Workshop summary

Uniform definition of asthma severity, control, and exacerbations: Document presented for the World Health Organization Consultation on Severe Asthma

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Asthma is a global health problem affecting around 300 million individuals of all ages, ethnic groups and countries. It is estimated that around 250,000 people die prematurely each year as a result of asthma. Concepts of asthma severity and control are important in evaluating patients and their response to treatment, as well as for public health, registries, and research (clinical trials, epidemiologic, genetic, and mechanistic studies), but the terminology applied is not standardized, and terms are often used interchangeably. A common international approach is favored to define severe asthma, uncontrolled asthma, and when the 2 coincide, although adaptation may be required in accordance with local conditions. A World Health Organization meeting was convened April 5-6, 2009, to propose a uniform definition of severe asthma. An article was written by a group of experts and reviewed by the Global Alliance against Chronic Respiratory Diseases review group. Severe asthma is defined by the level of current clinical control and risks as "Uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity (including impaired lung function or reduced lung growth in children)." Severe asthma includes 3 groups, each carrying different public health messages and challenges: (1) untreated severe asthma, (2) difficult-to-treat severe asthma, and (3) treatment-resistant severe asthma. The last group includes asthma for which control is not achieved despite the highest level of recommended treatment and asthma for which control can be maintained only with the highest level of recommended treatment. (J Allergy Clin Immunol 2010;126:926-38.)

Key words: *Asthma, severity, control, risk, definition, GARD*

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Asthma is a global health problem affecting around 300 million individuals of all ages, ethnic groups, and countries.[1] It is estimated that around 250,000 people die prematurely each year as a result of asthma.[1] However, due to geographical diversity, there is a considerable heterogeneity of asthma in terms of gene-environment interactions, pathophysiological mechanisms,

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environmental exposures, comorbidities, age, underlying disease severity, health care access, care received, psychological factors, responsiveness of disease to therapy, and burden of disease including asthma exacerbations and death as well as long-term chronic morbidity.[2]

Concepts of asthma severity and control are important in evaluating patients and their response to treatment as well as for public health, registries, and research (clinical trials, epidemiologic, genetic, and mechanistic studies), but the terminology applied is not standardized, and terms are often used interchangeably. A common international approach is favored to define severe asthma, uncontrolled asthma, and when the 2 coincide,[3] although adaptation may be required in accordance with local conditions.

In 2008, an American Thoracic Society (ATS)/European Respiratory Society (ERS) Task Force reported some new perspectives on asthma control and severity to achieve uniform reporting of clinical trials.[4] These concepts were appropriate for patients who have access to optimal drug treatments and to evaluate the response of patients to these interventions. Asthma in preschool children was not included, nor were aspects of severity related to public health issues and management in high-income countries or low-income and middle-income countries (LMICs).[5,6]

The first asthma guidelines were constructed on the idea that the practitioner first assessed and then graded asthma severity.[7] The major reasons to characterize asthma severity were to guide management and to identify people with asthma at risk of severe exacerbation. Unfortunately, the case definitions of asthma severity and control were not always clear, and over the last 2 decades, they varied between and within asthma management guidelines. Initially, asthma guidelines proposed a stepwise management according to disease severity[7] that was based on symptoms, the need for rescue medications, and lung function tests (eg, peak

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Abbreviations used

ATS: American Thoracic Society
COPD: Chronic obstructive pulmonary disease
DPI: Dry powder inhaler
EPR3: Expert Panel Report 3
ERS: European Respiratory Society
GINA: Global Initiative for Asthma
ICS: Inhaled corticosteroid
LABA: Long-acting ß$_2$-agonist
LMIC: Low-income and middle-income country
MDI: Metered-dose inhaler
NAEPP: National Asthma Education Prevention Program
OCS: Oral corticosteroid
PEF: Peak expiratory flow
PHC: Primary heath care
WHO-PEN: World Health Organization Package of Essential Interventions for Noncommunicable Diseases
WHO: World Health Organization

expiratory flow [PEF] rate and FEV_1). However, as it became increasingly recognized that categorizing asthma involved assessing both the severity of the underlying disease and its responsiveness to treatment,[8-10] later iterations of the guidelines viewed asthma severity according to the current treatment the patient was receiving.[11,12]

The classification of asthma by severity has raised concerns.[13-16] Severity is not a stable feature of asthma but may change with time, whereas the classification by disease severity suggests a static feature. Moreover, the term *severity* is used variably to indicate current symptoms, the resistance of symptoms to standard treatment, and future risk of death or exacerbations. Responsiveness to treatment is heterogeneous, even among patients with asthma of similar severity. Moreover, the use of severity as a single outcome measure has limited value in predicting which treatment will be required and the response to that treatment.[17,18] These considerations prompted some guideline committees to propose that asthma severity is no longer used as the basis for treatment decisions, and that the focus is more so to assess current clinical asthma control first[19] and then to adjust treatment accordingly in a stepwise manner.[11] The National Asthma Education Prevention Program (NAEPP)–Expert Panel Report 3 (EPR3) proposed that the concepts are linked: severity is the intrinsic intensity of the disease, control is the degree to which the manifestations of asthma are minimized by treatment, and responsiveness is the ease with which asthma control is achieved. EPR3 further proposed that severity and control incorporate 2 distinct domains: impairment (frequency and intensity of symptoms and functional limitations currently experienced) and risk (likelihood of exacerbations, progressive decline in lung function or, for children, reduced lung growth, or risk of medication side effects).[20,21]

A guideline for the management of asthma in LMICs has been published by The Union (International Union Against Tuberculosis and Lung Disease) based on the Global Initiative for Asthma (GINA) 1995 and adapted to the availability and affordability of medications[22] and the World Health Organization (WHO) Model List of Essential Medicines. An update was published in 2008.[23] In these guidelines, inhaled corticosteroids (ICSs) as potent anti-inflammatory drugs are proposed as the mainstay treatment for the management of asthma based on disease severity as assessed by symptoms and lung function measurement.

