



Asthma control and exacerbations: two different sides of the same coin

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Purpose of review

Optimal asthma management includes both the control of asthma symptoms and reducing the risk of future asthma exacerbations. Traditionally, treatment has been adjusted largely on the basis of symptoms and lung function and for many patients, this approach delivers both excellent symptom control and reduced risk. However, the relationship between these two key components of the disease may vary between different asthmatic phenotypes and disease severities and there is increasing recognition of the need for more individualized treatment approaches.

Recent findings

A number of factors which predict exacerbation risk have been identified including demographic and behavioural features and specific inflammatory biomarkers. Type-2 cytokine-driven eosinophilic airways inflammation predisposes to frequent exacerbations and predicts response to corticosteroids, and the usefulness of sputum eosinophilia as both a marker of exacerbation risk and biomarker for adjustment of corticosteroid treatment has been established for some time. However, attempts to develop surrogate markers, which would be more straightforward to deliver in the clinic, have been challenging.

Summary

Some patients with asthma have persistent symptoms in the absence of type-2 cytokine driven-eosinophilic airways inflammation due to noncorticosteroid responsive mechanisms (T2-low disease). Composite biomarker strategies using easily measured surrogate indicators of type-2 inflammation (such as fractional exhaled nitric oxide, blood eosinophil count and serum periostin levels) may predict exacerbation risk better but it is unclear if they can be used to adjust corticosteroid treatment. Biomarkers will be used to target novel biologic treatments but additionally may be used to optimize corticosteroid treatment dose and act as prognostics for exacerbation risk and potentially other important longer term asthma outcomes.

Keywords

asthma, biomarker, eosinophils, exacerbation, fractional exhaled nitric oxide, periostin

INTRODUCTION

Asthma is a clinical syndrome characterized by variable symptoms of wheeze, breathlessness, chest tightness and cough in association with bronchial hyperresponsiveness and reversible airflow obstruction. In addition to chronic symptoms, asthma is also associated with tendency to deteriorate in an abrupt or subacute manner. These events are usually referred to 'exacerbations' or 'attacks' which are serious events – they can be fatal, but at the very least have a major impact on quality of life in patients and have major health economic consequences globally. Severe asthma exacerbations have been defined by an American Thoracic Society/European Respiratory Society taskforce as 'events that require urgent action on the part of the patient and physician to prevent a serious outcome, such as hospitalization or death from asthma' [1]. In clinical trials, severe asthma

exacerbations generally refer to events which require the use of rescue systemic corticosteroids (or an increase from a stable maintenance dose) for at least 3 days, or a hospitalization or emergency room visit. The concept of 'asthma control' encapsulates both the level of 'day to day' control (including breakthrough symptoms and the extent to which activities of daily living are impaired) and the risk of future adverse events including loss of control,

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KEY POINTS

- In many patients, particularly with mild-to-moderate asthma, asthma symptoms correlate well with type-2 cytokine-driven eosinophilic airways inflammation ('concordant' disease) and increasing therapy (particularly, corticosteroid therapy) to achieve control of long-term symptoms will also reduce the risk of acute exacerbations. This is the approach advocated in current guidelines and serves many patients well.
- In other patients, particularly those with more severe disease, symptom severity is often dissociated from the degree of corticosteroid responsive type 2 airways inflammation ('discordant' disease). Patients with persistent symptoms due to noncorticosteroid responsive mechanisms (T2-low disease) will respond poorly to high-dose corticosteroids and are likely to receive an excessive corticosteroid burden, whereas patients with persistent type-2 cytokine-driven eosinophilic airways inflammation (T2-high disease) and minimal symptoms may be undertreated in terms of their elevated exacerbation risk.
- Novel strategies are required to target corticosteroid treatment in individual patients which will be easily deliverable in the clinic in place of sputum-guided treatment algorithms. A composite biomarker system using easily measured surrogate indicators of type-2 inflammation (such as FeNO, blood eosinophil count and serum periostin levels) can predict exacerbation risk independently of ACQ scores and lung function, but it is unclear if this approach can be used to adjust corticosteroid treatment. (Please see RASP-UK study for further information.)
- In the future, it is probable that biomarker-based strategies will facilitate a more individualized approach to asthma, particularly in those with more severe disease. Biomarkers will be used to target novel biologic treatments but additionally may be used to optimize corticosteroid treatment dose and act as prognostics for exacerbation risk and potentially other important longer term asthma outcomes.

exacerbations, accelerated decline in lung function and side-effects of treatment [1,2]. Although chronic symptoms and risk of acute exacerbations often coexist, in recent years the relationship between these two key facets of the asthma syndrome has become clearer and has challenged the current 'one-size-fits-all' pharmacological approach to asthma treatment, and is likely to change our approach to asthma management in the future.

