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Diagnosis and Management of Problematic Severe Asthma

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Abstract
This review will outline an evidence-based approach for diagnosing and managing children with problematic severe asthma (PSA). Children with PSA have uncontrolled asthma symptoms, despite maximal prescribed asthma treatment. These children have high morbidity and mortality and should be referred for specialist respiratory assessment and management. The first step in the assessment of a child with PSA is confirming the diagnosis of asthma using objective evidence. Following this, an assessment of inhaled corticosteroid adherence and a multi-disciplinary team approach is essential for separating difficult asthma (DA) from severe therapy resistant asthma (STRA). The majority of children have DA which entails uncontrolled asthma symptoms due to underlying modifiable factors including poor treatment adherence, poor inhaler technique, exposure to environmental allergens, co-morbid conditions and psycho-social factors. Approximately 20% of children with PSA have STRA, and have persistent asthma symptoms despite good treatment adherence and correction of modifiable factors. Children with STRA typically have multiple and severe aeroallergen sensitization, eosinophilic airway inflammation and high fraction exhaled nitric oxide (FeNO). Further investigation of children with STRA includes an assessment of systemic steroid responsiveness, this is important for confirming the diagnosis of STRA and guiding the choice of additional treatment. Biologics are an add on (immune targeted) therapy for STRA. The current biologics used in children target the T2 helper (Th2) pathway mediating eosinophilic, allergic asthma. **Conclusion.** Future clinical trials of biologics in children will be essential to help identify childhood specific biomarkers and to decide which biologic is best for which individual child.

Key Words: Paediatric ▪ Asthma.

Introduction

One in ten children in Europe have asthma (1). Most children with asthma have mild to moderate disease and can achieve good symptom control with low dose inhaled corticosteroids (ICS). However, approximately 2-5% of asthmatic children have problematic severe asthma (PSA) (2, 3). These children have uncontrolled symptoms despite being prescribed maximal standard pharmacological treatment, equivalent to step 4/5 of Global Initiative for Asthma (GINA) management guidelines (4). Children with PSA have an increased mortality, morbidity and despite their small number account for 50% of asthma related healthcare costs (5, 6). The UK National Review of Asthma Deaths observed that 17% of the asthma deaths were in patients with severe asthma, that by current international asthma management guidance, should have been under specialist respiratory care (7). For these reasons it is essential that these children are managed in a specialist setting by a multi-disciplinary team experienced in diagnosing and managing children with PSA. Current international guidance outlines when a child with problematic asthma should be referred to a respiratory specialist (4, 8).

This review will discuss the evidence based PSA pathway followed by Royal Brompton Hospital, London (9) for diagnosing and managing school aged children (6-16 years old) with PSA, with relevant reference to medical literature.

Problematic Severe Asthma

The umbrella term PSA describes all children with persistent asthma symptoms despite maximal standard pharmacological therapy (10). Unfortunately, multiple different terminologies have been used to describe children with severe asthma, which has made it difficult to compare disease outcomes in paediatric research studies. In order to unify terminology, the term PSA was proposed by the PSA in Childhood Initiative Group, a Global Allergy and Asthma European Network (GA2LEN) Task Force (10, 11) and has been adapted by the Royal Brompton Paediatric Severe Asthma diagnosis and management pathway.

Children with PSA have the following two features

i) poor symptom control defined as one or more of:
   - Chronic symptoms (most days for >3 months) or Childhood Asthma Control Test (C-ACT) score or Asthma Control Test (ACT) score <20 (12, 13)
   - Persistent Airflow obstruction (FEV_1 post bronchodilator <80%)
   - Recurrent severe asthma exacerbations (either ≥2 hospital admissions per year or ≥3 courses of high dose oral steroids for at least 3 days per year)
   - One intensive care admission requiring mechanical ventilation
ii) prescribed high-dose inhaled corticosteroids (equivalent to >800 μg/day of budesonide or fluticasone >500 μg /day) plus a long acting β2 agonist plus montelukast (or previous failed trial) or previous trial of other add on therapy such as theophylline OR require maintenance low dose oral corticosteroids. (As per GINA Asthma Step 4/5 Treatment and ERS/ATS Severe Asthma Guidance) (4, 8).

