

# Towards a personalised treatment approach for asthma attacks

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## ABSTRACT

Asthma attacks (exacerbations) are common, accounting for over 90 000 UK hospital admissions per annum. They kill nearly 1500 people per year in the UK, have significant associated direct and indirect costs and lead to accelerated and permanent loss of lung function. The recognition of asthma as a heterogeneous condition with multiple phenotypes has revolutionised the approach to the long-term management of the condition, with greater emphasis on personalised treatment and the introduction of the treatable traits concept. In contrast asthma attacks are poorly defined and understood and our treatment approach consists of bronchodilators and systemic corticosteroids. This review aims to explore the current limitations in the description, assessment and management of asthma attacks. We will outline the risk factors for attacks, strategies to modify this risk and describe the recognised characteristics of attacks as a first step towards the development of an approach for phenotyping and personalising the treatment of these critically important events. By doing this, we hope to gradually improve asthma attack treatment and reduce the adverse effects associated with recurrent courses of corticosteroids.

## INTRODUCTION

Asthma attacks (exacerbations) are common, accounting for over 90 000 UK hospital admissions per annum.<sup>1</sup> They kill nearly 1500 people per year in the UK,<sup>2</sup> have significant associated direct and indirect costs<sup>3</sup> and lead to accelerated and permanent loss of lung function.<sup>4</sup>

The recognition of asthma as a heterogeneous condition with multiple phenotypes has revolutionised the approach to the long-term management of the condition, with greater emphasis on personalised treatment and the introduction of the treatable traits concept.<sup>5</sup> In contrast, asthma attacks are poorly defined and understood and our treatment approach consists of bronchodilators and systemic corticosteroids.

This review aims to explore the current limitations in the description, assessment and management of asthma attacks. We will outline the risk factors for attacks, strategies to modify this risk and describe the recognised characteristics of attacks as a first step towards the development of an approach for phenotyping and personalising the treatment of these critically important events. By doing this, we hope to gradually improve asthma attack treatment and reduce the adverse effects associated with recurrent courses of corticosteroids.

## DEFINING ASTHMA ATTACKS

The Global Initiative for Asthma (GINA) 2019 definition states that asthma exacerbations are events

### Box 1 ATS/ERS statement definitions of severe and moderate asthma exacerbations<sup>7</sup>

- ▶ Severe asthma exacerbation: events that require urgent action on the part of the patient and physician to prevent a serious outcome, such as hospitalisation or death from asthma. The definition should include at least one of the following:
  - a. 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.
  - b. A hospitalisation or emergency department visit because of asthma, requiring systemic corticosteroids.
- ▶ Moderate asthma exacerbation: events that should result in a temporary change in treatment, in an effort to prevent the exacerbation from becoming severe. Should include one or more of the following:
  - a. Deterioration in symptoms.
  - b. Deterioration in lung function.
  - c. Increased use of short-acting  $\beta$ -agonist bronchodilator.

These features should last for 2 days or more, but not be severe enough to warrant systemic corticosteroid use and/or hospitalisation or emergency department visits for asthma.

that involve a progressive increase in symptoms (ie, dyspnoea, wheeze or chest tightness) and a progressive decrease in lung function that are 'sufficient to require a change in treatment'.<sup>6</sup> This is based on the 2009 American Thoracic Society/European Respiratory Society (ATS/ERS) definitions of severe and moderate exacerbations (box 1) which are usually used when defining exacerbations as an outcome measure in clinical trials.<sup>7</sup>

This definition of a severe exacerbation is inadequate because the event is retrospectively defined by the treatment received, rather than by any intrinsic characteristics of the event itself. The requirement for systemic corticosteroids should not be the sole determinant of whether an event is a severe exacerbation as factors such as patients' and physicians' assessment of severity and the availability and affordability of medical help will also influence what treatment is received. A more objective definition of moderate exacerbations for use in clinical



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trials has been proposed but not validated<sup>8</sup> and the ERS/ European Academy of Allergy and Clinical Immunology (EAACI) taskforce statement on severe exacerbations considered that the use of systemic corticosteroids for at least 5 days (rather than 3) may be more clinically relevant although this remains a largely subjective definition.<sup>9</sup>

An attempt to describe exacerbations in a more objective way has also been made in the development of a 'composite exacerbation endpoint' (CompEx) based on diary events recorded by asthma subjects during clinical trials.<sup>10</sup> Peak expiratory flow rate (PEFR), reliever use, symptoms and awakenings are combined in an algorithm and added to severe exacerbations defined by corticosteroid use. This methodology detected almost three times as many events as corticosteroid use alone allowing a reduction in clinical study size due to greater power. Although the exact significance of the additional events captured and the criteria used to define them can be debated, seasonal variation in CompEx events was preserved, there was a reduction in geographical variation in event rates and treatment effect was preserved or increased suggesting the events are clinically important.<sup>11</sup>

## RISK OF ASTHMA ATTACKS

### Attack rate

Recent epidemiological surveys of UK and US health records have reported asthma attack rates in unselected populations of asthma patients between 0.1 and 0.2 per patient per year.<sup>12 13</sup> Attack rates increased with asthma severity to ~0.5/patient/year in severe asthma (GINA Step 5).<sup>12</sup> In a study of over 50 000 patients, two-thirds of patients did not exacerbate over a 7-year period and half of those who exacerbated did so only once.<sup>13</sup> Only 370 (0.7%) 'frequent exacerbators' ( $\geq 1$  exacerbations per year) were identified most of whom (58%) had mild to moderate asthma. A study of ~2500 patients coded with asthma on high-dose inhaled corticosteroid/long-acting  $\beta$ -agonist (ICS/LABA) therapy reported severe exacerbation rates around 0.67/patient/year.<sup>14</sup>