THE RELATIONSHIP BETWEEN ASTHMA SYMPTOMS AND FUTURE EXACERBATION RISK IN ASTHMA

Several validated questionnaires of symptom control in asthma are available, with the Asthma

Control Test and Asthma Control Questionnaire (ACQ) used commonly in clinical practice and clinical trials [3,4]. When looking at large cohorts of patients, there is a relationship between current asthma symptom control and future risk of asthma exacerbation [5,6]. Bateman *et al.* [7] demonstrated in an analysis of 12 548 patients prescribed treatment at Global Initiative for Asthma (GINA) step 3/4 that the time to first severe exacerbation increased when patients were stratified by ACQ score and the risk was the highest in patients with an ACQ score of at least 1.5, which defines poorly controlled asthma using this instrument. Other clinical parameters have also been examined to try and predict future exacerbation risk. Perhaps not surprisingly, a history of prior asthma exacerbation, hospitalization and oral corticosteroid use are associated with exacerbation risk, but additionally markers of poor symptom control including high prescription use for short-acting β_2 -agonist treatment and recurrent physician visits are also related to future risk of exacerbation [8].

Although asthma symptom control is related to future exacerbation risk in studies of large asthma cohorts, is this the case for individual patients? And perhaps a more relevant but related question, can asthma control be used to define treatment requirements in all patients with asthma? In fact, the predictive value for the most commonly used instrument for measuring asthma control (ACQ) for an individual patient is relatively poor, with an area under receiver operator curve values of less than 0.7 for exacerbation-related outcomes [5]. Halder *et al.* [9] in an elegant study using cluster analysis described different phenotypes in mild and severe asthma populations and described 'concordant disease', in which asthma symptoms were related to eosinophilic airway inflammation (and by extension exacerbation risk [10]) and 'discordant disease' in which symptoms had little relation to airway inflammatory measures. In this latter group, which had greater representation in patients with severe asthma, there were both patients with minimal current symptoms but who had significant inflammation and exacerbation risk and patients with high symptom levels and minimal inflammation. We define severe asthma using a combination of persistent symptoms and high-dose corticosteroid treatment [11], and given symptoms are used to escalate treatment, in some ways, the greater representation of discordant disease in 'severe asthma' is hardly surprising. The obvious conclusion from this is that in some patients, escalating anti-inflammatory asthma treatment based on symptoms will be appropriate and effective (concordant disease) but in many others, using symptoms to define

treatment (particularly, corticosteroid dose) will lead to both inappropriate treatment escalation and undertreatment as symptoms are dissociated from inflammatory events in the airway and future exacerbation risk.

PHENOTYPES AND PERSONALIZING TREATMENT

Statistical approaches, such as cluster analysis using combinations of demographic, clinical, physiological and immunobiological variables, have defined phenotypes within asthma cohorts [9,12,13]. In parallel, using inflammatory biomarkers such as sputum analysis and transcriptomic profiling, it has been demonstrated that up to 50% of asthmatic patients have prototypic eosinophilic airway inflammation driven by 'Type 2' cytokines (T2-cytokines: interleukin-4, interleukin-5 and interleukin-13) and which has been termed 'T2-high asthma' [14²²]. It has also become clear that some of the pathophysiological features of asthma, including reversible airflow obstruction and bronchial hyper-responsiveness, can be present when there is no evidence of type-2 inflammation ('T2-low asthma'). An important additional observation from this work is that type-2 inflammation has been shown to respond well to corticosteroid therapy, whereas in the absence of this inflammatory profile, patients show little or no response to corticosteroid therapy [15²³]. This suggests that in some patients, persistent and chronic asthma symptoms are unlikely to be completely controlled with corticosteroid therapy, but the extent to which this may be clinically manifest will potentially vary from patient to patient.

