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Diagnosis and management of asthma in children

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ABSTRACT

Asthma is the commonest chronic respiratory condition of childhood worldwide, with around 14% of children and young people affected. Despite the high prevalence, paediatric asthma outcomes are inadequate and there are several avoidable deaths each year. Characteristic asthma features include wheeze, shortness of breath and cough. Asthma symptoms are typically triggered by a number of possible stimuli. There are several diagnostic challenges and as a result, both over and under diagnosis of paediatric asthma remain problematic.

Effective asthma management involves a holistic approach addressing both pharmacological and non-pharmacological management, as well as education and self-management aspects. Working in partnership with children and families is key in promoting good asthma outcomes. Education on trigger avoidance, modifiable risk factors and actions to take during acute attacks via personalised asthma action plans is essential.

This review aims to provide an overview of good clinical practice in the diagnosis and management of paediatric asthma. We discuss the current diagnostic challenges and predictors of life-threatening attacks. Additionally, we outline the similarities and differences in global paediatric asthma guidelines and highlight potential future developments in care. It is hoped that this review will be a useful tool for all health care providers working in a range of child health settings.

INTRODUCTION

Asthma is a chronic respiratory disease characterised by episodes of wheeze, cough, and shortness of breath. Around 14% of children worldwide have a diagnosis of asthma, making it the most common chronic respiratory disease of childhood(1).

Poor asthma control is associated with a number of negative effects on children and families. For example, they are more likely to be absent from school, have additional educational needs and have lower educational attainment(2). Caregivers also experience missed work days and financial challenges as a result(3). Some children will experience severe symptoms and life threatening attacks(4).

Paediatric asthma outcomes are poor overall and most pertinently there are several preventable deaths each year. Alarmingly, the National Review of Asthma Deaths (NRAD) in the United Kingdom found that in almost all paediatric cases, there were a number of significant avoidable contributing factors and that these deaths may have been preventable(5).

There are several factors that make the diagnosis and management of asthma in children challenging. The aim of this review is to explore these issues and highlight good clinical practice in the diagnosis and management of paediatric asthma.

PRESENTATION OF ASTHMA

Children with asthma typically present with a symptom triad of wheeze, shortness of breath and cough. However, ‘asthma’ is an umbrella term used to describe this collection of symptoms and when present should prompt practitioners to ask, “what type of asthma is this?”. There are a number of asthma subtypes that present and respond to treatment differently. Identification of the features of asthma and modifiable or treatable traits should only be the start of the diagnostic journey(6). Asthma symptoms are normally intermittent

in nature and may not be present at the time of clinical review, making the diagnosis challenging in some cases for health care professionals(7). Additionally, disease phenotypes are not fixed and may evolve over time necessitating ongoing review of symptoms and treatment(8).

Wheeze is a key feature of asthma and if not present, a diagnosis of asthma in a child is unlikely. Wheeze is an expiratory high-pitched whistle that occurs as a result of inflammation and narrowing of the small airways. Parental understanding of wheeze varies and clarifying what is meant when it is reported is key in making an accurate diagnosis(9).

The prevalence of 'preschool wheeze' is an additional challenge when diagnosing asthma in young children. In the first few years of life, many children will experience wheeze, however not all will go on to develop true asthma. The diagnosis of asthma should therefore be reviewed routinely, to identify true asthma and alter treatment where necessary(10). Favourable response to an appropriate trial of asthma treatment is an important confirmatory piece of diagnostic evidence.

Clinical examination may be normal in children and adolescents with asthma if they present during asymptomatic periods. During acute attacks, use of accessory muscles of respiration and widespread wheeze may be present(11). Chest hyperinflation may be identified in acute and chronic disease settings.

ASTHMA TRIGGERS

Asthma attacks commonly occur following exposure to one or several triggers. Viral respiratory infections remain the leading cause of asthma attacks in children(12), however there are a number of other known triggers (Table 1), including aeroallergens, second hand smoke exposure or changes in ambient air temperature or humidity. Identification

and documentation of specific asthma triggers should be part of routine care. Education on trigger recognition and avoidance is essential in providing good asthma care.

Table 1. Common asthma triggers

Viral respiratory tract infections(5)
Exercise(5, 13)
Weather changes in temperature and humidity(5, 13)
Domestic pollutants - e.g. pests, mould, dust mites(5)
Environmental pollutants - e.g. air pollution(5)
Secondhand smoke exposure(12, 13)
Pets and animals(12)
Strong odours(12)
Anxiety or strong emotions(13)
Drugs – e.g. non-steroidal anti-inflammatory drugs, beta-blockers(13)
Gastro-oesophageal reflux(13)

RISK FACTORS FOR ASTHMA

There are a number of risk factors that should be explored in the history of children who present with features of asthma. In symptomatic children, a personal or family history of atopic features, including asthma, eczema or rhinitis, supports a diagnosis of asthma. Some additional risk factors are outlined in Table 2. Education on modifiable risk factors, for example, exposure to second hand smoke and obesity, should be delivered routinely during consultations and asthma reviews.

Table 2. Asthma risk factors

Personal or family history of atopy - eczema, allergic rhinitis, nasal polyposis(14)
Family history of asthma(14)
Exposure to second hand smoke(14)
Preterm birth(15)
Low birth weight(16)
Obesity(17)
Poor housing quality/mould and dampness(5)

PAEDIATRIC ASTHMA PHENOTYPES

Asthma is a heterogeneous disease in which there are several phenotypes and underlying endotypes. Phenotypes are subtypes of asthma that share clinical characteristics such as symptom triggers, atopic features, disease severity and response to treatment. Endotypes are subtypes of asthma that are characterised by similar underlying biological mechanisms(18).

Key endotypes include ‘T2 high’ and ‘T2 low’ asthma. Identifying asthma phenotypes and endotypes can facilitate targeted treatment based on the pathophysiology occurring in a specific individual. For example, eosinophilic asthma (T2 high) is characterised by a number of different inflammatory biomarkers including high eosinophils, immunoglobulin (Ig) E and fractional exhaled nitric oxide (FeNO) levels(18), and typically responds well to inhaled corticosteroid (ICS) treatment(6). A number of biologic agents can be used in the management of asthma, under specialist supervision, and their use varies on asthma endotypes (Table 8)(19).

DIFFERENTIAL DIAGNOSES AND DIAGNOSTIC UNCERTAINTY

Misdiagnosis of asthma remains a major problem with rates of both under- and over-diagnosis being high(20). Overdiagnosis is problematic as it exposes children to unnecessary side effects of medications and runs the risk of trivialising asthma(6).

There are several conditions that may be associated with chronic cough, wheeze and/or shortness of breath in children and therefore present similarly to asthma (Table 3). Due to the difficulties with diagnosis, especially in young children where objective testing is not possible, the diagnosis of 'asthma' should be reviewed at each clinical presentation and interaction.

Table 3. Asthma differentials and clues in medical history

Differential diagnosis	Possible features of history
Cystic fibrosis(21, 22)	- Symptoms present from birth - Finger clubbing - Family History of cystic fibrosis or unexplained/atypical respiratory disease - Weight faltering - Gastrointestinal symptoms
Primary ciliary dyskinesia(22)	- Symptoms present from birth - Family history of unexplained respiratory symptoms - Persistent cough - Nasal symptoms
Chronic lung disease of prematurity/bronchopulmonary dysplasia(22)	- Premature
Bronchiectasis(21, 22)	- Persistent productive cough - Finger clubbing
Laryngeal dysfunction(22)	- Stridor - Abnormal cry
Gastro-oesophageal reflux disease or	- Vomiting

aspiration(21)	- Weight faltering - Recurrent infections
Structural abnormality - e.g. bronchomalacia, bronchogenic cyst(23)	- Present from birth - No variation to wheeze
Immunodeficiency(23)	- Weight faltering - Recurrent and/or atypical infections
Foreign body aspiration(23)	- Sudden onset - Unilateral chest features

DIAGNOSING ASTHMA IN CHILDREN

There is no single 'gold-standard' test that can be used to accurately diagnose asthma. In practice, a diagnosis should be made based on characteristic symptom patterns, evidence of variability in airflow limitation in the presence of airway inflammation, likelihood of alternative diagnoses and response to treatment. Getting the diagnosis correct is key for optimal management of paediatric asthma.

Lung function tests can be used to aid the diagnosis of asthma in children over the age of 5 years. Peak expiratory flow (PEF) and spirometry are commonly used to assess airflow obstruction and reversibility. PEF can be used to detect diurnal variation, which is a typical feature of asthma. The Global Initiative for Asthma (GINA) recommends the use of either PEF or spirometry in the diagnosis of asthma in children over 5 years(24). In children under 5 lung function testing is rarely practical out with a research setting. This makes diagnosis in this age group additionally challenging(15). Guidelines vary between countries and regions with regard to diagnostic criteria. An overview of the similarities and differences between these guidelines is displayed in Table 4.

