

REVIEW

Severe asthma in children—a review of definitions, epidemiology, and treatment options in 2019

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Abstract

Severe asthma is a relatively uncommon condition in children but one which causes morbidity, occasionally mortality, and is a challenging condition to manage. There are several definitions of severe asthma, which have a common theme of poor control despite high dose inhaled corticosteroid treatment. Depending on the definition chosen, the prevalence of severe childhood asthma may be up to 5% within populations with asthma. Collectively, there is some evidence that the treatments used in severe asthma are beneficial, but a solid evidence-base is lacking for many treatments and some treatments have recognized side effects. Evidence supporting the use of maintenance oral prednisolone and intramuscular triamcinolone is weak. Response to systemic corticosteroids is heterogeneous and recognizing phenotypes or endotypes may identify those most likely to gain maximal benefit from treatment. For children aged 6 to 11 years, the anti-IgE biologic omalizumab is effective and anti-IL-5 agent (mepolizumab) has recently been licenced in Europe (but not the US). Biologics, which are licenced for >11 year olds include omalizumab, mepolizumab, benralizumab, reslizumab, and dupilumab. There is plenty that the clinician can offer to the child and adolescent with severe asthma in 2019, including nontherapeutic and therapeutic interventions. To manage severe asthma, practitioners from broad specialities must establish and maintain a close therapeutic relationship with patients. Looking beyond 2019, more treatment options will emerge for severe childhood asthma, and clinical teams will need to continue weighing up benefits and harms.

KEYWORDS

asthma, biologics, child, corticosteroids, randomized controlled trial

1 | INTRODUCTION

Asthma is a common condition which is managed in many countries and in millions of children and adolescents according to regional, national, and international guidelines.^{1,2} The purpose of management is to increase preventative treatment in response to increasing symptoms and reduce treatment when symptoms are controlled. The reactive nature to childhood asthma management is associated with less-than-ideal control of symptoms³ and asthma exacerbations remain common, for example, in the UK, a child is admitted to hospital due to an asthma exacerbation every 20 minutes.⁴

In a proportion of children and adolescents, troublesome daily asthma symptoms and/or frequent asthma attacks can occur, and in this context, asthma is said to be “severe”. Severe childhood asthma is associated with morbidity, mortality and health care expense, and is a particularly challenging situation for the child and adolescent, their family, their health care team, and the wider health care system. The diagnosis and management of asthma remain predominantly subjective and this is especially true for severe asthma. Current guidelines^{1,2} are more appropriate for mild asthma and limited by the fact that, to date, clinical trials have not adequately addressed the treatment options for severe asthma in children.

The uncertainties surrounding the diagnosis and management of severe childhood asthma have been reviewed on a regular basis.⁵⁻¹² The aims of this review are (i) to describe the different definitions of severe asthma and to identify which components are common to all and which are not consistently included, (ii) to describe the epidemiology of severe asthma and (iii), knowing that the benefits and harm from commonly used inhaler medications and oral montelukast are described elsewhere^{1,2,13}, our final aim was to review the evidence of benefit and harm from the systemic medications currently used in severe asthma.

1.1 | Definitions of severe asthma

There is no uniformly accepted definition of asthma, so not unexpectedly, there are several definitions of severe asthma^{1,2,6,14-17} and these are described in Table 1. In addition to severe asthma, there are other terms such as “brittle” and “refractory” asthma, which are not defined but may be used interchangeably with severe asthma. The theme common to all the definitions of severe asthma is poor symptom control whilst all but one definition considered included high dose treatment (usually inhaled corticosteroid; ICS $\geq 400 \mu\text{g}$ budesonide or equivalent for children aged under 12 years and $\geq 1000 \mu\text{g}$ in older children²). Asthma attacks are included in four of the definitions of severe asthma described in table 1.

