Mechanisms and Management of Asthma

Exacerbations

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Abstract

Acute asthma remains an important medical emergency, the most frequent cause of acute admissions in children and a major source of morbidity for adults with asthma. In all ages with asthma the presence of exacerbations is an important defining characteristic of asthma severity. In this review we will assess the epidemiology of acute asthma, the triggers of acute exacerbations and the mechanisms that underlie these exacerbations. We will also assess current treatments that prevent exacerbations, with an emphasis on the role of type 2 airway inflammation in the context of acute exacerbations and the novel treatments that effectively target this. Finally we will review current management strategies of the exacerbations themselves.

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Introduction

Acute exacerbations of asthma remain a serious treatment challenge. They are a frequent cause of hospital admission or emergency room (ER) presentation, especially in children and according to the World Health Organisation, asthma was responsible for 383,000 deaths in 2015. Exacerbations are now considered to be key in defining the severity of the disease and their prevention is an important metric to measure success of asthma treatments (1). Definitions of acute asthma or exacerbations have varied over the years, and a more precise definition was required to standardise outcomes in clinical trials and clinical medicine. As a result, the ATS/ERS convened a task force to define exacerbations as well as asthma control (2). Consequently, a severe exacerbation was defined as; the use of corticosteroids for at least 3 days or a hospitalisation or ER visit because of asthma requiring corticosteroids. Moderate exacerbations were defined as an event that required a change in treatment to prevent it from becoming severe and not severe enough to warrant oral corticosteroids (OCS).

The interventions available for use in the setting of acute asthma are relatively limited, and the management of asthma exacerbations varies depending on severity and the treatment setting. Since the 1960s treatment for acute asthma has focused on the use of systemic corticosteroids and selective beta-2 agonists, and unfortunately there have been few new treatments trialled and little added of particular efficacy to the armamentarium of acute management with the exception of supportive measures. The treatment of asthma exacerbation currently begins with asthma self-management in the outpatient setting. As the severity of the presentation escalates, so do treatment regimens and the support required. Here we review the mechanisms that underpin acute asthma and its management.
What causes acute exacerbations

Epidemiology

Malcolm Sears succinctly summarized the data that describes the epidemiology of acute asthma, emphasizing the importance of age, sex and seasonality (Figure 1)(3). Acute asthma remains predominantly a disease of early childhood, with more boys affected before puberty, and then a switch occurs where females are more likely to suffer with acute asthma that persists throughout life. There is a peak of events when children return to school in autumn, with younger children and adults experiencing less pronounced increases following this and a smaller peak that occurs in those over 50 years in midwinter, with both of these peaks associated with the presence of virus infections (3).

These events seem to hold true across the developed world and are well illustrated by Australian data (4). The problem is greatest in childhood, with children being hospitalized at a prevalence of 495/100,000, compared to adults at 92/100,000. Deaths from asthma though were rare in 2016 with only 455 and two thirds of these were in those aged greater than 75 years. This epidemiological data also demonstrates how much asthma is also a disease of the social environment. In Australia, despite universal public healthcare the prevalence of acute asthma was higher in populations with a lower socioeconomic background, was two-fold greater amongst indigenous communities and higher in adults living in remote areas (4). Outcomes of studies of the relationships between asthma incidence and lower socioeconomic status (SES) have varied from no relationship (5) to increased risk (6). In general while asthma tends to be a disease of the developed world, explained in part through the hygiene hypothesis, when present, poverty is nearly always associated with worse outcomes (7). Lower SES has consistently been shown to be an independent risk for poor asthma control and exacerbations (8, 9) even when complicated by ethnicity (10). In developing nations, poverty or low SES is similarly associated with poor asthma
outcomes (11). The reasons for this are likely to be complex, including poor nutrition, access to health care, affordability of medicine, and exposure to cigarette smoke and/or pollution (7). While easy to dismiss as a problem to be solved by government and changes in social policy, well conducted, patient-centred interventions that focus on self-management can successfully deliver improved outcomes including reducing exacerbations (12).

