

WHO universal definition of severe asthma

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Purpose of review

In 2009, an expert panel met to propose a WHO definition of asthma severity and control, and criteria for describing exacerbations and their severity, which would be globally applicable. This review addresses their findings in the context of recent literature, and assesses the usefulness of these definitions in children in particular.

Recent findings

Severe asthma was 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 three groups, with different public health messages and challenges: untreated severe asthma, due to undiagnosed asthma or unavailability of therapy, difficult-to-treat severe asthma (due to adherence issues, inappropriate or incorrect use of medicines, environmental triggers or co-morbidity), and treatment-resistant severe asthma, including asthma for which control is not achieved despite the highest level of recommended treatment or asthma which is controlled only with the highest level of recommended treatment.

Summary

These definitions will enable more precise measurement of the burden of severe childhood asthma globally. International collaborations in epidemiological and mechanistic studies, and randomized controlled trials of treatment, will be facilitated. However, both pathophysiology and severity are influenced by a number of factors with wide global variation; international comparisons should be interpreted with caution.

Keywords

atopy, biomass fuels, severe asthma, steroid resistance, tobacco control

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Introduction

Although most children with asthma can be controlled with low doses of inhaled corticosteroids (ICS), if regularly and properly administered, a few remain with considerable morbidity and even mortality. The WHO convened an expert group to discuss the global nature of the problem of severe asthma, and come up with internationally applicable definitions. The purpose of this article is to review the WHO document in the context of recent literature on severe asthma in children, and assess the usefulness of the final definitions.

The global burden of asthma in children

Three hundred million people of all ages have asthma, and there are 250 000 premature deaths from asthma per year worldwide. Asthma is the commonest chronic illness in children. Moreover, although asthma was formerly considered to be uncommon in children in low or middle

income country (LMIC) settings, studies clearly indicate that the burden of childhood asthma in these areas is large and comparable to those in high income countries [1,2]. For example, the prevalence of asthma in African children, as assessed by self reported questionnaire in the ISAAC 3 study, is higher than the global average [3•]. Moreover, the prevalence of childhood asthma in LMICs is increasing, in contrast to that in high income settings where it has stabilized or is decreasing [1,2]. A consistent increase in asthma prevalence has been reported from both rural and urban settings in LMICs [4–9]. Furthermore, children in LMIC with asthma have been reported to have more severe symptoms than those in high income countries which may relate to many factors such as lack of diagnosis, access to care, affordability of therapy, environmental irritants, genetic susceptibility to more severe disease or a combination of these [10••]. For example, in many LMICs almost half of children who reported asthma in ISAAC 3 had severe symptoms. Furthermore, in many LMICs more than 30% of children with severe

asthma symptoms had never been diagnosed with asthma [10**].

The burden of chronic morbidity from childhood asthma is huge and costly. However, most of the chronic morbidity is preventable with effective use of simple medications. However, for those who do not have access to healthcare or medication (the majority) and those who have ongoing morbidity despite medications, the burden of personal misery and healthcare costs is enormous.

In April 2009, an expert panel was convened by the WHO in Geneva, and was tasked with proposing a WHO definition of asthma severity and control as well as criteria for describing exacerbations and their severity, which would be applicable in most circumstances in low, middle and high income countries to children and adults. The work of this group has been described in detail [11**]. Severe asthma was defined by the group 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).' There are three categories which may overlap, that are included in the definition.

- (1) Untreated severe asthma: asthma which is untreated either because of failure to make the diagnosis or because basic access to care or to medications and spacers are not available or affordable. This is an important group in LMICs [12,13,14*]; in addition to treatment access issues, there may be other factors such as exposure to tobacco or biomass fuels which exacerbate asthma [15]. Another issue may be lack of locally applicable asthma guidelines, failure to apply basic principles of asthma treatment, and lack of asthma education for families. It would be naïve to suggest that medications alone are the answer, but equally wrong to think that the problem cannot be tackled without medications. This category may also be found in parts of the so-called developed world in which the costs of medications are prohibitive and reimbursement of healthcare costs is inadequate. It could be argued that children in whom compliance with the medication regime is very poor despite access to medications could be placed in this category; we in fact place them in the 'difficult asthma' category.
- (2) Difficult-to-treat severe asthma: these patients have asthma which is not apparently responding to treatment, but often when appropriate asthma management is instituted the disease become controlled [16,17*,18**]. Problems may include adherence to treatment regimes, inappropriate or incorrect use of medication delivery devices, or adverse environmen-

tal circumstances [19,20**]. This category may be found in any setting.

