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. Severe asthma can be considered as difficult to treat or therapy resistant, or both. 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 recognised side-effects. Evidence supporting the use of maintenance oral prednisolone and intramuscular triamcinolone is weak. Response to corticosteroids is heterogeneous and recognising phenotypes or endotypes may identify those most likely to gain maximal benefit from treatment. For children aged 6-11 years the anti-IgE biologic omalizumab is effective an 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 non-therapeutic and therapeutic interventions. To manage severe asthma, practitioners from broad specialties 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.

INTRODUCTION

Asthma is a common condition which is managed in many countries and in millions of children and adolescents around the globe 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 symptoms[3] 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 healthcare expense, and is a particularly challenging situation for the child and young person, their family, their healthcare team and the wider healthcare 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.

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 one. 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 two themes common to all the definitions of severe asthma identified are poor symptom control and high dose treatment (usually inhaled corticosteroid, ICS ≥400 micrograms budesonide or equivalent for children aged under 12 years and ≥1000 micrograms in older children[2]). Asthma attacks are included in some but not all definitions of severe asthma.

Severe asthma can be broken down into two subcategories[6]. A substantial proportion of individuals with severe asthma has symptoms which are due to modifiable factors which include poor or non-adherence 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 beta agonists and leukotriene modifiers. There is a pressing need to categorise 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 "non-standard" 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 summarised here:

1. *Is this asthma?* Conditions such as dysfunctional breathing, vocal cord dysfunction are increasingly recognised in children aged five years and above, and are reviewed elsewhere [20,21]. Pertussis[22] and habitual cough[23] 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], but these are predominantly considerations for the under five year olds. Confirmation of the diagnosis 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 adolescents[24] and this can usually be easily identified and readily resolved. Addressing poor or non-adherence is less straight forward than addressing poor inhaler technique. Treatment non-adherence in asthma is reviewed elsewhere[25]. Briefly, adherence to medication is a complex behaviour and non-adherence 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, e.g. school avoidance. Adherence can be categorised as intentional or unintentional. Non-adherence 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 organisation in the day-to-day running of the household then attention to taking treatment is likely to be poor, and where there is scepticism or mistrust of healthcare professionals treatment adherence can be expected to be poor.

3. *Are there treatable co-morbidities?* Anxiety and allergic conditions such as rhinitis and eczema should be identified and managed since they can accompany and contribute towards poor quality of life for children and adolescents with severe asthma. Other conditions such as obesity, obstructive sleep apnoea and gastro-oesophageal 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 non-response to a dose of triamcinolone or a burst of 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 centres the role of airway biopsy in stratifying asthma treatment is being assessed[19].

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 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 paediatric age range, and in children aged less than five years is poorly understood. Anecdotally, in the under five years age group severe exacerbations occur with intercurrent upper respiratory tract infection against a back ground 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 asthma[26–30] indicate that severe asthma is more common in the 12-15 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) III[31] and the 99 children with severe asthma an initiative aimed at characterising severe asthma (U-BIOPRED)[32] were typically 11-12 years old and 55-60% were male. The complexity of the relationship between gender, 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 9-11 year olds with severe asthma were female increasing to 80% in the 15-17 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 versus prescribing of high dose inhaled corticosteroids (ICS) versus 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 one)[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 UK[36] (3 per million per annum) and Finland[37] (0.2 per million per annum), and this difference may reflect differences between healthcare systems. Birth cohort studies from Northern Europe estimate the prevalence of severe asthma is between 2 and 5 per thousand children or 2-5% of all children with asthma[38,39]. Consistent with these findings, studies using primary care prescribing data in England[40] and Scotland[41] 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].

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 stairway of escalating treatment. The mainstay of asthma treatment is inhaled corticosteroids and, when required, the addition of inhaled long acting beta 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 anti-reflux treatments.

Historically, "beyond the guidelines" treatments have followed an "ECG course" (figure one) 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 oral macrolides, cyclosporin, cytotoxic drugs such as methotrexate and azathioprine, gold salts, intravenous infusions of Immunoglobulin, subcutaneous beta-agonist treatment and, in those sensitised to fungi, oral antifungal therapy with itraconazole or voriconazole[8]. This process of "trial and error" is now less commonplace and today's novel therapies, for example biologics, emerge from a more robust scientific foundation.

Systemic corticosteroids

There is a high level of evidence that short bursts of oral corticosteroid (OCS) treatment (e.g. for three or five 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 one 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 minimise 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 paediatric 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, behaviour change and sleep disturbance)[43] and also for periods in excess of 14 days (weight gain, growth retardation, cushingoid features and susceptibility to infection)[44]. The potential for harm from maintenance OCS to be greater than benefit is highlighted in BTS/SIGN guideline[1] which states for adults (i.e. those aged >12 years): "add on low dose oral corticosteroids (7.5mg prednisolone daily) may be effective for some adults with severe asthma (Evidence D[i.e. based on very poor quality evidence]) but are associated with substantial side effects (Evidence B[i.e. based on good quality evidence])."

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 non-adherent with oral corticosteroid treatment[45]). 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 two. The third phase of the US Severe Asthma Research Program (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 three 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 an improvement in symptoms and a non-significant trend for improved pre bronchodilator FEV_1. The apparent lack of response to triamcinolone in children with non-severe asthma is likely to be explained by a small sample size with few symptoms and good initial FEV_1, and not necessarily by a lack of steroid-responsiveness. A second in a case series of 79 children[27], also sought to describe symptom and physiological outcomes four 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 categorised 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 series[28] 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 one month intervals. The number of exacerbations and hospital admissions during the treatment and post treatment phases fell relative to pre-treatment 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 summarised 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 series[29] 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 two 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.

Omalizumab

The anti-IgE antibody omalizumab has been used for the treatment of severe asthma in children aged 6-11 years since 2009, and in older children and adults since 2003. At least ten randomised 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 tumour necrosis factor), but a recent review noted that 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 trial[47] included in a recent review[46] found that the majority (59%) of potential participants were ineligible. The monthly

subcutaneous injection is uncomfortable, requires administration in a healthcare 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.

Mepolizumab

The anti-interleukin-5 molecule mepolizumab was licenced in Europe for use in children aged 6-11 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 headaches[48]; 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 6-11 year olds[49]. Inclusion criteria included: having an asthma diagnosis for more than 12 months; at least two exacerbations in the year prior to recruitment; receiving ≥400 micrograms budesonide daily (or equivalent); receiving an additional controller medication for more than three months; an FEV_1/FVC ratio of <0.8 and blood eosinophilia (>0.15x10^9/l on recruitment or >0.3 x10^9/l in the year prior to 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 likely that a randomised clinical trial will not 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" (i.e. either peak flow variability, bronchial hyperresponsiveness or bronchodilator response) and eosinophilia (i.e. elevated exhaled nitric oxide or blood eosinophilia). Treatment with one of three doses of mepolizumab was associated with between a 39-52% 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 12-82 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 twelve years and older, there are two other anti IL5 pathway specific therapies licensed (benralizumab and reslizumab). A recent review of the literature suggests that whilst 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].

