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Therapeutic strategies to reduce asthma exacerbations

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Asthma exacerbations can occur in patients with all degrees of asthma severity. They generally develop over 5 to 7 days and are most often initiated by an upper respiratory tract infection (usually with human rhinovirus) or by environmental allergen exposure in atopic subjects. Inhaled corticosteroids (ICSs) taken on a regular basis are very effective in reducing the risk of asthma exacerbations, and the combination of ICSs and long-acting inhaled β_2 -agonists further reduces this risk. In addition, use of the combination of the ICS budesonide and the long-acting inhaled β_2 -agonist formoterol, both as maintenance asthma treatment and also as rescue treatment (instead of a short-acting inhaled β_2 -agonist), has a significant further beneficial effect on asthma exacerbation risk. Other therapies that have been demonstrated to reduce severe asthma exacerbations are leukotriene receptor antagonists, which have been demonstrated to be effective most consistently in this regard in children, and anti-IgE mAbs, which are effective in subjects with difficult-to-treat allergic asthma. Approximately 50% of severe asthma exacerbations are eosinophilic in nature, whereas many of the remaining are neutrophilic. Several studies have demonstrated that making asthma treatment decisions based on minimizing airway eosinophil numbers (measured in induced sputum) can reduce the risks of severe exacerbations. In addition, treatment of patients with severe asthma with an anti-IL-5 mAb also reduces the number of severe asthma exacerbations, demonstrating a central role of eosinophils in many exacerbations. (*J Allergy Clin Immunol* 2011;■■■:■■■-■■■.)

Key words: Asthma, treatment, inhaled corticosteroids, leukotriene antagonist, long-acting β_2 -agonists, anti-IgE

Asthma exacerbations are common events in the lives of asthmatic patients. They pose the greatest risk for such patients, and they incur the greatest asthma-related treatment costs for the health care system and for society in general.¹ Asthma

Abbreviations used

HRV: Human rhinovirus

ICS: Inhaled corticosteroid

LABA: Long-acting inhaled β_2 -agonist

exacerbations range in severity from mild transient events lasting 1 to 2 days (previously called mild exacerbations) to severe life-threatening events. Mild exacerbations are now accepted to be part of poor current asthma control and have different therapeutic approaches to severe events.² A recently published American Thoracic Society/European Respiratory Society statement³ defines severe asthma exacerbations as events that require urgent action on the part of the patient and physician to prevent a serious outcome, such as hospitalization or death from asthma, and moderate exacerbations as events that should result in a temporary change in treatment in an effort to prevent the exacerbation from coming severe. Mild exacerbations were not differentiated because these episodes are only just outside the normal range of variation for the individual patient and difficult to distinguish from transient loss of asthma control.³

Severe asthma exacerbations can occur in patients with all degrees of asthma severity. Although their frequency can be increased in patients with difficult-to-control asthma, even patients considered to have mild, easy-to-treat asthma can experience severe asthma exacerbations,⁴ which are sometimes fatal.⁵ In a large clinical trial that enrolled patients with mild asthma who were followed for 1 year, the rate of severe exacerbations was almost 1 per patient per year.⁴

A common misperception of severe asthma exacerbations is that they are frequently sudden catastrophic events. In fact, almost all severe exacerbations develop over 5 to 7 days, with a gradual increase in asthma symptoms and deterioration in lung function before the exacerbation is recognized as an event requiring urgent intervention (*Fig 1*).^{6,7} Once treatment for the severe exacerbation is initiated, most will resolve over 7 to 10 days (*Fig 1*).⁷

Severe asthma exacerbations are very often preceded by an upper respiratory tract infection (usually with human rhinovirus [HRV])^{8,9} or by environmental allergen exposure in atopic patients.¹⁰ However, despite the fact that all children, including asthmatic patients, are infected with 1 or more strains of HRV each year, not all infections are associated with severe exacerbations. This has led to the speculation that HRV (or other respiratory tract viruses) acts as a cofactor in initiating acute severe events but that other conditions need to exist for this to happen and that respiratory tract viruses and environmental allergens interact to precipitate asthma exacerbations to an extent that neither alone can achieve. This is supported by epidemiologic evidence, which has indicated that the risks of being hospitalized with

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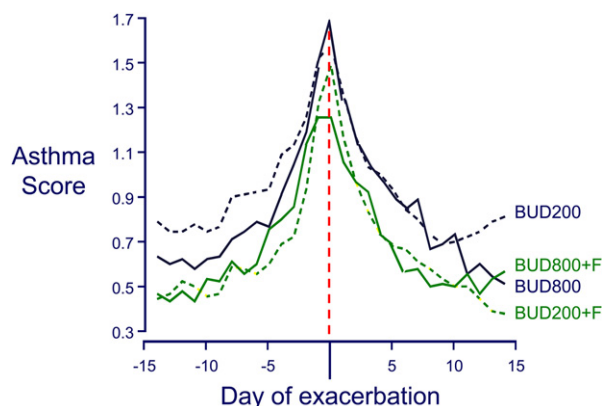