Patients with persisting airway eosinophilia/type-2 inflammation are prone to recurrent exacerbations, and targeting this inflammatory biology with either corticosteroids or specific antieosinophilic therapies targeting interleukin-5 causes a significant reduction in severe exacerbations in this group [16–18]. However, it is also clear from clinical trials that use specific anti-interleukin 5 treatments that severe exacerbations are reduced by around 50% in populations of patients with severe asthma who were selected because they are exacerbation prone and who have had evidence of persisting eosinophilia despite high-dose inhaled corticosteroid treatment [15²³,16,17]. This suggests that even in this population with severe disease, many of these severe exacerbations are potentially because of noneosinophilic events. The precise nature and character of these exacerbations needs to be further defined to allow specific targeting of the underlying mechanism to further reduce exacerbation rate.

CURRENT GUIDELINES AND HOW THINGS MAY CHANGE

The current paradigm of asthma management is based on the principle that good long-term symptom control equates to a lower risk of exacerbations. As discussed above, while this can be the case, this is not always so and current asthma guidelines have evolved to include assessment of both symptom control and future risk of exacerbation. The GINA guidelines offer helpful advice on assessing 'future risk' and identifying patients who are likely to exacerbate, as shown in Fig. 1 [2]. Studies published over the last year confirm that the risk factors cited here are continuing to be associated with poorer outcomes [19–21].

In addition, the GINA guidelines suggest that sputum-guided adjustment of corticosteroid treatment may be useful in patients with severe asthma, reflecting that in these patients, the discordance between corticosteroid responsive inflammation and symptoms is the greatest and that the side-effect profile of high-dose corticosteroid treatment is significant. In clinical trials, titrating corticosteroid against sputum eosinophilia has been shown to improve asthma control by reducing asthma exacerbations, but this strategy is difficult to deliver in real-world clinical settings [22,23]. Fractional exhaled nitric oxide (FeNO) is straightforward to measure, but when used as a single biomarker, it has been disappointing in titrating corticosteroids in patients with moderate asthma [24]. Periostin is a secreted matricellular protein from a number of tissues including airway epithelial cells, and is upregulated by T2 cytokines (IL-4 and IL-13) and is associated with airway eosinophilia in patients with severe asthma [23]. New algorithms for guiding corticosteroid treatment in patients with severe asthma are

Risk factors for exacerbations:

- Poor control of asthma symptoms
- Ever having been intubated due to asthma
- Having at least 1 severe exacerbation in last year
- Having a low FEV₁
- Incorrect inhaler technique
- Not being prescribed an inhaled corticosteroid
- Poor compliance with therapy
- Rhinosinusitis
- Food allergy
- Smoking (or smoke exposure)
- Obesity
- Pregnancy
- Sputum or blood eosinophilia
- Major psychological, social or economic problems

FIGURE 1. Risk factors for poor asthma outcomes – having one or more of these risk factors increases the risk of exacerbations even if symptoms are well controlled. (Reproduced from GINA Guidelines 2015 [2]).

needed, which are not solely based on clinical symptoms and lung function and which can be easily delivered in the clinic.

As part of the UK Medical Research Council funded Refractory Asthma Stratification Programme, the value of a composite biomarker strategy (using FeNO, blood eosinophils and serum periostin) to predict exacerbation risk in the placebo arms of clinical trials with lebrikizumab and omalizumab was examined in severe asthma [14²²,25]. This analysis demonstrated that the composite 'biomarker low' group had a very low severe exacerbation rate. Notably, the composite biomarker score was independent of asthma symptoms (measured by ACQ) and lung function again suggesting discordance between exacerbation risk and current asthma symptoms in patients with more severe asthma. Using a composite score in this manner, it may be possible to better quantify exacerbation risk in a similar way to how cardiologists stratify risk of cardiac ischaemia in patients with chest pain [26]. It remains to be seen if such composite algorithms can be used to titrate corticosteroid treatment in a similar manner to sputum eosinophilia, but one of the anticipated outcomes of biomarker-based adjustment of corticosteroid treatment is the identification of a patient group with T2-low severe asthma who have persistent symptoms and exacerbations which are not corticosteroid responsive and in whom T2 inflammation biomarkers (eosinophils, FeNO and periostin) are adequately controlled with moderate doses of inhaled corticosteroids. In a study in which corticosteroids were adjusted based on the presence or absence of sputum eosinophilia, one-third of patients had a sputum eosinophil count of less than 1.9% when repeatedly measured over 12 months despite corticosteroid withdrawal. It seems probable that this group represents a 'discordant disease' population where persistent symptoms have driven escalation of corticosteroid treatment beyond the point where there is any additional therapeutic benefit. There are currently few treatment options for these patients, representing a significant unmet medical need in which new targets need to be identified so novel drugs can be developed.