Severe asthma can be broken down into two subcategories.⁶ A substantial proportion of individuals with severe asthma have symptoms which are due to modifiable factors which include poor or nonadherence and/or poor inhaler technique, and these children and adolescents can be considered as having “difficult to treat asthma”. The second subcategory of severe asthma is termed “therapy-resistant asthma” and describes children and adolescents whose symptoms are resistant (or in some cases partially resistant) to standard treatments, such as inhaled and oral corticosteroids, long acting β agonists, and leukotriene modifiers. There is a pressing need to categorize individuals correctly since management approaches to these two subcategories of severe asthma are divergent. The management of difficult to treat asthma is rooted in education and psychology, whereas the management of therapy-resistant asthma is “nonstandard” pharmacological therapies. To further complicate matters, many individuals with therapy-resistant asthma also have characteristics of difficult to treat asthma. Ultimately, the diagnosis of severe asthma, and its difficult to treat asthma and therapy-resistant subcategories, is easiest made with the benefit of hindsight, but clinicians do not have this luxury during initial encounters with a patient whose asthma may be severe.

Faced with a child or adolescent with a possible severe asthma diagnosis, clinicians need to consider possibilities, which are more fully described elsewhere^{1,6-8,18,19} and summarized here:

1. *Is this asthma?* Conditions such as dysfunctional breathing, vocal cord dysfunction are increasingly recognized in children aged 5 years and above, and are reviewed elsewhere.^{20,21} Pertussis²² and habitual cough²³ are commonly treated with escalating asthma medications in school aged children. The “traditional” differential for asthma includes cystic fibrosis, primary ciliary dyskinesia, foreign body, immune deficiency, congenital airway pathologies such as tracheomalacia,¹

and these are predominantly considerations for the under-5-year olds. Confirmation of the diagnosis of severe asthma includes typical symptoms, fixed airflow limitation, and a response of symptoms and physiology to a defined period of supervised treatment.^{1,2}

2. *Is this difficult to treat asthma?* Inhaler technique is generally poor in children and adolescents²⁴ and this can usually be easily identified and readily resolved. Addressing poor or nonadherence is less straight forward than addressing poor inhaler technique. Treatment nonadherence in asthma is reviewed elsewhere.²⁵ Briefly, adherence to medication is a complex behavior and nonadherence can be due to a number of factors including denial of the diagnosis, fear of harm from the medication, lack of understanding about the importance of taking the medication, not considering asthma a priority, and having a secondary gain from the presence of symptoms, for example, school avoidance. Adherence can be categorized as intentional or unintentional. Nonadherence can include situations where medication is never taken, medication is discontinued (by the patient), and medication is taken but not as frequently as prescribed. Socioeconomic factors often contribute to poor adherence, and these include limited access to health care professionals and treatment. “Family factors” may also contribute to poor adherence, for example, if the family has little or no organization in the day-to-day running of the household, then attention to taking treatment is likely to be poor, and where there is skepticism or mistrust of health care professionals, treatment adherence can be expected to be poor.
3. *Are there treatable comorbidities?* Anxiety and allergic conditions such as rhinitis and eczema should be identified and managed since they can accompany and contribute toward poor quality of life for children and adolescents with severe asthma. Other conditions such as obesity, obstructive sleep apnea, and gastro-esophageal reflux disease (GORD) may accompany severe asthma but interventions aimed at reducing obesity or treating GORD have not been shown to improve asthma symptoms.¹⁹
4. *Are there avoidable adverse environmental exposures contributing to symptoms?* In the absence of a clear history of an exposure leading to symptoms, for example, contact with a cat or eating a peanut, this can be difficult to ascertain. A home visit may be revealing. Exposure to second hand smoke or visible mould in the bedroom may be contributory.
5. *Is this therapy-resistant asthma?* Consider corticosteroid resistance by nonresponse to a dose of intramuscular triamcinolone or a short (e.g. seven day) course of oral prednisone.
6. *Might a bronchoscopy and biopsy help?* This may be helpful in excluding a large airway pathology which is masquerading as asthma. In some centers, the role of airway biopsy in stratifying asthma treatment is being assessed.¹⁹

1.2 | Epidemiology of severe asthma

Studying the epidemiology of severe asthma is difficult due to its low prevalence, the use of different definitions, and the presence of only

TABLE 1 A summary of the definitions of severe asthma in children and young people

