Prevention and control of acute exacerbations are among the primary goals of asthma management. The consequences of acute exacerbations range, depending on the severity of the exacerbation, from impairment in the patient’s well-being and reductions in ability to perform normal daily activities to severe airflow limitation resulting in hospitalization and, in rare cases, death. The appropriate management of mild or moderate exacerbations—ideally, by preventing them—can check the development of uncontrolled asthma, which can be life threatening. Although severe exacerbations require emergency intervention and are typically managed in the hospital setting, the vast majority of exacerbations are mild or moderate and are managed by primary care providers or clinic-based respiratory specialists (eg, allergists). Clinic-based health care providers thus can play a pivotal role in reducing asthma-associated morbidity and mortality by monitoring the occurrences of exacerbations in their patients with asthma and tailoring pharmacotherapy to the severity of disease so that most exacerbations are prevented. This slide set considers the role of exacerbations as a marker of asthma severity and discusses pharmacotherapeutic approaches to preventing asthma exacerbations.

References

Asthma is caused by chronic airway inflammation, which is mediated primarily by immune cells such as mast cells, eosinophils, T lymphocytes, and neutrophils. In asthma, immune cells accumulate in the lungs and, with the respiratory epithelial cells, release cytotoxic and inflammatory mediators that cause edema, excessive mucus secretion, impairment of mucociliary clearance, and increased reactivity of respiratory smooth muscle. These inflammatory changes in the airways lead to obstruction of airflow and airway hyperresponsiveness, the two cardinal clinical characteristics of asthma. Some level of airway inflammation is chronically present even in patients with mild asthma; exacerbations of asthma are attributed to acute increases in inflammatory activity above this baseline of chronic inflammation.

References

The close correspondence between inflammatory changes in the lung and the occurrence of asthma exacerbations renders exacerbations an important marker of severity of inflammation in asthma. The occurrence of exacerbations reflects increases in inflammation; interventions that prevent asthma exacerbations do so by reducing inflammation.

These considerations underline the importance of (1) monitoring exacerbations as a gauge of disease severity; and (2) assessing the effects of medications on asthma exacerbations—as well as medication effects on the traditional end points of lung function and asthma symptoms—in choosing among pharmacotherapeutic interventions. The remainder of the slide set considers each of these issues in turn.
Asthma Exacerbations as Gauge of Disease Severity

- Exacerbations reflect increases in inflammation.
- Monitoring and controlling mild exacerbations is as important as monitoring and controlling severe exacerbations.
- Early detection of asthma exacerbations can be facilitated through partnership of the health care provider and patient.

Severe exacerbations of asthma constitute one of the most common respiratory emergencies in medical practice, but they account for only a small minority of total asthma exacerbations, most of which are mild in severity. In a recent survey conducted in a region of Australia, for example, asthma exacerbations resulting in hospitalization or death—that is, those that consume the majority of health care resources—accounted for fewer than 2% of total exacerbations; it was estimated that more than 98% of exacerbations were managed in primary care settings.

While much of the focus of asthma management is devoted to the most severe exacerbations, control of mild exacerbations is no less important in ensuring the patient’s well-being over the long term. The early detection of asthma exacerbations can be facilitated through partnership of the health care provider and the patient in tracking the patient’s clinical status. The National Heart, Lung, and Blood Institute (NHLBI) guidelines for asthma management (available on the Internet at www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm) describe practical means by which the patient and health care provider can detect exacerbations early by monitoring signs and symptoms of asthma, pulmonary function, and functional status and by considering these measures in the context of the patient’s history of asthma exacerbations. The guidelines recommend that self-monitoring of asthma symptoms be supplemented by lung function measurements such as PEF because some patients do not perceive worsening airway obstruction based on their symptoms until airway obstruction is advanced.

References


The frequency and severity of asthma exacerbations are monitored so that asthma therapy can be adjusted as appropriate to control and, whenever possible, to prevent asthma exacerbations. Although asthma exacerbations have historically been neglected as a main end point in clinical studies in favor of measures of lung function and symptoms, exacerbations are increasingly routinely included in clinical studies as a core outcome measure as recognition of their clinical and prognostic significance has grown.

