerbations in the previous year	Subcutaneous, 40 mg for children 6-11 years and 100 mg for age 12 and older every 4 weeks
Reslizumab	Binds to IL-5 ligand	≥ 18 years	Severe eosinophilic asthma, with baseline blood eosinophil count of ≥400 cells/microliter, at least one asthma exacerbation in the previous year, and reduced lung function with FEV ₁ <80% predicted	Intravenous, 3 mg/kg every 4 weeks
Benralizumab	Binds to IL-5 receptor	≥ 12 years	Severe asthma with an eosinophilic phenotype (suggested blood eosinophil count of ≥300 cells/microliter and at least two asthma exacerbations in the previous year)	Subcutaneous, 30 mg every 4 weeks for three doses, then 30 mg every 8 weeks
Dupilumab	Binds to IL-4 receptor alpha	≥ 6 years	Uncontrolled moderate-to-severe eosinophilic or oral corticosteroid dependent asthma (suggested blood eosinophil count ≥150 cells/microliter and exhaled nitric oxide ≥25 ppb)	Subcutaneous, 200 mg (after loading dose of 400 mg) or 300 mg (after loading dose of 600 mg) every 2 weeks

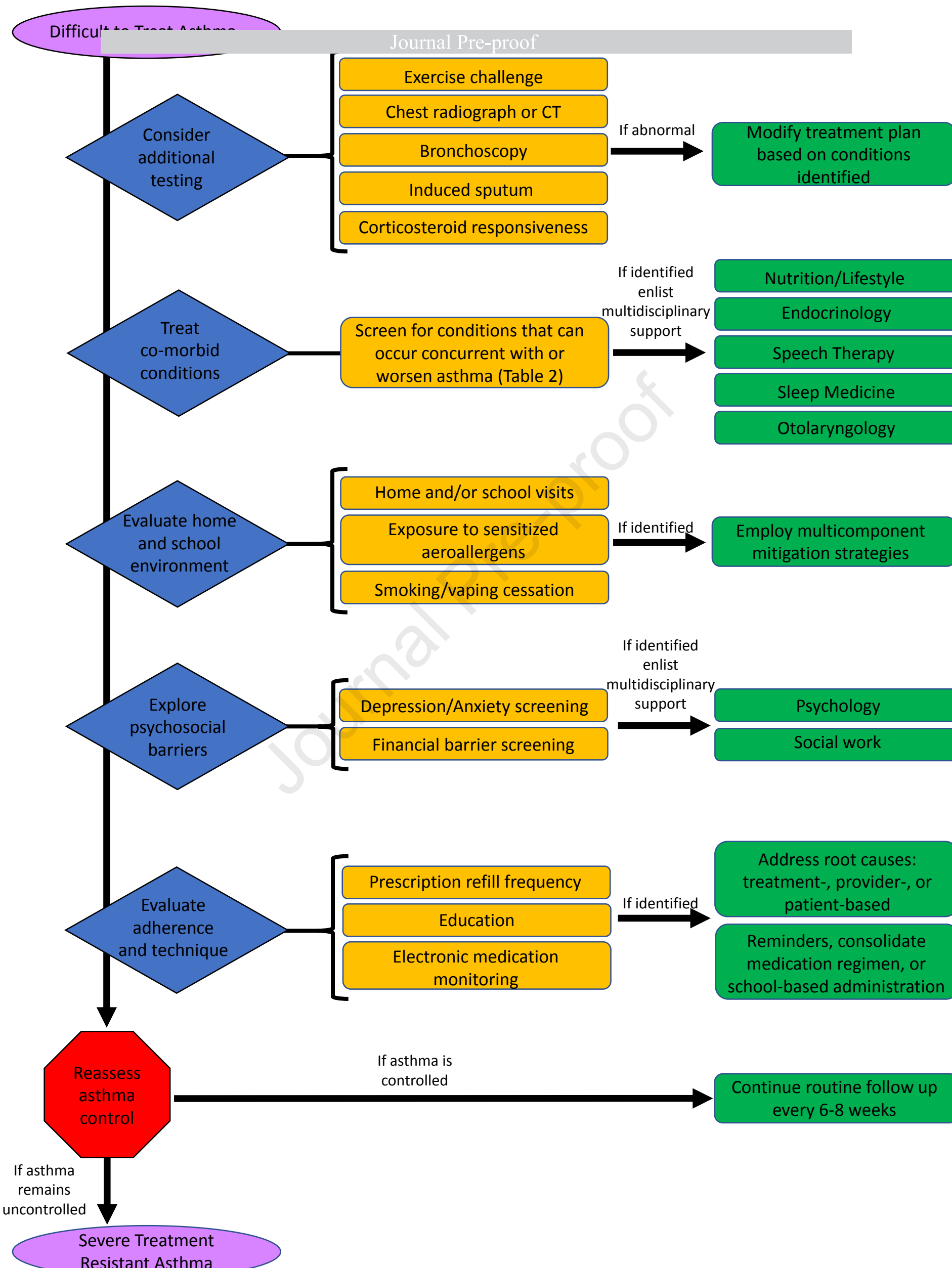
Table 1 ATS/ERS criteria for severe asthma.

