

# Diagnosis and management of asthma in children

Joanne Martin,<sup>1,2,3</sup> Jennifer Townshend,<sup>4</sup> Malcolm Brodrie <sup>1,4</sup>

**To cite:** Martin J, Townshend J, Brodrie M. Diagnosis and management of asthma in children. *BMJ Paediatrics Open* 2022;**6**:e001277. doi:10.1136/bmjpo-2021-001277

JT and MB contributed equally.

Received 1 March 2022

Accepted 13 April 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

<sup>1</sup>Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK

<sup>2</sup>Northern Foundation School, Health Education England North East, Newcastle upon Tyne, UK

<sup>3</sup>James Cook University Hospital, South Tees NHS Foundation Trust, Middlesbrough, UK

<sup>4</sup>Paediatric Respiratory Medicine, Great North Children's Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK

## Correspondence to

Dr Malcolm Brodrie; malcolm.brodrie@newcastle.ac.uk

## ABSTRACT

Asthma is the most common 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 overdiagnosis and underdiagnosis 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 aimed 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 healthcare 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.<sup>1</sup>

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.<sup>2</sup> Caregivers also experience missed work days and financial challenges as a result.<sup>3</sup> Some children will experience severe symptoms and life-threatening attacks.<sup>4</sup>

Taking the UK as an example, paediatric asthma outcomes are poor overall with considerable associated morbidity and high rates of emergency hospital admissions, and most pertinently, there are several preventable

## Key messages

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

deaths each year.<sup>5</sup> Alarming, 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.<sup>6</sup>

There are several factors that make the diagnosis and management of asthma in children challenging. The aim of this review was 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.<sup>7</sup> 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.<sup>8</sup> Additionally, disease phenotypes are not fixed and may evolve over time, necessitating ongoing review of symptoms and treatment.<sup>9</sup>

**Box 1 Common asthma triggers**

- ▶ Viral respiratory tract infections<sup>6</sup>
- ▶ Exercise<sup>6 59</sup>
- ▶ Weather changes in temperature and humidity<sup>6 59</sup>
- ▶ Domestic pollutants (eg, pests, mould and dust mites)<sup>6</sup>
- ▶ Environmental pollutants (eg, air pollution)<sup>6</sup>
- ▶ Secondhand smoke exposure<sup>13 59</sup>
- ▶ Pets and animals<sup>13</sup>
- ▶ Strong odours<sup>13</sup>
- ▶ Anxiety or strong emotions<sup>59</sup>
- ▶ Drugs (eg, non-steroidal anti-inflammatory drugs and beta blockers)<sup>59</sup>
- ▶ Gastro-oesophageal reflux<sup>59</sup>

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.<sup>10</sup>

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, but 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.<sup>11</sup> 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.<sup>12</sup> 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,<sup>13</sup> but there are a number of other known triggers (box 1), including aeroallergens, secondhand 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.

**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 box 2. Education

**Box 2 Asthma risk factors**

- ▶ Personal or family history of atopy: eczema, allergic rhinitis or nasal polyposis<sup>60</sup>
- ▶ Family history of asthma<sup>60</sup>
- ▶ Exposure to secondhand smoke<sup>60</sup>
- ▶ Preterm birth<sup>21</sup>
- ▶ Low birth weight<sup>61</sup>
- ▶ Obesity<sup>62</sup>
- ▶ Poor housing quality/mould and dampness<sup>6</sup>
- ▶ Air pollution<sup>63</sup>

on modifiable risk factors, for example, exposure to secondhand smoke or air pollution 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.<sup>14</sup>

**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.<sup>15</sup>

Key endotypes include ‘type 2-high’ and ‘type 2-low’ asthma.<sup>16</sup> Identifying asthma phenotypes and endotypes can facilitate targeted treatment based on the pathophysiology occurring in a specific individual.<sup>17</sup> For example, allergic or eosinophilic asthma that frequently starts in childhood is type 2-high and is characterised by eosinophilic airway inflammation, raised IgE and fractional exhaled nitric oxide (FeNO) levels.<sup>15</sup> Typically, type 2-high asthma responds well to inhaled corticosteroid (ICS) treatment.<sup>7</sup> 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).<sup>18</sup>

**DIFFERENTIAL DIAGNOSES AND DIAGNOSTIC UNCERTAINTY**

Misdiagnosis of asthma remains a major problem with rates of both underdiagnosis and overdiagnosis being high.<sup>19</sup> Overdiagnosis is problematic as it exposes children to unnecessary side effects of medications and runs the risk of trivialising asthma.<sup>7</sup>

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 1). 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 1** Asthma differentials and clues in medical history