FIG 1. Time of onset of the severe asthma exacerbations identified in the Formoterol and Corticosteroids Establishing Therapy study.⁷ Asthma symptom scores increased over 5 to 7 days before the exacerbations were recognized by the managing health care professional and treatment with oral corticosteroids was started (dashed line). The exacerbation resolved over 5 to 7 days on treatment. Redrawn from data in Tattersfield et al.⁶ BUD, Budesonide; F, formoterol.

severe asthma exacerbations are increased by allergen sensitization alone (risk ratio, 2.3; 95% CI, 1.0-5.4) and further increased by the combination of sensitization, high exposure to 1 or more allergens, and viral detection (risk ratio, 8.4; 95% CI, 2.1-32.8).¹¹

Although severe asthma exacerbations are usually relatively transient events, with full symptomatic recovery by the patient, they can be associated with a decrease in lung function, which does not fully recover after the exacerbation has been treated and is resolved.¹²

PREVENTION OF SEVERE ASTHMA EXACERBATIONS

The purpose of asthma treatment is to attempt to achieve total asthma control.^{13,14} Asthma control consists of 2 domains: current control (impairment), which reflects the day-to-day symptoms an asthmatic patient experiences and the burden imposed by these symptoms, and future risk, which consists of asthma exacerbations, irreversible decrease in lung function, and side effects from asthma medications.¹³ Thus the prevention of asthma exacerbations is an important component of establishing ideal asthma control.

Inhaled corticosteroids

The regular use of inhaled corticosteroids (ICSs) remains the most effective therapeutic strategy to reduce the risk of asthma exacerbations. This benefit was identified in studies conducted shortly after the introduction of ICSs¹⁵⁻¹⁷; however, the first prospective evaluation of a dose-response benefit of ICSs in a study in which severe asthma exacerbations were the primary outcome variable was reported in 1997.⁷ This study evaluated asthmatic patients already taking moderate doses of ICSs but with poorly controlled asthma. During a run-in period, all patients were treated with high doses of ICSs (budesonide, 1600 µg/d) to try to achieve good control and were then randomized to low (budesonide, 200 µg/d) or moderate (budesonide, 800 µg/d) doses of ICSs. The risks of severe asthma exacerbations were reduced by almost 50% in the group receiving the higher dose of budesonide,

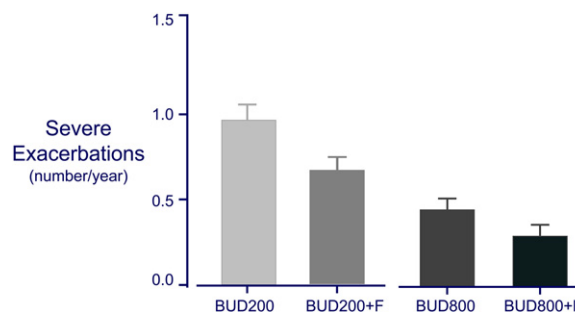


FIG 2. Number of severe asthma exacerbations (per patient per year) in the Formoterol and Corticosteroids Establishing Therapy study.⁷ A 4-fold increase in the ICS budesonide alone reduced severe asthma exacerbations by 50%. The addition of the LABA formoterol further reduced severe exacerbations when added to either the low or higher dose of budesonide. Reproduced with permission from Pauwels et al.⁷ BUD, Budesonide; F, formoterol.

from an annualized rate of 0.91 severe exacerbations per patient per year to 0.46 exacerbations per patient per year (Fig 2).⁷ An even larger magnitude of benefit was observed when a similar study was completed in patients with milder asthma who were not taking ICSs at the time of randomization, from 0.77 severe exacerbations per patient per year to 0.29 severe exacerbations per patient per year, a 74% reduction (Fig 3, group A).¹⁸

A similar benefit of ICS treatment in reducing severe asthma exacerbations has been demonstrated in pediatric asthmatic patients,¹⁹ and ICSs have been shown to be superior to the antileukotriene agent montelukast in this regard in children.²⁰ The corticosteroid budesonide has also been evaluated as a nebulized solution in very young children (age, 2-3 years) and again was demonstrated to be effective in reducing exacerbations,²¹ but this benefit was lost once the nebulized budesonide was discontinued. This lack of continuing benefit after discontinuation of ICSs has also been demonstrated in older children.²²

ICSs appear to achieve much of their clinical benefit from reducing the number and state of activation of airway eosinophils.^{23,24} Approximately 50% of severe asthma exacerbations are associated with an increase in airway eosinophil numbers,²⁵ whereas in others there is prominent airway neutrophilia.^{25,26} Several studies have shown that titrating the daily ICS dosage to normalize airway eosinophil numbers significantly reduces severe asthma exacerbations.^{27,28} The fact that ICSs do not reduce the numbers or activation of airway neutrophils and indeed prolong their survival²⁹ might largely explain why ICS treatment does not appear to eliminate the risk of all severe asthma exacerbations; although this has never been formally demonstrated, eosinophilic asthma exacerbations can, however, still occasionally occur in patients with difficult-to-treat asthma who are using ICSs.^{30,31}

Inhaled β_2 -agonists

All asthma treatment guidelines recommend rapid-acting inhaled β_2 -agonists for symptom relief.^{13,14,32} These have been with either short-acting drugs (short-acting β_2 -agonists, such as salbutamol or terbutaline) or long-acting drugs (long-acting inhaled β_2 -agonists [LABAs], such as formoterol). Interestingly, the use of formoterol as reliever therapy in patients receiving maintenance ICS therapy has been shown to reduce the risk of