### Risk factors for attacks

A number of risk factors for attacks have been recognised (table 1). The strongest of these is a previous attack, especially within the last 12 months.<sup>13</sup> Though other factors are undoubtedly important in terms of future risk, these have not been consistently identified in all studies. Asthma severity based on GINA Step or degree of airway obstruction appears to be associated with attack risk, but taken alone it is not a strong predictor<sup>15</sup> and frequently exacerbating patients and those admitted with severe life-threatening asthma attacks are more likely to have mild to moderate asthma.<sup>13 16</sup> Similarly, there is an association between asthma control and attack risk but poor control does not have a high predictive value for future attack<sup>17</sup>; ICS/LABA maintenance and reliever therapy significantly reduces attack risk but may have less effect on daily symptoms compared with ICS/LABA and short-acting  $\beta$ -agonist (SABA) therapy.<sup>18</sup> The strength of a previous attack as a risk factor for future attacks, in contrast to the inconsistencies of identified predictors for attack risk between different cohorts may imply a high degree of individual attack susceptibility determined by heterogeneous mechanisms. It has been suggested that serial measurements of airway obstruction, display 'self-similarity', that is, patterns of variability observed in previous measurements are a preserved characteristic of an individual's disease, which allow forecasting of future lung function and prediction of deteriorations.<sup>19</sup> Techniques such as detrended fluctuation analysis of PEFR measurements

**Table 1** Previously identified risk factors for asthma attacks in adults

Factor	Studies	
<b>Previous attacks</b>	$\uparrow$ Number of previous attacks/ED admissions/hospitalisations	22 25 83 89–91
<b>Disease severity</b>	$\downarrow$ FEV <sub>1</sub> / $\uparrow$ airway obstruction	23 89 90
	$\uparrow$ GINA Step	23
<b>Disease control</b>	High Asthma Control Questionnaire score	14 23
	Poor asthma control	91 92
<b>Treatment</b>	$\uparrow$ Reliever/SABA use	23 89
	$\uparrow$ Previous courses of oral corticosteroids	89
	Fixed dose steroid versus steroid in maintenance and reliever therapy	90
	Poor treatment adherence	93
	Incorrect inhaler technique	94
	Inhaler device polypharmacy	83
	Co-prescription of non-steroidal anti-inflammatory drugs	95
<b>Demographic factors</b>	Female gender	25 89 90 95
	Increased age	25 89 95
	Ethnicity: Black	91
<b>Comorbidities</b>	Smoking	22 89 95
	Gastro-oesophageal reflux disease	25 89 95–97
	Rhinitis, nasal polyps, eczema	89 95
	Rhinitis	25
	Chronic sinusitis	14 96 97
	Obesity	23 89 96 98
	Depression	83 95 97
	Vocal cord dysfunction	83
<b>Inflammation/phenotype</b>	$\uparrow$ Blood eosinophil count	89 95 96
	$\uparrow$ Bronchodilator responsiveness	96

Listed studies: Fuhlbrigge *et al.*,<sup>10</sup> Bateman *et al.*,<sup>23</sup> Patel *et al.*,<sup>90</sup> Blakey *et al.*,<sup>89</sup> Loymans *et al.*,<sup>22</sup> TENOR,<sup>31</sup> Kang *et al.*,<sup>25</sup> McDonald *et al.*,<sup>83</sup> Bateman *et al.*,<sup>32</sup> Engelkes *et al.*,<sup>93</sup> Melani *et al.*,<sup>94</sup> Price *et al.*,<sup>95</sup> Denlinger *et al.*,<sup>96</sup> ten Brinke *et al.*,<sup>97</sup> Fitzpatrick *et al.*<sup>98</sup>.

GINA, Global Initiative for Asthma; SABA, short-acting  $\beta$ -agonist.

have been used to calculate measures of temporal self-similarity which have demonstrated efficacy in predicting future attacks.<sup>20</sup>

### Risk stratification

Attack prevention has been recognised as a key priority by the latest GINA strategy.<sup>6</sup> It has been suggested that an individual's risk of asthma attack should be profiled and quantified in a similar fashion to the profiling and modification of cardiovascular risk factors for myocardial infarction (MI).<sup>21</sup> Using previously identified risk factors (table 1), several exacerbation risk-scoring systems have been developed.<sup>17 22 23</sup> However, a systematic review and attempt to externally validate existing scoring systems using primary and secondary care cohort data concluded their performance was not of a sufficiently high standard to be useful in clinical practice.<sup>24</sup>

Partly this may be due to the significant heterogeneity in asthma populations studied. Different risk factors for attack are

likely to be important in different severities or phenotypes of asthma.<sup>25</sup> For example, type-2 (T2) biomarkers were associated with exacerbation risk in severe refractory asthma but not in mild to moderate asthma.<sup>26</sup> Other reasons for the difficulty in identifying consistent risk factors for future attack may include: (1) the challenge in distinguishing between a 'true' asthma attack and a worsening of commonly related comorbidities such as chronic obstructive pulmonary disease (COPD)/vocal cord dysfunction/dysfunctional breathing, (2) the broad non-objective definition of an 'asthma exacerbation' and likely heterogeneity in the causal pathophysiology in comparison to the more consistent pathology underlying events such as an MI, (3) the infrequent occurrence of asthma attacks in many patients and relative lack of longitudinal data assessing attack risk beyond the course of a 12-month study period and (4) the possible (and understandable) over-representation in the literature of an exacerbation-prone phenotype who may have distinct mechanisms of disease (traits) compared with the majority of the asthma population.<sup>27</sup>

### Risk modification

Modification of attack risk may be achieved at a population level through therapeutic interventions known to reduce the overall attack risk which are summarised in table 2. Though a number of treatments are effective in reducing attack risk, the mechanisms by which they do this are poorly described and there are few clinically useful biomarkers to target treatment (*theranostic* biomarkers). Therefore, selection of appropriate interventions to minimise an individual's risk of attack when attending clinic is less established.

