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REVIEW

Defining moderate asthma exacerbations in clinical trials based on ATS/ERS joint statement

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Summary

Background: Exacerbations are a key outcome in clinical research, providing patient-relevant information about symptomatic control, health state and disease progression. Generally considered as an episode of (sub)acute deterioration of respiratory symptoms, a precise, clinically useful definition is needed for use in clinical trials.

Aim and methods: Focussing on moderate exacerbations, this opinion piece reviews landmark trials and current guidelines to provide a practical definition of a moderate exacerbation. Specifically, we adapt the ATS/ERS consensus statement of terminology Reddel et al. (2009) [1] which provides a conceptual (or 'theoretical') definition for moderate exacerbations, to an operational (or 'practical') criterion suitable for use in clinical research.

Results: The proposed definition for a moderate exacerbation requires ≥ 1 of the following criteria combined with a change in treatment: a) nocturnal awakening(s) due to asthma requiring SABA for 2 consecutive nights or an increase of ≥ 0.75 from baseline in daily symptom scores on 2 consecutive days; b) increase from baseline in occasions of SABA use on 2 consecutive days (minimum increase: 4 puffs/day); c) $\geq 20\%$ decrease in PEF from baseline on at least

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2 consecutive mornings/evenings or $\geq 20\%$ decrease in FEV₁ from baseline and/or d) visit to the emergency room/trial site for asthma treatment not requiring systemic corticosteroids.

Conclusion: A clinically and patient-relevant, operational definition of moderate exacerbations is needed. The proposed definition has been endorsed by the EMA Scientific Advice Working Party in 2011 and needs to be trialled in forthcoming clinical studies.

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Introduction

Exacerbations are increasingly recognised as a cornerstone for evaluating the management of asthma and gauging the success of interventions to reduce future risk. The Global Initiative for Asthma (GINA) guidelines recommend regular monitoring, and state that moderate exacerbations should be treated accordingly before they become severe [2]. The ostensible value of moderate exacerbations is as an intermediary stage at which physician intervention can mitigate progression to severe exacerbation. However, neither GINA, consensus guidelines from the World Health Organisation, the National Asthma Education and Prevention Task Force nor the NHLBI/NIAID Asthma Outcomes Workshop publication on Exacerbations [3] provide guidance on how to stratify severity or how to define a moderate exacerbation.

Currently, moderate exacerbations are largely defined subjectively according to the patients' experience and the physician-led changes in clinical management; in contrast, clinical trials with patient-relevant endpoints require consistent, prospective, clearly defined endpoints to compare study interventions. Without such clinically relevant data, the evidence on which best practice is based becomes considerably weakened, creating a circular problem. Based on the definitions of previous studies, this position paper attempts to provide a definition for moderate exacerbations that can be trialled, reviewing key work and guidelines to provide context.

Exacerbations as an endpoint in clinical trials: reviewing the evidence

Critical clinical studies have used a variety of definitions, examples of which are summarised in Table 1 [4–18], it is noteworthy that no core, landmark studies have used a

single, coherent definition of exacerbation. The diverse terminology invalidates comparison of endpoints between studies and complicates pooling of data for meta-analyses [19]; it also undermines perspectives in the aetiology, risk factors and associations for exacerbations, which are critical for developing strategies of symptom control.

In the current literature, exacerbations are sometimes described by change in medication (most frequently, an increase in inhaled steroid use), but across clinical research as a whole, the utility of medication type or dose in reducing the risk of progression to severe exacerbation may itself be the subject of the investigation. For this reason, exacerbations should be defined by other clinical criteria as well. Other key criteria include lung function (PEF or FEV₁ – which have been questioned regarding their usefulness as patient relevant outcomes), though notably thresholds vary, and indices of symptom worsening such as nocturnal awakening due to asthma.

A few general points can also be made about the level of stratification from the studies summarised below (Table 1). The emphasis in clinical research has, historically, focussed on severe exacerbations, which can be more clearly defined around the criterion of hospitalisation. Less mention is made of mild exacerbations, possibly because these are difficult to distinguish from intra- and inter-patient variability of baseline symptoms. Moderate exacerbations, however, are also not clearly defined in milestone studies; this may in part be because the interest in them as an endpoint is relatively recent. However, the advantages of a definition for moderate exacerbation go beyond clarity of trial reporting to improve outcomes for patients; intervention at the moderate stage could prevent patients from developing a severe exacerbation, which may require more intense treatment including hospitalisations. Accordingly, any intervention which reduces moderate exacerbations

Table 1 Defining asthma exacerbations in previous clinical trials. The studies listed in Table 1 used different criteria for exacerbations and most were published before the ATS/ERS Task Force recommendations in 2009. Since then, harmonisation in definitions of severe exacerbations has been attempted in clinical trials, but a uniform definition is still lacking.

