

# Repeated exacerbation of asthma: An intrinsic phenotype of uncontrolled asthma

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## ABSTRACT

Asthma is a chronic disease of the airways affecting a large number of people across the globe. Uncontrolled asthma poses an emotional as well as the physical burden on patients and results in a great economic burden. “Exacerbation-prone phenotype” asthmatics are a cluster of patients who may suffer from more frequent and severe exacerbations than other asthmatics. Factors such as inadequate symptom control, improper adherence to medications, and incorrect use of inhalers are responsible for frequent asthma exacerbations. Caring for the patient with “exacerbation-prone asthma” needs participation from both the doctor as well as the patient. Self-management, improving knowledge about the disease, control of comorbidities, and a stepwise approach with the use of a single inhaler maintenance and reliever therapy in patients with severe asthma could help in delivering better care for the “exacerbation-prone phenotype” of asthmatics.

**KEY WORDS:** Exacerbation-prone, inhalers, phenotype, severe asthma

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Asthma is a chronic disease affecting the airways. Inflammation and hyperresponsiveness of the bronchial tubes and hindrance to airflow lead to the symptoms of asthma.<sup>[1]</sup> An alarming 334 million people around the world are afflicted by this respiratory illness.<sup>[2]</sup> Asthma is responsible for lowering the quality of life, curtailing daily activities, reduction in lung function, and absenteeism from school or work.<sup>[2]</sup> A large number of patients experience emotional and functional restraints due to asthma.<sup>[3]</sup> It poses a considerable socioeconomic burden and often leads to the use of a large amount of health-care resources.<sup>[2,4]</sup> Approximately, four out of every 100 adults around the globe suffer from asthma.<sup>[5]</sup> However, the prevalence of asthma varies between countries. While Vietnam records a low prevalence of 1.0%, Austria and Sweden have the highest prevalence rates of 21.5% and 20.2%, respectively.<sup>[5]</sup> The

exact prevalence of asthma in India remains elusive. The World Health Organization reports that India harbors about 15–20 million asthmatics and of these, 10%–15% are children.<sup>[6]</sup> Almost three out of every 100 adults in India are affected with asthma.<sup>[5]</sup> It was estimated that an appalling 139.45 billion Indian rupees have been spent on the treatment of asthma in the year 2015 alone.<sup>[7]</sup> Every year, nearly 15 million disability-adjusted life years are lost as a result of asthma, which accounts for 1% of the global disease burden.<sup>[2]</sup> Nearly 489,000 lives are lost to this chronic disease annually.<sup>[8]</sup> Low- and middle-income countries such as Africa, Oceania, and Southeast Asia contribute to a vast majority of the deaths due to asthma.<sup>[9]</sup>

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Asthma poses an emotional as well as the physical burden on patients in India. The Asia Pacific-asthma insights and management (AP-AIM) study found that more than 75% of asthmatics in India endured fatigue due to the disease. The Indian Study on Epidemiology of Asthma, Respiratory Symptoms and Chronic Bronchitis in adults found that the prevalence of asthma varied across the nation, ranging from 0.4% in Secunderabad to as high as 4.8% in Kolkata.<sup>[10,11]</sup> Among Indian children, prevalence rates of 2.3% and 3.3% have been noted in the age groups of 6–7 years and 13–14 years, respectively. Almost an equal number had missed school or work during the past year, amounting to an average loss of 16.5 days. The productivity of the patients also dropped to almost half when symptoms of asthma were present.<sup>[11,12]</sup> Female gender, increasing age, low socioeconomic status, tobacco smoking, and family history in a first-degree relative were associated with a higher chance of developing this chronic disease.<sup>[13]</sup>

