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REVIEW ARTICLE

Insights from Overviewing Selective International Guidelines for Pediatric Asthma

Kam L.E. Hon[1,*], Daniel K.K. Ng[2], Wa K. Chiu[3] and Alexander K.C. Leung[4]

[1]*Department of Pediatrics, The Chinese University of Hong Kong and The CUHK Medical Centre, Hong Kong, China;* [2]*Department of Pediatrics, The Hong Kong Sanitorium & Hospital, Hong Kong, China;* [3]*Department of Pediatrics and Adolescent Medicine, United Christian Hospital, Hong Kong, China;* [4]*Department of Pediatrics, The University of Calgary and The Alberta Children's Hospital, Calgary, Alberta, Canada*

Abstract: ***Background*:** Asthma is a chronic atopic and inflammatory bronchial disease characterized by recurring symptoms, episodic reversible bronchial obstruction and easily triggered bronchospasms. Asthma often begins in childhood. International guidelines are widely accepted and implemented; however, there are similarities and differences in the management approaches. There is no national guideline in many cities in Asia. This review aims to provide a practical perspective on current recommendations in the management of childhood asthma, specifically in the following aspects: diagnosis, classification of severity, treatment options, and asthma control, and to provide physicians with up-to-date information for the management of asthma.

***Methods*:** We used the PubMed function of Clinical Queries and searched keywords of "Asthma", "Pediatric" AND "Guidelines" as the search engine. "Clinical Prediction Guides", "Etiology", "Diagnosis", "Therapy," "Prognosis," and "Narrow" scope were used as filters. The search was conducted in November 2022. The information retrieved from this search was used in compiling the present article.

***Results*:** Diagnosis is clinically based on symptom pattern, response to therapy with bronchodilators and inhaled corticosteroids, and spirometric pulmonary function testing (PFT). Asthma is classified in accordance with symptom frequency, peak expiratory flow rate (PEFR), forced expiratory volume in one second (FEV1), and atopic *versus* nonatopic etiology, where atopy means a predisposition toward a type 1 hypersensitivity reaction. Asthma is also classified as intermittent or persistent (mild to severe). Unfortunately, there is no disease cure for asthma. However, symptoms can be prevented by trigger avoidance and suppressed with inhaled corticosteroids. Antileukotriene agents or long-acting beta-agonists (LABA) may be used together with inhaled corticosteroids if symptoms of asthma are not controlled. Rapidly worsening symptoms are usually treated with an inhaled short-acting beta-2 agonist (SABA, *e.g.*, salbutamol) and oral corticosteroids. Intravenous corticosteroids and hospitalization are required in severe cases of asthma attacks. Some guidelines also provide recommendations on the use of biologics and immunotherapy.

***Conclusion*:** Asthma is diagnosed clinically, with supporting laboratory testing. Treatment is based on severity classification, from intermittent to persistent. Inhaled bronchodilator and anti-inflammatory corticosteroid form the main stay of management.

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1. INTRODUCTION

Asthma is an inflammatory disease of the bronchial airways with recurring and variable symptoms, episodic reversible airway obstruction, and easily triggered bronchospasms [1-10]. Symptomatology includes episodic expiratory wheezing, dry coughing, shortness of breath and chest tightness. Asthma usually gets worse at night or with exertion [1-3]. Younger children may complain of nonfocal chest pain. Asthma is associated with significant mortality and morbidity worldwide [3, 11]. Most of the asthma deaths occurred in the developing nations [1, 2]. Asthma often begins before 6 years of age, and the rates of asthmatic attacks have significantly increased since the 1960s [1, 2, 12] Asthma is caused by a combination of environmental and genetic factors [1, 2]. Environmental factors primarily include exposure to pollution and aeroallergens [1, 2]. Diagnosis is clinically based on symptom pattern, therapeutic response with bronchodila-

*Address correspondence to this author at the Department of Pediatrics The Chinese University of Hong Kong and The CUHK Medical Centre, Hong Kong, China; Tel: 852 35052982; Fax: 852 26360020;
E-mail: ehon@hotmail.com

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Table 1. Overview of international guidelines for pediatric asthma.

Criteria	China 2020/2021[10][21][22][23][24]	GINA 2021[10][25]	NHLBI 2020[26]	+ERS-ATS 2020[27]	NICE 2021[28]	BTS-SIGN[29]	+EAACI 2020[30]	TSANZ 2020[31]
Diagnosis							-	-
History	Y	Y	N	N	Y	Y	N	Y
Physical examination	Y	Y	N	N	Y	Y	N	Y
Investigations	Y	Y	Y	Y	Y	Y	N	Y
Asthma Severity								
Classification of severity	Y	Y	N*	Y	N	Y	Y	Y
Treatment							-	-
Non-pharmacological Considerations							-	-
Prevention/self-management	Y	Y	Y	N	Y	Y	N	Y
Alternative therapies	Y	Y	N	N	N	Y	N	N
Pharmacological Interventions							-	-
Young children	Y	Y	Y	Y	Y	Y	N	Y
Older children/adolescents	Y	Y	Y	Y	Y	Y	Y	Y
Monitoring Asthma Control							-	-
Dose adjustments	Y	Y	Y	N	Y	Y	N	Y
Monitoring and assessments	Y	Y	Y	N	Y	Y	N	Y

Y: Recommended; N: Not recommended/limited evidence
Note: * Previously defined in NHLBI Expert Panel Report 2007
+ ERS-ATS 2020 and EAACI 2020 provide recommendations for the management of severe asthma and the use of biologicals

tors and inhaled corticosteroids, and spirometric pulmonary function testing (PFT) [13]. Asthma is classified based on the frequency of respiratory symptoms, peak expiratory flow rate, forced expiratory volume in one second (FEV1), and atopic *versus* non-atopic etiology, where atopy refers to a type 1 hypersensitivity predisposition [14]. Asthma is a chronic recurring disease, and management is primarily focused on control rather than disease cure [1, 2]. Symptoms can be prevented by trigger avoidance, and suppressed with inhaled corticosteroids [4, 9, 10, 15-17] Long-acting beta agonists (acronym as LABA) or antileukotriene agents (such as montelukast) may be used in addition to inhaled corticosteroids if asthma symptoms remain uncontrolled [10, 16-19]. Treatment of rapidly worsening symptoms is generally with an inhaled short-acting beta-2 agonist (SABA) and oral corticosteroids [4, 9]. Intravenous corticosteroids in hospital may be required in severe cases of asthma attacks [4, 9].

There is no national management guideline in many cities in Asia. This review aims to provide a practical perspective on current recommendations in the management of childhood asthma, specifically in the following aspects: diagnosis, classification of severity, treatment options, and asthma control, and to provide physicians with up-to-date information for the management of this disease.

The cited international guidelines are widely accepted and implemented; however, there are similarities and differences in the management approaches [20]. Major international guidelines are tabulated for comparison. These international guidelines provide updated recommendations on the management of childhood asthma, especially for many Asian cities where unified national guidelines are not available.

2. METHODS

We used the PubMed function of Clinical Queries and searched keywords of “Asthma”, “Pediatric” AND “Guidelines” as the search engine. “Clinical Prediction Guides”, “Etiology”, “Diagnosis”, “Therapy” and “Prognosis” were used as filters. “Narrow” scope was used. Conducted in November 2022, the retrieved information was used in the compilation of this article.

