

Definitions of asthma exacerbations

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Purpose of review

During the past decade exacerbations of asthma have increasingly been recognized as a primary outcome parameter in clinical research. However, comparison of results is hampered by the use of different definitions for asthma exacerbations in published reports. The purpose of this review is to describe the consequences of using different definitions and to propose possible solutions.

Recent findings

The use of different definitions of asthma exacerbations not only influences incidence rates, but also affects patient identification and risk assessment. The American Thoracic Society/European Respiratory Society and the World Health Organization independently proposed consensus definitions based on clinical symptoms and management. This needs to be complemented by a prospective definition that may support clinicians in their treatment decisions.

Conclusion

Currently there is no commonly accepted definition for asthma exacerbations. A prospective definition is desirable. This could be obtained by phenotyping asthma exacerbations based on clinical signs, lung function parameters and possibly other biomarkers.

Keywords

asthma exacerbation, definition, outcome measures, prevalence

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Introduction

Asthma is a chronic lung disease affecting millions of individuals of all ages and ethnicities all over the world [1]. Asthma is a heterogeneous disease that is characterized by airway inflammation associated with variable airflow limitation and symptoms such as wheezing, cough and shortness of breath. A major challenge for physicians is the episodic character of the clinical and physiological abnormalities of asthma over time and the within-patient and between-patient variability.

Exacerbations of asthma are episodes of (sub)acute worsening of asthmatic symptoms. The majority of asthma exacerbations are preceded by (viral) upper airway infections [2]. Other examples of triggers are allergen exposure and weather conditions [3]. This causes epithelial and inflammatory activity leading to contraction of smooth muscles, airway oedema and increased mucus production, resulting in airway narrowing and airflow limitation. Exacerbations are a major burden for patients' wellbeing [4] and usually result in doctor's consultation and medication prescription, occasional hospitalization or even death [5]. Exacerbations account for a considerable amount of healthcare utilization for asthma and accompanying costs [6,7]. In addition, severe exacer-

bations may lead to impaired long-term prognosis by accelerating lung function decline [8]. Therefore, the prevention of exacerbations is one of the major treatment goals in current asthma guidelines [1,9,10]. It is not surprising that exacerbations have become the primary outcome in several clinical trials evaluating new therapeutic strategies.

Estimation of incidence rates

Incidence rates of asthma exacerbations vary considerably depending on the level of healthcare organization of the examined populations. At the level of mortality registration, fortunately, the number of fatal asthma exacerbations has decreased during the past decades to 0.23 per 100 000. This is likely to be due to the introduction of inhaled corticosteroids (ICS) in the maintenance therapy of the disease [11^{*}]. Furthermore, the number of Emergency Department (ED) visits because of asthma exacerbations has been declining gradually from 9.7 per 1000 in 1999 to 6.7 per 1000 in 2005, accounting for 1.8–1.2% of the total number of ED visits, respectively [12]. Among those, 10% is hospitalized and 90% is discharged [12]. Furthermore, a Canadian study [13] showed that 33% of the patients received oral corticosteroids (OCS) after discharge from the ED.

In a primary care population who had had an exacerbation during the previous year (defined as a temporary increase in ICS or a course of OCS), 23% of asthmatic patients experienced an episode of deteriorating asthma control during a period of 12 months. Half of these cases resulted in a course of OCS [14[•]]. A deteriorating control of asthma was defined as a fall in peak expiratory flow (PEF) of more than 15% on two consecutive days or more than 30% on one day [14[•]]. In unselected primary care populations, the incidence of exacerbations is likely to be lower.

Definitions of exacerbation

When getting towards definitions, it needs to be appreciated that there are two types of definition. First, there are conceptual definitions. These are precise descriptions of the meaning of a word. Secondly there are operational definitions. These describe the presence or quantity of defined objects by derivable properties. As this review discusses the asthma exacerbations as outcome parameters, we will confine ourselves to the operational definition.

The mixed usage of the terms ‘asthma severity’, ‘(loss of) control’ and ‘exacerbation’ is confusing and should be abandoned [15]. To clarify this issue, ‘control’ is recommended to be used in terms of the extent to which the symptoms of asthma have been reduced by treatment, and includes assessment of current clinical control and future risk. Furthermore, ‘severity’ describes the intensity of treatment necessary to achieve control [16].

When checking the literature, several terms such as acute (severe) asthma, asthma attack and status asthmaticus are being used interchangeably for exacerbations. The common denominator is that an exacerbation is generally regarded as an episode of deterioration of symptoms. Table 1 [8,17–26] shows illustrative examples of definitions of asthma exacerbations, used in the very recent literature during 2010 and 2009.

