Over the last decade, asthma has been shown to be a chronic inflammatory disease. Even the mild asthmatic is known to have inflammatory changes in the airways. This knowledge has concentrated the research for new medications on methods to prevent or decrease the cascading inflammatory process. Initially, it was thought that research focusing on multiple mediators secreted during this inflammatory process would be beneficial. The high efficacy in clinical trials of drugs that block the synthesis or activity of the leukotriene (LT) family of mediators has modified that view.

Leukotrienes emerged in 1979 when they were identified as the slow-reacting substances of anaphylaxis (SRS-A). The past 20 years of research has expanded the knowledge of their role in the pathophysiology of asthma. As pro-inflammatory enzymes, leukotrienes are released when the mast cell erupts, causing a cascading series of events. LTs are the metabolites of the fatty acid arachidonate and are produced through the activity of 5-lipoxygenase (5-LO) and 5-lipoxygenase activating protein (FLAP). The inflammatory cascade results in the release of the unstable intermediate enzyme LTA4. LTA4 may be converted to LTB4 or LTC4 depending on the specific cell type. The role of LTB4 is unclear in asthma.

The action of the specific enzymes in the tissues and circulation results in further conversion of LTA4 to LTC4 to LTD4 and LTE4. LTC4, LTD4, and LTE4 are collectively referred to as the cysteinyl leukotrienes (CysLT). Their role as mediators has been the subject of multiple research studies over the past several years.

What occurs in asthma?
The submucosa is impacted by the leukotrienes through several factors. An increase in eosinophils occurs. The effect on bronchiolar smooth muscle results in bronchoconstriction. An over-production of mucus occurs as the leukotrienes affect the mucous (mucus-secreting) glands. They also play a role in mucociliary clearance and vascular permeability.

The CysLTs are implicated as particularly important mediators in the pathophysiology of asthma. Their bronchoconstriction effect has been shown to be 1,000 times more potent than...
histamine or methacholine in both normal and asthmatic subjects. Montelukast and zafirlukast are CysLT receptor antagonists. A reduction or prevention of LTD4-induced bronchoconstriction occurs as well as the attenuation of the early and late phase response after allergen and exercise challenge.

Cysteinyl LT antagonists in bronchial challenge

What is the effect of cysteinyl LT antagonists in bronchial challenge studies? Montelukast and zafirlukast appear to antagonize the CysLT receptors equally well in normal and asthmatic airways. Oral administration of the drug appears more effective than when given by inhalation. Bronchoconstriction induced by common triggers such as exercise, cold air, allergen, and aspirin is also reduced. The inflammatory cells in the airway wall release bronchoconstrictor substances with exercise. LTs play an important role in this response. The decrease in FEV1, post-exercise is less when patients are treated with CysLT antagonists. The recovery time post-exercise is substantially decreased.

Allergen challenges result in a mast cell-dependent early response followed by a late response in about 50 percent of the patients. This late reaction results in an infiltration of the airway by neutrophils, eosinophils, and T cells along with swelling of the airway wall. CysL Ts are responsible for a major portion of the airway obstruction observed in the early response, and at least one-half of the late response is attributed to the cysteinyl LTs.

What is the effect of CysLT antagonists on baseline lung function? Cysteinyl LT antagonists have been shown to produce bronchodilatation in stable asthma. This finding suggests that they contribute to the basal airway tone.

Impact on asthma disease management

The 1997 National Heart, Lung, and Blood Institute (NHLBI) National Asthma Education and Prevention Program’s Expert Panel Report II: Guidelines for the Diagnosis and Management of Asthma (EPR-2) recommend leukotriene modifiers (zafirlukast and zileuton, a 5-LO inhibitor) as being acceptable pharmacologic controller agents for mild, persistent asthma symptoms in patients over 12 years of age. However, these agents were introduced to the general medical community just prior to release of the 1997 NHLBI EPR-2 asthma guidelines, so committee members had limited clinical experience with them during guideline development. Recent literature suggests that leukotriene modifiers may be appropriate to enhance control of persistent symptoms experienced by asthmatics.

Zafirlukast and montelukast are orally available leukotriene receptor antagonists. A study published in 1998 with montelukast therapy confirmed the previous association of cysteinyl receptor antagonists and protection against exercise-induced bronchoconstriction in a group 15 to 45 years of age. Frequently, patients may have only exercise-induced bronchoconstriction. A significant improvement was observed in the maximal FEV1 decrease post-exercise and the time required to return to within 5 percent of baseline lung function. Similar results were demonstrated in the 6- to 14-year-old group.

