Asthma represents one of the most common chronic conditions affecting children. Effective therapies exist, but some children continue to have treatment-resistant asthma. Management of this is a significant challenge and evidence for the treatment of asthma at the severe end of the spectrum is lacking. However, a structured approach to assessment and management can be used to improve patient outcomes. For the minority in whom symptoms persist, further investigations, alternative anti-inflammatory drugs or more novel therapies, such as anti-IgE, may need to be considered and these are best carried out by a specialist pediatric pulmonologist. Further developments in the use of noninvasive biomarkers to help individualize treatment will be helpful in the future treatment of severe asthma.

Asthma is one of the most common chronic conditions affecting childhood. The Global Initiative for Asthma (GINA) [1], a project conducted in collaboration with the National Heart, Lung and Blood Institute and The WHO, estimated that approximately 300 million people in the world currently have asthma and that this prevalence is increasing. Asthma continues to cause significant morbidity and mortality and consumes a substantial amount of resources; medical, financial and social.

Effective treatments exist for asthma and in the majority of cases symptoms are controlled. However, a subgroup of patients have difficult asthma, which means they do not respond adequately to conventional treatment, and this treatment-resistant asthma poses a challenge to those managing it.

The exact incidence of treatment-resistant asthma is unknown and this is largely due to the difficulties in making a diagnosis of asthma and the variations in diagnostic criteria. It is however estimated that around 5–10% of asthmatic patients have treatment-resistant asthma [2].

This article will focus on the management of this group of patients in the school-age population.

**Definitions of treatment-resistant asthma**

Various terms are used to describe treatment-resistant asthma: severe persistent, severe refractory, difficult, corticosteroid resistant or corticosteroid dependent and life threatening.

Indeed several task forces have been established to address the various issues pertaining to this group of patients, including formulating a consensus on how best to define, evaluate and optimize management.

The National Asthma Education and Prevention Program (NAEPP) [3] and GINA [1] guidelines assess disease severity on the basis of asthma symptoms, short-acting bronchodilator requirements, asthma exacerbations and baseline lung function measurements before treatment. However, there are difficulties with using these parameters to assess severity as patients’ subjective reporting of asthma symptoms (e.g., frequency, severity and medication usage) may correlate poorly with objective data such as pulmonary function measurements. In one prospective study of children aged 5–18 years with asthma, forced expiratory volume in 1 s (FEV₁) was generally normal even in severe persistent asthma whilst a reduction in the percentage of the forced vital capacity (FVC) exhaled in the first 1 s of the forced expiration (FEV₁/FVC ratio) was observed in increasing asthma severity [4].

The European Respiratory Society task force employed similar measures to define difficult/therapy-resistant asthma, and in addition to quantification of symptoms the definition includes the amount of inhaled anti-inflammatory treatment required to achieve control of asthma [2]. They define difficult/therapy-resistant asthma as that which is poorly controlled with ongoing chronic symptoms, episodic exacerbations and a continued requirement for short-acting β₂-agonists despite a daily dose of at least budesonide 800 µg or equivalent for 6 months or longer [2]. There is also an emphasis on the importance of a period of observation of at least 6–12 months in order to allow for a more accurate diagnosis, assessment of disease severity and asthma control on therapy.

In 2000, the American Thoracic Society (ATS) developed a consensus definition for severe asthma [5], which takes into account medication...
requirements, clinical symptoms, frequency of exacerbations and the degree of airflow limitation, and in addition incorporates a combination of major and minor criteria to help identify patients with severe, refractory asthma. Unlike traditional guideline-based assessment of disease severity, this classification strategy includes other elements of asthma control such as healthcare utilization, which may more accurately identify patients with severe asthma. It assumes exclusion of other conditions, and that existing exacerbating factors have been addressed and that there are no confounding issues from poor adherence. The group agreed two major and seven minor criteria (Box 1), with refractory asthma being defined as one or both major criteria and at least two minor criteria.

Recently, a European consensus of pediatric pulmonologists highlighted the fact that the nomenclature for this group still remains confusing, thus making it difficult to compare studies [6]. We agree that there is an urgent need for a common international approach to nomenclature, and classification, to facilitate collaborative trials and develop appropriate investigation and treatment algorithms.

**Incidence**

A significant proportion of the population worldwide currently have asthma [1]. Prevalence is highest in developed countries (UK >15%, USA 10.9% and Canada 14.1%) [7]. The UK has one of the highest asthma prevalence rates where it is estimated that 3.4 million people have asthma requiring treatment and this includes approximately one in every seven children aged 2–15 years (1.5 million) [7]. Despite the very high incidence of asthma, the number of individuals with treatment-resistant asthma is relatively small, estimated to be approximately 5–10% of adult asthmatics. Data on children are less precise. If we use a definition of high-dose inhaled corticosteroids (ICS; >800 µg budesonide/day) and the concurrent use of add-on therapy (long-acting β2-agonist, leukotriene receptor antagonist) as a definition for treatment resistant asthma, approximately 3.5% of asthmatic children aged 5–11 years in the UK, would fulfill this criteria [8].

**Assessment of treatment-resistant asthma**

**Need for structured approach to assessment**

Patients with treatment-resistant asthma represent a heterogeneous group and many may have complicating coexisting conditions. There is therefore a need for a systematic and structured clinical approach to the assessment of treatment resistant asthma (Box 2). Various factors need to be considered, in particular if higher doses of steroids or additional therapies are thought to be required. In particular, it is of importance to establish whether a child has poor control because of nonadherence to medication or because of other contributing diagnoses or whether the child is truly resistant to standard asthma treatments [6].

Patients with difficult and treatment-resistant asthma should be referred to a pediatric pulmonologist for further evaluation and management (Box 3).