From Table 1 three different ways to define an exacerbation can be derived. The first type is based on increased symptoms, for example, resulting in a symptom score or use of rescue medications, possibly recorded in a diary. The second possibility of a definition is a fall in lung function parameters, such as forced expiratory volume in 1 second (FEV1) or PEF, expressed in a percentage from predicted or from personal best. The third option is to define it based on healthcare utilization, for example, medication prescription, unscheduled doctor’s visit, ED visit or hospitalization. Table 1 also shows the pros and cons of the types of definitions.

Implications of using different definitions: lessons from Chronic Obstructive Pulmonary Disease (COPD)

There is little doubt that the widely differing definitions are affecting the reported incidence rates. Although one

Key points

- There is a wide variability in definitions for asthma exacerbations used in research.
- The use of different definitions of exacerbations affects estimates of incidence and hampers meta-analysis.
- A prospective definition is warranted, based on clinical signs, lung function parameters and possibly biomarkers.

might expect that the number of exacerbations will generally be higher if it is based on having increased symptoms for two consecutive days than if based on an ED visit or hospitalization, the reverse may be true due to severe under-reporting of symptom-based exacerbations [27^{••}]. We were unable to find reports about the implications of different definitions of asthma exacerbations on incidence rates. However, these terminology problems are very similar in COPD [28[•]], as Calverley *et al.* [29] stated: ‘agreeing on a comprehensive definition has been surprisingly difficult and is limited by the lack of studies in which different approaches to defining an exacerbation have been compared.’ Indeed, a pharmaco-economic analysis of the costs of exacerbations of COPD was hampered by nonconsistent approaches to define exacerbations [30[•]]. The use of symptom-based and event-based approaches resulted in substantially different conclusions regarding the occurrence of an exacerbation. This created difficulties in interpreting results across multiple studies in COPD [30[•]]. Similarly, the use of a symptom-defined (increase of complaints for 2 consecutive days) versus a healthcare-defined exacerbation (need for antibiotics and/or oral corticosteroids) affected the incidence of COPD exacerbations [31]. During 1 year, 127 patients completed day-by-day diary cards assessing symptoms, quality of life and healthcare utilization. During the year 296 symptom-defined (increased symptom score for 2 consecutive days) and 351 healthcare-defined exacerbations were identified. Notably, the majority of the exacerbations were not associated with a visit to a physician, even though unplanned doctors’ visits are often used as a definition of exacerbations. Amongst exacerbations based on healthcare definitions only 41% were also identified by the symptom-based definition [31]. Vice versa, amongst the symptom-defined exacerbations, 54% was also recognized in the healthcare-defined group. This illustrates the implications of using different definitions of exacerbations, albeit in COPD.

Proposed definitions

To overcome the above problems of using different definitions, expert committees of two leading international societies that are focussed on respiratory research and healthcare developed consensus definitions and classifi-

Table 1 Variability of definitions of asthma exacerbation encountered across a sample of recent research papers

[Reference] Definition of asthma exacerbation	Symptoms	Lung function	Healthcare utilization			Comments
			Medication	Visits	Other	
[8] The primary outcome was time to the first severe asthma-related events (SAREs), defined as events requiring hospitalization or emergency treatment due to worsening of asthma, or death due to asthma. Emergency treatment was defined as treatment of acute airway obstruction with systemic corticosteroids and nebulized or parenteral bronchodilators given at a healthcare institution. This most stringent definition of a severe asthma exacerbation was selected to ensure uniformity in the 32 countries enrolling patients in the trial	No	No	Yes	Yes	No	Good attempt to specify defining terms, although assignment of cause of death may be difficult
[17] Additional outcomes included the numbers of severe asthma exacerbations (i.e. those requiring systemic corticosteroids or doubling of ICS dose)	No	No	Yes	No	No	No criteria given for 'requiring'; 'doubling of ICS dose' precludes higher doses
[18] Asthma exacerbations were also evaluated, and two definitions were used: need for systemic steroids, or need for systemic steroids or doubling of ICS dose	No	No	Yes	No	No	'Need' not specified; 'doubling' precludes higher dosages
[19] The primary outcome was the number of patients with asthma exacerbations of moderate intensity; that is requiring a short course of oral corticosteroids	No	No	Yes	No	No	No specification of 'requiring' or 'short'
[20] Searches were also limited to randomized clinical trials (RCTs) that included the following outcome measures: . . . , . . . , and exacerbations (not specified)	No	No	No	No	No	
[21] Severe exacerbations were defined as requiring medical intervention [hospital admission, emergency department presentation, unscheduled doctor visit or the use of oral corticosteroids (OCS)]. Mild exacerbations were defined as those managed by the patient and self-reported as increased symptoms or medication use [inhaled corticosteroids (ICS) or B2-agonists], or using a written action plan	Yes	No	Yes	Yes	Yes	No lower limit of self-reported increase; 'written action plan' not specified
[22] An acute asthma exacerbation was defined as at least one OCS treatment (prescription for <22 days filled within 7 days of a physician visit), asthma-related ED visit , or asthma-related hospitalization . Subacute lack of asthma control (SALAC) was defined as more than 4 physician visits for asthma (or ≥ 2 /quarter) or more than 5 SABA prescriptions during 1 year	No	No	Yes	Yes	No	Prescription may be more valid than 'use' since the clinician assesses the indication. Also, it is easier to document; 'asthma' not specified
[23] The secondary outcomes included . . . , and episodes of poor asthma control (EPACs) defined by any of the following events occurring any time during the follow-up period: a decrease in PEFr more than 30% over baseline; increased use of metered dose inhaler of the short acting β_2 agonist by more than four metered doses a day; use of oral corticosteroid; or any unscheduled asthma healthcare visit	No	Yes	Yes	No	No	EPAC's have characteristics of exacerbations
[24] Predetermined secondary outcome measures included . . . , . . . , asthma exacerbations (defined as increased asthma symptoms resulting in the use of oral glucocorticoids or the increased use of inhaled glucocorticoids or other asthma medications), . . .	Yes	No	Yes	No	No	'Increased', 'asthma symptoms', and 'asthma medications' not specified; 'asthma medications' not specified
[25] An exacerbation was defined as a course of oral corticosteroids, hospital admission, or emergency department attendance for asthma during the outcome year	No	No	Yes	Yes	No	Minimal dosages/duration of course not specified; 'asthma' not defined
[26] Severe exacerbations were defined as deterioration in asthma requiring emergency hospital treatment/admission or according to investigator opinion	No	No	Yes	Yes	No	Treatment not specified; 'according to investigator opinion' inherently unspecified