Rather than considering and treating asthma attacks as uniform events, a greater degree of complexity in their profiling is required to determine whether these events have distinct phenotypes or traits and, if so, whether these are related to the stable disease phenotype. Personalised risk profiling based on the phenotypes, and ultimately endotypes, of asthma in periods of stability and during attacks has the potential to markedly improve forecasting of an individual's attack risk and direct targeted intervention to mitigate this risk. Novel strategies including biomarker-based methods of attack risk profiling need further assessment.<sup>28 29</sup>

Targeted biological treatment of persistent T2-high airway inflammation leads to significant reductions in attack frequency, but further studies are required to determine more precise theranostic biomarkers and improve specificity of treatment selection. Profiling of remaining attacks in these patients will lead to novel insights into mechanisms of exacerbation and should inform further treatment targeting to reduce attack frequency further still. Patients prone to viral attacks may require a different targeted approach to therapy; for example, results from clinical and mechanistic studies suggest omalizumab can reduce the seasonal peak in attacks thought to be secondary to viral infection by reducing susceptibility to respiratory viruses (table 2).<sup>30 31</sup> Appropriate preventative treatment for T2-low attacks and those triggered by bacteria, pollution or other recognised triggers is unclear and requires further study.

### HETEROGENEITY OF ASTHMA ATTACKS

To better define attacks we need to understand more about how these events can be described and categorised. Some of the previously identified determinable characteristics of attacks and their relation to underlying aetiology are now considered and summarised in figure 1.

### Recognised attack 'triggers'

Several triggers for asthma attacks have been identified and discussed in detail elsewhere.<sup>32</sup> This section will provide a brief summary of the main recognised triggers to contextualise further discussion regarding attack phenotyping.

#### Viruses

The presence of viral DNA has been detected in ~80% of adult asthma attacks<sup>33</sup> making them the most commonly identified trigger of exacerbations. Rhinoviruses (RV), particularly subtypes A and C are the most commonly detected organisms in adults,<sup>34</sup> followed by influenza virus, respiratory syncytial virus and coronavirus.<sup>33</sup> Subjects with asthma may be more susceptible to viral infections owing to impaired expression of interferons (antiviral cytokines), and there is ample in vitro evidence to support this hypothesis<sup>35</sup> although not all studies are concordant.<sup>36</sup>

#### Allergens

Inhalation of allergens is undoubtedly an important factor in the development of asthma attacks and sensitisation to various allergens including cats, dust mites, mould and cockroaches has been recognised as a risk factor for acute presentation requiring emergency treatment of asthma.<sup>37</sup> Whether aeroallergen exposure at normal environmental levels in a sensitised individual is a sufficient independent stimulus to trigger a severe attack is more difficult to establish due to the inherent difficulties in verifying and quantifying personal levels of exposure. Indirect evidence for such an effect is provided by observations of seasonal peaks in exacerbation rates correlating with high grass pollen counts.<sup>38</sup> However, excluding the effects of other potential 'co-triggers'<sup>39</sup> in such studies is difficult. Epidemics of asthma attacks secondary to exposure of high doses of airborne allergen have been described including 'thunderstorm' asthma which occurs due to exposure to high levels of grass pollen in sensitised individuals.<sup>40</sup>

Accumulating evidence suggests a synergistic effect between allergic sensitisation and viral infection in provoking attacks.<sup>35</sup>

#### Bacteria

The frequency of asthma attacks triggered by bacterial infection is unclear. The atypical organisms *Chlamydomphila* and *Mycoplasma pneumoniae* have been detected in widely varying proportions of asthma patients with acute asthma symptoms<sup>41</sup> with this variation likely secondary to the differing serological testing methods used in these studies. More recent studies have isolated bacteria alone from sputum and nasopharyngeal swab samples in patients with severe asthma exacerbations in up to 45% of cases using PCR-based techniques.<sup>42</sup>

The role of bacteria in asthma attacks is unlikely to be fully elucidated until unbiased whole genome sequencing studies of the airway microbiota are performed before, during and after attacks. Interactions between viruses and bacteria may be important in the development of an attack<sup>43</sup> and significant rates of bacterial/viral coinfection have been noted<sup>42</sup> with some in vitro evidence demonstrating viral impairment of the antibacterial function of human alveolar macrophages.<sup>44</sup>

#### Other potential triggers

Less commonly described triggers for attacks include exposure to non-steroidal anti-inflammatory drugs (NSAIDs) or high doses of inhaled irritants, air pollution, perimenstrual asthma, stress and treatment non-adherence.<sup>45</sup>