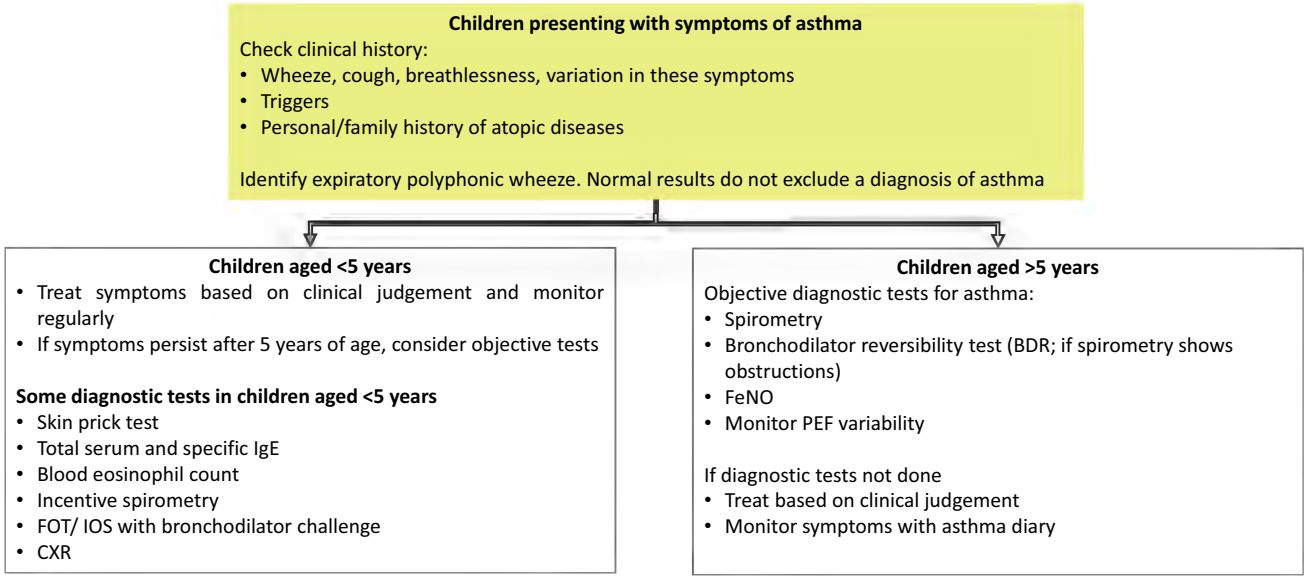
3. RESULTS

We reviewed guidelines from selected countries including guidelines from China [Chinese guidelines 2016 & Chinese Children's Asthma Action Plan (CCAAP)] [10, 21-24]. US [Global Initiative for Asthma (GINA 2021)] [10, 25], National Asthma Education and Prevention Program, The National Heart, Lung, and Blood Institute (NAEPP-NHLBI 2020) Updates [26], European Respiratory Society/American Thoracic Society (ERS/ATS) [27], United Kingdom, European Union National Institute for Health and Care Excellence (NICE 2021) [28], The joint British Thoracic Society and Scottish Intercollegiate Guidelines Network (BTS/SIGN 2019) [29], European Association of Allergy & Immunology (EAACI) Biologicals Guidelines 2020 [30], and The Thoracic Society of Australia and New Zealand National Asthma Committee (TSANZ/NAC) Australian Asthma Handbook (Box **1**) [31].

Table 2. Positive thresholds for objective diagnostic tests in children.

Diagnostic Tests	China[10][21][22][23][24]	GINA[10][25]	NHLBI[26]	NICE[28]	BTS-SIGN[29]	TSANZ[31]
Spirometry (FEV1/FVC)* < LLN	<80%	<90%	-	≤70%	Y	Y
PEF variability >20%	≥13%	>13%	-	>20%	N	-
Forced oscillation test > ULN	-	-	-	-	-	-
BDR (FEV1 improvement[†]) **FEF 25-75% ??** **FE**	≥12%	>12%	-	≥12%	Y	Y
FeNO (pbb) >ULN	Y	N	Y	≥35	Y	N
Blood/sputum eosinophil > 150??	Y	-	-	-	N	-
Skin prick/IgE test	Y	Y	-	N	N	Y
Exercise challenge (FEV1)* > 10%	-	>12%	-	Y	-	-
CXR	May exclude structural abnormalities but not for routine clinical practice					

Some guidelines recommend conducting specific diagnostic tests but do not specify thresholds; these are indicated as 'Y'. 'N' indicates not recommended/limited evidence
Note: *Expressed as % from expected
BDR: Bronchodilator reversibility; CXR: Chest X-ray; FeNO: Fractional exhaled nitric oxide; FEV1/FVC: forced expiratory volume in one second/forced vital capacity; FEV1: forced expiratory volume in one second; IgE: Immunoglobulin E; PEF: Peak expiratory flow; ppb, parts per billion.



Adapted from NICE UK[28]

Fig. (1). Diagnostic algorithm for pediatricasthma. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

3.1. Guidelines

An overview of these International Guidelines for the Management of Pediatric Asthma is summarized (Table **1**). In these guidelines, asthma diagnosis is based clinically on obtaining a supporting history, physical examination, and relevant investigations. Interestingly, several guidelines do not rely on history and physical examination, including the recent National Heart, Lung, and Blood Institute (NHLBI) 2020, European Respiratory Society/American Thoracic Society ERS/ATS 2020 and EAACI 2020 guidelines. Classification of asthma severity is generally recommended. Treatment is based on non-pharmacological considerations and pharmacological interventions. Non-pharmacological management in terms of prevention/self-management and alternative therapies is not unanimous. Alternative therapies are generally not recommended. Pharmacological interventions are similar among these guidelines, with recommendations for young children and older children/adolescents. Monitoring of asthma control is generally recommended, with exception of the ERS/ATS 2020 and EAACI 2020 guidelines.

3.2. Diagnosis

Guidelines are in agreement with the clinical and objective approaches in diagnosing childhood asthma as adopted by NICE UK (Fig. **1**). International guidelines for asthma diagnosis are compared (Table **2**). In general, guidelines are in agreement with the clinical and objective approaches to diagnosing childhood asthma. Spirometry or Peak Expiratory

Flow (PEF) variability is generally recommended but the thresholds are not in agreement.

3.2.1. Peak Expiratory Flow (PEF) Variability and Bronchodilator Response (BDR) of FEV1 Improvement

Diurnal PEF variability is the daily amplitude percent mean (from twice daily readings) [10, 21-23]. For diurnal variability, the upper 95% confidence limit in healthy children is 12.3%. Diurnal PEF >13% is generally regarded as excessive for children, according to GINA [10].

In adults with typical asthma symptoms, Variation in FEV1 of more than 12% and 200 mL from baseline is consistent with asthma. Predicted normal ranges for PEF and FEV1 have limitations as there are no specific ranges in children. Hence, the patient's recorded best reading is considered as their normalcy according to GINA [10, 21-23].

Those with atypical clinical manifestations (such as no obvious wheezing or clinical signs), should have at least one of the following: (1) confirmed reversible airflow limitation such as: (a) positive bronchodilator reversibility test result: ≥ 12% increase in FEV1 15 min after inhalation of rapid-acting β2 agonists (such as albuterol 200 -400 μg *via* metered dose inhaler); (b) improvement in pulmonary ventilation after anti-inflammatory treatment: ≥ 12% increase in FEV1 after being treated with inhaled corticosteroids and/or anti-leukotrienes for 4 to 8 weeks; (2) positive bronchial provocation test; (3) diurnal PEF variability (for 2 consecutive weeks of monitoring) ≥ 13%. Those who meet criteria 1-2 or 2-3 can be diagnosed with asthma [10, 21-23].

3.2.2. Fractional Exhaled Nitric Oxide (FeNO) in Parts Per Billion (pbb)

FeNO is not considered useful for asthma diagnosis according to GINA [10]. Although no prospective studies have confirmed the exact value of non-invasive airway inflammation markers such as induced sputum eosinophil count and FeNO in the diagnosis of childhood asthma, continuous monitoring of these markers can help to assess the level of asthma control and guide the development of optimal asthma treatment regimens according to the Chinese guidelines and recommendations [10, 21-24].

3.2.3. Blood/Sputum Eosinophil

School-age children can usually cooperate with the sputum induction test. Increased level of eosinophils in induced sputum is associated with the degree of airway obstruction and its reversibility, the severity of asthma, and the allergy status [10, 21-23]. Although no prospective studies have confirmed the exact value of non-invasive airway inflammation markers such as induced sputum eosinophil count and FeNO in the diagnosis of childhood asthma, continuous monitoring of these markers can help to assess the level of asthma control and guide the development of optimal asthma treatment regimens [10, 21-23].

3.3. Asthma Severity

The severity of asthma is evaluated by the medications and treatment required to control symptoms and exacerbation and is generally classified as mild, moderate and severe. There are some variations in terms of the classification of disease severity. They are tabulated for reference, Table **3a** for China, Table **3b** for GINA, and Table **3c** for NHLBI, respectively [10, 21-23]. Many of these guidelines further classify severe asthma based on its phenotype (Table **4**).

For GINA, currently, asthma severity is retrospectively assessed from the therapeutic level needed to control symptoms [10]. The severity of asthma can be assessed once the patient has been on an effective level of controlled treatment for a few months. Asthma severity may change over time [10]. For NHLBI, severity is classified as intermittent and persistent (mild, moderate and severe) [7, 32-34] NICE does not include details on asthma severity [28]. The severity of asthma is evaluated by the level of treatment required to control exacerbation and symptoms. To consolidate, asthma severity can be classified based on the conglomeration of all these guidelines (Table **5**) [10, 21-23, 28, 29, 32-34].

Table 3a. Classification of asthma severity in children - China[21][22][23][24].