**Is asthma the correct diagnosis?**

It is essential to firstly determine that the diagnosis of asthma has been established. No single gold-standard test exists. A typical history will suggest episodic wheeze associated with breathlessness, chest tightness and cough. As asthma

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**Box 1. American Thoracic Society workshop consensus for the definition of treatment-resistant asthma**

**Major characteristics**

- In order to achieve control to a level of mild-to-moderate persistent asthma:
  - Treatment with continuous or near continuous (≥50% of year) oral corticosteroids
  - Requirement for treatment with high-dose ICS

**Minor characteristics**

- Requirement for daily treatment in addition to ICS (e.g., long-acting β-agonist, theophylline or leukotriene antagonist)
- Short-acting β-agonist use on a daily or near daily basis
- Persistent airway obstruction (FEV₁ <80% predicted; diurnal PEF variability >20%)
- One or more emergency visits for asthma per year
- Three or more oral steroid courses per year
- Prompt deterioration with ≤25% reduction in oral or ICS dose
- Previous near fatal asthma event

**Definition of treatment-resistant asthma requires one or both major criteria and two minor criteria.**

**FEV₁**: Forced expiratory volume in 1 s; **ICS**: Inhaled corticosteroids; **PEF**: Peak expiratory flow.
is an inflammatory disorder characterized by airway hyper-responsiveness and variable airflow limitation, which is often reversible, some measurements of airway physiology may help to confirm the diagnosis. These include peak expiratory flow measurements, spirometry with flow volume loops, bronchodilator reversibility tests and challenge testing. Measurements of inflammatory markers such as determining exhaled nitric oxide (eNO) levels in the clinic setting may provide additional support.

Confirm adherence
One of the most common reasons for poor response to asthma therapy is poor adherence to treatments. But adherence to inhaled therapy is very difficult to assess and the true scale of noncompliance is difficult to estimate. One pediatric study designed to assess this issue found compliance to be poor with a discrepancy between reported use of inhaled therapy and that recorded by an electronic monitoring device reflecting actual use [9]. Of 24 children aged 8–12 years monitored over a 13-week period, reported compliance with inhaled corticosteroid treatment was 94.5%; however, actual compliance recorded by the electronic device was only 58.4%. In addition, time corrected compliance (doses taken within the correct time window) was even lower at 32%. In total, 92% of patients exaggerated the use of their ICS. A total of eight children had an exacerbation during the 13-week study serious enough to warrant prescription of oral corticosteroids. Perhaps not surprisingly, the median raw compliance value with ICS, in this eight, was only 13.7% compared with 68.2% in the nonexacerbating group (p = 0.008).

In a study of 71 children attending a tertiary pediatric respiratory center with problematic asthma, 48% had medication issues on asthma nurse home visits; such as lack of medications available for inspection at home and out of date medications [10].

The reasons for poor compliance appear to be complex and multifactorial. These may include a poor general understanding of the underlying asthma as a disease process, or for parents, a fear of the side effects associated with the prolonged use of corticosteroids. The issue also becomes more complicated as children approach adolescence. Denial of being asthmatic, the dislike of being different and or the awkwardness of having to use inhalers around their friends may represent some of the issues surrounding poor compliance in this age group [11].

One of the main approaches to improving compliance to therapy is through a strong emphasis on asthma education; by providing information regarding the disease itself as well as its treatments and the methods of treatment delivery to optimize management [12]. Laboratory measurements of blood theophylline and prednisolone concentrations may assist in the assessment of compliance if these are prescribed. Enquiries regarding prescription collection (from primary and secondary care) and inhaler usage may also be helpful as markers of adherence. A period of elective hospital admission may be required to optimize management and to review whether supervised therapy results in better control, and also to investigate and manage exacerbating factors.

Evaluation of exacerbating factors
Asthma can be perceived to be difficult to control and treatment resistant if there is continued and chronic exposure to exacerbating factors that aggravate asthma symptoms. In this situation, a careful search for the presence of such factors that could be contributing to the lack of response to treatment should be undertaken. This may involve enlisting the help of the asthma nurse who can arrange home visits to review the home environment and this can prove invaluable [10]. Exacerbating factors can be those that are readily recognizable by patients and parents but some may not be immediately obvious and will require some time before these are identified and measures to address them can be carried out.

Box 2. Approach to treatment-resistant asthma.
- Confirm diagnosis of asthma
- Asthma education and inhaler technique
- Establish adherence and improve compliance to prescribed therapies
- Evaluate environmental triggers
- Optimize standard asthma therapy according to asthma guidelines
- Exclude alternative/concomitant diagnoses
- Individualize assessment of treatment-resistant asthma
- Optimize treatment and delivery of care
- Monitor and assess response to therapy and clinical stability of disease

Box 3. When to refer to a pediatric pulmonologist.
- Poor baseline control despite prescribed high-dose inhaled corticosteroid therapy
- Frequent rescue oral corticosteroid use/hospitalization
- Severe exacerbation requiring hospital high dependency or pediatric intensive care unit admission
- Need for alternate day or daily oral corticosteroids to achieve control of asthma
- Growth impairment
- Evidence of adrenal suppression
Common allergens within the household include house dust mite, pets (both those kept indoors and out), cockroaches and various moulds and aspergillus. Allergens can be difficult to eliminate from the environment and recommendations regarding allergen reduction should only be made to those in whom sensitization to an allergen has been demonstrated. House dust mite allergen in particular can be difficult to reduce significantly without extensive measures in the home (e.g., removing carpets, covering mattresses and regular washing). When children are placed in very low house dust mite allergen environments (e.g., spending prolonged periods in a sanatorium in Davos, Switzerland or in hospital) significant improvements can be seen both clinically in symptom reduction and by reductions in bronchial reactivity to histamine [13]. These effects are harder to achieve in the home situation. The endearing household pet who is every bit a part of the family can be difficult to remove, but serious consideration needs to be placed on this and if not at the very least to prevent pets from entering the patients bedroom, living areas and the replacement of a deceased pet. Exposure to environmental tobacco smoke also adversely affects the health of children with asthma and it has been associated with both reduced lung function and increased frequency of asthma exacerbations. Parental reports appear to be reliable when used to screen for exposure to environmental tobacco smoke in children with asthma and the smoking status of parents of these children should be established at consultation [14].