Both in moderate and chronic asthma studies, leukotriene receptor antagonists have been shown to cause clinically significant bronchodilatation, which has an additive effect with a beta agonist. It also improves FEV1, decreases symptoms, and decreases beta-agonist inhaler use. Many of these findings suggest a continuous release of leukotrienes in a particular group of patients. This continues to reinforce the understanding of the role of
LTD4 and LTE4 mediators in the pathogenesis of asthma. Integrating therapeutic interventions with the patient’s lifestyle is an essential component of asthma disease management. The potential impact of an oral, once-a-day medication on asthma control cannot be overstated. Montelukast sodium has been shown to have a rapid onset, long duration, and is well tolerated. Zafirlukast reduced asthma symptoms, decreased as-needed beta-agonist use, and improved pulmonary function without increasing the number of adverse events in patients with chronic, stable asthma. Both drugs carry a caution about a rare inflammatory condition, Churg-Strauss syndrome. The leukotriene-receptor antagonists do offer another tool in the armamentarium against asthma.

A 1998 study began to investigate the influence of LTD4 on human airway smooth muscle (HASM) proliferation and extracellular matrix protein expression. The study demonstrated no effect on the proliferation of HASM cells, but it produced a marked potentiation of mitogenesis elicited by the epidermal growth factor (EGF) and thrombin. The potential impact of this study is an understanding of the mechanisms of airway remodeling in asthma and the factors that contribute to this irreversible component of asthma.

Because LTD4 has the ability to potentiate growth factor-induced mitogenesis of HASM cells, it raises the possibility that cysteinyl LTs play a role in the structural changes that occur in asthma. Further study is needed to demonstrate the impact of CysLT receptor antagonists on the changes in lung architecture in asthma.

**Conclusion**

Cysteinyl LTs are important in the pathogenesis of asthma as inflammatory mediators. The symptoms of asthma triggered by environmental, allergen, or physiologic stimuli are reduced with CysLT antagonists and LT synthesis inhibitors. Improvements in lung function occur both at baseline and in response to bronchial-challenge testing. They also exhibit an additive effect to beta-2 agonists as well as a steroid-sparing effect. Given orally, improved patient adherence to the prescribed therapeutic intervention is a possibility.

Asthmatics should continue to use appropriate rescue medications in addition to the leukotriene antagonists. Also, the need for systemic or inhaled corticosteroids may still exist. The cysteinyl LTs are the first new class of drugs released in the

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**References**

Asthma Pharmacology  
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past 25 years to treat asthma. Demonstrating further benefits of this new class of drugs is a challenge respiratory therapists should embrace to improve the care of the asthmatic population.

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Mechanical Ventilation  
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Generally, the newer generation of ventilators do not deliver helium mixtures well because their internal gas-metering devices are not calibrated to such mixtures. Volume measurements (both inspiratory and expiratory) are usually subject to error. Therefore, it may be more reasonable to use pressure-limited, time-cycled modes of ventilation when using heliox. However, great care must be exercised when using mechanical ventilators to deliver low-density gases.

Airways Inflammation  
Inflammation of the airways should be treated with steroids. As mentioned above, the therapist should closely monitor the interactions between steroids and other drugs being used. While there is a potential for reduced side effects with the use of topical steroids, no health care facility can avoid parenteral administration of steroids in status asthmaticus.

Finally, mucous plugging in the ventilated asthmatic needs to be treated. This is most easily done with hydration, both systemic and to the airways. As noted above, an 8 mm or larger endotracheal tube should be used whenever possible. Heated humidification of the ventilator circuit is extremely important. Therapeutic bronchoscopy may be indicated to treat segmental or lobar collapse. This is a treatment that is far from benign and should be done only by those who are familiar with both the technique and the risks associated with it.

Successful, safe ventilation of the patient suffering from status asthmaticus is challenging, but by no means impossible.

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Clearing Airways  
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bronchospasm. A bronchodilator should always be given in conjunction with the administration of these agents. Guaiifenesin acts by irritating the stomach lining, resulting in stimulation of the vagus nerve. As the vagus nerve is stimulated, the bronchial glands begin to secrete fluid. This fluid will dilute the mucous blanket, thinning out secretions and facilitating expectoration. Critics feel that guaiifenesin is no more effective than water.

Increasing hydration is perhaps the best method to thin secretions and prevent mucous plugging. Unless contraindicated, a patient with thick, retained, or plug-type secretions would benefit from increasing water intake to 10 to 12 eight- to 10-ounce glasses per day. Coffee, tea, and cola with caffeine will promote water loss. Antihistamines, cough suppressants, and diuretics dry the body out and will make secretions more difficult to expectorate.

Increased water intake when using these substances is recommended. Alcohol should always be avoided, as this will enhance dehydration. Fruit juices and carbonated beverages will add a degree of hydration but cannot be expected to deliver the same effect as water.

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