**Table 2** Preventative treatments to reduce risk of asthma attacks

Agent	Patient group/phenotype	Efficacy for attack reduction	Mechanisms for attack reduction	Theranostic biomarker
<b>T2-targeted treatment</b>				
ICS	Asthma (not phenotyped)	Exacerbation rate ↓50% versus placebo <sup>99</sup>	<b>Reduces 'eosinophilic' exacerbations</b> ICS dose titration according to sputum eosinophil count significantly reduces eosinophilic exacerbation frequency but the rate of non-eosinophilic exacerbations was unchanged. <sup>69</sup>	Sputum eosinophil count <sup>100</sup>
Omalizumab	Adults and children with moderate to severe asthma on ICS	Exacerbation odds ↓45% (absolute risk reduction 10%) over 16–60 weeks Meta-analysis (10 studies, n=3261) <sup>101</sup>	<b>Reduces IgE-mediated allergic inflammation</b> blocks IgE–receptor interaction on mast cells, basophils and antigen-presenting cells by selectively binding free IgE. <sup>102</sup> <b>Reduces susceptibility to viral exacerbations</b> <sup>30 31</sup> Enhances interferon (IFN)-α responses to rhinovirus (RV) via an unknown mechanism, limiting viral replication and ↓ detection of RV in nasal mucus, ↓ duration and severity of RV infection and ↓ rate of RV-associated illness.	Some evidence suggests that high levels of T2 biomarkers more likely to respond <sup>103</sup> though not all studies are concordant <sup>104</sup>
Mepolizumab (anti-IL-5)	Severe asthma Evidence of eosinophilic airway inflammation	Exacerbation rate ↓ 50% <sup>105</sup>	<b>Reduces 'eosinophilic' exacerbations</b> Exacerbations in mepolizumab patients associated with a lower sputum eosinophil count, fewer symptoms and a reduced OCS treatment response than comparative events in placebo group <sup>106</sup> suggesting residual events consistent with 'non-eosinophilic' exacerbations. <b>No evidence for specific benefit on viral exacerbations</b> Not assessed in initial phase III studies. No effect on postinfective fall in lung function or loss of asthma control <sup>107</sup> in patients with mild asthma experimentally infected with RV. Mepolizumab-treated patients had a significantly enhanced viral load in comparison to placebo group.	Blood eosinophils ≥0.15 x 10 <sup>9</sup> /L <sup>108</sup>
Dupilumab (anti-IL-4/IL-13 receptor)	Moderate to severe asthma and high T2 biomarkers	Exacerbation rate ↓ 50% <sup>109</sup>	<b>No evidence for specific benefit on inflammatory exacerbation subtype</b> <b>Possible effect on viral exacerbations</b> Trend towards lower rates of viral URTI, bronchitis and influenza in treatment group compared with placebo group.	FeNO <sup>109</sup> Blood eosinophils <sup>109</sup>
<b>Other treatment</b>				
LAMA, eg, tiotropium	Asthma (not phenotyped)	Exacerbation risk ↓ 33% in addition to ICS <sup>110</sup>	<b>Unclear</b> ? due to effects on airway inflammation/mucus hypersecretion <sup>111</sup>	None
LABA, eg, formoterol	Asthma (not phenotyped)	Exacerbation risk ↓ ~50% in addition to ICS <sup>112</sup>	<b>Unclear</b> ?synergistic effect with ICS on allergen-induced airway inflammation. <sup>113</sup>	None
Leukotriene antagonists (montelukast)	Adults with asthma (not phenotyped)	Exacerbation odds ↓40% (compared with placebo) <sup>114</sup>	<b>Viral exacerbations</b> Possible selective treatment benefit for viral exacerbations. <sup>115</sup>	None
Azithromycin	Severe asthma non-eosinophilic subgroup <sup>116</sup> Uncontrolled asthma: eosinophilic and non-eosinophilic <sup>117</sup>	Exacerbation/ LRTI rate ↓ by 0.6/6 months exacerbation rate ↓ by ~0.8/patient year	<b>Unclear</b> Various mechanisms proposed <sup>118</sup> including: ▶ Antiviral effects. ▶ Reduction in airway load of <i>Haemophilus influenzae</i> . ▶ Reduced levels of gastro-oesophageal reflux.	None
Self-management plan (monitoring PEF/ symptoms with written action plan)	Adults with asthma (not phenotyped)	Risk of hospitalisation ↓ 36% compared with usual care <sup>119</sup>	Based on early recognition of increasing symptoms or reduction in peak flow (figure 3) as trigger to escalate asthma management and reduce clinical severity of 'peak' attack.	Not applicable
<b>Potential future treatments</b>				
Tezepelumab (anti-TSLP)	Uncontrolled asthma: T2 high and T2 low subgroups	Exacerbation rate ↓ 62% <sup>120</sup>	<b>No evidence for specific benefit on inflammatory exacerbation subtype</b> <b>Viral exacerbations</b> Effect on virally induced exacerbations not assessed in trial. In vitro: TSLP released by airway epithelial cells infected by RSV promoting a T2 inflammatory response <sup>121</sup> suggesting suppression of this pathway may prove effective.	Effect regardless of T2 biomarker levels

Continued



Table 2 Continued

Agent	Patient group/phenotype	Efficacy for attack reduction	Mechanisms for attack reduction	Theranostic biomarker
Fevipirant and timapirant (prostaglandin D2 receptor antagonists)		Unknown (phase III study of fevipirant in progress)	Fevipirant significantly ↓ eosinophilic airway inflammation in patients with moderate to severe persistent eosinophilic asthma. <sup>122</sup> Timapirant resulted in a significant ↓ in the rate of respiratory tract infections, <sup>123</sup> hence may be effective in reducing viral exacerbations.	? Sputum eosinophils

FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; IFN-α, interferon α; IL, interleukin; LABA, long-acting β-agonist; LAMA, long acting muscarinic antagonist; LRTI, lower respiratory tract infection; OCS, oral corticosteroid; PEFR, peak expiratory flow rate; RSV, respiratory syncytial virus; RSV, respiratory syncytial virus; RV, rhinovirus; T2, type 2; TSLP, thymic stromal lymphopoietin; URTI, upper respiratory tract infection.