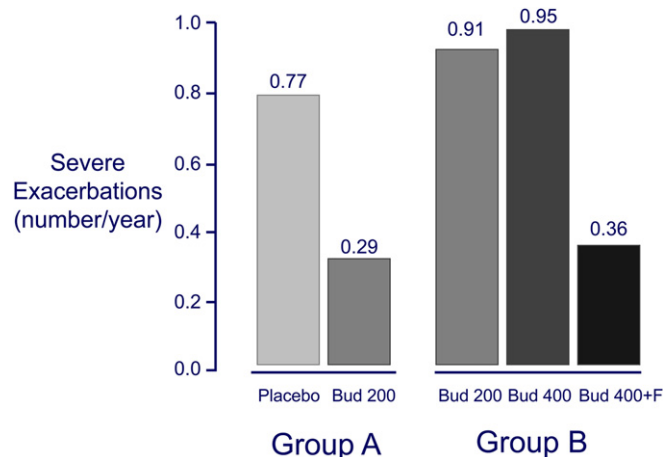


FIG 3. Number of severe asthma exacerbations (per patient per year) in the Optimal Management of Asthma study.¹⁸ The study consisted of 2 populations: group A, who were steroid naïve at the time of study enrollment, and group B, who were already receiving low-dose ICS treatment at the time of study enrollment. In group A low-dose budesonide alone markedly reduced severe exacerbations, whereas in group B doubling the dose of budesonide alone did not reduce severe exacerbations, but adding the LABA formoterol did reduce severe exacerbation risk. Redrawn from data in O'Byrne et al.¹⁸ BUD, Budesonide; F, formoterol.

severe exacerbations when compared with terbutaline.³³ However, none of the inhaled β_2 -agonists, which provide rapid bronchodilation and symptom relief, have been convincingly shown to treat the underlying asthmatic inflammatory process.³⁴ Indeed, the regular use of salbutamol has been demonstrated to increase the airway inflammatory response to inhaled allergens,³⁵ and overuse of β_2 -agonists when used as monotherapy in asthma has been associated with severe asthma exacerbations, resulting in asthma hospitalizations and even increased asthma mortality.^{36,37} Thus although rapid-acting inhaled β_2 -agonists are very effective bronchodilators and useful for the relief of asthma symptoms, their use should be intermittent and, with good asthma control, infrequent. Concerns about the adverse effects of using inhaled LABAs has resulted in a “black box” warning about their use being associated with increasing severe asthma-related events and even asthma death in some countries, including the United States and Canada.

Combination inhalers with ICSs and LABAs

Concerns about the use of LABAs as monotherapy for asthma and the evidence of a deleterious effect that exists for some patients³⁸ in the early 1990s resulted in the development of a clinical trial being designed, which examined whether combinations of ICSs and LABAs change the risks of severe asthma exacerbations when compared with ICS treatment alone.⁷ As described above, the patient population was asthmatic patients with poorly controlled asthma and a history of prior severe exacerbations. The study demonstrated that the combination of the ICS budesonide and the LABA formoterol significantly reduced the risks of both mild and severe asthma exacerbations when compared with the same doses of the ICS alone. The annualized rate of severe exacerbations was reduced from 0.46 per patient per year with the higher dose of budesonide alone to 0.34 per patient per year⁷ when this dose was combined with a LABA (Fig 2). This

benefit of combination therapy with ICSs and LABAs on reducing severe exacerbations has been reproduced in many studies with this and other combinations of ICSs and LABAs (Fig 3, group B).³⁹⁻⁴¹

The mechanism by which the combination of ICSs/LABAs reduces asthma exacerbations remains unclear. A clinical model of a mild asthma exacerbation is allergen inhalation challenge in patients with mild asthma.⁴² Allergen challenge induced transient eosinophilic and basophilic airway inflammation,^{43,44} which is associated with airflow obstruction (the early and late asthmatic responses) and a transient change in airway hyperresponsiveness.⁴⁵ The ability of the combination of ICSs/LABAs to attenuate these allergen-induced responses when compared with an ICS alone has been reported.⁴⁶ This study demonstrated that the combination was significantly superior to the ICS alone in reducing allergen-induced airway eosinophilia, as well as the physiological consequences of allergen inhalation. Thus the benefits of the anti-inflammatory effects of the ICS, together with the LABA as a bronchodilator and a functional antagonist (protecting against bronchoconstrictor stimuli), and the synergism of the combination on airway eosinophilic inflammation might explain the added benefit in reducing severe exacerbations.

Combination inhalers with ICSs and LABAs as maintenance and reliever therapy

A hypothesis has been developed that has postulated that using a combination inhaler containing both an ICS and a rapid-onset LABA for both regular maintenance therapy and reliever therapy would be advantageous when compared with using an inhaled β_2 -agonist as needed. This implies that the additional anti-inflammatory effect of the ICS, which is achieved when the combination is used for symptom relief, would provide additional clinical benefit, particularly in reducing the risks of severe asthma exacerbations, which are known to be associated with worsening airway inflammation, as well as increasing symptoms.