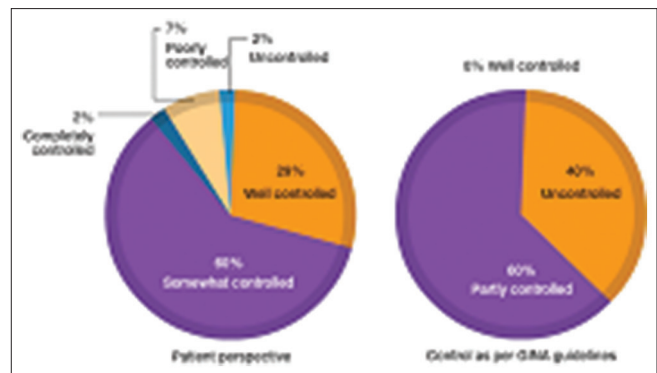
The World Health Survey noted that 9.63% of the population surveyed in India reported an episode of wheezing during the past year.<sup>[5]</sup> Such a high prevalence could be due to inadequate control of asthma in the Indian population. Uncontrolled asthma poses a larger economic burden than when the disease is under control.<sup>[2]</sup> Therefore, a better understanding of the risk factors, pathophysiology, and treatment of uncontrolled asthma is essential to lower the socioeconomic burden due to uncontrolled asthma.

### Asthma control among patients in India

Negligible data about hospital admission rates due to asthma in low- and middle-income countries are available.<sup>[2]</sup> It has been observed that a large number of asthmatics in India exaggerate their control over the disease.<sup>[3]</sup> The AP-AIM study surveyed 400 asthmatic patients in India and found that 91% of the patients were of the impression that their disease was well controlled. However, when the level of control in these patients was assessed objectively using the Global Initiative for Asthma (GINA) guidelines, it was noted that not even one of them had well-controlled asthma, and 40% were suffering from uncontrolled asthma. Among those who claimed to have a good asthma control over the past 1 month, 63% and 38% had insufficiently controlled and uncontrolled asthma, respectively [Figure 1]. An average of 8.4 exacerbations was found to be reported by asthmatic patients in India every year, each episode lasting for about 4 days.<sup>[11]</sup>

Salvi *et al.* found that 67% of the asthmatic patients in India had suffered an exacerbation during the previous year.<sup>[3]</sup> This clearly shows that asthma control is inadequate in India.<sup>[11]</sup>

The terms “uncontrolled” and “severe” are associated with a lack of clarity among patients as well as doctors with regard to asthma. “Level of control” refers to the extent of reduction in symptoms, as well as chances of developing adverse events. An increased chance of developing exacerbations goes hand in hand with lack



**Figure 1:** Patient perception versus the Global Initiative for Asthma guidelines-defined asthma control<sup>[13]</sup>

of control of symptoms.<sup>[14]</sup> “Severity” on the other hand, is gauged by the level or intensity of treatment that is necessary to control the exacerbation.<sup>[14,15]</sup> “Severe asthma exacerbations” have been defined by the American Thoracic Society to be an event which necessitates urgent action to prevent grave outcomes due to asthma, such as death or hospitalization.<sup>[15]</sup>

Exacerbations must be considered separately from the level of control when evaluating asthma. This is because exacerbations may occur in spite of adequate symptom control and activity limitation. Increase in maintenance medications may not always prevent such exacerbations.<sup>[16]</sup> As most of the asthma-related deaths are preventable, an understanding of the pathophysiology leading to exacerbations will go a long way in reducing morbidity and improving the quality of life of patients with severe asthma exacerbations.

### EXACERBATION-PRONE ASTHMA

Being a heterogeneous disease having varied pathophysiology, there exist distinguishable clusters of patients who share clinical, demographic, and/or pathophysiological characteristics known as “phenotypes.”<sup>[14]</sup> One such phenotype, the “exacerbation-prone phenotype” may suffer from more frequent and severe exacerbations in comparison to other asthmatics.<sup>[1,17]</sup> A patient is said to have suffered from a severe exacerbation if any of the following are present: (I) Systemic steroids had been used to treat the attack, or the maintenance dose required to be escalated for at least for 3 days; (II) An emergency visit due to asthma had to be made to a health-care facility, during which systemic steroids were administered.<sup>[15]</sup> It is necessary to understand more about this subgroup of patients because of a higher morbidity and mortality among them.<sup>[17,18]</sup>