All asthma guidelines propose that for an individual patient, the practitioner should perform a periodic assessment of asthma control and adjust treatment accordingly.[11,12,20,23-25] This is particularly important in children, in whom remission of asthma is common.

Three important issues regarding the current global situation for asthma management have led to the proposal for the uniform definition of severe asthma. First, health care provision in different countries is disparate, especially in LMICs, which have limited or no access to chronic medical care or asthma therapies. Second, with appropriate management,[11,12,20,23-25] the control of asthma can be achieved adequately in most patients. Third, direct and indirect costs for asthma are substantial, in particular in low-resource settings.[26,27] Thus, a standardized definition of severe asthma will promote efficient identification and treatment of patients. These patients will benefit from treatment, and, in turn, this will ease the burden of the disease on patients, their families, and society.

The proposal for a uniform definition of asthma severity, control, and exacerbations has taken into account the GINA 2006 revision,[11] the 2007 NAEPP-EPR3,[20] The Union 2008 guide,[23] and the 2008 ATS/ERS Task Force report[4] and has considered the previous definitions of the 2 ERS[28] and ATS Task Forces,[8] in which the terms "severe," "therapy-resistant asthma," "refractory asthma," or "difficult-to-control asthma" were applied to patients with symptomatic asthma on current treatment.

GOAL OF THE WHO CONSULTATION

The goal of the WHO Consultation on Severe Asthma (Geneva, April 6-7, 2009) was to propose a WHO definition of asthma severity and control as well as criteria for describing exacerbations and their severity, which should be applicable in most circumstances in low-, middle-, and high-income countries.

MANAGEMENT OF ASTHMA

Diversity of asthma management across the world

The management of asthma differs widely and is dependent on patients' centered problems (socioeconomic and cultural barriers) as well as national, economic, and health provider settings. In high-income countries, most antiasthma treatments are available and, for the majority of patients, are affordable. Therefore, asthma management in these countries is possible using guidelines formulated without respect to medication availability, cost, and affordability. However, in many LMICs, essential medicines may be available but are rarely affordable.[29,30] In these settings, patients and health care providers are used to short-term continuous treatments for most communicable diseases and do not easily understand the need for long-term treatments. In the primary health care (PHC) settings of LMICs, only syndromic approaches for major noncommunicable diseases are applicable.[31,32] In many LMICs, the availability of objective pulmonary function testing such as spirometry and PEF measurement is also problematic, although the availability and use of PEF has recently been recommended to all PHC facilities (WHO Package of Essential Interventions for Noncommunicable Diseases [WHO-PEN]).[33] Hence, both adequate treatments and organized health care systems are needed, as well as an appropriate communication to health care providers and patients.

TABLE I. WHO model list of essential medicines for asthma and COPD[34]

☐ Beclometasone	Inhalation (aerosol): 50-250 μg (dipropionate) per dose
Epinephrine (adrenaline)	Injection: 1 mg (as hydrochloride or hydrogen tartrate) in 1 mL ampoule
Ipratropium bromide	Inhalation (aerosol): 20 μg/metered dose
☐ Salbutamol	Inhalation (aerosol): 100 μg (as sulfate) per dose)
	Injection: 50 μg (as sulfate)/5 mL ampoule
	Oral liquid: 2 mg/5 mL
	Respirator solution for use in nebulizers: 5 mg (as sulfate)/mL

The square box symbol (☐) is primarily intended to indicate similar clinical performance within a pharmacologic class. The listed medicine should be the example of the class for which there is the best evidence for effectiveness and safety. In some cases, this may be the first medicine that is licensed for marketing; in other instances, subsequently licensed compounds may be safer or more effective. Where there is no difference in terms of efficacy and safety data, the listed medicine should be the one that is generally available at the lowest price, based on international drug price information sources.

WHO model list of essential medicines

The current Model List of Essential Medicines was prepared by a WHO Expert Committee in March 2007 and represents its 15th edition[34] (Table I).

In principle, essential medicines are those that satisfy the priority health care needs of the population, and they are selected in regard to disease prevalence, evidence on efficacy and safety, and comparative cost-effectiveness. Although a central repository of treatments for severe asthma worldwide is clearly desirable, selection, updating, and assessment of the efficacy of current and novel medicines are difficult tasks, and cost-effectiveness assessments for different areas of the world are most likely impossible. Furthermore, the requirements and methodology for the assessment and grading of evidence are more demanding and require up-to-date methodology, which necessitates significant resources.

Assuring quality of inhalation products

To minimize adverse reactions, maximize efficacy, and increase the speed and duration of effect at the site of action, inhalation from a pressurized metered-dose inhaler (MDI), a dry powder inhaler (DPI), or a spacer is the recommended route of administration for the majority of medicines for asthma or chronic obstructive pulmonary disease (COPD; corticosteroids, $ß_2$-agonists, and anticholinergics). However, these recommendations imply that only high-quality drugs meeting strict criteria set by drug regulatory authorities are made available. Inhalation dosage forms, such as MDIs and DPIs, are complex, consisting of the active drug substance in an appropriate formulation and a mechanical device component that delivers the formulation to the patient. The formulation of MDIs is contained in canisters under pressure and contains propellants, such as chlorofluorocarbons or hydrofluoroalkans, for aerosolization. In accordance with the Montreal Protocol, the use of chlorofluorocarbons in inhalers is being phased out and replaced by hydrofluoroalkans or by devices that do not use propellants.[35,36] Several hydrofluoroalkan-MDIs are efficient, but hydrofluoroalkans have characteristics that make them different and more difficult to use as propellants than chlorofluorocarbons. The technology to manufacture hydrofluoroalkan-propelled inhalation aerosols is evolving. Many of the inhalation aerosols are suspensions, making it difficult to manufacture them and maintain their quality through the life of the product. The formulation of DPIs generally contains lactose as a bulking agent. Issues related to the use of lactose include varying stability of the product in various temperatures and relative humidity conditions experienced in the world.