-	Mild	Moderate	Severe
Symptom frequency	Few/month - 1-2 times/week	Few/week - daily	Few/week - throughout the day
Night awakenings	None or minimal	Few/month	≥1 night/week
Asthma-related impairment	<6 yrs: Speaks in sentences, pulse <100 beats/min, no cyanosis, wheezing ≥6 yrs: Dyspnea when walking, can lie down, speaks in sentences, may be anxious or irritable. Slightly increased pulse rate, wheeze (scattered, end expiratory)	≥6 yrs: dyspnea when speaking, prefers sitting to lying, speaks in phrases, often anxious or irritable, may have use of accessory neck muscles and 3- concave sign. Slightly increased pulse rate, wheeze (scattered, end-expiratory)	<6 yrs: anxious, irritable, drowsy or unconcious. Speaks in single words, pulse >200 (0-3 yrs) or >180 (4-5 yrs) beats/min, cyanosis, weaken/absent wheezing >6 yrs: dyspnea at rest, sits hunched forward, speaks in single words, often anxious or irritable, have use of accessory neck muscles and 3-concave sign. Significantly increased pulse rate, wheeze (loud diffused, biphasic)
Lung function: FEV1; FEV1/FVC	Not Specified	Not specified	Not specified
Lung function: PEF	≥6 yrs: after SABA treatment: > 80	≥6 yrs: before SABA >50 - 80, after SABA > 60 - 80	≥6 yrs: before SABA ≤ 50%, after SABA ≤ 60%
Blood oxygen saturation	<6 yrs: before treatment: ≥0.92 ≥6 yrs: 0.90~0.94	≥6 yrs: 0.90~0.94	<6 yrs: before treatment: <0.92 ≥6 yrs: 0.90

Abbreviations: FEV1/FVC: forced expiratory volume in one second/forced vital capacity; FEV1: forced expiratory volume in one second; IgE: Immunoglobulin E; NA: Not available; PEF: Peak expiratory flow; SABA: Short-acting beta-agonist; Yrs: years.

Table 3b. Classification of asthma severity in children - Gina[10][25].

● Currently, asthma severity is assessed retrospectively from the level of treatment required to control symptoms and exacerbations. It can be assessed once the patient has been on controlled treatment for several months, and if appropriate treatment step down has been attempted to find the patient's minimum effective level of treatment. Asthma severity is not a static feature and may change over months or years[10].
● Asthma severity can be assessed when the patient has been on controlled treatment for several months:

Mild	Moderate	Severe
Infrequent symptoms *e.g.*, twice a month or less Currently defined as asthma that is well controlled with Step 1 or 2 treatment *i.e.* with as-needed ICS formoterol alone, or with low-intensity maintenance, controlled treatment such as low dose ICS, LTRAs or chromones. For patients prescribed as needed ICS-form, the frequency of use should be considered to represent well-controlled asthma has not et been determined. GINA does not yet distinguish between so-called 'intermittent' and mild-persistent asthma. GINA is currently reviewing the definition of mild asthma.	Asthma symptoms several times a week-once a day or need for reliever twice a month or more Well-controlled with step 3 or step 4 treatment *e.g.*, low or medium dose ICS-LABA	Troublesome symptoms most days Night awakening once a week or more, and low lung function Asthma that remains uncontrolled despite optimized treatment with high dose ICS-LABA, or that requires high dose ICS-LABA to prevent it from becoming 'uncontrolled'. While many patients with uncontrolled asthma may be difficult to treat due to inadequate or inappropriate treatment, or persistent problems with adherence or comorbidities such as chronic rhinosinusitis or obesity, the ERS/ATS task force on severe asthma considered the definition of severe asthma should be reserved for patients with refractory asthma and hose in whom response to treatment of comorbidities is incomplete.

Abbreviations: FEV1/FVC: forced expiratory volume in one second/forced vital capacity; FEV1: forced expiratory volume in one second; IgE: Immunoglobulin E; NA: Not available; PEF: Peak expiratory flow; SABA: Short-acting beta-agonist; Yrs: years.

Table 3c. Classification of asthma severity in children - NHLBI[15, 26].

-	Intermittent	Mild	Moderate	Severe
Symptom frequency	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
Night awakenings	0-4 yrs: none 5-17 yrs: ≤2x/mth	0-4 years: 1-2x/month 5-17 years: 3-4x/month	0-4 yrs: 3-4x/month 5-17 yrs: >1x/week but not nightly	0-4 yrs: >1x/week 5-17 yrs: 7x/week
Asthma-related impairment	No interference with normal activity	Minor interference with activity	Some limitation on activity	Extremely limited in activity
Lung function: FEV1; FEV1/FVC	5-11 yrs: Normal FEV1 between exacerbations, FEV1 >80% predicted, FEV1/FVC >85% 12-17 yrs: Normal FEV1 between exacerbations, FEV1 >80% predicted, FEV1/FVC normal	5-11 yrs: FEV1 >80% predicted, FEV1/FVC >80% 12-17 yrs: FEV1 ≥80% predicted, FEV1/FVC normal	5-11 yrs: FEV 60-80% predicted, FEV1/FVC 75-80% 12-17 yrs: FEV1 >60% but <80% predicted, FEV1/FVC reduced by 5%	5-11 yrs: FEV <60% predicted, FEV1/FVC <75% 12-17 yrs: FEV<60% predicted, FEV1/FVC reduced 5%
Lung function: PEF	-	-	-	-
Blood oxygen saturation	-	-	<90% indicates serious distress	<90% indicates serious distress

Abbreviations: FEV1/FVC: forced expiratory volume in one second/forced vital capacity; FEV1: forced expiratory volume in one second; IgE: Immunoglobulin E; NA: Not available; PEF: Peak expiratory flow; SABA: Short-acting beta-agonist; Yrs: years.

Table 4. Classification of severe asthma and its phenotype.

-	GINA 2021[a]	EAACI[b]	ERS-ATS 2020[c]	TSANZ 2020[d]	BTS-SIGN
Definition of severe asthma	Uncontrolled asthma (also called severe refractory asthma or severe treatment-resistant asthma) despite the highest level of recommended treatment (ie, high-dose ICS + second controller and/or systemic CS[a], ICS + LABA [Australian Asthma Handbook level ≥4][d]), or that requires such maintenance treatment, to prevent it from becoming uncontrolled.				Defined as more than two asthma attacks/year or persistent symptoms, requiring SABA more than twice/week despite specialist-level therapy
Severe asthma phenotypes	• For children, adolescents with severe asthma uncontrolled despite GINA step 4-5 or NAEPP/NHLBI step 5 therapies, we recommend the addition of tiotropium[c] • Anti-IL4/13 is also indicated for systemic corticosteroid dependent severe asthmatics regardless of eosinophilic status[c] • ERS-ATS suggests against the use of chronic macrolide treatment in children[c]				

(Table 4) contd….

-	GINA 2021[a]	EAACI[b]	ERS-ATS 2020[c]	TSANZ 2020[d]	BTS-SIGN
Type 2 inflammation	• bEos ≥150µl, and/or, FeNO ≥20 ppb and/or, sputum eosinophil ≥2%, • Asthma is clinically allergen-driven, and/or the need for maintenance OCS (repeat bEos and FeNO up to 3 times on lowest possible OCS dose)			See criteria for individual biologics	This recommendation does not apply to individuals taking biologic agents, except for omalizumab
• Allergic severe asthma	• Serum total IgE levels 30-1300 IU/mL not adequately controlled on ICS and/or other background controllers[b] • Considering specific eosinophil (≥ 260 /µl) and FeNO (≥19.5 ppb) cutoffs to identify adolescents or adults with the greatest likelihood or response to anti-IgE therapy[c]				-
• Eosinophilic severe asthma	• Sputum eosinophil count of >1% or an asthma-related peripheral blood eosinophil count of ≥150 cells/µL, or a FeNO≥20 ppb[b]				

EAACI recommendations for severe asthma is derived from that of GINA and ERS-ATS guidelines; China, NICE, NHLBI had no specific definition for severe asthma
Abbreviations: ERS-ATS, European Respirology Society-American Thoracic Society; GINA, Global initiative for Asthma; NAEPP, National Asthma Education and Prevention Program; NHLBI, National Heart, Lung and Blood Institute (US National Institute of Health); NICE, National Institute of Health Care Excellence, UK; SIGN, Scottish Intercollegiate Guidelines Network; TSANZ, Thoracic Society of Australia and New Zealand
bEos: Blood eosinophil; CS: corticosteroid; FeNO: Fractional exhaled nitric oxide; ICS: Inhaled corticosteoroid; LABA: Long-acting beta2 agonist; ppb; part per billion; SABA: Short-acting beta-agonist

Table 5. Classification of asthma severity in children.