**Onset phase**

**Clinical observations**

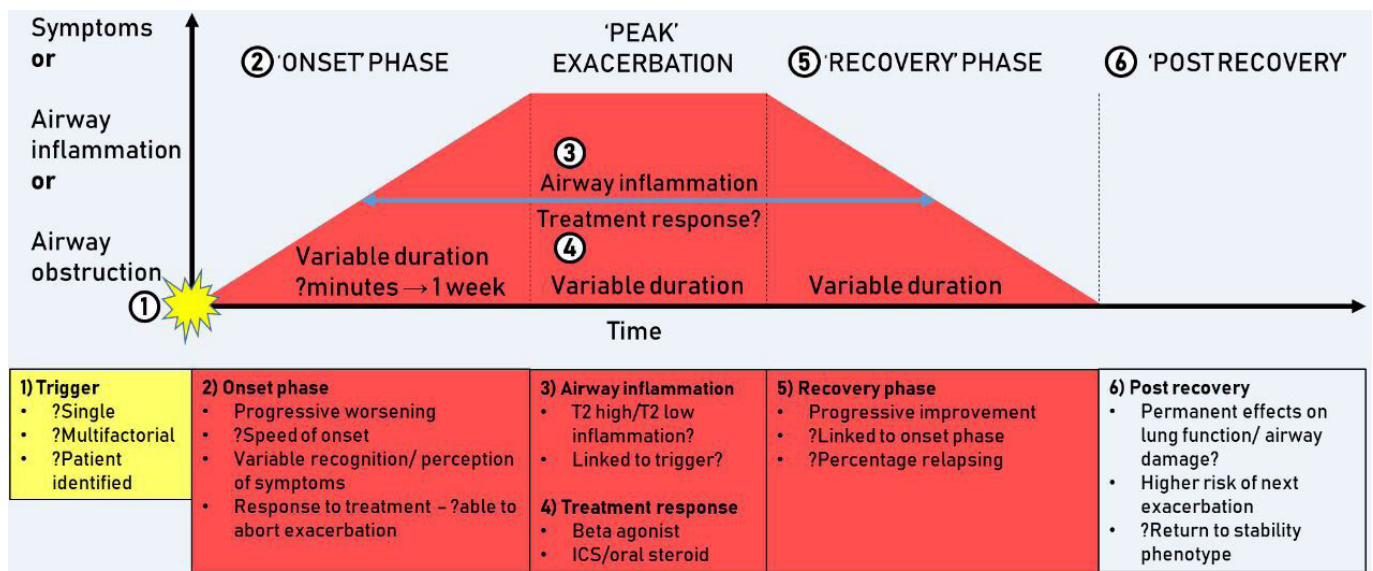
Clinical studies have described ‘sudden-onset’ attacks (presentation within hours of symptom onset) in 6%–20% of cases.<sup>46–49</sup> Both ‘sudden’ and ‘slow’ onset groups report upper respiratory tract infections (URTIs) as exacerbation triggers in >75% of cases although the sudden-onset group more commonly reported exacerbations triggered by allergens, exercise or stress.<sup>46</sup> Some patients with rapid-onset exacerbations reported obvious triggers such as NSAIDs or respiratory irritants<sup>48</sup> which may trigger acute bronchospasm. Despite similar initial PEFRs, patients with ‘sudden-onset’ exacerbations demonstrated a significantly larger improvement in PEFR following initial treatment.<sup>46</sup> Other features of slow-onset and rapid-onset attacks from clinical studies and histology studies reviewing cases of fatal asthma<sup>50–53</sup> are summarised in figure 2.

There are several difficulties in interpreting these studies including: the varying cut-off times used to distinguish fast-onset and slow-onset attacks, the reliance on patient-reported triggers for attacks with a lack of objective testing (particularly viral PCR), the lack of contemporaneous measures of airway inflammation and the difficulty in distinguishing rapid-onset asthma attacks from differential causes of acute dyspnoea such as vocal cord dysfunction. However, these studies are useful in highlighting the variation in the reported/perceived onset phase of attacks and that broadly two clinical attack phenotypes

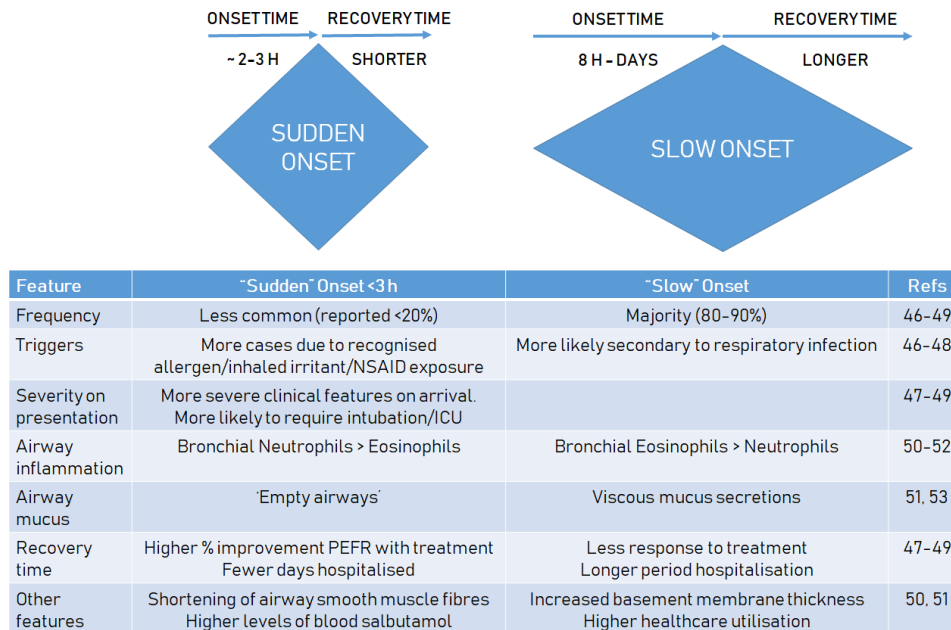
of fast-onset, fast recovery (≤10%) and slower-onset, slower recovery (≥90%) have been observed.

**Observational studies**

Detailed data characterising the physiological changes associated with attacks come from the Formoterol and Corticosteroids Establishing Therapy (FACET) study.<sup>54</sup> Severe exacerbations were defined as events requiring an investigator-prescribed course of oral corticosteroid (OCS) or a deterioration of morning PEFR >30% from mean baseline on 2 consecutive days. On retrospective review of PEFR data, a gradual reduction in PEFR was observed from ~7 days prior to the ‘peak’ of the exacerbation with a more rapid fall (as per the PEFR exacerbation definition) in the 2–3 days preceding peak exacerbation (figure 3). The worsening of symptoms demonstrated a similar pattern to PEFR with β-agonist use increasing in a similar fashion. The exacerbation events felt to require OCS (~70% of total) were associated with more symptoms and smaller PEFR changes (on average about half the magnitude) than those defined by PEFR criteria (30%) meaning decisions to treat with OCS (making these events severe exacerbations by default) were mostly made on the basis of symptoms rather than ‘objective’ PEFR criteria. It is possible some patients had an increased perception of symptoms with a lower relative change in PEFR or that these two different definitions of exacerbation



**Figure 1** Summary figure illustrating determinable clinical, physiological and biochemical characteristics of asthma attacks. ICS, inhaled corticosteroid; T2, type 2.