Current asthma treatment guidelines also advocate a standardized treatment approach to management of exacerbations, including the use of systemic corticosteroids. Indeed, as outlined above, a pragmatic definition of severe exacerbation for clinical trial purposes includes the requirement for rescue systemic corticosteroids based on physician judgement. However, accepting that not all asthma symptoms are corticosteroid responsive, that corticosteroid response is predicted by type 2/eosinophilic inflammation and that antieosinophilic

strategies only reduce severe exacerbations by up to 50%, it seems probable that using systemic corticosteroids in all acute severe exacerbations is not required. However, the key challenge will be providing a solid evidence base and 'near patient' testing to allow systemic corticosteroids to be withheld in an acutely unwell symptomatic patient. Prospectively following a 'T2-low' severe asthma population would also allow the exacerbation inflammatory profile and stability of the phenotype to be explored. Our current knowledge of the mechanism and phenotype of 'noneosinophilic' exacerbations is low but is fundamental to understanding and targeting exacerbations in this group.

There are other clinical and behavioural factors which may further impact the relationship between current symptoms and future risk of exacerbation particularly in severe disease. Nonadherence to corticosteroid therapy is a major clinical problem, present in 30–50% of patients with difficult-to-control asthma. Nonadherence can be intentional or nonintentional, is poorly detected by physicians and asthma nurses and is associated with poor asthma outcomes and increased healthcare costs [27]. Initial identification of patients who should respond to corticosteroid treatment is relatively straightforward and FeNO greater than 47 ppb provides a simple means of predicting corticosteroid response in patients with undiagnosed respiratory symptoms [28]. In patients with difficult-to-control asthma, those who have a FeNO more than 45 ppb have a high risk of exacerbation [29], and thus, a simple FeNO measurement identifies a 'risk high' group. It also generates the key clinical question as to whether failure to control their disease is because of nonadherence to inhaled corticosteroid treatment or whether they are adherent with high-dose inhaled corticosteroid treatment and have relative corticosteroid-resistant T2-high asthma. These latter patients frequently require systemic corticosteroids to achieve disease control, but the availability of many new biologic therapies targeting T2-high disease in the next 5 years will generate many interesting questions, including differential efficacy between monoclonal antibodies targeting IL-5 / IL-5R (mepolizumab, benralizumab and reslizumab), IL-13 (lebrikizumab and tralokinumab) and IL-4R α (dupilumab). Other strategies targeting the T2-axis, including anti-CrTh2 and novel anti-immunoglobulin E therapies (quilizumab, Medi-4212 and QGE031), will also be targeting overlapping patient groups; identifying which patients respond better to different classes of drugs may require 'head-to-head' studies. Many of these new therapies are expected to come to market with a companion diagnostic or predictive biomarker(s) of clinical response.