Sources of the definition	Exact wording	Is this feature of severe asthma mentioned?		
		High-dose therapy	Poor control	Exacerbations
Global Initiative for Asthma 2017 ²	Asthma that requires step 4 or 5 treatment, for example, high dose ICS/LABA, to prevent it becoming uncontrolled, or asthma that remains uncontrolled despite this treatments	Yes	Yes	No
British Thoracic Society and Scottish Intercollegiate Guidelines Network Guideline for the Treatment of Asthma ¹ 2016	A prior diagnosis of asthma exists, and asthma-like symptoms and asthma attacks persist, despite prescription of high-dose asthma therapy	Yes	Yes	Yes
European Respiratory Society/American Thoracic Society guidelines on definition, evaluation and treatment of severe asthma ³ 2014	Asthma which requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming "uncontrolled" or which remains "uncontrolled" despite this therapy	Yes (ICS)	Yes	No
Problematic Severe Asthma in Childhood Initiative group ⁴ 2010	School-age children who, despite prescribed therapy of ≥ 800 mg/day inhaled corticosteroid (budesonide or equivalent), have undergone trials of at least two of three controllers (long-acting β -agonist, leukotriene receptor antagonist and oral theophylline) and still have symptoms When poor control is due to one or more of the following: associated diagnoses (comorbid conditions), poor adherence to treatment regimens, or adverse psychological and environmental factors When factors that make the child difficult to treat cannot be identified	Yes	Yes	No
World Health Organisation ⁵ 2010	Difficult-to-treat asthma Severe therapy-resistant asthma	No	Yes (morbidity)	Yes
American Thoracic Society and Severe Asthma Research Programme 2000 ⁶	Refractory asthma (after excluding other conditions, obvious environmental triggers and non-adherence) requires ≥ 1 major and ≥ 2 minor criteria Major criteria 1. Continuous/near continuous oral corticosteroid treatment 2. High dose inhaled corticosteroids Minor criteria 1. Daily treatment with additional preventer, for example, long acting β agonist 2. Daily/near daily short acting β agonist treatment 3. Persistent airway obstruction, for example, $FEV_1 < 80\%$ 4. At least one urgent care visit per year 5. At least three "bursts" of oral corticosteroid treatment per year 6. Prompt deterioration after reduction in maintenance oral or inhaled corticosteroid treatment 7. Past history of a near fatal asthma episode	Yes	Yes (minor criteria 2)	Yes

(Continues)

TABLE 1 (Continued)

Sources of the definition	Exact wording	Is this feature of severe asthma mentioned?		
		High-dose therapy	Poor control	Exacerbations
European Respiratory Society Task Force on Difficult/therapy-resistant asthma, 1999 ⁷	Difficult/therapy-resistant asthma is that which is poorly controlled in terms of chronic symptoms, episodic exacerbations, persistent and variable airways obstruction and a continued requirement for short-acting beta2-agonists despite delivery of a reasonable dose of inhaled corticosteroids. Patients may require courses of oral corticosteroids or a regular dose of oral corticosteroids to maintain reasonable control of the disease. Rarely, control of asthma may be totally uninfluenced by corticosteroid therapy.	Yes	Yes	Yes

a few whole population studies. Key questions include what is the average age of a child with severe asthma? Is there a difference in prevalence between males and females? And what is the prevalence of severe asthma?

Severe asthma occurs across the pediatric age range, and in children aged less than 5 years, it is poorly understood. Anecdotally, in the under-5-years age group, severe exacerbations occur with intercurrent upper respiratory tract infection against a background of relatively well-controlled symptoms, and this pattern is generally considered as distinct from severe asthma in older children. Cases series of treatment with intramuscular triamcinolone for severe asthma²⁶⁻³⁰ indicate that severe asthma is more common in the 12 to 15 year age group but there is no consistent male or female majority (Table 2). The 188 children with severe asthma in the Severe Asthma Research Program (SARP) III³¹ and the 99 children with severe asthma an initiative aimed at characterizing severe asthma (U-BIOPRED)³² were typically 11- to 12-years old and 55%-60% were male. The complexity of the relationship between sex, age, and asthma severity is demonstrated in an observational study of asthma, which concluded that the proportion of asthmatic patients recruited who had severe asthma increased in boys as they became older (34% in the youngest and 59% in the oldest age group) but the proportion did not increase significantly as girls became older (33% and 52%, respectively).³³ This study also found that among White children, 54% of 9- to 11-year olds with severe asthma were female, increasing to 80% in the 15- to 17-year age group but this was not seen among Black females.³³