FeNO and allergy testing are additional tools that can be used to aid the diagnosis of asthma(21, 25, 26). FeNO is used to detect and quantify eosinophilic airway inflammation

with levels elevated in those with eosinophilic asthma and normal in non-eosinophilic asthma(27). Allergy testing (skin prick testing or measurement of specific-IgE levels) is not routinely carried out in the diagnostic process; however, it is recommended in a number of clinical guidelines and may identify individual triggers(25, 26, 28, 29).

There are several other aspects that make paediatric asthma diagnosis challenging. Most diagnoses are made in primary care where there is little access to spirometry, FeNO or allergy testing. Additionally, the symptom onset for most cases of paediatric asthma occurs before the age of 3 years(30) when lung function testing cannot be used to aid diagnosis. In this age group, response to an asthma treatment trial is useful to aid diagnostic decision making and is recommended in a number of national guidelines(29, 31-33).

Table 4. Summary of paediatric asthma national guidelines – focusing on diagnosis.

Guideline	Year	Diagnostic criteria	Recommended objective testing	When to refer to a specialist	When to consider alternative diagnoses	Identification of high risk patients
NICE Guidelines (United Kingdom)(21)	2017	Under 5 years Findings in clinical history and examination that are suggestive of asthma Over 5 years Findings in clinical history and examination that are suggestive of asthma *and* either spirometry demonstrating obstructive airflow and bronchodilator reversibility *or* a FeNO level of 35 ppb or more	Over 5 years Spirometry and bronchodilator reversibility *or* FeNO 1st line. Additional tests PEF, bronchial challenge test with histamine or methacholine	Children who are not responding to treatment and cannot complete objective testing If there is obstructive spirometry but negative bronchodilator reversibility and negative FeNO	When children have symptoms of asthma but normal objective testing results	Repeated attacks, poor adherence and psychosocial problems
Global Initiative for Asthma (Global)(24)	2021	6 years and over Findings in clinical history that are suggestive of asthma *plus* evidence of variability in expiratory airflow limitation with either spirometry and bronchodilator reversibility, repeated PEF measurements, positive exercise challenge or positive bronchial challenge	6 years and over Either spirometry, PEF, exercise challenge *or* bronchial challenge to detect variability in lung function	Diagnostic uncertainty, previous life threatening attack, no/poor response to asthma treatment	Atypical asthma features, atypical clinical examination findings - e.g. cardiac murmurs	Multiple attacks, poor asthma symptom control, persistent variability in lung function
Canadian Thoracic Society (Canada)(33)	2021	Aged 1-5 years More than one presentation of asthma like symptoms *plus* a response to asthma treatment trial Over 6 years Findings in clinical history that are suggestive of asthma *plus* spirometry showing obstructive expiration and demonstration	Over 6 years Spirometry and bronchodilator reversibility (1st line). Additional tests that may be useful - peak flow variability, bronchial challenge and exercise challenge	Diagnostic uncertainty, severe asthma, previous life threatening attack, need for allergy testing, any hospitalisation as a result of asthma		-

		of reversibility of airflow limitation of at least 12%				
National Asthma Council Australia (Australia)(31)	2021	Aged 1-5 years Findings in clinical history and examination that are suggestive of asthma *plus* a response to treatment trial with SABA and/or ICS 6 years and over Findings in clinical history and examination that are suggestive of asthma *plus* spirometry demonstration of reversibility of airflow limitation of at least 12%	Aged 1-5 years None 6 years and over Spirometry 1st line. Bronchial challenge test and exercise testing to be considered if spirometry results does not show a reversibility of airflow limitation of at least 12%	When child has characteristic asthma symptoms and diagnosis is not clear from objective testing results	Atypical asthma features No response to treatment trials Results of objective testing do not suggest asthma	-
Asthma and Respiratory Foundation NZ (New Zealand)(32)	2020	Aged 1-11 Findings in clinical history that are suggestive of asthma *plus* a response to asthma treatment trial	Aged 5-11 years Spirometry should be considered if asthma symptoms are atypical or in those with typical asthma symptoms that do not respond to a treatment trial	When there is no response to asthma treatment trials and/or there is diagnostic uncertainty	Atypical asthma features	Monitor number of attacks in the last 12 months. Monitor health care use (excessive healthcare use suggests uncontrolled disease). Monitor medication use (more inhalers suggests uncontrolled disease)
Irish College of General Practitioners (Ireland)(34)	2020	Under 6 years Findings in clinical history that are suggestive of asthma Over 6 years Findings in clinical history that are suggestive of asthma *plus* evidence of obstructive airflow limitation and reversibility with bronchodilators	Under 6 years Treatment trial Over 6 years PEF *or* spirometry.	Parental concern or request, failure to respond to treatment trial, failure to thrive, diagnostic uncertainty		Those with frequent unplanned health attendances/admissions and requiring excess medication such as inhalers frequently or oral steroids
The Japanese Society of Allergology (Japan)(29)	2020	All ages Findings in clinical history that are suggestive of asthma *plus* a response to asthma treatment trial	Lung function testing (non-specified), skin prick testing, bronchodilator reversibility testing, bronchial challenge	Poor response to multiple agent therapy or multiple courses of oral steroids	Atypical asthma features, no response to treatment trial or atypical results on objective testing	Number of attacks in the last year, previous ICU admission for asthma, patient comorbidities

International Consensus on Pediatric Asthma (Global)(26)	2015	Under 5 years Findings in clinical history that are suggestive of asthma Over 5 years Findings in clinical history that are suggestive of asthma *plus* spirometry with bronchodilator reversibility demonstration of reversibility of airflow limitation of at least 12%	Over 5 years Spirometry 1st line. PEF is useful for aiding. FeNO and skin prick testing for detecting allergic asthma can be useful.			
GEMA (Spain)(25)	2009	Under 6 years Findings in clinical history that are suggestive of asthma Over 6 years Findings in clinical history that are suggestive of asthma *plus* spirometry with bronchodilator reversibility demonstration of reversibility of airflow limitation of at least 12%	6 years and over Spirometry with combined bronchodilator reversibility. FeNO and allergy testing may be useful if diagnosis is unclear			Poor asthma symptom control and frequent attacks
Ministry of Health (Singapore)(28)	2008	All ages Findings in clinical history and examination that are suggestive of asthma	No objective testing normally required for diagnosis. PEF at every consultation and spirometry at least annually in children over 6 years to assess asthma severity. Tests that may be considered - CXR to exclude foreign bodies and chronic LRTIs, skin prick testing to detect atopy and exercise testing to assess exercise induced asthma	High risk patients with poor control, young age and poor response to treatment trial, when requiring high doses of steroids to control symptoms	-	-

MANAGEMENT OF ASTHMA IN CHILDREN

The management of asthma is multifactorial and to optimise disease control a number of pharmacological, non-pharmacological and self-management aspects need to be considered.

1. Pharmacological management

The pharmacological management of asthma involves two key components; maintenance and reliever therapies. Maintenance therapies are the mainstay of asthma management and the treatment aim is that no reliever therapies are required. Use of reliever therapy suggests asthma control is poor.

An overview of maintenance and reliever therapies is outlined in Tables 5 and 6 respectively. A stepwise approach to asthma management is encouraged and pharmacological management varies on age, symptom control and the national guideline used. An overview of management approach in a number of national guidelines is summarised in Table 7.

GINA guidelines recommend dual ICS and short-acting beta-2 agonist (SABA) therapy to children over the age of 5(24). SABA monotherapy was previously the main management starting point, however compared with combined treatment, SABA monotherapy has been shown to be associated with asthma mortality(35). SABA monotherapy is now only recommended by GINA for use in children aged 5 or less(24).

Single Maintenance and Reliever Therapy (SMART) inhalers are combined inhalers offering both maintenance and reliever therapy in those with asthma. These inhalers contain a number of maintenance and reliever therapies in different combinations. The use of these inhalers have been shown to reduce the risk of asthma attacks and ED admissions(36), improve lung function and decrease the need for reliever therapy(37). There is limited evidence in the effectiveness of SMART inhalers in children, however

children over 12 years may be prescribed a SMART inhaler, which acts as both a maintenance and reliever therapy, if symptoms are not well controlled(38).

Table 5. Maintenance therapies

Maintenance therapies	Comments
Inhaled corticosteroids (ICS)	Currently used as a first line maintenance agent in a number of national guidelines(21, 24, 32, 34). When using ICS, the lowest possible dose to effectively control symptoms should be used to prevent possible adverse effects of reduced growth and risk of adrenal suppression.
Long-acting beta-2 agonists (LABA)	Used as an add on therapy when dual ICS and SABA (short-acting beta-2 agonists) therapy is ineffective. In comparison to SABA, bronchodilation duration is prolonged to 12 hours.
Leukotriene receptor antagonists (LTRA) (e.g. montelukast)	Used as an add on therapy in those who have poor symptom control despite ICS and LABA treatments(21, 24, 25, 29, 31, 33). There have been a number of concerns raised regarding possible adverse reactions to montelukast. These include neuropsychiatric features ranging from poor sleep to suicidal ideation(39).
Long-acting muscarinic antagonists (LAMA) (e.g. tiotropium)	Used as an add on therapy in those who have poor symptoms control despite ICS and LABA therapies.
Oral theophylline	Used as an add on therapy, usually in those with uncontrolled symptoms despite several maintenance and reliever therapies. Monitoring of plasma level required on initiation of treatment and dose changes.

