ASTHMA AND NEW EFFECTIVE TREATMENTS

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Executive Summary *Asthma affects individuals differently. Consequently, one treatment does not fit all. This article looks at traditional methods of managing this disease, as well as describing some of the newer medications being used, and possible alternative treatments that are currently being investigated.*

Introduction

Asthma affects an estimated 235 million people worldwide[1] (over 18 million people over age 18 in the US)[2]. It affects all age groups. It is under-diagnosed and under-treated, and is a concern for rising treatment costs as well as a significant burden on health care systems. It is also one of the leading causes of absences from work or school and is the most common chronic disease among children[3].

What Is It?

Asthma is a condition that is characterized by completely reversible airway obstruction at some point in the clinical history. It is chronic and affects the airways–the bronchial tubes that carry air in and out of the lungs. In most cases, there is no known cause, although it can be triggered by allergens or certain occupational exposure (allergic asthma), or by infections, cold air, exercise or some medications (nonallergic asthma).

Types of Asthma

Allergic (extrinsic)[4]: This is the most common type of asthma and is typically caused by the sufferer inhaling or ingesting an allergen such as pet dander, pollen, dust mites, etc. People with allergic asthma often have other allergic diseases such as eczema, hay fever, or food and drug allergies.

Nonallergic (intrinsic): This asthma is considered non-seasonal. Some of the common causes are colds, sinus infections, throat infections, teeth or gum infections, chronic sinusitis, among other things (i.e., anything other than allergens). This type of asthma is more likely to become chronic.

Eosinophilic[5]: This is a somewhat rare subgroup of asthma and is usually diagnosed in adulthood. It presents with eosinophilia: a high eosinophil level in either blood or sputum. Eosinophils are a type of disease-fighting white blood cell.

There are several other subgroups of asthma but they all still fall under one of the main types listed above.

Severity of Asthma

The severity or degree of asthma is of particular importance and is judged based on:
a) How much symptoms affect the sufferer's life.
b) How well the sufferer's lungs work.
c) The risk of having an asthma attack and death.

Asthma may be classified as:
Intermittent: Symptoms usually occur 2 or fewer days per week. These symptoms typically do not limit normal daily activity and do not wake up a person at night. Lung function is normal or near normal. People with intermittent asthma may only need to use short-acting beta-antagonists (SABA) when they have symptoms.

Mild persistent: At this degree, symptoms occur more than twice per week but not daily. These symptoms may slightly limit daily activity and may occasionally cause the person to wake at night. The lung function is near normal and daily medication is at a low dose.

Moderate persistent: With this severity, symptoms occur every day and cause limitations in daily activity. Asthma sufferers at this level will typically wake up

at least once a week because of their symptoms. This is significant enough that an inhaled corticosteroid and a second medication such as a long-acting beta-antagonist (LABA) are required. People with moderate asthma have decreased lung function.

Severe persistent: People with severe persistent asthma have asthma symptoms throughout each day. Their symptoms will cause daily activity to be extremely limited with nightly wake-ups. Lung function in these people is severely decreased. These sufferers are seen by an asthma specialist and often take a high-dose inhaled corticosteroid with a LABA.

How Is It Diagnosed?

A diagnosis of asthma is made when a person's doctor reviews his medical history, and does a physical examination and a lung function test called spirometry- a common office test to assess how well the lungs work by measuring how much air is inhaled, how much is exhaled, and how quickly it is exhaled. (A chest X-ray typically will not show if a person has asthma, but it may be able to tell if there is something else that could be causing symptoms similar to asthma.) Lung function tests are difficult to do in children younger than 5 years, so in these cases, doctors rely on medical histories, signs and symptoms, and physical exams to make a diagnosis.

Pathophysiology

In asthma, the airways become inflamed, causing them to become swollen and very sensitive. When this happens, the airways react and the muscles around them tighten, restricting the air flow into the lungs. This produces recurrent periods of wheezing, chest tightness, shortness of breath and coughing (especially at night, during exercise or when laughing).

Traditional Treatment

Asthma itself cannot be prevented. There is no actual cure; however, there are ways to control the disease and potentially prevent some of the symptoms. Aside from trying to identify any triggers (other than healthy exercise), there are many treatment options that have been around for a while. Successful management of asthma is attained by controlling the inflammation of the airways, thereby reversing the symptoms before they get out of hand.

Treatment is very important especially when symptoms are severe. Without proper management and treatment, some severe symptoms can be fatal. In fact, if there is poor control of the asthma or the disease is severe, this could lead to acute severe asthma, which was formerly known as status asthmaticus. This is an acute exacerbation of asthma that remains unresponsive to initial treatment with bronchodilators. It is then a medical emergency that requires immediate recognition and treatment.