In terms of environmental interventions, one potential limitation with most studies are that they tend to focus on reducing exposure to single allergens rather than on improving the indoor environment as a whole. The Inner-City Asthma Study investigated the benefits of a multifaceted, targeted, home based, environmental intervention for inner-city children with asthma [15]. A total of 937 children with atopic asthma aged 5–11 years were enrolled from seven major US cities to a randomized, controlled trial of an environmental intervention that lasted 1 year. This involved an educational and remediation program targeting both environmental allergens as well as tobacco smoke. Interventions were based on established models of behavioral change and were tailored to each child’s sensitization depending on skin prick test positivity and environmental risk profile. The study reported a sustained reduction in both indoor allergen levels and reported asthma-associated morbidity in the intervention group. The effect of the observed reduction in symptoms from this intervention was felt to be comparable to that described in placebo controlled studies of inhaled corticosteroids.

Anxiety and depressive symptoms are also recognized exacerbating factors, which can adversely affect asthma control. One telephone survey from Seattle (WA, USA) utilized child health status asthma and anxiety depression questionnaires to further investigate this [16]. A total of 767 asthmatics aged 11–17 years were surveyed and the researchers found that the presence of an anxiety or depressive disorder in this group of patients was associated with an increase in reported asthma symptoms. Indeed, as the number of anxiety depressive symptoms increased, the mean number of asthma symptoms increased accordingly. Of the study participants, approximately 10% had an anxiety disorder, 3% had a depressive disorder and approximately 5% had both these conditions. A thorough search for any psychological factors, particularly in the older child or adolescent, will be important and should prompt referral to a pediatric psychologist for further assessment and management.

Is there an alternative or concomitant diagnosis? Alternative diagnoses in wheezy children unresponsive to therapy are well-recognized and revisiting the history and undertaking investigations as appropriate may unveil an alternative disorder mimicking asthma. Asthma is a very common disorder and therefore it is not unusual for someone with a rare disorder to also have asthma. Occasionally asthma symptoms are not controlled as a patient also has another diagnosis. The need for additional, more detailed investigations will depend on the history, signs and symptoms (Box 4). For example, fiber-optic bronchoscopy with bronchoalveolar lavage (BAL) allows a review of anatomy to exclude structural abnormalities, determination of bacterial colonization and/or infection by respiratory pathogens and investigation of the possibility of aspiration. High-resolution computed tomography (HRCT) of the chest may exclude other underlying pathologies such as bronchiectasis. If the history is suggestive, pH monitoring may be indicated to exclude gastroesophageal reflux.

One study of adult patients referred to a tertiary treatment center for difficult to treat asthma found that 12% did not have asthma [17]. In a study of
young children under 5 years of age with severe recurrent wheeze, around one third of children had abnormal bronchoscopies that identified structural abnormalities and just over half had abnormalities on pH study and lipid laden macrophages on BAL specimens in keeping with a diagnosis of gastroesophageal reflux disease (GERD) [18]. Another recent study of 102 children (mean age: 11 years) from a difficult asthma clinic, found that 51% had alternative or additional diagnoses, which was more common in the nonatopic than the atopic children [19]. Following assessment, eight children were thought to be not suffering from difficult asthma at all. Additional or alternative diagnoses included bronchiectasis, primary ciliary dyskinesia, Job's syndrome, vascular ring, severe sinusitis, severe gastro esophageal reflux, immune abnormalities and vocal cord dysfunction.

The concomitant presence of upper airway disease can complicate management. Vocal cord dysfunction, which is a condition characterized by paradoxical adduction of the vocal cords, can often either mimic or coexist with asthma. In the adult refractory asthma clinic setting, approximately 10% will have vocal cord dysfunction and not asthma and approximately 30% will have both vocal cord dysfunction and asthma [20]. In a pediatric clinic one would expect vocal cord dysfunction to be less common, but it is probably under recognized, particularly in the adolescent population. Diagnosis depends on maintaining a high index of suspicion and direct visualization of the vocal cords and demonstrating the abnormality when symptomatic. Close liaison with the ear, nose and throat specialist is important and most patients will benefit from ongoing input from both teams.

It is well established that gastroesophageal reflux can coexist with asthma, however, a causative relationship is still unclear. There are some adult studies that report benefits in treating gastroesophageal reflux [21] and others that do not [22]. A double blind, randomized controlled study in 770 moderate-to-severe stable adult asthmatics found that acid suppression with esomeprazole, 40 mg given twice-daily over a 16-week period, conferred benefits over placebo but only in those with both GERD and nocturnal respiratory symptoms. In this group it improved both morning and evening peak expiratory flow rate. However, patients without GERD or nocturnal respiratory symptoms were unlikely to benefit from esomeprazole therapy. The investigators report esomeprazole to be safe and well-tolerated in this asthma population. However, in another study of inadequately controlled asthmatics without symptoms of GERD, 40 mg esomeprazole twice daily for 24 weeks conferred no benefit over placebo [22]. Data to support acid suppressive therapy in the management of difficult asthma in the pediatric population is scant. A very small study of 38 asthmatic children with some symptoms of GERD and a reflux index of 5 or more on pH monitoring reported no improvement in asthma symptom score, quality of life score, improvement in lung function or reduction in use of bronchodilators following 20 mg esomeprazole daily for 12 weeks compared with placebo [23]. On a practical level, we would suggest a targeted trial of antireflux therapy to ascertain whether individual patients would benefit from this, particularly if they were clinically symptomatic.