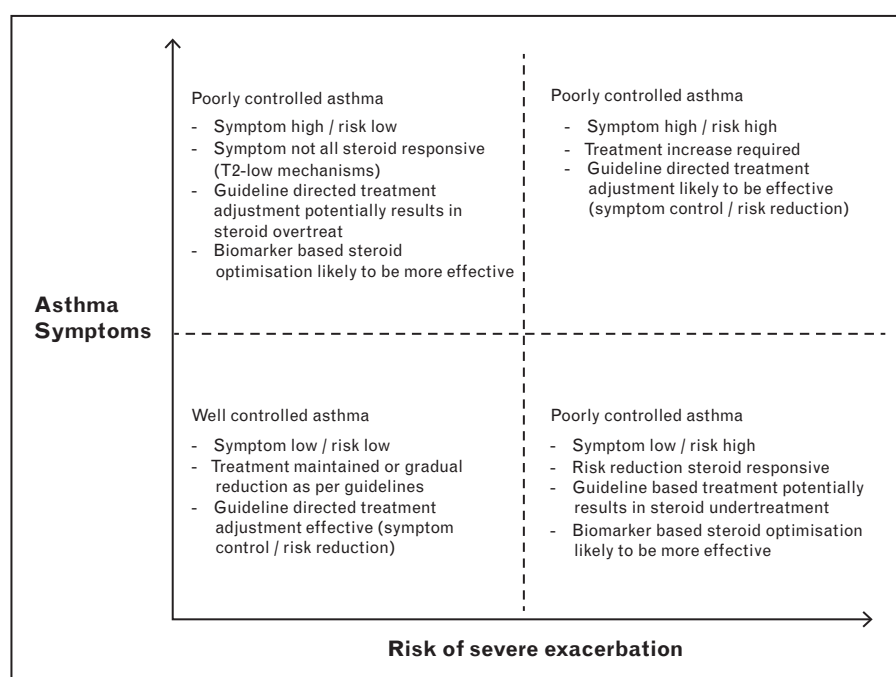


FIGURE 2. Conceptual diagram of the relationship between asthma symptoms and risk of exacerbation in severe asthma. In severe asthma and those with ‘discordant disease’ (dissociation between symptoms and future risk), symptom-based treatment strategies will potentially lead to underuse of anti-inflammatory treatment in a ‘risk-high’ population and treatment escalation in patients with symptoms due to noncorticosteroid responsive mechanisms.

Extrapulmonary factors including tobacco smoking [30], psychological dysfunction [31], rhinosinusitis/nasal polyps [32], obesity [33] and gastro-oesophageal reflux disease [34] have been associated with recurrent severe exacerbations, and current management guidelines advocate identification and management of these conditions [2]. In identifying determinants of not attaining ‘well controlled asthma’ in the Gaining Optimal Asthma control (GOAL) study, the greatest odds ratio was current smoking when compared with never smokers (odds ratio 2.8) [35]. In a study of risk-factors for recurrent exacerbations in difficult to control asthma, the greatest risk was associated with the presence of physiological dysfunction (odds ratio 10.8) [34]. Thus, it is important to remember that current asthma symptoms and exacerbation risk are impacted by extrapulmonary and behavioural factors which further complicate the relationship between these important asthma outcomes.

CONCLUSION

Asthma is a heterogeneous clinical syndrome which includes a number of different pathophysiological endotypes. It seems likely that the relationship between current asthma symptoms and asthma exacerbation risk will be different within these different endotypes.

The ‘one-size fits all’ approach advocated in current treatment guidelines with progressive escalation of corticosteroid treatment has been instrumental in standardizing asthma care globally and improving outcomes for many patients, and continues to serve many patients well, particularly those with milder ‘concordant’ disease with an excellent treatment response to low or moderate dose asthma therapy.

However, in other patients, particularly in severe asthma and those with ‘discordant disease’, symptom-based treatment strategies can potentially lead to under-use of anti-inflammatory treatment in a ‘risk-high’ population and also treatment escalation in patients with noncorticosteroid responsive mechanisms causing persistent symptoms as illustrated in Fig. 2. In this latter group, excessive corticosteroid treatment is likely to contribute further to morbidity with no additional therapeutic benefit. In the future, moving to biomarker-based strategies, which can be easily delivered in the clinic, to ‘optimize’ corticosteroid treatment in these patients will be a major advance. In parallel, further defining the pathophysiological mechanisms in ‘T2-low’ asthma and ‘non-eosinophilic’ exacerbations will provide a greater understanding of best management in this group.

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Conflicts of interest

There are no conflicts of interest.

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

- of special interest
- of outstanding interest

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Summary of composite biomarker stratification data for exacerbation and dissociation from persistent symptoms in severe asthma.

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Summary of current position of biomarkers in predicting exacerbation risk and response to novel biologic therapies.