

Management of severe asthma in children

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Abstract

The majority of children with asthma are classified as mild/moderate and can be successfully managed with regular inhaled corticosteroids and bronchodilators. However, more than 5% of asthmatic children continue to have sub-optimal control despite apparently appropriate therapy. These children suffer significant morbidity including poor school attendance, adverse effects on family life and consume disproportionate health care resources. True therapy resistant asthma is rare in children and paediatricians should focus on ensuring the correct diagnosis, identifying and managing modifiable risk factors for difficult to control asthma before using the label severe asthma. Management of severe asthma requires a multidisciplinary approach. Symptomatic children on Step 4 (less than 5 years) or Step 5 (more than 5 years) of British Thoracic Society/SIGN Asthma Guideline or in children with diagnostic uncertainty should be referred to the local tertiary paediatric respiratory service.

Keywords adherence; allergy; asthma; children; difficult; severe

Introduction

Asthma is a chronic inflammatory disease characterized by airway hyper-responsiveness and variable airflow obstruction manifesting as recurrent episodes of wheeze, breathlessness, cough and chest tightness. Asthma remains a clinical diagnosis. One in 11 children in UK has a diagnosis of asthma with the vast majority controlled by low doses of medication including inhaled bronchodilators and corticosteroids. They are managed successfully in Primary or sometimes Secondary care. A small proportion of asthmatic children have poorly controlled disease despite treatment with high dose inhaled steroids. The World Health Organization (WHO) defines severe asthma as: "Uncontrolled asthma which can result in the risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity (including impaired lung function or reduced lung growth in children)".

The British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN) guidelines define difficult asthma as persistent and/or frequent symptoms despite

treatment with 400 mcg/day budesonide or equivalent of inhaled corticosteroids (ICS) in children less than 5 years or 800 mcg/day (500 mcg fluticasone) of ICS in children more than 5 years. Despite effective therapies and such evidence based guidelines many children and adults with asthma fail to achieve satisfactory control of their symptoms. The Environment and Child birth cohort study from Norway estimates 4.5% of children with asthma have severe disease. Although evidence for the management of children with severe asthma is sparse and, current practice is based on extrapolation of data from adult studies and research in children with mild to moderate asthma, there is consensus that severe asthma in children requires a multidisciplinary, stepwise approach involving considerable health care time and resource. This frequently involves the use of high doses of anti-asthma medications and of poly-pharmacy exposing these children to adverse drug effects. Paediatric asthma deaths in the UK peaked in the mid-1960s but children with poorly controlled asthma remain at risk of fatal exacerbations. In 2010 there were 16 asthma related deaths in children aged less than 14 years in UK and confidential enquires continue to highlight the increased risk amongst those classified as severe.

Severe asthma classification

Asthma severity classifications are utilized in the stepwise approach advocated in the various national and international guidelines. The goal of such guidelines is no or minimal symptoms, without exacerbations and the opportunity to lead a normal lifestyle with no impairment to activity accompanied by normal or near normal lung function in the face of little or no use of rescue bronchodilator therapy. However, the evidence base is insecure and differentiates poorly between the various levels of severity. There is a poor correlation between symptoms and measures of lung function and asthma severity. Such classifications are open to the criticism that they reflect the concept of asthma control rather than measure the severity of the underlying disease.

Approach to the patient with severe asthma

Table 1 highlights three groupings commonly utilized in evaluating children referred with 'severe asthma'. Terms including 'chaotic asthma', 'refractory asthma' 'brittle asthma' are best avoided.

Is the diagnosis right?

Asthma is a clinical diagnosis. It is characterized by episodic respiratory symptoms predominantly wheeze which can be associated with cough, breathlessness and chest tightness in absence of an alternative explanation. Children are often atopic and symptoms improve with adequate treatment. The BTS/SIGN guideline recommends diagnosis of asthma on the basis of high, intermediate and low probability. A thorough history and examination is key to the diagnosis of asthma. Spirometry and bronchodilator reversibility should be performed in children older than 6 years. Spirometry demonstrates small-medium airway obstruction in asthma. However, it may be normal even in patients with severe asthma. A detailed Peak flow diary is useful in some children to provide longitudinal trends.

Careful evaluation for alternate diagnosis should be carried out in children with 'low probability' of asthma or in children with poor response to standard asthma management (Table 2).