### Potential contributing factors for frequent exacerbations

Several factors precipitate frequent exacerbations of asthma; inadequate symptom control is the most important of them.<sup>[14,19]</sup> Patients are often ignorant regarding the correct symptoms of asthma or exacerbations. If patients are not educated about asthma, or if an objective measurement of

lung function is not performed, they may wrongly perceive their symptoms to be greater than or lesser than the actual severity.<sup>[20]</sup> When symptoms are underestimated, patients may fail to take adequate controller medication, which in the long run, results in an overuse of relievers.<sup>[20]</sup>

Improper adherence to medications leads to poor disease control, disease progression, emergency hospital visits, requirement for stronger medication and increased health-care costs.<sup>[20]</sup> Other factors such as psychological impairment, smoking, chronic sinusitis, rhinitis, viral infections of the respiratory tract, gastroesophageal reflux, and sleep disturbances also contribute to the poor control of asthma.<sup>[20-22]</sup> Appropriate choice of an inhaler and perfecting the technique of using the device is also crucial for adequate disease control.<sup>[23]</sup> Physicians contribute to the growing pool of uncontrolled asthmatics by misdiagnosis of the disease, insufficient knowledge about the latest guidelines and inadequate patient education.<sup>[20]</sup>

### Why is phenotypic characterization necessary?

Since asthma is a hereditary disease, it might be possible that a genetic influence is associated with the severity of the disease. Some investigators have observed an excess decline in lung function in patients exhibiting variants of the ADAM33, FCER1B, interleukin 4 (IL4), and IL4RA genes.<sup>[24,25]</sup> Others have suggested that an epigenetic mechanism might be held responsible for the disproportionate increase in the incidence and severity of asthma over the past few years.<sup>[26]</sup> It has been postulated that certain marks on the human genome may be more susceptible to modification by exposure to environmental factors, thereby bringing about the various phenotypes of this disease.<sup>[27]</sup> If so, understanding the “exacerbation-prone phenotype” as a distinct entity will aid in guiding the treatment and enhancing our knowledge of the natural history, inherent mechanisms, and prognosis of the disease.<sup>[28]</sup>

Within asthmatics, the responsiveness to treatment may vary from person to person. While some patients respond quickly to low-dose treatment, others may show a poor response. This poor response may be due to the presence of confounding factors other than asthma.<sup>[16]</sup> Ambiguity also exists regarding the structural changes that occur in the lungs, and the reason for abnormalities in smooth muscles and epithelial cells in patients with severe asthma.<sup>[28]</sup> Some studies state that the airway inflammation present in severe asthma may differ from that of mild or moderate disease. Neutrophils, as well as eosinophils, might be present in severe disease, as opposed to the presence of eosinophils alone in mild or moderate asthma.<sup>[29]</sup> Patients identified with the “xacerbation-prone” phenotype may need to be protected from precipitating factors such as respiratory viruses and allergens and other triggering factors.<sup>[28]</sup> Better knowledge about these mechanisms which appear to be unique to patients with severe asthma could help in treating and preventing this chronic disease.

## EVIDENCE FOR A MORE INTRINSIC PHENOTYPE OF REPEATED EXACERBATION OF ASTHMA

The studies conducted in the recent past suggest the existence of the “exacerbation-prone phenotype” of asthma.<sup>[4,30,31]</sup> Outcomes and Treatment Regimens Study evaluated the characteristics of patients with severe asthma. The risk of developing exacerbations in this subset of patients was not related to the severity of the disease or any other demographic factors. However, inadequate control of the disease was found to be associated with the chance of developing future exacerbations.<sup>[30]</sup> These patients reported a high use of medication, frequent visits to health-care facilities, and perception of a poor quality of life. Risk of developing exacerbation in the future was found to be strongly associated with having a history of recent exacerbations.<sup>[30]</sup>

Another study, the severe asthma research program surveyed patients with severe, moderate and mild asthma.<sup>[4]</sup> It was observed that most of the patients with severe asthma were using an additional controller medicine and short-acting beta-agonist (SABA) daily, a required emergency oral corticosteroid (OCS) therapy, and had unrelenting airflow obstruction.<sup>[4]</sup> Frequent visits to a health-care facility, sinusitis, gastroesophageal reflux disease, and aspirin sensitivity were also observed in these patients.<sup>[4]</sup> Both Moore *et al.* and Chipps *et al.* emphasize that the occurrence of exacerbations in the recent past, which require emergency services, is a reliable predictor of developing future exacerbations.<sup>[4,30]</sup>