Reference	Design, patients (n) and intervention	Primary outcome measurement	Definition of exacerbation	Incidence of exacerbation
Sears MR et al., 1990 [4].	24-week double-blind, placebo-controlled, randomised cross-over study Patients with stable asthma (n = 89) Fenoterol versus placebo	Control defined by daily morning and evening PEF, symptoms diaries, use of additional bronchodilator medication and requirement for prednisone	Exacerbations mentioned as a symptom in the study, but not defined	57/64 subjects showed a clear difference in degree of control of asthma between the fenoterol and placebo periods
Evans DJ et al., 1997 [5].	12-week randomised, controlled, double-blind, parallel group study Patients with asthma (n = 62) treated with either: 1. Inhaled budesonide 400 µg (low dose) + theophylline 250 or 375 mg (depending on body weight) or 2. Inhaled budesonide 800 µg (high dose)	Lung function: peak expiratory flow, FEV1, and forced vital capacity (FVC) and the reversibility of abnormalities in FEV1. Patient diaries recording twice daily entries of three PEF measurements, albuterol usage, and severity of symptoms	Exacerbations were defined as: Mild: two consecutive days with any of the following: decrease in morning PEF by more than 20% of base line, nocturnal symptoms, or the need for more than four puffs of albuterol or Severe: decrease in morning PEF by more than 30% on two consecutive days.	Mild exacerbations: range 0–11; median 3 in high dose budesonide range 0–13; median 2 in the group given low-dose budesonide plus theophylline. Severe exacerbations: Three exacerbations during the study (two in the given high-dose budesonide group and one in the low dose group).
The FACET study Pauwels RA et al., 1997 [6].	1 yr randomised, double-blind, controlled trial with 4 treatment arms Patients with asthma >6 months, treated with inhaled glucocorticosteroid (>3 months) 1. Budesonide 100 µg + placebo 2. Budesonide 100 µg + 12 µg formoterol 3. Budesonide 400 µg + placebo 4. Budesonide 400 µg + 12 µg formoterol	The rates of severe and/or mild exacerbations per patient per year.	A severe exacerbation was defined as one requiring treatment with oral glucocorticosteroids, as judged by the investigator, or a decrease in the peak expiratory flow as measured in the morning to more than 30% below the baseline value on two consecutive days. 73% of severe exacerbations were identified clinically by the investigators. The baseline peak expiratory flow was defined as the mean peak expiratory flow in the morning during the last 10 days of the run-in period. Days with mild exacerbations were defined as days when one of the following occurred: a peak expiratory flow in the	The number of severe exacerbations for treatment groups 1–4 was: 153, 125, 90 and 57 respectively, and for mild exacerbations: 5953, 3980, 4289, 2241.

(continued on next page)

Table 1 (continued)

Reference	Design, patients (n) and intervention	Primary outcome measurement	Definition of exacerbation	Incidence of exacerbation
			morning that was more than 20% below the base-line value; the use of more than three additional inhalations of terbutaline per 24 h as compared with the base-line period; or awakening at night due to asthma. Single, isolated days of mild exacerbations were not counted. The base-line value was the mean value for the variable during the last 10 days of the run-in period.	
Tattersfield AE et al., 1999 [7].	Subset analysis of the FACET study (above) explored characteristics and risk factors for the severe exacerbations observed (n = 425): a gradual fall in PEF over several days, followed by more rapid changes over 2–3 days; parallel use of rescue-medication and symptom increase; higher incidence in female patients			
The START study Pauwels RA et al., 2003 [8]. O'Byrne PM et al., 2009 [9]. and O'Byrne PM et al., 2010 [10].	3-yr, randomised, double-blind, placebo-controlled trial Patients with mild persistent asthma <2 years (n = 7165) Placebo versus 400 µg, or 200 µg inhaled budesonide	Time to first serious asthma-related event (SARE)	Part of a composite definition, SARE. This was defined as events requiring hospitalisation 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 glucocorticosteroids and nebulised or parenteral bronchodilators administered in a health-care setting.	198 of 3568 patients on placebo and 117 of 3597 on budesonide had at least one severe asthma exacerbation; hazard ratio 0.56 (95% CI 0.45–0.71, p < 0.0001).
The STAY study O'Byrne PM et al., 2005 [11]. and O'Byrne PM et al., 2007 [12].	1 yr, randomised, controlled, double-blind, parallel-group study Patients with asthma treated with ICS and a history of exacerbations (n = 2760) Patients treated with: 1. Terbutaline 0.4 mg + budesonide/formoterol (BD), 80/4.5 µg 2. Terbutaline 0.4 mg + budesonide 320 µg (BD) 3. Budesonide/formoterol (BD), 80/	Time to first severe exacerbation	Severe asthma exacerbations were defined as a deterioration in asthma resulting in hospitalisation/emergency room treatment, oral steroid treatment (or an increase in ICS [via a separate inhaler] and/or other additional treatment for children aged 4–11 years), or morning peak expiratory flow of 70% or less of baseline on 2 consecutive days. Mild exacerbations were	Events per patient year for groups 1, 2 and 3 respectively: 0.68, 0.68 and 0.36