Differential diagnosis	Possible features of history
Cystic fibrosis <sup>49 64</sup>	<ul style="list-style-type: none"> <li>▶ Symptoms present from birth.</li> <li>▶ Finger clubbing.</li> <li>▶ Family history of cystic fibrosis or unexplained/atypical respiratory disease.</li> <li>▶ Weight faltering.</li> <li>▶ Gastrointestinal symptoms.</li> </ul>
Primary ciliary dyskinesia <sup>64</sup>	<ul style="list-style-type: none"> <li>▶ Symptoms present from birth.</li> <li>▶ Family history of unexplained respiratory symptoms.</li> <li>▶ Persistent cough.</li> <li>▶ Nasal symptoms.</li> </ul>
Chronic lung disease of prematurity/bronchopulmonary dysplasia <sup>64</sup>	<ul style="list-style-type: none"> <li>▶ Premature.</li> </ul>
Bronchiectasis <sup>49 64</sup>	<ul style="list-style-type: none"> <li>▶ Persistent productive cough.</li> <li>▶ Finger clubbing.</li> </ul>
Laryngeal dysfunction <sup>64</sup>	<ul style="list-style-type: none"> <li>▶ Stridor.</li> <li>▶ Abnormal cry.</li> </ul>
Gastro-oesophageal reflux disease or aspiration <sup>49</sup>	<ul style="list-style-type: none"> <li>▶ Vomiting.</li> <li>▶ Weight faltering.</li> <li>▶ Recurrent infections.</li> </ul>
Structural abnormality, for example, bronchomalacia and bronchogenic cyst <sup>65</sup>	<ul style="list-style-type: none"> <li>▶ Present from birth.</li> <li>▶ No variation to wheeze.</li> </ul>
Immunodeficiency <sup>65</sup>	<ul style="list-style-type: none"> <li>▶ Weight faltering.</li> <li>▶ Recurrent and/or atypical infections.</li> </ul>
Foreign body aspiration <sup>65</sup>	<ul style="list-style-type: none"> <li>▶ Sudden onset.</li> <li>▶ Unilateral chest features.</li> </ul>

### 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.<sup>20</sup> Once a child is old enough to reliably perform lung function testing, it is recommended that this be 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.<sup>21</sup> 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 2](#). 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.<sup>22</sup> 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 2](#)). FeNO monitoring may also be useful in titrating dosage of ICS in those with an established diagnosis of asthma.<sup>23</sup>

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.<sup>24–27</sup>

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.<sup>28</sup> 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<sup>29</sup> 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.<sup>27 30–32</sup>

### 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.

#### 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 3 and 4](#), 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

**Table 2** 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 (UK) <sup>49</sup>	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 <i>and</i> either spirometry demonstrating obstructive airflow and bronchodilator reversibility <i>or</i> a FeNO level of 35 ppb or more	Over 5 years: Spirometry and bronchodilator reversibility <i>or</i> FeNO first line. Additional tests, PEF, bronchial challenge test with histamine or methacholine	Children who are not responding to treatment and/or 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) <sup>20</sup>	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 <i>or</i> 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, for example, cardiac murmurs
Canadian Thoracic Society (Canada) <sup>32</sup>	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 (first 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) <sup>30</sup>	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 first line Bronchial challenge test and exercise testing to be considered if spirometry results do 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 Zealand) <sup>31</sup>	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

Continued

Table 2 Continued

Guideline	Year	Diagnostic criteria	Recommended objective testing	When to refer to a specialist	When to consider alternative diagnoses
Irish College of GPs (Ireland) <sup>50</sup>	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) <sup>27</sup>	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
International Consensus on Pediatric Asthma (global) <sup>25</sup>	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 first line PEF is useful for aiding. FeNO and skin prick testing for detecting allergic asthma can be useful.		
GEMA (Spain) <sup>24</sup>	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) <sup>26</sup>	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.

CXR, chest X-ray; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; LRTI, lower respiratory tract infection; NICE, National Institute for Health and Care Excellence; PEF, peak expiratory flow; ppb, parts per billion; SABA, short-acting beta agonist.

management approach in a number of national guidelines is summarised in [table 5](#).