The case-control study by Koga *et al.* compared patients suffering from multiple exacerbations with those who did not. He noted that some clinical characteristics were shared by most of the patients suffering from frequent exacerbations. A longer duration of disease, higher dose of OCSs and inhaled corticosteroids (ICS), frequency of hospital admissions, presence of chronic sinusitis, allergy to nonsteroidal anti-inflammatory drugs (NSAIDs) were associated with multiple exacerbations [Table 1].<sup>[19]</sup> A reduction in the reversibility of forced expiratory volume-1 (FEV<sub>1</sub>) after bronchodilator administration and FEV<sub>1</sub>/forced vital capacity (FEV<sub>1</sub>/FVC) ratio was also evident.<sup>[19]</sup>

Barreiro *et al.* noted that a lower perception of dyspnea was evident in patients who had suffered a near-fatal attack of asthma compared with those who did not. It was also observed in the study that, different mechanisms were responsible for exercise limitation in both groups of patients. Patients with a near-fatal attack stopped exercising due to leg discomfort, whereas the other group stopped because of breathlessness.<sup>[32]</sup> van Veen *et al.* compared alveolar nitric oxide between patients with severe and mild-to-moderate asthma. Within patients suffering from severe asthma, greater level of airway

**Table 1: Comparison of patient characteristics among asthmatics with and without multiple exacerbations<sup>[19]</sup>**

	ME	Control	P
n	32	37	
Age	46.7±18.4	44.4±15.7	0.55
Male (%)	6 (27.3)	11 (34.4)	0.44
Duration of asthma (years)	29.1±18.0	11.0±13.1	0.008*
Family history of asthma (%)	17 (53.1)	12 (32.4)	0.13
Childhood asthma (%)	8 (25.0)	7 (18.9)	0.75
Admissions (%)	23 (71.9)	9 (24.3)	0.0002*
Visit on ambulance (%)	12 (37.5)	3 (8.1)	0.008*
ICS (µg/day)	1037.5±452.8	621.6±257.3	0.0005*
Oral steroid (%)	9 (28.1)	1 (2.7)	0.008*
Nasal allergy (%)	16 (50.0)	24 (64.9)	0.31
Chronic sinusitis (%)	11 (34.4)	4 (10.8)	0.038*
NSAIDs intolerance (%)	11 (34.4)	2 (5.4)	0.006*

\*P<0.05 was considered significant. ME: Multiple exacerbations, ICS: Inhaled corticosteroids, NSAIDs: Nonsteroidal anti-inflammatory drugs

inflammation, and dysfunction was evident in patients taking continuous OCS; this evidence supports the fact that airway inflammation by itself is not related to the severity of asthma.<sup>[33]</sup>

A prospective analysis by Miller *et al.* as well observed that asthma exacerbations in the recent past and inadequate control were associated with developing exacerbations in the future. Patients who were exposed to triggering factors had a body mass index more than 30 and had lower predicted FVC% were at an increased risk of exacerbations. The study concluded that the pathophysiology behind exacerbations possibly differ from those concerning other aspects of asthma.<sup>[31]</sup> Thus, it is possible that there exists a subgroup of patients suffering from asthma who are more prone than others to develop exacerbations regardless of conventional therapy.<sup>[1]</sup>

### CHARACTERISTICS OF THE REPEATED EXACERBATION OF ASTHMA PHENOTYPE

Patients prone to exacerbations may have a lower perception of dyspnea, which predispose them to severe attacks of asthma.<sup>[32]</sup> They may often deny the symptoms of asthma and evade medications or preventive strategies.<sup>[34]</sup> Meltzer EO *et al.* used the Asthma Control Questionnaire (ACQ), a tool which could measure the degree of asthma control, to predict the possibility of developing exacerbations in patients with moderate to severe asthma. The study showed that the probability of developing an exacerbation in the ensuing 2 weeks increased with every 1-point increase in the ACQ score, use of SABA and presence of symptoms at night.<sup>[35]</sup> Frequent emergency visits to the hospital within the last 1 year and use of higher doses of oral and inhaled steroids were found to be indicative of poor disease control, which in turn led to exacerbations.<sup>[22,36,37]</sup> Greater chances of exacerbations were also noted in patients with use of SABA more than 400 µg/day.<sup>[22]</sup> A high variability in peak expiratory flow, quick fall in the prebronchodilator