Table 1 (continued)

Reference	Design, patients (n) and intervention	Primary outcome measurement	Definition of exacerbation	Incidence of exacerbation
	4.5 µg with Budesonide/formoterol as needed		defined as 2 consecutive days with either a morning PEF of 80% or less of baseline, as-needed use [of] two or more inhalation[s] per day above baseline, or awakenings caused by asthma.	
Rabe KF et al., 2006 [13].	1 yr, double-blind, parallel-group study with three treatment arms Patients using inhaled corticosteroids (n = 3394) Budesonide-formoterol (maintenance) plus as needed medication: 1. Terbutaline (0.4 mg) 2. Formoterol (4.5 µg) 3. Budesonide-formoterol combination at 160 µg + 4.5 µg	Time to first severe exacerbation	A severe exacerbation was defined as deterioration in asthma resulting in emergency treatment or hospitalisation or the need for oral steroids for 3 days or more (as judged by the investigator).	The rates of severe exacerbations were 37, 29, and 19 per 100 patients/year for treatment groups 1, 2 and 3 respectively
Kuna P et al., 2007 [14].	6-month, randomised double-blind controlled trial Patients ≥ 12 years with asthma for ≥ 6 months (n = 4399) using ICS ≥ 3 months Budesonide/formoterol (160/4.5 µg, OD plus additional inhalations as needed, [SMART] vs salmeterol/fluticasone (25/125 µg BID inhalation with terbutaline as needed) vs budesonide/formeterol (320/9 µg OD inhalation with terbutaline as needed)	The primary variable was the time to first severe exacerbation	Severe exacerbations were defined as deterioration in asthma resulting in hospitalisation or emergency room (ER) treatment, or the need for oral steroids for ≥ 3 days (as judged by the investigator). A mild exacerbation day was defined as a day with any one of the following: morning PEF ≥ 20% below baseline, daily as-needed medication use ≥ 2 inhalations above baseline or a night with an asthma-related awakening, calculated from diary-card data. A mild exacerbation was defined as two consecutive mild exacerbation days satisfying the same criterion.	There was a 33% reduction in hazard ratio for a first severe exacerbation with SMART compared with salmeterol/fluticasone, and a 26% reduction compared with budesonide/formeterol and terbutaline
Maneechotsesuwan K. 2007 [15].	12-week randomised double-blind controlled trial Patients with moderate stable asthma (n = 24)	The onset of exacerbation following withdrawal of corticosteroid	An exacerbation was defined as at least one of three criteria: (1) a drop in morning peak flow ≥ 20% below baseline	The fast withdrawal of inhaled corticosteroids led to an increase in sputum neutrophils and IL-8 <i>(continued on next page)</i>

Table 1 (continued)