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 study [53] recruited 1902 participants aged at least 12 years who were randomised 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; FEV_1 <80% (or ≤90% for 12-17 year olds); bronchodilator reversibility (>12% or 200mls); poor symptom control (Asthma Control Questionnaire score ≥1.5); and an asthma attack requiring systemic glucocorticosteroid treatment in the last year. The 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 two week's treatment and thereafter throughout the study, also they had a mean increase of 140mls in FEV_1 compared to the placebo

group. Eosinophilia (i.e. >300 eosinophils per cubic millimetre) occurred in 4% of participants who received dupliumab and 0.6% who received placebo, the clinical significance of this is uncertain.

Gastro-oesophageal reflux treatment

Gastro-oesophageal reflux disease (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 esomeprazole[54] 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 randomised controlled trial explored the benefit of a proton pump inhibitor (Lansoprazole) in poorly controlled (not severe) asthma in 306 children aged 6-17 years[56]. Eligibility criteria included receiving a dose of ICS >175 micrograms/day fluticasone (or equivalent), evidence of airway reversibility or hyperresponsiveness, need for short acting beta agonist treatment more than two 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 24 weeks there were no differences in asthma outcomes between those who received lansoprasole compared to placebo. Unexpectedly the active medication was associated with increased risk for respiratory infection.

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 highlighted ongoing areas of uncertainty in the definition, the epidemiology and the medical treatment of severe asthma (table three). 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 inhaled corticosteroid 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 non-medicinal interventions there are new "uncertainties" such as temperature-controlled laminar airflow[60] 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 (e.g. teachers) and personalising care.

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 (e.g. 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?

REFERENCES

1. British Thoracic Society Scottish Intercollegiate Guidelines Network. BTS/SIGN British guideline on the management of asthma. 2016; Available at: https://www.brit-thoracic.org.uk/standards-of-care/guidelines/btssign-british-guideline-on-the-management-of-asthma/. Accessed 19th Dec 2018.

2. Global Initiative for Asthma. 2017 GINA Report, Global Strategy for Asthma Management and Prevention. 2017; Available at: http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/. Accessed 1st April 2017.

3. Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. *Eur Respir J* 2000; 16: 802-7.

4. Asthma UK. Asthma facts and FAQs. 2017; Available at: http://www.asthma.org.uk/asthma-facts-and-statistics. Accessed 08/31, 2017.

5. Bush A, Saglani S. Management of severe asthma in children. *Lancet* 2010; 376: 814-25.

6. Hedlin G, Bush A, Lodrup Carlsen K, Wennergren G, De Benedictis FM, Melen E, Paton J, Wilson N, Carlsen K, Problematic Severe Asthma in Childhood Initiative group Problematic severe asthma in children, not one problem but many: a GA2LEN initiative. *Eur Respir J* 2010; 36: 196-201.

7. Lodrup Carlsen KC, Hedlin G, Bush A, Wennergren G, de Benedictis FM, de Jongste JC, Baraldi E, Pedroletti C, Barbato A, Malmstrom K, et al. Assessment of problematic severe asthma in children. *Eur Respir J* 2011; 37: 432-40.

8. Bush A, Pedersen S, Hedlin G, Baraldi E, Barbato A, de Benedictis F, Lodrup Carlsen KC, de Jongste J, Piacentini G, PSACI (Problematic Severe Asthma in Childhood Initiative) group.. Pharmacological treatment of severe, therapy-resistant asthma in children: what can we learn from where? *Eur Respir J* 2011; 38: 947-58.

9. Giovannini-Chami L, Albertini M, Scheinmann P, de Blic J. New insights into the treatment of severe asthma in children. *Paediatr Respir Rev* 2015; 16: 167-73.

10. Goldstein S. Unlocking the Puzzle of Severe Asthma in Children. *J Allergy Clin Immunol Practice* 2017; 5: 420-1.

11. Ramratnam SK, Bacharier LB, Guilbert TW. Severe Asthma in Children. *J Allergy Clin Immunol Practice* 2017; 5: 889-98.

12. Larenas-Linnemann D, Nieto A, Palomares O, Pitrez PM, Cukier G. Moving toward consensus on diagnosis and management of severe asthma in children. *Cur Med Res Opinion* 2018; 34: 447-58.

13. Leung JS, Johnson DW, Sperou AJ, Crotts J, Saude E, Hartling L, Stang A. A systematic review of adverse drug events associated with administration of common asthma medications in children. *PLoS ONE* 2017; 12: e0182738.

14. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, Adcock IM, Bateman ED, Bel EH, Bleecker ER et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43: 343-73.

15. Bousquet J, Mantzouranis E, Cruz AA, Ait-Khaled N, Baena-Cagnani CE, Bleecker ER, Brightling CE, Burney P, Bush A, Busse WW, et al. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. *J Allergy Clin Immunol* 2010; 126: 926-38.

16. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. American Thoracic Society. *Am J Respir Crit Care Med* 2000; 162: 2341-51.

17. Chung KF, Godard P, Adelroth E, Ayres J, Barnes N, Barnes P, Bel E, Purney P, Chanez P, Connett G, et al. Difficult/therapy-resistant asthma: the need for an integrated approach to define clinical phenotypes, evaluate risk factors, understand pathophysiology and find novel therapies. ERS Task Force on Difficult/Therapy-Resistant Asthma. European Respiratory Society. *Eur Respir J* 1999; 13: 1198-208.

18. Guilbert TW, Bacharier LB, Fitzpatrick AM. Severe asthma in children. *J Allergy Clin Immunol Practice* 2014; 2: 489-500.

19. Bush A, Fleming L, Saglani S. Severe asthma in children. *Respirology* 2017; 22: 886-97.

20. Barker N, Ugonna K, Thevasagayam R, Kirkby J. Practical guide to the management of dysfunctional breathing. *Paediatr Child Health* 2018; 28: 149-151.

21. de Groot EP. Breathing abnormalities in children with breathlessness. *Paediatr Respir Rev* 2011; 12: 83-7.

22. Harnden A, Grant C, Harrison T, Perera R, Brueggemann AB, Mayon-White R, Mant D. Whooping cough in school age children with persistent cough: prospective cohort study in primary care. *Brit Med J* 2006; 333: 174-7.