FEV<sub>1</sub>/FVC ratio, low FEV<sub>1</sub> was also associated with frequent asthma attacks.<sup>[29,36]</sup>

Higher sputum eosinophil count (>25%) and sputum neutrophil count may be present in the “exacerbation-prone” patients, because of the inability of the treatment to reduce inflammation in the airways.<sup>[29,36,38]</sup> Neutrophilic inflammation has been associated with a lack of response to steroids.<sup>[39]</sup> Likewise, eosinophil cationic protein, IL8, and myeloperoxidase levels were observed to be elevated in severe asthmatics.<sup>[29]</sup> Unsatisfactory control of airway inflammation when ICS is tapered could lead to inadequate asthma control and exacerbations.<sup>[38]</sup> A blood eosinophil count more than 400/µL was seen to be associated with the chance of developing two or more exacerbations in the forthcoming year.<sup>[22]</sup> Elevated C-reactive protein levels and exhaled nitric oxide more than 45 parts per billion could also serve as predictors of exacerbation-prone disease.<sup>[29,36]</sup> Alveolar nitric oxide measures the inflammation of the peripheral airways, also helps to determine the severity of the disease.<sup>[33]</sup> Sensitivity to aspirin has been noted to be associated with severe asthma, probably due to remodeling of the airways.<sup>[30,40,41]</sup>

### EVIDENCE-BASED APPROACH FOR THE TREATMENT OF REPEATED EXACERBATION OF ASTHMA

**Approach to the patient with “exacerbation-prone asthma”**  
Caring for the patient with “xacerbation-prone asthma” needs participation from both the doctor as well as the patient. Self-management and knowledge about the disease go a long way in achieving adequate control.<sup>[14]</sup> To begin with, the presence of asthma must be confirmed, excluding any other respiratory conditions.<sup>[14]</sup> Factors that might have an impact on asthma control such as triggering factors, improper adherence to medications, improper inhalation technique, and comorbidities should be tackled before classifying the disease as severe asthma.<sup>[28]</sup> The severity of asthma must be assessed based on the type of treatment taken by the patient over the past few months.<sup>[14]</sup> Once diagnosed, follow-up of exacerbation-prone patients is very important. Enquiries should be made regarding the use of OCS, number of episodes of exacerbation, and admission to a health-care facility. Lung function tests, ACQs, and measure of airway inflammation need to be assessed at each follow-up.<sup>[28]</sup> The evaluation of exhaled nitric oxide levels and sputum cell counts are noninvasive methods of measuring airway inflammation.<sup>[28]</sup>

The treatment strategy for asthma aims to accomplish and sustain disease control with the lowest possible medication. GINA recommends a stepwise approach for the treatment of asthma. Initially, SABA is started, followed by the addition of a low dose of ICS if the disease is not controlled.<sup>[14]</sup> Subsequent steps involve increasing the dose of ICS, and adding a long-acting beta-agonists (LABA); along with the use of a SABA during poor control.<sup>[14]</sup>