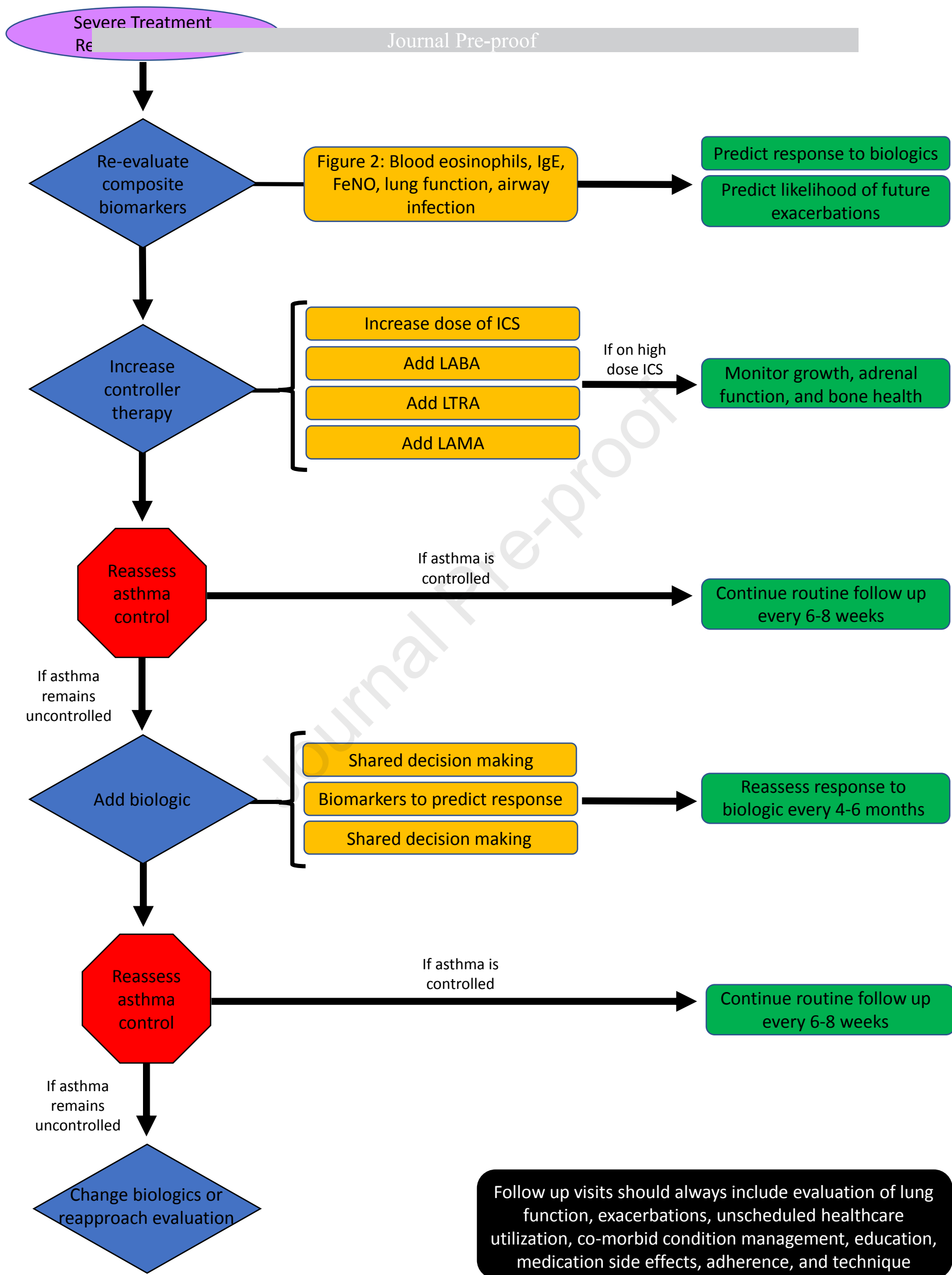
Treatment with high-dose inhaled corticosteroids (ICS): For children 6-12 years: ≥ 800 mcg of beclomethasone equivalent/day For children 12 years and older: ≥ 2000 mcg of beclomethasone equivalent/day
PLUS
Using, or having had a failed trial of, long-acting β -2 agonists (LABA), a leukotriene receptor antagonist (LTRA), and sometimes low dose (anti-inflammatory) theophylline
AND ALSO: Uncontrolled asthma, defined as one or more of-
Poor symptom control (Asthma Control Questionnaire (ACQ) consistently ≥ 1.5 or Asthma Control Test (ACT) < 20 .
Frequent severe asthma attacks, defined as ≥ 2 courses of systemic corticosteroids (≥ 3 days each) in the previous year
≥ 1 serious attacks, namely least one hospitalization, intensive care unit stay or mechanical ventilation in the previous year
Airflow limitation defined as a forced expiratory volume in 1 s (FEV_1) $< 80\%$ predicted (in the presence of reduced FEV_1 /forced vital capacity (FVC) ratio defined as less than the lower limit of normal) following a withhold of both short- and long-acting bronchodilators
An additional criterion used in paediatrics is persistent airflow limitation (PAL), defined as failure to improve spirometry to within the normal range despite a course of systemic corticosteroids and acute administration of short-acting β -2 agonist (SABA).