Biologics	Use as an add on therapy, under specialist care, in those who have poorly controlled symptoms despite being on several maintenance and reliever therapies. A number of biologic agents are available (Table 8). Various individual biologics have been shown to reduce attacks, improve lung function and reduce oral corticosteroid use(19).

Table 6. Reliever therapies

Reliever therapies	**Comments**
Short-acting beta-2 agonists (SABA)	Currently used as a first line reliever agent in a number of national guidelines. Effects of bronchodilation last for up to 4 hours. SABAs work by rapidly relaxing the smooth muscle of small airways, providing quick relief from asthma symptoms.
Oral corticosteroids	Used as a short-term therapy during asthma attacks to reduce airway inflammation and ease symptoms. Repeated short-term courses of oral steroids suggest poor chronic symptom control and should trigger a review of maintenance therapy.

2. Non-pharmacological management

Non-pharmacological aspects of asthma management include providing education on modifiable risk factors and comorbidities to caregivers and conducting annual asthma reviews to assess control and future risk.

Education is key to improving caregiver and child understanding of asthma and its management. Clear information regarding modifiable risk factors, such as smoke exposure, domestic pollutants and obesity, should be given. Short term educational interventions aimed to improve self-management have been shown to increase medication adherence(40), improved symptom control and reduced mortality(41).

All young people with asthma should have asthma reviews at least annually. These reviews should focus on current symptom control and management, previous attacks, triggers, modifiable risk factors and personal asthma action plans (PAAPs). Asthma reviews are opportunities to assess child and caregiver understanding of asthma and provide education if necessary.

3. Self-management

Self-management aspects of paediatric asthma management include asthma education and PAAPs. PAAPs are written documents that are given to young people and/or caregivers that advise them on day to day asthma management and what to do in the event of an attack(42). Action plans should be created with patient/caregiver input, shared with relevant individuals (e.g. school teachers) and should be reviewed and updated regularly. PAAPs have been shown to reduce ED attendance, missed school days and increase caregiver confidence when managing attacks(43). The 2018 Annual Asthma Survey found that over 50% of children with asthma in the United Kingdom had no PAAP and around 20% of caregivers did not seek medical advice during acute asthma attacks, highlighting large gaps in education(44).

Table 7. Summary of paediatric asthma national guidelines – focusing on management

Guideline	Year	1st line management	Add on therapies*	Treatment withdrawal
NICE Guidelines (United Kingdom)(21)	2017	Aged 1-4 years SABA monotherapy Aged 5-16 years SABA monotherapy	Aged 1-4 years 2nd line - low dose ICS 3rd line - low dose ICS and LTRA 4th line - referral to paediatrics for specialist management Aged 5-16 years 2nd line - low dose ICS 3rd line - low dose ICS and LTRA 4th line - low dose ICS and LABA 5th line - high dose ICS and LABA 6th line - referral to paediatrics for specialist management	Consider withdrawing maintenance treatment after 3 months of stable asthma. Only consider stopping ICS on those who are on ICS monotherapy
Global Initiative for Asthma (Global)(24)	2021	Aged 5 years and under SABA monotherapy Aged 6-11 years Combined low dose ICS+SABA (as needed) Adolescents Combined low dose ICS+SABA (as needed)	5 years and under 2nd line - low dose ICS 3rd line - medium dose ICS *or* low dose ICE and LTRA 4th line - refer to paediatrics for expert advice Aged 6-11 years 2nd line - low dose ICS 3rd line - low dose ICS and LABA *or* medium dose ICS *or* daily SMART combined ICS/LABA. Refer for expert advice 4th line - refer for phenotype assessment Adolescents 2nd line - low dose ICS 3rd line - medium dose ICS 4th line - medium/high dose ICS +/- LAMA. Refer for phenotype assessment	Stepping down treatment should be considered when both asthma symptoms and lung function have been stable for a period of 3 months or more
Canadian Thoracic Society (Canada)(33)	2021	Aged 1-5 years SABA monotherapy Aged 6 -11 SABA monotherapy Age 12+ SABA monotherapy	Aged 1-5 years 2nd line – ICS and LTRA 3rd line - high dose ICS and LTRA 4th line - referral to paediatrics for specialist management Aged 6 -11 2nd line - ICS and LTRA 3rd line - high dose ICS and LTRA 4th line - high dose ICS, LTRA and LABA 5th line - high dose ICS, LTRA, LABA and oral steroids Age 12+ 2nd line – ICS and LTRA 3rd line – ICS, LTRA and LABA 4th line - high dose ICS, LTRA, LABA and tiotropium	After asthma has been well controlled for a period of 3-6 months

National Asthma Council Australia (Australia)(31)	2021	Aged 1-5 years SABA monotherapy Aged 6 and over SABA monotherapy	Age 1-5 years 2nd line - low dose ICS *or* LTRA 3rd line - low dose ICS and LTRA 4th line - referral to paediatrics for specialist management Age 6 and over 2nd line - low dose ICS *or* LTRA 3rd line - low dose ICS and LTRA *or* high dose ICS *or* ICS/LABA combination 4th line - referral to paediatrics for specialist management	Step down of treatment should be considered when symptoms have been well controlled for a period of at least 6 months
Asthma and Respiratory Foundation NZ (New Zealand)(32)	2020	Aged 1-4 years SABA and low dose ICS Aged 5-11 years SABA monotherapy	Age 1-4 years 2nd line - low dose ICS and LTRA 3rd line - referral to paediatrics for specialist management Age 5-11 years 2nd line – SABA and low dose ICS 3rd line – LABA and low dose ICS 4th line - LABA, high dose ICS, LTRA and referral to paediatrics for specialist management	If child has been stable for 3 months or more on treatment, step down with an incremental approach
Irish College of General Practitioners (Ireland)(34)	2020	Aged 6-11 ICS and SABA (ICS only to be taken when SABA is used as a reliever) Adolescents ICS and SABA (ICS only to be taken when SABA is used as a reliever)	Aged 6-11 2nd line – low dose ICS *or* LTRA (if ICS is not appropriate) 3rd line - low dose ICS and LABA *or* high dose ICS 4th line - medium dose ICS, LABA and referral to paediatrics for management advice 5th line - refer to paediatrics for phenotype assessment Adolescents 2nd line – low dose ICS 3rd line - low dose ICS and LABA 4th line - medium dose ICS and LABA *or* low dose ICS, LABA and LAMA 5th line - refer to paediatrics for phenotype assessment	
The Japanese Society of Allergology (Japan)(29)	2020	Aged 1-5 years SABA monotherapy Aged 6-15 years SABA monotherapy	Age 1-5 years 2nd line - low dose ICS *or* LTRA or Disodium cromoglycate (DSCG) 3rd line - medium dose ICS 4th line - high dose ICS and LTRA Age 6-15 years 2nd line - low dose ICS *or* LTRA 3rd line - medium dose ICS *or* combined low dose ICS/LABA 4th line - high dose ICS *or* combined medium dose ICS/LABA	-
International Consensus on Pediatric	2015	Quotes GINA and NICE guidelines	Quotes GINA and NICE guidelines	

Asthma (Global)(26)				
GEMA (Spain)(25)	2009	<u>Aged 3 and under</u> SABA monotherapy <u>Aged 3 and over</u> SABA monotherapy	<u>Aged 3 and under</u> 2nd line - low dose ICS *or* LTRA 3rd line - moderate dose ICS *or* low dose ICS and LTRA 4th line - moderate dose ICS and LTRA 5the line - high dose ICS and LTRA. Consider adding LABA 6th line - oral steroids <u>Aged 3 and under</u> 2nd line - low dose ICS *or* LTRA 3rd line - moderate dose ICS or low dose ICS and LTRA *or* low dose ICS and LABA 4th line - moderate dose ICS and LTRA *or* moderate dose ICS and LABA 5th line - high dose ICS and LABA. Consider adding LTRA and theophyllines 6th line – consider oral steroids and omalizumab	
Ministry of Health (Singapore)(28)	2008	No stepwise approach outlined	No stepwise approach outlined	Consider stepping down treatment when symptoms are stable for 3 to 6 months considering the child's risk of poor outcomes. Do not stop ICS
South African Thoracic Society (South Africa)(45)	2007	<u>Adolescents</u> SABA + low dose ICS	<u>Adolescents</u> 2nd line – LABA andICS 3rd line - LABA, low dose ICS and LTRA/LABA *or* high dose ICS or LABA, low dose ICS and theophyllines. Consider oral corticosteroids 4th line - referral to specialist	-