GINA guidelines recommend dual ICS and short-acting beta-2 agonist (SABA) therapy to children over the age of 5.<sup>20</sup> 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.<sup>33</sup> SABA monotherapy is now only recommended by GINA for use in children aged 5 or less.<sup>20</sup> As seen in [table 5](#), GINA recommends symptom-driven ICS use, compared with daily ICS use, as initial therapy in children over 6 years of

**Table 3** Maintenance therapies

Maintenance therapies	Comments
ICS	Currently used as a first-line maintenance agent in a number of national guidelines <sup>20 31 49 50</sup> ; 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.
LABA	Used as an add-on therapy when dual ICS and SABA therapy is ineffective. In comparison to SABA, bronchodilation duration is prolonged to 12 hours.
Leucotriene receptor antagonists (eg, montelukast)	Used as an add-on therapy in those who have poor symptom control despite ICS and LABA treatments <sup>20 24 27 30 32 49</sup> . 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. <sup>66</sup>
Long-acting muscarinic antagonists (eg, 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 6). Various individual biologics have been shown to reduce attacks, improve lung function and reduce oral corticosteroid use. <sup>18</sup>

ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonists; SABA, short-acting beta-2 agonist.

age. In comparison to daily ICS use, symptom-driven use has demonstrated a similar exacerbation risk and reduces the risk of ICS adverse effects.<sup>34</sup>

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 emergency department (ED) admissions,<sup>35</sup> improve lung function and decrease the need for reliever therapy.<sup>36</sup> There is limited evidence in the effectiveness of SMART inhalers in children, but 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.<sup>37</sup>

There are a number of biologic agents (table 6) 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 vary 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.<sup>17</sup>

### 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

**Table 4** Reliever therapies

Reliever therapies	Comments
SABAs	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.

SABA, short-acting beta-2 agonist.

**Table 5** Summary of paediatric asthma national guidelines: focusing on management

Guideline	Year	First-line management	Add-on therapies*	Treatment withdrawal
NICE Guidelines (UK) <sup>49</sup>	2017	Aged 1–4 years: SABA monotherapy Aged 5–16 years: SABA monotherapy	Aged 1–4 years: second line: low-dose ICS, third line: low-dose ICS and LTRA, fourth line: referral for specialist management Aged 5–16 years: second line: low-dose ICS, third line: low-dose ICS and LTRA, fourth line: low-dose ICS and LABA; fifth line: high-dose ICS and LABA; sixth 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.
GINA (global) <sup>20</sup>	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: second line: low-dose ICS, third line: medium-dose ICS or low-dose ICE and LTRA, fourth line: refer for expert advice Aged 6–11 years: second line: low-dose ICS; third line: low-dose ICS and LABA or medium-dose ICS or daily SMART combined ICS/LABA; refer for expert advice; fourth line: refer for phenotype assessment Adolescents: second line: low-dose ICS; third line: medium-dose ICS; fourth line: medium-dose/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) <sup>32</sup>	2021	Aged 1–5 years: SABA monotherapy Aged 6–11: SABA monotherapy Age 12+: SABA monotherapy	Aged 1–5 years: second line: ICS and LTRA, third line: high-dose ICS and LTRA, fourth line: referral for specialist management Aged 6–11: second line: ICS and LTRA; third line: high-dose ICS and LTRA; fourth line: high-dose ICS, LTRA and LABA; fifth line: high-dose ICS, LTRA, LABA and oral steroids Age 12+: second line: ICS and LTRA; third line: ICS, LTRA and LABA; fourth 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 <sup>30</sup>	2021	Age 1–5 years: SABA monotherapy Aged six and over: SABA monotherapy	Age 1–5 years: second line: low-dose ICS or LTRA; third line: low-dose ICS and LTRA; fourth line: referral for specialist management Age 6 and over: second line: low-dose ICS or LTRA; third line: low-dose ICS and LTRA or high-dose ICS or ICS/LABA combination; fourth 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) <sup>31</sup>	2020	Aged 1–4 years: SABA and low-dose ICS Aged 5–11 years: SABA monotherapy	Age 1–4 years: second line: low-dose ICS and LTRA, third line: referral for specialist management Age 5–11 years: second line: SABA and low-dose ICS; third line: LABA and low-dose ICS; fourth line: LABA, high dose ICS, LTRA and referral for specialist management	If the child has been stable for 3 months or more on treatment, step-down with an incremental approach.
Irish College of General Practitioners (Ireland) <sup>50</sup>	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: second line: low-dose ICS or LTRA (if ICS is not appropriate); third line: low-dose ICS and LABA or high dose ICS; fourth line: medium-dose ICS, LABA and referral to paediatrics for management advice; fifth line: refer to paediatrics for phenotype assessment Adolescents: second line: low-dose ICS; third line: low-dose ICS and LABA; fourth line: medium-dose ICS and LABA or low dose ICS, LABA and LAMA; fifth line: refer to paediatrics for phenotype assessment	
The Japanese Society of Allergology (Japan) <sup>27</sup>	2020	Age 1–5 years: SABA monotherapy Age 6–15 years: SABA monotherapy	Age 1–5 years: second line: low-dose ICS or LTRA or disodium cromoglycate, third line: medium-dose ICS, fourth line: high dose ICS and LTRA Age 6–15 years: second line: low-dose ICS or LTRA, third line: medium-dose ICS or combined low-dose ICS/LABA, fourth line: high-dose ICS or combined medium dose ICS/LABA	–