Components of Severity		Mild	Moderate	Severe
Symptom frequency[(10)(25)(26)]		>2 days/week but not daily	Daily	Throughout the day
Night awakenings[(26)]		1-2 times/month	3-4 times/month or more than once/week	More than once a day or >7 times/week
Symptom control[(21)(22)(23)(24)(10)(25)(26)]		Well-controlled with GINA Step 1 and 2 or initiation of NHLBI step 2 treatment	Well-controlled with step 3 and 4 treatment or initiation of NHLBI step 3 treatment	Required high-dose ICS-LABA (or uncontrolled with ICS-LABA) or NHLBI step 3 and 4 treatment
Asthma-related impairment[(26)]		Minor	Some limitation	Extreme
Lung Function (for children aged ≥5 yrs)				
FEV1; FEV1/FVC[(26)]		FEV1≥80%; FEV1/FVC>80% (5-11 years), normal (12-17 yrs)	FEV=60-80%; FEV1/FVC=75-80% (5-11 years), reduced by 5% (12-17 yrs)	FEV<60%; FEV1/FVC<75% (5-11 yrs), reduced by 5% (12-17 yrs)
PEF (before SABA, after SABA)[(28)]		NA, >80%	>50-80%, >60-80%	≤50%, ≥60%
Blood oxygen saturation[(10)(21)(22)(23)(24)]	Children <5 yrs	≥92%	≥92%[7]	<92%
	Children ≥5 yrs	90-95%	90%	<90%

Note: Chinese guidelines[(10)(21)(22)(23)(24)]; GINA[(10)(25)]; NHLBI[(26)], BTS-SIGN[(28)]. NICE did not include details on asthma severity. ERS-ATS guideline was specific to severe asthma.
Abbreviations: FEV1/FVC: forced expiratory volume in one second/forced vital capacity; FEV1: forced expiratory volume in one second; IgE: Immunoglobulin E; NA: Not available; PEF: Peak expiratory flow; SABA: Short-acting beta-agonist; Yrs: years.

3.4. Pharmacological Treatment

3.4.1. GINA and China Guidelines

The two guidelines are similar (Table **6a**) [10, 21-23, 35] Stepwise management for asthma differs according to age groups. These guidelines recommend SABA or short-acting beta agonist as needed as a reliever for all steps, except GINA recommendations for adolescents (Track 2) [25]. Short course oral corticosteroid (OCS) may be needed for patients presenting with severe uncontrolled asthma.

3.4.2. NHLBI Guideline

The guideline recommends SABA as needed as a reliever for all steps (Table **6b**) [7, 32-34].

3.4.3. BTS-SIGN & TSANZ Guidelines

Stepwise management for asthma differs according to age groups in BTS-SIGN & TSANZ (Table **6c**) [29, 31].

3.4.4. NICE Guidelines

The NICE guideline recommends stepwise management for asthma differs according to age groups (Table **6d**) [28].

3.4.5. Guideline Updates

Treatment for adolescents now shows two 'Tracks' in the GINA 2021 guideline [25, 36].

Track 1: Using ICS-formoterol as symptom reliever is recommended by GINA due to the fact that the risk of severe exacerbation is reduced compared with usage of a SABA reliever [25, 36].

Track 2: Using SABA reliever is an alternative approach if Track 1 is not preferred by a patient without exacerbations with their current asthma therapy.

The guideline for children aged 6-11 years has been updated to include low-dose budesonide-formoterol Maintenance And Reliever Therapy or MART.

Table 6a. Stepwise management for asthma differs according to age groups - China & Gina[10][21][22][23][24][3].

Guideline	Severity	Treatment Steps: Preferred Treatment		
		Young Children (<6 Years)	**Older Children (6-11 Years)**	**Adolescents (12-17 Years)**
China[21][22][23][24]	**Mild persistent**	1. None	1. None	
	Mild persistent	2. Low-dose ICS • *Other options: LTRA; Intermittent High-dose ICS*	2. Low-dose ICS • *Other options: LTRA; Intermittent High-Dose ICS*	
	Moderate persistent	3. Medium dose ICS • *Other options: Low-dose ICS + LTRA*	3. Low-dose ICS-LABA • *Other options: Low-dose ICS + LTRA; Medium- and high-dose ICS; Low-dose ICS + extended-release theophylline*	
	Severe persistent	4. Medium- and high-dose ICS + LTRA • *Other options: Medium- and high-dose ICS/LABA; Medium- and high- dose ICS + extended-release theophylline; Medium and high-dose ICS + LTRA (or LABA) and lowest dose oral corticosteroid*	4. Med- and High-dose ICS-LABA • *Other options: Medium- and high-dose ICS + LTRA; Medium- and high-dose ICS + extended-release theophylline; Medium- and high-dose ICS/LABA + LTRA or extended-release theophylline*	
		-	5. Med- and high-dose ICS-LABA + LTRA and/or EX theophylline + lowest dose OCS • *Other options: Medium- and high-dose ICS/LABA + LTRA and/or extended-release theophylline + anti-IgE therapy*	
Gina[10][25]	**Mild infrequent** (symptoms less than twice a month)	1. None	1. ICS PRN + SABA • *Other options: daily low dose ICS*	1. PRN Low-dose ICS-formoterol (Track 1); ICS whenever SABA is taken (Track 2)
	Mild persistent (symptoms twice a month or more, but less than daily)	2. Daily low-dose ICS	2. Daily low-dose ICS • *Other options: daily LTRA*	2. PRN Low-dose ICS-formoterol (Track 1) or Low-dose ICS (Track 2)
	Moderate persistent (symptoms most days, or waking with asthma once a week or more)	3. Double low-dose ICS	3. Low-dose ICS-LABA or med-dose ICS or very low-dose MART • *Other options: low dose ICS + LTRA*	3. Low-dose ICS-formoterol (Track 1) or ICS-LABA (Track 2)
	Severe (symptoms most days, or waking with asthma once a week or more, and low lung functions)	4. Refer to specialist	4. Med-dose ICS-LABA or low-dose ICS- formoterol (MART); refer to specialist • *Other options: Add tiotropium or add LTRA*	4. Med-dose ICS-formoterol (Track 1)* or ICS-LABA (Track 2)*
		-	5. Refer for phenotypic assessment ± higher dose of ICS-LABA or add-on anti-IgE • *Other options: Add-on anti-IL5, or add-on low dose OCS, but consider side effects*	5. As above, add on LAMA; refer for phenotypic assessment; ± anti-IgE, -IL5/5R, -IL4R • *Consider High-dose ICS-formoterol (Track 1) or High-dose ICS-LABA*

Note: All guidelines recommend SABA as-needed as a reliever for all steps, except GINA recommendations for adolescents (Track 2).* Short course OCS may be needed for patients presenting with severe uncontrolled asthma.

Table 6b. Stepwise management for asthma differs according to age groups - NHLBI[26].

Guideline	Severity	Treatment Steps: Preferred Treatment		
		Young Children (<6 Years)	**Older Children (6-11 years)**	**Adolescents (12-17 years)**
NHLBI[26]	**Intermittent**	1. Short course ICS + PRN SABA	1. PRN SABA	1. PRN SABA
	Mild (If uncontrolled with current treatment and symptoms are increasing in intensity/frequency)	2. Daily low-dose ICS • *Other options: Daily montelukast or cromolyn and PRN SABA*	2. Daily low-dose ICS and PRN SABA • *Other options: Daily LTRA, or Cromolyn, or Nedocromil, or Theophylline, and PRN SABA* • *Other options: subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy*	2. Daily low-dose ICS or PRN concomitant ICS + SABA • *Other options: Daily LTRA and PRN SABA or Cromolyn, or Nedocromil, or Zileuton, or Theophylline, and PRN SABA* • *Other options: subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy*
	Moderate (If uncontrolled with current treatment and symptoms are increasing in intensity/frequency)	3. Daily medium-dose ICS	3. Daily and PRN low-dose ICS-formoterol • *Other options: Daily medium-dose ICS and PRN SABA or Daily low-dose ICS-LABA, or daily low-dose ICS + LTRA, or daily low-dose ICS +Theophylline, and PRN SABA* • *Other options: subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy*	3. Daily and PRN combination low-dose ICS-formoterol • *Other options: Daily medium-dose ICS and PRN SABA* • *Other options: Daily low-dose ICS-LABA, or daily low-dose ICS + LAMA, or daily low-dose ICS + LTRA, and PRN SABA* • *Other options: Daily low-dose ICS + Theophylline or Zileuton, and PRN SABA* • *Other options: subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy*
	Severe (If uncontrolled with current treatment and symptoms are increasing in intensity/frequency)	4. Daily medium-dose ICS-LABA • *Other options: Daily medium-dose ICS + montelukast* and PRN SABA*	4. Daily and PRN med-dose ICS-formoterol • *Other options: Daily medium-dose ICS-LABA and PRN SABA or Daily medium-dose ICS + LTRA or daily medium-dose IC + Theophylline, and PRN SABA* • *Other options: subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy*	4. Daily and PRN combination med-dose ICS-formoterol • *Other options: Daily medium-dose ICS-LABA or daily medium-dose ICS + LAMA, and PRN SABA* • *Other options: Daily medium-dose ICS + LTRA, or daily medium-dose ICS + Theophylline, or daily medium-dose ICS + Zileuton, and PRN SABA* • *Other options: subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy*
		5. Daily high-dose ICS-LABA • *Daily high-dose ICS + montelukast* and PRN SABA*	5. Daily high-dose ICS-LABA and PRN SABA • *Other options: Daily high-dose ICS + LTRA or daily high-dose ICS + Theophylline, and PRN SABA*	5. Daily med-high-dose ICS-LABA • *Daily medium-high dose ICS-LABA or daily high-dose ICS + LTRA, and PRN SABA* • *Consider adding Asthma Biologics (e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13)*
		6. Daily high-dose ICS-LABA (or ICS) + OCS • *Daily high-dose ICS + montelukast*+ oral systemic corticosteroid and PRN SABA*	6. Daily high-dose ICS-LABA + OCS + PRN SABA • *Other options: Daily high-dose ICS + LTRA* + oral systemic corticosteroid or daily high-dose ICS + Theophylline* + oral systemic corticosteroid, and PRN SABA* • *Other options: Consider Omalizumab*	6. Daily high-dose ICS-LABA + OCS • *Consider adding Asthma Biologics (e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13)*