The evaluation of this hypothesis was possible with the combination inhaler containing budesonide/formoterol. This is because formoterol has an onset of bronchodilator action within the first minute,⁴⁷ with a similar efficacy and safety to salbutamol, even in patients with acute severe asthma,⁴⁸ and its pharmacological characteristics demonstrate a dose-response effect in which increasing doses provide additional benefit,⁴⁹ which is not the case with salmeterol.^{49,50}

This approach has been evaluated in several large studies that have consistently demonstrated that the combination of budesonide/formoterol for both maintenance and symptom relief reduces severe exacerbations requiring medical intervention and exposure to oral steroids, reducing reliever medication use and nighttime symptoms, including awakenings, and improves lung function when compared with either budesonide/formoterol or a 4-fold higher dose of budesonide for maintenance therapy, both with short-acting β_2 -agonists for relief.⁵¹⁻⁵³ The benefits were seen in both children⁵⁴ and adults⁵¹ with moderate to severe asthma not controlled with moderate doses of ICSs (some also receiving LABAs) at randomization, all of whom have had a previous history of severe asthma exacerbations. This benefit was also achieved with lower maintenance doses of ICSs in the combination arm by using ICSs/LABAs as maintenance and reliever. In addition, the benefit of using another combination of

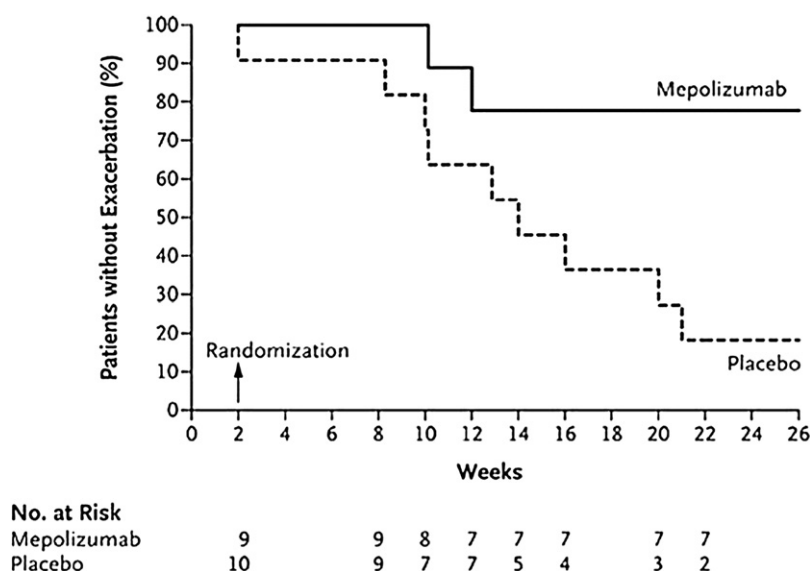


FIG 4. Kaplan-Meier analysis of the proportion of patients without an asthma exacerbation. Both patient groups had a structured reduction of maintenance oral prednisone during the study. The mepolizumab-treated patients did not experience an eosinophilic asthma exacerbation during the study, whereas this occurred in 9 of 10 patients receiving placebo. Reproduced with permission from Nair et al.³¹

ICSs/LABAs (beclomethasone and formoterol) as reliever therapy has been shown in a milder population of asthmatic patients.⁵⁵

The mechanism by which the combination of ICSs/LABAs containing formoterol reduces the risk of severe asthma exacerbations is not yet explained. Asthma exacerbations generally develop over a period of 5 to 7 days, before the exacerbation is recognized and treatment is initiated, during which patients experience deteriorating symptoms and lung function (Fig 1).⁶ This suggests that there is an opportunity to intervene early with an increase in ICS dose for several days before the exacerbation becomes severe enough to require medical intervention. However, studies that have doubled the maintenance dose of ICSs well into the course of an exacerbation have failed to show added benefits.^{56,57} These interventions have usually been in response to a fixed increase in symptoms and a decrease in lung function (as dictated by study protocol), which is likely too late for the increased dose of ICS to have benefit. It is plausible but not yet proved that using the combination containing an ICS/formoterol for maintenance and relief more effectively treats the worsening inflammation because ICSs are always delivered when the combination is used to relieve the increase in symptoms, which occur early in the development of an exacerbation. Although this treatment approach has been approved for use in almost all countries, it is not approved in the United States.