Manufacturing of inhalation products is complicated because of the nature of the dosage form. There are various guidance documents issued by regulatory agencies that advise the industry on producing quality inhalation products.[37-40] The critical elements of inhalation dosage forms are assurance of consistent particle size, distribution of the active moiety, dose content uniformity throughout the life of the product, spray pattern and plume geometry, controls for impurities, degradation products, extractability, and leachability. For DPIs, additional critical elements include control for water and moisture content. Ruggedness and reliability of the product under conditions of patients' use are important for all inhalation dosage forms.

The catastrophic failure of an MDI or DPI resulting in little, no, or excess delivery of the active drug substance will place patients with asthma at substantial risk. Failure of an MDI or DPI containing a controller drug such as ICS may go unnoticed by patients because their asthma may not worsen acutely. Furthermore, propellants and excipients in MDIs or lactose in DPIs, which make up the bulk of the drug product formulation, may give the sensation that patients are receiving the drug, whereas in reality they may be getting no active drug substance. Such failures of MDIs and DPIs have been reported in developed countries and have resulted in market withdrawal of products,[41] regulatory action,[42] and public concern.[43]

The Union Asthma Drug Facility provides quality-assured hydrofluoroalkan inhalers subjected to specific testing and then certified by using a quality assurance system based on WHO norms and standards.[5]

Health care providers should also be cognizant that inhalation dosage forms are complex and should keep in mind the possibility of device failure or improper use when encountering patients who seem to have worsening asthma despite compliance with medications.

Efficacy and effectiveness of interventions for asthma management

Studies at the community level on the effectiveness of good asthma care in whole populations reveal a considerable reduction of both hospitalizations and deaths[44-48] as a result of initiating recommended treatment. All of these intervention programs are also cost-effective.[45] Such public health strategies for asthma include affordability and accessibility to controller treatments, education of patients and parents, and cooperation between PHC centers. Some studies have been carried out in LMICs or deprived populations (eg, the US Inner City Asthma in Children,[49] Belo Horizonte and Porto Alegre [studies in children, Brazil],[50] and Salvador [study in adults, Brazil][51]). A pilot study conducted in several LMIC sites found that after 1 year of the effective asthma treatment of applying The Union asthma management approach,[22] and of using essential medicines,[5] asthma control improved dramatically.[52]

PROPOSAL FOR A UNIFORM DEFINITION OF ASTHMA SEVERITY

Components of asthma severity

The concepts of asthma severity, control, and responsiveness are linked.[20,21] Asthma severity is the intrinsic severity of the

TABLE II. Components of asthma severity[20]

1. Level of control
Current clinical control (impairment): symptoms and functional limitations over previous 2-4 wk
Exacerbations over previous 6-12 mo, including number, severity, and use of systemic corticosteroid
2. Level of current treatment prescribed, inhalation technique, and compliance with treatment
3. Responsiveness to treatment
4. Risk

TABLE III. Level of asthma control in patients ≥5 years of age

Control level	Well controlled†	Partially controlled†	Poorly controlled†
Daytime symptoms in the past 2-4 wk	≤2 d/wk but not more than once a day	>2 d/wk or more than once a day but ≤2 d/wk	Throughout the day
Limitations of activities in the past 2-4 wk	None	Some limitation	Extremely limited
Nocturnal symptoms/awakenings in the past 2-4 wk	None	≤2 nights/wk	>2 nights/wk
Need for short-acting inhaled ß$_2$-agonists in the past 2-4 wk	≤2 d/wk	>2 d/wk	Several times a day
Lung function			
FEV$_1$ or PEFR*	≥80% predicted or personal best	60% to 79% predicted or personal best	<60% predicted or personal best
FEV$_1$/FVC (<11 y of age)	≥80%	75% to 80%	<75%
Exacerbations (requiring oral or systemic corticosteroids)‡	0-1/y	2/y	Frequent (>2/y)
	Consider severity and interval since last exacerbation		

FVC, Forced vital capacity; *PEFR,* peak expiratory flow rate.
Adapted with permission from GINA 2006[11] and 2007 NAEPP-EPR3.[20]
Any of the components places the patient in the category.
*FEV$_1$ or PEF may be ≥80% predicted in patients with severe persistent asthma.
†For well-controlled asthma, all components should be present; for partially or poorly controlled asthma, any of the components places the patient in the category.
‡Currently there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control or severity.

disease process, asthma control is the degree to which therapy goals are met, and responsiveness is the ease with which asthma control is achieved by therapy. The definition of asthma severity includes all these components, as depicted in Table II.

Level of control. The level of asthma control incorporates current clinical control and exacerbations (Table III). Current clinical control, or extent of impairment, is the frequency and intensity of symptoms and functional limitations that a patient experiences or has recently experienced as a consequence of asthma and includes measures of day and night symptoms, use of reliever therapy, activity limitations, and lung function. The period for which current clinical control should be assessed is proposed to be the previous 2 to 4 weeks for adults and at least 4 weeks for children. The number of asthma exacerbations requiring oral systemic corticosteroids (for more than 3 days) in the previous year should also be considered in evaluating overall asthma control.

