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Title: Where does worsening asthma end and an asthma exacerbation begin?

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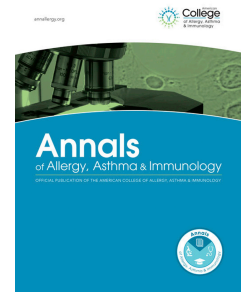
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Title Page

Title: Where does worsening asthma end and an asthma exacerbation begin?

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Abbreviations:

ATS: American Thoracic Society
ERS: European Respiratory Society
FACET: Formoterol and Corticosteroids Establishing Therapy
GINA: Global Initiative for Asthma
NIH: National Institutes of Health

PACT: Pediatric Asthma Controller Trial

PEF: Peak expiratory flow

SABA: short-acting beta-agonist

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When does worsening asthma end, and an asthma exacerbation begin?

Asthma exacerbations serve as a marker of disease risk and necessity of asthma therapy. Frequency of exacerbation, in particular severe exacerbations requiring emergency room visits, or hospitalizations, are used as an indication of risk,¹ and a measure of response to asthma therapy.¹ Exacerbations, in combination with symptoms and quality of life over time, are often noted as the measures of asthma control. Prevention of future exacerbations is cited as an important reason for asthma controller therapy.¹ In addition, asthma exacerbations are often used as a primary outcome in asthma intervention studies.² It has been argued that “exacerbations are the most important [asthma] outcome, because they constitute the greatest risk to patients, are a cause of anxiety to patients and their families, result in the greatest stress on health care providers, and generate the greatest cost to the health care system.”³ In addition, data suggest that airway remodeling leading to chronic irreversible airflow obstruction is driven by asthma exacerbations. As exacerbations play such a major role in defining asthma risk, therapy and outcomes, a uniform definition for asthma exacerbations is of primary importance.

Exacerbations are in theory “episodic flare-ups of asthma that can be life-threatening and carry a significant burden to patients and the community.”¹ However the definition of exacerbations varies dramatically. It has been noted that “almost no two studies define asthma exacerbations in the same way.”² A recent expert group organized by the National Institutes of Health (NIH) recommended that asthma exacerbations be defined as worsening asthma that requires the use of oral corticosteroids (or increased dose of oral corticosteroids in an asthmatic already on oral steroids) in order to “prevent a serious outcome.”² They did not include clinical symptoms in this

definition, but noted in their literature review that over 15 different definitions of asthma exacerbations exist.

In contrast, some guidelines include clinical criteria in the definition of asthma exacerbations. For example the 2018 Global Initiative for Asthma (GINA) update includes symptoms, such as shortness of breath, wheeze, cough, or chest tightness, in the definition of exacerbations, in addition to a decrease in lung function.¹

The inclusion of symptomatic criteria blurs the lines between worsening asthma and an asthma exacerbation. As the recent NIH expert panel noted, “the ability to distinguish between poorly controlled asthma and an exacerbation is difficult and is characterized by vague and inconsistent terminology.”² Many research studies, in addition to the GINA strategy, include clinical symptoms (or increased short-acting beta-agonist use [SABA]) in the definition of exacerbations.² And yet, it has been shown in both pediatric and adult asthmatics that clinical symptoms, and hence increased SABA use, typically precede a defined exacerbation by a few days.

This was well demonstrated in the NHLBI Childhood Asthma Research and Education Network PACT (Pediatric Asthma Controller Trial) study, which randomized 285 mild-to-moderate asthmatic children aged 6-14 years to one of three asthma controller therapies (inhaled fluticasone, inhaled fluticasone/salmeterol, or oral montelukast) and examined factors associated with exacerbations (defined as systemic corticosteroid use or emergency care).⁴ The PACT study noted that increasing symptoms and frequent albuterol use preceded an acute exacerbation by up

to several days, although this indicator had a poor positive predictive value for exacerbations. This was also demonstrated in the adult asthmatic population in the FACET (Formoterol and Corticosteroids Establishing Therapy) study, a randomized double blind trial that was designed to compare low and high-dose inhaled budesonide therapy with and without formoterol in the prevention of asthma exacerbations (defined as systemic corticosteroid therapy or drop of morning peak expiratory flow (PEF) by more than 30%) in 852 adult asthmatics.⁵ An analysis of the 425 exacerbations with 242 asthmatic patients that occurred during this year-long study found that an increase in symptom scores and albuterol use preceded exacerbations by 5 to 7 days with a more rapid increase over the 2-3 days preceding the exacerbation.⁵

We believe it is important to differentiate asthma worsenings, or loss of control, from asthma exacerbations. A joint statement by the American Thoracic Society (ATS) and European Respiratory Society (ERS) in 2009 on asthma control and exacerbations dealt with this paradox by further stratifying exacerbations as either moderate or severe.³ Severe exacerbations were defined as “events that require urgent action...to prevent a serious outcome” and could include systemic corticosteroid use (for at least 3 days duration) or a hospital/emergency room visit. In contrast, moderate exacerbations were defined as “an event that, when recognized, should result in a temporary change in treatment, in an effort to prevent the exacerbation from becoming severe” and could include worsening symptoms or lung function, or increased bronchodilator use. Under this definition, one could include worsening asthma in the category of a moderate exacerbation, with increased treatment required to prevent a severe exacerbation.

In the authors' opinion, an increase in clinical symptoms and/or need for reliever therapy is what defines asthma worsening, and offers a window of opportunity for treatment to prevent an asthma exacerbation. The use of symptom and reliever criteria in the definition of an asthma worsening will allow for focused study of interventions (such as, but not limited to, short or long acting beta-agonist use, inhaled corticosteroid dose, inhaled corticosteroid/long acting beta-agonist use, addition of a long acting muscarinic antagonist or leukotriene receptor antagonist) to prevent progression to asthma exacerbations as defined by the ATS/ERS. Similarly, use of clear criteria such as initiation of (or increasing) systemic corticosteroids or need for emergency department care or hospitalization for an asthma exacerbation allows for this distinction. Moving forward, a standard definition of asthma worsenings and for asthma exacerbations would serve both our asthmatic patients, as well as the ongoing research that determines their therapies.

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