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1. Not asthma	<i>The diagnosis is wrong</i>
2. Difficult to treat asthma	<i>Mild asthma exacerbated by one or more co-morbidities (asthma plus) and those with reversible factors such as poor adherence poor inhaler technique or excessive allergen exposure</i>
3. Severe therapy resistant asthma	<i>Continued symptoms despite trial of various medications and addressing reversible factors</i>

Table 1

The term 'wheeze' is often used by parents to describe other respiratory sounds including stridor and rattly breathing. Alternative diagnosis should be sought particularly in non-atopic children with a diagnosis of poorly controlled asthma and in young patients. In a study of 102 children investigated for problematic severe asthma, 10 out of 14 non-atopic children had alternative diagnosis.

Isolated cough is not a feature of paediatric asthma (cough variant asthma) and asthma medication should not be prescribed in these children. A prospective review of 81 children with chronic cough showed none of these children had asthma as their sole final diagnosis. Studies have also shown that in children with isolated cough, airway inflammation is not consistent with asthma.

CT chest is a useful biomarker in adult severe asthma but evidence of its value in paediatric severe asthma is poor and should be arranged only if a diagnosis other than asthma is suspected.

Difficult to treat asthma

Why is there poor symptom control?

Children with asthma of varying severity accompanied by other co-morbid conditions (asthma plus) such as obesity, chronic rhino-sinusitis, gastroesophageal reflux, psychological factors or potentially reversible factors including poor adherence, inhaler technique or continued exposure to allergens are included under the umbrella term "difficult to treat asthma". Children should not have escalation of asthma medication until associated conditions have been thoroughly addressed.

Is there a co-morbid condition? – Asthma plus

Asthmatic children often have conditions which escalate the severity of their asthma termed 'asthma plus'.

Is the child receiving/taking their medication?

Poor adherence to daily medication is the commonest cause for poor symptom control. Children are surprisingly frequently left to administer their own medication without adequate supervision. Inability to see immediate effect of daily medications is thought to be the major contributing factor for poor adherence. Adherence to treatment should be checked at every possible opportunity and difficulties encountered by children or carers in remembering and administering medications should be addressed with repeated education and practical tips and incorporated into a clear Asthma Management Plan. Prescription uptake should be assessed by contacting the General Practitioner and a home visit by the asthma or respiratory nurse is of immense value. The accessibility, use by date, dose and type of medications can all be assessed during such visits. Home visit by

Alternative diagnosis

Symptom/sign	Possible diagnosis	Investigation
Wet cough	Cystic fibrosis	Sweat test
	Immunodeficiency	Immunoglobulins, vaccine response antibodies, T cell subsets
	Primary ciliary dyskinesia Bronchiectasis	Nasal ciliary biopsy, nasal nitric oxide CT chest
Stridor	Tracheo-bronchomalacia	CT chest with contrast, bronchoscopy
	Vascular rings, mediastinal mass, foreign body	
Wheeze	Foreign body, aspiration	Bronchoscopy, barium studies
Breathlessness	Dysfunctional breathing	Psychology assessment
	Pulmonary hypertension	Cardiology assessment
Dry cough	Post viral, infection	X-ray chest
	Psychogenic	
Symptoms from infancy	Cystic fibrosis, PCD Chronic lung disease	Appropriate investigations
Developmental delay	Recurrent aspiration GORD	Barium studies, pH study

Table 2

asthma/respiratory nurse should be considered in all poorly controlled patients. Education represents a significant component in children's lives and regular interaction with the school nurse is useful. Use of social media sites, email etc. to advocate adherence should be explored. The patient and parents should be involved at every stage and medications/delivery systems should be 'personalized' as far as possible to improve concordance to treatment. Chan et al. reported improved compliance, less health utilization and better symptom control in 60 children managed by Web based case management and education compared to 60 children whose asthma was managed by standard outpatient based education and management.