- (3) Treatment-resistant severe asthma (also known as severe, therapy-resistant asthma, or treatment refractory asthma). Children in this category have severe asthma even with optimal management and after all conventional asthma medications have been given, or are controlled only with the highest level of asthma therapy, giving an unacceptable risk of side-effects. When making international comparisons, it is important to ensure which medications are considered conventional and available. The therapeutic trials performed will be different in countries where, for example, long-acting β -2 agonists (LABAs) are not available compared with those in whom they can routinely be prescribed. It follows that the definition may need to be modified in different countries, and it is essential that it should always be clear, particularly if comparisons between countries are being made.

It is important to distinguish the very different and legitimate purposes for which these definitions may be used. Thus in a LMIC defining the prevalence of severe asthma may draw attention to the lack of diagnosis, basic medication or spacer devices, the need to improve healthcare delivery, the need to curtail the activities of the tobacco industry, and the need for education about environmental hazards, such as biomass fuels. In a developed world setting, with good access to asthma medications, it may be used as a basis for defining the rare subgroups of asthmatics with severe, therapy-resistant asthma, so that the molecular and cellular mechanisms can be determined and novel therapies developed.

Finally, it is essential to realize that asthma is really a spectrum of clinical features, rather than a precise diagnosis, rather like 'chronic renal failure'; an end-point of many different processes. Thus the disease may show marked pathophysiological differences across the world. An obvious example is atopic sensitization, which is common in childhood asthma in the UK. In Porto Alegre, Brazil, by contrast asthma is usually nonatopic, and strongly associated with early respiratory viral infection [21]. Thus when making comparisons between countries, it should not be assumed that the disease is the same.

Initial assessment of the child with suspected asthma

Throughout the world, when asthma of any severity is suspected, a number of simple steps should be undertaken, and this is particularly true for severe asthma. The term 'problematic severe asthma' has been suggested as an umbrella term to cover patients who are thought to

have asthma which is not responding to therapy, but who have not yet undergone specialist assessment [16,17^{*}]. It should be noted that the level of training of specialists, and access to diagnostic testing, will show large global variation. The group 'problematic severe asthma' contains the categories 'wrong diagnosis' ('not asthma at all') and 'asthma with co-morbidities' ('asthma plus'), as well as the three groups discussed above ('untreated severe asthma', 'difficult-to-treat severe asthma', and 'treatment-resistant severe asthma').

The differential diagnosis of asthma is extensive, and beyond the scope of this chapter. The main diagnoses will show global variation in prevalence, so beyond recommending an appropriate diagnostic work up, it is not possible to be prescriptive for all healthcare settings across the world. Likewise, the prevalence of important co-morbidities, although less studied, is likely to show global variation. These include gastro-esophageal reflux, rhinosinusitis, obesity, food allergy and dysfunctional breathing and other psychological issues. It is important to exclude important co-morbidity [22^{*}]. Assuming that appropriate work-up has been done as clinically indicated, and the child is diagnosed as having asthma, an assessment of severity is now appropriate.

Assessment of asthma severity

The linked domains of asthma severity (the intrinsic severity of the disease process, which may vary over time), control (the degree to which symptoms are minimized by therapy), and responsiveness (the ease with which therapy leads to asthma control) should be assessed [23,24], as summarized below:

- (1) Level of control:
 - (a) current clinical control (impairment): symptoms and functional limitations over previous 2–4 weeks;
 - (b) exacerbations over previous 6–12 months, including number, severity and use of systemic corticosteroids.
- (2) Level of current treatment prescribed, inhalation technique and compliance with treatment.
- (3) Responsiveness to treatment.
- (4) Risk.

Unfortunately, most criteria are arbitrary and not evidence based. Severity may also be assessed historically, when asthma is untreated, and during therapy. There may be no relationship between the two, in particular in the child who has severe untreated asthma, but who responds rapidly to low-dose ICS.

Level of control

This comprises symptoms and functional limitation over a 2–4-week period, and exacerbations over the previous 6–12 months (both time periods arbitrary). Proposals for defining acceptable levels of bronchodilator use (e.g. less than twice/week) have been made, but are essentially arbitrary. It is probable that assessing several different end-points, rather than relying on a single test, is best for assessing control [25,26,27^{*},28]. In particular in children, spirometry is an insensitive end-point [29]. There is emerging evidence that, although poorly controlled patients will complain of symptoms, many apparently well controlled patients under-estimate the effect of asthma on their lives [30–32]. There is no uniform agreement on the definition of an exacerbation of childhood asthma, but an operational definition could be life-threatening, requiring admission to intensive care; very severe, requiring admission and intravenous therapy; severe, requiring admission but no intravenous therapy; moderate, requiring out-patient prescription of oral corticosteroids; and mild, not requiring the prescription of oral corticosteroids. For many purposes, just defining an exacerbation as meriting any prescription of oral corticosteroids will be adequate.