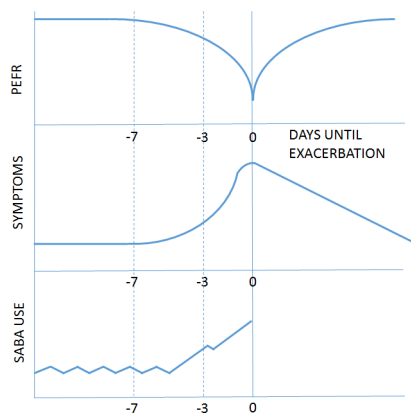


**Figure 2** Asthma attack phenotypes noted from clinical observations/histological studies.<sup>50-53</sup> ICU, intensive care unit; NSAID, non-steroidal anti-inflammatory drug; PEFR, peak expiratory flow rate.

actually represent different 'types' of exacerbation with potentially different underlying pathology.

It is worth considering, however, that the mean PEFR, symptom and  $\beta$ -agonist data presented in the FACET study figures (figure 3) disguise marked individual variability between patients. This individual variability in rescue inhaler use prior to exacerbation has been demonstrated in studies using electronic monitoring of  $\beta$ -agonist use.<sup>55 56</sup>

A smaller study (n=41)<sup>57</sup> also monitored symptoms and PEFR prior to exacerbations, defined as hospitalisations for asthma treatment, decrease in personal best PEFR >30% or increased symptoms for >48 hours with lack of response to usual medications and starting or doubling of ICS/OCS. In contrast to the FACET results, worsening symptoms occurred prior to a reduction in PEFR. Investigators noted the lack of significant diurnal variation in PEFR preceding exacerbation.



**Figure 3** Composite diagram illustrating average observed changes in peak expiratory flow rate (PEFR), symptoms and short-acting  $\beta$ -agonist (SABA) use prior to attacks with peak of exacerbation occurring on day 0. Adapted from FACET (Formoterol and Corticosteroids Establishing Therapy),<sup>54</sup> Bardin *et al*,<sup>59</sup> Jackson *et al*<sup>60</sup> and Pilcher *et al*<sup>55</sup> studies.

Another key study detailing the pattern of pathophysiological airway changes during exacerbation by Reddel *et al*<sup>58</sup> described marked differences in peak flow patterns between exacerbation episodes and periods of poor control. Exacerbation was characterised by a linear fall in PEFR with little diurnal variability and an impaired  $\beta$ -agonist response compared with the high diurnal variability and bronchodilator reversibility seen during periods of poor control. Most of the exacerbations in this study were associated with symptoms of URTI although confirmatory viral PCR testing was not performed.

#### Viral attacks

Experimentally induced RV infections in patients with asthma resulted in significant reductions in PEFR and FEV<sub>1</sub>, developing over a period of 6-7 days (figure 3)<sup>59 60</sup> with worsening symptoms and an increase in airways hyper-reactivity<sup>59</sup> consistent with the study of Reddel *et al*.<sup>58</sup>

#### Airway inflammation

##### Clinical observations

The inflammatory phenotypes of patients hospitalised with asthma attacks have been studied. Hasegawa *et al*<sup>61</sup> demonstrated 19/47 (40%) of such patients had a blood eosinophilia (blood eosinophil count  $\geq 0.3 \times 10^9/L$ ) during their hospital admission although the clinical characteristics of this group and the 'non-eosinophilic' group were not significantly different. A cluster analysis of 218 Chinese patients hospitalised with exacerbations identified four distinct clusters.<sup>62</sup> Two of these demonstrated neutrophilic/mixed granulocytic airway inflammation in sputum cell counts in younger patients with early-onset asthma and mild airway obstruction (cluster 1; ~25%) and older late-onset patients with more severe airway obstruction (cluster 3; ~37%). The other two clusters had eosinophil predominant airway inflammation with cluster 2 (~22%) composed mostly of female patients with the most severe degree of airway obstruction post exacerbation and arterial hypoxia on admission and cluster 4 (~17%) composed exclusively of male smoking

subjects. Unfortunately exacerbation triggers were not recorded and lung function and inflammation measures were assessed at varying times (3–10 days) post exacerbation meaning at least 3 days of systemic steroid treatment had been administered prior to obtaining measurements/samples.

Bronchial biopsies from intubated patients admitted to ITU with sudden-onset severe exacerbations revealed markedly higher tissue densities of neutrophils and eosinophils in the epithelium and subepithelium than those seen in stable asthma and control groups.<sup>63</sup> A greater increase in neutrophils than eosinophils and greater expression of neutrophil chemoattractants (CXCL5&8) and their receptors (CXCR1&2) was observed. The disproportionate influx of neutrophils corresponds with the predominant neutrophilic inflammation noted in ‘rapid-onset’ cases of fatal asthma<sup>52</sup> and the inflammatory profile in bronchoalveolar lavage (BAL) from mechanically ventilated patients with severe asthma.<sup>64</sup> Again, the potential confounding effect on these results of high-dose steroid treatment causing a selective reduction in eosinophilic airway inflammation prior to sampling requires consideration.

### Observational studies

Few data are available regarding the inflammatory nature of asthma attacks. In one study in adults assessing sputum differential counts, exacerbations were predominantly neutrophilic in nature (18/22, 82%).<sup>65</sup> The cause, however, was not clear as PCR for *Chlamydomydia pneumoniae* was negative in 99% of samples and no other pathogens were tested for. By contrast, a small study of adult patients hospitalised with exacerbations<sup>66</sup> reported 9/10 had sputum eosinophilia and demonstrated improvements with prednisolone treatment in FEV<sub>1</sub> and blood eosinophilia within 24 hours and sputum eosinophils within 48 hours. Another study of 18 patients with severe refractory asthma with exacerbations requiring OCS observed a significant overall increase in sputum eosinophils during exacerbation prior to OCS treatment with no change in sputum neutrophils. This was paralleled by mixed T helper (Th)1/Th2 activation during exacerbations (which was Th2-biased in the group at baseline) and further suppression of regulatory T cells (Tregs) compared with baseline.<sup>67</sup> Bjornsdottir *et al*<sup>68</sup> identified three distinct patterns of gene expression during exacerbation when compared with the stable state. One of these involved genes associated with innate immunity (despite no symptoms consistent with infection) with interleukin (IL) 15-mediated innate T-cell activation, the second was consistent with an allergen-driven immune response and the third expression profile differed least from the stable state and could not be attributed to a specific biological pathway.