*SABA reliever therapy as required at any stage

Table 8. Biologic agents used in the management of asthma

Biologic	Route and frequency	Mechanism of action	Effect on asthma symptoms	Effect on attacks and mortality	Safety concerns/Common adverse reactions
Omalizumab	S/C injection every 4 weeks	$IgG1_K$ antibody that binds to the Fc portion of IgE, resulting in the inability of IgE to bind to the IgE receptor on mast cells(46). This reduces the concentration of free circulating IgE and consequently mast cell degranulation(47)	Improved asthma symptoms(48)	Reduce asthma attacks(48, 49)	Mild injection site reactions, headache, pyrexia, abdominal pain, gastroenteritis and nasopharyngitis(50)
Dupilumab	S/C injection every 2 weeks	Binds to alpha component of IL-4 receptor blocking IL-4 and IL-13 stimulation of B-cells(51)	Improved asthma symptoms and quality of life(52)	Reduced asthma attacks(53)	Mild injection site reactions and eosinophilia(53)
Mepolizumab	S/C injection every 4 weeks	Binds to IL-5 cytokines resulting in reduced peripheral eosinophilia and reduced airway inflammation(54)	Improved asthma symptoms and quality of life(55)	Reduced asthma attacks(55, 56)	Headache, attack of asthma symptoms and bronchitis(57, 58)
Reslizumab	IV infusion every 4 weeks	Binds to IL-5 cytokines resulting in reduced peripheral eosinophilia and reduced airway inflammation(54)	Improved asthma symptoms and quality of life(59)	Reduced asthma attacks(59)	Attack of asthma symptoms, nasopharyngitis and upper respiratory tract infections(60)
Benralizumab	S/C injection every 4 weeks for the first 3 doses and then every 8 weeks	Binds to alpha component of IL-5 receptor resulting in reduced eosinophil activation from IL-5(61)	Improved asthma symptoms and quality of life(62)	Reduced asthma attacks(62)	Headache, sinusitis, nasopharyngitis and pyrexia(62)

Withdrawing management/stepping down

Asthma control should be reviewed at every medical contact. When asthma symptoms are well controlled on pharmacological therapy, stopping or stepping down medication should be considered to protect young people from unnecessary adverse effects.

The GINA 2021 guidelines advise that clinicians should consider stepping down asthma management to the lowest effective treatment regimen when good symptom control has been achieved for at least 3 months(24). When stepping down treatment an individualised risk-benefit approach should be taken with focus on the child's medical history including frequency of oral corticosteroid use, frequency of asthma attacks and previous intensive or high dependency care admissions(63).

WHEN TO REFER TO A SPECIALIST

Most paediatric asthma cases are diagnosed in primary care without the input of general paediatricians or paediatric respiratory physicians(5). However, a number of children with asthma may need to be referred to specialists for diagnostic or management input. Common indications for specialist referral include no or poor response to asthma treatments, inconclusive objective testing, poor symptom control with appropriate treatment, frequent oral corticosteroid use or the occurrence of a severe asthma attack(21, 24, 29, 31, 32, 34).

Health care professionals must consider any safeguarding implications at all paediatric asthma reviews as part of delivering holistic care. Unexplained or frequent ‘do not attend’ appointments or suspicion of poor medical management at home should be flagged and acted upon locally.

PREDICTORS OF LIFE-THREATENING ATTACKS

The following features have been shown to increase the likelihood of future severe attacks and particular attention should be given to these factors during asthma reviews.

1. Previous attack: The strongest risk factor for a future asthma attack is a personal history of a previous attack. One large systematic review and meta-analysis found that children with a recent history of ED attendance with an asthma attack were up to 5.8 times more likely to have another ED attendance and up to 3 times more likely to be admitted to hospital with a future asthma attack(64).

2. Frequent SABA use and prescription requests: Frequent use of SABA reliever therapy suggests poor control of asthma symptoms. If asthma symptoms are well controlled, no more than two SABA inhalers should be required annually(65). The UK NRAD found that excess SABA prescription and use was prominent in individuals who died of asthma attacks. For those with data available, around 40% had been prescribed 12 or more SABA inhalers in the 12 months before death(5).

POST-ATTACK REVIEW

Asthma attacks should be viewed as never events. It is essential that a post-attack review is conducted to review asthma maintenance treatment, as this is likely to be suboptimal. Failure to review patients post-attack, and alter treatment where appropriate, is likely to predispose to future attacks, which could be life-threatening. Management of the current attack should be reviewed to ensure treatment is appropriate and symptoms are resolving. Some individuals may require additional courses of oral corticosteroids to settle symptoms(6).

Current NICE quality standards (UK) state that all individuals hospitalised with an asthma attack should receive a follow up review in primary care within 2 working days of

discharge(21), to review maintenance management and ensure resolution of symptoms. However, the 2018 National Asthma Survey completed in the UK found that 64% of respondents had no primary care follow up post-attack and most patients were not aware that this was required(44).

Salbutamol weaning

Salbutamol weaning plans are commonly used by a number of healthcare organisations following discharge after an asthma attack. These plans direct caregivers to provide regular SABA therapy, often in a reducing regime, in the days following discharge. There have been a number of concerns raised with regards to these plans with some believing that providing regular SABA therapy may potentially mask deterioration and could delay care givers seeking medical advice(66). Healthcare professionals should enquire about salbutamol weaning plans during post-attack reviews and urge caregivers to seek medical advice if they have concerns or the effects of SABA are not lasting the 4 hours of duration.

FUTURE DEVELOPMENTS IN CARE

The management of paediatric asthma is changing over time with, just as two examples, developments in technology and service structure.

1. Technology. The growing use of technology in asthma care has huge potential to improve clinical outcomes. Smartphone applications can be used to provide medication reminders to users and this has been shown to increase ICS adherence(67). Applications can also be used to provide educational content to young people and care givers(68), as well as store personal asthma action plans(69). ‘Smart’ inhalers, not to be confused with SMART inhalers, are devices that can provide audio reminders to users and record when they are used. One paediatric study found that

the use of 'smart' inhalers increased treatment adherence to 84%, compared to 30% in the control group(70).

2. Diagnostic hubs. In the UK, regional diagnostic hubs for asthma care have been recommended in NHS England's Long Term Plan(71). Implementation of diagnostic hubs is hoped to result in earlier and more accurate asthma diagnoses by improving access to objective testing and specialised interpretation. Hubs are designed to improve asthma outcomes by enabling most appropriate treatment initiation and monitoring. There is currently no evidence in the literature of the clinical effects of diagnostic hubs being used in the management of paediatric asthma.

CONCLUSIONS

Paediatric asthma outcomes are currently poor and many deaths are preventable. The aim should be to avoid asthma attacks occurring with appropriate maintenance therapy and they should be viewed as never events. In order to improve outcomes, accurate diagnosis and management are essential. Good asthma care extends beyond providing medication and should include education, as well as supported self-management advice. The use of PAAPs remains poor and a significant number of young people with asthma do not have one. Post-attack asthma reviews are a key opportunity to review maintenance medication and current symptom control.

KEY MESSAGES

1. Paediatric asthma outcomes are poor and many deaths are preventable
2. Diagnosing asthma in childhood can be challenging and the diagnosis should be reviewed during follow up to ensure it is correct
3. Asthma attacks should be viewed as never events. Post-attack reviews are essential to optimise maintenance therapy and prevent future attacks
4. Education is key to improving asthma outcomes
5. Personalised Asthma Action Plans are essential and a significant number of children with asthma do not have one

COMPETING INTERESTS

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Diagnosis and management of asthma in children

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ABSTRACT

Asthma is the commonest chronic respiratory condition of childhood worldwide, with around 14% of children and young people affected. Despite the high prevalence, paediatric asthma outcomes are inadequate and there are several avoidable deaths each year. Characteristic asthma features include wheeze, shortness of breath and cough, which are typically triggered by a number of possible stimuli. There are several diagnostic challenges and as a result, both over and under diagnosis of paediatric asthma remain problematic.

Effective asthma management involves a holistic approach addressing both pharmacological and non-pharmacological management, as well as education and self-management aspects. Working in partnership with children and families is key in promoting good outcomes. Education on how to take treatment effectively, trigger avoidance, modifiable risk factors and actions to take during acute attacks via personalised asthma action plans is essential.

This review aims to provide an overview of good clinical practice in the diagnosis and management of paediatric asthma. We discuss the current diagnostic challenges and predictors of life-threatening attacks. Additionally, we outline the similarities and differences in global paediatric asthma guidelines and highlight potential future developments in care. It is hoped that this review will be useful for health care providers working in a range of child health settings.

INTRODUCTION

Asthma is a chronic respiratory disease characterised by episodes of wheeze, cough, and shortness of breath. Around 14% of children worldwide have a diagnosis of asthma, making it the most common chronic respiratory disease of childhood[1].

Poor asthma control is associated with a number of negative effects on children and families. For example, they are more likely to be absent from school, have additional educational needs and have lower educational attainment[2]. Caregivers also experience missed work days and financial challenges as a result[3]. Some children will experience severe symptoms and life threatening attacks[4].