The temptation to combine chronic symptoms and functional impairment with exacerbations in a global 'control score' should be resisted. They do overlap (except probably in the true episodic viral wheeze in preschool children), in that a high level of chronic symptoms, chronic impairment of lung function, a high number of allergic triggers [33^{*},34^{*}], and failure to prescribe low-dose ICS [35,36] are all associated with an increased risk of exacerbations in school age children. However, excellent asthma control between viral infections does not prevent severe viral induced exacerbations, and there is no evidence that increasing the dose of inhaled corticosteroids between exacerbations is a useful strategy. In a tertiary research context in a high income setting, normalizing sputum eosinophils may be a helpful strategy [37,38], and in adults, the use of the anti-interleukin (IL)-5 monoclonal mepolizumab is beneficial [39,40]. Furthermore, most healthcare providers would be concerned about a child with a single attack of asthma that was so severe as to require ventilation, even if there were no other asthma symptoms after the attack.

Level of current treatment prescribed

This is an area which will vary throughout the world, depending on medication availability and cost. In a high income setting severe asthma would be defined as inadequate levels of control (including ongoing exacerbations) despite the prescription of ICS (500 µg/day Fluticasone or 800 µg/day Beclomethasone equivalent) and LABA, leukotriene receptor antagonist (LTRA) and probably low-dose oral theophylline, or failed trials of

these medications. In LMICs, only the most basic medications may be available, with LABAs or LTRAs unavailable or unaffordable. Thus for purposes of comparison, context must be given, and the available medications must be stated. The basic asthma 'kit' in a developing world context is as follows:

- (1) beclomethasone/budesonide pMDI;
- (2) salbutamol pMDI;
- (3) plastic bottle with/out mask as a spacer;
- (4) prednisolone.

Responsiveness to treatment

This relates to the level of medication required to obtain control. For example, a child may have very severe symptoms when not treated, but rapidly obtain control on low-dose ICS; thus 'untreated severe asthma' is converted to mild disease. Children may be responsive to treatment, but only at a level which is likely to lead to severe side-effects. The problem of poorly responsive patients is discussed in more detail below.

Risk

There are a number of elements to this important domain. These are risk of failure of normal lung growth (children) or accelerated decline in lung function (adults); risk of future loss of asthma control; risk of future exacerbations; risk of phenotype change from episodic, viral to multitrigger (mainly preschool children) [41[•]]; and the risk of harm from medications. This last is of most immediate concern; a child with good asthma control on very high-dose oral corticosteroids is at high risk of unacceptable side-effects, and must be considered to have severe asthma.

Sorting out the problem: what type of severe asthma?

The WHO document defines three different groups, which we discuss in turn: 'untreated asthma', 'difficult-to-treat asthma', and 'treatment-resistant severe asthma'. This last is referred to as 'severe, therapy-resistant asthma' in the GA2LEN network.

Untreated asthma

This is frequently due to undiagnosed asthma in children in LMICs. When asthma has been diagnosed, then poor access to care, medicines or spacers or unaffordability may make appropriate treatment of asthma impossible, thus effectively untreated or under treated (see below, Medication issues).

Difficult-to-treat asthma

In high income settings, many children with asthma that is apparently not controlled will improve if basic manage-

ment is correctly instituted. The five important areas are medication issues, the environment, asthma education, co-morbidity, and psychological problems [17[•], 18^{••}, 20^{••}]. The methods of assessment will vary across the world; in a UK context, nurse led home visits have proved to be very valuable.

Medication issues: is the best use being made of what is available?

In high income countries, these may be important in up to 50% of children with apparently uncontrolled severe asthma. Problems worldwide may include failure to access available medication because of ignorance, or cost; failure to use medication regularly, even though it is available within the home; and failure to use an appropriate medication delivery device. In this context, the provision of a plastic bottle spacer should be attainable everywhere.

Environmental issues

These include irritants and allergens, and the relative contributions of the two vary across the world, in part depending on the importance of atopy. Passive exposure to tobacco smoke must be addressed, and indoor use of biomass fuels. The avoidance of relevant allergens (if any) should be addressed. It is of course one thing to identify a problem, and quite another to tackle it. There may be no alternative way of cooking food.