**Triggers for acute asthma**

The seasonal variation in asthma exacerbations especially in children has already been described, particularly the marked increase that accompanies the return to school in Autumn. This has been linked strongly with the presence of rhinovirus (RV) infection and lack of preventer use in Canadian children aged 5-15 years (13). Less intense peaks have also been seen in mid-winter in older adults and patients with chronic obstructive pulmonary disease and associated with influenza (14). While other factors contribute to this seasonal variation in acute asthma, in school-age children, the community prevalence of RV is the strongest predictor (15). Associations between respiratory infections and acute asthma has been recognised for centuries, as described in 1864 by Henry Salter (himself an asthmatic) “the most prominent and frequent of all exciting causes is what is commonly called *taking cold* ... The asthma consequent on cold on the chest (bronchitis) is of a most painful and distressing kind; unlike that produced by cold directly, it often lasts for days”. The ability to identify viruses by polymerase chain reactions (PCR), demonstrated that they were associated with 80-85% of asthma exacerbations in children (16) and the majority in adults (17), with RV the most common. While true to Salter’s description exacerbations associated with viral infections have also been shown to cause more severe disease (18).

Recently it has been shown that certain RV strains are more closely linked to acute asthma. In children the newly identified RV-C strain was detected in 59.4% and was associated with more severe disease (19). In childhood, RV-C strains seem particularly capable of causing exacerbations,
while infections with RV-A strains require a higher viral titre to trigger an exacerbation, whereas RV-B strains seem relatively benign (20). RV-C binds to epithelial cells via the cadherin-related family member 3 protein, with a missense single nucleotide polymorphism (rs6967330, C529Y) linked to greater cell-surface expression (21). This mutation has also been linked to childhood severe asthma exacerbations (22), and recently this enhanced risk was found to be due to RV-C associated exacerbations in two separate birth cohorts (23). While this strong association has been seen in children with acute asthma and RV-C, it does not seem to hold true for adults where RV-A dominates and RV-C was rarely identified in Australian (24) and US cohorts (25).

Environmental factors also influence asthma exacerbations. A Canadian study showed that after adjusting for season and air pollution a doubling in grass pollen levels and fungal spore counts increased asthma admissions (26). A US study also showed a potential relationship between mould spore levels and asthma deaths (27), and a metaanalysis linked outdoor pollen exposure to acute asthma events (28). More recently an Australian study demonstrated three separate peaks of asthma admissions, the first two related to virus infection, but the third in late spring correlated with high grass pollen counts and high humidity, implicating thunderstorms as a trigger (29). Acute thunderstorm asthma events are extreme examples of this phenomena, where high pollen counts combine with atmospheric conditions that induce severe acute asthma epidemics (30, 31), associated with intense type 2 airway inflammation (32)(Figure 1).

**Exacerbation prone asthma phenotype**

Within populations the risk of asthma exacerbations is not equal. In children a history of previous severe exacerbations appears to be the strongest predictor along with poor asthma symptom control and disease severity (33-35). This risk though appears to vary by season, with exacerbations occurring in autumn and winter (usually viral) predicted by a history of previous
exacerbations, and those in spring and summer by dose of inhaled corticosteroids (ICS) required for control (36). This suggests that events triggered by allergy may be better controlled by regular use of ICS.

In adults, analysis of three clinical trials of greater than 7,000 subjects with asthma who had their treatment with ICS/long acting beta-agonist (LABA) therapy optimized, exacerbations were predicted by disease severity, asthma symptom control and a history of smoking (37). Unlike in childhood, in adults, comorbid disease is also an important additional factor. This has been consistently seen with chronic rhinosinusitis, body mass index, and psychological dysfunction (38, 39). In adults with severe asthma the complexity of this situation needs to be appreciated if effective strategies are to be designed to prevent exacerbations. Using registry data McDonald et al., demonstrated that 24 individual treatable traits could be identified in the domains of; pulmonary, extrapulmonary and behavioural factors that were over represented in those with severe asthma and were related to risk of exacerbation (40). In the context of severe asthma a single approach that only focuses on asthma disease control then is unlikely to be sufficient to improve patient outcomes.

**Poor asthma control and type 2 airway inflammation in acute asthma**

One key independent factor that emerges as an ongoing risk for exacerbations and provides insight into the pathophysiology of acute asthma is the presence of refractory type 2 airway inflammation. Type 2 inflammation is characterized by the release of the cytokines interleukin (IL)-5, IL-4 and IL-13 produced by T-helper type-2 (Th2) cells and innate lymphoid cells of type 2 (ILC2 cells) and is associated with airway eosinophilia and elevated levels of exhaled nitric oxide.