Where it is described, severe asthma prevalence diminishes as more stringent definitions are applied, e.g. asthma mortality vs prescribing of high dose ICS vs self-reported severity. Routinely collected data indicate that the incidence of mortality from asthma in children is between 0 and 2 per million children per annum in European countries (Figure 1),³⁴ but mortality may be as high as 7 per million per annum in some non-European countries.³⁵ The international differences in mortality is illustrated when comparing data from the UK³⁶ (3 per million per annum) and Finland³⁷ (0.2 per million per annum), and this difference may reflect differences between health care systems. Birth cohort studies from northern Europe estimate the prevalence of severe asthma is between 2 and 5 per thousand children or 2 to 5% of all children with asthma.^{38,39} Consistent with these findings, studies using primary care prescribing data in England⁴⁰ and Scotland⁴¹ also found that approximately 5% of children with asthma were prescribed very high dose ICS. A European study also found that 5% of parents of children with asthma scored their child's asthma as being severe.³ When using self-reported questionnaires, the prevalence of severe asthma symptoms (defined as ≥ 4 attacks of wheeze or ≥ 1 night per week sleep disturbance from wheeze or wheeze affecting speech in the past 12 months) in adolescents ranges between 38% and 51% with the higher proportions being seen in low- and middle-income countries.³⁵

1.3 | Systemic medications used for severe asthma

In the absence of high quality evidence, guidelines cannot say which medications should be considered beyond the "top step" of the

TABLE 2 Details of case reports where intramuscular triamcinolone was used as part of asthma management

Studies	Number of participants	Dose of triamcinolone used and interval	Outcome after treatment
Phipatanakul et al ²⁶	188 children (mean 11.5 y, range 6-17 y, overall 62% male)	One dose, 1 mg/kg up to a maximum of 40 mg	Assessment three weeks after treatment found reduced FeNO and blood eosinophils in all participants. In addition, among 111 participants with severe asthma, treatment was associated with increased symptom score. FEV ₁ did not change after treatment
Koo et al ²⁷	79 cases (age and sex distribution not stated)	40 or 80 mg (if < or ≥30 kg) one dose given	Exhaled nitric oxide, sputum eosinophilia, and admissions for asthma were reduced in White children
Panickar et al ²⁸	5 cases given one dose (mean 9 y, range 5-13 y, 2 female) 8 given 2-5 doses (mean 13 y, range 12-15 y, 5 female)	20-100 mg at four weekly intervals	>1 dose was associated with reduced admissions and exacerbations even after cessation of treatment. A single dose was associated with reduced exacerbations.
Kapur et al ²⁹	7 cases (mean 12, range 8-16 y, 6 female)	≤60 mg (usually 40 mg) interval between doses not stated	No improvement in 2 cases. Self-reported improvement in 3 cases. Overall improvement in FEV ₁ . All reported adverse effects. Treatment discontinued in two due to adverse effects
Krupp et al ³⁰	5 cases (8-15 y, sex distribution not stated)	60-120 mg interval between doses not stated	The collective number of admissions fell to zero

stairway of escalating treatment. The mainstay of asthma treatment is ICSs and, when required, the addition of inhaled long acting β agonists, leukotriene receptor antagonists, and theophylline.^{1,2} When these treatments are considered to be inadequate, treatment options mentioned in guidelines include long term oral corticosteroids, intramuscular omalizumab (an anti-IgE antibody), and antireflux treatments.

Historically, “beyond the guidelines” treatments have followed an “ECG course” (Figure 2) where there is a spark of interest (P-wave)

followed by a wave of enthusiasm, shortly followed by a rapid loss of enthusiasm (QRS complex). Finally, there is a small amount of use in some contexts and regions (T-wave) before practice ceases completely. Historically, experimental “beyond the guidelines” therapies, which have been through the “ECG course” include cyclosporin, cytotoxic drugs such as methotrexate and azathioprine, gold salts, intravenous infusions of immunoglobulin, subcutaneous β -agonist treatment and, in those sensitized to fungi, oral antifungal therapy with itraconazole or voriconazole.⁸ This process of “trial and error” is

