Review Article

Review on Moderate to Severe Asthma in Primary Care, Review Article

Abstract:

Asthma is a chronic condition characterized by wheezing, coughing, and shortness of breath due to airway inflammation and hyper-responsiveness. Severe asthma accounts for a considerable amount of asthma-related costs, although being less common than milder asthma. According to a review of US studies, the expenses for people with severe asthma are roughly 1.7- to 5-fold higher than for people with mild asthma. A subspecialized severe asthma services provides the benefit of an organized, variety of approaches to validate the diagnosis, asthma severity and phenotype, and risk factors and comorbidities management. This multimodal approach frequently comprises a team of respiratory physicians, nurses, and support health specialists, such as physiotherapists, speech therapists, nutritionists, and clinical psychologists. In addition to evaluation and monitoring for common comorbidities, they provide physician review, lung function testing, blood tests, inhaler optimization, and general illness awareness. This review aims to overview approach to diagnosis and management of moderate to severe asthma in primary care settings.

Introduction

Asthma is a chronic condition characterized by wheezing, coughing, and shortness of breath due to airway inflammation and hyper-responsiveness. The term "asthma" refers to a group of illnesses that have similar symptoms but differ in their underlying etiology and prognosis. Depending on the age of onset, clinical signs might indicate one of several phenotypes of the disease, each with its own set of diagnostic, management, and therapy problems. It is hoped that a better understanding of the various subtypes of asthma will help us better evaluate, manage, and cure the symptoms.[1-3]

Asthma is often assumed to be an illness that starts in childhood. Despite the fact that asthma is most typically diagnosed in children, it can manifest clinically at any age. Indeed, according to a national survey, 3.1 percent each year who diagnosed with asthma are over 65 years old which is not significantly different from those between

the ages of 18 and 34 where 4.0 percent are diagnosed per year. Asthma occurrence in adults over 65 years of age is reported to be 7%, which is comparable to the total prevalence. Prematurity, early lung infections, sinusitis, tobacco consumption, and obesity are linked to diagnosis of asthma in adults. As a result, an older patient's beginning of chronic cough should not prevent the physician from examining asthma.[4-7]

According to the National Health Interview Survey–2012, roughly 40 million people in the USA have had asthma at some point in their lives, this comprises about 13 % of the total population .and 8% are currently having asthma which includes about 26 million patient . Incidences for young adults aged 18-24 years are higher (10.3 percent) when compared to older people. 5% to 10% of the entire adult asthma populations are diagnosed with severe asthma.[8,9] Severe asthma accounts for a considerable amount of asthma-related costs, although being less common than milder asthma. According to a review of US studies, the expenses for people with severe asthma are roughly 1.7- to 5-fold higher than for people with mild asthma.[10-12]. Asthma is substantially more common in women (10.4%) than in men (6.2%), in those living in poverty (11.8%), and in those who identify as an ethnic or racial minority, particularly black race (10.2%) and Puerto Rican Hispanic ethnicity (14.9 percent). The incidence varies greatly per state, ranging from 4.9 percent to 12.7 percent. Despite the availability of a wide range of treatment options, over half of individuals with asthma report having one or more attacks in the previous year, emphasising the significance of symptom management and disease control.[13]

Severe asthma is a diverse condition that is described as a treatment-resistant disease characterized by persistent symptoms or recurrent acute episodes despite the use of standard medications. It means patients with "difficult-to-treat" asthma, in which a variety of factors contribute to poor management of the disease , as well as patients with "biologically severe" asthma, who remain to have poor control yet after alternative diagnoses have been ruled out and contributory factors have been optimized. There are now successful, focused biological medicines aimed at targeting the underlying pathogenic pathways for some people with physiologically severe asthma. Many individuals with difficult-to-treat asthma, on the other hand, have risk factors that exacerbate symptoms, and by carefully managing these variables, they can achieve significant enhancement. As a result, it's critical to establish care models that best address the complex and varied needs of people with severe asthma, with the overall goal of enhancing patient outcomes for all.[14-19]

The vast number of asthma patients is treated by primary care physicians, placing them at the forefront of asthma management, allowing them to identify at-risk patients and give appropriate medication and awareness. In a 2012 survey, reported that just 22% of asthma patients were managed by a specialist on a regular basis, and 48% of patients had never seen a specialist. As a result, it's critical for healthcare professionals to conduct routine asthma management evaluations and ask patients the right questions in order to keep track of asthma severity. Patients with asthma should be referred to specialists by primary care providers who do not do pulmonary function testing on a regular basis.[20-23] According to an Australian survey, up to 45 percent of community members had uncontrolled asthma, resulting in frequent hospitalizations and unscheduled medical visits. However, just half of the patients had seen a general practitioner in the previous year, and only 10% had had a specialist evaluation.[24]