**A phenotypic approach**

Once the diagnosis is established, concurrent diagnoses addressed and adherence to therapy ensured, one needs to attempt to answer what it is that has made this child’s asthma so difficult to treat. There has been increasing interest in a targeted and tailored approach that takes each individual’s asthmatic characteristics into account when considering the further management of patients with treatment-resistant asthma. Phenotyping asthma refers to the process of identifying an apparently associated cluster of clinical and or pathophysiologival features in patients with asthma. Several key physiologic components to asthma should be considered such as bronchial hyper-reactivity, persistent airflow limitation and airway inflammation [24].

Bronchial hyper-reactivity appears to arise from a variety of different pathways. Although it has traditionally been linked closely with airway inflammation, the two perhaps should not be

**Box 4. Alternative or concomitant diagnoses of asthma.**

- Bronchiectasis
- Bronchiolitis obliterans
- Cystic fibrosis
- Allergic rhinitis
- Extrinsic allergic alveolitis
- Primary ciliary dyskinesia
- Gastroesophageal reflux
- Vocal cord dysfunction
- Hyperventilation/panic disorder
- Developmental abnormalities of the airway
- Recurrent aspiration
- Immune dysfunction
- Inhaled foreign body
- Tracheobronchomalacia
- Hypersensitivity pneumonitis
- Reflux esophagitis
regarded as synonymous as the underlying pathogenetic mechanisms appear far more complex than this suggests.

Bronchoscopic studies have implicated eosinophils in the pathology of airway inflammation in asthma. However, eosinophilic airway inflammation may not be the sole determinant of asthma as it is increasingly recognized that other inflammatory cells may play a role giving rise to noneosinophilic forms of asthma. Furthermore, noninflammatory asthma phenotypes have also been described.

Persistent airflow limitation in asthma is another important consideration in the management of difficult asthma and may explain why certain phenotypes do not respond as well to conventional modalities of treatment. It is important to establish this, after all there is no point in escalating treatment if there is no further capacity for it to dilate the airway. Congenital causes of reduced airway caliber defects may arise as a result of prenatal exposure to maternal smoking or perhaps as a result of maternal atopy or hypertension while acquired causes may include postinfective obliterative bronchiolitis, gastroesophageal reflux and aspiration. In addition, other factors that alter lung mechanics and compliance may be important.

The above can be assessed in each child by the use of: symptom diaries (± home peak flow monitoring) to assess symptoms; spirometry both before and after a high-dose steroid course and $\beta_2$-agonists to assess air-flow limitation and bronchial hyper-responsiveness; eNO and sputum induction (and/or bronchoscopic lavage/airway biopsy) to assess airway inflammation, again before and after a high-dose steroid course.

Several distinct pediatric asthma phenotypes have been described and there is an argument for then directing further treatment according to the phenotype.

In clinical practice, some phenotypes appear to be concordant (there is agreement between symptoms and measure of inflammation) and some appear to be discordant (symptoms and inflammation markers being incongruous to

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**Box 5. Investigation of treatment-resistant asthma.**

**Assessment of severity/inflammation**
- Symptom score chart
- Morning and evening peak expiratory flow diary
- Need for $\beta_2$-agonist reliever therapy
- Spirometry
- Biomarkers of inflammation – exhaled nitric oxide, induced sputum analysis
- Quality of life assessment
- Bronchial responsiveness (to histamine/methacholine)

**Assessment of treatment responsiveness**
- Assessment of inhaler technique
- Assessment of compliance to therapy
- Bronchodilator responsiveness (reversibility to $\beta_2$-agonist)
- Corticosteroid responsiveness (response to prednisolone/triamcinolone)

**Other tests – indicated by history & examination**
- Chest radiograph
- High-resolution computed tomography of the lungs
- Full blood count (eosinophil count)
- Total serum IgE and IgE to specific allergens
- Skin prick test
- Serum IgG, IgA, IgM and IgG subclasses
- Fibreoptic bronchoscopy with bronchoalveolar lavage
- Bronchial biopsy
- 24-h esophageal pH monitoring
- Barium swallow
- Psychological assessment
- Sweat test and genetic assessment of CFTR mutations (if indicated)
- Examination of nasopharyngeal airways
- Computed tomography of sinuses
- Ciliary function

*CFTR: Cystic fibrosis transmembrane conductance regulator.*
each other) [25]. This may lend further support
to suggest that airway inflammation may not
be the only mediator in the histopathology of
asthma and it is likely that other inflammation
independent factors might contribute. In a study
of 40 children with difficult asthma, 28 children
completed successful sputum induction, how-
ever only nine of these had abnormal sputum
cytology despite being symptomatic; implying
the mechanism for their symptoms may be non-
inflammatory [26]. Despite the normal sputum
cellularity, however, most had elevated eNO.

Another case series reported their findings on
six pediatric patients referred with difficult to
control asthma who underwent bronchoscopy
with endobronchial biopsies to further charac-
terize their underlying disease process [27]. They
observed extensive airway remodeling (thick-
ened basement membrane, smooth muscle
hyperplasia, goblet cell and submucous gland
hyperplasia) but minimal histological evidence
of airway inflammation. However, patients had
significant lung-function lability but were still
able to achieve normal FEV₁ despite significant
subbasement membrane thickening.