Continued



Table 5 Continued

Guideline	Year	First-line management	Add-on therapies*	Treatment withdrawal
International Consensus on Paediatric Asthma (global) <sup>25</sup>	2015	Quotes GINA and NICE guidelines	Quotes GINA and NICE guidelines	
GEMA (Spain) <sup>24</sup>	2009	Age 3 and under: SABA monotherapy Age 3 and over: SABA monotherapy	Age 3 and under: second line: low-dose ICS or LTRA; third line: moderate-dose ICS or low-dose ICS and LTRA; fourth line: moderate-dose ICS and LTRA; fifth line: high-dose ICS and LTRA; consider adding LABA; sixth line: oral steroids Age 3 and under: second line: low-dose ICS or LTRA; third line: moderate-dose ICS or low dose ICS and LTRA or low dose ICS and LABA; fourth line: moderate-dose ICS and LTRA or moderate-dose ICS and LABA; fifth line: high-dose ICS and LABA; consider adding LTRA and theophyllines; sixth line: consider oral steroids and omalizumab	
Ministry of Health (Singapore) <sup>26</sup>	2008	No stepwise approach outlined	No stepwise approach outlined	Consider stepping down treatment when symptoms are stable for 3–6 months considering the child's risk of poor outcomes. Do not stop ICS.
South African Thoracic Society (South Africa) <sup>67</sup>	2007	Adolescents: SABA +low-dose ICS	Adolescents : second line: LABA and ICS; third line: LABA, low-dose ICS and LTRA/LABA or high dose ICS or LABA, low dose ICS and theophyllines. Consider oral corticosteroids; fourth line: referral to specialist	-

\*SABA reliever therapy as required at any stage.

GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; LTRA, leucotriene receptor antagonist; NICE, National Institute for Health and Care Excellence; SABA, short-acting beta agonist; SMART, single maintenance and reliever therapy.

medication adherence,<sup>38</sup> improve symptom control and reduce mortality.<sup>39</sup>

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<sup>40</sup> and associated with poor disease control.<sup>41</sup>

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.<sup>42</sup>

### 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.<sup>43</sup> Action plans should be created with patient/caregiver input, shared with relevant individuals (eg, school teachers) and should be reviewed and updated regularly. PAAPs have been shown to reduce ED attendance and missed school days and to increase caregiver confidence when managing attacks.<sup>44</sup> The 2018 Annual Asthma Survey found that over 50% of children with asthma in the UK had no PAAP, and around 20% of caregivers did not seek medical advice during acute asthma attacks, highlighting large gaps in education.<sup>45</sup>

Diet and exercise are additional important self-management aspects within paediatric asthma care. A number of short-term exercise interventions have demonstrated improvements in lung function and symptom control.<sup>46</sup> Healthy eating interventions can help reduce body mass index and improve the quality of life of both young people and their caregivers.<sup>47</sup>

### Withdrawing management/stepping down

Asthma control should be reviewed at every medical contact. When asthma symptoms are well controlled on

**Table 6** 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	Subcutaneous injection every 4 weeks	IgG1 <sub>k</sub> antibody that binds to the Fc portion of IgE, resulting in the inability of IgE to bind to the IgE receptor on mast cells. <sup>68</sup> This reduces the concentration of free circulating IgE and consequently mast cell degranulation. <sup>69</sup>	Improved asthma symptoms <sup>70</sup>	Reduced asthma attacks <sup>70,71</sup>	Mild injection site reactions, headache, fever, abdominal pain, gastroenteritis and nasopharyngitis <sup>72</sup>
Dupilumab	Subcutaneous injection every 2 weeks	Binds to alpha component of IL-4 receptor blocking IL-4 and IL-13 stimulation of B-cells <sup>73</sup>	Improved asthma symptoms and quality of life <sup>74</sup>	Reduced asthma attacks <sup>75</sup>	Mild injection site reactions and eosinophilia <sup>75</sup>
Mepolizumab	Subcutaneous injection every 4 weeks	Binds to IL-5 cytokines resulting in reduced peripheral eosinophilia and reduced airway inflammation <sup>76</sup>	Improved asthma symptoms and quality of life <sup>77</sup>	Reduced asthma attacks <sup>77,78</sup>	Headache, attack of asthma symptoms and bronchitis <sup>79,80</sup>
Reslizumab	Intravenous infusion every 4 weeks	Binds to IL-5 cytokines, resulting in reduced peripheral eosinophilia and reduced airway inflammation <sup>76</sup>	Improved asthma symptoms and quality of life <sup>81</sup>	Reduced asthma attacks <sup>81</sup>	Attack of asthma symptoms, nasopharyngitis and upper respiratory tract infections <sup>82</sup>
Benralizumab	Subcutaneous injection every 4 weeks for the first three doses and then every 8 weeks	Binds to alpha component of IL-5 receptor, resulting in reduced eosinophil activation from IL-5 <sup>83</sup>	Improved asthma symptoms and quality of life <sup>84</sup>	Reduced asthma attacks <sup>84</sup>	Headache, sinusitis, nasopharyngitis and fever <sup>84</sup>

\*Detailed appraisal of the evidence base for their use is provided in the individual management guidelines and has been recently reviewed.<sup>17</sup> IL, interleukin.