Antileukotrienes

Drugs that inhibit the synthesis of the cysteinyl leukotrienes or their receptors have been demonstrated to be effective in the treatment of asthma.^{58,59} Initial studies of the efficacy of this class of asthma medication focused on their ability to improve lung function and reduce symptoms^{60,61} or reduce exercise-induced⁶² or allergen-induced^{63,64} bronchoconstriction. More recently, antileukotrienes have been shown to reduce the risks of asthma

exacerbations, both in preschool⁶⁵ and older⁶⁶ children. Many severe asthma exacerbations in children occur shortly after return to school after the summer vacation.⁶⁷ This increase is associated with viral respiratory tract infections (particularly HRV), and the leukotriene receptor antagonist montelukast has been shown to reduce this increase.⁶⁶ There are also studies demonstrating that antileukotrienes reduce asthma exacerbations in adults,^{61,68} and clinical benefit has been described in using montelukast in the management of acute episodes in the emergency department.⁶⁹

Anti-IL-5 mAbs

Approximately 50% of severe asthma exacerbations are eosinophilic in nature,²⁵ whereas many of the remaining exacerbations are neutrophilic. Several studies have demonstrated that making asthma treatment decisions based on minimizing airway eosinophil numbers (measured in induced sputum) can reduce the risks of severe exacerbations.^{27,28} Some patients (approximately 40% to 50%) with difficult-to-treat asthma have persistent airway eosinophilia despite treatment with high-dose ICSs or sometimes with oral corticosteroids. The treatment of these difficult-to-treat patients with airway eosinophilia with the anti-IL-5 mAb mepolizumab has been shown to reduce the number of severe asthma exacerbations,^{30,31} demonstrating a central role of eosinophils in causing asthma exacerbations in these patients (Fig 4). Treatment with the anti-IL-5 mAb was initially not thought to provide any clinical benefit in patients with difficult-to-treat asthma in this study.⁷⁰ This is because the patients randomized were not selected as having persistent airway eosinophilia. However, even in this study, there was a nonsignificant trend toward a reduction in severe asthma exacerbations with treatment with mepolizumab. However, this therapy is not yet approved in any country for the treatment of difficult-to-treat asthma.

Anti-IgE mAb

An mAb directed against IgE, omalizumab, is available for the treatment of allergic asthma, and asthma treatment guidelines recommend its use in adults with difficult-to-treat asthma who are sensitized to environmental allergens. Omalizumab has been effective in reducing asthma exacerbation risk in this patient population^{71,72} and more recently in inner-city allergic asthmatic children and adolescents.⁷³ The antibody is, in general, well tolerated, but reports have identified rare episodes of anaphylaxis after administration.^{74,75} This occurs in less than 0.1% of treated patients.⁷⁴ Its high cost has also limited its use in patients with difficult-to-treat asthma.

Bronchial thermoplasty

The most recent approach to the treatment of difficult-to-treat asthma is bronchial thermoplasty, which has been approved in some countries. This requires the patient to undergo fiberoptic bronchoscopy, and the central airways are treated with radiofrequency energy that is converted to heat (65°C) in the airway wall. This heat ablates airway smooth muscle without causing any other damage to the airways.^{76,77} Initial studies of this treatment demonstrated clinical benefit in reducing symptoms and improving lung function and reducing mild asthma exacerbations.^{78,79} A subsequent study has also demonstrated a significant reduction in severe asthma exacerbations.⁸⁰ This treatment approach is associated with occasional need for hospitalization of patients after fiberoptic bronchoscopy,⁷⁷ but long-term follow-up has not raised any safety concerns, and the clinical benefit appears to be maintained.⁷⁹

CONCLUSIONS

Severe asthma exacerbations can occur in any asthmatic patient and have potential long-term consequences with regard to a decrease in lung function. ICS treatment is very effective in reducing severe exacerbations when used as monotherapy, and the combination of an ICS with a LABA provides even more protection. In patients with a history of severe exacerbations, using ICS/LABA combinations, which contain the LABA formoterol, both as maintenance and rescue treatment has been shown to be superior to any treatment approach, which uses β_2 -agonist alone as rescue treatment. In patients with childhood asthma, treatment with a leukotriene receptor antagonist reduces virus-induced asthma exacerbations. Patients with difficult-to-treat asthma with persisting airway eosinophilia despite combination treatment might demonstrate a reduction in asthma exacerbation risk with the use of an anti-IL-5 mAb, whereas in difficult-to-treat patients with allergic asthma, a similar benefit might be obtained with an anti-IgE mAb. The most recent innovation has been the demonstration that bronchial thermoplasty reduced the exacerbation risk in patients with difficult-to-treat asthma.

The recognition of the importance and effect of severe asthma exacerbations has resulted in their enumeration being included in almost all large clinical trials of asthma treatment and their reduction as a pivotal outcome variable. Also, all treatment guidelines now recognize that elimination of exacerbation risk is a requirement for good asthma control.

What do we know?

- Regular use of ICSs is the single most effective way to reduce the risk of severe asthma exacerbations.
- Additional benefit can be obtained with the regular use of combinations of ICSs and LABAs.
- In patients with a history of previous severe asthma exacerbations, using a combination of an ICS and the rapid-onset LABA formoterol further reduces the risk of severe exacerbations.
- Other treatment approaches that have been demonstrated to reduce severe exacerbation risk include the use of a leukotriene receptor antagonist or omalizumab, an mAb directed against IgE; mepolizumab, an mAb directed against IL-5; or bronchial thermoplasty.

What is still unknown?

- Some severe asthma exacerbations are characterized by an airway neutrophilic response. The efficacy of current treatment approaches in preventing this type of asthma exacerbation remains unclear.
- The mechanisms by which asthma treatments reduce exacerbation risk are unknown.
- Severe asthma exacerbations are associated with a more rapid loss of FEV₁. This effect is attenuated by the regular use of ICSs. Whether other asthma treatments, which reduce exacerbation risk, have a similar benefit remains unknown.