Taking the United Kingdom as an example, paediatric asthma outcomes are poor overall with considerable associated morbidity, high rates of emergency hospital admissions and most pertinently there are several preventable deaths each year[5]. Alarmingly, the National Review of Asthma Deaths (NRAD) found that in almost all paediatric cases, there were a number of significant avoidable contributing factors and that these deaths may have been preventable[6].

There are several factors that make the diagnosis and management of asthma in children challenging. The aim of this review is to explore these issues and highlight good clinical practice in the diagnosis and management of paediatric asthma.

PRESENTATION OF ASTHMA

Children with asthma typically present with a symptom triad of wheeze, shortness of breath and cough. However, ‘asthma’ is an umbrella term used to describe this collection of symptoms and when present should prompt practitioners to ask, “what type of asthma is this?”. There are a number of asthma subtypes that present and respond to treatment differently. Identification of the features of asthma and modifiable or treatable traits should

only be the start of the diagnostic journey[7]. Asthma symptoms are normally intermittent in nature and may not be present at the time of clinical review, making the diagnosis challenging in some cases[8]. Additionally, disease phenotypes are not fixed and may evolve over time necessitating ongoing review of symptoms and treatment[9].

Wheeze is a key feature of asthma and if not present, a diagnosis of asthma in a child is unlikely. Wheeze is an expiratory high-pitched whistle that occurs as a result of inflammation and narrowing of the small airways. Parental understanding of wheeze varies and clarifying what is meant when it is reported is key in making an accurate diagnosis[10].

The prevalence of 'preschool wheeze' is an additional challenge when diagnosing asthma in young children. In the first few years of life, many children will experience wheeze, however not all will go on to develop true asthma. The diagnosis of asthma should therefore be reviewed routinely, to identify true asthma and alter treatment where necessary[11]. Favourable response to an appropriate trial of asthma treatment is an important confirmatory piece of diagnostic evidence.

Clinical examination may be normal in children and adolescents with asthma if they present during asymptomatic periods. During acute attacks, use of accessory muscles of respiration and widespread wheeze may be present[12]. Chest hyperinflation may be identified in acute and chronic disease settings.

ASTHMA TRIGGERS

Asthma attacks commonly occur following exposure to one or several triggers. Viral respiratory infections remain the leading cause[13], however there are a number of other known triggers (Table 1), including aeroallergens, second hand smoke exposure or changes in ambient air temperature or humidity. Identification and documentation of

specific asthma triggers should be part of routine care. Education on trigger recognition and avoidance is essential.

Table 1. Common asthma triggers

Viral respiratory tract infections[6]
Exercise[6, 14]
Weather changes in temperature and humidity[6, 14]
Domestic pollutants - e.g. pests, mould, dust mites[6]
Environmental pollutants - e.g. air pollution[6]
Secondhand smoke exposure[13, 14]
Pets and animals[13]
Strong odours[13]
Anxiety or strong emotions[14]
Drugs – e.g. non-steroidal anti-inflammatory drugs, beta-blockers[14]
Gastro-oesophageal reflux[14]

RISK FACTORS FOR ASTHMA

There are a number of risk factors that should be explored in the history of children who present with features of asthma. In symptomatic children, a personal or family history of atopic features, including asthma, eczema or rhinitis, supports a diagnosis of asthma. Some additional risk factors are outlined in Table 2. Education on modifiable risk factors, for example, exposure to second hand smoke and obesity, should be delivered routinely during consultations and asthma reviews. A range of social determinants that are linked to poverty impact on outcomes and the health of children with asthma[15].

Table 2. Asthma risk factors

Personal or family history of atopy - eczema, allergic rhinitis, nasal polyposis[16]
Family history of asthma[16]
Exposure to second hand smoke[16]
Preterm birth[17]
Low birth weight[18]
Obesity[19]
Poor housing quality/mould and dampness[6]
Air pollution [20]

PAEDIATRIC ASTHMA PHENOTYPES

Asthma is a heterogeneous disease in which there are several phenotypes and underlying endotypes. Phenotypes are subtypes of asthma that share clinical characteristics such as symptom triggers, atopic features, disease severity and response to treatment. Endotypes are subtypes of asthma that are characterised by similar underlying biological mechanisms[21].

Key endotypes include 'Type 2-high' and 'Type 2-low' asthma[22]. Identifying asthma phenotypes and endotypes can facilitate targeted treatment based on the pathophysiology occurring in a specific individual[23]. For example, allergic or eosinophilic asthma that frequently starts in childhood, is Type 2-high and characterised by eosinophilic airway inflammation, raised immunoglobulin (Ig) E and fractional exhaled nitric oxide (FeNO) levels[21]. Typically Type 2-high asthma responds well to inhaled corticosteroid (ICS) treatment[7]. A number of biologic agents can be used in the management of asthma, under specialist supervision, and their use varies on asthma endotypes (Table 8)[24].

DIFFERENTIAL DIAGNOSES AND DIAGNOSTIC UNCERTAINTY

Misdiagnosis of asthma remains a major problem with rates of both under- and over-diagnosis being high[25]. Overdiagnosis is problematic as it exposes children to unnecessary side effects of medications and runs the risk of trivialising asthma[7].

There are several conditions that may be associated with chronic cough, wheeze and/or shortness of breath in children and therefore present similarly to asthma (Table 3). Due to the difficulties with diagnosis, especially in young children where objective testing is not possible, the diagnosis of 'asthma' should be reviewed at each clinical presentation and interaction.

Table 3. Asthma differentials and clues in medical history

Differential diagnosis	Possible features of history
Cystic fibrosis[26, 27]	- Symptoms present from birth - Finger clubbing - Family History of cystic fibrosis or unexplained/atypical respiratory disease - Weight faltering - Gastrointestinal symptoms
Primary ciliary dyskinesia[27]	- Symptoms present from birth - Family history of unexplained respiratory symptoms - Persistent cough - Nasal symptoms
Chronic lung disease of prematurity/bronchopulmonary dysplasia[27]	- Premature
Bronchiectasis[26, 27]	- Persistent productive cough - Finger clubbing
Laryngeal dysfunction[27]	- Stridor

	- Abnormal cry
Gastro-oesophageal reflux disease or aspiration[26]	- Vomiting - Weight faltering - Recurrent infections
Structural abnormality - e.g. bronchomalacia, bronchogenic cyst[28]	- Present from birth - No variation to wheeze
Immunodeficiency[28]	- Weight faltering - Recurrent and/or atypical infections
Foreign body aspiration[28]	- Sudden onset - Unilateral chest features

DIAGNOSING ASTHMA IN CHILDREN

There is no single 'gold-standard' test that can be used to accurately diagnose asthma. In practice, a diagnosis should be made based on characteristic symptom patterns, evidence of variability in airflow limitation in the presence of airway inflammation, likelihood of alternative diagnoses and response to treatment. Getting the diagnosis correct is key for optimal management of paediatric asthma.

Lung function tests can be used to aid the diagnosis of asthma in children over the age of 5 years. Peak expiratory flow (PEF) and spirometry are commonly used to assess airflow obstruction and reversibility. PEF can be used to detect diurnal variation, which is a typical feature of asthma. The Global Initiative for Asthma (GINA) specifically recommends the use of either PEF or spirometry in the diagnosis of asthma in children over 5 years[29]. Once a child is old enough to reliably perform lung function testing it is recommended that this is undertaken if the diagnosis of asthma has not been previously confirmed. In children under 5 lung function testing is rarely practical outside a research setting. This makes diagnosis in this age group additionally challenging[17]. Guidelines vary between countries and regions with regard to diagnostic criteria. An overview of the

similarities and differences between these guidelines is displayed in Table 4. Lung function testing is frequently used to monitor progress of children with asthma as part of their care. Objective testing should be repeated if there is poor response to treatment or diagnostic uncertainty.

FeNO is used to detect and quantify eosinophilic airway inflammation with levels elevated in those with eosinophilic asthma[30]. Once staff are trained, and provided equipment is available, FeNO is a practically useful test that is quick to perform in school-aged children. The exact positioning of FeNO testing varies between guidelines worldwide (Table 4). FeNO monitoring may also be useful in titrating dosage of ICS in those with an established diagnosis of asthma.[31]

Allergy testing (skin prick testing or measurement of specific-IgE levels) is not routinely carried out in the diagnostic process; however, it is recommended in a number of clinical guidelines and may identify individual triggers[32-35].

There are several aspects that make paediatric asthma diagnosis challenging. Most diagnoses are made in primary care where there is often limited access to objective testing at present. Despite guideline recommendations objective testing is frequently only available in secondary or tertiary care settings where equipment and trained staff are available. The COVID-19 pandemic has served to exacerbate these issues and increase backlogs. Various solutions have been proposed, including community diagnostic hubs [36]. In some healthcare systems the cost of undergoing objective testing is a cause of health inequalities.