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.<sup>20</sup> 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.<sup>48</sup>

### 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.<sup>6</sup> 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.<sup>20 27 30 31 49 50</sup> A key element of specialist care is a multidisciplinary team consisting of a number of professionals, including specialist nurses, psychologists, physiologists and pharmacists.

Healthcare 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 on 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 three times more likely to be admitted to the hospital with a future asthma attack.<sup>51</sup>
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.<sup>52</sup> The UK NRAD found that excess SABA prescription and use were 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.<sup>6</sup>

### POSTATTACK REVIEW

Asthma attacks should be viewed as never events. It is essential that a postattack review is conducted to review asthma maintenance treatment, as this is likely to be suboptimal. Failure to review patients post attack, and to 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.<sup>7</sup>

Current NICE quality standards (UK) state that all individuals hospitalised with an asthma attack should receive a follow-up review in primary care within two working days of discharge,<sup>49</sup> 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.<sup>45</sup>

### 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 regard to these plans with some believing that providing regular SABA therapy may potentially mask deterioration and could delay caregivers seeking medical advice.<sup>53</sup> Healthcare professionals should enquire about salbutamol weaning plans during postattack 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.<sup>54</sup> Applications can also be used to provide educational content to young people and caregivers,<sup>55</sup> as well as store PAAPs.<sup>56</sup> ‘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 with 30% in the control group.<sup>57</sup>

2. Diagnostic hubs. In the UK, regional diagnostic hubs for asthma care have been recommended in NHS England's Long Term Plan.<sup>58</sup> 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 limited and a significant number of young people with asthma do not have one. Postattack asthma reviews are a key opportunity to review maintenance medication and current symptom control.

**Contributors** All authors conceived the ideas for the article. JM wrote the first draft that was then commented on by JT and MB.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** MB received investigator-led research grants from Pfizer and Roche Diagnostics; speaker fees paid to Newcastle University from Novartis, Roche Diagnostics and TEVA; and travel expenses to educational meetings Boehringer Ingelheim and Vertex Pharmaceuticals.

**Patient consent for publication** Not applicable.

**Ethics approval** Not applicable.

**Provenance and peer review** Commissioned; externally peer reviewed.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