REFERENCES

1. Barnett SB, Nurmagambetov TA. Costs of asthma in the United States: 2002-2007. *J Allergy Clin Immunol* 2011;127:145-52.
2. O'Byrne PM, Parameswaran K. Pharmacological management of mild or moderate persistent asthma. *Lancet* 2006;368:794-803.
3. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009;180:59-99.
4. Gauvreau GM, Parameswaran KN, Watson RM, O'Byrne PM. Inhaled leukotriene E(4), but not leukotriene D(4), increased airway inflammatory cells in subjects with atopic asthma. *Am J Respir Crit Care Med* 2001;164:1495-500.
5. Robertson CF, Rubinfeld AR, Bowes G. Deaths from asthma in Victoria: a 12-month survey. *Med J Aust* 1990;152:511-7.
6. Tattersfield AE, Postma DS, Barnes PJ, Svensson K, Bauer CA, O'Byrne PM, et al. Exacerbations of asthma: a descriptive study of 425 severe exacerbations. The FACET International Study Group. *Am J Respir Crit Care Med* 1999;160:594-9.
7. Pauwels RA, Lofdahl CG, Postma DS, Tattersfield AE, O'Byrne P, Barnes PJ, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. *N Engl J Med* 1997;337:1405-11.
8. Johnston SL, Pattermore PK, Sanderson G, Smith S, Campbell MJ, Josephs LK, et al. The relationship between upper respiratory infections and hospital admissions for asthma: a time-trend analysis. *Am J Respir Crit Care Med* 1996;154:654-60.
9. Johnston SL, Pattermore PK, Sanderson G, Smith S, Lampe F, Josephs L, et al. Community study of role of viral infections in exacerbations of asthma in 9-11 year old children. *BMJ* 1995;310:1225-9.
10. Boulet LP, Cartier A, Thomson NC, Roberts RS, Dolovich J, Hargreave FE. Asthma and increases in nonallergic bronchial responsiveness from seasonal pollen exposure. *J Allergy Clin Immunol* 1983;71:399-406.
11. Green RM, Custovic A, Sanderson G, Hunter J, Johnston SL, Woodcock A. Synergism between allergens and viruses and risk of hospital admission with asthma: case-control study. *BMJ* 2002;324:763.