Reference	Design, patients (n) and intervention	Primary outcome measurement	Definition of exacerbation	Incidence of exacerbation
	Budesonide (400 µg b.i.d.) or placebo		(mean of the last 7 days run-in period) on 2 consecutive days; (2) waking due to asthma on 2 consecutive nights, and requiring rescue medication; (3) $\geq 50\%$ increase in 24-h rescue medication use on at least 2 consecutive days compared to mean use during the last 7 days of the run-in period, which also exceeded the equivalent of four puffs of terbutaline. FEV1 was then measured within 24 h of the exacerbation.	concentrations. Following this, patients experienced exacerbation of asthma.
The GOAL study Bateman ED et al., 2008 [16].	1 yr, randomised double-blind controlled trial Patients with uncontrolled asthma (n = 3421) Salmeterol/fluticasone propionate vs fluticasone propionate	Totally or well-controlled asthma, defined as a composite endpoint; the absence of an exacerbation was necessary for control	Defined as a deterioration in asthma requiring treatment with an oral corticosteroid or an emergency department visit, and/or hospitalisation	In patients achieving well-controlled or totally controlled asthma, at least well-controlled asthma was maintained for a median of almost 3 and 6 months, and for more than 85% and 95% of weeks of follow-up, respectively.
2009 – ATS/ERS Task force recommendations [1]				
Nathan RA et al., 2010 [17].	26-week multicentre, double-blind, double-dummy, randomized, placebo-controlled trial Patients (n = 781) with uncontrolled asthma on medium dose inhaled corticosteroids Mometasone furoate/formoterol (200/10 µg) versus its monocomponents versus placebo, all b.i.d.	The time to first asthma deterioration and the bronchodilatory effect of MF/F versus MF.	An asthma deterioration was defined as any one of the three following events: (1) an occurrence of any clinically judged deterioration that resulted in emergency treatment, hospitalization due to asthma, or treatment with additional excluded asthma medication (i.e., systemic corticosteroids); (2) a $\geq 0\%$ decrease from the average of the two predose FEV1 measurements taken just before the first dose of randomized study medication; or (3) a $\geq 30\%$ decrease from the	The combined drug group was superior to its individual components or placebo for both of the primary endpoints.

Table 1 (continued)

Reference	Design, patients (n) and intervention	Primary outcome measurement	Definition of exacerbation	Incidence of exacerbation
Meltzer EO et al., 2012 [18].	26-week, multicentre, double-blind, placebo-controlled study Patients (n = 746) with poorly controlled asthma on low-dose inhaled corticosteroids Mometasone furoate/formoterol (100/10 µg) versus its monocomponents versus placebo, all b.i.d.	Time to first asthma deterioration and change in forced expiratory volume in 1 s (FEV1)	respective aver-age A.M. or P.M. PEF baseline measurements (obtained over the 7 days immediately before receiving the first dose of randomized study medication) for at least 2 consecutive days. An asthma deterioration was defined as a clinically judged deterioration (i.e. asthma attack resulting in emergency treatment, hospitalisation or treatment with additional, excluded asthma medication (i.e. systemic corticosteroids)) or a meaningful reduction in lung function (i.e. a decrease in FEV1 of >20% from baseline at any study visit or a decrease in PEF of >30% from baseline for ≥2 days consecutively at any time during the treatment period).	The combined drug group was superior to its individual components or placebo for both of the primary endpoints.

Legend: Full reference details of studies are provided in the reference list. Classification of exacerbations is given as direct quotations from the published texts, for clarity.

might also influence the frequency and/or severity of severe exacerbations.

A clear definition of moderate exacerbation: contributions to future clinical research and understanding

A combined ATS/ERS Task Force reviewed the Cochrane library database for publications from 1998 to 2004 (studies included, n = 327). Its primary objective was to standardise terminology used in asthma research to support data collection methods in future clinical trials, with a particular focus on definitions of asthma control, severity and exacerbation [1].

Definitions for each measure took into account the following: the congruity of information (is the measure consistent with existing understanding of asthma?); the extent of a given measure to support treatment aims (for example, did the measure achieve good control of symptoms or a reduced risk to patients?); the characteristics of the measure relevant to its use in clinical studies (how easy

it is to reproduce the measure, assess it and how does it associate with other measures?) and the feasibility of use (will use of the measure be limited by measures such as safety, accessibility and/or cost?). The resulting comprehensive review proposed a precise definition for mild, moderate and severe exacerbations, that has been published by the ATS/ERS Task Force (Callout Box 1). The authors concluded that 'more work is needed to develop simple feasible criteria for defining exacerbations in clinical practice' [1].

Theoretical classifications such as the ATS/ERS definitions are useful but invariably retrospective, as they depend largely on treatment decisions such as drug use. This may be sufficient in clinical practice, but for clinical trials, a more specific, prospective definition is needed to ensure consistency [19]. In chronic obstructive pulmonary disease, data suggest that comparing symptom-defined as opposed to healthcare-defined exacerbation rates results in clinically relevant differences in incidence levels [20] with a resultant impact on economic and care burden [21,22]. Furthermore, patients might adjust medication inappropriately in response to perceived symptom changes [23].

Callout Box 1. Defining moderate exacerbations: The ATS/ERS consensus statement (direct quotation from Reddel et al., 2009 [1]).