Reference 6 - Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014; 43: 343-73.

Figure 1.







CME EXAM

MS# & Article title: 21-00995, Difficult-to-treat Asthma Management in Children

Author(s): Andrew Bush, Anne Fitzpatrick, Sejal Saglani, Stanley Szefer

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Learning objectives:

1. To understand the role of a multi-disciplinary assessment in the assessment of children with problematic severe asthma.
2. To appreciate the modes of action of and indications for the novel biologics in children with eosinophilic asthma.
3. To understand that not all asthma requires ever more anti-eosinophilic strategies, but instead deploy alternative strategies.
4. To realize that asthma attacks are not a trivial inconvenience, but a major red flag, and thus the importance of a focused response.

Questions:

1. Which of the following statements about definitions of severe asthma is correct?
 - a. Aspects of risk are included in most definitions of severe asthma.
 - b. Severe asthma due to failure of diagnosis or lack of availability of treatment is an exclusively low- and middle-income country problem.
 - c. Most children referred for therapy with biologics in fact need to get the basics right.
 - d. Inhaled steroid dose of fluticasone equivalent 2000 mcg/day is part of the definition of severe asthma.

Answer: C

Explanation: Poor adherence is among the commonest issues identified and therefore it is important to get the basic evaluation correct before proceeding to more expensive therapies. Pockets of deprivation leading to severe asthma can occur in high income countries. Most definitions of severe asthma are based on levels of prescribed medications. The level of fluticasone equivalent stated in the definition of severe asthma is 1000 mcg/day.

2. Which of the following clinical features is best used to define severe asthma in the ERS/ATS criteria?
 - a. Six courses/year of oral prednisolone
 - b. One episode of ventilation for an asthma attack

- c. Asthma control test (ACT) score <15
- d. FEV1 percent predicted persistently less than 70%

Answer: B

Explanation: One episode of ventilation is among the clinical features used to define severe asthma in the ERS/ATS criteria along with two courses/year of prednisolone define severe and asthma control test score <20/25, and persistent airflow limitation defined by FEV1 percent predicted persistently less than 80%.