12. O'Byrne PM, Pedersen S, Lamm CJ, Tan WC, Busse WW. Severe exacerbations and decline in lung function in asthma. *Am J Respir Crit Care Med* 2009;179:19-24.
13. Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma—summary report 2007. *J Allergy Clin Immunol* 2007;120(suppl):S94-138.
14. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, Fitzgerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J* 2008;31:143-78.
15. Juniper EF, Kline PA, Vanzieleghe MA, Ramsdale EH, O'Byrne PM, Hargreave FE. Effect of long-term treatment with an inhaled corticosteroid (budesonide) on airway hyperresponsiveness and clinical asthma in nonsteroid-dependent asthmatics. *Am Rev Respir Dis* 1990;142:832-6.
16. Juniper EF, Kline PA, Vanzieleghe MA, Ramsdale EH, O'Byrne PM, Hargreave FE. Long-term effects of budesonide on airway responsiveness and clinical asthma severity in inhaled steroid-dependent asthmatics. *Eur Respir J* 1990;3:1122-7.
17. Dahl R, Lundback B, Malo JL, Mazza JA, Nieminen MM, Saarelainen P, et al. A dose-ranging study of fluticasone propionate in adult patients with moderate asthma. International Study Group. *Chest* 1993;104:1352-8.
18. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med* 2001;164:1392-7.
19. Bisgaard H. Use of inhaled corticosteroids in pediatric asthma. *Pediatr Pulmonol Suppl* 1997;15:27-33.
20. Covar RA, Szefer SJ, Zeiger RS, Sorkness CA, Moss M, Mauger DT, et al. Factors associated with asthma exacerbations during a long-term clinical trial of controller medications in children. *J Allergy Clin Immunol* 2008;122:741-7.
21. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefer SJ, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;354:1985-97.
22. Strunk RC, Sternberg AL, Szefer SJ, Zeiger RS, Bender B, Tonascia J. Long-term budesonide or nedocromil treatment, once discontinued, does not alter the course of mild to moderate asthma in children and adolescents. *J Pediatr* 2009;154:682-7.
23. Gibson PG, Salto N, Borgas T. Airway mast cells and eosinophils correlate with clinical severity and airway hyperresponsiveness in corticosteroid-treated asthma. *J Allergy Clin Immunol* 2000;105:752-9.
24. Brightling CE, Green RH, Pavord ID. Biomarkers predicting response to corticosteroid therapy in asthma. *Treat Respir Med* 2005;4:309-16.
25. Turner MO, Hussack P, Sears MR, Dolovich J, Hargreave FE. Exacerbations of asthma without sputum eosinophilia. *Thorax* 1995;50:1057-61.
26. Fahy JV, Kim KW, Liu J, Boushey HA. Prominent neutrophilic inflammation in sputum from subjects with asthma exacerbation. *J Allergy Clin Immunol* 1995;95:843-52.
27. Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;360:1715-21.
28. Jayaram L, Pizzichini MM, Cook RJ, Boulet LP, Lemiere C, Pizzichini E, et al. Determining asthma treatment by monitoring sputum cell counts: effect on exacerbations. *Eur Respir J* 2006;27:483-94.
29. Cox G. Glucocorticoid treatment inhibits apoptosis in human neutrophils. Separation of survival and activation outcomes. *J Immunol* 1995;154:4719-25.
30. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009;360:973-84.
31. Nair P, Pizzichini MM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009;360:985-93.
32. British Thoracic Society and Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma: a national clinical guideline. London (UK): BMJ Publications; 2009.
33. Tattersfield AE, Lofdahl CG, Postma DS, Eivindson A, Schreurs AG, Rasidakis A, et al. Comparison of formoterol and terbutaline for as-needed treatment of asthma: a randomised trial. *Lancet* 2001;357:257-61.
34. McIvor RA, Pizzichini E, Turner MO, Hussack P, Hargreave FE, Sears MR. Potential masking effects of salmeterol on airway inflammation in asthma. *Am J Respir Crit Care Med* 1998;158:924-30.
35. Gauvreau GM, Jordana M, Watson RM, Cockcroft DW, O'Byrne PM. Effect of regular inhaled albuterol on allergen-induced late responses and sputum eosinophils in asthmatic subjects. *Am J Respir Crit Care Med* 1997;156:1738-45.
36. Suissa S, Ernst P, Boivin JF, Horwitz RI, Habbick B, Cockcroft D, et al. A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. *Am J Respir Crit Care Med* 1994;149:604-10.
37. Spitzer WO, Suissa S, Ernst P, Horwitz RI, Habbick B, Cockcroft D, et al. The use of beta-agonists and the risk of death and near death from asthma. *N Engl J Med* 1992;326:501-6.
38. Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *BMJ* 1993;306:1034-7.
39. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med* 2004;170:836-44.
40. Stanford RH, Fuhlbrigge A, Riedel A, Rey GG, Stempel DA. An observational study of fixed dose combination fluticasone propionate/salmeterol or fluticasone propionate alone on asthma-related outcomes. *Curr Med Res Opin* 2008;24:3141-8.
41. Papi A, Paggiaro PL, Nicolini G, Vignola AM, Fabbri LM. Beclomethasone/formoterol versus budesonide/formoterol combination therapy in asthma. *Eur Respir J* 2007;29:682-9.
42. O'Byrne PM, Dolovich J, Hargreave FE. Late asthmatic responses. *Am Rev Respir Dis* 1987;136:740-51.
43. Gauvreau GM, Watson RM, O'Byrne PM. Kinetics of allergen-induced airway eosinophilic cytokine production and airway inflammation. *Am J Respir Crit Care Med* 1999;160:640-7.
44. Gauvreau GM, Lee JM, Watson RM, Irani AM, Schwartz LB, O'Byrne PM. Increased numbers of both airway basophils and mast cells in sputum after allergen inhalation challenge of atopic asthmatics. *Am J Respir Crit Care Med* 2000;161:1473-8.
45. O'Byrne PM. Allergen-induced airway hyperresponsiveness. *J Allergy Clin Immunol* 1988;81:119-27.
46. Kelly MM, O'Connor TM, Leigh R, Otis J, Gwozd C, Gauvreau GM, et al. Effects of budesonide and formoterol on allergen-induced airway responses, inflammation, and airway remodeling in asthma. *J Allergy Clin Immunol* 2010;125:349-56.
47. Palmqvist M, Persson G, Lazer L, Rosenborg J, Larsson P, Lotvall J. Inhaled dry-powder formoterol and salmeterol in asthmatic patients: onset of action, duration of effect and potency. *Eur Respir J* 1997;10:2484-9.
48. Balanag VM, Yunus F, Yang PC, Jorup C. Efficacy and safety of budesonide/formoterol compared with salbutamol in the treatment of acute asthma. *Pulm Pharmacol Ther* 2006;19:139-47.
49. Palmqvist M, Ibsen T, Mellen A, Lotvall J. Comparison of the relative efficacy of formoterol and salmeterol in asthmatic patients. *Am J Respir Crit Care Med* 1999;160:244-9.
50. Woolcock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. *Am J Respir Crit Care Med* 1996;153:1481-8.
51. O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005;171:129-36.
52. Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet* 2006;368:744-53.
53. Bousquet J, Boulet LP, Peters MJ, Magnussen H, Quirarte J, Martinez-Aguilar NE, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. *Respir Med* 2007;101:2437-46.
54. Bisgaard H, Le RP, Bjammer D, Dymek A, Vermeulen JH, Hultquist C. Budesonide/formoterol maintenance plus reliever therapy: a new strategy in pediatric asthma. *Chest* 2006;130:1733-43.
55. Papi A, Canonica GW, Maestrelli P, Paggiaro P, Olivieri D, Pozzi E, et al. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. *N Engl J Med* 2007;356:2040-52.
56. FitzGerald JM, Becker A, Sears MR, Mink S, Chung K, Lee J. Doubling the dose of budesonide versus maintenance treatment in asthma exacerbations. *Thorax* 2004;59:550-6.
57. Harrison TW, Osborne J, Newton S, Tattersfield AE. Doubling the dose of inhaled corticosteroid to prevent asthma exacerbations: randomised controlled trial. *Lancet* 2004;363:271-5.
58. Drazen JM, Israel E, O'Byrne PM. Treatment of asthma with drugs modifying the leukotriene pathway. *N Engl J Med* 1999;340:197-206.
59. O'Byrne PM, Israel E, Drazen JM. Antileukotrienes in the treatment of asthma. *Ann Intern Med* 1997;127:472-80.
60. Israel E, Rubin P, Kemp JP, Grossman J, Pierson W, Siegel SC, et al. The effect of inhibition of 5-lipoxygenase by zileuton in mild-to-moderate asthma. *Ann Intern Med* 1993;119:1059-66.
61. Reiss TF, Chervinsky P, Dockhorn RJ, Shingo S, Seidenberg B, Edwards TB. Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma: a multicenter, randomized, double-blind trial. Montelukast Clinical Research Study Group. *Arch Intern Med* 1998;158:1213-20.
62. Manning PJ, Watson RM, Margolskee DJ, Williams VC, Schwartz JI, O'Byrne PM. Inhibition of exercise-induced bronchoconstriction by MK-571, a potent leukotriene D4-receptor antagonist. *N Engl J Med* 1990;323:1736-9.