Assessing subjects with both severe asthma as well as mild to moderate disease; severity and asthma symptom control independently predicted exacerbation risk, but so too did sputum eosinophilia or elevated exhaled nitric oxide (41). While adult onset asthma is often not associated
with atopy, a large number, especially those with more severe disease have evidence of type 2 immune activation, with elevated sputum eosinophils and increased levels of exhaled nitric oxide (42). More recently blood eosinophils have been identified as a good predictor of airway eosinophils (43). In population samples of adults, elevated blood eosinophils are associated with increased risk of exacerbations. In 2,392 subjects with asthma, a blood eosinophil count of >0.4 x10⁹/ml independently predicted exacerbation risk with an odds ratio of 1.31 (95%CI 1.07 to 1.6) (44). This remained an independent predictor for exacerbations, even in those with poor asthma symptom control (45), and showed the strongest association with the most severe exacerbations that result in hospital admission (odds ratio; 5.14, 95%CI, 1.76 to 14.99) (46). Combining elevated blood eosinophils together with exhaled nitric oxide may further define those at greatest risk of future asthma exacerbations (47). The presence of active type 2 airway inflammation and its measurement with biomarkers, such as blood eosinophils and exhaled nitric oxide provides a clear indication of risk for future exacerbations.

**Non-type 2 airway inflammation in acute asthma**

While the role of type 2 airway inflammation in acute asthma is becoming much clearer, other immune processes are likely to also be important and future treatments will likely rely upon a clearer understanding of these (48). Acute exacerbations, especially those associated with virus infection have been shown to be associated with neutrophilic inflammation (49), though this may differ in children where there is more evidence of eosinophilic inflammation (50). Dysregulation of innate immune responses, including activation of inflammasome pathways and airway neutrophilia have been seen to be distinct in asthma with non-type 2 inflammation (51, 52), with recent mechanistic and clinical studies implicating non-type 2 airway inflammatory mechanisms play a key role in exacerbations, with microRNAs and inflammasomes more likely involved in virus infection as well as contributing to corticosteroid resistant processes (53, 54).
Management of exacerbations

Controlling type 2 airway inflammation

Control of type 2 airway inflammation is critical in preventing exacerbations (Table 1). Treatment with ICS remains the cornerstone strategy for the majority with asthma and is effective in most at reducing the risk of exacerbations, including the risk of death (55-57). Using either OCS or ICS, adjusted to suppress airway eosinophilia in asthma has been shown to effectively reduce the risk of exacerbations (58, 59). More recently biologic treatments that target specific aspects of type 2 immune responses in those with severe asthma and ICS refractory type 2 airway inflammation have been shown to reduce asthma exacerbations. Treatment of patients with severe allergic asthma with Omalizumab, a monoclonal antibody to IgE, reduces exacerbations in those with severe disease despite optimal doses of ICS/long acting beta-agonist (60). In subjects with severe asthma and refractory eosinophilia, monoclonal antibody therapy against IL-5 reduced exacerbation frequency by approximately half (61). While treatment with Dupilumab, a monoclonal therapy against IL-4 and IL-13, similarly reduced asthma exacerbations though only in those with persistent type 2 airway inflammation, as measured by either increased blood eosinophils or exhaled nitric oxide, despite treatment with ICS (62, 63).

Adjusting ICS/OCS

Control of type 2 airway inflammation prevents exacerbations, but also improves outcomes during an exacerbation. Treatment with systemic steroids, including 1-6 days of prednisone or dexamethasone, effectively reduced relapse rates in acute asthma in children (64). Similarly, in adults, systemic steroids reduced acute relapse rates, though the course of prednisone needed to be at least 7-10 days in duration, with shorter courses being ineffective.
Treatment with ICS cannot be used in place of OCS (66), but may prevent the need to use OCS in acute asthma. Quon et al., showed that doubling the maintenance dose of ICS at the start of an exacerbation was insufficient to prevent the use of OCS (67). More recently, however, Oborne et al., assessed whether a quadruple dose of ICS could prevent exacerbations needing OCS (68). Although they failed to reach their primary outcome, possibly because their platform event filler-triggered action plan provided a delayed response, those who did increase their ICS used less OCS.