Additionally, the symptom onset for most cases of paediatric asthma occurs before the age of 3 years[37] when lung function testing cannot be used to aid diagnosis. In this age group, response to an asthma treatment trial is useful to aid diagnostic decision making and is recommended in a number of national guidelines[35, 38-40].

Table 4. Summary of paediatric asthma national guidelines – focusing on diagnosis.

Guideline	Year	Diagnostic criteria	Recommended objective testing	When to refer to a specialist	When to consider alternative diagnoses
NICE Guidelines (United Kingdom)[26]	2017	Under 5 years: Findings in clinical history and examination that are suggestive of asthma Over 5 years: Findings in clinical history and examination that are suggestive of asthma *and* either spirometry demonstrating obstructive airflow and bronchodilator reversibility *or* a FeNO level of 35 ppb or more	Over 5 years: Spirometry and bronchodilator reversibility *or* FeNO 1st line. Additional tests PEF, bronchial challenge test with histamine or methacholine	Children who are not responding to treatment and cannot complete objective testing If there is obstructive spirometry but negative bronchodilator reversibility and negative FeNO	When children have symptoms of asthma but normal objective testing results
Global Initiative for Asthma (Global)[29]	2021	6 years and over: Findings in clinical history that are suggestive of asthma *plus* evidence of variability in expiratory airflow limitation with either spirometry and bronchodilator reversibility, repeated PEF measurements, positive exercise challenge or positive bronchial challenge	6 years and over: Either spirometry, PEF, exercise challenge *or* bronchial challenge to detect variability in lung function	Diagnostic uncertainty, previous life threatening attack, no/poor response to asthma treatment	Atypical asthma features, atypical clinical examination findings - e.g. cardiac murmurs
Canadian Thoracic Society (Canada)[40]	2021	Aged 1-5 years: More than one presentation of asthma like symptoms *plus* a response to asthma treatment trial Over 6 years : Findings in clinical history that are suggestive of asthma *plus* spirometry showing obstructive expiration and demonstration of reversibility of airflow limitation of at least 12%	Over 6 years Spirometry and bronchodilator reversibility (1st line). Additional tests that may be useful - peak flow variability, bronchial challenge and exercise challenge	Diagnostic uncertainty, severe asthma, previous life threatening attack, need for allergy testing, any hospitalisation as a result of asthma	
National Asthma Council Australia (Australia)[38]	2021	Aged 1-5 years Findings in clinical history and examination that are suggestive of asthma *plus* a response to treatment trial with SABA and/or ICS 6 years and over Findings in clinical history and examination that are suggestive of asthma *plus* spirometry demonstration of reversibility of airflow limitation of at least 12%	Aged 1-5 years: None 6 years and over: Spirometry 1st line. Bronchial challenge test and exercise testing to be considered if spirometry results does not show a reversibility of airflow limitation of at least 12%	When child has characteristic asthma symptoms and diagnosis is not clear from objective testing results	Atypical asthma features No response to treatment trials Results of objective testing do not suggest asthma
ARF NZ (New	2020	Aged 1-11: Findings in clinical history that are suggestive of asthma *plus* a response to asthma treatment trial	Aged 5-11 years: Spirometry should be considered if asthma symptoms are atypical or in those with typical	When there is no response to asthma treatment trials	Atypical asthma features

Zealand)[39]			asthma symptoms that do not respond to a treatment trial	and/or there is diagnostic uncertainty	
Irish College of GPs (Ireland)[41]	2020	Under 6 years: Findings in clinical history that are suggestive of asthma Over 6 years: Findings in clinical history that are suggestive of asthma *plus* evidence of obstructive airflow limitation and reversibility with bronchodilators	Under 6 years: Treatment trial Over 6 years: PEF *or* spirometry.	Parental concern or request, failure to respond to treatment trial, failure to thrive, diagnostic uncertainty	
The Japanese Society of Allergology (Japan)[35]	2020	All ages: Findings in clinical history that are suggestive of asthma *plus* a response to asthma treatment trial	Lung function testing (non-specified), skin prick testing, bronchodilator reversibility testing, bronchial challenge	Poor response to multiple agent therapy or multiple courses of oral steroids	Atypical asthma features, no response to treatment trial or atypical results on objective testing
Int. Consensus on Ped. Asthma (Global)[33]	2015	Under 5 years: Findings in clinical history that are suggestive of asthma Over 5 years: Findings in clinical history that are suggestive of asthma *plus* spirometry with bronchodilator reversibility demonstration of reversibility of airflow limitation of at least 12%	Over 5 years: Spirometry 1st line. PEF is useful for aiding. FeNO and skin prick testing for detecting allergic asthma can be useful.		
GEMA (Spain)[32]	2009	Under 6 years: Findings in clinical history that are suggestive of asthma Over 6 years: Findings in clinical history that are suggestive of asthma *plus* spirometry with bronchodilator reversibility demonstration of reversibility of airflow limitation of at least 12%	6 years and over Spirometry with combined bronchodilator reversibility. FeNO and allergy testing may be useful if diagnosis is unclear		
Ministry of Health (Singapore)[34]	2008	All ages: Findings in clinical history and examination that are suggestive of asthma	No objective testing normally required for diagnosis. PEF at every consultation and spirometry at least annually in children over 6 years to assess asthma severity. Tests that may be considered - CXR to exclude foreign bodies and chronic LRTIs, skin prick testing to detect atopy and exercise testing to assess exercise induced asthma	High risk patients with poor control, young age and poor response to treatment trial, when requiring high doses of steroids to control symptoms	-

Resources, in terms of equipment and appropriately trained staff to perform testing in children are substantial limitations in primary care at present. Ideally PEF, spirometry and FeNO could be performed in primary care. With the addition of skin prick testing and blood work in secondary care and bronchial challenge and exercise testing reserved for tertiary care. Abbreviations: NICE: National Institute for Health and Care Excellence; FeNO: Fractional exhaled Nitric Oxide; ppb:

parts per billion; PEF: Peak Expiratory Flow; SABA: Short-Acting Beta Agonist; ICS: Inhaled CorticoSteroid; ICU: Intensive Care Unit; CXR: Chest X-Ray; LRTI: Lower Respiratory Tract Infection.

MANAGEMENT OF ASTHMA IN CHILDREN

The management of asthma is multifactorial and to optimise disease control a number of pharmacological, non-pharmacological and self-management aspects need to be considered.

1. Pharmacological management

The pharmacological management of asthma involves two key components; maintenance and reliever therapies. Maintenance therapies are the mainstay of asthma management and the treatment aim is that no reliever therapies are required. Use of reliever therapy suggests asthma control is poor.

An overview of maintenance and reliever therapies is outlined in Tables 5 and 6 respectively. A stepwise approach to asthma management is encouraged and pharmacological management varies on age, symptom control and the national guideline used. An overview of management approach in a number of national guidelines is summarised in Table 7.

GINA guidelines recommend dual ICS and short-acting beta-2 agonist (SABA) therapy to children over the age of 5[29]. SABA monotherapy was previously the main management starting point, however compared with combined treatment, SABA monotherapy has been shown to be associated with asthma mortality[42]. SABA monotherapy is now only recommended by GINA for use in children aged 5 or less[29]. As seen in Table 7, GINA recommends symptom-driven ICS use, compared to daily ICS use, as initial therapy in children over 6 years of age. In comparison to daily ICS use, symptom-driven use has demonstrated a similar exacerbation risk and reduces the risk of ICS adverse effects[43].

Single Maintenance and Reliever Therapy (SMART) inhalers are combined inhalers offering both maintenance and reliever therapy in those with asthma. These inhalers contain a number of maintenance and reliever therapies in different combinations. The

use of these inhalers have been shown to reduce the risk of asthma attacks and ED admissions[44], improve lung function and decrease the need for reliever therapy[45]. There is limited evidence in the effectiveness of SMART inhalers in children, however children over 12 years may be prescribed a SMART inhaler, which acts as both a maintenance and reliever therapy, if symptoms are not well controlled[46].

There are a number of biologic agents (Table 8) that may be used in the management of paediatric asthma. These are endotype-specific, targeted therapies that should be used only under the supervision of specialists. Their availability and cost varies between countries and different healthcare systems. Detailed appraisal of the evidence base for their use is provided in the individual management guidelines and has been recently reviewed[23].