Assessment of the Child Referred with PSA

Confirming Asthma Diagnosis

The first step in the assessment of a child with PSA is to confirm the diagnosis of asthma (8). Approximately 50% of children with PSA have an existing co-morbidity, associated diagnosis, or have been wrongly diagnosed as having asthma (14). National Institute of Clinical Excellence (NICE) Asthma guidelines advise the use of symptom history and objective tests to diagnose asthma (15). It is essential to not simply rely on the history to confirm the diagnosis, but also to use objective tests for diagnosing asthma, as outlined below.

Lung Function Tests

- Spirometry- all children aged 5 and over should have spirometry. An FEV_1/FVC ratio <70% is positive for obstructive airways disease.
- Bronchodilator reversibility (BDR)- if obstructive spirometry (FEV_1/FVC ratio <70%) then BDR testing is needed to determine if it is fixed or reversible obstructive airways disease. A BDR test result is positive for reversibility if increase in FEV_1 ≥12%.
- Peak expiratory flow variability- A 2 to 4 week period of PEFR monitoring is advised if the diagnosis is uncertain after spirometry, BDR and FeNO (see below). PEFR monitoring should be done if a. normal spirometry and b. obstructive spirometry (FEV_1/FVC Ratio <70%) with negative BDR test (not reversible obstructive spirometry) and raised FeNO ≥35ppb. Spontaneous variability in PEFR ≥20% is positive for reversible obstructive airways disease.

Airway Inflammation Tests

- Fractional exhaled nitric oxide (FeNO)- FeNO testing, is an approximate measure of eosinophilic airway inflammation (16). FeNO measurement should be considered if either normal spirometry or obstructive spirometry and negative BDR testing. A FeNO result of ≥ 35ppb is supportive for airway inflammation in children.

Airway Hyper-responsiveness Tests

- Airway Challenge- Airway hyper-responsiveness can be demonstrated by direct methacholine or histamine challenge, or indirect airway challenge using exercise, mannitol or hypertonic saline. The National Institute for Health

and Care Excellence (NICE) guidance does not recommend airway hyper-responsiveness testing in children. However, in specialist respiratory centres if diagnostic uncertainty remains after lung function testing and airway inflammation testing, it is an important additional test to consider.

Initial Investigations

Tests for Atopic Status

Asthma of all severity in children is typically allergic and hence it is important to question a diagnosis of asthma if there is no objective evidence of atopic sensitisation, particularly if the child has a chronic wet cough. Alternative diagnoses that may present as wrongly labelled or misdiagnosed severe asthma, are listed in Table 1. An assessment of the child's atopic status using patient history and objective tests is also important for identifying asthma triggers in children with asthma. Objective atopic testing may be undertaken by measurement of serum total IgE and serum specific IgE tests or skin prick testing to common allergens: food allergens (peanut, milk, egg), common aeroallergens (cat, dog, grass, tree, house dust mite) and moulds *(Alternaria alternata, Penicillium notatum and Cladosporium herbarum)*.

A small proportion of children (<15%) have non-atopic severe asthma (14, 17). Risk factors associated with non-allergic asthma include family history of asthma, eczema or rhinitis; lower respiratory tract infections in childhood, damp or mould in home environment, obesity and parental smoking (18). Despite, differences in atopic status, both allergic and non-allergic asthma in adults has been shown to have similar bronchial mucosal changes and immunocellular changes (19). Investigations to support asthma diagnosis and establish airway inflammatory phenotype are essential in non-atopic children to enable targeted treatment.

Other Tests

Additional tests that should be considered as part of an initial severe asthma assessment include chest x-ray (CXR), sweat test, vitamin D level and urinary cotinine. A CXR in a child with severe asthma may show non-specific radiological findings such as hyperinflation and peri-bronchial wall thickening. However, a CXR is most useful for investigating alternative diagnoses. A high resolution CT (HRCT) should be considered if there is an atypical asthma presentation i.e. abnormal carbon monoxide transfer factor, excessive mucus production, rapid decline in lung function, non-atopic (8). A sweat test should also be considered to exclude cystic fibrosis in those without objective evidence of an asthma diagnosis.