A subspecialized severe asthma services provides the benefit of an organized, variety of approaches to validate the diagnosis, asthma severity and phenotype, and risk factors and comorbidities management. This multimodal approach frequently comprises a team of respiratory physicians, nurses, and support health specialists, such as physiotherapists, speech therapists, nutritionists, and clinical psychologists. In addition to evaluation and monitoring for common comorbidities, they provide physician review, lung function testing, blood tests, inhaler optimization, and general illness awareness. It expands educational and self-management opportunities, as well as access to modern biological medicines. These services are now encouraged as they showed positive results on improving the symptoms of the disease, quality of life and decreased incidences of disease exaggeration [25-29]

The word "asthma" originates from the Greek meaning short of breath, meaning that any patient with breathlessness was asthmatic. The term was refined in the latter part of the 19th Century with the publication of a treatise by Henry Hyde Salter entitled "On Asthma and its Treatment". In this scholarly work Salter defined asthma as "Paroxysmal dyspnoea of a peculiar character with intervals of healthy respiration between attacks", a description that captures his concept of a disease in which the airways narrow due to contraction of their smooth muscle. .[72] His book contains remarkably accurate illustrations of the airways in asthma and bronchitis as well as the cellular appearance of asthmatic sputum some 30 years before Paul Ehrlich described aniline stains for eosinophils (eosin) and mast cells (toluidine blue). He also described black coffee as a treatment for asthmatic spasms, a drink with a high content of theobromine, a derivative of theophylline and theophylline itself. This extraordinary insight into asthma stems from Dr Salter himself suffering from asthma himself. Thus, by the late

nineteenth century, physicians adopted the view that asthma was a distinct disease which had a specific set of causes, clinical consequences, and requirements for treatment. [73-74] .

Definition and pathogenesis of severe asthma

Historically, asthma was thought to be a condition caused by increase in the activity of the airway smooth muscle, or bronchoconstriction, in reaction to environmental stimuli. Even in people with just occasional symptoms or new-onset asthma, chronic airway inflammation is now regarded a characteristic of the condition. The incidence of symptoms, the extent of functional disability, and the rate of asthma attacks were all used to determine the severity of asthma. More recent practice guidelines reflect increased knowledge of the basic pathophysiology of asthma, so the previous factors are considered only as elements of asthma management, and the severity of asthma disease is categorized by the type and dosage of medicines a patient needs to maintain proper disease control. As a result, symptom control is evaluated separately from and then incorporated into the criteria of asthma severity.[30,31].

The International European Respiratory Society (ERS) and the American Thoracic Society (ATS) updated the concept of severe asthma in 2014. Severe asthma in people aged 6 and up is defined by the ERS/ATS guidelines as either (1) asthma that needs treatment with medium- to high-dose inhaled corticosteroids (ICS) and one or more additional medicines (eg, long-acting 2-agonist, , leukotriene modifier, and theophylline) or systemic corticosteroids for minimum 6 months According to these criteria, uncontrolled asthma requires at least one of the following symptoms: unsatisfactory symptom control, recurrent acute exacerbations, major exacerbation (requiring hospitalization), or airflow limitation.[32] .Although asthma has a bigger influence on physical than mental functioning, poorly controlled asthma is linked to poor school performance, attention, and focus, as well as an increase in depression and anxiety symptoms. Furthermore, airway remodeling can result in airway functional impairment and the evolution of chronic obstructive pulmonary disease (COPD). Taking oral corticosteroids to treat severe uncontrolled asthma has its own set of side effects, including osteoporosis, slowed growth in children, and increased risk of cataract and inflammation [30,31,33,34]

Assessment and evaluation of Asthma

The combination of patient symptoms and respiratory function testing is required for a reliable diagnosis of asthma. [35]. As the symptoms of asthma are sometimes ambiguous and can be triggered by other diseases, it's crucial to rule out disorders that resemble asthma, especially in older people who are more subjected to have other illnesses.[36]

History:

Asthma symptoms include wheezing, tightness of the chest, and coughing. These symptoms are frequently recurrent in nature and can vary in strength. Changes in stimulators such as allergens, irritants, or respiratory illnesses are related to changes in symptoms. Bronchoconstriction in reaction to exercise can cause symptoms of asthma. At rest, people with uncontrolled illness may experience persistent symptoms. The presence of chest tightness as the primary presenting symptom should raise suspicions of heart illness. Asthmatics frequently suffer from rhinitis and sinusitis, where allergic rhinitis is a predisposing factor for developing asthma. Upper airway symptoms should be assessed, as they are regarded to represent diverse presentations of a shared allergic pathogenesis.[35,36]