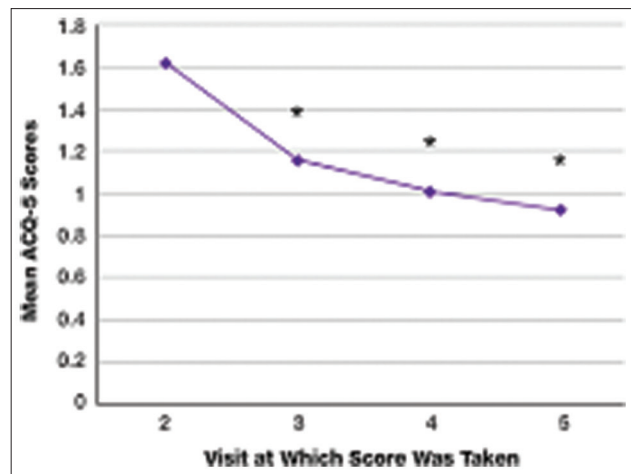
A leukotriene receptor antagonist or theophylline may be added if symptoms persist.<sup>[14]</sup> Bronchodilators and ICS form the backbone of treatment for severe asthma. However, there are cases in which corticosteroids may not be effective in the treatment of severe asthma.<sup>[28]</sup> This is because corticosteroids are advantageous when the inflammatory response is predominantly eosinophilic.<sup>[42]</sup> In a neutrophilic airway inflammation, ICS may be of little use.<sup>[43]</sup> In many instances, SABAs are overused to achieve fast relief from symptoms. Unreasonable use of SABAs has been observed to be frequently associated with inadequate disease control.<sup>[44-46]</sup> This could be because high doses of beta-agonists interfere with the action of corticosteroids, thereby failing to check disease progression.<sup>[47]</sup>

### Role of single inhaler maintenance and reliever therapy

As an increase in adverse events was noticed when LABA and corticosteroids were dispensed separately, a newer single inhaler maintenance and reliever therapy approach was introduced in patients who suffered from uncontrolled asthma.<sup>[48-51]</sup> Formoterol is the only LABA that can be used for maintenance and reliever, due to its quick onset of action and a long bronchodilator effect.<sup>[51]</sup> Budesonide and beclomethasone are the only two ICS approved by GINA for use as single inhalation therapy.<sup>[52]</sup> A low dose of budesonide/formoterol may be administered for maintenance and can be temporarily increased during an exacerbation.<sup>[53]</sup> Using single inhaler maintenance and reliever therapy has shown benefit in reducing exacerbations compared to fixed dose therapy as well as compared to high dose ICS therapy.

Different trials were conducted to observe the exacerbations of asthma in patients with the single inhaler therapy in comparison to the patients with fixed-dose therapy. The observations from the AHEAD trial showed that single inhaler maintenance and reliever therapy is more effective than the ICS/LABA fixed-dose combination therapy. The pattern of severe exacerbations was observed in patients, and the trial stated that single inhaler therapy provided greater protection to patients at times of asthma worsening. The results from COMPASS trial showed that the single inhaler therapy prolonged first severe exacerbations in the patients when compared with the fixed-dose treatment groups. Single inhaler maintenance and reliever therapy help asthmatics to avoid using SABA, decrease total corticosteroid dose taken over time, prevent exacerbations at a lower cost and better treatment adherence.<sup>[52-54]</sup>

The single inhaler maintenance and reliever therapy Asia study analyzed the effect of budesonide/formoterol therapy in patients with inadequately controlled asthma in five countries across Asia.<sup>[55]</sup> A total of 162 patients from India were part of this study. An appreciable improvement in the symptoms, control of the disease, and quality of life were observed 4 weeks from the start of the therapy. An increase in lung function and symptom-free intervals and decrease in sleep disturbances and the use of reliever medications were reported by patients [Figure 2].<sup>[55]</sup> A recent Cochrane



**Figure 2:** Mean Asthma Control Questionnaire-5 scores after beginning the treatment with SMART.<sup>[55]</sup> \*Denotes significant difference from the baseline level. Visit 2 = baseline

review found LABA/ICS combination therapy to be more beneficial than an increment in the dose of ICS to reduce the risk of exacerbations in patients with uncontrolled asthma. Beneficial effects of single inhaler maintenance and reliever therapy were seen at a lower overall steroid dose compared to fixed-dose combinations. Better lung function, control of symptoms and adherence to therapy were achieved with this combination therapy.<sup>[56]</sup> Several investigators have demonstrated the efficacy of using the budesonide/formoterol combination therapy in patients who have uncontrolled asthma, and it is also included in the GINA guidelines.<sup>[14,57,58]</sup>