## ORCID ID

Malcolm Brodli <http://orcid.org/0000-0003-4591-8299>

## REFERENCES

- Zar HJ, Ferkol TW. The global burden of respiratory disease-impact on child health. *Pediatr Pulmonol* 2014;49:430-4.
- Fleming M, Fitton CA, Steiner MFC, et al. Educational and health outcomes of children treated for asthma: Scotland-wide record linkage study of 683716 children. *Eur Respir J* 2019;54:1802309.
- Nichols M, Miller S, Treiber F, et al. Patient and parent perspectives on improving pediatric asthma self-management through a mobile health intervention: pilot study. *JMIR Form Res* 2020;4:e15295.
- FitzGerald JM, Barnes PJ, Chipps BE, et al. The burden of exacerbations in mild asthma: a systematic review. *ERJ Open Res* 2020;6:00359-2019.
- Levy ML, Fleming L, Warner JO, et al. Paediatric asthma care in the UK: fragmented and fatally fallible. *Br J Gen Pract* 2019;69:405-6.
- Physicians RCo. *The National review of asthma deaths (NRAD)*, 2014.
- Bush A, Pavord ID. The *Lancet* Asthma Commission: treating children in primary care. *Prescriber* 2018;29:28-32.
- McCormack MC, Enright PL. Making the diagnosis of asthma. *Respir Care* 2008;53:583-90.
- Kuruville ME, Lee FE-H, Lee GB. Understanding asthma phenotypes, Endotypes, and mechanisms of disease. *Clin Rev Allergy Immunol* 2019;56:219-33.
- Michel G, Silverman M, Strippoli M-PF, et al. Parental understanding of wheeze and its impact on asthma prevalence estimates. *Eur Respir J* 2006;28:1124-30.
- Fainardi V, Santoro A, Caffarelli C. Preschool wheezing: trajectories and long-term treatment. *Front Pediatr* 2020;8:240.
- Townshend J, Hails S, McKean M. Diagnosis of asthma in children. *BMJ* 2007;335:198-202.
- Gautier C, Charpin D. Environmental triggers and avoidance in the management of asthma. *J Asthma Allergy* 2017;10:47-56.
- Keet CA, Matsui EC, McCormack MC, et al. Urban residence, neighborhood poverty, race/ethnicity, and asthma morbidity among children on Medicaid. *J Allergy Clin Immunol* 2017;140:822-7.
- Licari A, Castagnoli R, Brambilla I, et al. Asthma Endotyping and biomarkers in childhood asthma. *Pediatr Allergy Immunol Pulmonol* 2018;31:44-55.
- Fahy JV. Type 2 inflammation in asthma--present in most, absent in many. *Nat Rev Immunol* 2015;15:57-65.
- Brusselle GG, Koppelman GH. Biologic therapies for severe asthma. *N Engl J Med* 2022;386:157-71.
- McGregor MC, Krings JG, Nair P, et al. Role of biologics in asthma. *Am J Respir Crit Care Med* 2019;199:433-45.
- Kavanagh J, Jackson DJ, Kent BD. Over- and under-diagnosis in asthma. *Breathe* 2019;15:e20-7.
- Asthma Gf. Global strategy for asthma management and prevention. Available: <https://ginasthma.org/gina-reports/2021>
- Been JV, Lugtenberg MJ, Smets E, et al. Preterm birth and childhood wheezing disorders: a systematic review and meta-analysis. *PLoS Med* 2014;11:e1001596.
- Berry M, Morgan A, Shaw DE, et al. Pathological features and inhaled corticosteroid response of eosinophilic and non-eosinophilic asthma. *Thorax* 2007;62:1043-9.
- Petsky HL, Kew KM, Chang AB. Exhaled nitric oxide levels to guide treatment for children with asthma. *Cochrane Database Syst Rev* 2016;11:CD011439.
- Plaza Moral V, Alonso Mostaza S, Alvarez Rodríguez C, et al. Spanish guideline on the management of asthma. *J Investig Allergol Clin Immunol* 2016;26 Suppl 1:1-92.
- Papadopoulos NG, Arakawa H, Carlsen K-H, et al. International consensus on (icon) pediatric asthma. *Allergy* 2012;67:976-97.
- Health SMO. Management of asthma. Available: [https://www.moh.gov.sg/docs/librariesprovider4/guidelines/cpg\\_asthma.pdf20082008](https://www.moh.gov.sg/docs/librariesprovider4/guidelines/cpg_asthma.pdf20082008)
- Arakawa H, Adachi Y, Ebisawa M, et al. Japanese guidelines for childhood asthma 2020. *Allergol Int* 2020;69:314-30.
- Sylvester KP, Youngs L, Rutter MA, et al. Early respiratory diagnosis: benefits of enhanced lung function assessment. *BMJ Open Respir Res* 2021;8.
- Devonshire AL, Kumar R. Pediatric asthma: principles and treatment. *Allergy Asthma Proc* 2019;40:389-92.
- Australia TNAC. Australian asthma Handbook. Available: <https://www.nationalasthma.org.au/health-professionals/australian-asthma-handbook20212021>
- Zealand AaRFN. New Zealand child asthma guidelines: a quick reference guide. Available: <https://www.asthmafoundation.org.nz/resources/nz-child-asthma-guidelines20202020>
- Yang CL, Hicks EA, Mitchell P, et al. Canadian Thoracic Society 2021 Guideline update: Diagnosis and management of asthma in preschoolers, children and adults. *Canadian Journal of Respiratory, Critical Care, and Sleep Medicine* 2021;5:348-61.
- Suissa S, Ernst P, Benayoun S, et al. Low-Dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000;343:332-6.
- Muneswarao J, Hassali MA, Ibrahim B, et al. It is time to change the way we manage mild asthma: an update in GINA 2019. *Respir Res* 2019;20:183.
- Scicchitano R, Aalbers R, Ukena D, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. *Curr Med Res Opin* 2004;20:1403-18.
- Sobieraj DM, Weeda ER, Nguyen E, et al. Association of inhaled corticosteroids and long-acting  $\beta$ -Agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma. *JAMA* 2018;319:1485.