23. Wright MF, Balfour-Lynn I. Habit-tic cough: Presentation and outcome with simple reassurance. *Pediatr Pulmonol* 2018; 52: 512-6.

24. Gillette C, Rockich-Winston N, Kuhn JA, Flesher S, Shepherd M. Inhaler Technique in Children With Asthma: A Systematic Review. *Academ Pediatr* 2016; 16: 605-15.

25. Klok T, Kaptein AA, Brand PLP. Non-adherence in children with asthma reviewed: The need for improvement of asthma care and medical education. *Pediatr Allergy Immunol* 2015; 26: 197-205.

26. Phipatanakul W, Mauger DT, Sorkness RL, Gaffin JM, Holguin F, Woodruff PG, Ly NP, Bacharier LB, Bhakta NR, Moore WC, et al. Effects of Age and Disease Severity on Systemic Corticosteroid Responses in Asthma. *Am J Respir Crit Care Med* 2017; 195: 1439-48.

27. Koo S, Gupta A, Fainardi V, Bossley C, Bush A, Saglani S, Fleming L. Ethnic Variation in Response to IM Triamcinolone in Children With Severe Therapy-Resistant Asthma. *Chest* 2016; 149: 98-105.

28. Panickar JR, Kenia P, Silverman M, Grigg J. Intramuscular triamcinolone for difficult asthma. *Pediatr Pulmonol* 2005; 39: 421-5.

29. Kapur AS, Madge P, Davies PL, Paton JY. A Retrospective Analysis of IM Triamcinolone as a Therapy for "Difficul to Control" Asthma in Children. *Arch Dis Child* 2012; 97 (Suppl 1)(A29).

30. Krupp NL, Weist A, Fiscus C. Monthly Triamcinolone Acetonide for Severe Refractory Life-Threatening Asthma in Children. *J Allergy Clin Immunol* 2016; AB212: 690.

31. Teague WG, Phillips BR, Fahy JV, et al. Baseline Features of the Severe Asthma Research Program (SARP III) Cohort: Differences with Age. *J Allergy Clin Immunol Practice* 2018; 6: 545,554.e4.

32. Fleming L, Murray C, Bansal AT, Hashimoto S, Bisgaard H, Bush A, Frey U, Hedlin G, Singer F, van Aalderen WM, et al. The burden of severe asthma in childhood and adolescence: results from the paediatric U-BIOPRED cohorts. *Eur Respir J* 2015; 46: 1322-33.

33. Chipps BE, Szefler SJ, Simons FER, Haselkorn T, Mink DR, Deniz Y, Lee JH, TENOR Study Group. Demographic and clinical characteristics of children and adolescents with severe or difficult-to-treat asthma. *J Allergy Clin Immunol* 2007; 119: 1156-63.

34. World Health Organisation. European Health Information Gateway. SDR (0-14), Asthma, per 100,000. 2018; Available at: https://gateway.euro.who.int/en/indicators/hfamdb_126-sdr-0-14-asthma-per-100-000/. Accessed 4th December 2018.

35. Asher I, Pearce N. Global burden of asthma among children. *Int J Tuberculosis Lung Dis* 2014; 18: 1269-78.

36. Royal College of Physicians. Why asthma still kills. 2015; https://www.rcplondon.ac.uk/projects/outputs/why-asthma-still-kills 2015. Accessed 19th Dec 2018..

37. Kivisto JE, Karjalainen J, Kivela L, Huhtala H, Protudjer JLP. Very low asthma death incidence among Finnish children from 1999 to 2015. *Pediatr Pulmonol* 2018; 53: 1009-13.

38. Nordlund B, Melen E, Schultz ES, Gronlund H, Hedlin G, Kull I. Prevalence of severe childhood asthma according to the WHO. *Respir Med* 2014; 108: 1234-7.

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

40. Turner S, Thomas M, von Ziegenweidt J, Price D. Prescribing trends in asthma: a longitudinal observational study. *Arch Dis Child* 2009; 94: 16-22.

41. Elkout H, Helms PJ, Simpson CR, McLay JS. Changes in primary care prescribing patterns for paediatric asthma: a prescribing database analysis. *Arch Dis Child* 2012; 97: 521-5.

42. Smith M, Iqbal S, Elliott TM, Everard M, Rowe BH. Corticosteroids for hospitalised children with acute asthma. *Cochrane Database of Systematic Reviews* 2003;-2003.

43. Aljebab F, Choonara I, Conroy S. Systematic review of the toxicity of short-course oral corticosteroids in children. *Arch Dis Child* 2016; 101: 365-70.

44. Aljebab F, Choonara I, Conroy S. Systematic Review of the Toxicity of Long-Course Oral Corticosteroids in Children. *PLoS ONE* 2017; 12: e0170259.

45. Gamble J, Stevenson M, McClean E, Heaney LG. The prevalence of nonadherence in difficult asthma. *Am J Respir Crit Care Med* 2009; 180: 817-22.

46. Chipps BE, Lanier B, Milgrom H, Deschildre A, Hedlin G, Szefler SJ, Kattan M, Kianifard F, Ortiz B, Haselkorn T, et al. Omalizumab in children with uncontrolled allergic asthma: Review of clinical trial and real-world experience. *J Allergy Clin Immunol* 2017; 139: 1431-44.

47. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, Gruchalla RS, Kattan M, Teach SJ, Pongracic JA, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med* 2011; 364: 1005-15.

48. Menzella F, Lusuardi M, Galeone C, Taddei S, Facciolongo N, Zucchi L. Mepolizumab for severe refractory eosinophilic asthma: evidence to date and clinical potential. *Ther Adv Chronic Dis* 2016; 7: 260-77.

49. Glaxosmithkline. 200363-Pharmacokinetics and pharmacodynamics of mepolizumab administered subcutaneously in children. 2018; Available at: https://www.gsk-studyregister.com/studies?conditions=&locationCountryInternal=&pcode=&Status=&Keyword=200363&ageRange=&gender=&phases=&studyType=&SortField=Location_Distance&SortOrder=asc&page=0. Accessed 4th Dec 2018.

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

51. Ortega HG, Liu MC, Pavord ID, Brusselle GC, Fitzgerald JM, Chetta A, Humbert M, Katz LE, Keene ON, Yancey SW et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014; 371: 1198-207.

52. Busse W, Chupp G, Nagase H, Albers FC, Doyle S, SHen Q, Bratton DJ, Gunsoy NB. Anti-IL-5 treatments in patients with severe asthma by blood eosinophil thresholds: Indirect treatment comparison. *J Allergy Clin Immunol* 2019; 143: 190,200.e20.