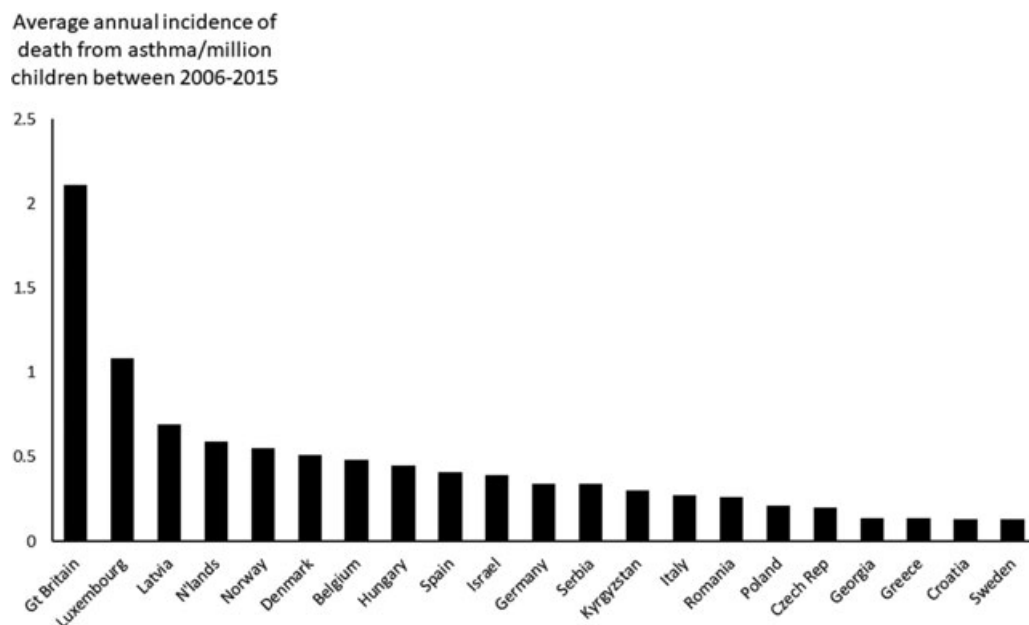
**FIGURE 1** The incidence of asthma morbidity in 21 countries in the World Health Organisation European Region averaged between 2006 and 2015. Only countries where data were available in each year and where at least 1 year had an incidence which was not zero. Data were available between 2006 and 2015 and the incidence was zero throughout from the following countries: Cyprus, Estonia, Israel, Lithuania, and Malta



FIGURE 2 Schematic “ECG” summarizing the ups and downs of enthusiasm for many novel treatments, which have been used for severe asthma in the past, but which are no longer used.⁸ In this metaphor, treatment is first proposed as being potentially of use (P-wave), then followed by a surge of enthusiasm (upwards limb of the QRS complex) followed by reality (downwards limb of the QRS complex), then a short burst of use by a few enthusiast (T-wave) after which the medication is never used

now less commonplace and today's novel therapies, for example, biologics, emerge from a more robust scientific foundation.²

1.4 | Systemic corticosteroids

There is a high level of evidence that short bursts of oral corticosteroid (OCS) treatment (eg, for 3 or 5 days) are effective in reducing the severity and duration of an asthma exacerbation in children.⁴² This experience has been extrapolated to the different setting of chronic poorly controlled asthma symptoms, and some children and adolescents can receive maintenance daily or alternate daily OCS treatment for periods in excess of 1 month. There is absence of evidence for efficacy of “maintenance” OCS despite this treatment being in asthma guidelines.^{1,2} Maintenance OCS treatment should ideally be under the supervision of a respiratory expert who can minimize the risk for wrong diagnosis and likely distinguish difficult to treat asthma from therapy-resistant asthma, but the use of maintenance OCS in severe childhood asthma remains an evidence-free area. Most experienced pediatric pulmonologists can readily recall a (typically adolescent) patient who required maintenance OCS prescriptions for a period of months to gain symptom control and then were successfully weaned off their OCS.