Note: Guideline recommend SABA as-needed as a reliever for all steps.

Table 6c. Stepwise management for asthma differs according to age groups – BTS-SIGN & TSANZ[7,9]

Guideline	Severity	Treatment Steps: Preferred treatment		
		Young children (<6 years)	Older children (6-11 years)	Adolescents (12-17 years)
BTS-SIGN[28]	**Suspected asthma**	1. Very low-to-low-dose ICS	1. Very low-to-low-dose ICS	
	Mild	2. LTRA	2. Very low-dose ICS (as regular preventer) • *Other options: once-a-day inhaled corticosteroids at the same total daily dose can be considered if good control is established*	
	Moderate (If uncontrolled with current treatment and symptoms are increasing in intensity/frequency)	3. Very low dose ICS + LTRA • *Other options: recheck the diagnosis, assess adherence to existing medication and check technique*	3. Very low-dose ICS + LABA or LTRA • *Other options: consider single combination inhaler as MART as an alternative approach to introduction of a fixed-dose twice-daily combination inhale that might suit some individuals*	
	Severe (If uncontrolled with current treatment and symptoms are increasing in intensity/frequency)	4. Low-dose ICS • *Other options: consider adding a theophylline*	4. Low-dose ICS or add on LABA (stop if no response) or LTRA • *Other options: if control remains inadequate after stopping a LABA, and increasing dose of ICS, consider sequential trials of add-on therapy, i.e LTRA or theophyllines*	
		5. Refer to specialist	5. Refer to specialist	
TSANZ[31]	**Intermittent-Mild**	1. None (<12 mo); PRN SABA (1-5yrs)	1. PRN SABA	1. PRN SABA
	Mild (symptoms twice a month or more, but less than daily)	2. Low-dose ICS	1. Low-dose ICS • *Other options: montelukast/chromones*	2. Daily low-dose ICS
	Moderate (symptoms most days, or waking with asthma once a week or more)	3. Low-dose ICS • *Other options: montelukast* • *Other options: ICE high paediatric dose (consult with a specialist before increasing dose in <5 years)*	2. High-dose ICS • *Other options: Low-dose ICS-LABA* • *Other options: Low-dose ICS + montelukast*	3. Daily and PRN ICS-LABA
	Severe (symptoms most days, or waking with asthma once a week or more)	3. Refer to specialist	3. Refer to specialist	4. Daily med-high-dose ICS-LABA + PRN low-dose ICS

All guidelines recommend SABA as-needed as a reliever for all steps.
BTS-SIGN recommends the following medicines as short-acting bronchodilators: inhaled short-acting B2 agonists, inhaled ipratropium bromide, and theophyllines.

Table 6d. NICE - stepwise management for asthma differs according to age groups - NICE[28].

Guideline	Severity	Treatment Steps: Preferred Treatment	
		Young Children (<5 years)	Older Children (5-16 years)
NICE[28]	**Intermittent-mild** (including suspected asthma or newly diagnosed)	1. SABA as reliever therapy	1. SABA alone as reliever therapy
	Moderate-severe (if uncontrolled with current treatment and symptoms are increasing in intensity/frequency)	2. Moderate dose ICS (trial for 8 wks)	2. Low-dose ICS
		3. Low-dose ICS	3. Low dose ICS + LTRA (trial for 4-8 weeks)
		4. Low dose ICS + LTRA	4. Low-dose ICS + LABA (stop LTRA)
		5. Stop LTRA; Refer to specialist	5. Low-dose ICS + MART
		-	6. Medium-dose ICS + MART • *Other options: Consider changing MART to fixed-dose ICS and LABA, with SABA as reliever therapy*
		-	7. Seek advice from a healthcare professional with expertise in asthma • *Other options: High-dose ICS with SABA as reliever therapy; trial of an additional drug*

Note: Guideline recommends SABA as-needed as reliever for all steps, except GINA recommendations for adolescents (Track 2).* Short course OCS may be needed for patients presenting with severe uncontrolled asthma.

Table 7. The stepwise management for asthma differs according to age groups.

Guideline	Severity	Treatment Steps: Preferred Treatment		
		Young Children (<6 Years)	Older Children (6-11 Years)	Adolescents (12-17 Years)
China[21][22][23][24]	Mild persistent	1. None	1. None	
	Mild persistent	2. Low-dose ICS	2. Low-dose ICS	
	Moderate persistent	3. Medium does ICS	3. Low-dose ICS-LABA	
	Severe persistent	4. Medium- and high-dose ICS + LTRA	4. Med- and High-dose ICS-LABA	
		-	5. Med- and high-dose ICS-LABA + LTRA and/or EX theophylline + lowest dose OCS	
GINA[10][25]	Mild infrequent	1. None	1. ICS PRN + SABA	1. PRN Low-dose ICS-formoterol (Track 1); ICS whenever SABA is taken (Track 2)
	Mild persistent	2. Daily low-dose ICS	2. Daily low-dose ICS	2. PRN Low-dose ICS-formoterol (Track 1) or ICS (Track 2)
	Moderate persistent	3. Double low-dose ICS	3. Low-dose ICS-LABA or med-dose ICS or very low-dose MART	3. Low-dose ICS-formoterol (Track 1) or ICS-LABA (Track 2)
	Daily symptoms, ≥1 night/week	4. Refer to specialist	4. Med-dose ICS-LABA or low-dose ICS-formoterol (MART); refer to specialist	4. Med-dose ICS-formoterol (Track 1)* or ICS-LABA (Track 2)*
		-	5. Refer for phenotypic assessment ± higher dose of ICS-LABA or add-on anti-IgE	5. High-dose ICS-formoterol (Track 1) or ICS-LABA (Track 2); add on LAMA; refer for phenotypic assessment; ± anti-IgE, -IL5/5R, -IL4R
NHLBI[26]	Intermittent	1. Short course ICS	1. PRN SABA	1. PRN SABA
	Mild	2. Daily low-dose ICS	2. Daily low-dose ICS	2. Daily low-dose ICS or PRN concomitant ICS + SABA
	Moderate	3. Daily medium-dose ICS	3. Daily and PRN low-dose ICS-formoterol	3. Daily and PRN low-dose ICS-formoterol
	Severe	4. Daily medium-dose ICS-LABA	4. Daily PRN med-dose ICS-formoterol	4. Daily PRN med-dose ICS-formoterol
		5. Daily high-dose ICS-LABA	5. Daily high-dose ICS-LABA	5. Daily med-high-dose ICS-LABA + LAMA
		6. Daily high-dose ICS-LABA (or ICS) + OCS	6. Daily high-dose ICS-LABA + OCS	6. Daily high-dose ICS-LABA + OCS
BTS-SIGN[28]	Suspected asthma	1. Very low-to-low-dose ICS	1. Very low-to-low-dose ICS	
	Confirmed asthma: move up/down depending on control	2. LTRA	2. Very low-dose ICS (as regular preventer)	
		3. Very low dose ICS + LTRA	3. Very low-dose ICS +LABA or LTRA	
		4. Low-dose ICS	4. Low-dose ICS or add on LABA (stop if no response) or LTRA	
		5. Refer to specialist	5. Refer to specialist	
NICE[28]	Suspected asthma	1. SABA + reliever	1. SABA alone	1. PRN SABA alone
	If uncontrolled with SABA (symptoms >3 times/week, night awakening) - move up/-down depending on control	2. Moderate dose ICS (trial for 8 wks)	2. Low-dose ICS or add-on LTRA (trial for 4-8 wks)	2. Low-dose ICS
		3. Low-dose ICS	3. Low dose ICS + LABA	3. Low-dose ICS-LABA
		4. Low dose ICS + LTRA	4. Low-dose ICS + MART or med-dose ICS (± MART)	4. Medium-high-dose ICS-LABA
		5. Stop LTRA; Refer to specialist	5. Refer to specialist	5. Refer to specialist
TSANZ[31]	Recurrent wheeze	1. None (<12 mo); PRN SABA (1-5yrs)	1. PRN SABA	1. PRN SABA
	Symptoms every 4-6 weeks or ≤1/week, and/or nighttime symptoms >2/mth (>6yrs) - move up/down depending on control	2. Low-dose ICS	1. Low-dose ICS or montelukast/chromones	2. Daily low-dose ICS
		3. Low-dose ICS + montelukast	2. High-dose ICS or Low-dose ICS-LABA or low-dose ICS + montelukast	3. Daily and PRN ICS-LABA
		-	3. Refer to specialist	4. Daily med-high-dose ICS-LABA + PRN low-dose ICS