Treatment becomes very individualized as each person's level of disease and reaction to symptoms vary. Individuals must work closely with their doctors to determine the best possible course of treatment. Depending on the type of asthma diagnosis, treatment will typically start off with the lowest possible dose of the applicable medication, and then tweaked to the best possible course to control the asthma and reduce the occurrence of symptoms. Ongoing monitoring of asthma is also important as the degree of control can vary over time and with changes in the surroundings. If this occurs, then adjustments to the medication can be made as needed.

Therefore, each person who has asthma should have an Asthma Action Plan – doctor-prescribed steps on what medications are needed, when they are to be taken, and how to adjust if the asthma starts to get out of control.

Traditional treatments have been used to achieve control, along with regular follow-up care. Until now, treatments have been basically in two camps: controllers (or preventers), which are used to reduce airway inflammation and which should be taken regularly to reduce or prevent symptoms; and relievers, which help to alleviate acute attacks. See below for definitions of controller and reliever treatments.

Controllers are long-term therapies which are taken on a daily basis. If not taken regularly, the inflammation could return. *Relievers* (short-acting beta$_2$-agonists or SABAs) are a short-term treatment for flare-ups as they only relieve the tightening of the airway, but not the underlying cause of the inflammation. They are taken to provide fast relief of acute symptoms.

More often than not, medication is taken by way of a corticosteroid inhaler device; however, a pill form is also available. The inhaled corticosteroids (ICS) have been the most effective long-term therapy for persistent asthma.

As with many medications, there are potential side effects, but the benefits of taking inhaled corticosteroids and preventing asthma attacks far outweigh the risk of side effects.

What new treatments are on the horizon and what does future asthma care look like?

New Treatments

As previously mentioned, treatment has typically focused on the use of inhalers or anti-inflammatory pills. Yet even with all the current variety of treatments, there are still many sufferers of serious asthma who cannot get the necessary help that they need. As a result, researchers continue to look to new ways to offer/discover new treatments.

Oral medications

Leukotriene modifiers or leukotriene receptor antagonists are a new class of oral medications. Leukotrienes are potent inflammation-inducing molecules produced by the immune system and other tissues and cells in response to immunological and nonimmunological stimuli. These are much more potent than histamines and their effects last longer. Leukotriene modifiers neutralize the actions of leukotrienes and have been around for about 20 years. Some examples include montelukast (Singulair), zafirlukast (Accolate) and zileuton (Zyflo), which are taken in pill form once every day.

These medications are used for long-term control and prevention of asthma symptoms. They should not be used to relieve immediate asthma symptoms.

Biologics

For severe asthma sufferers, there is a group of medications that are known as biologics. These are an add-on option. They do not replace the existing controller or reliever medications. These medications currently used for asthma are antibodies and are designed to help control the disease by shutting down lung inflammation or other processes that lead to asthma attacks. They are not used for rapid relief. Biologics target two types of severe asthma: *allergic* (IgE-mediated) asthma and *eosinophilic* asthma.

As mentioned above, *allergic* asthma is triggered by allergens. In this type of asthma, the body produces large amounts of a protein called IgE (immunoglobulin E). For individuals who suffer from this severe type of asthma, and who are not controlled with standard therapies, a biologic medication could be used to block the action of IgE. An example of this type of biologic is omalizumab (Xolair) which has been around for about 10 years[6].

In *eosinophilic* asthma, where the eosinophil cells play a significant role in causing airway inflammation and increasing the risk of an asthma attack, there are more recently introduced biologic medications that reduce the body's production of eosinophils. Mepolizumab (Nucala) and reslizumab (Cinqair) were both FDA approved in November 2015[7] and in March 2016[8] respectively.

Biologics are administered by a doctor or nurse, subcutaneously or intravenously, every 2 to 4 weeks.

A very new biologic which just received FDA approval in late 2017 is benralizumab (Fasenra)[9]. This is another add-on maintenance treatment for patients with severe asthma age 12 years and older, and with an eosinophilic phenotype. It is a monoclonal antibody that recruits natural killer cells causing direct, rapid and near-complete depletion of eosinophils. Benralizumab is administered subcutaneously once every 4 weeks for the first three doses and then once every 8 weeks.

All of these medications and treatments will help doctors determine the best course of action for the patient on a more individualized basis depending on the type of asthma and the severity.