What is clear is that oral corticosteroid treatment is known to have adverse effects in children when used in short bursts (vomiting, behavior change, and sleep disturbance)⁴³ and also for periods in excess of 14 days (weight gain, growth retardation, cushingoid features, and susceptibility to infection e.g. varicella zoster virus).⁴⁴ The potential for harm from maintenance OCS to be greater than benefit is highlighted in BTS/SIGN guideline,¹ which states for adults (ie, those aged >12 years): “add on low dose oral corticosteroids (7.5 mg prednisolone daily) may be effective for some adults with severe asthma (Evidence D [ie, based on very poor quality evidence]) but are associated with substantial side effects (Evidence B [ie, based on good quality evidence]).”

1.5 | Intramuscular triamcinolone

Intramuscular treatment with triamcinolone may have a role in identifying steroid-responsive asthma, and may also provide treatment in severe asthma, where adherence to inhaled and/or oral corticosteroids is in question (approximately 50% of adults with

severe asthma are nonadherent with oral corticosteroid treatment⁴⁵). Evidence supporting the use of this systemic treatment in children is limited to case series where different doses of triamcinolone are used,^{26–30} see Table 2. The third phase of the US SARP III included the largest case series, where triamcinolone was used to treat asthma symptoms. The aim of the study was to identify determinants of steroid-responsiveness in 188 children and 526 adults, who had extensive physiological assessments before and 3 weeks after a single dose of triamcinolone. Triamcinolone treatment was associated with significant falls in exhaled nitric oxide and blood eosinophil count. Among 111 children with severe asthma, there was improvement in symptoms and a nonsignificant trend for improved prebronchodilator FEV₁. The apparent lack of response to triamcinolone in children with nonsevere asthma is likely to be explained by a small sample size with few symptoms and good initial FEV₁, and not necessarily by a lack of steroid-responsiveness. A second case series of 79 children,²⁷ also sought to describe symptom and physiological outcomes 4 weeks after a single dose of intramuscular triamcinolone, which was given as part of a well-described pathway of care. Children had improved symptom score (as evidenced by Asthma Control Test) and spirometry, and the differences were more clearly seen in children categorized as White compared to Black. Sputum eosinophilia, exhaled nitric oxide, and intensive care unit admissions were all reduced after treatment but only among White children.

A third prospectively recruited case series²⁸ identified children with an “unacceptably high level” of symptoms and admissions despite regular short bursts or continuous oral corticosteroid treatment and where adherence was considered adequate (including checking on the number of inhalers collected). Individuals were given either one treatment of triamcinolone or repeated treatments at 1-month intervals. The number of exacerbations and hospital admissions during the treatment and posttreatment phases fell relative to pretreatment among those with repeated triamcinolone treatments. Among those given a single treatment with triamcinolone, exacerbations but not hospital admissions were reduced. In all participants, the number of day's treatment with oral corticosteroid fell close to zero. Side effects were minimal and limited to the injection site. The authors conclude “Whether its [i.e. Triamcinolone] efficacy is due to improved compliance, or an improved anti-inflammatory profile compared with oral steroids, remains unclear”.

Two retrospective case series published as separate abstracts^{29,30} and which are summarized in Table 2, report beneficial and adverse treatment outcomes in a total of 12 children.

Collectively, these data should be considered with caution since their "open label" design, absence of placebo, and (in two cases^{29,30}) their retrospective design mean that it is not reasonable to infer beyond doubt that any benefits arose from triamcinolone treatment. The worrying side effects reported in one series²⁹ should be considered, albeit other case series did not mention side effects^{27,30} and the fourth study mentioned only minor local effects.²⁸ As with most asthma treatments, response to triamcinolone is not homogeneous and results from one study indicate that a response may be more clearly seen in White children compared to Black.²⁷ When adherence to maintenance oral corticosteroid treatment is uncertain and the child or young person is experiencing severe or life-threatening asthma exacerbations, then it would be reasonable to start a short trial of triamcinolone treatments to demonstrate whether symptoms are steroid responsive. If there is no response to at least 2-months treatment and/or side effects develop, then treatment might be discontinued. If there is a response (in asthma control and number of exacerbations), then strategies to improve inhaled or oral corticosteroid adherence should be explored.