Psychological and behavioural factors

Psychological dysfunction is associated with fatal and near fatal asthma and more than half of the children referred for evaluation of poorly controlled asthma have evidence of psychological distress. Psychological factors such as anxiety and depression are common in severe asthmatics. The extent to which persistent symptoms of asthma result in psychological morbidity or pre-existing psychological factors contribute to severity of asthma is not clear. Airway eosinophilic response to allergens is amplified by stress. Psychological factors influence asthma by neuro-

immunological mechanisms, induction of steroid resistance and indirectly by poor adherence to medications. In children issues such as bullying and safeguarding should be explored and referral to the local psychology services should be considered to address psycho-social issues and improve adherence before escalation of treatment. Local asthma and school nurses may help to identify and facilitate discussion with patients and carers regarding psychological issues. Although evidence is lacking regarding its usefulness and cost effectiveness a small observational study in children has shown improved treatment adherence in a joint asthma clinic with a child psychiatrist.

Dysfunctional breathing

Dysfunctional breathing including vocal cord dysfunction (VCD) and hyperventilation may co-exist with asthma or 'mimic' asthma and may be difficult to differentiate from exercise induced asthma. VCD is common in adolescent females, in high achievers, environments leading to excessive social pressures and competitive athletes. The symptoms usually appear suddenly with 'breathlessness' and 'tightness in the throat' rather than 'chest tightness'. Symptoms are not present at night. Diagnosis is by direct laryngoscopy by ENT surgeon (performed during symptomatic phase) showing adduction of vocal cords during inspiration. Spirometry performed during symptoms may confirm extra-thoracic obstruction particularly with flattening of the inspiratory loop. It is important to recognize this condition and offer breathing exercise by trained physiotherapists or psychologist. A study by Bracken et al. showed 15% of a paediatric severe asthma cohort showed evidence of VCD.

Is the inhaler device/technique right?

Bracken et al. showed that 15% of poorly controlled asthmatic children were using an inappropriate delivery device. It is not uncommon to find a 6 year old using a 'spacer' device with mask instead of mouth piece. Even in patients who have progressed to this level of severity it is good practice to check inhaler devices/drugs and review inhaler technique at every clinic visit. Prescribing age appropriate inhaler devices and offering patients a choice of appropriate inhaler devices may improve compliance.

Allergen avoidance/exposure to tobacco smoke

Continued exposure to allergen results in sensitized patients having poor symptom control and steroid resistance mediated by IL2 and IL4. Studies involving home visits by asthma nurses have shown half of poorly controlled asthmatic children live with pets to which they are sensitized and in majority no pet avoidance measures were taken. Apart from pets, continued exposure to house dust mite in sensitized children, exposure to allergens at school, damp and moulds all contribute to poor asthma control. House dust mite avoidance measures including washing bed linen and toys at high temperatures, use of high particulate filter vacuum cleaner, protective mattress covers, non-carpeted flooring, minimal soft furnishings and adequate ventilation may improve asthma control. Admitting children to hospital where they are taken away from exposure to household allergens may demonstrate improvement in symptoms. This will also provide an opportunity to review inhaler technique and administration of medications along with supervision of treatment.

Exposure to environmental tobacco smoke results in increased asthma exacerbations and bronchial hyper-responsiveness. Studies in adults have shown steroid resistance in active smokers. Bracken et al. reported in their cohort that 25% of severe asthmatic children had exposure to tobacco smoke. Mackay et al. have reported reduction in hospital admissions due to childhood asthma after introduction of legislation banning smoking in public places in Scotland. Passive and active smoking, smoking 'inside' or 'outside' the house possibly has same effect on children and smoking cessation advice and support for household members should be provided at every opportunity.

Role of Rhino-sinusitis and Gastroesophageal reflux

Adult studies have shown better asthma control with concomitant treatment of rhino-sinusitis. Although similar studies are not available in the paediatric population, the cellular mechanisms in both the processes involve eosinophils. The 'united airway disease hypothesis' proposes upper and lower airway diseases are both manifestation of a single inflammatory process.

The role of gastroesophageal reflux in severe asthma is complex. Bronchial hyper-responsiveness in gastro-oesophageal reflux may be mediated by neural activity in lower oesophagus. Chronic respiratory symptoms and medications such as theophyllines can exacerbate reflux. The outcome of treatment with anti-reflux medication in asthmatic children is disappointing. If there is a clear history of gastroesophageal reflux, a trial of medications for 8–12 weeks may be considered.

Obesity

Obesity has a complex relationship with asthma. Breathlessness, immobility and obstructive sleep apnoea may all result in difficulty in assessing the severity of asthma. Oral corticosteroids may result in weight gain and obese children may have steroid resistance. Prospective studies in obese children and adults have shown reduction in forced vital capacity and increased hospitalization rates following acute asthma exacerbations but not worse asthma severity, quality of life or increased health care utilization. Local services providing weight reduction programs should be explored as a health promotion measure before escalating treatment.