Approximately 30% of asthmatic children have vitamin D deficiency (serum 25 (OH)D <75nmol/L) (20). Vitamin D has been proposed to have immunomodulatory effects, including antiviral and anti-inflammatory effects (21). A Cochrane Systematic Review of vitamin D in children with asthma, identified 7 randomised controlled trials including a total of 435 children. Only one trial that included 22 children measured the rate of asthma exacerbations. Overall the systematic review reported vitamin D in adults and children reduced the rate of exacerbations requiring steroids (rate ratio 0.64, 95% CI 0.46 to 0.90). However, this review also included pre-school children (22) and mainly adults. In adult asthmatics, there is convincing evidence that vitamin D supplementation can prevent asthma exacerbations (23). However, the evidence base for recommendation of vitamin D supplementation to prevent asthma exacerbations in children is limited due to small study sample sizes (24).

Passive smoke exposure in asthmatic children can trigger asthma exacerbations (25). Asthmatic children with passive smoke exposure have more frequent emergency healthcare attendances and are twice as likely to have an asthma exacerbation requiring a hospital admission (25). Hospital admission data analysis has shown that banning smoking in public places in Scotland resulted in an 18% reduction in hospital admissions (95% CI 14.7 to 21.8; P<0.001) for asthma exacerbations in children (26). Urinary or salivary cotinine level is an objective marker of passive smoke exposure

and can be used to motivate carers to stop smoking and assess whether smoking has ceased in a household.

Table 1. Differential Diagnoses to Consider when Assessing Children with Problematic Severe Asthma

Dysfunctional breathing
Tracheo-bronchomalacia
Foreign body
External airway compression
Aspiration
Bronchiectasis
Obliterative bronchiolitis
Hypersensitivity Pneumonitis
Cystic Fibrosis
Primary Ciliary Dyskinesia

Multidisciplinary Assessment

Once a diagnosis of asthma has been confirmed, further management and assessments must be undertaken using a multidisciplinary team approach. The Royal Brompton multidisciplinary paediatric asthma team is composed of specialist asthma physiotherapists, dieticians, physiologists, clinical psychologists, specialist asthma nurses, safeguarding nurses, social workers and medical doctors. A multidisciplinary team approach is also essential to determine if the child has Difficult Asthma (DA) or Severe Therapy Resistant Asthma (STRA). This guides the direction of further management towards addressing modifiable factors or the need for further investigations to determine choice of add on treatments.

Definitions

Difficult Asthma

Children with DA have poor asthma symptom control due to underlying modifiable factors. Over 50% of children with PSA have difficult to treat asthma and symptoms improve after identifying and addressing modifiable factors (27). These modifiable factors include poor treatment adherence, poor inhaler technique, exposure to environmental allergens, co-morbid conditions and psycho-social factors (27).

Severe Therapy Resistant Asthma

Children with STRA have ongoing asthma symptoms despite good adherence to high dose inhaled corticosteroids and correction of modifiable factors. Children with STRA are immunophenotypically different to children with DA (28), STRA children are resistant to high-dose inhaled corticosteroids and have persistent eosinophilic airway inflammation, high FeNO and airway remodeling (14). The majority of children (85%) with STRA will be positive for one or more allergen have very severe and multiple allergen sensitization, and typically have worse disease severity with co-existing food allergies (29).

Assessments to Exclude Difficult Asthma

Basic Inhaler Technique and Objective Assessments of Adherence to ICS

Non-adherence to inhaled corticosteroids is strongly associated with poor asthma control, increased morbidity and mortality (7). Therefore, a thorough assessment of adherence to treatment is vital, to enable interventions to improve adherence, as well as distinguish STRA from DA. This includes assessing inhaler technique and reviewing suitability of spacer device used. Approximately 40% of children have poor inhaler technique and 15% use the wrong device (27). Incorrect administration of medication is common but is easily rectifiable with expert guidance.

Good adherence is defined as at least 80% administration of prescribed inhaled corticosteroid doses (30), moderate adherence 60-80% and poor adherence <60% administration of prescribed doses (31). Adherence can be measured by an assessment of prescription uptake, which is carried out by contacting the child's local pharmacy or primary care physician to check prescription records. Prescription uptake in half of asthmatic

children referred for specialist input is suboptimal (<80%) (27). A prescription uptake assessment may be sufficient to assess adherence, since poor prescription refill and uptake confirms poor adherence. However, good uptake does not equate to good adherence as there is little relationship between prescription uptake and actual administration of medication. Therefore, adherence is better assessed objectively by using electronic monitoring devices which attach to corticosteroid inhalers. These devices record timing and number of actuations (32). Newer devices are also able to record inhalation of the drug.