- 37 UK A. Maintenance and reliever therapy (Mart), 2021. Available: <https://www.asthma.org.uk/advice/inhalers-medicines-treatments/inhalers-and-spacers/mart/>
- 38 Boutopoulos B, Koumpagioti D, Matziou V, *et al.* Interventions on adherence to treatment in children with severe asthma: a systematic review. *Front Pediatr* 2018;6:232.
- 39 Guevara JP, Wolf FM, Grum CM, *et al.* Effects of educational interventions for self management of asthma in children and adolescents: systematic review and meta-analysis. *BMJ* 2003;326:1308–9.
- 40 Gillette C, Rockich-Winston N, Kuhn JA, *et al.* Inhaler technique in children with asthma: a systematic review. *Acad Pediatr* 2016;16:605–15.
- 41 Capanoglu M, Dibek Misirlioglu E, Toyran M, *et al.* Evaluation of inhaler technique, adherence to therapy and their effect on disease control among children with asthma using metered dose or dry powder inhalers. *J Asthma* 2015;52:838–45.
- 42 Searle A, Jago R, Henderson J, *et al.* Children's, parents' and health professionals' views on the management of childhood asthma: a qualitative study. *NPJ Prim Care Respir Med* 2017;27:53.
- 43 Ducharme FM, Bhogal SK. The role of written action plans in childhood asthma. *Curr Opin Allergy Clin Immunol* 2008;8:177–88.
- 44 Lakupoch K, Manuyakorn W, Preutthipan A, *et al.* The effectiveness of newly developed written asthma action plan in improvement of asthma outcome in children. *Asian Pac J Allergy Immunol* 2018;36:88–92.
- 45 UK A. The reality of asthma care in the UK. Available: <https://www.asthma.org.uk/578f5bcf/globalassets/get-involved/external-affairs-campaigns/publications/annual-asthma-care-survey/annual-asthma-survey-2018/asthmauk-annual-asthma-survey-2018-v7.pdf> 2018
- 46 Wanrooij VHM, Willeboordse M, Dompeling E, *et al.* Exercise training in children with asthma: a systematic review. *Br J Sports Med* 2014;48:1024–31.
- 47 Lu KD, Forno E. Exercise and lifestyle changes in pediatric asthma. *Curr Opin Pulm Med* 2020;26:103–11.
- 48 Kallenbach JM, Frankel AH, Lapinsky SE, *et al.* Determinants of near fatality in acute severe asthma. *Am J Med* 1993;95:265–72.
- 49 (NICE) NifHaCE. Asthma: diagnosis, monitoring and chronic asthma management. Available: <https://www.nice.org.uk/guidance/ng80/resources/asthma-diagnosis-monitoring-and-chronic-asthma-management-pdf-183768797562120172021>
- 50 Dermot Nolan DM. Asthma - Diagnosis, Assessment and Management in General Practice Quick Reference Guide. Available: <https://www.icgp.ie/speck/properties/asset/asset.cfm?type=LibraryAsset&id=B913F962%2DC2B7%2D4C24%2D817B66C37E2F8A90&property=asset&revision=tip&disposition=inline&app=icgp&filename=Asthma%5F%2D%5FDiagnosis%5F%5FAssessment%5Fand%5FManagement%5Fin%5FGeneral%5FPractice%5FQRG%2Epdf>
- 51 Ardura-Garcia C, Stolbrink M, Zaidi S, *et al.* Predictors of repeated acute Hospital attendance for asthma in children: a systematic review and meta-analysis. *Pediatr Pulmonol* 2018;53:1179–92.
- 52 Nwaru BI, Ekström M, Hasvold P, *et al.* Overuse of short-acting  $\beta_2$ -agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. *Eur Respir J* 2020;55:1901872.
- 53 Keeley D, Baxter N. Conflicting asthma guidelines cause confusion in primary care. *BMJ* 2018;360:k29.
- 54 Mosnaim G, Li H, Martin M, *et al.* A tailored mobile health intervention to improve adherence and asthma control in minority adolescents. *J Allergy Clin Immunol Pract* 2015;3:288–90.
- 55 Katwa U, Rivera E. Asthma management in the era of Smart-Medicine: devices, gadgets, Apps and telemedicine. *Indian J Pediatr* 2018;85:757–62.
- 56 Burbank AJ, Lewis SD, Hewes M, *et al.* Mobile-based asthma action plans for adolescents. *J Asthma* 2015;52:583–6.
- 57 Chan AHY, Stewart AW, Harrison J, *et al.* The effect of an electronic monitoring device with audiovisual reminder function on adherence to inhaled corticosteroids and school attendance in children with asthma: a randomised controlled trial. *Lancet Respir Med* 2015;3:210–9.
- 58 UK A. Recovery and reset for respiratory: restoring and improving basic care for patients with lung disease. Available: <https://www.asthma.org.uk/283059c7/globalassets/campaigns/publications/restarting-basic-care-final.pdf> 2020