Moderate asthma exacerbations

1. A moderate asthma exacerbation is an event that, when recognised, should result in a temporary change in treatment, in an effort to prevent the exacerbation from becoming severe.
2. 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 hospitalisation. ER visits for asthma (e.g. for routine sick care), not requiring systematic corticosteroids, may be classified as moderate exacerbations.
3. The magnitude of change in these outcomes will differ depending on the population studied and each individual patient's baseline variation.

Translating clinical definitions to an operational setting: a new definition

Therefore, the ATS/ERS definition of a moderate asthma exacerbation should be translated into an operational format suitable for a clinical trial environment (Callout Box 2). This proposed definition of a moderate asthma exacerbation suitable for use in clinical trials was endorsed by the European Medicines Agency Scientific Advice Working Party in February 2011. In constructing this definition, not only a change in medication, but also the clinical observations that precede a change in treatment, providing clear thresholds for diagnosis across four key criteria were taken into account.

Although the validity of these criteria compared with other criteria still need to be tested prospectively, the individual criteria in Box 2 have been used before with variations in other studies. It is noteworthy that small differences in criteria can make a large difference in exacerbation rates [1]. To move the field forward, methodology will have to be developed to evaluate the utility of different criteria in various combinations.

The hypothesis that this adapted ATS/ERS definition of a moderate exacerbation can be used in clinical research is currently under investigation in a phase III controlled trial of allergy immunotherapy (MITRA trial, ALK, Horsholm,

Denmark) with the primary endpoint being a reduction in the risk for an asthma exacerbation. Moderate and severe exacerbations were defined as described by the ATS/ERS Task Force [1]. Studies exploring exacerbations in asthma have largely focused on severe exacerbations, but it might be more relevant to capture information about moderate exacerbations, thus exploring the potential for earlier interventions to mitigate disease progression and maintain and/or improve control and prevent future severe exacerbations.

Such future trials will be needed to review the success of the proposed definition. In order to achieve more widespread acceptance, the definition will need to be used far more widely; for example, trialling for different drug classes. It will also be necessary to explore how the moderate exacerbation endpoint works across key subgroups, for example: pregnant women; those with particularly severe asthma; the elderly, the paediatric population; adolescents and those with complications in asthma. Refining this definition to support use in especially vulnerable patient groups may include strategies for gathering information from patients who have difficulty in expressing their symptoms and/or where there may be difficulty in collecting classic metric data. Future research and wider participation should reveal these answers, and may also provide further elucidation of operational definitions for

Callout Box 2. Defining moderate exacerbations: The MITRA study protocol (direct quotation from Virchow et al., 2013 [24]).

A moderate exacerbation is defined as ≥ 1 of criteria a)–d) fulfilled and leading to a change in treatment:

- a) Nocturnal awakening(s) due to asthma requiring SABA for 2 consecutive nights or increase of ≥ 0.75 from baseline in daily symptom score on 2 consecutive days
- b) Increase from baseline in occasions of SABA use on 2 consecutive days (minimum increase: 4 puffs/day)
- c) $\geq 20\%$ decrease in PEF same from baseline on at least 2 consecutive mornings/evenings or $\geq 20\%$ decrease in FEV1 from baseline
- d) Visit to the emergency room/trial site for asthma treatment not requiring systemic corticosteroids

mild and severe exacerbations. It remains unclear to what extent the results of this analysis will be generalisable to other populations such as those with poor pulmonary function, different age and at greater risk for exacerbations, but using such a definition would be a starting point for further comparative analysis.

Conclusion

Exacerbations are increasingly likely to be a focal endpoint in clinical trials as they represent a patient- and healthcare system-relevant endpoint. Accordingly, there is a clear need for a standard definition. This will enable comparison of treatments and procedures, meta-analysis to strengthen the evidence-base, and will improve trial quality. Furthermore, many physicians may welcome a practical, observation-led definition of moderate exacerbation that enables them to identify patients at risk of developing severe exacerbations, and to develop strategies to prevent this.

Contributorship statement

VB, FDB, PK, CL, JLP and HHV contributed to the initial development of the MITRA trial protocol and VB, FDB, PK, CL, JLP, HHV and JCV to its further development and completion. All authors contributed to the development of the operational definition of moderate asthma exacerbations, and to the development of the outline and all stages of drafting and revision of the manuscript. JCV was lead author and takes responsibility for its overall content.

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Competing interests

JCV, NVB, FdB, JLP, PK have participated in advisory boards for ALK and have received honoraria for lectures. CL and HHV are employees of ALK.

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