Table 5. Maintenance therapies

Maintenance therapies	**Comments**
Inhaled corticosteroids (ICS)	Currently used as a first line maintenance agent in a number of national guidelines[26, 29, 39, 41]. When using ICS, the lowest possible dose to effectively control symptoms should be used to prevent possible adverse effects of reduced growth and risk of adrenal suppression.
Long-acting beta-2 agonists (LABA)	Used as an add on therapy when dual ICS and SABA (short-acting beta-2 agonists) therapy is ineffective. In comparison to SABA, bronchodilation duration is prolonged to 12 hours.
Leukotriene receptor antagonists (LTRA) (e.g. montelukast)	Used as an add on therapy in those who have poor symptom control despite ICS and LABA treatments[26, 29, 32, 35, 38, 40]. There have been a number of concerns raised regarding possible adverse

	reactions to montelukast. These include neuropsychiatric features ranging from poor sleep to suicidal ideation[47].
Long-acting muscarinic antagonists (LAMA) (e.g. tiotropium)	Used as an add on therapy in those who have poor symptoms control despite ICS and LABA therapies.
Oral theophylline	Used as an add on therapy, usually in those with uncontrolled symptoms despite several maintenance and reliever therapies. Monitoring of plasma level required on initiation of treatment and dose changes.
Biologics	Use as an add on therapy, under specialist care, in those who have poorly controlled symptoms despite being on several maintenance and reliever therapies. A number of biologic agents are available (Table 8). Various individual biologics have been shown to reduce attacks, improve lung function and reduce oral corticosteroid use[24].

Table 6. Reliever therapies

Reliever therapies	**Comments**
Short-acting beta-2 agonists (SABA)	Currently used as a first line reliever agent in a number of national guidelines. Effects of bronchodilation last for up to 4 hours. SABAs work by rapidly relaxing the smooth muscle of small airways, providing quick relief from asthma symptoms. Should be delivered via an age-appropriate spacer device or only if requiring supplemental oxygen via a nebuliser. Older children may be able to

	use a handheld device without a spacer if trained and deemed competent in using it effectively.
Oral corticosteroids	Used as a short-term therapy during asthma attacks to reduce airway inflammation and ease symptoms. Repeated short-term courses of oral steroids suggest poor chronic symptom control and should trigger a review of maintenance therapy.

2. Non-pharmacological management

Non-pharmacological aspects of asthma management include providing education on modifiable risk factors and comorbidities to caregivers and conducting annual asthma reviews to assess control and future risk.

Education is key to improving caregiver and child understanding of asthma and its management. Clear information regarding modifiable risk factors, such as smoke exposure, domestic pollutants and obesity, should be given. Short term educational interventions aimed to improve self-management have been shown to increase medication adherence[48], improve symptom control and reduce mortality[49].

All young people with asthma should have asthma reviews at least annually. These reviews should focus on current symptom control and management, previous attacks, triggers, modifiable risk factors and personal asthma action plans (PAAPs). Asthma reviews are opportunities to assess child and caregiver understanding of asthma and provide education if necessary. Annual asthma reviews are also opportunities to assess inhaler technique (including spacer use) and provide education on this if necessary. Poor inhaler technique is common in young people with asthma[50] and associated with poor disease control[51].

Taking time to understand the perceptions of young people and their caregivers in relation to their asthma diagnosis and management is important and exploring such perceptions may enhance engagement during consultations, subsequently improving outcomes for young people[52].

3. Self-management

Self-management aspects of paediatric asthma management include asthma education and PAAPs. PAAPs are written documents that are given to young people and/or caregivers that advise them on day to day asthma management and what to do in the event of an attack[53]. Action plans should be created with patient/caregiver input, shared with relevant individuals (e.g. school teachers) and should be reviewed and updated regularly. PAAPs have been shown to reduce ED attendance, missed school days and increase caregiver confidence when managing attacks[54]. The 2018 Annual Asthma Survey found that over 50% of children with asthma in the United Kingdom had no PAAP and around 20% of caregivers did not seek medical advice during acute asthma attacks, highlighting large gaps in education[55].

Diet and exerice are additional important self-management aspects within paediatric asthma care. A number of short term exercise interventions have demonstrated improvements in lung fuction and symptom control[56]. Healthy eating interventions can help reduce BMI and improve the quality of life of both young people and their caregivers[57].

Table 7. Summary of paediatric asthma national guidelines – focusing on management

Guideline	Year	1st line management	Add on therapies*	Treatment withdrawal
NICE Guidelines (United Kingdom)[26]	2017	Aged 1-4 years SABA monotherapy Aged 5-16 years SABA monotherapy	Aged 1-4 years: 2nd line: low dose ICS; 3rd line: low dose ICS and LTRA; 4th line: referral for specialist management Aged 5-16 years: 2nd line: low dose ICS; 3rd line: low dose ICS and LTRA; 4th line: low dose ICS and LABA; 5th line: high dose ICS and LABA; 6th line - referral for specialist management	Consider withdrawing maintenance treatment after 3 months of stable asthma. Only consider stopping ICS on those who are on ICS monotherapy
Global Initiative for Asthma (Global)[29]	2021	5 years and under SABA monotherapy 6-11 years Combined low dose ICS+SABA (as needed) Adolescents Combined low dose ICS+SABA	5 years and under: 2nd line: low dose ICS; 3rd line: medium dose ICS *or* low dose ICE and LTRA; 4th line: refer for expert advice Aged 6-11 years: 2nd line: low dose ICS; 3rd line: low dose ICS and LABA *or* medium dose ICS *or* daily SMART combined ICS/LABA. Refer for expert advice; 4th line: refer for phenotype assessment Adolescents: 2nd line: low dose ICS; 3rd line: medium dose ICS; 4th line: medium/high dose ICS +/- LAMA. Refer for phenotype assessment	Stepping down treatment should be considered when both asthma symptoms and lung function have been stable for a period of 3 months or more
Canadian Thoracic Society (Canada)[40]	2021	Aged 1-5 years SABA monotherapy Aged 6 -11 SABA monotherapy Age 12+ SABA monotherapy	Aged 1-5 years: 2nd line – ICS and LTRA; 3rd line - high dose ICS and LTRA; 4th line - referral for specialist management Aged 6 -11: 2nd line - ICS and LTRA; 3rd line: high dose ICS and LTRA; 4th line: high dose ICS, LTRA and LABA; 5th line: high dose ICS, LTRA, LABA and oral steroids Age 12+: 2nd line: ICS and LTRA; 3rd line: ICS, LTRA and LABA; 4th line: high dose ICS, LTRA, LABA and tiotropium	After asthma has been well controlled for a period of 3-6 months
National Asthma Council Australia [38]	2021	Aged 1-5 years SABA monotherapy Aged 6 and over SABA monotherapy	Age 1-5 years: 2nd line: low dose ICS *or* LTRA; 3rd line: low dose ICS and LTRA; 4th line: referral for specialist management Age 6 and over: 2nd line: low dose ICS *or* LTRA; 3rd line: low dose ICS and LTRA *or* high dose ICS *or* ICS/LABA combination; 4th line: referral for specialist management	Step down of treatment should be considered when symptoms have been well controlled for a period of at least 6 months
Asthma and Respiratory Foundation NZ (New Zealand)[39]	2020	Aged 1-4 years SABA and low dose ICS Aged 5-11 years SABA monotherapy	Age 1-4 years: 2nd line: low dose ICS and LTRA; 3rd line: referral for specialist management Age 5-11 years: 2nd line: SABA and low dose ICS; 3rd line: LABA and low dose ICS; 4th line: LABA, high dose ICS, LTRA and referral for specialist management	If child has been stable for 3 months or more on treatment, step down with an incremental approach
Irish College of General Practitioners (Ireland)[41]	2020	Aged 6-11 ICS and SABA (ICS only to be taken when SABA is used as a reliever)	Aged 6-11: 2nd line: low dose ICS *or* LTRA (if ICS is not appropriate); 3rd line: low dose ICS and LABA *or* high dose ICS; 4th line: medium dose ICS, LABA and referral to paediatrics for management advice; 5th line: refer to paediatrics for phenotype assessment	

		Adolescents ICS and SABA (ICS only to be taken when SABA is used as a reliever)	Adolescents: 2nd line: low dose ICS; 3rd line: low dose ICS and LABA; 4th line: medium dose ICS and LABA *or* low dose ICS, LABA and LAMA; 5th line: refer to paediatrics for phenotype assessment	
The Japanese Society of Allergology (Japan)[35]	2020	Aged 1-5 years SABA monotherapy Aged 6-15 years SABA monotherapy	Age 1-5 years: 2nd line: low dose ICS *or* LTRA or Disodium cromoglycate (DSCG); 3rd line: medium dose ICS; 4th line: high dose ICS and LTRA Age 6-15 years: 2nd line: low dose ICS *or* LTRA; 3rd line: medium dose ICS *or* combined low dose ICS/LABA; 4th line: high dose ICS *or* combined medium dose ICS/LABA	-
International Consensus on Pediatric Asthma (Global)[33]	2015	Quotes GINA and NICE guidelines	Quotes GINA and NICE guidelines	
GEMA (Spain)[32]	2009	Aged 3 and under SABA monotherapy Aged 3 and over SABA monotherapy	Aged 3 and under: 2nd line: low dose ICS *or* LTRA; 3rd line: moderate dose ICS *or* low dose ICS and LTRA; 4th line: moderate dose ICS and LTRA; 5th line: high dose ICS and LTRA. Consider adding LABA; 6th line: oral steroids Aged 3 and under: 2nd line: low dose ICS *or* LTRA; 3rd line: moderate dose ICS or low dose ICS and LTRA *or* low dose ICS and LABA; 4th line: moderate dose ICS and LTRA *or* moderate dose ICS and LABA; 5th line: high dose ICS and LABA. Consider adding LTRA and theophyllines; 6th line: consider oral steroids and omalizumab	
Ministry of Health (Singapore)[34]	2008	No stepwise approach outlined	No stepwise approach outlined	Consider stepping down treatment when symptoms are stable for 3 to 6 months considering the child's risk of poor outcomes. Do not stop ICS
South African Thoracic Society (South Africa)[58]	2007	Adolescents SABA + low dose ICS	Adolescents : 2nd line: LABA and ICS; 3rd line: LABA, low dose ICS and LTRA/LABA *or* high dose ICS or LABA, low dose ICS and theophyllines. Consider oral corticosteroids; 4th line: referral to specialist	-