A prospective cohort study in asthmatic children attending a specialist paediatric severe asthma clinic used electronic monitoring devices (EMD) to monitor adherence to prescribed inhaled corticosteroid treatment (32). Ninety-three children had EMD monitoring for a median number of 92 days (range 56-200 days) (32). The median adherence to prescribed inhaled corticosteroids was 74% (range 21-99%). Disappointingly, nearly 60% of patients had suboptimal adherence (<80%), despite being aware that adherence was being monitored. After the adherence monitoring intervention, the study identified four patient groups based on adherence and asthma symptoms post intervention. These four groups were a. STRA group (18%) with good adherence but persistent poor control, b. good adherence and improved symptom control group (24%), the monitoring most likely improved adherence and resulted in improved asthma symptoms, c. over-treated group (26%), who had sub-optimal adherence but good control, suggesting that the patient was being over-treated with high dose inhaled corticosteroids, d. poor asthma symptom control group with sub-optimal adherence (32%) in whom the adherence monitoring intervention made no difference to their adherence. This study demonstrated the utility of objective monitoring of inhaled corticosteroids to measure adherence and distinguish difficult asthmatics from severe therapy resistant asthmatics.

FeNO suppression testing is an alternative strategy for measuring inhaled corticosteroid adherence. It has been used in adults as a marker of clinical response to treatment with inhaled corticosteroids (33). In FeNO suppression testing FeNO levels are measured before and after a period of directly observed therapy (DOT) with inhaled corticosteroids. Heaney et al., used remote DOT and FeNO suppression to assess adherence. Study participants had one week of remotely monitored directly observed therapy, in which high dose inhaled corticosteroids were administered daily. The FeNO suppression test was positive if a 42% decrease in FeNO was observed (34). Two hundred and one people in the study completed the test and over half (N=130) had positive suppression tests (33). FeNO suppression is a useful alternative approach to using electronic monitoring devices, which are expensive, often lost and also require a longer period of monitoring.

Adherence monitoring is important, not only to prevent overprescribing, but to identify patients with DA. Furthermore, information from adherence monitoring can be used to motivate families and children to improve adherence and modify their behaviour. In cases where support from the multidisciplinary team, including psychologist is not successful at improving adherence, directly observed therapy of inhaled corticosteroids at school can be implemented and in cases with significant concern a social services referral may be considered (35). Patients that are steroid responsive but have persistent poor adherence despite intervention are called 'refractory difficult asthmatics' (36).

Assessment of Home Environment

As part of a child's initial PSA assessment at the Royal Brompton Hospital the respiratory clinical nurse specialist undertakes a home visit (27). A home visit enables a first-hand assessment of smoke exposure, allergen exposure (house dust mite, mould, pets) and available medication in the house. It also provides opportunity for the family to talk with the nurse about the impact of managing a child with asthma on the family, difficulties they are experiencing in doing so, and for the specialist nurse to give advice on minimising environ-

mental triggers. In addition, the nurse may contact the school nurse and primary care physician for information on medication prescriptions, asthma inhaler use at school, participation in school sports, school attendance and any social concerns about the family (35).

Assessment of Co-Morbidities

Co-morbid conditions can complicate asthma management and lead to overtreatment or worsening of asthma symptoms. Appropriate assessment and investigation for co-morbid conditions is vital. The most common co-morbidities are chronic allergic rhinosinusitis and gastro-oesophageal reflux.

Gastro-oesophageal Reflux Disease

Gastro-oesophageal reflux disease (GORD) is associated with chronic respiratory disease (37). Approximately 20 to 80% of asthmatic children have GORD (38). The lack of large longitudinal randomized controlled studies and the inconsistency in GORD definition used, makes it difficult to accurately estimate the prevalence of GORD in asthma, determine a causal relationship and determine the impact of GORD on asthma symptoms (38). In a small randomized controlled trial of lansoprazole in children with poorly controlled asthma and asymptomatic gastro-oesophageal reflux, no effect on asthma control was observed (39). The current evidence suggests there may be an association between GORD and asthma, but there is no evidence for gastro-oesophageal reflux treatment improving asthma symptoms or outcomes in paediatrics.