A more flexible approach that adjusted ICS dose in response to symptoms has been shown to be more successful. Formoterol/budesonide combinations have shown utility in the setting of mild asthma exacerbations and loss of asthma control when used as maintenance and reliever therapy (69). The formoterol component in Symbicort has a rapid onset of action of 1-3 minutes and also a prolonged duration of action (70). The short onset of action is particular to formoterol containing inhalers, and allows it to be used as reliever therapy. This has a role in the setting of mild asthma exacerbations, where, instead of typical short acting bronchodilators, formoterol/budesonide combination inhalers lead to symptomatic bronchodilation along with the administration of extra ICS. Ideally, this extra ICS may be sufficient to target steroid-responsive inflammation that may be at the heart of the current exacerbation. As a result, adjustable dosing of budesonide formoterol is linked with better exacerbation control long-term (71). More recently this approach was used to show that as required use of Formoterol/budesonide, in those with mild intermittent disease also effectively reduced exacerbations and the need for OCS (72, 73).

Definitive treatment in the setting of severe exacerbations currently involves therapy with OCS. Their use is associated with reduced recurrent asthma exacerbations, and emergency department and hospital admissions (74). Given that exacerbations are thought to often involve eosinophilic inflammation beyond what is typically managed with maintenance therapy in the patient’s day-to-day life, systemic corticosteroids effectively target this inflammation. They have
been shown to induce apoptosis in eosinophils, reduce mucus hypersecretion in the airways and prevent the recruitment of eosinophils. All of this contributes to their importance as a major therapy in the treatment of acute asthma exacerbations (75).

Self-management

The Global Strategy for Asthma Management and Prevention (GINA), along with most international respiratory societies, recommend self-management strategies to reduce the impact of acute exacerbations in all groups (1). This involves patient education and the provision of an individualised written asthma action plan. An action plan should include a description of regular maintenance therapy, and instructions for the escalation of therapy depending on either a worsening of symptoms or a change in peak flow monitoring (for examples see https://www.nationalasthma.org.au/health-professionals/asthma-action-plans/asthma-action-plan-library). Action plans that include instructions using 2-4 action points and the use of both ICS and when to initiate OCS improved health outcomes including reductions in hospital admissions (76).

Bronchodilators

Since the advent of metered dose inhalers for the treatment of bronchoconstriction, beta-adrenergic bronchodilators have formed the mainstay of treatment of acute exacerbations. In the outpatient setting, patients are instructed to increase their use of short-acting bronchodilators in conjunction with their symptoms. Given their potential to mask symptoms and delay seeking of medical attention, it is important to adequately educate patients on the need to pursue further treatment, typically with increasing doses of corticosteroids (77). While important during the
acute management of the symptoms of an exacerbation, typically bronchodilators do not treat the underlying inflammation that underpin the exacerbation, particularly eosinophilic inflammation.

Because of their short onset of action, short-acting bronchodilators are used in this setting, most commonly beta-2-agonists but also short-acting anti-muscarinics. Both act on airway smooth muscle to promote bronchodilation. This is mediated by beta-adrenergic stimulation of smooth muscle to enact bronchodilation or cholinergic antagonism to relieve bronchial constriction that is under parasympathetic activity (78, 79). Treatment is primarily symptomatic, as bronchodilation does not target the underlying inflammation that drives the exacerbation.

**Magnesium**

Typically, the use of magnesium sulfate is limited to those situations where asthma exacerbation is refractory to treatment with bronchodilators and steroids alone. Parenteral administration is used as it has greater bioavailability compared to oral magnesium (80). A Cochrane review demonstrated reduced hospital admissions and a small improvement in lung function with the use of magnesium sulfate in the emergency department (81). A review by Ling et al., did not demonstrate any reduction in hospital admissions with the use of nebulized magnesium, and thus there is not a clear benefit of nebulised administration at this point (82). Another Cochrane review assessed comparisons between the administration of inhaled magnesium sulfate and b2-agonist with b2-agonist alone also did not show any improvement in lung function or hospital admission rate (83). These findings seem to be equivalent in children (84).

**Treating infection and non-type 2 inflammation**

Infection plays a crucial role in triggering acute asthma. Experimental studies show impaired innate immune responses to virus infections in asthma (85), and that infections induce microRNAs and inflammasome activation that suppress responses to corticosteroids(53, 54).
Investigators sought to determine if treatment at the time of a cold with nebulised interferon would reduce exacerbation severity in those with a history of virus-induced acute asthma. Treatment though did not improve the severity of acute asthma symptoms overall, except in those with pre-existing poor control and more severe disease (86). In contrast to acute exacerbations of COPD, there is no evidence that antibiotics improve outcomes in acute asthma (87). This is likely since the majority of exacerbations are associated with viral infections. Macrolide antibiotics have been used to reduce the frequency of exacerbations of asthma and other airways disease and are proposed to have anti-inflammatory effects. In a trial of 278 adults with asthma treatment with the ketolide Telithromycin was shown to improve asthma symptom scores (88), but it was later withdrawn due to toxicity. A similar trial attempted to assess add on azithromycin to see if this would improve asthma symptoms acutely, the trial failed to demonstrate a difference, though the investigators had to exclude 10 subjects for everyone randomised as they had already received antibiotics (89). Azithromycin has also been used in preschool children (1-3 years) presenting with acute wheezing illnesses, but has had mixed results, with one trial demonstrating a reduction in length of symptoms (90), and another failing to show improvement in clinical outcomes (91). Antimicrobials, instead, should be reserved for those cases where there is clinical suspicion for bacterial infection that would require treatment in conjunction with treatment of the asthma exacerbation (1).