1.6 | Omalizumab

The anti-IgE antibody, omalizumab, has been used for the treatment of severe asthma in children aged 6 to 11 years since 2009, and in older children and adults since 2003. At least 10 randomized controlled trials in children have explored the efficacy of omalizumab in a range of settings including "persistent asthma", "severe asthma," and "moderate-to-severe atopic asthma," and the consensus is that treatment is safe and effective in reducing asthma exacerbations (especially in the September peak in asthma exacerbations), reducing ICS dose and reducing symptoms.⁴⁶ When first introduced, there were concerns about anaphylaxis and increased risk for malignancies (mostly extrapolated from anxieties about infliximab, an antibody specific for tumor necrosis factor), but a recent review noted that the risk of anaphylaxis was approximately 0.2% per treatment and there was no excess of malignancies.⁴⁶ Omalizumab is not suitable for all patients, the largest trial⁴⁷ included in a recent review⁴⁶ found that the majority (59%) of potential participants were ineligible. The monthly subcutaneous injection is uncomfortable, requires administration in a health care setting with nursing observations, and is expensive. What remains to be clarified is whether it is superior to high dose ICS, and how and when treatment should be discontinued.

1.7 | Mepolizumab

The anti-interleukin-5 molecule, mepolizumab, was licenced in Europe for use in children aged 6 to 11 in August 2018, and has been licenced for use in older children in the US and Europe since 2015. Experience with this "mab" in adults was initially mixed, with some studies finding improved asthma outcomes but most studies reported severe head-

aches⁴⁸; a definitive trial found that mepolizumab was effective in reducing asthma exacerbations and a licence was granted in 2015.⁴⁸

The license in Europe for children is based only on safety data from a single study of 36 6- to 11-year olds.⁴⁹ Inclusion criteria included having an asthma diagnosis for more than 12 months; at least two exacerbations in the year before recruitment; receiving $\geq 400 \mu\text{g}$ budesonide daily (or equivalent); receiving an additional controller medication for more than 3 months; an FEV₁/FVC ratio of < 0.8 and blood eosinophilia ($> 0.15 \times 10^9/\text{l}$ on recruitment or $> 0.3 \times 10^9/\text{l}$ in the year before recruitment). In keeping with the adult experience, headaches were a common side effect. Clinical improvements were not sought in this phase II trial, so the efficacy of this treatment remains uncertain in children. Given the challenge in recruiting children fulfilling these inclusion criteria, it is unlikely that a randomized clinical trial against placebo will be carried out.

Data from studies in adults (but including participants as young as 12 years) have demonstrated the efficacy of mepolizumab for reducing risk of asthma exacerbations. The DREAM study enrolled 621 participants (159 received a placebo), who had at least two asthma attacks in the previous year, "airway variability" (ie, either peak flow variability, bronchial hyperresponsiveness, or bronchodilator response) and eosinophilia (ie, elevated exhaled nitric oxide or blood eosinophilia). Treatment with one of three doses of mepolizumab was associated with between a 39% to 52% reduction in the rate of exacerbations, but there was no improvement in asthma control between the placebo and treatment groups.⁵⁰ The MENSA study recruited 576 participants aged 12 to 82 years, of whom 191 received placebo treatment and who had very similar characteristics to the DREAM study (namely, two recent asthma attacks, airway variability, and eosinophilia). There was approximately a 50% reduction in asthma exacerbations for those treated with mepolizumab compared to placebo and also a small improvement in asthma symptoms (but which was not greater than the minimal clinically important change).⁵¹

For patients aged 12 years and older, there are two other anti IL5 pathway-specific therapies licensed (benralizumab and reslizumab). A recent review of the literature suggests that while all three anti IL-5 pathway-specific therapies are more effective than placebo in reducing exacerbations and improving symptom control, mepolizumab has the greatest benefit.⁵²

1.8 | Dupilumab

Dupilumab is an IL-4 and IL-13 antibody which is licensed in the US and European Union for the management of severe asthma in individuals who are aged 12 years and older. The LIBERTY ASTHMA QUEST study⁵³ recruited 1902 participants aged at least 12 years, who were randomized to either placebo or one of two subcutaneous doses of dupilumab given at two weekly intervals over a 12-month period. Inclusion criteria included prescribed medium-high dose ICS treatment; prescribed an additional controller; FEV₁ $< 80\%$ (or $\leq 90\%$ for 12-17 year olds); bronchodilator reversibility ($> 12\%$ or 200 mls); poor symptom control (Asthma Control Questionnaire score ≥ 1.5); and an asthma attack requiring systemic glucocorticosteroid treatment in the last year. The