Asthma education

Appropriate asthma education for healthcare workers, caregivers and the patient is important to maximize adherence and ensure optimal use of devices and therapy. Such education should be appropriate to the culture and language of patients. In some LMIC there is considerable stigma associated with a diagnosis of asthma and much misinformation about the safety of pMDIs – addressing such caregiver concerns is crucial to obtaining good adherence.

Co-morbidity

Management of co-morbid conditions such as allergic rhinitis is important in achieving asthma control with the least medication.

Psychological factors

Any physical illness may lead to psychological problems, including depression and anxiety in child or carer, and the over-estimation or under-estimation of symptoms. Dysfunctional breathing patterns, such as hyperventilation or vocal cord dysfunction may commonly complicate asthma.

In summary, patients are placed in the 'difficult-to-treat' asthma category ('difficult asthma' in the GA²LEN nomenclature [18^{••}]) if their poor asthma control is

due to difficulty with accessing or using medications; if the home environment is such that medications are likely to be ineffective; if there is poor understanding of the illness and its management; or if there is untreated psychological or other co-morbidity. Children who do not have access to ICS, and have to rely on oral corticosteroids with the inherent risk of side-effects, are placed in this category. Children in this category may be just as needy as those in the 'severe therapy-resistant group'; poverty may need to be tackled, an educational program put in place, or the home environment improved. The key issue in this group is that the problem is not optimally addressed just by increasing medications, or, by using increasingly experimental and risky therapies.

Treatment-resistant severe asthma ('severe, therapy-resistant asthma' in the GA²LEN nomenclature)

This category comprises two groups. The first is those children who remain symptomatic despite high doses of available medications, including oral corticosteroids. The second group achieve control, but only at the cost of unacceptably high doses of medication. In children, it can be argued whether these two groups are in fact ends of a spectrum, in that most children will improve if given enough oral corticosteroid, since steroid resistance is a spectrum. These children should have undergone a detailed evaluation to rule out other diagnoses, and to try to identify and reverse any causes of secondary steroid resistance such as ongoing allergen exposure, active or passive tobacco smoke exposure, or, particularly in high income countries, obesity [18[•],20^{••},22[•],41[•]].

Uniform definition of severe asthma

In summary, based on the definitions above, the WHO has provided a uniform definition of severe asthma. This 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 three 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:
 - (a) Asthma for which control is not achieved despite the highest level of recommended treatment: refractory asthma and corticosteroid-resistant asthma.
 - (b) Asthma for which control can be maintained only with the highest level of recommended treatment.

Beyond the definitions: how to sub-phenotype asthma

The establishment of a definition is only the first step. It is clear that the definitions above comprise a number of phenotypes. The ultimate aim must be to understand the mechanisms of each of these phenotypes. How this is done will depend on the resources available. Broadly, phenotyping may be hypothesis driven or data driven. Each has its disadvantages. Hypothesis driven phenotyping means the investigators impose their own prejudices on the data, whereas data driven analyses rely on the application of mathematical techniques such as cluster analysis, or principle component analysis to large groups of patients [42,43]. This latter may be more objective, but crucially depends on the right data set being analysed. What is clear is that clarity of definition must precede the essential international collaboration which is the only way that mechanisms of therapy resistance in asthma will be sorted out.

Special issues in young children

These were addressed in a recent Task Force of the European Respiratory Society [44]. The current WHO document did not add much to this report. It is arguable whether the term 'asthma' is appropriate in very young children, in whom evidence of inflammation is lacking. Operationally, the most useful categorization of pre-school wheeze is on symptoms: 'episodic, viral' and 'multiple trigger'.

Summary and conclusion: how has the WHO document advanced the field?

If, as has been strongly argued elsewhere, international collaboration is needed, then the first step has to be uniformity of definition. However, there are important caveats. Asthma may be a different disease in parts of the developing world, with atopy in particular being less important than in the developed world. The level of specialist training, and access to medications and diagnostic testing may be different. Thus even the careful application of the definitions does not mean that a child unresponsive to 800 µg/day Beclomethasone equivalent in Buenos Aires is the same as one in Liverpool. Nonetheless, these definitions have important applications. Clearly they will be a powerful tool for public health planning, and estimating the morbidity and financial costs of not making basic asthma medications widely available within a given country, and facilitate comparisons with neighbouring regions with similar incomes. There is potential for the development of international registries, clinical trials, exploration of mechanisms of disease, and epidemiological studies. However, the need for careful assessment of comparability of the problem of

severe asthma in different countries will be needed before international collaborations are undertaken in any of these fields.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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