*SABA reliever therapy as required at any stage

Abbreviations: SABA: Short-Acting Beta Agonist; ICS: Inhaled CorticoSteroid; LTRA: LeukoTriene Receptor Antagonist; LABA: Long-Acting Beta Agonist; LAMA: Long-Acting Muscarinic Antagonists

Table 8. Biologic agents used in the management of asthma

Biologic	Route and frequency	Mechanism of action	Effect on asthma symptoms*	Effect on attacks and mortality*	Safety concerns/Common adverse reactions*
Omalizumab	S/C injection every 4 weeks	$IgG1_K$ antibody that binds to the Fc portion of IgE, resulting in the inability of IgE to bind to the IgE receptor on mast cells[59]. This reduces the concentration of free circulating IgE and consequently mast cell degranulation[60]	Improved asthma symptoms[61]	Reduce asthma attacks[61, 62]	Mild injection site reactions, headache, pyrexia, abdominal pain, gastroenteritis and nasopharyngitis[63]
Dupilumab	S/C injection every 2 weeks	Binds to alpha component of IL-4 receptor blocking IL-4 and IL-13 stimulation of B-cells[64]	Improved asthma symptoms and quality of life[65]	Reduced asthma attacks[66]	Mild injection site reactions and eosinophilia[66]
Mepolizumab	S/C injection every 4 weeks	Binds to IL-5 cytokines resulting in reduced peripheral eosinophilia and reduced airway inflammation[67]	Improved asthma symptoms and quality of life[68]	Reduced asthma attacks[68, 69]	Headache, attack of asthma symptoms and bronchitis[70, 71]
Reslizumab	IV infusion every 4 weeks	Binds to IL-5 cytokines resulting in reduced peripheral eosinophilia and reduced airway inflammation[67]	Improved asthma symptoms and quality of life[72]	Reduced asthma attacks[72]	Attack of asthma symptoms, nasopharyngitis and upper respiratory tract infections[73]
Benralizumab	S/C injection every 4 weeks for the first 3 doses and then every 8 weeks	Binds to alpha component of IL-5 receptor resulting in reduced eosinophil activation from IL-5[74]	Improved asthma symptoms and quality of life[75]	Reduced asthma attacks[75]	Headache, sinusitis, nasopharyngitis and pyrexia[75]

*Detailed appraisal of the evidence base for their use is provided in the individual management guidelines and has been recently reviewed[23].

Withdrawing management/stepping down

Asthma control should be reviewed at every medical contact. When asthma symptoms are well controlled on pharmacological therapy, stopping or stepping down medication should be considered to protect young people from unnecessary adverse effects.

The GINA 2021 guidelines advise that clinicians should consider stepping down asthma management to the lowest effective treatment regimen when good symptom control has been achieved for at least 3 months[29]. When stepping down treatment an individualised risk-benefit approach should be taken with focus on the child's medical history including frequency of oral corticosteroid use, frequency of asthma attacks and previous intensive or high dependency care admissions[76].

WHEN TO REFER TO A SPECIALIST

Most paediatric asthma cases are diagnosed in primary care without the input of general paediatricians or paediatric respiratory physicians[6]. However, a number of children with asthma may need to be referred to specialists for diagnostic or management input. Common indications for specialist referral include no or poor response to asthma treatments, inconclusive objective testing, poor symptom control with appropriate treatment, frequent oral corticosteroid use or the occurrence of a severe asthma attack[26, 29, 35, 38, 39, 41]. A key element of specialist care is a multidisciplinary team consisting of a number of professionals, including specialist nurses, psychologists, physiologists and pharmacists.

Health care professionals must consider any safeguarding implications at all paediatric asthma reviews as part of delivering holistic care. Unexplained or frequent ‘do not attend’ appointments or suspicion of poor medical management at home should be flagged and acted upon locally.

PREDICTORS OF LIFE-THREATENING ATTACKS

The following features have been shown to increase the likelihood of future severe attacks and particular attention should be given to these factors during asthma reviews.

1. Previous attack: The strongest risk factor for a future asthma attack is a personal history of a previous attack. One large systematic review and meta-analysis found that children with a recent history of ED attendance with an asthma attack were up to 5.8 times more likely to have another ED attendance and up to 3 times more likely to be admitted to hospital with a future asthma attack[77].

2. Frequent SABA use and prescription requests: Frequent use of SABA reliever therapy suggests poor control of asthma symptoms. If asthma symptoms are well controlled, no more than two SABA inhalers should be required annually[78]. The UK NRAD found that excess SABA prescription and use was prominent in individuals who died of asthma attacks. For those with data available, around 40% had been prescribed 12 or more SABA inhalers in the 12 months before death[6].

POST-ATTACK REVIEW

Asthma attacks should be viewed as never events. It is essential that a post-attack review is conducted to review asthma maintenance treatment, as this is likely to be suboptimal. Failure to review patients post-attack, and alter treatment where appropriate, is likely to predispose to future attacks, which could be life-threatening. Management of the current attack should be reviewed to ensure treatment is appropriate and symptoms are resolving. Some individuals may require additional courses of oral corticosteroids to settle symptoms[7].

Current NICE quality standards (UK) state that all individuals hospitalised with an asthma attack should receive a follow up review in primary care within 2 working days of

discharge[26], to review maintenance management and ensure resolution of symptoms. However, the 2018 National Asthma Survey completed in the UK found that 64% of respondents had no primary care follow up post-attack and most patients were not aware that this was required[55].

Salbutamol weaning

Salbutamol weaning plans are commonly used by a number of healthcare organisations following discharge after an asthma attack. These plans direct caregivers to provide regular SABA therapy, often in a reducing regime, in the days following discharge. There have been a number of concerns raised with regards to these plans with some believing that providing regular SABA therapy may potentially mask deterioration and could delay care givers seeking medical advice[79]. Healthcare professionals should enquire about salbutamol weaning plans during post-attack reviews and urge caregivers to seek medical advice if they have concerns or the effects of SABA are not lasting the 4 hours of duration.

FUTURE DEVELOPMENTS IN CARE

The management of paediatric asthma is changing over time with, just as two examples, developments in technology and service structure.

1. Technology. The growing use of technology in asthma care has huge potential to improve clinical outcomes. Smartphone applications can be used to provide medication reminders to users and this has been shown to increase ICS adherence[80]. Applications can also be used to provide educational content to young people and care givers[81], as well as store personal asthma action plans[82]. ‘Smart’ inhalers, not to be confused with SMART inhalers, are devices that can provide audio reminders to users and record when they are used. One paediatric study found that

the use of 'smart' inhalers increased treatment adherence to 84%, compared to 30% in the control group[83].

2. Diagnostic hubs. In the UK, regional diagnostic hubs for asthma care have been recommended in NHS England's Long Term Plan[84]. Implementation of diagnostic hubs is hoped to result in earlier and more accurate asthma diagnoses by improving access to objective testing and specialised interpretation. Hubs are designed to improve asthma outcomes by enabling most appropriate treatment initiation and monitoring. There is currently no evidence in the literature of the clinical effects of diagnostic hubs being used in the management of paediatric asthma.

CONCLUSIONS

Paediatric asthma outcomes are currently poor and many deaths are preventable. The aim should be to avoid asthma attacks occurring with appropriate maintenance therapy and they should be viewed as never events. In order to improve outcomes, accurate diagnosis and management are essential. Good asthma care extends beyond providing medication and should include education, as well as supported self-management advice. The use of PAAPs remains poor and a significant number of young people with asthma do not have one. Post-attack asthma reviews are a key opportunity to review maintenance medication and current symptom control.

KEY MESSAGES

1. Paediatric asthma outcomes are poor and many deaths are preventable
2. Diagnosing asthma in childhood can be challenging and the diagnosis should be reviewed during follow up to ensure it is correct
3. Asthma attacks should be viewed as never events. Post-attack reviews are essential to optimise maintenance therapy and prevent future attacks
4. Education is key to improving asthma outcomes
5. Personalised Asthma Action Plans are essential and a significant number of children with asthma do not have one

COMPETING INTERESTS

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