Rhinosinusitis

Approximately 60-80% of children with asthma have allergic rhinitis (40). Evidence from cohort studies in children with asthma shows an association between allergic rhinitis and poor asthma control, and that intranasal corticosteroids may have a beneficial effect on asthma control (41). It is important to optimally treat nasal symptoms to ensure they do not compromise asthma symptom control. However, there is limited evidence to support this relationship and randomized controlled trials of intranasal corticosteroids would be the best way of determining the relationship between allergic rhinitis symptoms and asthma symptoms.

Obesity

Epidemiological studies have demonstrated an association between obesity in childhood and asthma (42-45). Further evidence from meta-analysis of prospective cohort studies has shown a two-fold increase in the incidence of asthma in childhood if obese (42). Conversely, children with asthma are at an increased risk of obesity because of daily inhaled corticosteroids, and reduced activity levels because of concerns about triggering asthma symptoms (45, 46). The current evidence suggests that the relationship between asthma and obesity is bi-directional, and that asthma can cause obesity, but can also be triggered by obesity. The proposed underlying mechanisms for obesity associated asthma are complex and include altered systemic inflammation and metabolic dysregulation (47). In a paediatric asthma cohort study, a non-atopic Type 1 (Th1) helper driven endotype, was observed in obese asthmatic children (48). Obesity in asthmatic children is associated with worse asthma control, lung function, quality of life, increased risk of asthma exacerbations and reduced response to inhaled corticosteroids (49-52). Though obesity can worsen reflux symptoms, it is important to not overtreat, and consider that gastro-oesophageal reflux is more prevalent in obesity and may result in increased perceived asthma symptoms (53). Similarly, physical deconditioning in obesity due to lack of exercise, may also result in mislabeling of symptoms as asthma (54). A multi-disciplinary team input for children with severe asthma is important to reliably assess asthma symptoms, prevent obesity by encouraging physical activity and support children that are obese to lose weight.

Dysfunctional Breathing

Dysfunctional breathing is defined as recurrent or chronic changes in breathing pattern, which results in respiratory and non-respiratory symptoms, such as chest or throat tightness, shortness of breath, wheeze and anxiety (55). It is a blanket term that encompasses vocal cord dysfunction, breathing pattern disorder and hyperventilation syndrome (56). The Nijmegen Questionnaire (NQ) is a validated screening tool for dysfunctional breathing in adults, and is also used for screening in children, but has not been validated (57, 58). The prevalance of dysfunctional breathing was 5% in a cross-sectional survey of 203 hospital outpatient children with mild to moderate asthma, this was associated with worse asthma symptom control (59). An assessment by a specialist physiotherapist is useful to identify and treat breathing pattern disorders. Breathing exercises are recommended for adults, though the same exercises are age-adapted and used in children, there is limited available evidence in children (53). However, a cohort study of 169 children with asthma and dysfunctional breathing observed that a breathing exercise intervention had a significant improvement in asthma symptoms and a reduction in dysfunctional breathing screening score (60).

Psychosocial Factors

Co-existent psychosocial factors are associated with poor asthma symptom control. Psychosocial factors were associated with a quarter of asthma deaths identified in the National Review of Asthma Deaths (7). An estimated 25% of children with asthma have anxiety and or depression, these children have a higher rate of emergency department attendances for asthma symptoms (61). The healthcare beliefs of the child and their family, as well as symptom perception all influence adherence to prescribed treatment and engagement with healthcare intervention. Questionnaires can be used to provide a baseline understanding of impact of asthma on the child and their family. This includes the Asthma Control Test (ACT), Childhood Asthma Control Test and Paediatric Asthma Quality of Life Questionnaire (PAQLQ) for children aged 12 years and older (12, 13, 62). Ultimately, input from a paediatric psychologist is invaluable in identifying psychosocial concerns and working together with the family and the rest of the team to support the family in the form of tailored support, involvement of social services and schools if necessary and individual counselling (35).

After the comprehensive multidisciplinary assessment children with modifiable factors are classified as DA. Those with persistent symptoms despite good treatment adherence and absence of modifiable factors are classified as STRA. The latter group require further investigation. It is important to remember that even children categorized as DA, may have persistent symptoms after modifiable factors have been addressed and if so, should be managed as STRA.