Note: All guidelines recommend SABA as-needed as reliever for all steps, except GINA recommendations for adolescents (Track 2).* Short course OCS may be needed for patients presenting with severe uncontrolled asthma.

Treatment of vitamin D insufficiency in pregnant patients with asthma is suggested as primary asthma prevention in children.

Focus updates are also made for the NHLBI 2020 guideline. In children aged 0-4 years, a short course of daily ICS (as opposed to PRN SABA) is recommended at the onset of a respiratory infection [4, 15, 26, 35, 37]. In children aged ≥12 years with uncontrolled persistent asthma, adding LABA (instead of LAMA or long acting muscarinic antagonists) to ICS is preferred [10, 21-24].

SCIT (Subcutaneous immunotherapy) but not (SLIT) sublingual immunotherapy is recommended as an adjunct treatment to standard pharmacotherapy in children aged ≥5 years with mild-to-moderate asthma.

The use of SLIT for childhood asthma is generally not recommended as there is insufficient evidence [10, 17, 21-23, 28, 32-34, 38].

3.4.6. The Age-based Stepwise Management for Asthma

The stepwise management of asthma differs according to age groups. Minor variations in the recommendations for SABA and ICS across these guidelines are tabulated (Table **7**).

Use of selected biologics (*e.g.*, omalizumab (anti-IgE), benralizumab (anti-IL5), mepolizumab (anti-IL5) and dupilumab (anti-IL4)) requires specialist evaluations. The guidelines for use of two biologics, omalizumab and benralizumab are included in this overview (Table **8**) [28].

3.4.7. Complimentary Therapies

Recommendations on the use of other therapeutic interventions for asthma including oxygen therapy, traditional Chinese medicine (TCM), breathing exercises and vitamin D supplementation have been reviewed [39]. They are also recommended by some of the guidelines (Table **9**) [28].

Table 8. Guidelines concerning two biologics.

-	GINA 2021[a]/ EAACI 2020[b/] ERS-ATS 2020[c]	TSANZ[d(31)]	NICE[(28)]	NHLBI	BTS-SIGN 2019	China Guideline21
-	**Children ≥6 Years Old***					
Omalizumab (Anti-IgE)	• **Uncontrolled severe allergic asthma** (children 6-11 yrs old) • **Moderate to severe allergic asthma** (in patients ≥6[a] or 12-17[b,c] years) uncontrolled on step 4-5 treatment. [a]bEos ≥260µl or FeNO ≥20 ppb; Baseline IgE does not predict response [b]Total IgE level of 30-700 IU/mL (US) 30-1500 IU/mL (EU) ± one perennial aeroallergen [c]bEos ≥260 μL^{-1}, FeNO ≥19.5 ppb	• Add-on treatment for **uncontrolled severe allergic asthma*** in children aged ≥6 years despite daily high-dose ICS • Management of **moderate to severe allergic asthma**[d] adolescents aged ≥12 years already using ICS [d]Past or current evidence of atopy, documented by skin prick testing or an *in vitro* measure of specific IgE, that is no more than 1 year old AND total serum IgE ≥30 IU/mL.	Severe persistent confirmed **allergic IgE-mediated asthma**** in patients who need continuous/frequent treatment with OCS (≥4 courses in the last year)	Conditional recommendation as **step 5 and 6 treatment** in children aged ≥5 years old	Omalizumab SC may be considered in eligible patients with a high oral corticosteroid burden, especially those with **moderate or severe allergic asthma.**	• It has a good effect on IgE-mediated allergic asthma. • Suitable for children aged ≥6 years with **severe persistent allergic asthma** whose serum IgE is significantly elevated and cannot be controlled with high-dose ICS and LABA
	Children ≥12 Years Old*					
Benralizumab (Anti-IL5)	Benralizumab is recommended in the children with uncontrolled **severe eosinophilic asthma**[a,b] [a]bEos ≥150 or ≥300µL [b]high-dose ICS + LABA with baseline bEos >300 or >150 cells/µL for OCS-dependent patients	Add-on treatment for uncontrolled **severe eosinophilic asthma**[§] in patients aged ≥12 years [d]bEos ≥300 cells per µL (≥150 cells per µL while receiving treatment with oral corticosteroids) in the last 12 months	**Severe eosinophilic asthma**[e] [e]bEos ≥300µl and ≥4 exacerbations (or bEos ≥400µl and ≥3 exacerbations) requiring systemic CS in the last 12 mths; or had continuous OCS of prednisolone 5mg/day over the previous 6 mths or	*No specific recommendations for the use of biologics (ie, anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13) in asthma in Steps 5 and 6 for children ages ≥12 years*	May be considered in eligible patients with and a high oral corticosteroid burden, particularly those with **severe eosinophilic asthma**	*No recommendations for the use of mepolizumab as an add-on therapeutic option for asthma*

Abbreviations: bEos: Blood eosinophil; CS: corticosteroid; FeNO: Fractional exhaled nitric oxide; ICS: Inhaled corticosteoroid; LABA: Long-acting beta2 agonist; OCS: Oral corticosteroid; ppb; part per billion; SABA: Short-acting beta-agonist

Note: * ** TSANZ 'uncontrolled severe allergic asthma' GINA 'allergic IgE-mediated asthma'

Table 9. Complimentary therapies.

Therapy	China[21][22][23][24]	GINA[10][25]	NHLBI[26]	NICE[28]	BTS-SIGN[28]	TSANZ[9]
Oxygen therapy (for worsening asthma)	R	R	-	-	R	R
Yearly influenza and childhood vaccination (influenza vaccination recommended in moderate to severe asthma only)	-	R	R	-	R	R
Traditional Chinese Medicine (TCM) TCM emphasises treatment based on symptom differentiation and must be selected according to the specific situation of the child in clinical practice. Nevertheless, there is still a lack of robust evidence on the various formulations and the efficacy of these treatments in childhood asthma[1,2]	R	-	-	-	IE	IE/NR
Breathing exercises Breathing exercises including the Buteyko method and Papworth method, may be a useful supplement to asthma pharmacotherapy for symptoms and quality of life, but they do not reduce exacerbation risk of have consistent effects on lung function[10][25]	-	IE	-	-	IE	IE
Vitamin D supplementation Several cross-sectional studies have shown that serum levels of Vitamin D are linked to impaired lung function, higher exacerbation frequency and reduced corticosteroid response. Vit D supplementation may reduce the rate of asthma exacerbation requiring treatment with systematic corticosteroids.[3] However further research is required on whether the effects of Vit D supplementation are confided to people with lower baseline Vit D status and into the effects on people with frequent severe asthma attacks.[7]	-	IE	-	-	IE	IE

Abbreviations: R: Recommended; NR: Not recommended; IE: insufficient/limited evidence.
Note: NICE, ATS-ERS and EAACI did not provide specific recommendations for alternative therapies for childhood asthma.

Table 10. Non-pharmacological considerations.