- 59 Win PH, Hussain I. Asthma triggers: what really matters? *Clinical Asthma* 2008:149–56.
- 60 Tarasidis GS, Wilson KF. Diagnosis of asthma: clinical assessment. *Int Forum Allergy Rhinol* 2015;5 Suppl 1:S23–6.
- 61 Mu M, Ye S, Bai M-J, *et al.* Birth weight and subsequent risk of asthma: a systematic review and meta-analysis. *Heart Lung Circ* 2014;23:511–9.
- 62 Egan KB, Ettinger AS, Bracken MB. Childhood body mass index and subsequent physician-diagnosed asthma: a systematic review and meta-analysis of prospective cohort studies. *BMC Pediatr* 2013;13:121.
- 63 Holst GJ, Pedersen CB, Thygesen M, *et al.* Air pollution and family related determinants of asthma onset and persistent wheezing in children: nationwide case-control study. *BMJ* 2020;370:m2791.
- 64 Ullmann N, Mirra V, Di Marco A, *et al.* Asthma: differential diagnosis and comorbidities. *Front Pediatr* 2018;6:276.
- 65 Townshend J, Hails S, McKean M. Management of asthma in children. *BMJ* 2007;335:253–7.
- 66 Dixon EG, Rugg-Gunn CE, Sellick V, *et al.* Adverse drug reactions of leukotriene receptor antagonists in children with asthma: a systematic review. *BMJ Paediatr Open* 2021;5:e001206.
- 67 Society SAT. Guidelines for the management of chronic asthma in adolescents and adults. Available: [https://pulmonology.co.za/wp-content/uploads/2016/11/Guideline\\_8.pdf](https://pulmonology.co.za/wp-content/uploads/2016/11/Guideline_8.pdf) 20072016
- 68 Doroudchi A, Pathria M, Modena BD. Asthma biologics: comparing trial designs, patient cohorts and study results. *Ann Allergy Asthma Immunol* 2020;124:44–56.
- 69 Galli SJ, Tsai M. Ige and mast cells in allergic disease. *Nat Med* 2012;18:693–704.
- 70 Busse WW, Morgan WJ, Gergen PJ, *et al.* Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med* 2011;364:1005–15.
- 71 Kulus M, Hébert J, Garcia E, *et al.* Omalizumab in children with inadequately controlled severe allergic (IgE-mediated) asthma. *Curr Med Res Opin* 2010;26:1285–93.
- 72 Corren J, Kavati A, Ortiz B, *et al.* Efficacy and safety of omalizumab in children and adolescents with moderate-to-severe asthma: a systematic literature review. *Allergy Asthma Proc* 2017;38:250–63.
- 73 Kau AL, Korenblat PE. Anti-interleukin 4 and 13 for asthma treatment in the era of endotypes. *Curr Opin Allergy Clin Immunol* 2014;14:570–5.
- 74 Corren J, Castro M, Chanez P, *et al.* Dupilumab improves symptoms, quality of life, and productivity in uncontrolled persistent asthma. *Ann Allergy Asthma Immunol* 2019;122:41–9.
- 75 Castro M, Corren J, Pavord ID, *et al.* Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med* 2018;378:2486–96.
- 76 Tan LD, Bratt JM, Godor D, *et al.* Benralizumab: a unique IL-5 inhibitor for severe asthma. *J Asthma Allergy* 2016;9:71–81.
- 77 Ortega HG, Liu MC, Pavord ID, *et al.* Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med Overseas Ed* 2014;371:1198–207.
- 78 Pavord ID, Korn S, Howarth P, *et al.* Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380:651–9.
- 79 Khatri S, Moore P, Gibson PG, *et al.* Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma. *J Allergy Clin Immunol* 2019;143:1742–51.
- 80 Gupta A, Ikeda M, Geng B, *et al.* Long-Term safety and pharmacodynamics of mepolizumab in children with severe asthma with an eosinophilic phenotype. *J Allergy Clin Immunol* 2019;144:1336–42.
- 81 Wechsler M, Hickey L, Garin M. Efficacy of Reslizumab treatment in Exacerbation-Prone patients with severe eosinophilic asthma. 8. The Journal of Allergy and Clinical Immunology: In Practice, 2020.
- 82 Virchow JC, Katial R, Brusselle GG, *et al.* Safety of Reslizumab in uncontrolled asthma with eosinophilia: a pooled analysis from 6 trials. *J Allergy Clin Immunol Pract* 2020;8:540–8.
- 83 Kolbeck R, Kozhich A, Koike M, *et al.* MEDI-563, a humanized anti-IL-5 receptor alpha mAb with enhanced antibody-dependent cell-mediated cytotoxicity function. *J Allergy Clin Immunol* 2010;125:1344–53.
- 84 Harrison TW, Chanez P, Menzella F, *et al.* Onset of effect and impact on health-related quality of life, exacerbation rate, lung function, and nasal polyposis symptoms for patients with severe eosinophilic asthma treated with benralizumab (ANDHI): a randomised, controlled, phase 3B trial. *Lancet Respir Med* 2021;9:260–74.