63. Taylor IK, O'Shaughnessy KM, Fuller RW, Dollery CT. Effect of cysteinyl-leukotriene receptor antagonist ICI 204,219 on allergen-induced bronchoconstriction and airway hyperreactivity in atopic subjects. *Lancet* 1991;337:690-4.
64. Hamilton AL, Watson RM, Wyile G, O'Byrne PM. Attenuation of early and late phase allergen-induced bronchoconstriction in asthmatic subjects by a 5-lipoxygenase activating protein antagonist, BAYx 1005. *Thorax* 1997;52:348-54.
65. Bisgaard H, Zielen S, Garcia-Garcia ML, Johnston SL, Gilles L, Menten J, et al. Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. *Am J Respir Crit Care Med* 2005;171:315-22.
66. Johnston NW, Mandhane PJ, Dai J, Duncan JM, Greene JM, Lambert K, et al. Attenuation of the September epidemic of asthma exacerbations in children: a randomized, controlled trial of montelukast added to usual therapy. *Pediatrics* 2007;120:e702-12.
67. Johnston NW, Johnston SL, Duncan JM, Greene JM, Keadze T, Keith PK, et al. The September epidemic of asthma exacerbations in children: a search for etiology. *J Allergy Clin Immunol* 2005;115:132-8.
68. Bjerner L, Bisgaard H, Bousquet J, Fabbri LM, Greening AP, Haastela T, et al. Montelukast and fluticasone compared with salmeterol and fluticasone in protecting against asthma exacerbation in adults: one year, double blind, randomised, comparative trial. *BMJ* 2003;327:891.
69. Ramsay CF, Pearson D, Mildenhall S, Wilson AM. Oral montelukast in acute asthma exacerbations: a randomised, double-blind, placebo-controlled trial. *Thorax* 2011;66:7-11.
70. Flood-Page P, Swenson C, Faierman I, Matthews J, Williams M, Brannick L, et al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. *Am J Respir Crit Care Med* 2007;176:1062-71.
71. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001;108:184-90.
72. Busse WW, Massanari M, Kianifard F, Geba GP. Effect of omalizumab on the need for rescue systemic corticosteroid treatment in patients with moderate-to-severe persistent IgE-mediated allergic asthma: a pooled analysis. *Curr Med Res Opin* 2007;23:2379-86.
73. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med* 2011;364:1005-15.
74. Cox L, Platts-Mills TA, Finegold I, Schwartz LB, Simons FE, Wallace DV. American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Report on omalizumab-associated anaphylaxis. *J Allergy Clin Immunol* 2007;120:1373-7.
75. Lin RY, Rodriguez-Baez G, Bhargava GA. Omalizumab-associated anaphylactic reactions reported between January 2007 and June 2008. *Ann Allergy Asthma Immunol* 2009;103:442-5.
76. Miller JD, Cox G, Vincic L, Lombard CM, Loomas BE, Danek CJ. A prospective feasibility study of bronchial thermoplasty in the human airway. *Chest* 2005;127:1999-2006.
77. Cox PG, Miller J, Mitzner W, Leff AR. Radiofrequency ablation of airway smooth muscle for sustained treatment of asthma: preliminary investigations. *Eur Respir J* 2004;24:659-63.
78. Cox G, Thomson NC, Rubin AS, Niven RM, Corris PA, Siersted HC, et al. Asthma control during the year after bronchial thermoplasty. *N Engl J Med* 2007;356:1327-37.
79. Pavord ID, Cox G, Thomson NC, Rubin AS, Corris PA, Niven RM, et al. Safety and efficacy of bronchial thermoplasty in symptomatic, severe asthma. *Am J Respir Crit Care Med* 2007;176:1185-91.
80. Castro M, Rubin AS, Laviolette M, Fiterman J, De Andrade LM, Shah PL, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. *Am J Respir Crit Care Med* 2010;181:116-24.