Jayaram *et al*<sup>69</sup> observed approximately equal numbers of eosinophilic (sputum differential  $\geq 3\%$ ) and non-eosinophilic exacerbations in a group of 102 subjects with asthma while trying to minimise the ICS dose required to achieve good asthma control. The symptom burden associated with both exacerbation ‘types’ was the same, but non-eosinophilic exacerbations were associated with a less marked reduction in pre-bronchodilator FEV<sub>1</sub>.

Experimentally induced exacerbations through withdrawal of steroid treatment have been studied using methods originally described by Gibson *et al*.<sup>70</sup> These studies, which included subjects on medium-dose to high-dose ICS<sup>70</sup> and those with severe refractory asthma on high-dose ICS<sup>71</sup> or oral steroids,<sup>72</sup> generally demonstrated increases in sputum eosinophilia with steadily worsening symptoms. Increasing measures of airway obstruction (described as ‘mild exacerbations’) which peaked

between 2 and 6 weeks (variability that may have been related to differing rates of ICS/OCS withdrawal) were also observed. These results suggest that uncontrolled eosinophilic inflammation eventually results in exacerbation-like events with a longer ‘onset phase’ than those provoked by viral infections.

Results from these studies indicate that the inflammatory profiles of clinically observed asthma attacks are heterogeneous in nature. Further more detailed studies carefully assessing exposures/trigger factors are required and the resultant endotypic mechanisms underlying these heterogeneous phenotypes require further elucidation.

### Viral attacks

Experimental RV infection has been demonstrated to induce neutrophilic airway inflammation in the asthmatic airways in the bronchial mucosa,<sup>73</sup> BAL<sup>74</sup> and sputum.<sup>75</sup> The degree of neutrophilic inflammation appears to be associated with levels of the neutrophil chemoattractant IL-8.<sup>74</sup> However, significant increases in eosinophil numbers in BAL<sup>75</sup> and bronchial mucosa<sup>76</sup> have also been observed during RV infection. More recent evidence suggests RV infection of bronchial epithelial cells may activate T2 inflammatory pathways through cytokines such as IL-25 and IL-33<sup>60,77</sup> causing release of mediators including IL-5 and IL-13 from T2 innate lymphoid cells and leading to augmentation of allergic inflammation and airway eosinophilia.<sup>78</sup>

The results of these experimental studies, though important, may not reflect the complexity of the pathology underlying ‘real-life’ viral attacks. These can be caused by a number of different viruses in patients with more severe, uncontrolled asthma who may develop severe exacerbations rather than the mild to moderate exacerbation events (not requiring OCS treatment) usually observed in controlled conditions. Some studies of patients with asthma with confirmed ‘wild-type’ viral infections have reported these are associated with increased sputum neutrophil counts.<sup>79,80</sup> Wark *et al*<sup>80</sup> reported patients with viral exacerbations had a greater degree of airway obstruction and risk of hospitalisation than those with non-infective exacerbations who were noted to have significantly increased sputum eosinophil counts. However, two studies by Bjerregard *et al*<sup>81,82</sup> found no difference in the proportions of inflammatory phenotypes (eosinophilic vs non-eosinophilic) of patients with viral (PCR-positive) or non-viral (PCR-negative) exacerbations. In contrast to the findings above, patients with eosinophilic exacerbations had a significantly lower % predicted FEV<sub>1</sub> at baseline and were more likely to require supplemental oxygen.

### Summary

Though data in this area are limited, these studies clearly demonstrate the variability in the phenotypes of attacks. Clinical observations suggest the rate of attack onset may vary and may depend on the initial trigger. Attacks secondary to known triggers such as viral infection vary in their inflammatory profile and this may be due to the interaction of the ‘stable-state’ inflammatory phenotype with the additional inflammatory burden induced during an attack. Larger scale studies attempting to objectively detail relevant trigger exposure, symptom perception, speed of onset and relevant biomarkers are required to allow more detailed phenotyping/endotyping of attacks.

### Treatment response

The acute treatment of attacks corresponding to their identified phenotypic characteristics is summarised in table 3.