In terms of preventing exacerbations targeting non-type 2 immune mechanisms there have been mixed results (Table 2). In adults with moderate to severe asthma regular azithromycin reduced exacerbation risk in those with and without eosinophilic airway inflammation in an Australian study (92), but not in a European study (93). Tiotropium a long acting anticholinergic bronchodilator has also been shown to reduce exacerbation risk in those on ICS/LABA, in adults and children with asthma, while long acting beta agonists alone have not (94). Omalizumab as discussed reduces exacerbations, but recent evidence suggests part of its effect may be by
improving antiviral immune responses (95). However monoclonal antibodies that targeted TH-17 (96) and tumour necrosis factor-alpha (97) failed to reduce exacerbations.

**Conclusions**

Treatment of asthma exacerbations using the therapies described is successful for a large proportion of patients. Indeed, as a result, over the course of the last 100 years, the mortality rate from asthma exacerbations has declined considerably. This has largely been due to the recognition of corticosteroids as a cornerstone of treatment of asthma exacerbations. Despite these improvements, there remains a significant ongoing mortality rate due to asthma that appears to have reached a plateau in the developed world. With the advent of precision medicine and targeted therapies, there have been many new insights into the management of chronic disease in asthma, however, this has not yet been seen with exacerbations. We remain hopeful that further advances will see further decline in mortality due to asthma – whether this be due to advances in chronic therapy, acute and exacerbation management, or even, potentially, cure.
### Table 1 Preventing acute asthma

<table>
<thead>
<tr>
<th>Therapeutic</th>
<th>Mechanism of action</th>
<th>Clinical effect</th>
<th>Asthma phenotype</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICS</td>
<td>Effective in control of type 2 airway inflammation, probable effects on non-specific features of inflammation.</td>
<td>Reduced exacerbations, improved asthma symptoms, reduced airway reactivity.</td>
<td>Arguably effective in all with asthma, effect clearly greatest in those with Type 2 immune activation.</td>
<td>(56, 64-68, 74, 75, 98, 99)</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>Monoclonal antibody against IgE, prevents IgE crosslinking and allergen induced activation. In-vitro evidence that it improves antiviral responses in plasmacytoid dendritic cells.</td>
<td>Reduced exacerbations, improved asthma symptoms.</td>
<td>Moderate to severe allergic asthma, poor control or exacerbations despite ICS/LABA.</td>
<td>(95, 99-101)</td>
</tr>
<tr>
<td>Therapies that target IL-5 pathways (Mepolizumab, Benzralizumab, Reslizumab)</td>
<td>Monoclonal antibody that blocks the action of IL-5 on recruitment of immune cells, in particular eosinophils.</td>
<td>Reduced exacerbations, improved asthma symptoms.</td>
<td>Severe asthma with refractory eosinophilic inflammation despite ICS</td>
<td>(61)</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>Monoclonal antibody that blocks the action of IL-4/13.</td>
<td>Reduced exacerbations, improved asthma symptoms, improved lung function.</td>
<td>Moderate to severe asthma, with evidence of active type 2 airway inflammation, either elevated exhaled nitric oxide or blood eosinophils.</td>
<td>(62, 63)</td>
</tr>
<tr>
<td>Tezepelumab</td>
<td>Monoclonal antibody that blocks the action of TSLP.</td>
<td>Reduced exacerbations, improved lung function.</td>
<td>Adults with moderate to severe asthma, at this stage not limited to an inflammatory phenotype (based on 1 RCT).</td>
<td>(102)</td>
</tr>
<tr>
<td>Tiotropium</td>
<td>Long acting antimuscarinic agent, blocking the action of acetylcholine on airway smooth muscle and goblet</td>
<td>Reduced exacerbations, improved lung function and asthma symptoms</td>
<td>Recommended in those &gt;12 years as add on to ICS/LABA, may be effective in those with milder disease</td>
<td>(94)</td>
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<tr>
<td><strong>Azithromycin</strong></td>
<td>Macrolide antibiotic, with potential anti-inflammatory effects</td>
<td>Mixed results. May reduce exacerbation frequency.</td>
<td>Adults with moderate to severe asthma, not limited to those with type 2 immune activation.</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: ICS (inhaled corticosteroid) LABA (long acting beta agonist).
# Table 2: Treating acute asthma