53. Castro M, Corren J, Pavord ID, Maspero S, Wenzel S, Rabe KF, Busse WW, Ford L, Sher L, Fitzgerald JM, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. *N Engl J Med* 2018; 378: 2486-96.

54. Kiljander TO, Harding SM, Field SK, Stein MR, Nelson HS, Ekelund J, Illueca M, Beckman O, Sostek MB. Effects of esomeprazole 40 mg twice daily on asthma: a randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2006;173:1091-7.

55. American Lung Association Asthma Clinical Research Centers, Mastronarde JG, Anthonisen NR, Castro M, Holbrook JT, Leone FT, Teague WG, Wise RA. Efficacy of Esomeprazole for Treatment of Poorly Controlled Asthma; a Randomized Controlled Trial. *N Engl J Med* 2009; 360:1487–1499.

56. Writing Committee for the American Lung Association Asthma Clinical Research Centers, Holbrook JT, Wise RA, Gold BD, Blake K, Brown ED, Castro M, Dozor AJ, Lima JJ, Mastronarde JG, et al. Lansoprazole for children with poorly controlled asthma: a randomized controlled trial. *J Am Med Assoc* 2012; 307: 373-81.

57. Chan AHY, Stewart AW, Harrison J, Camargo CAJ, Black PN, Mitchell EA. The effect of an electronic monitoring device with audiovisual reminder function on adherence to inhaled corticosteroids and school attendance in children with asthma: a randomised controlled trial. *Lancet Respir Med* 2015; 3: 210-9.

58. Klok T, Kaptein AA, Duiverman EJ, Brand PL. It's the adherence, stupid (that determines asthma control in preschool children)! *Eur Respir J* 2014; 43: 783-91.

59. Shields M, Alqahtani F, Rivey M, McElnay J. Using remote directly observed therapy (R-DOT) for optimising asthma therapy. *Eur Respir J* 2017; 50, suppl 61: OA3448.

60. Boyle RJ, Pedroletti C, Wickman M, Bjermer L, Valovirta E, Dahl R, Von Berg A, Zetterstrom O, Warner JO, 4A Study Group. Nocturnal temperature controlled laminar airflow for treating atopic asthma: a randomised controlled trial. *Thorax* 2012; 67: 215-21.

61. Murray CS, Foden P, Sumner H, Shepley E, Custovic A, Simpson A. Preventing Severe Asthma Exacerbations in Children. A Randomized Trial of Mite-Impermeable Bedcovers. *Am J Respir Crit Care Med* 2017; 196: 150-8.

FIGURE LEGENDS

Figure one. Schematic "ECG" summarising 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.

Figure two. 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 one year had an incidence which was not zero. Data were available between 2006-2015 and the incidence was zero throughout from the following countries: Cyprus, Estonia, Israel, Lithuania and Malta.

Table one. A summary of the definitions of severe asthma in children and young people

Source of the definition		Exact wording	Mention		
			High dose therapy	Poor control	Exacerbations
Global Initiative for Asthma 2017[2]		Asthma that requires step 4 or 5 treatment, e.g. 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	Problematic Severe Asthma	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 b-agonist, leukotriene receptor antagonist and oral theophylline) and still have symptoms	Yes	Yes	No
	Difficult-to-treat asthma	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			
	Severe therapy-resistant asthma	When factors that make the child difficult to treat cannot be identified			
World Health Organisation[5] 2010		'Uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity	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, e.g. long acting beta agonist 2. Daily/near daily short acting beta agonist treatment 3. Persistent airway obstruction, e.g. FEV_1 <80% 4. At least one urgent care visit per year 5. A 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 fata asthma episode	Yes	Yes (minor criteria 2)	Yes
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 b2-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

Table two. Details of case reports where intramuscular triamcinolone was used as part of asthma management.

Study	Number of participants	Dose of triamcinolone used and interval	Outcome after treatment
Koo et al[1]	79 cases (age and sex distribution not stated)	40 or 80mg (if < or ≥30 kg) one dose given	Exhaled nitric oxide, sputum eosinophilia and admissions for asthma were reduced in white children
Panikar[2]	5 cases given one dose (mean 9 years, range 5-13 years, 2 female) 8 given 2-5 doses (mean 13 years, range 12-15 years, 5 female)	20-100 mg at 4 weekly intervals	>1 dose was associated with reduced admissions and exacerbations even after ending treatment. A single dose was associated with reduced exacerbations.
Kapur[3]	7 cases (mean 12, range 8-16 years, 6 female)	≤60 mg (usually 40mg) 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 [4]	5 cases (8-15 years, sex distribution not stated)	60-120 mg interval between doses not stated	The collective number of admissions fell to zero
Phipatanakul[5]	188 children (mean 11.5 years, range 6-17 years, overall 62% male)	One dose, 40mg/kg up to a maximum of 40mg	Assessment three weeks after treatment found reduced FeNO and blood eosinophils in all participants. Additionally, among 111 participants with severe asthma, treatment was associated with increased symptom score. FEV_1 did not change after treatment.

Table three. A summary of the evidence for efficacy and side effects of medications included in this review. 1=evidence from systematic review or randomised control trials, 2=evidence from open label trial, 3=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

	Efficacy?	Side effects?
Prednisolone	3+	1+++
Triamcinolone	3+	3++
Omalizumab	1+++	3+
Mepolizumab	No data	2++
Lanzoprazole	1-	3+

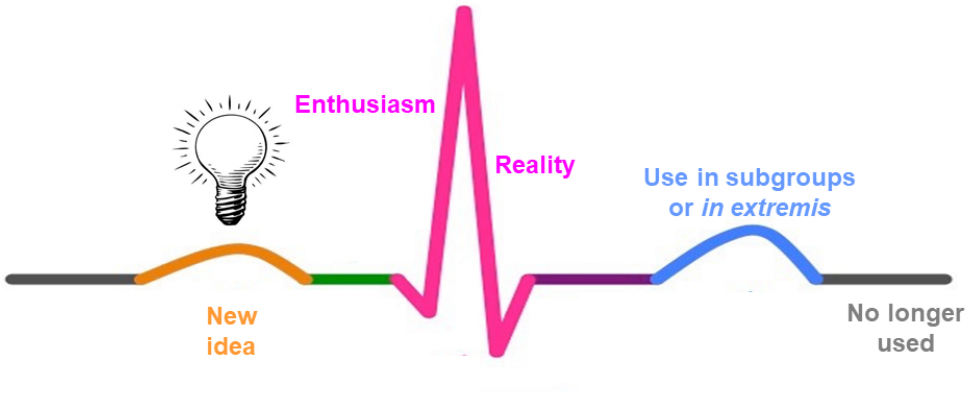

Figure one. Schematic "ECG" summarising the ups and downs of enthusiasm for many novel treatments which have been used for severe asthma in the past, but which are no longer used8. In this metaphor, treatment is first proposed as being potentially of use (P wave), then followed by a surge of enthusiasm (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.