Further evaluation of the various histopath-
ological processes underlying asthma will be
important but endobronchial biopsies to obtain
histological specimens requires an invasive proce-
dure and so opportunities for this will be limited.
The use of HRCT scanning has been evaluated as
a noninvasive marker of airway remodeling, but
so far, unlike in adults, no relationship between
bronchial wall thickening observed on HRCT
and reticular basement membrane thickening on
endobronchial biopsies has been established in
children with difficult asthma [28].

Management of
treatment-resistant asthma
Optimizing standard
asthma management

This is an important aspect of management and
conventional asthma management needs to be
optimized prior to escalation of therapies and
consideration of additional treatments. A retro-
spective survey found that optimizing therapy
in a structured environment in patients referred
with difficult asthma (aged >6 years) resulted in
an improvement in asthma symptom control in
51 out of 60 patients [29]. This was a result of the
implementation of close supervision, treatment
adherence and the avoidance of external triggers of
asthma in a rehabilitation center (poor treatment
adherence n = 32; parental smoking n = 22; aller-
gen exposure n = 10). Of the remaining patients,
symptom control remained poor in five patients
and an alternative diagnosis other than asthma
was made in four other patients.

Monitoring control

Regular follow-up and review to monitor pro-
gress and control is essential. This is important in
order to monitor both response to treatment and
to titrate asthma treatments, but also to consider
reducing therapy once control has been achieved.

Enquiries into asthma control by direct
questioning of asthma symptoms need to be
phrased carefully as nonspecific questions may
serve to underestimate symptoms. The use of a
series of well-validated questions can be useful,
for example questions from the asthma con-
trol test (Box 6) [30]. In addition, this provides a
score with which to monitor control.

However, it is well recognized that there are
many aspects of a child’s health that need to be
taken into account when assessing their entire
wellbeing. The physical health only represents one
aspect and the other areas, such as social, educa-
tion and emotional status, are equally important.
Quality of life scores represent a useful measure
to assess patient-related outcomes and perhaps
the most widely used is the Pediatric Asthma Quality
of Life Questionnaire (PAQLQ) [31]. This con-
stitutes a 23-item questionnaire (identified by chil-
dren as troublesome in their daily lives) and has
been shown to be sensitive in detecting changes in
health status either as a result of natural fluctua-
tions in asthma control or as a result of treatment.
It has also been shown to accurately distinguish

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**Box 6. Asthma Control Test.**

- How much of the time did your asthma keep you from getting as much done at school, work
  or home?
- How often do you have shortness of breath?
- How often do your asthma symptoms wake you up at night or earlier than usual?
- How often have you used your rescue inhaler or nebulizer medication?
- How would you rate your asthma control?

*These five questions refer to the preceding 4 weeks. Items are scored on a scale of 1 to 5. A total score of 25 indicates
perfect control. A score of 20–24 indicates that asthma may be well controlled, but further advice should be sought.
A score of less than 20 should prompt an asthma review.*
between these groups of patients with those whose asthma control remains stable with reproducible results of good internal consistency and test retest reliability. Direct measurements of health-related quality of life such as this are invaluable to assist in the assessment of the full impact of asthma on the lives of children with asthma. In addition it may also assist in the follow-up and assessment of the effectiveness of therapy.

**Drug delivery devices**

Inhaled drugs are the mainstay of asthma treatment. Delivery can be given either via nebulization or an age appropriate inhaler device. The pressurized metered dose inhaler and a valve holding chamber, with the addition of a face mask for the younger child, remains an excellent standard delivery device for children [32]. Other devices include the breath actuated metered dose inhaler and the dry powder inhalers, which represent more portable alternatives for the older child and with correct inhaler technique, there are no major differences between these devices in terms of drug delivery [33]. It is however, important that inhaler technique be assessed at every opportunity and a switch to a more appropriate device should be considered if required to achieve more efficient drug delivery. There is little doubt that the type of inhaler is just as important as the class of medication prescribed in the long-term management of asthma. The choice of inhaler device needs to be age appropriate, acceptable to the individual and the user technique reviewed regularly.

**Noninvasive markers of asthma control**

The development of accurate surrogate inflammatory biomarkers to assist in disease activity monitoring will be important, especially if these are sensitive enough to allow titration of treatments and can be incorporated into more targeted algorithms to assist in overall asthma management. Currently, international guidelines suggest adjusting inhaled corticosteroid maintenance therapy on the basis of symptoms, the need for β₂-agonist rescue medication and the results of lung function tests. There has recently been increased interest in the use of induced sputum eosinophil counts [34] and eNO [35] as noninvasive inflammatory markers to guide asthma management, particularly in adults.

Sputum eosinophils as a marker of airway inflammation has been investigated in both adult [32] and pediatric studies [36,37]. In children, a change in the number of eosinophils in sputum has been shown to be significantly associated with symptoms [36]. In a study of 40 children with stable asthma eligible for ICS reduction, treatment reduction was successful in all children who had no eosinophils in induced sputum before the attempted reduction [37]. Furthermore, the percentage of sputum eosinophils was a significant predictor of failed reduction of ICS. Currently the use of sputum induction is limited to tertiary practice and as a research tool, because of the expertise and time required particularly in processing the sputum.

There is increasing use of eNO measurements in clinical practice and this investigation appears to be safe, easy to perform and reproducible as a noninvasive marker of airway inflammation. It appears to be a good surrogate marker for eosinophilic airway inflammation and low levels may suggest alternative noneosinophilic pathologies [38]. Normal values in children (aged 4–17 years) range from 15 to 25 ppb and this appears to increase by 1 ppb per year of life. It is increasingly used in pediatric asthma clinics to complement conventional tests such as spirometry. At present, the use of eNO with repeated measurements at follow-up visits may be more useful than comparison with population-based normal ranges and further studies are required to further validate cutoff levels, diurnal variations of these values and to further describe influencing factors and repeatability. However, in children with asthma its use has proved helpful in predicting exacerbations during steroid dose reduction [35] and in predicting relapse after stopping ICS [39].