Until recently, strong emphasis has been placed on lung function measures such as PEF and FEV$_1$ before and after bronchodilator as a measure of asthma control or asthma severity. There is an inconsistent relationship between lung function measures and symptoms or exacerbation frequency as patient-centered outcome measures.[10] Therefore, it is important for a comprehensive assessment to capture multiple asthma endpoints, including lung function.

Questionnaires for assessing asthma control have been developed. These tools score asthma indices as continuous variables and thus provide numeric values to distinguish different levels of control (eg, Asthma Control Test,[53] Childhood Asthma Control Test, Asthma Control Questionnaire,[54] Asthma Therapy Assessment Questionnaire,[55] Royal College of Physicians Questionnaire,[56] Asthma Control Scoring System[57]). Most of these instruments do not include a measure of lung function.

For PHC centers, WHO has developed a minimal set of criteria to assess noncommunicable diseases including asthma (WHO-PEN) that can be used for determining the level of asthma control. The components of asthma control used in this declaration are daytime symptoms, nighttime symptoms, needs for rescue medications, limitations of daily physical activity, exacerbations requiring oral or injectable corticosteroid, and PEF.

Risk. The concept of asthma risk[20] is intended to capture the following:

- The likelihood of asthma exacerbations.
- And/or the development of chronic morbidity including progressive loss of pulmonary function over time (or for children, reduced lung growth). Low lung function is a risk for severe disease.[10]
- And/or the risk of adverse reactions from asthma medication.[58]
- In children, a phenotypic switch from episodic (viral) wheezing to multitrigger wheezing should also be a component of asthma risk.[59]

Exacerbations

Exacerbations (commonly referred to as *asthma attacks* or *acute asthma*) are episodes of progressive increase in shortness of breath, cough, wheezing, chest tightness, or a combination of these symptoms. Exacerbations are characterized by decreases in expiratory airflow (PEF or FEV$_1$). However, PEF variability does not usually increase during an exacerbation, although it may do so leading up to or during the recovery from an exacerbation.[60] The severity of exacerbations ranges from mild to life-threatening and can be evaluated based on both symptoms and lung function. Exacerbations should be considered separately

TABLE IV. Diagnoses that may masquerade as severe asthma

Children
Tuberculosis
Obliterative bronchiolitis
Vocal cord dysfunction
Exercise-induced laryngeal obstruction syndrome
Tracheomalacia or bronchomalacia
Inhaled foreign body
Cystic fibrosis
Recurrent aspiration (particularly in children with neuromuscular or neurodevelopmental issues), including incoordinate swallow and gastroesophageal reflux disease
Developmental abnormalities of the upper airway
Congenital malformations, eg, bronchogenic cyst
Primary ciliary dyskinesia and other causes of noncystic fibrosis bronchiectasis
Persistent bacterial bronchitis
Vascular ring and pulmonary artery sling
Bronchial tumor, particularly carcinoid
Adults
COPD
Vocal cord dysfunction
Exercise-induced laryngeal obstruction syndrome
Tuberculosis
Bronchiectasis
Hyperventilation syndrome (dysfunctional breathing)
Cystic fibrosis
Tracheobronchomalacia
Recurrent aspiration
Sleep apnea syndrome
Congestive heart failure
Tumors in or impinging on central airways
Hypersensitivity pneumonitis
Inhaled foreign bodies
Bronchial amyloidosis
As part of the asthmatic diathesis
Allergic bronchopulmonary aspergillosis
Pulmonary eosinophilic syndromes

Adapted with permission from Chung KF, et al. Difficult/therapy-resistant asthma: the need for an integrated approach to define clinical phenotypes, evaluate risk factors, understand pathophysiology and find novel therapies. ERS Task Force on Difficult/Therapy-Resistant Asthma. European Respiratory Society. Eur Respir J 1999;13:1198-208.[28]

from current clinical control (impairment) when evaluating overall asthma control because exacerbations may occur even if the patient has adequate day-to-day control of symptoms and minimal activity limitations. Such exacerbations may or may not be prevented by escalating maintenance therapy.

In GINA 2006[11] and NAEPP-EPR3 2007,[20] moderate or severe asthma exacerbations are those that require treatment with systemic corticosteroids. More frequent and intense exacerbations, requiring urgent, unscheduled care, an emergency department visit, hospitalization, or intensive care unit admission, indicate poorer overall disease control.

Responsiveness to therapy

Responsiveness to therapy is the ease with which asthma control is achieved by therapeutic interventions. The degree of responsiveness to therapy will determine the amount of medication required to achieve asthma control (as defined in Table III) and is considered a key element of assessing severity during treatment (Table II).

Several levels of responsiveness to treatment are recognized:

- Responsive patients will show an improvement of many measures of asthma control. Some of these patients may maintain control with minimal, low-dose treatment as established during the step-down process described in the disease management guidelines. Other patients will need step-up therapy according to guidelines to respond fully to treatment. Many previously untreated patients with a history of poorly controlled asthma respond well to therapy with controllers such as ICS and achieve good control of their asthma. With adequate treatment, such patients who initially may have untreated severe asthma no longer have severe disease.
- Patients with difficult-to-treat severe asthma represent an asthma category in which partial or poor response to treatment[58] reflects the presence of factors other than asthma alone. Issues to address include poor access to medical treatment,[61] poor adherence to medication, poor inhalation methods, environmental exposure such as passive smoking or allergen exposure, psychosocial issues (including dysfunctional breathing), and comorbidities (Tables IV and V). Patients taking only oral corticosteroids (OCSs) due to the unavailability of ICS may also be considered as having difficult-to-treat severe asthma because of the increased risks of treatment side effects. Tobacco smoking has major effects on asthma control and a future risk of reduced lung function and exacerbations.[62] The role of gastroesophageal reflux in asthma control is debatable.[63]