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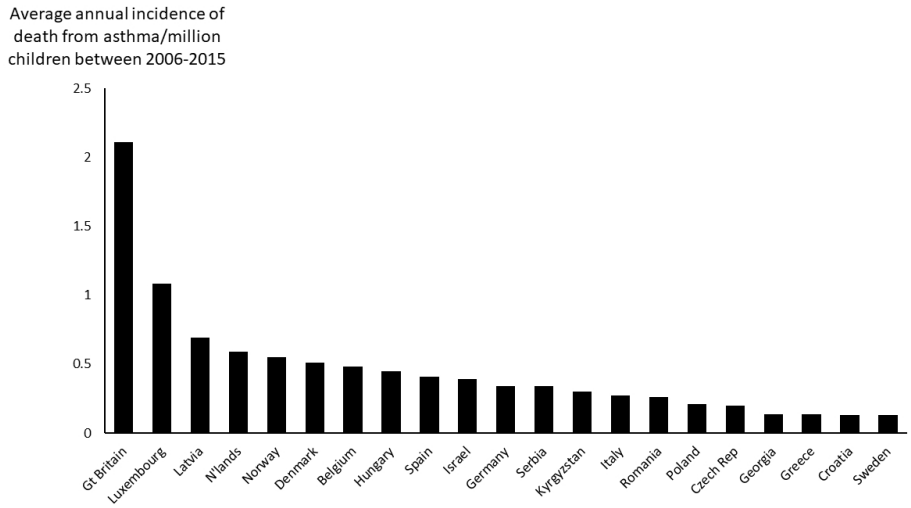

Figure two. The incidence of asthma morbidity in 21 countries in the World health Organisation European Region averaged between 2006 and 2015. Only countries where data were available in each year and where at least one year had an incidence which was not zero. Data were available between 2006-2015 and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

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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 and adolescents 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, and some definitions also include regular exacerbations. Severe asthma can be considered as difficult to treat or therapy resistant or both. The prevalence of severe asthma within populations of children and adolescents with asthma may be up to 5% depending on the definition chosen. 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 recognised side-effects. Evidence supporting the use of maintenance oral prednisolone and intramuscular triamcinolone is weak but there is evidence of adverse effects. Response to corticosteroids is heterogeneous and recognising phenotypes ~~(which may include ethnicity)~~ or endotypes ~~(which may include eosinophilia)~~ may identify those most likely to gain maximal ~~ise~~ benefit from treatment. There is a robust evidence base describing the efficacy and side effects for the anti-IgE biologic omalizumab. A second biologic, an anti-IL-5 agent mepolizumab, has recently been licenced in Europe (but not the US) for children aged 6-11 years based on safety data but without efficacy data. Biologics which are licenced for use in patients over 11 years old include omalizumab, mepolizumab, benralizumab, reslizumab and dupilumab. A randomised controlled trial found that proton pump inhibitor treatment does not improve asthma control but may have side effects. There is plenty that the clinician can offer to the child and adolescent with severe asthma in 2019, including non-therapeutic and therapeutic interventions. To manage severe asthma, practitioners from broad specialties 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.

INTRODUCTION

Asthma is a common condition which is managed in many countries and in millions of children and ~~young people~~adolescents around the globe 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 symptoms[3] 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 ~~young people~~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 healthcare expense, and is a particularly challenging situation for the child and young person, their family, their healthcare team and the wider healthcare 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.

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 one. 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 two themes common to all the definitions of severe asthma identified are poor control and high dose treatment (usually inhaled corticosteroid, ICS ≥400 micrograms budesonide or equivalent for children aged under 12 years and ≥1000 micrograms in older children[2]). Asthma attacks are included in some but not all definitions of severe asthma.

Severe asthma can be broken down into two subcategories[6]. A substantial proportion of individuals with severe asthma has symptoms which are due to modifiable factors which include poor or non-adherence 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 beta agonists and leukotriene modifiers. There is a pressing need to categorise 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 "non-standard" 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 summarised here:

1. *Is this asthma?* Conditions such as dysfunctional breathing, vocal cord dysfunction are increasingly recognised in children aged five years and above, and are reviewed elsewhere [20,21]. Pertussis[22] and habitual cough[23] 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], but these are predominantly considerations for the under five year olds. Confirmation of the diagnosis 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 adolescents[24] and this can usually be easily identified and readily resolved. Addressing poor or non-adherence is less straight forwards than addressing poor inhaler technique. Treatment non-adherence in asthma is reviewed elsewhere[25]. Briefly, adherence to medication is a complex behaviour and non-adherence 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, e.g. school avoidance. Adherence can be categorised as intentional or unintentional. Non-adherence 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 organisation in the day-to-day running of the household then attention to taking

treatment is likely to be poor, and where there is scepticism or mistrust of healthcare professionals ~~and~~ treatment adherence can be expected to be poor.

3. *Are there treatable co-morbidities?* Anxiety and allergic conditions such as rhinitis and eczema should be identified and managed since they can accompany and contribute towards poor quality of life for children and adolescents with severe asthma. Other conditions such as obesity, obstructive sleep apnoea and gastro-oesophageal 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 non-response to a dose of triamcinolone or a burst of 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 centres the role of airway biopsy in stratifying asthma treatment is being assessed[19].

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 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 paediatric age range, and in children aged less than five years is poorly understood. Anecdotally, in the under five years age group severe exacerbations occur with

intercurrent upper respiratory tract infection against a back ground 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 asthma[26–30] indicate that severe asthma is more common in the 12-15 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) III[31] and the 99 children with severe asthma an initiative aimed at characterising severe asthma (U-BIOPRED)[32] were typically 11-12 years old and 55-60% were male. The complexity of the relationship between gender, 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 9-11 year olds with severe asthma were female increasing to 80% in the 15-17 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 versus prescribing of high dose inhaled corticosteroids (ICS) versus 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 one)[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 UK[36] (3 per million per annum) and Finland[37] (0.2 per million per annum), and this difference may reflect differences between healthcare systems. Birth cohort studies from Northern Europe estimate the prevalence of severe asthma is between 2 and 5 per thousand children or 2-5% of all children with asthma[38,39]. Consistent with these findings, studies using primary care prescribing data in England[40] and Scotland[41] 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].

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 stairway of escalating treatment. The mainstay of asthma treatment is inhaled corticosteroids and, when required, the addition of inhaled long acting beta agonists, ~~and~~ 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 anti-reflux treatments.