**Phenotypic directed management**

There has recently been an emerging interest in determining individualized treatment plans according to asthma phenotype (see earlier for assessment). Several different phenotypes have been described and the various treatment approaches are discussed later [24].

**Steroid-sensitive asthma**

This appears to be the most common phenotype of asthma. It describes the child who becomes asymptomatic with normal lung function and with no airway inflammation on airway biopsy and/or BAL whilst on high-dose systemic-steroid therapy. The minimum safe dose of maintenance steroids should be used and a steroid sparing agent considered if this proves difficult.

**Steroid-resistant, eosinophilic asthma**

This phenotype describes the child who continues to be symptomatic with biopsy and or BAL evidence of eosinophilic inflammation despite high-dose systemic-steroid therapy (i.e., depot intra-muscular triamcinolone). Complex pathways
appear to be involved and as yet are poorly understood. Alternative anti-inflammatory agents such as ciclosporin should be considered and steroids (initially oral and then inhaled) reduced to the minimum tolerated.

**Steroid-resistant, noneosinophilic inflammatory phenotype asthma**

This phenotype describes those patients who are symptomatic and poorly responsive to steroids and who on biopsy and/or BAL show evidence of neutrophil predominant inflammation. It is uncertain as to whether reducing these neutrophil numbers actually improves symptoms. Assuming that this is desirable, possible agents to trial include macrolide antibiotics (which block IL-8 production) or oral theophyllines (which enhance neutrophil apoptosis). Further research to determine the exact role of neutrophils in the pathogenesis of asthma and to ascertain whether neutrophilia reduction mechanisms contribute to control will be important before specific recommendations can be made in the targeted therapy of this particular asthma phenotype.

**Noninflammatory, persistent bronchial hyper-reactivity**

Patients with this phenotype remain symptomatic despite therapy and have marked bronchodilator reversibility but no evidence of residual airway inflammation on bronchoscopy, BAL and/or biopsy. This suggests that the underlying airway inflammation may be more easily treated than bronchial hyper-reactivity, but again the molecular basis of this remains unclear. It is doubtful that continually increasing doses of anti-inflammatory drugs will be beneficial in this situation. The use of subcutaneous infusions of terbutaline in these patients has been reported with some success.

**Alternative therapeutic approaches**

Inhaled corticosteroids and β₂-agonist bronchodilators continue to be the mainstay of asthma therapy. However, when maximal recommended doses of these treatments are reached and yet asthma control remains suboptimal, alternative strategies need to be considered (Box 7).

**Leukotriene modifiers**

Leukotrienes are recognized to be important in the pathogenesis of asthma and currently available leukotriene modifiers include the leukotriene receptor antagonists; montelukast, zafirlukast, pranlukast and also the 5-lipoxygenase inhibitor; zileuton, which exerts its effect by inhibiting leukotriene synthesis. Montelukast (Singulair®) is a leukotriene receptor blocker that is licensed for pediatric use across the pediatric age range. It can be particularly beneficial in those patients with asthma and concomitant allergic rhinitis and a trial of this as add on therapy to inhaled corticosteroid should be considered in those who continue to be symptomatic [40]. A 4–6-week trial of montelukast would be reasonable to assess its impact on asthma control and in the event of little or no perceived benefit after this trial period, montelukast should be discontinued.

**Theophylline**

Theophylline has previously been used in the treatment of asthma but it has its drawback with its dangerous side effects in overdose. However, in addition to producing bronchodilation, theophylline also has anti-inflammatory effects [41], which include inhibition of neutrophil activation and it therefore may have a role in the management of difficult asthma. It is worth considering a trial of theophylline particularly if a prevalence of neutrophilia is demonstrated in the presence of apparent steroid resistance. It has the benefits of allowing serum drug monitoring to facilitate titration to achieve therapeutic drug efficacy, and in addition, this may also be used as a surrogate marker of compliance. Levels should be taken 1–2 h postadministration in those taking standard preparations and 4–6 h postdose in those taking modified release preparations.

**Macrolides**

Macrolides are a class of antibiotics that appear to have antimicrobial activity as well as anti-inflammatory and immune modulating effects. Erythromycin, clarithromycin and azithromycin are examples of macrolides in clinical use. There are a number of studies investigating their role in both asthma and cystic fibrosis, where airway remodeling as a result of chronic inflammation appears to play an important role [42]. Certainly in adult studies, macrolides appear to be effective in reducing bronchial hyper-responsiveness in asthmatics with a more significant improvement

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**Box 7. Alternative therapeutic strategies.**

- Leukotriene modifiers
- Theophylline
- Macrolides
- Oral steroids
- Monoclonal anti-IgE antibody
- Steroid sparing agents
- Subcutaneous terbutaline infusion
in FEV₁ observed in those with evidence of atypical bacteria colonization or infection [43]. Less evidence is available for their use in children and one study showed no ICS sparing effect in children with moderate-to-severe asthma [44]. Nonetheless, macrolides may still have a possible role in the management of these children and a therapeutic trial of this can be considered in those with treatment-resistant asthma. As previously discussed, it may confer a particular benefit in those patients with a neutrophil predominant phenotype.