ER, emergency room; ICS, inhaled corticosteroids; n.a., not applicable; OCS, oral corticosteroids; SCS, systemic corticosteroids. References [8, 17–26].

cation of asthma exacerbations, aimed to standardize definitions for future clinical trials and clinical practice.

The European Respiratory Society (ERS) in collaboration with the American Thoracic Society (ATS) proposed the following consensus definitions for severe and moderate asthma exacerbations [32^{••}]:

The definition of a severe asthma exacerbation for clinical trials should include at least one of the following:

- (1) Use of systemic corticosteroids (tablets, suspension, or injection), or an increase from a stable maintenance dose, for at least 3 days. For consistency, courses of corticosteroids separated by 1 week or more should be treated as separate severe exacerbations.
- (2) A hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids.

The definition of a moderate asthma exacerbation should include one or more of the following: deterioration in symptoms, deterioration in lung function, and increased rescue bronchodilator use. These features should last for 2 days or more, but not be severe enough to warrant systemic corticosteroid use and/or hospitalization. Emergency room visits for asthma (e.g. for routine sick care), not requiring systemic corticosteroids may be classified as moderate exacerbations.

A definition of a mild asthma exacerbation is not justifiable with present methods of analysis, because the symptoms or changes in flow rates during these episodes will be only just outside the normal range of variation for the individual patient and may reflect transient loss of asthma control rather than the early stages of a severe exacerbation.

The World Health Organization (WHO) also recognized the problem and proposed the following [33^{••}]:

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 FEV1). 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. The severity of exacerbations ranges from mild to life-threatening and can be evaluated based on both symptoms and lung function.

The differences between ERS/ATS and WHO can be explained by different objectives. The former was primarily developed for clinical research, whereas the latter should be applicable in clinical circumstances in low, middle and high-income countries. Each of the proposed

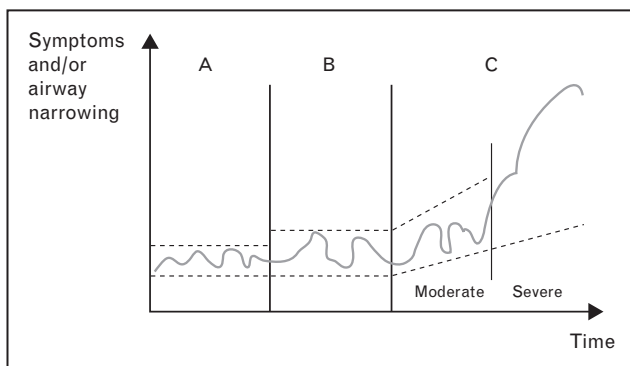
definitions has its drawbacks. WHO leaves much room for interpretation and has no clear classification of severity of the exacerbation. ERS/ATS is more specific, and has a severity classification, but is largely based on medication prescription. It lacks value for usage in clinical practice, because of essentially being retrospective (as acknowledged by the authors themselves). In addition, it relies on doctor's decisions, which by themselves may not be inadequate, but are likely to vary between physicians and time points. There are guidelines that help to differentiate between moderate and severe exacerbations, based on signs and symptoms such as the alertness of the patient and the ability to speak full sentences, but also objective variables such as respiratory rate, heart rate, peak flow and saturation [1,9]. However, these parameters have not been assessed systematically and are therefore just general guides [1,9]. It needs to be emphasized that adherence to guidelines on asthma management is poor [34[•]]. Therefore, a suitable definition for clinical practice has to be prospective. In addition, it would preferably be based on objective, quantitative and easily obtainable signs, leaving little room for (mis)interpretation.