Historically, "beyond the guidelines" treatments have followed an "ECG course" (figure one) 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 oral macrolides, cyclosporin, cytotoxic drugs such as methotrexate and azathioprine, gold salts, intravenous infusions of Immunoglobulin, subcutaneous beta-agonist treatment and, in those sensitised to fungi, oral antifungal therapy with itraconazole or voriconazole[8]. This process of "trial and error" is now less commonplace and today's novel therapies, for example biologics, emerge from a more robust scientific foundation.

Systemic corticosteroids

There is a high level of evidence that short bursts of oral corticosteroid (OCS) treatment (e.g. for three or five 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 ~~young people~~adolescents can receive maintenance daily or alternate daily OCS treatment for periods in excess of one 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 minimise 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 paediatric 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, behaviour change and sleep disturbance)[43] and also for periods in excess of 14 days (weight gain, growth retardation, cushingoid features and susceptibility to infection)[44]. The potential for harm from maintenance OCS to be greater than benefit is highlighted in BTS/SIGN guideline[1] which states for adults (i.e. those aged >12 years): "add on low dose oral corticosteroids (7.5mg prednisolone daily) may be effective for some adults with severe asthma (Evidence D) but are associated with substantial side effects (Evidence B)."

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 non-adherent with oral corticosteroid treatment[45]). 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 two. ~~In the largest case series, part of T~~the third phase of the US Severe Asthma Research Program (SARP III) ~~i~~included the largest case series where triamcinolone was used to treat asthma symptoms. ~~I, 188~~

~~children and 526 adults had extensive physiological assessments before and three weeks after a single dose of triamcinolone.~~ 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 three 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 an improvement in symptoms and a non-significant trend for improved pre bronchodilator FEV_1. The apparent lack of response to triamcinolone in children with non-severe asthma is likely to be explained by a small sample size with few symptoms and good initial FEV_1, and not by a lack of steroid-responsiveness. A second in a case series of 79 children[27], also sought to describe symptom and physiological outcomes four 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 categorised 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 series[28] 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 one treatment of triamcinolone or repeated treatments at one moth intervals. The number of exacerbations and hospital admissions during the treatment and post treatment phases fell relative to pre-treatment 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 summarised 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 series[29] 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 two 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.

Omalizumab

The anti-IgE antibody omalizumab has been used for the treatment of severe asthma in children aged 6-11 years since 2009, and in older children and adults since 2003. At least ten randomised 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 tumour necrosis factor), but a recent review noted that 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 trial[47] included in a recent review[46] found that the majority (59%) of potential participants were ineligible. The monthly subcutaneous injection is uncomfortable, requires administration in a healthcare 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.

Mepolizumab

The anti-interleukin-5 molecule mepolizumab was licenced in Europe for use in children aged 6-11 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 headaches[48]; 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 6-11 year olds[49]. Inclusion criteria included: having an asthma diagnosis for more than 12 months; at least two exacerbations in the year prior to recruitment; receiving ≥400 micrograms budesonide (or equivalent); receiving an additional controller medication for more than three months; an FEV_1/FVC ratio of <0.8 and blood eosinophilia (>0.15x10^9/l on recruitment or >0.3 x10^9/l in the year prior to 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 likely that a randomised clinical trial will not 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" (i.e. either peak flow variability, bronchial hyperresponsiveness or bronchodilator response) and eosinophilia (i.e. elevated exhaled nitric oxide or blood eosinophilia).

Treatment with one of three doses of mepolizumab was associated with between a 39-52% 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 12-82 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 twelve years and older, there are two other anti IL5 pathway specific therapies licensed (benralizumab and reslizumab). A recent review of the literature suggests that whilst all three anti IL-5 pathway specific therapies are more effective than placebo in reducing exacerbations and improving symptom control, mepolizumab has the greater benefit[52].

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 study [53] recruited 1902 participants aged at least 12 years who were randomised 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; FEV_1 <80% (or ≤90% for 12-17 year olds); bronchodilator reversibility (>12% or 200mls); poor symptom control (Asthma Control Questionnaire score ≥1.5); and an asthma attack requiring systemic glucocorticosteroid treatment in the last year. The primary outcome was exacerbation rate and, as seen~~m~~ 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 two week's treatment and thereafter

throughout the study, also they had a mean increase of 140mls in FEV_1 compared to the placebo group. Eosinophilia (i.e. >300 eosinophils per cubic millimetre) occurred in 4% of participants who received dupliumab and 0.64% who received placebo, the clinical significance of this is uncertain.

Gastro-oesophageal reflux treatment

Gastro-oesophageal reflux disease (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 esomeprazole[54] but this same medication is not associated with improved lung function or symptoms in the absence of GORD symptoms[54,55]. ~~but,~~ Despite the relationship not being thought to be causal[1], a trial of GORD treatment is sometimes used in children with severe asthma. The evidence base for this practice is very narrow. One randomised controlled trial has explored the benefit of a proton pump inhibitor (Lansoprazsole) in poorly controlled (not severe) asthma in 306 children aged 6-17 years[56]. Eligibility criteria included receiving a dose of ICS >175 micrograms/day fluticasone (or equivalent), evidence of airway reversibility or hyperresponsiveness, need for short acting beta agonist treatment more than two days a week and two asthma exacerbations in the past year. Children and ~~young people~~adolescents with overt GORD symptoms were excluded. Just over 40% of participants tested had evidence of GORD. After 24 weeks there were no differences in asthma outcomes between those who received lansoprasole compared to placebo. Unexpectedly the active medication was associated with increased risk for respiratory infection.

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 highlighted ongoing areas of uncertainty in the definition, the epidemiology and the medical

treatment of severe asthma (table three). 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 inhaled corticosteroid 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 non-medicinal interventions there are new "uncertainties" such as temperature-controlled laminar airflow[60] 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 (e.g. teachers) and personalising care.

Research needs

These are some areas where further research might advance the care for children and ~~young people~~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 (e.g. 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 ~~and omalizumab~~ be stopped?

REFERENCES

1. British Thoracic Society Scottish Intercollegiate Guidelines Network. BTS/SIGN British guideline on the management of asthma. 2016; Available at: https://www.brit-thoracic.org.uk/standards-of-care/guidelines/btssign-british-guideline-on-the-management-of-asthma/. Accessed 19th Dec 2018.

2. Global Initiative for Asthma. 2017 GINA Report, Global Strategy for Asthma Management and Prevention. 2017; Available at: http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/. Accessed 1st April 2017.

3. Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. *Eur Respir J* 2000; 16: 802-7.

4. Asthma UK. Asthma facts and FAQs. 2017; Available at: http://www.asthma.org.uk/asthma-facts-and-statistics. Accessed 08/31, 2017.