Other considerations

Anaphylaxis can masquerade as severe life threatening asthma. Unrecognized allergies particularly food allergy should be excluded and consideration of the need for emergency epinephrine considered particularly after life-threatening events. Salicylate sensitivity and endocrine factors may rarely be of importance. In the majority of patients improved asthma control can be achieved through addressing the above issues (Figure 1).

On-going care

Management of children with severe asthma requires a multi-disciplinary and holistic approach. Asthma nurses play an important role in management. Once the clinician is happy with the diagnosis of asthma and has addressed issues which may contribute to poor asthma control the aim of treatment is to control symptoms allowing the child to lead a normal active life and prevent asthma exacerbations. Improving the level of asthma control is likely to require several clinic visits to enable

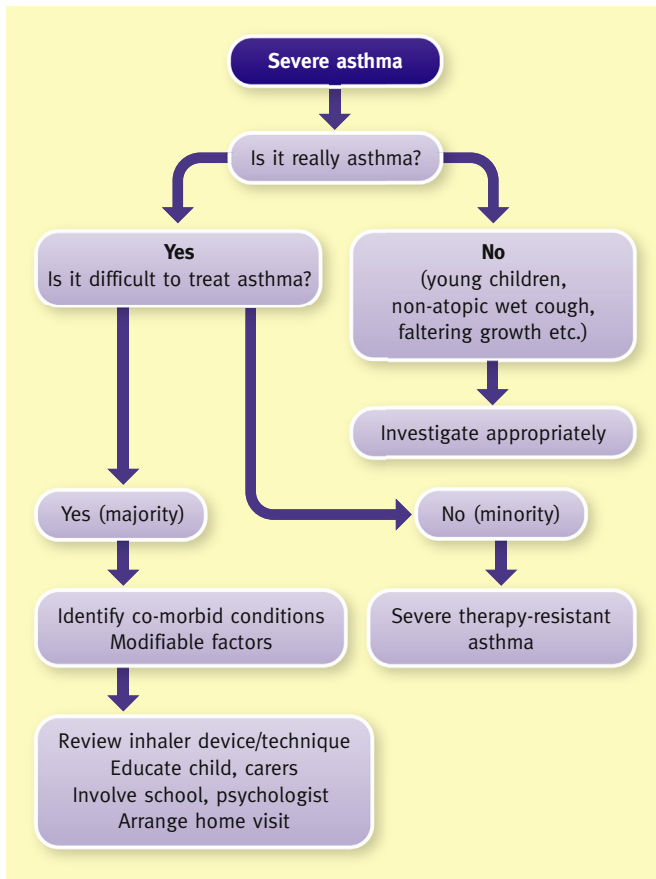


Figure 1 Assessment of children with severe asthma

a comprehensive work-up, eliminate aggravating factors and assess therapeutic responses. During this time written self-management plans, structured symptom based questionnaires and repeated assessments of Quality of Life can aid management and assist patient orientated goals to be identified and achieved.

Therapy resistant asthma

Children with suspected therapy resistant asthma by definition includes patients whose asthma is poorly controlled despite appropriate efforts to address co-morbidities and modifiable factors. They are usually investigated and managed in conjunction with tertiary respiratory centres. These patients may require further investigations including more complex lung function testing, measurement of exhaled nitric oxide (FeNO), bronchodilator reversibility, chest CT, immunology, allergy tests and flexible bronchoscopy. Flexible bronchoscopy enables exclusion of structural airway abnormalities such as tracheo-bronchomalacia and vascular rings. Bronchoalveolar lavage (BAL) cellularity may help in differentiating eosinophilic and neutrophilic asthma phenotypes. 'Neutrophilic asthma' although seen in adults, is uncommon in paediatric population and the diagnosis of asthma should be reconsidered in cases where BAL shows predominant neutrophils. Management is then 'personalized' after investigation and multidisciplinary team input.

The key question at this point is whether the child's asthma is steroid responsive. Should there be evidence of steroid resistance then steroid treatments can be reduced and alternative

therapeutic approaches explored. Clinical outcome measures after a 2-week trial of oral corticosteroid along with lung function and measures of inflammation are conventional approaches to this question. The most common phenotype seen at this point is of substantial improvement with such a trial with or without ongoing oral corticosteroids.