<table>
<thead>
<tr>
<th>Class</th>
<th>Example</th>
<th>Effect</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>SABA/SAMA</td>
<td>1. Inhaled bronchodilator</td>
<td>Symptomatic relief: Beta-2-agonist leading to smooth muscle cell relaxation allowing for bronchodilation Anti-cholinergic relieves parasympathetic bronchoconstriction</td>
<td>(79)</td>
</tr>
<tr>
<td></td>
<td>Salbutamol MDI (100mcg/puff) 2-4 puffs q1h PRN Atrovent MDI (17mcg/puff) 2 puffs q4h PRN (up to q20min in ED acutely)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICS/LABA or ICS</td>
<td>2. Inhaled corticosteroid</td>
<td>Treat steroid-responsive inflammation in mild to moderate asthma exacerbations. Potentially avoids the necessity of systemic corticosteroids.</td>
<td>(68, 69, 72, 73)</td>
</tr>
<tr>
<td></td>
<td>Budesonide/formoterol via dry powder device (200/6mcg) 1-2 puffs as needed (max. 8/day) Ciclesonide (160) 4 puffs TID</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral steroids</td>
<td>2. Systemic corticosteroid</td>
<td>Treat steroid-responsive inflammation in asthma exacerbation. Reduces relapse and hospitalization rates.</td>
<td>(64, 65, 74)</td>
</tr>
<tr>
<td></td>
<td>Adults Prednisone 37.5 to 50mg daily for 7 days Children &gt;6 years give prednisone 1 mg/kg (maximum 50 mg) orally for 3 days.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>3. Elemental magnesium</td>
<td>Smooth muscle relaxation/bronchodilation</td>
<td>(81)</td>
</tr>
<tr>
<td></td>
<td>Magnesium sulfate 2g IV over 20 minutes</td>
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</table>

Table 2: Summary of treatment modalities for asthma exacerbation. In the acute setting, the use of Class 1 medications for symptom relief is standard, in addition to Class 2 to target inflammation at the heart of an acute exacerbation and prevent relapse. Class 3 medications are typically used in refractory situations, or where there is clinical need for treatment of comorbidities or ongoing supportive management. SABA (Short acting bronchodilator), SAMA (short acting antimuscarinic). ICS (inhaled corticosteroid) LABA (long acting beta agonist).
Figure 1: Acute exacerbations of asthma follow a pattern of seasonal variation. A number of peaks of acute asthma activity occurs. There is a marked increase that accompanies the return to school in Autumn. This has been linked strongly with the presence of rhinovirus (RV) infection and lack of preventer use in school children with asthma. A less intense peak has also been seen in mid-winter in older adults and patients with chronic obstructive pulmonary disease and associated with influenza and other winter related respiratory tract infections. Exposure to allergens however is also important. After adjusting for season and air pollution a doubling in grass pollen levels and fungal spore counts is also associated with increased asthma admissions. This is associated with a third peak in late spring correlated with high grass pollen counts and high humidity, seen through a combination of high ambient pollen counts and weather events like thunderstorm.

Legend Figure 1
Figure 1: Acute exacerbations of asthma follow a pattern of seasonal variation. A number of peaks of acute asthma activity occurs. There is a marked increase that accompanies the return to school in Autumn. This has been linked strongly with the presence of rhinovirus (RV) infection and lack of preventer use in school children with asthma. A less intense peak has also been seen in mid-winter in older adults and patients with chronic obstructive pulmonary disease and associated with influenza and other winter related respiratory tract infections. Exposure to allergens however is also important. After adjusting for season and air pollution a doubling in grass pollen levels and fungal spore counts is also associated with increased asthma admissions. This is associated with a third peak in late spring correlated with high grass pollen counts and high humidity, seen through a combination of high ambient pollen counts and weather events like thunderstorm.
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