5. Bush A, Saglani S. Management of severe asthma in children. *Lancet* 2010; 376: 814-25.

6. Hedlin G, Bush A, Lodrup Carlsen K, Wennergren G, De Benedictis FM, Melen E, Paton J, Wilson N, Carlsen K, Problematic Severe Asthma in Childhood Initiative group Problematic severe asthma in children, not one problem but many: a GA2LEN initiative. *Eur Respir J* 2010; 36: 196-201.

7. Lodrup Carlsen KC, Hedlin G, Bush A, Wennergren G, de Benedictis FM, de Jongste JC, Baraldi E, Pedroletti C, Barbato A, Malmstrom K, et al. Assessment of problematic severe asthma in children. *Eur Respir J* 2011; 37: 432-40.

8. Bush A, Pedersen S, Hedlin G, Baraldi E, Barbato A, de Benedictis F, Lodrup Carlsen KC, de Jongste J, Piacentini G, PSACI (Problematic Severe Asthma in Childhood Initiative) group.. Pharmacological treatment of severe, therapy-resistant asthma in children: what can we learn from where? *Eur Respir J* 2011; 38: 947-58.

9. Giovannini-Chami L, Albertini M, Scheinmann P, de Blic J. New insights into the treatment of severe asthma in children. *Paediatr Respir Rev* 2015; 16: 167-73.

10. Goldstein S. Unlocking the Puzzle of Severe Asthma in Children. *J Allergy Clin Immunol Practice* 2017; 5: 420-1.

11. Ramratnam SK, Bacharier LB, Guilbert TW. Severe Asthma in Children. *J Allergy Clin Immunol Practice* 2017; 5: 889-98.

12. Larenas-Linnemann D, Nieto A, Palomares O, Pitrez PM, Cukier G. Moving toward consensus on diagnosis and management of severe asthma in children. *Cur Med Res Opinion* 2018; 34: 447-58.

13. Leung JS, Johnson DW, Sperou AJ, Crotts J, Saude E, Hartling L, Stang A. A systematic review of adverse drug events associated with administration of common asthma medications in children. *PLoS ONE* 2017; 12: e0182738.

14. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, Adcock IM, Bateman ED, Bel EH, Bleecker ER et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43: 343-73.

15. Bousquet J, Mantzouranis E, Cruz AA, Ait-Khaled N, Baena-Cagnani CE, Bleecker ER, Brightling CE, Burney P, Bush A, Busse WW, et al. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. *J Allergy Clin Immunol* 2010; 126: 926-38.

16. Proceedings of the ATS workshop on refractory asthma: current understanding, recommendations, and unanswered questions. American Thoracic Society. *Am J Respir Crit Care Med* 2000; 162: 2341-51.

17. Chung KF, Godard P, Adelroth E, Ayres J, Barnes N, Barnes P, Bel E, Purney P, Chanez P, Connett G, et al. Difficult/therapy-resistant asthma: the need for an integrated approach to define clinical phenotypes, evaluate risk factors, understand pathophysiology and find novel therapies. ERS Task Force on Difficult/Therapy-Resistant Asthma. European Respiratory Society. *Eur Respir J* 1999; 13: 1198-208.

18. Guilbert TW, Bacharier LB, Fitzpatrick AM. Severe asthma in children. *J Allergy Clin Immunol Practice* 2014; 2: 489-500.

19. Bush A, Fleming L, Saglani S. Severe asthma in children. *Respirology* 2017; 22: 886-97.

20. Barker N, Ugonna K, Thevasagayam R, Kirkby J. Practical guide to the management of dysfunctional breathing. *Paediatr Child Health* 2018; 28: 149-151.

21. de Groot EP. Breathing abnormalities in children with breathlessness. *Paediatr Respir Rev* 2011; 12: 83-7.

22. Harnden A, Grant C, Harrison T, Perera R, Brueggemann AB, Mayon-White R, Mant D. Whooping cough in school age children with persistent cough: prospective cohort study in primary care. *Brit Med J* 2006; 333: 174-7.

23. Wright MF, Balfour-Lynn I. Habit-tic cough: Presentation and outcome with simple reassurance. *Pediatr Pulmonol* 2018; 52: 512-6.

24. Gillette C, Rockich-Winston N, Kuhn JA, Flesher S, Shepherd M. Inhaler Technique in Children With Asthma: A Systematic Review. *Academ Pediatr* 2016; 16: 605-15.

25. Klok T, Kaptein AA, Brand PLP. Non-adherence in children with asthma reviewed: The need for improvement of asthma care and medical education. *Pediatr Allergy Immunol* 2015; 26: 197-205.

26. Phipatanakul W, Mauger DT, Sorkness RL, Gaffin JM, Holguin F, Woodruff PG, Ly NP, Bacharier LB, Bhakta NR, Moore WC, et al. Effects of Age and Disease Severity on Systemic Corticosteroid Responses in Asthma. *Am J Respir Crit Care Med* 2017; 195: 1439-48.

27. Koo S, Gupta A, Fainardi V, Bossley C, Bush A, Saglani S, Fleming L. Ethnic Variation in Response to IM Triamcinolone in Children With Severe Therapy-Resistant Asthma. *Chest* 2016; 149: 98-105.

28. Panickar JR, Kenia P, Silverman M, Grigg J. Intramuscular triamcinolone for difficult asthma. *Pediatr Pulmonol* 2005; 39: 421-5.

29. Kapur AS, Madge P, Davies PL, Paton JY. A Retrospective Analysis of IM Triamcinolone as a Therapy for "Difficul to Control" Asthma in Children. *Arch Dis Child* 2012; 97 (Suppl 1)(A29).

30. Krupp NL, Weist A, Fiscus C. Monthly Triamcinolone Acetonide for Severe Refractory Life-Threatening Asthma in Children. *J Allergy Clin Immunol* 2016; AB212: 690.

31. Teague WG, Phillips BR, Fahy JV, et al. Baseline Features of the Severe Asthma Research Program (SARP III) Cohort: Differences with Age. *J Allergy Clin Immunol Practice* 2018; 6: 545,554.e4.

32. Fleming L, Murray C, Bansal AT, Hashimoto S, Bisgaard H, Bush A, Frey U, Hedlin G, Singer F, van Aalderen WM, et al. The burden of severe asthma in childhood and adolescence: results from the paediatric U-BIOPRED cohorts. *Eur Respir J* 2015; 46: 1322-33.

33. Chipps BE, Szefler SJ, Simons FER, Haselkorn T, Mink DR, Deniz Y, Lee JH, TENOR Study Group. Demographic and clinical characteristics of children and adolescents with severe or difficult-to-treat asthma. *J Allergy Clin Immunol* 2007; 119: 1156-63.