Towards a prospective definition

Temporary deterioration of symptoms and airflow limitation are characteristic for exacerbations of asthma. Previous studies elegantly described courses with a (sub)acute onset, a progressive phase and a recovery period of about 9–14 days after initiation of treatment [35,36]. When using such diurnal PEF variations an exacerbation is distinguishable from poor asthma control [35,36]. This has shown that exacerbations also occur when patients are adequately controlled [35]. It remains to be established from prospective measurements whether gradual and acute onset exacerbations should be discriminated [37].

The temporal events in uncontrolled and exacerbated asthma as derived from previous studies are schematically depicted in Fig. 1. Situation A represents controlled asthma with limited day-to-day variation of symptoms and/or airway narrowing. Situation B represents loss of control, for example, because of nonadherence or therapy resistance. In these circumstances, most guidelines recommend the next treatment step [37]. However, this situation may persist for a longer period as patients do not always seek medical attention [38]. An arbitrary line to differentiate between situations A and B on the Y-axis could be an Asthma Control Questionnaire score of $0.75 \leq \text{ACQ} \leq 1.50$ [39,40[•]]. In situation C symptoms progress, often causing patients to seek medical care. It is well recognized that exacerbations can have ascending severities, but it remains to be established whether or not moderate and severe exacerbations are serial events.

Figure 1 Schematic representation of the level of symptoms (or airway narrowing) of an asthmatic patient



Situation A represents a controlled situation with an acceptable range of experienced complaints, with a day-to-day variation. Situation B represents an uncontrolled situation; however, this situation may be sustained. Situation C represents a progressive increase of symptoms (exacerbation) from moderate to severe [36], which may occur acutely [35]. Dotted lines represent arbitrary confidence intervals.

If moderate and severe exacerbations are temporally related, therapeutic intervention may prevent deterioration to a (severe) exacerbation, but this remains to be established by prospective studies. Interestingly, the temporal fluctuations in parameters, such as peak flow (PEF), may by themselves include predictive information about the progression to exacerbations [41]. Therefore, fluctuation analysis could be complementary when defining the future risk and/or severity of exacerbations. A combined prospective analysis of the dynamics of symptoms, lung function and possible biomarkers may eventually provide adequate predictive capacity for the development of exacerbations.

Biomarkers

It is tempting to consider the usage of (noninvasive) biomarkers as a complementary predictor of asthma exacerbations.

Sputum eosinophils have potential for being biomarkers for exacerbations. Sputum eosinophils predict the loss of clinical control and/or the development of exacerbations following inhaled steroid tapering, in both asthmatic adults [42,43] and children [44]. More importantly, a randomized controlled trial [45] showed that adjusting therapy based on monitoring sputum eosinophil counts leads to a five-fold reduction in exacerbation rate in asthma as compared with current standard therapy without increasing the inhaled steroid doses. This effect size has not been matched by any novel drug or any traditional, indiscriminative treatment regimen. These data were confirmed by showing increases in time to first exacerbation when using a sputum strategy, particularly

in patients with moderate to severe asthma [46]. Perhaps expectedly, the sputum strategy was not effective for noneosinophilic (presumably virus-driven) exacerbations. However, obtaining sputum cells, by induction, is quite comprehensive and for the time being not suitable for routine care during exacerbations. There are surrogate markers for eosinophilic inflammation, such as serum eosinophilic cationic protein [47] and exhaled nitric oxide [48]. Unfortunately, using the latter for guiding therapy has not led to significant reductions in asthma exacerbations [48].

Conclusion

There is a wide variability in the usage of definitions of asthma exacerbations. This affects not only the estimation of incidence and prevalence rates but also patient identification, risk assessment and current and future meta-analyses. The development of a definition is hampered by the wide variability in signs and symptoms, which are not consistent with airway obstruction. Therefore, multivariate and modern fluctuation analysis should be considered for prospective definitions of asthma exacerbations. This may include biomarkers, for which real-time desktop measures are still lacking. Therefore, prospective phenotyping of asthma exacerbations in terms of symptoms, lung function parameters and other biomarkers is necessary to obtain a definition of asthma exacerbation that can be used for research purposes as well as clinical practice.

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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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