TABLE V. Factors that may contribute to the gain or loss of control in asthma

Poor compliance/adherence to therapy
Inhaler misuse and use of inappropriate inhalation devices
Inadequate medical facilities
Poor access to medical facilities
Inadequate assessment of disease control by the clinician
Inadequate treatment
Low patient expectations
Psychosocial and emotional factors
Allergic rhinitis and rhinosinusitis
Exposure to allergens
Smoking (active or passive)
Exposure to irritants and chemicals
Indoor/outdoor pollution
Viral respiratory tract infections

Adapted with permission from Chung KF, et al. Difficult/therapy-resistant asthma: the need for an integrated approach to define clinical phenotypes, evaluate risk factors, understand pathophysiology and find novel therapies. ERS Task Force on Difficult/Therapy-Resistant Asthma. European Respiratory Society. Eur Respir J 1999;13:1198-208.[28]

- Patients with treatment-resistant severe asthma represent 2 categories of responsiveness
  - Partially or poorly controlled asthma despite high-dose ICS or a high-dose ICS–long-acting ß$_2$-agonist (LABA) combination (when LABAs are available and affordable) and frequent or chronic use of systemic corticosteroids. This category has previously been referred to as "refractory asthma" or "severe asthma."[8] For a patient to fall into this category, all reasonable efforts to eliminate other, nonasthma diagnoses must have been made. Moreover, asthma diagnosis and factors that may contribute to a loss of asthma control should be re-evaluated (Tables IV and V). Patients with treatment-resistant severe asthma are considered to be relatively insensitive to ICS or OCS.[64,65] This insensitivity is not an absolute phenomenon but varies from patient to patient. Some patients in this category may also be labeled as *corticosteroid-dependent* because asthma control may deteriorate when the maintenance dose of ICS or OCS is reduced. There are currently no validated tests that measure corticosteroid sensitivity. Furthermore, it is now recognized that many factors may contribute to decreased corticosteroid responsiveness, including obesity and tobacco smoke; eliminating some of these factors may improve treatment responsiveness. New treatments that improve corticosteroid sensitivity in severe asthma may become available.[66]
  - Well-controlled asthma that requires the highest level of recommended treatment to maintain control. This requirement for high doses of medication and multiple medications suggests a component of treatment resistance or insensitivity. Furthermore, from a clinical and public health perspective, although the asthma is controlled, the patients are at high risk for severe exacerbations if treatment is inappropriately reduced or becomes unavailable.

Assessment of severity

The ATS/ERS Task Force on the definition of asthma severity and control proposed not to retain a definition of severity in patients in the absence of treatment because pretreatment features do not usually predict subsequent response to therapy.[4] However, many (if not most) people with asthma in the world, particularly in LMICs, do not have access to effective medications (medications may be unavailable or unaffordable or the individual may not have received a diagnosis or been prescribed appropriate treatment). To help with disease management and to allow for appropriate epidemiologic assessments, it is important that disease severity be determined in the absence of treatment if patients are currently untreated.

Asthma severity may be influenced by genetic and environmental factors, the underlying disease activity, and the patient's disease pathobiological processes. These differ between patients with differing phenotypes, which may be further described using a combination of pathological and physiological markers.[4] These markers might also serve as surrogate disease measures for gauging future risk and are discussed further in the section "Subphenotyping of severe/uncontrolled asthma." It is possible that the phenotypes of severe untreated and severe asthma differ during treatment.

Asthma severity is thus measured either before treatment is initiated, for the untreated patients, or during treatment.

Before treatment, the historical severity should be assessed by reviewing the patient's history of asthma control over a sufficient period (ideally 6-12 months) to better assess the intrinsic severity of the disease and to avoid seasonal variations. It may be evaluated using the criteria used for the assessment of asthma control (Table III). Using these criteria, a patient would be considered to have untreated severe asthma if the history indicated partially or poorly controlled asthma over a sufficient period.

During treatment, the level of severity is determined by correlating it with the minimal level of medications required to maintain asthma control (see section "Responsiveness to therapy"). Assessment of adherence to prescribed treatment is essential, for example, by sensitive inquiry, prescription monitoring, or tablet counting. Risks should also be assessed (Table II). Although data are lacking to correlate specific levels of risk to severity, in general, the greater the frequency and intensity of the side effects of medication or occurrence of exacerbations, or the documentation of progressive lung function or reduced lung growth, the higher the level of asthma severity. Generally, the duration over which disease severity should be assessed is between 6 and 12 months.

UNIFORM DEFINITION OF SEVERE ASTHMA

Severe asthma is defined by the level of current clinical control and risks as "Uncontrolled asthma which can result in risk of frequent severe exacerbations (or death) and/or adverse reactions to medications and/or chronic morbidity (including impaired lung function or reduced lung growth in children)."

Severe asthma includes 3 groups, each carrying different public health messages and challenges:

1. Untreated severe asthma.
2. Difficult-to-treat severe asthma.
3. Treatment-resistant severe asthma. This group includes the following:
   - Asthma for which control is not achieved despite the highest level of recommended treatment: refractory asthma and corticosteroid-resistant asthma.
   - Asthma for which control can be maintained only with the highest level of recommended treatment.

This document also includes wheezing disorders in preschool children. Although there is dispute as to the age at which the label

asthma can properly be applied,[59] for the purpose of the document, infants and preschool children with wheeze not related to a specific underlying diagnosis such as cystic fibrosis are included.

The definitions help support the treatment of patients with asthma including both the level of current clinical control and the risk of deterioration. They may be particularly useful for the following:

- Primary health care, according to the 2008 to 2013 Action Plan for the Global Strategy for the Prevention and Control of Noncommunicable Disease.[33,67]
- Public health planning in different health care systems.
- Helping in the development of standard registries of severe asthma.
- Fostering comparability of information collected for research including health economics.