TABLE 3 A summary of the evidence for efficacy and side effects of medications included in this review

	Efficacy?	Side effects?
Prednisolone	1+	3+++
Triamcinolone	1+	1++
Omalizumab	3+++	3+
Mepolizumab	No data	2++
Lansoprazole	3–	3+

Note. 3, evidence from systematic review or randomized control trials; 2, evidence from open label trial; and 1, anecdotal evidence or case series. The minus sign indicates no evidence of efficacy, the plus signs indicate the magnitude of efficacy and of side effects.

primary outcome was exacerbation rate and, as seen for other “-mabs,” the rate of exacerbations was reduced by approximately half (47.7%) in those receiving active treatment compared to placebo. The dupilumab group had improved symptom scores after 2 week's treatment and thereafter throughout the study, also they had a mean increase of 140 mls in FEV₁ compared to the placebo group. Eosinophilia (ie, >300 eosinophils per cubic millimetre) occurred in 4% of participants who received dupilumab and 0.6% who received placebo, the clinical significance of this is uncertain.

1.9 | Gastro-esophageal reflux treatment

GORD is commonly present in adults and children with asthma. In the adult literature, there was evidence of benefit (in terms of improved lung function), when patients with night-time respiratory symptoms and GORD were treated with esomeprazole⁵⁴ but this same medication was not associated with improved lung function or reduced symptoms in the absence of GORD symptoms.^{54,55} Despite the relationship not being thought to be causal,¹ a trial of GORD treatment is sometimes used in children with severe asthma. An evidence base for this practice is lacking. One randomized controlled trial explored the benefit of a proton pump inhibitor (lansoprazole) in poorly controlled (not severe) asthma in 306 children aged 6 to 17 years.⁵⁶ Eligibility criteria included receiving a dose of ICS >175 µg/day fluticasone (or equivalent), evidence of airway reversibility or hyperresponsiveness, need for short acting β agonist treatment more than 2 days a week, and two asthma exacerbations in the past year. Children and adolescents with overt GORD symptoms were excluded, but just over 40% of participants tested had evidence of GORD after oesophageal pH testing. After 24 weeks, there were no differences in asthma outcomes between those who received lansoprazole compared to placebo. Unexpectedly, the active medication was associated with an increased risk for respiratory infection.

2 | CONCLUSIONS

Severe asthma in children will continue to be a clinical challenge and brings a risk of morbidity and mortality due to the disease itself and also potentially from the treatment offered. This review has high-

lighted ongoing areas of uncertainty in the definition, the epidemiology, and the medical treatment of severe asthma (Table 3). The future is likely to continue to bring more treatment options for severe asthma, which may offer benefit but also may prove to be a “flat line” after the ECG course. For example, the roles of long acting muscarinic agonists, macrolide antibiotics, and bronchial thermoplasty in children are unknown at present, but will likely be explored in future. There is a sound evidence base that electronic logging of ICS treatment leads to improved asthma outcomes, and such meters may become more commonly used in clinical practice.^{57,58} Directly observed inhaler treatment using video conference technology may also be useful in some situations.⁵⁹ Among other nonmedicinal interventions, there are new “uncertainties” such as temperature-controlled laminar airflow⁶⁰ and old “uncertainties” such as dust mite impermeable bedding.⁶¹ Severe asthma will always test clinical teams and sometimes call for difficult decisions to be made. Key to management are involving the asthma team, speaking to other professionals involved (eg, teachers), and personalizing care.

2.1 | Research needs

These are some areas where further research might advance the care for children and adolescents with severe asthma.

- What is the prevalence and incidence of severe asthma in children (using different definitions)?
- What objective tests are most effective in distinguishing between difficult to treat and therapy-resistant asthma (eg, spirometry, plasma prednisolone concentration, inhaler logging devices, directly observed therapy)?
- How and when should treatment with maintenance oral corticosteroids and intramuscular triamcinolone or biologics begin and when might they be stopped?

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