Testing of Children with Severe Therapy Resistant Asthma

Blood Tests

If not previously done earlier in the assessment the following blood tests should be undertaken: serum Total IgE, blood eosinophil count, Vitamin D level and specific IgE antibody measurements to common aeroallergens (cat, dog, mixed grass, mixed tree, *Penicillium notatum, Alternaria alternata, Aspergillus fumigatus*), food allergens (peanut, egg, milk). Total serum IgE and eosinophil count are particularly important for guiding choice of biologic.

Sputum Induction

Sputum induction enables a safe, non-invasive assessment of airway cellularity and airway inflammatory phenotype. Sputum induction is a GINA recommended assessment in adults and adolescents with severe asthma (4). Sputum eosinophil guided management in adults with a confirmed asthma diagnosis has been shown to be beneficial.

A Cochrane systematic review of sputum eosinophil guided asthma therapy included 5 randomised controlled trials in adults and showed a significant reduction in frequency of asthma exacerbations in adults OR 0.57 (95% CI 0.38 to 0.86). The review included one randomized controlled trial in 54 children that did demonstrate a reduction in exacerbations but did not reach statistical significance 0.76 (95% CI 0.54 to 1.04) P=0.09. Currently, there is insufficient evidence for sputum eosinophil guided management in children. However, sputum is an important tool for assessing inflammatory phenotype; this will be increasingly important when choosing immune directed biologic therapy.

Fibreoptic Bronchoscopy

Bronchoscopy is an invasive procedure that enables assessment of inflammation and airway remodeling. It also enables direct assessment of airway structure, sampling of lower airway infection, inflammatory cells using lavage and airway histology assessment by biopsy. The results obtained can be used to immunophenotype the airways.

Assessment of Response to Systemic Corticosteroids and Additional Add on Treatments

Approximately 20% of children with severe asthma have true STRA, these children require further assessment to determine pathological phenotype and determine if systemic corticosteroid responsive (32). This can be assessed by giving a single dose of intramuscular triamcinolone and measuring change in asthma symptoms, spirometry (FEV_1, FEV_1/FVC Ratio), BDR, FeNO, sputum and bronchoalveolar lavage eosinophils before and 1 month after treatment (63). The pattern of response to treatment with systemic corticosteroid may help to decide the optimal add-on therapy for the individual child. For example, a significant improvement in exhaled nitric oxide after triamcinolone has been shown to be a predictor of positive response to omalizumab (63).

Long-Acting Muscarinic Antagonists for STRA

Tiotropium bromide is a long-acting muscarinic antagonist which causes bronchodilation by non-specific blocking of the muscarinic acetylcholine receptor, therefore inhibiting smooth muscle contraction as well as mucus secretion (64). A Phase-III double blind randomized controlled trial of tiotropium bromide plus maintenance ICS treatment in children over 12 years old with severe asthma showed a numerical improvement in FEV_1, but this was not statistically significant (48). A similar phase-III trial of once-daily Respimat (tiotropium) 5 μg in children 6-11 years old with severe asthma on ICS plus one or more other treatments showed a statistically significant increase in FEV_1. The addition of tiotropium may limit loss of asthma control and improve FEV_1. Tiotropium use is therefore recommended as an additional treatment by ATS/ERS Severe Asthma Management Guidelines for children with severe asthma on Step 4/5 of GINA treatment (65, 66). However, it should be given as a trial of therapy, and if no improvement in symptoms or lung function is seen in the individual child, then it should be stopped.

Biologics

Severe asthma in children is a heterogeneous disease. The advent of the recent biologic era, and "omics" analyses (such as transcriptomics, proteomics, metabolomics, genomics) and increasing understanding of disease inflammatory pathways and mechanisms, has highlighted the need to develop biomarker guided severe asthma therapy. The majority of children have allergic eosinophilic asthma, mediated by a T2 helper (Th2) molecular pathway; including IgE production and inflammatory mediator cytokines IL-4, IL-5 and IL-13. Biomarkers that indicate activation of this pathway include FeNO, blood eosinophils and broncho-alveolar lavage or sputum eosinophilia. Biologics are an add on (immune targeted) treatment therapy for severe asthma that reduce asthma exacerbations. The current biologics used in children target the Th2 pathway mediating allergic asthma.