**Oral steroids**

A trial of maintenance daily or alternate day regime of oral corticosteroids, usually prednisolone, is often warranted in the child whose asthma is very difficult to control. For some patients, there will be substantial improvements in their asthma control over time and for this group of patients, it is important to ensure close monitoring and weaning of steroid dose to safer levels of treatment. The use of oral corticosteroids, particularly at higher doses however, can be associated with significant systemic adverse effects on growth, adrenal function, metabolic and bone profile and hence other approaches should be considered before concluding that long-term steroids are required. Often high-dose oral steroids are used for a limited time (2 weeks) in order to assess their effect and phenotype the asthma. In this situation, occasionally intramuscular triamcinolone is used as an alternative in order to ensure compliance with treatment [45].

**Recombinant IgG₁, monoclonal anti-IgE antibody**

Omalizumab is a hybridized, murine, monoclonal antibody directed at the Fc portion of human IgE. It is recommended for use in severe persistent IgE mediated asthma. It may be considered in those children with persistently difficult asthma in whom other strategies have failed. It has been licensed for use in children over 12 years of age for some time and more recently this has been extended to those 6 years and above with an IgE level of up to 1500 IU/l in the UK. It needs to be given subcutaneously on either a fortnightly or a monthly basis according to IgE levels and bodyweight. The INNOVATE randomized controlled trial studied the effect of omalizumab as an add-on therapy in people with inadequately controlled severe asthma from a difficult to treat patient population (n = 419, aged 12–75 years) [46]. The findings suggested that the addition of omalizumab was not only effective in reducing the frequency of significant asthma exacerbations but also the severity of asthma exacerbations and also emergency hospital visits. In a more recent study of children age 6–12 years, 627 children with moderate-to-severe asthma were randomized to omalizumab or placebo [47]. Over a period of 52 weeks, omalizumab reduced exacerbations by 43% and severe exacerbations by 50% compared with placebo.

It is important to recognize that currently omalizumab treatment is a very costly option. Given the cost of this treatment many centers would consider it unjustified to start therapy if families were unwilling to consider targeting known exacerbating factors, such as pet relocation in a known allergic individual or smoking cessation. Some may also consider that poor compliance with standard therapy is also a contraindication to starting omalizumab therapy. However, a study in adults, investigating adherence and persistence with omalizumab compared with inhaled combination therapy found that both adherence and persistence were twice as good over a 12-month period than with the inhaled therapy [48]. In addition, in studies in adolescent asthmatics, in which adherence to treatment is generally recognized to be poor, significant benefits have been reported with omalizumab compared with placebo [49]. It has been recognized that its benefits may take up to 4 months to take effect. Most centers recommend a trial of treatment lasting at least 16 weeks where agreed outcomes would be monitored before and after the trial, and maintenance therapy only recommended if shown to be effective.

**Steroid-sparing measures**

Ciclosporin, an immunosuppressive drug commonly used post organ transplantation, may be useful in the management of patients with treatment-resistant asthma. It mediates its effects by inhibiting T-helper lymphocytes and has been reported to improve lung function [50] and confer a steroid sparing effect in adult asthmatics [51]. There have not been any controlled trials of its use in pediatric patients but there have been published case series that have reported benefits in its use in pediatric patients with treatment resistant asthma [52]. A therapeutic trial of ciclosporin will require meticulous attention to monitoring drug dosage titrated according to trough whole blood ciclosporin concentrations. Regular serum electrolytes and creatinine measurements will also be required as the main side effect of ciclosporin is nephrotoxicity and hence an assessment of
renal function prior to treatment is required. If the response to ciclosporin is good, then there should be an attempt to wean the dose of maintenance steroids to the minimum dose tolerated. Low-dose ciclosporin may need to be maintained thereafter as there are reports that the benefit of ciclosporin appears to be lost once treatment is discontinued [52]. In addition to ciclosporin, other steroid sparing measures that have been tried include methotrexate, gold salts and intravenous γ-globulin. All these agents have the potential for serious side effects and careful monitoring is essential in their use. Further large-scale studies will be required to further evaluate the use of ciclosporin as well as these other agents in the management of pediatric patients with treatment-resistant asthma.

Subcutaneous terbutaline
Subcutaneous terbutaline has been reported to be useful in the management of adult asthmatics [53] with severe asthma and occasionally in children [54]. It can be delivered either via a continuous or by intermittent injections. There have been published case series reporting effectiveness of long-term subcutaneous terbutaline in some patients with brittle asthma [53] and also in patients who show considerable diurnal air flow variations allowing subsequent reduction in steroid doses [55]. Side effects include tremor, which is common but usually transient, and bruising or infection at the injection site. Initiation of a trial of this therapy should be commenced in hospital where treatment response and possible side effects can be monitored.

Future developments & novel therapies

Bronchial thermoplasty
Bronchial thermoplasty represents a possible treatment option for the management of treatment resistant asthma, currently only tested in adults. It refers to the delivery of a controlled amount of thermal energy to the airway wall during bronchoscopy resulting in a prolonged reduction in smooth muscle mass. The Asthma Intervention Research Trial (AIR2) reviewed this in a sham controlled trial in severe adult asthmatics and found that it resulted in improvements in quality of life scores and reduced both the number of severe exacerbations per year as well as the number of emergency room visits [56]. In addition, in patients with moderate-to-severe asthma, bronchial thermoplasty was found to exert a positive effect by reducing symptoms, asthma exacerbations and also by improving quality of life and lung function [57]. Further trials and studies will be required to further assess this new modality before it translates to increased clinical use.

Newer drugs
There are recent exciting new drug developments in the management of difficult asthma as research continues to unveil a deeper understanding of the molecular and inflammatory mechanisms underlying this condition. Not only are there improvements in existing therapies such as faster onset once-daily combination drugs but there are also improvements in drug pharmacokinetics and in improving safety profiles of existing therapies.