Treatment options in therapy resistant asthma

Pharmacotherapy in this group is based on experience in small numbers of patients with the use of immuno-modulatory drugs often with varied safety profile. Treatment options may be further dictated by the level of steroid responsiveness identified. Therapy should be aimed at improving symptoms, school attendance with minimal side effects with the lowest possible dose of medication. Therapy in this group of patients often does not improve lung function.

Use of high dose inhaled steroids (up to 2000 µg/day of beclomethasone equivalent), or using Symbicort (SMART regimen). Studies in adults have shown reduction in exacerbation rate with Symbicort (budesonide/formoterol) as a single device maintenance and reliever therapy (SMART). In children older than 10 years with good technique with a Turbohaler a trial of such a regime may be appropriate. Low or higher dose daily oral prednisolone therapy may help achieve control. Intramuscular Triamcinolone ensures adherence to therapy and Panicker et al. demonstrated short term benefits (reduced exacerbation rate, hospitalization) in children. Growth and particularly adrenal function should be carefully monitored in children on high dose inhaled or long term oral corticosteroid therapy particularly during the 'weaning' phase. Additional monitoring of blood pressure, bone health and metabolic status should be undertaken.

Steroid sparing drugs: Omalizumab is an anti-IgE monoclonal antibody recommended as add on therapy by National Institute of Health and Clinical Excellence (NICE) for children 6 years or older with persistent allergic asthma. It is administered as subcutaneous injection every 2–4 weeks for an initial trial period of 16 weeks. A large randomized double blind, placebo control study involving 419 adolescents and young adults showed 25% reduction in days with asthma symptoms. Recently Brodie et al. have shown corticosteroid sparing effect of Omalizumab in a cohort of 34 children. Median daily dose of prednisolone reduced from 20 mg to 5 mg, asthma control and quality of life improved during 16 week trial period with Omalizumab. Apart high cost, Omalizumab should be administered in hospital setting (risk of anaphylaxis). Children may miss school for hospital visits. It is not ideal in patients with high levels of needle anxiety.

Azithromycin has anti-inflammatory property and is beneficial in adult asthmatics with neutrophilic airway inflammation. Severe asthma in children is predominantly eosinophilic and other diagnosis should be considered in presence of neutrophilic airway inflammation in children. There is no evidence for prescribing Azithromycin routinely in children with moderate-severe asthma.

Unlicensed treatments: subcutaneous Terbutaline as a continuous infusion is useful in selective cases where there is chronic variation in peak flow measurement and presence of significant bronchodilator reversibility.

Immuno-modulatory drugs such as Azathioprine, Ciclosporine and Methotrexate may be useful in selected patients with severe side effects of steroids but the evidence is limited to small case series. These drugs may control the symptoms and allow reduction in dose of systemic steroids but not improve lung function. Children on immuno-modulatory drugs require close monitoring for drug toxicity.

Novel drugs/future therapies

A number of novel therapies in asthma are in development including cytokine specific monoclonal antibody therapies such as anti-interleukin 5 and anti-TNF but are likely to be very expensive and are best considered experimental at this time. Other therapies include laminar air flow systems such as Protexo directed at reducing nocturnal allergen exposure and bronchial thermoplasty currently being explored in adult patients.

Conclusion

Management of children with severe asthma requires a multi-disciplinary approach. However, the importance of getting the basics right cannot be over-emphasized and will remain the foundation of management for the foreseeable future. The carers and child should be involved in every stage of management. Not all children with “difficult to control” asthma have “severe” asthma. Thorough assessment and addressing issues around adherence, inhaler technique, psychology, allergen exposure coupled with improved management with conventional medications results in improvement in the majority of children. Modifiable risk factors should be identified and addressed before escalation of treatment. Management should be personalized to each child and referral to tertiary paediatric service should be considered not only in children with severe asthma but also where the diagnosis is in doubt. ♦

FURTHER READING

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Practice points

- True therapy resistant asthma is rare in children
- Diagnosis of severe asthma should be reviewed in children with poor symptom control, atypical features and non-atopic children
- Modifiable factors should be addressed before escalation of therapy
- Asthmatic children with poor symptom control despite therapy with high dose inhaled steroids should be referred to tertiary paediatric respiratory service