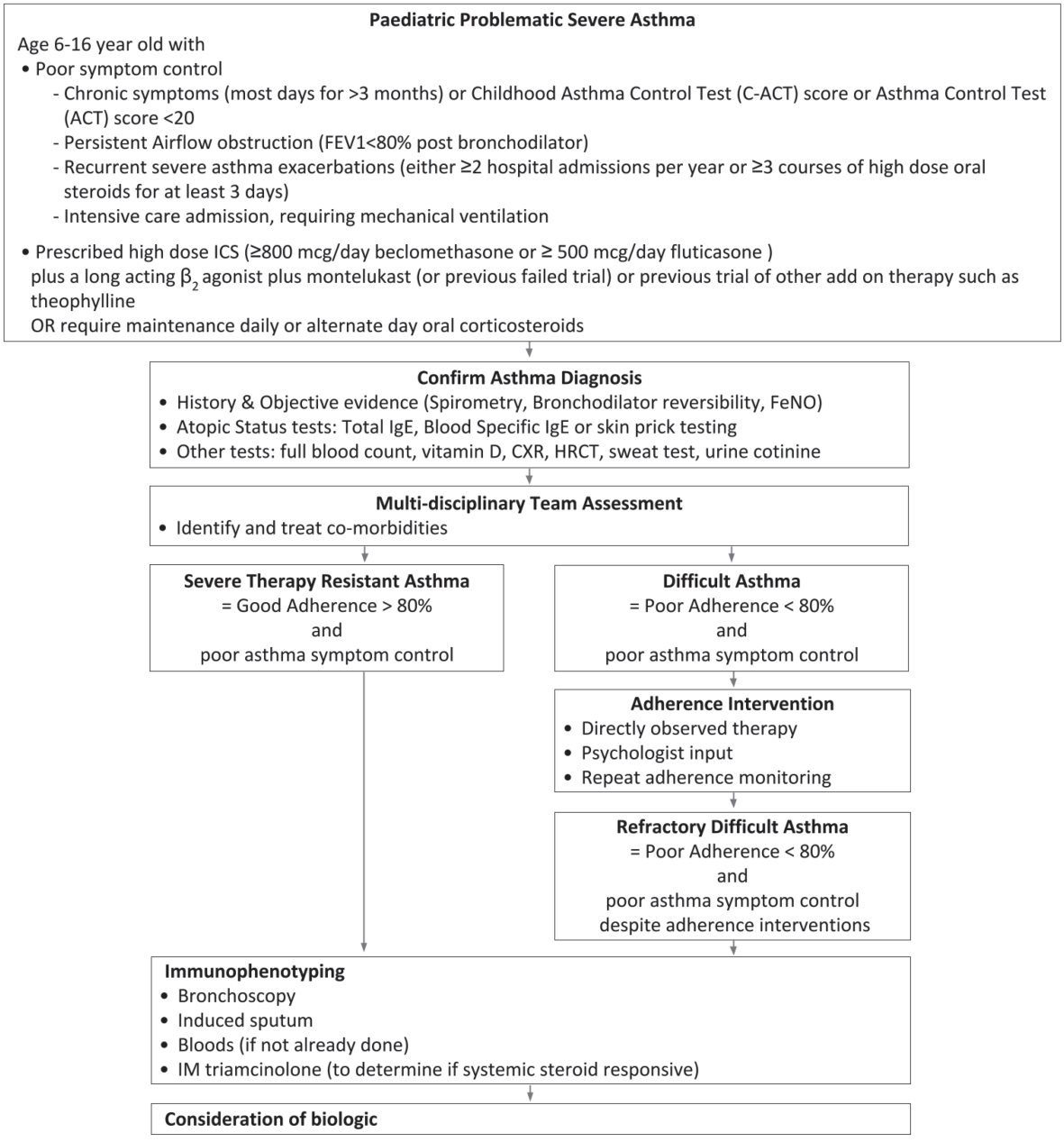

Figure 1. Paediatric Problematic Severe Asthma Assessment Pathway.