**Table 3** Acute treatment of asthma attacks

Attack phenotypic characteristic	Agent	Strategy	Patient group/phenotype (all with asthma <sup>Δ</sup> )	Efficacy for treatment of attacks	Mechanism for treatment effect
Airway obstruction	β <sub>2</sub> -agonists	Increasing dose	Adults	Recommended as part of acute treatment Increasing β <sub>2</sub> -agonist use described prior to hospital attendance with severe exacerbation <sup>56</sup> Effectiveness of SABA ↓ during exacerbation	β-adrenergic receptor stimulation → smooth muscle relaxation → bronchodilation Loss of effectiveness of SABA during attack: ▶ Subgroup of patients (<33%) with poor PEFR response to salbutamol described with ↑ airway obstruction, ↑ symptom duration and ↑ healthcare utilisation <sup>124</sup> ▶ ↓ β <sub>2</sub> -agonist FEV <sub>1</sub> response during exacerbations—during viral exacerbations β <sub>2</sub> -adrenoceptor function is impaired <sup>58</sup>
	Short-acting anticholinergics	Systematic review: inhaled anticholinergics + β <sub>2</sub> -agonists in emergency management of asthma <sup>125</sup>	Adults	Recommended in acute severe asthma Risk of admission ↓ 28%	Decreased cholinergic tone → smooth muscle relaxation → bronchodilation
	Magnesium	Systematic review: intravenous magnesium sulfate in acute asthma <sup>126</sup>	Adults	Recommended in acute severe asthma with poor initial response to inhaled bronchodilators odds of admission ↓ 27% (significant study heterogeneity/threshold for magnesium unclear)	Smooth muscle relaxation → bronchodilation
Airway inflammation	Inhaled steroids	Doubling dose: ▶ Based on symptom score, PEFR <80% <sup>127</sup> ▶ Based on symptom score, morning PEFR ↓ ≥15% <sup>128</sup>	Age ≥13 years Attack within ≤12/12 Age ≥16 years Attack within ≤12/12	No effect on requirement for OCS No effect on requirement for OCS	No treatment effect observed
		Quadrupling dose during deteriorations in asthma control <sup>84</sup>	Adults Attack within ≤12/12	Chance of exacerbation over 12-month period (hazard rate) ↓ 20%	Unknown
		Quintupling ICS dose for 7 days at the early signs of loss of asthma control <sup>129</sup>	5–11 year old children	No effect	No treatment effect observed
		Systematic review <sup>130</sup> : pre-emptive high-dose ICS in viral wheeze/asthma episodes (vs placebo)	Children ≤6 years with intermittent asthma/viral triggered wheeze n=422	Exacerbation rate ↓ 35%	<b>Reduction in (likely) virally triggered exacerbations</b> Mechanism unclear
	Pooled RCT data <sup>131</sup> : inhaled budesonide/formoterol (SMART) versus fixed ICS strategy (assumption SMART group ↑ ICS dose during attack via ↑ reliever use)	Child and adult patients step 2–4 treatment ≥1 attack in last 12/12 Suboptimal control during run-in. n=12 507	↓ 36% in 'cold-related' exacerbations with SMART versus other strategies	<b>Reduction in (likely) virally triggered exacerbations</b> Mechanism unclear	
	Meta-analysis <sup>132</sup> : systemic corticosteroids versus systemic corticosteroids + ICS for acute asthma treatment in ED	Child and adult patients admitted to ED with acute asthma 25 studies, n=2733	Odds of admission ↓ 27%	Unknown	
	Oral steroids	Cochrane review <sup>133</sup> : early ED treatment of acute asthma with systemic corticosteroids	Child and adult patients, n=863	Odds of admission ↓ 60%	Unknown
	Cochrane review: steroids to prevent relapse post-attack <sup>134</sup>	6 trials, n=374	Odds of relapse in week post-exacerbation ↓ 62%	Unknown	
Airway infection	Antibiotics	Cochrane review <sup>135</sup> : antibiotics for exacerbations of asthma	6 studies (3 adult and 3 children aged 1–18 years), n=681	No effect (significant heterogeneity in study design/patient selection)	No treatment effect observed
	Inhaled IFN-β treatment	14-day treatment with inhaled IFN-β within 24 hours of developing cold symptoms <sup>136</sup>	Adults Previous viral attack and ≥1 viral attack in last 24 months, n=147	No effect on 1 <sup>0</sup> outcome (ACQ). Morning PEFR ↑ in treatment group and both measures ↑ in severe asthma subgroup	? Due to impaired IFN expression in severe asthma <sup>35</sup>

ACQ, Asthma Control Questionnaire; ED, emergency department; ICS, inhaled corticosteroid; IFN-β, interferon β; OCS, oral corticosteroid; PEFR, peak expiratory flow rate; RCT, randomised controlled trial; SABA, short-acting β-agonist; SMART, steroid in maintenance and reliever therapy.

Though extrapulmonary features may also be important in exacerbation,<sup>83</sup> they are not considered within the scope of this review.

**Acute treatment: future directions**

Currently, limited information is available to allow phenotypic specific treatment of acute asthma attacks and so systemic

steroids and increased bronchodilators are recommended for all severe attacks. Peak flow is the only marker of airway obstruction regularly measured, although this may not be a sensitive marker of patient-reported attacks,<sup>54</sup> and is often not measured by patients despite symptom worsening.<sup>84</sup> The use of more sophisticated effort-independent measures of obstruction such



as focused oscillometry in attacks requires evaluation. The most accessible marker of airway inflammation acutely, the blood eosinophil count, is useful in predicting steroid responsiveness in stable disease but its significance in acute asthma is unknown. Other potential biomarkers such as exhaled nitric oxide<sup>85</sup> and volatile organic compounds<sup>86</sup> which are being actively explored in the management of stable asthma may also have a role in the treatment of acute attacks. The ability of near patient testing devices based on rapid PCR techniques to detect common respiratory viruses is improving and may prove a valid strategy for appropriately directed antiviral therapy.<sup>87</sup> An approach based on detection of blood gene expression signatures<sup>88</sup> could also prove efficacious in distinguishing between bacterial, viral and non-infectious causes of exacerbations to guide acute treatment.

## SUMMARY

In summary, asthma attacks are critically important events linked to excessive morbidity and mortality. There are many challenges to be overcome to improve outcomes relating to attacks. These include a limited and subjective definition of these events and a lack of understanding about their underlying complexity which have hindered efforts to stratify patient attack risk and mitigate this risk by targeting appropriate preventative treatment. Acutely, asthma attacks are all managed in the same way despite questionable efficacy of current interventions in some patient groups.

We believe that there is convincing evidence of heterogeneity in acute asthma attacks as there is in stable asthma and that over the next decade we will see improved treatment of asthma attacks, moving away from high-dose corticosteroids for all towards a phenotype-directed personalised treatment approach which has transformed the management of severe stable asthma in recent years.

Further studies are required in this area to: (1) explore and validate more sensitive and specific criteria to define attacks with the aim of producing standardised objective definitions of attack, (2) further elucidate the mechanisms/characteristics of attacks in well-phenotyped patients across the spectrum of asthma severity and in those taking biological treatment, including superior characterisation and quantification of allergic, environmental, viral and bacterial (through DNA-based techniques) exposures, (3) identify robust, easily measured markers of impending attack to allow timely intervention to abort these and (4) ultimately investigate selective targeting of acute and preventative treatment for attack based on improved understanding and detection of attack phenotypes.

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