A decision tree (Fig 1) represents how to characterize the 3 groups of severe asthma (untreated severe asthma, treatment-resistant severe asthma, and difficult-to-treat severe asthma). The characterization of severe asthma is based on successive assessments of asthma control, which can be evaluated by using different methods according to the setting and management strategies, including applying the criteria in Table III or using WHO-PEN. Patients with poorly controlled asthma are at risk of developing severe exacerbations and chronic morbidity. Many patients consulting for severe asthma do not have asthma, and some patients with mild/moderate asthma present with another condition (eg, bronchiectasis, dysfunctional breathing, vocal cord dysfunction, and so forth) that is causing severe symptoms in addition to their background asthma.[68]

SUBPHENOTYPING OF SEVERE/UNCONTROLLED ASTHMA

Asthma is a complex, multidimensional disease with marked heterogeneity. Tools to phenotype individual asthma subtypes are now being developed to characterize the various patterns of triggers that induce symptoms, different clinical presentations of the disease, and different inflammatory markers (Fig 2). Phenotyping subtypes can be used to characterize and predict disease severity, progression, and response to treatment and may help identify targets for treatment. Heterogeneity also exists within each dimension of the disease (eg, eosinophils and asthma severity),[69,70] across diseases (eg, eosinophils in asthma and COPD), and in relation to comorbidities.[2,71] Phenotypes may also change over time both within and across countries.

Phenotype heterogeneity may be hypothesis-driven or hypothesis-generating (multiple logistic regression[2,72]; cluster analysis[71,73]). However, it is necessary to commence with a WHO definition that can be applied worldwide. The subphenotyping of severe asthma may then be attempted with the following approaches:

- Use and develop markers of asthma and asthma severity.
- Explore specific mechanistic characteristics such as innate immunity,[74] inflammation, remodeling,[75,76] small airways,[77] neural inflammation, epithelial dysfunction,[78] and so forth.[69,71,79,80]
- Identify specific subcategories such as brittle, exacerbation-prone, aspirin-intolerant, neutrophilic, fixed and persistent eosinophilic inflammation despite corticosteroid, and the more widely recognized disorders such as bronchopulmonary allergic aspergillosis, Churg-Strauss syndrome, and persistent bacterial infection with *Chlamydia* and *Mycoplasma*.
- Differentiate causative agents: exacerbation provoked by viruses, allergens, occupational agents, chemicals, environmental tobacco smoke, irritants, and pollutants.
- Consider the impact of comorbidities such as atopic dermatitis, food allergy, rhinitis,[81] rhinosinusitis, gastroesophageal reflux, and so forth.[82,83]
- Apply the science of endophenotyping to genomics, pharmacogenomics, and envirogenomics to guide treatment and personalized medicine in asthma.

ASTHMA AND WHEEZING IN CHILDREN

Childhood asthma represents a serious problem worldwide with increasing trends in LMICs.[84] In childhood asthma, specific factors need to be considered including environmental factors (eg, sensitization to allergens, early-age smoking and environmental tobacco smoke, early-life infections, food allergy), correct use of medications (eg, spacers) and fear of ICS. Moreover, asthma severity in children may be very different from that in adults (eg, baseline airway caliber often normal, highly responsive to viral infections, exercise, foods).

The roots of much adult airway disease lie antenatally and in the very early preschool years, hence the importance of this age group. Antenatal factors, in particular maternal smoking and maternal atopic status,[85,86] but also other factors such as environmental pollutant exposure,[87,88] maternal diabetes, use of antibiotics,[89] and possibly transgenerational effects of grandparental smoking, affect infant lung health and immune responses in cord blood. Taken together, these affect the severity of viral infections in the preschool years, in particular rhinovirus, and these are associated with wheeze persisting into mid-childhood.[90,91] Infants who will later develop persistent wheeze are born with essentially normal lung function, but will have developed airway obstruction by age 4 to 6 years.[92,93] Airway wall histology is normal at age 1 year, and bronchoalveolar lavage predominantly shows a neutrophilic phenotype.[94] By age 2.5 years and even earlier,[95,96] structural airway wall changes and eosinophilic inflammation have started to appear.[97] The epidemiologic evidence also underscores the importance of the early years.[98] It has been shown by a succession of overlapping studies that lung function tracks from age 6 years into late middle age.[93,99]

There is poor agreement on the definitions of different phenotypes of preschool wheezing disorders. An ERS Task Force[59] proposed the use of the following terms: *episodic (viral) wheeze* to describe children who wheeze intermittently with upper respiratory viral infections and who feel well between episodes, and *multiple-trigger wheeze* for children who wheeze both during and outside discrete viral episodes. Although there was no consensus, the ERS Task Force proposed that the term *asthma* should probably not be used in preschool children because data regarding underlying inflammation are lacking.[59] Tools to predict progression to persistent asthma in childhood are not yet available for widespread clinical use,[100-102] and there are no disease-modifying strategies to prevent this progression from happening.[103-106] In the preschool child, alternative diagnoses are more common, and medication delivery may be much more difficult. Some medications may not have the same efficacy in preschool and older children (eg, LABAs).