The 2019 GINA guidelines suggest considering biologics at step 5 (4). Though evidence is limited, and refractory DA group have not been a focus of clinical trials; children with refractory DA and unresponsive to strategies to improve treatment adherence, should also be considered for biologics, in order to prevent a fatal attack.

Omalizumab

Omalizumab (Xolair) is a subcutaneous injection licensed by European Medicines Agency (EMA) and US Federal Drug Administration (FDA) for use in children with allergic STRA (67). It is an anti-immunoglobulin E (IgE) humanised monoclonal antibody. It binds to circulating free IgE, which

consequently neutralises IgE and results in down-regulation of IgE receptors on mast cells, basophils and dendritic cells and results in reduced Th2 inflammatory cytokines (68). Three randomised controlled trials in children (N=1381) have compared omalizumab with placebo in children with PSA. The main effect of omalizumab is a reduction in exacerbations. The number of asthma exacerbations was lower for children on omalizumab (26.7% vs. 40.6%) (69). However, one-third of children do not have a clinical response to omalizumab and a further third of patients are not eligible for omalizumab under the current prescribing guidance because of the narrow serum IgE range recommended by the manufacturer. Of note, its efficacy has not been tested in children with true STRA, only in those with PSA.

Mepolizumab, Reslizumab and Benralizumab

Mepolizumab is an anti IL-5 monoclonal antibody subcutaenous injection. It prevents IL-5 mediated eosinophil activation and reduces eosinophil survival (70). It is licensed in Europe for use as an add on treatment in children with severe asthma aged 6-16 years old. Although adult data shows that mepolizumab is both safe and efficacious, there have been a limited number of children in clinical trials and no efficicacy trials in children aged 6-11 years old. However, a non-randomised open label trial of mepolizumab in children aged 6-11 has demonstrated similar pharmacodynamics to adults and that it is safe to use in this age group (71). Current prescribing guidelines include severe asthma with poor symptom control despite good adherence to treatment, blood eosinophil count ≥300/μl and 4 or more courses of oral steroids in last 12 months or daily oral steroids for last 6 months. The MENSA and DREAM trials showed a reduction in exacerbations and blood eosinophil count, but included only 34 children aged 12 to 17 years old (72).

Reslizumab, like mepolizumab is also an anti-IL-5 monoclonal antibody, but is less attractive for children as it has to be administered using the intravenous route. It is not yet licenced for use in children in Europe. Benralizumab is an IL-5Rα receptor antibody and also does not currently have a licence for children in Europe. There have not been any clinical efficacy trials in children for either drug. Anti-IL-5 or anti-IL-5Rα treatment is recommended for adults with blood eosinophils ≥300/μL in GINA guidelines if on step 4/5 of asthma management and persistent poor asthma control (73). The latest ATS/ERS severe asthma guidelines advise a lower eosinophil threshold of ≥150/μL for adults (49). The literature has focussed on blood eosinophils as a marker, rather than other markers of eosinophilic inflammation (such as sputum eosinophils) due to ease of obtaining a blood eosinophil count. Randomised clinical trials in children are needed to help determine IL-5 monoclonal antibody treatment thresholds, utility of biomarkers and efficacy.

Conclusion

Approximately 2-5% of all children with asthma have PSA. It is essential that children with PSA are referred to a specialist paediatric respiratory centre for confirmation of diagnosis, a step-wise multidisciplinary team assessment and ongoing management, including consideration of additional steroid sparing treatments, such as biologics. Firstly, the diagnosis of asthma must be confirmed, using history and objective tests. In tandem a multidisciplinary assessment is essential to assess for co-morbidities, identify modifiable environmental factors and assess treatment adherence. 50-80% of children have poor treatment adherence and a smaller number have true STRA. Biologics are a new and important additional treatment, however clinical trials to date in children have been limited in size, the only randomized controlled trials of biologics in children of all ages have been with omalizumab, but even then, none have included only children with STRA. However, only two-thirds of children with STRA are eligible for omalizumab because of the narrow serum IgE range in which it can be prescribed. This means additional biologics are important and needed for children. However, trials of efficacy are lacking and biomarkers of eosinophilic inflammation and markers to predict

response for different paediatric phenotypes are currently lacking but are urgently needed to guide future choice of biologic.

Conflict of Interest: The authors declare that they have no conflict of interest.

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