Trigger Avoidance	Patient Education	Adolescent to Adult Care	Asthma Action Plan
Triggers[10][21][22][23][24][25] • Indoor/outdoor allergens/pollution • Anxiety/stress exercise • Medications that may make asthma worse	• Ways to **avoid triggers** that induce exacerbations • Encourage **self management** based on clinical symptoms and results of PEF monitoring (see asthma action plan) • Encourage **adherence to medications**, appointments and correct inhaler technique[10][25] • Consider **medication options** and effects of long-term use[7]	• **By mid-adolescence** (around 14-16 years old), patients should be treated as an adult[9] • For **pubescent girls**, assess whether flare-ups are affected by the menstrual cycle; consider hormonal management or refer for investigation for girls with predictable perimenstrual worsening of asthma symptoms[9]	**Written plans on actions to take if asthma deteriorates**, including seeking emergency help, starting oral steroids (which may include provision of an emergency course of steroid tablets), restarting or temporarily increasing fourfold (as opposed to just doubling) ICS, as appropriate to clinical severity.[6,9][28] The Chinese Asthma Action plan is **categorised based on symptoms or PEF**[2] • Green (PEF ≥ 80% predicted value) • Yellow (PEF at 60% - 80% the expected value) • Red (PEF< 60%)
Lifestyle			
• Manage **comorbid conditions** and psychosocial factors • Promote **natural delivery**, encourage **breastfeeding**, avoid use of broad-spectrum antibiotics in children <1 year, **weight reduction in obese/overweight children** to reduce likelihood of respiratory symptoms suggestive of asthma.[28] • Encourage a **healthy diet** high in fruits and vegetables and **regular physical activity** for its general health benefits.[10][25]			

Note: Chinese guidelines[1,2]; GINA[3]; NHLBI[126] ; BTS-SIGN[28]
Abbreviations: ICS: Inhaled corticosteroid; PEF: Peak expiratory flow.

3.5. Non-pharmacologic Treatment

Additional strategies may be considered to support symptom control or reduce the risk of future asthma exacerbations. Trigger avoidance, patient education, adolescent to adult care, lifestyle issues, and asthma action plan are recommended by some of the guidelines (Table **10**) [28].

3.6. Monitoring of Asthma Control

Asthma management may require adjustment to medication regimens through a control-based management cycle. This includes timely step-up and step-down of treatment, along with regular monitoring.

Table 11. Monitoring asthma control in children with asthma.

Asthma Monitoring Tools	China[21][22][23][24]	GINA[10][25]	NHLBI[26]	NICE[28]	BTS-SIGN[28]	TSANZ [31]
Self-monitoring	Asthma diary	2-week diary	-	-	-	-
PEF measurements	Record daily PEF in an asthma diary	Short-term monitoring	Children ≥4 years	Children ≥5 years	Children ≥5 years	-
Spirometry	-	Children ≥5 years	Children ≥12years	Children ≥5 years	Children ≥5 years	Every 1-2 years
FeNO	As part of an ongoing monitoring strategy	As part of an ongoing monitoring strategy	Children ≥5 years; as part of an ongoing monitoring strategy	Not for routine monitoring*	Only in specialist asthma clinic	Children ≥5 years; as part of an ongoing monitoring strategy
Sputum eosinophils	N/IE	N/IE	-	-	N/IE	-
Adherence and compliance	Observe at every consultation, when inhaler is changed or when asthma control deteriorates. Consider poor adherence, inhaler technique, environmental factors, and comorbid conditions before escalating treatment					

Note: *Only for patients who are symptomatic despite using ICS
Abbreviations: ** FeNO is not recommended for children <5 years and is supported as a part of an on-going monitoring strategy and not to be used alone as a basis for ICS treatment. In children, FeNO-guided treatment significantly reduces exacerbations rates in children however
R: Recommended; N/IE: Not recommended/insufficient evidence. ACQ (>5 yrs), C-ACT (4-11 yrs), mini AQLQ (7-11yrs) C-ACS, Asthma Control Score for children; ATAQ, Asthma Therapy Assessment Questionnaire; CASI, Composite Asthma Severity Index; deNO, Fractional exhaled nitric oxide; PCAS, Primary care Asthma Control Screening; PEF, Peak expiratory flow, Test for Respiratory and Asthma Control in Kids

3.6.1. Step Up Treatment

Step up of treatment is indicated if control is not achieved after reviewing patient adherence, their inhaler technique and control of triggering factors [28]. Considerations for step-up include:

(i) Short-term increase for 1-2 weeks in maintenance ICS dose during viral infections or seasonal allergen exposure (GINA guideline).

(ii) If frequency of symptoms increases (from less than twice a month, to twice a month or more) or if exacerbations continue to occur, step up to daily low dose ICS.

(iii) Use SABA as needed, dependent on severity of symptoms:

Up to 3 treatments at 20-minute internals (NHLBI guideline) [7]
Consider moving up if already using ≥3 doses a week (BTS-SIGN guideline).

(iv) Consider adding LTRA in combination with ICS (TSANZ guideline).

(v) If no clear benefit or control is observed within 4-6 weeks, the clinician should consider alternative diagnosis, adjusting therapy (NHLBI guideline) [7] or referral to a specialist for assessment before stepping up (TSANZ guideline) [31]. Thereafter reassess every 2-6 weeks (TSANZ guideline) [31].

Patients with difficult-to-treat asthma have inadequately controlled symptoms despite optimization of step 4 therapy for 1-3 months [24, 40]. At each visit, inhaler technique and patient compliance to drug adherence must be assessed. In these patients, asthma mimics such as tracheal tumors and vocal cord dysfunction have to be considered. These patients should be evaluated for the possibility of allergic bronchopulmonary aspergillosis. Oral corticosteroids at low dose and for short duration should be considered if asthma symptoms are uncontrolled despite maximization of step 4 therapy. Drug-related adverse effects should also be simultaneously monitored.

3.6.2. Step Down Treatment

When symptoms are well-controlled for at least 3 months (China, NHLBI, NICE guidelines) [7] or 6 months (with close supervision within 4-6 weeks; TSANZ guideline [31]):

(i) Reduce ICS dose by 25-50% if using medium- and high-dose ICS alone according to China guideline [35].

(ii) Switch to once-daily low-dose ICS. Complete cessation of ICS can be considered if using low-dose ICS alone according to China guideline [35].

(iii) If using an ICS with LABA, reduce ICS dose first by 50%. Only discontinue LABA once low-dose ICS is achieved according to China guideline [35].

3.6.3. Asthma Control Assessment

Asthma control assessment is a key element of asthma care (Table **11**). Self-monitoring by asthma diary for children is only recommended by the CHINA and GINA guidelines. The Chinese guideline encourages children to adhere to daily PEF measurements, monitor changes in their symptoms, and record these in their asthma diaries [37].

CONCLUSION

According to some of the major guidelines, few conclusions can be made [3, 7].

Diagnosis

The diagnosis of asthma should be considered in a patient with recurrent or episodic breathlessness, cough, wheezing or chest tightness without an alternative diagnosis for these symptoms. Paradoxically, none of the signs and symptoms are specific for the diagnosis of asthma, and the absence of symptoms at presentation does not refute its diagnosis. Therefore, several guidelines do not base the diagnosis of asthma on symptomatology.

Spirometry

Importantly, a normal spirometry study does not refute asthma. However, spirometry should be performed to confirm diagnosis, assess severity and monitor asthma control [37, 41-43]. The ratio of FEV1 to forced vital capacity (FVC) (*i.e.*, FEV1/FVC) below the 5th percentile of reference population values should preferentially be used to diagnose the presence of obstruction of airflow. A fixed cut-off of FEV1/FVC less than 0.75 for older individuals and less than 0.8 for younger patients may be used to confirm the diagnosis of airway obstruction. Testing for reversibility of airflow obstruction following the usage of bronchodilator medication is useful for asthma diagnosis if a spirometry study shows airflow limitation. PEF meters may be used to assess bronchodilator reversibility if spirometry evaluation is not available. Importantly, bronchodilator reversibility is neither necessary for diagnosing or excluding asthma. Furthermore, PEF measurements and FEV1 measurements are not interchangeable. Patients and their families should be encouraged to practice self-monitoring of PEF for optimizing asthma control.

Routine bronchoprovocation testing is no longer advocated for asthma diagnosis [44-46] Methacholine challenge testing is useful to exclude asthma when spirometry is normal. The chest radiograph is not routinely necessary unless complications or an alternate diagnosis is suspected.

Quantification of eosinophil in sputum can guide inhaled corticosteroid therapy in adults with moderate to severe asthma, thereby reducing the risk of exacerbations in these patients [47-51] Eosinophils <2% are considered normal, and more than 2% are suggestive of eosinophilic inflammation instead of neutrophilic inflammation.

Routine FENO or exhaled breath fractional nitric oxide measurement is not advocated in the management of asthma [52-56] Routine evaluations of allergic status by quantifications of total Immunoglobulin E (IgE), specific IgE to common aeroallergens, and allergic skin prick testing are not advocated for asthma diagnosis or its management. These tests are usually performed in specialized centers when specific triggers are considered.