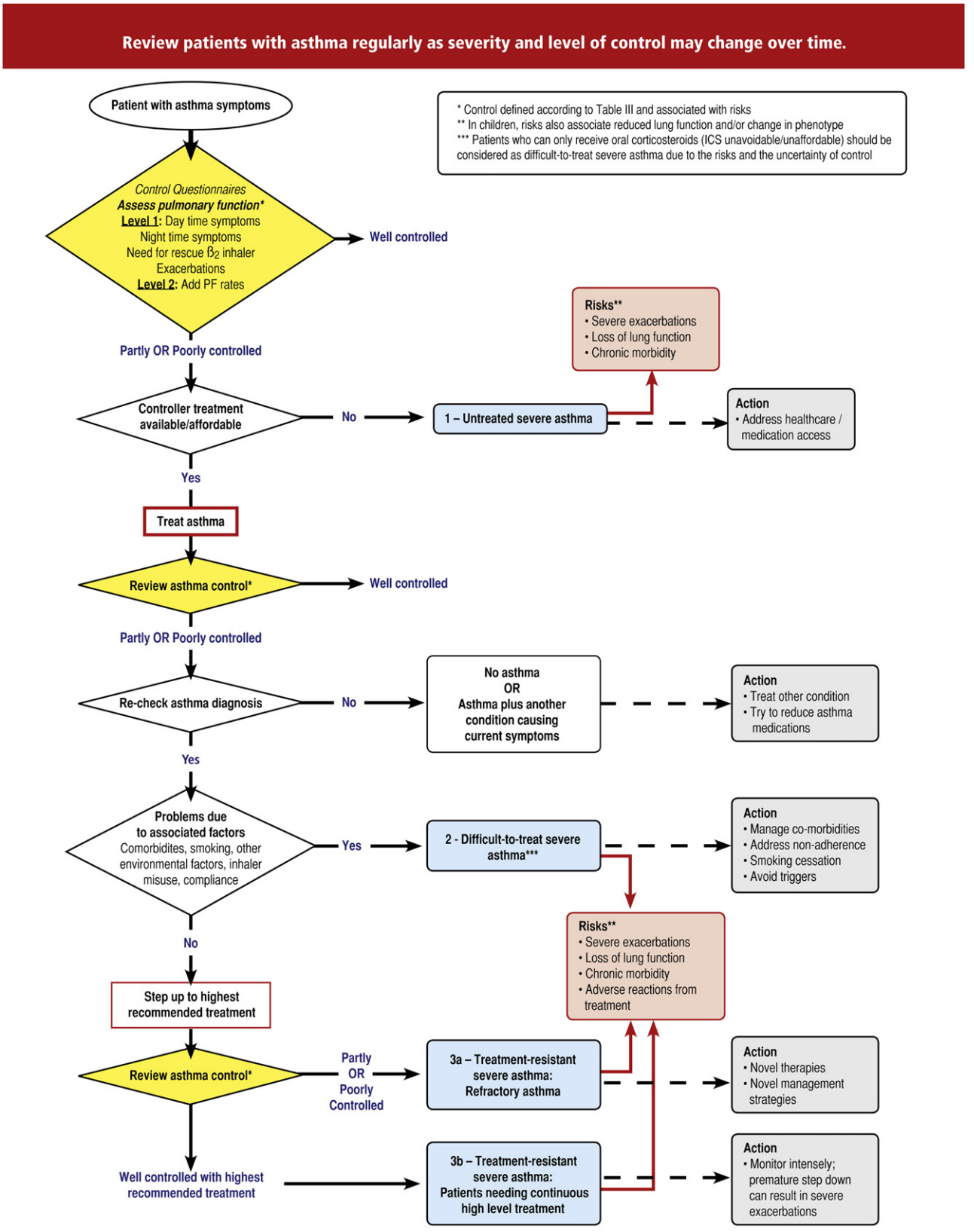

FIG 1. Decision-making steps for characterizing severe asthma, with correlating action steps for clinical management. *PF*, Pulmonary function.

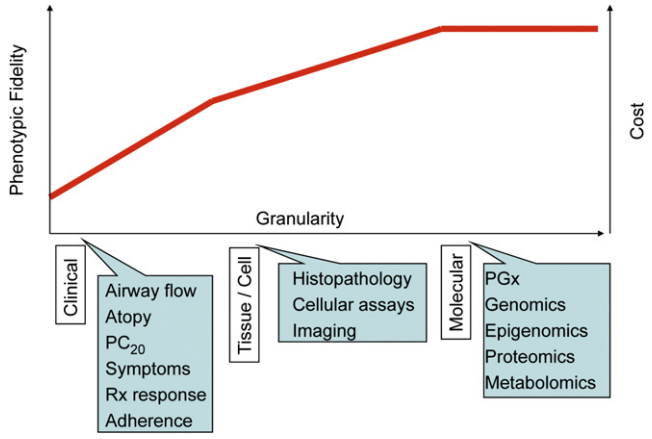

FIG 2. Increasing detail and precision for phenotypic characterization to provide a more comprehensive and integrated understanding of asthma by taking into account multidimensional features. Although costs escalate with increasing granularity, comprehensive phenotyping may reveal subclinical phenotypes with distinct pathophysiologic pathways for individualizing patient treatment. *PGx,* A designation for pharmacogenomics; *Rx,* pharmacologic.

The definition of severe asthma as reported is applicable in this age group, but difficult-to-treat severe asthma and treatment-resistant severe asthma are proposed to be listed as "problematic severe asthma" until a detailed evaluation has separated the 2.[107]

Although most children with asthma are easy to treat with medications that are both safe and effective, some remain symptomatic despite using high doses of medications.[108] The nomenclature for this group is confusing, and studies are difficult to compare because of the variety of terms that are currently used.[3] The approach to "problematic severe asthma" varies with the age of the child. In school children and adolescents, guidelines usually propose an approach similar to that in adults for the definition of control and severity[20] (Tables II and III).

The phenotypes of "problematic severe asthma" show age-related differences. Initially, episodic (viral) exacerbations are common; subsequently, a multitrigger phenotype becomes prominent.

In children ≥5 years, as in adults, severe asthma includes untreated severe asthma, difficult-to-control asthma, and treatment-resistant severe asthma. However, it should be noted that comorbidities may differ in children and adults and that asthma-inducing precipitous and severe exacerbations (sometimes referred to as *brittle asthma*) may be more common. Phenotypes of severe asthma in children vary from those of adults and change more rapidly. It is therefore necessary to reassess phenotypes at regular intervals.