34. World Health Organisation. European Health Information Gateway. SDR (0-14), Asthma, per 100,000. 2018; Available at: https://gateway.euro.who.int/en/indicators/hfamdb_126-sdr-0-14-asthma-per-100-000/. Accessed 4th December 2018.

35. Asher I, Pearce N. Global burden of asthma among children. *Int J Tuberculosis Lung Dis* 2014; 18: 1269-78.

36. Royal College of Physicians. Why asthma still kills. 2015; https://www.rcplondon.ac.uk/projects/outputs/why-asthma-still-kills 2015. Accessed 19th Dec 2018..

37. Kivisto JE, Karjalainen J, Kivela L, Huhtala H, Protudjer JLP. Very low asthma death incidence among Finnish children from 1999 to 2015. *Pediatr Pulmonol* 2018; 53: 1009-13.

38. Nordlund B, Melen E, Schultz ES, Gronlund H, Hedlin G, Kull I. Prevalence of severe childhood asthma according to the WHO. *Respir Med* 2014; 108: 1234-7.

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

40. Turner S, Thomas M, von Ziegenweidt J, Price D. Prescribing trends in asthma: a longitudinal observational study. *Arch Dis Child* 2009; 94: 16-22.

41. Elkout H, Helms PJ, Simpson CR, McLay JS. Changes in primary care prescribing patterns for paediatric asthma: a prescribing database analysis. *Arch Dis Child* 2012; 97: 521-5.

42. Smith M, Iqbal S, Elliott TM, Everard M, Rowe BH. Corticosteroids for hospitalised children with acute asthma. *Cochrane Database of Systematic Reviews* 2003;-2003.

43. Aljebab F, Choonara I, Conroy S. Systematic review of the toxicity of short-course oral corticosteroids in children. *Arch Dis Child* 2016; 101: 365-70.

44. Aljebab F, Choonara I, Conroy S. Systematic Review of the Toxicity of Long-Course Oral Corticosteroids in Children. *PLoS ONE* 2017; 12: e0170259.

45. Gamble J, Stevenson M, McClean E, Heaney LG. The prevalence of nonadherence in difficult asthma. *Am J Respir Crit Care Med* 2009; 180: 817-22.

46. Chipps BE, Lanier B, Milgrom H, Deschildre A, Hedlin G, Szefler SJ, Kattan M, Kianifard F, Ortiz B, Haselkorn T, et al. Omalizumab in children with uncontrolled allergic asthma: Review of clinical trial and real-world experience. *J Allergy Clin Immunol* 2017; 139: 1431-44.

47. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, Gruchalla RS, Kattan M, Teach SJ, Pongracic JA, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med* 2011; 364: 1005-15.

48. Menzella F, Lusuardi M, Galeone C, Taddei S, Facciolongo N, Zucchi L. Mepolizumab for severe refractory eosinophilic asthma: evidence to date and clinical potential. *Ther Adv Chronic Dis* 2016; 7: 260-77.

49. Glaxosmithkline. 200363-Pharmacokinetics and pharmacodynamics of mepolizumab administered subcutaneously in children. 2018; Available at: https://www.gsk-studyregister.com/studies?conditions=&locationCountryInternal=&pcode=&Status=&Keyword=200363&ageRange=&gender=&phases=&studyType=&SortField=Location_Distance&SortOrder=asc&page=0. Accessed 4th Dec 2018.

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

51. Ortega HG, Liu MC, Pavord ID, Brusselle GC, Fitzgerald JM, Chetta A, Humbert M, Katz LE, Keene ON, Yancey SW et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014; 371: 1198-207.

52. Busse W, Chupp G, Nagase H, Albers FC, Doyle S, SHen Q, Bratton DJ, Gunsoy NB. Anti-IL-5 treatments in patients with severe asthma by blood eosinophil thresholds: Indirect treatment comparison. *J Allergy Clin Immunol* 2019; 143: 190,200.e20.

53. Castro M, Corren J, Pavord ID, Maspero S, Wenzel S, Rabe KF, Busse WW, Ford L, Sher L, Fitzgerald JM, et al. Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma. *N Engl J Med* 2018; 378: 2486-96.

54. Kiljander TO, Harding SM, Field SK, Stein MR, Nelson HS, Ekelund J, Illueca M, Beckman O, Sostek MB. Effects of esomeprazole 40 mg twice daily on asthma: a randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2006;173:1091-7.

55. American Lung Association Asthma Clinical Research Centers, Mastronarde JG, Anthonisen NR, Castro M, Holbrook JT, Leone FT, Teague WG, Wise RA. Efficacy of Esomeprazole for Treatment of Poorly Controlled Asthma; a Randomized Controlled Trial. *N Engl J Med* 2009; 360:1487–1499.

56. Writing Committee for the American Lung Association Asthma Clinical Research Centers, Holbrook JT, Wise RA, Gold BD, Blake K, Brown ED, Castro M, Dozor AJ, Lima JJ, Mastronarde JG, et al. Lansoprazole for children with poorly controlled asthma: a randomized controlled trial. *J Am Med Assoc* 2012; 307: 373-81.

57. Chan AHY, Stewart AW, Harrison J, Camargo CAJ, Black PN, Mitchell EA. The effect of an electronic monitoring device with audiovisual reminder function on adherence to inhaled corticosteroids and school attendance in children with asthma: a randomised controlled trial. *Lancet Respir Med* 2015; 3: 210-9.

58. Klok T, Kaptein AA, Duiverman EJ, Brand PL. It's the adherence, stupid (that determines asthma control in preschool children)! *Eur Respir J* 2014; 43: 783-91.

59. Shields M, Alqahtani F, Rivey M, McElnay J. Using remote directly observed therapy (R-DOT) for optimising asthma therapy. *Eur Respir J* 2017; 50, suppl 61: OA3448.

60. Boyle RJ, Pedroletti C, Wickman M, Bjermer L, Valovirta E, Dahl R, Von Berg A, Zetterstrom O, Warner JO, 4A Study Group. Nocturnal temperature controlled laminar airflow for treating atopic asthma: a randomised controlled trial. *Thorax* 2012; 67: 215-21.

61. Murray CS, Foden P, Sumner H, Shepley E, Custovic A, Simpson A. Preventing Severe Asthma Exacerbations in Children. A Randomized Trial of Mite-Impermeable Bedcovers. *Am J Respir Crit Care Med* 2017; 196: 150-8.

FIGURE LEGENDS

Figure one. Schematic "ECG" summarising 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.

Figure two. 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 one year had an incidence which was not zero. Data were available between 2006-2015 and the incidence was zero throughout from the following countries: Cyprus, Estonia, Israel, Lithuania and Malta.