Long-term controller medications for asthma include inhaled corticosteroids, long-acting bronchodilators, and leukotriene modifiers. In keeping with the inflammatory etiology of asthma, anti-inflammatory pharmacotherapy is the cornerstone of asthma management. Inhaled corticosteroids are the standard of long-term controller therapy for the inflammatory component of persistent asthma because of their robust efficacy and potent anti-inflammatory activity.

Long-acting bronchodilators cause prolonged bronchodilation by relaxing airway smooth muscle. They are not directly anti-inflammatory and are not recommended as monotherapy for exacerbations. Long-acting β₂-agonists are often used in combination with anti-inflammatory therapy to provide control of symptoms.

Leukotriene-modifying agents are a relatively new class of therapy, the role of which in asthma management remains to be defined. In clinical trials conducted to date, leukotriene modifiers have been shown to produce modest improvements in symptoms and to reduce the need for short-acting β₂-agonists in mild to moderate asthma. The effects of each of these classes of therapy on asthma exacerbations have been assessed.

**Reference**

Effect of Inhaled Corticosteroid Versus Leukotriene Modifier

- Randomized, double-blind, multicenter study
- Patients with persistent asthma receiving maintenance inhaled corticosteroids were switched to fluticasone propionate (88 mcg twice daily; n = 221) or zafirlukast (20 mg twice daily; n = 216) for 6 weeks.


Although the effects of each of the main classes of controller therapy on asthma exacerbations have been studied, the comparative efficacy of these classes of long-term controller therapy at preventing asthma exacerbations has not been extensively assessed in head-to-head trials. Furthermore, the comparator trials that have been conducted are generally underpowered to detect differences among treatments in asthma exacerbations.

However, the results of one recent study suggest that the inhaled corticosteroid fluticasone propionate more effectively prevents asthma exacerbations than does the leukotriene receptor antagonist zafirlukast. Kim et al studied patients with persistent asthma who were receiving maintenance treatment with inhaled steroids and switched their therapies to either a low dose of inhaled fluticasone propionate (88 mcg twice daily; n=221) or zafirlukast (20 mg twice daily; n=216) for 6 weeks.

Reference

The results demonstrate that besides being more effective than zafirlukast at improving pulmonary function, asthma symptoms, and health-related quality of life, inhaled fluticasone propionate was more effective than zafirlukast at preventing asthma exacerbations, defined as worsening asthma symptoms requiring the use of rescue medication in addition to albuterol. Significantly fewer patients in the fluticasone propionate group (n = 5, or 2%) compared with the zafirlukast group (n = 14, or 6%) experienced an exacerbation (P = 0.035).

Reference
Whereas half of the exacerbations with inhaled fluticasone propionate were managed at the physician’s office and half were managed at home, the majority of exacerbations with zafirlukast required intervention by a health care provider (10/16 in the physician’s office and 1/16 in the emergency room). Possibly, the greater efficacy of inhaled fluticasone propionate compared with the leukotriene receptor antagonist at preventing exacerbations is attributed to the more widespread anti-inflammatory effects of the corticosteroid.

Reference
If asthma remains poorly controlled on low-dose inhaled corticosteroids, therapeutic alternatives include increasing the dose of the inhaled corticosteroid or adding another long-term controller medication such as a long-acting β₂-agonist. The addition of a long-acting β₂-agonist to an inhaled corticosteroid regimen has consistently been shown to be more effective at improving lung function and alleviating asthma symptoms than has increasing the dose of the inhaled corticosteroid. Results of several recent investigations extend these data by demonstrating that adding a long-acting β₂-agonist to an inhaled corticosteroid regimen is also more effective at preventing asthma exacerbations than increasing the dose of the inhaled corticosteroid.