The safety of the single inhaler therapy was examined by a double-blind trial conducted in patients with asthma. The patients were randomized into six groups, one group received budesonide/formoterol maintenance and reliever therapy ( $n = 5584$ ) and the other groups were treated with budesonide plus SABA ( $n = 2210$ ), budesonide/formoterol plus SABA ( $n = 3143$ ), budesonide/formoterol plus formoterol ( $n = 1137$ ), and salmeterol/fluticasone plus SABA ( $n = 2272$ ) respectively. The risks for asthma-related adverse events and the discontinuation due to the adverse events were reduced with budesonide/formoterol maintenance and reliever therapy ( $n = 41$ ,  $n = 25$  respectively) when compared to the budesonide plus SABA, budesonide/formoterol plus SABA, budesonide/formoterol plus formoterol, and Salmeterol/fluticasone plus SABA fixed-dose therapies ( $n = 121$ ,  $n = 85$ , respectively). The study concluded that the budesonide/formoterol maintenance and reliever therapy is safer with a decreased risk of adverse events in patients when compared with the fixed-dose alternatives.<sup>[59]</sup>

### Role of other drugs

Other drugs such as anti-leukotrienes, leukotriene receptor antagonists, and monoclonal antibodies have been tried in patients with severe asthma. Zafirlukast, a leukotriene receptor antagonist, was found to reduce the chance of developing exacerbations and ameliorate

pulmonary function in patients who were on a high dose of ICS.<sup>[60]</sup> Antileukotrienes have been suggested for the treatment of severe asthmatics who are sensitive to NSAIDs.<sup>[61,62]</sup> Omalizumab, a recombinant humanized anti-Immunoglobulin-E antibody, has been found to reduce exacerbations and hospital visits in patients who suffer severe exacerbations in spite of using high-dose ICS and LABA.<sup>[63,64]</sup>

Comorbidities associated with severe asthma exacerbations such as smoking, potential triggering factors, intake of NSAIDs, recurrent respiratory tract infections, and chronic sinusitis need to be kept in check in patients who are prone to exacerbations. A close interaction between the health-care providers and the patient is necessary where the patient is educated about asthma, the various medications prescribed, correct use of inhaler and self-monitoring. A written asthma action plan should be provided to the patient to help them know how to distinguish a true exacerbation, and how to respond to it.<sup>[14]</sup> With adequate research, it might be possible to identify the “exacerbation-prone phenotype” of asthma with the help of genetic markers and deliver better care for these patients.

## CONCLUSION

Asthma is a chronic disease affecting the airways. Inflammation and hyperresponsiveness of the bronchial tubes and hindrance to airflow leads to the symptoms of asthma. Exacerbations must be considered separately from the level of control when evaluating asthma, because exacerbations may occur despite adequate symptom control, increase in maintenance medication and activity limitation. There exists a cluster of patients with the “exacerbation-prone phenotype,” who suffer from more frequent and severe exacerbations than other asthmatics. Inadequate symptom control, improper adherence to medication, psychological impairment, smoking, chronic sinusitis, rhinitis, viral infections of the respiratory tract, gastroesophageal reflux, and sleep disturbances are potential contributing factors for severe exacerbations. A lower perception of dyspnea, use of higher doses of steroids or SABA, high variability in peak expiratory flow, quick fall in the prebronchodilator FEV<sub>1</sub>/FVC ratio, low FEV<sub>1</sub>, higher sputum eosinophil and neutrophil count, and an increase in exhaled nitric oxide levels are predictors of exacerbation-prone disease. The single inhaler maintenance and reliever therapy are beneficial in the treatment of exacerbation-prone asthma. In this therapy, formoterol and budesonide are dispensed together to be used as a reliever and controller. In conclusion, close interaction between the health-care providers and patients, good self-management, awareness about the asthma, control of precipitating factors along with adequate therapy will help exacerbation-prone patients to better cope up with asthma. The single inhaler therapy helps in decreasing the risk of future exacerbations in asthma

patients, and it should be adopted as a standard care for asthma management.

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## Conflicts of interest

Dr. Nila Velayudhan and Dr Jayakumar G are employees of AstraZeneca Pharma India Ltd.

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