Long-acting bronchodilators
Long-acting bronchodilators such as salmeterol and formoterol have a duration of action that lasts for greater than 12 h. They have complementary actions to corticosteroids and should be delivered together as a combination inhaler. This has proved an effective available therapy for asthma. Longer acting β2-agonists that have a duration of action greater than 24 h are under development, and these include indacaterol, carmoterol and GSK-159797 [58]. Combination therapy of one of these longer acting β2-agonists together with inhaled corticosteroids with increased duration of action is envisaged to confer additional advantages as this should improve treatment compliance and is hoped to represent an emerging therapeutic option in asthma.

Newer inhaled corticosteroids
There have also been developments to produce corticosteroids with improved safety profiles. A new corticosteroid, ciclesonide, which becomes activated to des-ciclesonide in the lung is an example of a prodrug that appears to have less systemic effects, possibly as a result of its long term retention in the lung and no oral bioavailability [59].

Cytokine inhibitors
More novel therapies include cytokine inhibitors as they play a key role in chronic inflammation. These include blocking antibodies to IL-5, IL-13 for example and also cytokine inhibitors such as etanercept and infliximab. There has also been an interest in the use of anti-inflammatory cytokines such as IL-10, which has a broad spectrum of anti-inflammatory effects as well as chemokine antagonists, for example chemokine (C–C motif) receptor 3 (CCR)3, which is predominantly expressed on eosinophils and CCR4 on Th2 cells [58,59].
NK1/NK2 receptor antagonists

There is evidence that the tachykinins substance P and neurokinin A may contribute to airway inflammation and hence, may be implicated in the pathophysiology of asthma, the former by microvascular leakage, mucus secretion, and inflammatory cell responses and the latter by bronchoconstriction [60]. Therefore, several tachykinin NK1 and NK2 receptor antagonists have been developed and begun to be tested in adult asthmatics. At present, more research is required to determine the precise role of tachykinins and their receptors and to establish their position in the treatment of asthma.

As with all new therapies, research is initially aimed at adults and it will be some time before any effective treatments in adults find their way into pediatric practice.

Conclusion

The cornerstone of drug treatment for asthma management has been β2-agonists for relief of bronchoconstriction and inhaled corticosteroids for suppression of inflammation. These are usually successful 90–95% of the time, however as discussed previously the remainder of patients respond poorly. Recent advances in the understanding of airway inflammation have provided areas of research for development of novel therapies. These potential therapies might herald the arrival of patient-specific interventions reflecting the recognition of distinct asthma phenotypes.

Continued work on the evaluation of non-invasive monitoring, in particular of airway inflammation to further establish the asthma phenotype, will aid our understanding of the underlying mechanisms of the disease, natural history, progression of disease and prognosis and will help guide asthma treatments. It will also no doubt shed light on the development of novel interventions and guide future research directions into asthma therapies.

Future perspective

Further phenotypes may continue to emerge as interest in this area expands. An enhanced understanding of the complex pathophysiological mechanisms associated with asthma will also facilitate further work in the development of immunomodulators such as those that modulate regulatory T and T-helper cell functions and novel biologic therapies directed against the inflammatory pathways for the treatment of severe asthma. Although specific targeted therapy according to phenotypes, may be central to the successful management of treatment-resistant asthma, it is equally possible that there is a need to target multiple pathways, with combination therapies, before optimal control can be achieved.

Financial & competing interests disclosure

Clare S Murray has received honoraria for advisory work from GlaxoSmithKline and Chiesi, travel grants from GlaxoSmithKline and Novartis, grant money from GlaxoSmithKline and holds company shares in GlaxoSmithKline and AstraZeneca. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Treatment-resistant asthma is seen in a small minority of patients with asthma.
- Management remains a challenge and the emphasis should be on a structured and thorough approach to assessment and management.
- A distinction needs to be made between those with poor control associated with poor adherence or alternative/concomitant diagnoses and those with true treatment-resistant asthma.
- Children with this condition should be managed by pediatric pulmonologists with access to specialist pediatric services.
- Alternative approaches to therapy exist and these include the use of recombinant monoclonal anti-IgE antibody, macrolide antibiotics and selected immunosuppressive agents.
- More recently, there has been increasing interest in the phenotyping of asthma and the use of individualized phenotype-specific targeted therapy.
- Emerging areas for research include the development of novel therapies such as T-cell immunomodulators and biologic therapies against specific inflammatory pathways, for example, with cytokine inhibitors (to IL-5 and IL-13) and chemokine antagonists (CCR3).
- The development of accurate noninvasive inflammatory biomarkers of asthma control will be invaluable, especially if these prove sensitive enough to allow titration of treatments and allow incorporation into more targeted algorithms to assist in overall asthma management.
Bibliography

Papers of special note have been highlighted as:
• of interest
** of considerable interest

** Excellent overview of an integrated approach to the management of therapy-resistant asthma from a European perspective.
** This working party consensus includes a clear classification strategy to more accurately identify patients with severe asthma.
** Observational study of children with difficult asthma describing their clinical characteristics and their response to corticosteroids.
** Well-conducted large-scale double-blind randomized controlled study describing the benefits of acid suppression with esomeprazole in a subgroup of adult asthmatics.
** Describes tertiary pediatric experiences in phenotyping asthma and a protocol approach to phenotype-specific therapy.
** Describes a well-validated Asthma Quality of Life Questionnaire for pediatric use.
Good review of the new targets under J. Allergy Clin. Immunol. There has been increasing use of...


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• There has been increasing use of omalizumab in clinical practice and this article describes its benefits as an add-on therapy in moderate-to-severe asthma in children.


• Good review of the new targets under development with potential for future clinical use.