3. Which of the following is the predominant pathophysiological phenotype of childhood severe therapy resistant asthma?
- a. Non-atopic, eosinophilic inflammation
 - b. Non-atopic, neutrophilic inflammation
 - c. Allergic, eosinophilic airways disease, despite high dose inhaled corticosteroids (ICS)
 - d. Persistent airflow limitation

Answer: C

Explanation: The majority of children (>85%) with true severe therapy resistant asthma have aeroallergen sensitization and a predominant airway eosinophilia

4. Which of the following is a priority in the management of a child with predominant neutrophilic airway inflammation?
- a. Trial of anti-IL17 antibody therapy
 - b. Trial of macrolide therapy
 - c. Identify airway bacterial infection and trial of targeted antibiotics
 - d. Trial of anti-CXCR2 therapy

Answer: C

Explanation: The most common reason for neutrophilic inflammation in children with difficult-to-control or true severe therapy resistant asthma is the presence of bacterial airway infection. This must be identified and treated with targeted antibiotics before considering any anti-neutrophilic therapies. Neutrophilic asthma is very rare in children.

5. Which of the following will contribute very little as part of a composite biomarker to phenotype severe therapy resistant asthma?
- a. Blood eosinophils
 - b. Exhaled nitric oxide
 - c. Total serum IgE
 - d. Blood neutrophils

Answer: D

Explanation: There is little to no evidence of a relationship between blood and airway neutrophils. One of the biggest gaps in our knowledge and unmet needs for severe asthma is a non-invasive biomarker for airway neutrophilia.

6. A 10-year old child with difficult-to-treat asthma remains symptomatic after receipt of a low-dose inhaled corticosteroid and a long-acting beta agonist. Which of the following is the most appropriate next step?
- Prescribe a long-acting muscarinic antagonist (e.g., tiotropium).
 - Increase the dose of the inhaled corticosteroid.
 - Evaluate potential co-morbidities.
 - Initiate biologic therapy.

Answer: C

Explanation: Most children with asthma respond well to a low dose inhaled corticosteroid plus one other controller medication if administered regularly and correctly. Only a few children benefit from increasing the dose of the inhaled corticosteroid. If a child is not responding to low-dose standard medication, the most appropriate next step is to look for extra-pulmonary co-morbidities and social/environmental factors to correct.

7. Which of the following treatment approaches is the most efficacious for a child with difficult-to-treat asthma who remains symptomatic despite daily use of inhaled corticosteroids?
- Doubling the dose of the inhaled corticosteroid
 - Addition of a long-acting muscarinic antagonist (e.g., tiotropium)
 - Addition of a long-acting beta agonist (e.g., salmeterol)
 - Addition of a leukotriene receptor antagonist (e.g., montelukast)

Answer: C

Explanation: Long-acting beta agonists are the preferred secondary treatment and are superior to leukotriene receptor antagonists for improvement of lung function and symptoms. Long-acting muscarinic antagonists are not more efficacious than long-acting beta agonists and have a less favorable benefit-harm profile. Doubling the dose of the inhaled corticosteroid also has an unfavorable benefit-harm profile and increases the risk of adrenal suppression.

8. The recently proposed definition of clinical remission includes absence of symptoms for which of the following timeframes?
- 3 months
 - 6 months

- c. 12 months
- d. 24 months

Answer: C

Explanation: Menzies-Gow and colleagues conducted a Delphi process to come up with a definition of remission that could be considered for regulatory agencies in describing benefits of medications, such as asthma biologics. For clinical remission, they decided on a period of 12 months with absence of symptoms to describe clinical remission. This would cover the pertinent seasons of the year and assure an adequate period of time for evaluation.

Reference:

Menzies-Gow A, Bafadhel M, Busse WW, Casale TB, Kocks JWH, Pavord ID, et al. An expert consensus framework for asthma remission as a treatment goal. *J Allergy Clin Immunol* 2020;145:757-765.