Possible Future Treatments

Fevipiprant is a new drug currently being investigated by Novartis Pharmaceuticals, as reported in *The Lancet*[10]. It is being touted as the first new asthma pill in almost 20 years which shows promise in significantly reducing the severity of asthma. It is an oral prostaglandin DP_2 receptor (CRTh2) antagonist, potentially for help in allergic asthma uncontrolled on low-dose inhaled corticosteroids. It is reported to be the first asthma treatment to use a dual pathway approach by inhibiting eosinophils while stopping inflammation in the airway lining and repairing any damage. At the time of the writing of this article, it is not an approved medication as it is undergoing Phase 3 trials. According to Professor Christopher Brightling, University of Leicester, UK, who led the research, *"This new treatment, Fevipiprant, could likewise help to stop preventable asthma attacks, reduce hospital admissions and improve day-to-day symptoms – making it a 'game changer' for future treatment."*[11]

HMGB1[12] - A study done at the University of Leicester in the UK has identified a breakthrough in the cause of airway narrowing. The scientists discovered that an active form of a key protein, HMGB1, is increased and related to narrowing of the airway in people with severe asthma. They have shown that HMGB1 is increased in the mucous from the airways of people with severe asthma. This could now enable drug makers to specifically target the protein in future treatment for non-allergy related asthma.

Worms - And now stretching even further into the future – A study published in *Immunity Journal*[13] in November 2017 and funded by Asthma UK found that worms could possibly prevent asthma. The research apparently found that parasitic worms that live in the intestines release a protein molecule called HpARI. This protein prevents its host from having an allergic reaction. The press release through Asthma UK[14] indicated that people who live in countries where parasitic worms are common are "less likely to have asthma. In South East Asia, less than 1 in 20 people have asthma as diagnosed by a doctor. Whereas in the UK, 1 in 11 people have the condition." This study was done on mice, but there are findings that show that it could be applied to human lungs. The researchers hope that in the next 5-10 years, scientists could use this protein as the basis for asthma treatments.

Conclusion

Treatment, whether new or traditional, of asthma is still primarily focused on controlling the symptoms of the disease. Individuals with asthma, especially the severe sufferers, should be regularly following their Asthma Action Plan, staying compliant with their medications, and having regular follow-ups with their attending physician. The need for monitoring and possible adjustment of the treatment, including combining different treatments, will be key in keeping the symptoms at bay.

Being aware of all these different types of treatment is important in underwriting individuals with asthma. However, you will also need to take into account the severity of the disease, the frequency of attacks, when the last attack occurred, and the responsiveness to the treatment. Pulmonary function test results during an asthma attack will tell you how bad the individual is during an attack, but it is more important to see whether the lung function gets back to normal after the attack. Underwriting an individual with a history of acute severe asthma (status asthmaticus) should be done very carefully.

Notes

1 World Health Organization www.who.int/respiratory/asthma/en/.
2 Centers for Disease Control and Prevention. www.cdc.gov/nchs/fastats/asthma.htm.
3 World Health Organization www.who.int/respiratory/asthma/en/.
4 https://asthma.net/living/extrinsic-vs-intrinsic/.
5 https://asthma.net/living/subgroups-what-is-eosinophilic/.
6 Omalizumab www.fda.gov/Drugs/DrugSafety/ucm414911.htm.
7 Nucala www.drugs.com/history/nucala.html.
8 Cinqair www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm491980.htm.
9 Benralizumab www.astrazeneca.com/media-centre/press-releases/2017/fasenra-benralizumab-receives-us-fda-approval-for-severe-uncontrolled-eosinophilic-asthma-14112017.html.
10 *The Lancet* www.thelancet.com/journals/lanres/article/PIIS2213-2600(16)30179-5/abstract.
11 Professor Christopher Brightling www.pharmatimes.com/news/novartis_fevipiprant_hailed_a_game-changer_in_asthma_treatment_1092300.
12 *The Journal of Allergy and Clinical Immunology* – March 2017 www.jacionline.org/article/S0091-6749(17)30047-7/fulltext.
13 *Immunity Journal* www.cell.com/immunity/fulltext/S1074-7613(17)30426-0.
14 Asthma UK www.asthma.org.uk/about/media/news/press-release-worms-could-cure-asthma-new-study-shows/.

About the Author

Merv Gillson, FALU, FLMI, ALHC, has over 40 years of experience in the insurance industry with the past 25 years or so in the underwriting area. He is currently Senior Underwriting Specialist and Claims Manager at LOGiQ3 with responsibilities stretching from risk selection, quality assurance, training, mentoring for life... as well as overseeing Claims. Merv is a firm believer in giving back to the industry with over 15 years on the ALU committee and serving as Chair of the Canadian Institute of Underwriters (CIU) in 2014 and 2015.

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