Oxygen Saturation

Oxygen saturation is assessed by pulse oximetry measurement during an acute attack of asthma. Exacerbations that are not severe generally do not require any investigation, except pulse oximetry and PEF. Patients with a PEF < 60% of predicted (or personal best, and patients with an oxygen saturation of less than 92% should be transferred to and treated in the emergency department and admitted to the hospital. An arterial blood gas analysis ought to be performed to evaluate oxygenation and carbon dioxide retention. Oxygen is administered and titrated to maintain a SpO_2 between 93% and 95% [57-59] $PaCO_2$ should be closely monitored in patients if more than >8 L/min of oxygen is needed.

Medications

ICSs should be used as controller medication in stable asthma. They are of equal efficacy when used in low-to-moderate equipotent doses in the majority of patients. ICS is usually started at low to moderate doses and used at the lowest possible doses. High-dose ICS use should generally be avoided to reduce the risk of both systemic and local side effects. LABA monotherapy is not used in patients with stable asthma. LABA added to ICS should be used when symptoms are not controlled despite moderate doses of ICS monotherapy.

Leukotriene modifiers do not have a role in acute asthma. Beyond the acute phase, leukotriene agonist (LTRA) monotherapy is inferior to ICS monotherapy. LTRA monotherapy is an alternative to ICS monotherapy in children with mild asthma if the parents (steroid phobia) or patients (not tolerating the inhaler device) are unwilling to use ICS. A LABA is better than LTRAs as an add-on to ICS. Addition of LTRA to ICA/LABA in patients with uncontrolled asthma may be beneficial. Tiotropium may also be considered as add-on therapy to ICS/LABA if asthma remains uncontrolled despite moderate-to-high doses of ICS/LABA.

Monotherapy with methylxanthine is inferior to ICS monotherapy. Doubling the dose of ICS when stepping up from ICS monotherapy is as effective as ICS with methylxanthine. ICS with methylxanthine is inferior to the combination therapy of ICS/LABA.

SABA is a rescue medication for the treatment of asthma. SAM or short-acting muscarinic antagonist is not an add-on/alternative to SABA as a reliever drug. LABA monotherapy (*i.e.*, formoterol) should not be used as a reliever because of safety concerns. Oral beta-agonists (such as Procaterol) should not be used as rescue drugs. ICS/LABA combination (formoterol-based) in a single inhaler as both maintenance and reliever medication is preferred.

Bronchodilators

Fast-acting inhaled beta-2 agonists (*e.g.*, ventolin or salbutamol) are bronchodilators used for acute asthma exacerbation [60]. Combined salbutamol and ipratropium bromide produce synergistic bronchodilation than either drug alone. Ipratropium is indicated in all patients with severe asthma exacerbations (*e.g.*, 500 μg once followed by 250 μg q4-6 h). A higher-metered-dose inhaler (MDI) used with a spacer device is equally effective as a nebulizer for acute asthmatic attacks. Nebulized drugs can be delivered to children unable to use MDI with a spacer. The nebulizer should be switched back to a spacer once the patient's asthma is sta-

bilized. Continuous nebulization (2.5 mg salbutamol given every 15 min) is more efficacious than intermittent nebulization (2.5 mg salbutamol administered every 20 min) of fast-acting SABA. The subsequent dosage of nebulized salbutamol should be 2.5 mg every two to four hours for optimal clinical response. There is no added benefit with formoterol over salbutamol. Thus, formoterol is not advocated for routine use in the management of acute asthma.

Theophylline and parenteral beta-2 agonists are not routinely used due to increased adverse reaction profiles. They confer no additional advantage over inhaled SABA unless in exceptional circumstances, such as in an ICU setting where inhaled drugs are not effective.

Corticosteroids

Systemic corticosteroids are indicated in all patients with acute asthmatic attacks that are severe. The oral route and the parenteral route are equally effective, except in critically ill children who could not tolerate or those with contraindications to feeding per orally. Oral glucocorticosteroids (1-2 mg/kg of prednisolone equivalent per day for 5-7 days are sufficient in the majority of patients. There is no need to taper systemic steroids if given for < 3 weeks. In less severe asthma exacerbations, patients are initially managed with 4 to 6 puffs of 100 µg salbutamol given every 30 min. Once daily dose of oral prednisone (dosage 1-2mg/kg) should be administered for 5-7 days if there is no response to inhaled salbutamol within an hour. ICSs give no additional advantage when administered along with oral or systemic corticosteroids and are therefore, not advocated in acute asthmatic attacks. Inhaled steroids are usually stepped up at discharge for 2-4 weeks in addition to oral corticosteroids.

Monoclonal Antibody

Omalizumab can be used as an adjunct to ICS in moderate-to-severe asthma patients with (1) elevated serum levels of IgE and (2) sensitization to at least one perennial aeroallergen (*i.e.*, a positive skin test).

Immunotherapy

Immunotherapy for a single allergen may give a modest benefit to mild-to-moderate asthma patients with demonstrable cutaneous allergy to the specific antigen. Immunotherapy for multiple allergens is not currently recommended based on current evidence. Immunotherapy carries severe risks and potentially life-threatening reactions, and it should only be practiced in specialized centers. Immunotherapy is contraindicated in severe or poorly controlled asthma, and in patients with FEV1 less than 70% due to higher risks of fatal reactions.

Pulmonary Rehabilitation Therapy

Pulmonary rehabilitation therapy may improve quality of life and exercise capacity [61-66]. Although often advocated, current evidence is not sufficient to demonstrate the efficacy of influenza or pneumococcal vaccination for patients with asthma [67-70] There is no role for oral antibiotics in the prevention of attacks or exacerbations of asthma [71-73]. Pretreatment with bronchodilator drugs (any of the SABA, LABA and SAMA) and anti-inflammatory medications (LTRA but not ICS) is efficacious in reducing the fall in FEV1 in exercise induced asthma. Regular use of LTRAs or ICSs can prevent exercise-induced asthma. LABA by long-term regular administration, may induce tolerance and is associated with an increase in adverse effects and should not be used as prophylaxis for EIA. The management of aspirin-induced asthma (AIA) should not be different from that of asthma except for the avoidance of NSAIDs. Symptoms of occupational asthma can be improved by both removal and reduction of exposure.

Removal of exposure is better than reduction of exposure if feasible.

Cessation of smoking is advocated for all asthmatic patients who smoke. Patients with difficult asthma and comorbidities (such as gastro-esophageal reflux disease, obstructive sleep apnea, obesity and rhinitis) should be treated accordingly. Optimal self-management involving self-monitoring, patient education, regular review and follow-up, and usage of a written asthma action plan in combination is advocated in asthma management.

AUTHORS' CONTRIBUTIONS

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

LIST OF ABBREVIATIONS

AIT	=	Allergen Immunotherapy
BD	=	Twice Daily
BDR	=	Bronchodilator Responsiveness
bee's	=	Blood Eosinophil
BHR	=	Bronchial Hyperresponsiveness
Bpm	=	Beats per Minute
C-ACT	=	Childhood-Asthma Control Test
CCAAP	=	Chinese Children's Asthma Action Plan
CXR	=	Chest X-ray
DPI	=	Dry Powder Inhaler
EAACI	=	European Academy of Allergy and Clinical Immunology
ED	=	Emergency Department
ERS-ATS	=	European Respirology Society-American Thoracic Society
FDC	=	Fixed-dose Combination
FeNO	=	Fractional Exhaled Nitric Oxide

FEV1/FVC = Forced Expiratory Volume in One Second/-Forced Vital Capacity

FEV1 = Forced Expiratory Volume in One Second

GINA = Global Initiative for Asthma

HDM = House Dust Mite

ICS = Inhaled Corticosteroids

IgE = Immunoglobulin E

LABA = Long-acting beta2 Agonist Agonist

LAMA = Long-acting Muscarinic Antagonists

LTRA = Leukotriene Receptor Antagonist

MART = Maintenance and Reliever Therapy

MDI = Metered Dose Inhaler

min = Minute

mth = Month

NAC = National Asthma Council (Australia)

NAEPP = National Asthma Education and Prevention Program

NHLBI = National Heart, Lung and Blood Institute (US National Institute of Health); NICE = National Institute of Health Care Excellence, UK

OCS = Oral Corticosteroid

Paed = Paediatric

PEF = Peak Expiratory Flow

PICU = Paediatric Intensive Care Unit

pMDI = Pressurized Metered-dose Inhaler

PRN = As-needed Dosing

SABA = Short-acting Beta-agonist

SCIT = Subcutaneous Immunotherapy

SIGN = Scottish Intercollegiate Guidelines Network

SLIT = Sublingual Immunotherapy

SpO2 = Peripheral Capillary Oxygen Saturation

TSANZ = Thoracic Society of Australia and New Zealand

URTI = Upper Respiratory Tract Infection

Wk = Week(s)

X = Time(s)

Yrs = Year(s)

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CONFLICT OF INTEREST

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