In preschool children, recurrent, episodic (viral) wheeze appears to be the most common pattern. Morbidity including hospitalization is common for respiratory viral infections. However, allergic asthma may develop very early in life. Pathophysiology in this age group is different from that in adults,[59] responses to different drugs differ,[109] and adverse effects of corticosteroids on growth and bone maturation in children mean that different treatment strategies are needed.[110] A family history of asthma and the presence of allergy are important for symptom persistence into mid-childhood.

In LMICs, asthma in children is highly prevalent, may be more severe than in high-income countries, and is often undiagnosed, in particular because of the lack of training of health care professionals.

APPLICABILITY OF THE PROPOSED DEFINITIONS OF SEVERE ASTHMA

Public health

For public health purposes, a uniform definition of severe asthma is needed to identify those patients who require particular attention, to ensure appropriate treatment and regular monitoring, and to improve adherence to treatment to reduce the use of emergency departments and hospitalizations. The aim is to optimize health care planning and policies. This definition will also contribute to accurate estimates of the prevalence of severe asthma and provide support for more precise calculations on the needs for medications in a country. On the basis of the prevalence of severe asthma, the risk of health resource use and deaths is associated with lack of proper management.

Clinical practice

These WHO definitions provide a framework upon which decisions can be made as to who needs targeting for treatment or improved treatment, especially in LMICs.

Registries on severe asthma

Severe asthma registries provide a foundation to generate a greater understanding of public health need, and to define phenotypic heterogeneity. They are used for the surveillance of severe asthma.

Several national registries for severe asthma in adults and children already exist, and some are planned. Although there is considerable commonality between these registries, there are also differences. The establishment of an internationally agreed severe asthma definition will facilitate the alignment of current registries. Such a definition will also provide the opportunity to develop a single registry to capture core information in both developed and developing countries.

Clinical trials

For clinical trials, clarity is essential as to which definitions have been used—severity assessed before treatment or after treatment—and also, which treatment was used.

Research on asthma mechanisms and genetics

There is an urgent need for more research into severe asthma. We need to improve our understanding of the underlying causes of the disease in order to develop new strategies with an aim to control and therefore eradicate severe asthma. A global definition and a collaborative approach to epidemiologic, genetic, and mechanistic research are important. As highlighted, the challenges for the groups of severe asthma are different. Difficult-to-treat severe asthma requires further research into the role of the comorbidities, cofactors, and psychosocial issues discussed. Strategies need to be developed to improve psychosocial issues and determine their relative importance in contributing to the severity of disease. For treatment-resistant severe asthma, more detailed cellular and molecular phenotyping is needed to identify new targets for the potential development of novel therapies and

TABLE VI. Proposals for the management of severe asthma

To manage severe asthma
Accurate diagnosis (need PEF or spirometry)
Accurate assessment of severity
Assessment and prevention of risk factors
Assessment and control of comorbidities
Appropriate therapy (ICS, short-acting ß$_2$-agonists and LABAs), given with an appropriate drug delivery device
Assessment of control (WHO-PEN, asthma control questionnaires, symptoms, and so forth)
Ongoing support in self-management and patient education
Well-trained health professionals

to target current therapies. Different levels of phenotype characterization (granularity) can be applied to assess phenotypic characterization in patients with severe asthma (Fig 2). For the success of such approaches, it is important to develop global partnerships and platforms to ensure the application of standard methodology, protocols to promote sharing of samples, data to create methods, and infrastructures to collect data and samples from different countries.

Epidemiologic studies

In epidemiologic population studies, it is often difficult to assess severity because many patients are undertreated based on guideline recommendations. The WHO definition of severe asthma accounts for these patients and articulates time frames for the appropriate assessment of severity and control. Thus, the definition will facilitate epidemiologic research and comparisons across studies in different populations.

Control usually refers to events occurring recently (over the last 2-4 weeks), whereas severity refers to those occurring over a long period (eg, 6-12 months).

Applicability to developed and developing countries

A WHO definition of severe asthma is needed and should be applicable to the local and geographic conditions of all countries, phenotypes, risk factors, and availability and affordability of treatment, differing widely around the world. Research must be planned to evaluate the phenotypes of severe asthma in different countries.

Conclusion

Severe asthma broken down into untreated severe asthma, difficult-to-treat asthma, and therapy-resistant asthma remains a major global health problem, particularly in areas or jurisdictions where recommended treatments are not available or affordable, as well as in patients not receiving adequate treatment. Severe asthma is associated with uncontrolled asthma and the increased risk of developing severe and life-threatening exacerbations as well as chronic morbidity such as decline in lung function or reduced lung growth (in children). ICSs represent the mainstay treatment for the prevention and control of severe asthma, and it has been shown that in places where national or local intervention programs exist, there is a considerable cost-effective reduction in asthma hospitalizations and deaths as well as an improved quality of life overall. Children need particular attention because the onset of asthma occurs most frequently in childhood, and management has lifelong consequences on productivity and quality of life. Severe asthma should be managed by appropriate measures as depicted in Table VI. Through the mobilization of health care systems and professionals and access to appropriate medications, it should be possible to reduce the burdens associated with severe/uncontrolled asthma. For people with severe asthma in whom severity cannot be improved with existing therapies, new forms of treatment including preventive strategies are necessary and could be discovered through the global collaboration of databases and biobanks of these patients.

Although some patients still present with severe asthma despite adequate current management, the following declaration should guide future asthma programs worldwide:

- Reduce the burden of severe asthma in children.
- Zero tolerance for asthma deaths.

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