For example, Matz et al combined data from two double-blind studies of 925 patients who remained symptomatic on a low dose (88 mcg twice daily) of the inhaled corticosteroid fluticasone propionate. Patients were randomized to receive either supplementary treatment with the long-acting β₂-agonist salmeterol (42 mcg twice daily) in addition to low-dose fluticasone propionate or to receive a higher dose of fluticasone propionate (220 mcg twice daily) for 24 weeks.

References

The results show that over the 24-week treatment period, patients receiving salmeterol in addition to fluticasone propionate experienced significantly fewer asthma exacerbations, defined as any asthma event that required treatment with oral or parenteral corticosteroids, than did the higher-dose fluticasone propionate group. The percentage of patients experiencing one or more exacerbations over the 24-week period was 8.8% for the group given the fluticasone propionate-salmeterol combination compared with 13.8% for the group given a higher dose of fluticasone propionate \((P = 0.017)\). The fluticasone propionate-salmeterol combination was superior to the higher-dose fluticasone propionate regimen regardless of degree of baseline airway obstruction (ie, mild to moderate obstruction with a baseline FEV\(_1\) of >60% to 85% of predicted value, or severe obstruction with a baseline FEV\(_1\) of 40% to 60% of predicted value). In addition to fewer exacerbations, the fluticasone propionate-salmeterol group demonstrated a significantly longer time to first exacerbation than did the group receiving a higher dose of fluticasone propionate \((P<0.05)\). These findings show that the combination of an inhaled corticosteroid and a long-acting \(\beta_2\)-agonist is more effective in preventing asthma exacerbations than increasing the dose of the inhaled corticosteroid.

**Reference**
Effect of Adding a Long-Acting $\beta_2$-Agonist Versus Adding a Leukotriene Modifier

- Randomized, double-blind, parallel-group clinical trial
- 447 patients remaining symptomatic on a low dose (88 mcg twice daily) of inhaled fluticasone propionate
- Patients randomized to receive fluticasone propionate (100 mcg twice daily) plus either salmeterol (50 mcg twice daily) or oral montelukast (10 mg once daily)

Recent findings also suggest that asthma exacerbations may be more effectively prevented with an inhaled corticosteroid/long-acting $\beta_2$-agonist combination than with an inhaled corticosteroid/leukotriene modifier combination. In a randomized, double-blind clinical trial, Nelson et al. compared the efficacy and tolerability of fluticasone propionate 100 mcg plus salmeterol 50 mcg twice daily with that of fluticasone propionate 100 mcg twice daily plus oral montelukast 10 mg once daily in patients with asthma who remained symptomatic on low-dose inhaled corticosteroid therapy.

Reference
The results demonstrate that besides producing significantly greater improvements in lung function and asthma symptoms, the fluticasone propionate/salmeterol combination more effectively prevented asthma exacerbations than did the fluticasone propionate/montelukast combination. The incidence of asthma exacerbations, defined as any requirement for rescue asthma medications, over the 12-week treatment period was significantly lower in the fluticasone propionate/salmeterol group (2%; \( P = 0.031 \)) compared with the fluticasone propionate/montelukast group (6%; \( P = 0.031 \)).

Reference
Conclusions

- By partnering with the patient in monitoring asthma severity and by choosing judiciously among pharmacotherapies for controlling exacerbations, clinic-based physicians can contribute to reductions in asthma morbidity and mortality.

- Addition of a long-acting $\beta_2$-agonist to an inhaled corticosteroid regimen confers more effective control of asthma exacerbations than:
  - Increasing the inhaled corticosteroid dose
  - Adding a leukotriene modifier

Considered together, these data provide new practical and theoretical insights about optimizing control of the inflammation that leads to asthma exacerbations. By partnering with the patient in monitoring asthma severity and by choosing judiciously among the pharmacotherapeutic options for controlling exacerbations, health care providers are better placed than ever before to contribute to reductions in asthma morbidity and mortality.

The clinical data show that the addition of a long-acting $\beta_2$-agonist to an inhaled corticosteroid regimen provides more effective control of asthma exacerbations than does (1) increasing the dose of the inhaled corticosteroid; or (2) the addition of the leukotriene modifier montelukast.