Any possible exposures that aggravate the patient's respiratory problems should be tested by physician. The presence of identifiable triggers raises the likelihood of underlying asthma. Allergens are well-known triggers that might be seasonal (usually outdoors) or persistent (typically indoor). Outdoor allergen exposure is widely different across the United States in terms of distribution and timing. Outdoor allergies are primarily pollen-based and can come from a variety of sources, including trees, and weeds, and can be detected at different periods throughout the year. Dust mites, cockroaches, molds, and animal dander from pets are examples of perennial allergies. Cigarette smoking, secondhand smoke exposure, perfumes or strong scents, excess heat or cold , exercise, or psychosocial strain are among non-allergic triggers. Occupational exposures can cause the onset of asthma or exacerbate the symptoms of asthma that already exist . It's crucial to ask about employment exposures in relation to asthma diagnosis and symptom variation by asking about changes in symptoms between weekdays and weekends. Environmental sensitivity is suggested by changes in respiratory symptoms while travel, which supports an asthma diagnosis. [37-40]

Physical Examination

The physical examination is most helpful in determining whether or not there are any concomitant or mimicking conditions. A pulmonary examination in an asthmatic patient is frequently unremarkable. Expiratory wheezing is possible; however it is neither sensitive nor unique to this disease. Inspiratory wheeze is unusual and could indicate a different or additional condition. Crackles, on the other hand, should prompt you to examine other possibilities. Patients may exhibit symptoms of rhinitis or postnasal drip. Eczema can be discovered with a skin examination. Finally, to check for evidence of heart failure, a cardiac examination should be conducted. [37-40]

Tests

Spirometry is an essential diagnostic tool used when both the history of the patient and its physical evaluation point to asthma as a potential diagnosis. Spirometry should be performed before and after administration of bronchodilator to check for the two major criteria for asthma diagnosis: expiratory airflow obstruction and airflow variability. Spirometry that shows both airflow obstruction and complete reversal of airflow obstruction after bronchodilator delivery confirms an asthma diagnosis. Spirometry is typically normal when asthma is adequately treated since variability in symptoms and airflow limitation is a significant aspect of asthma. Additionally, due of increased disease symptoms during presentation, some individuals with asthma who present with expiratory airflow obstruction may not entirely reverse following bronchodilator administration. These other illnesses should be examined because partial reversibility is also a characteristic of COPD or asthma-COPD overlap. In such cases, spirometry is unable to reliably differentiate between asthma and COPD.
A ratio of fractional exhaled volume in the first second (FEV1) to total volume forcefully expelled (FVC) less than the lower limit of normal (LLN) indicates the presence of airflow blockage. Because the LLN compensates for the projected fall in FEV1/FVC that happens with ageing, it is preferable over adopting a set threshold (e.g., 70%). The term "post-bronchodilator response" refers to an increase in FEV1 or FVC of more than 12% and more than 200 mL after using a bronchodilator. These limits are set by guidelines that emphasize that the clinical situation should be considered when evaluating test results. For example, a patient who improves their FEV1 by 10% after a bronchodilator and also improves their FEV1 before the bronchodilator following a trial of inhaled corticosteroids (ICS) would have had a clinically meaningful response that is highly compatible with a diagnosis of asthma.[41-43]

When spirometry indicates normal results but physician still consider the diagnosis of asthma, spirometry must be repeated at a later time point, because minimally single episode of obstruction must be documented to confirm the conclusion of asthma. If reversibility on spirometry cannot be determined, sequential testing with a peak flow meter can be used to establish variability in airflow limitation. Over the course of two weeks, the patient is told to record the best of three attempted peak flows twice daily (usually in the morning and late evening) or more frequently during periods of respiratory discomfort. Variable airflow limitation can be diagnosed by a 7-day average of each day's largest to smallest recorded value, divided by the day's average.[42]

Bronchoprovocation tests, such as a methacholine challenge, for measuring the hyper-responsiveness of airways has a poor sensitivity for asthma, as other respiratory disorders, such as COPD, and the general population, where the prevalence has ranged from 4% to 37%, have been linked to airway hyper-responsiveness. As a result, this test is no longer used to verify asthma, although it does have a function in excluding asthma in some groups due to its high negative predictive value, which has been observed to approach 100%.[44-46]

A progressive diagnostic strategy involving spirometry or peak flow testing to determine blockage and variable airflow limitation is used mainly unless the patient shows exaggerated symptoms on administration. When patients are already using asthma drugs, identifying asthma-related blockage might be difficult. According to a recent Canadian study, up to one-third of those who have been diagnosed with asthma by a doctor do not actually have it. These patients were less likely to have received formal testing for airflow limitation, and the outcomes of the study highlight the importance of objective testing in asthma diagnosis.[47]

In most cases, radiographic studies and blood tests are not required in the diagnostic process until there is a suspicion of a different diagnosis. Elevations in eosinophils, immunoglobulin E (IgE), or allergen-specific IgE, while useful in detecting allergic illness and evaluating advanced therapy, are neither sensitive nor specific for the initial diagnosis of asthma. Although fractional exhaled nitric oxide (FeNO) is a sign of eosinophilic airway inflammation, it is rarely used in asthma diagnosis. [47]

Management:

To enhance disease control and address underlying inflammation while reducing side effects from prescribed drugs, successful care necessitates ongoing review over time. Symptoms, risk of worsening, drug tolerance and adherence, and comorbidities should all be assessed at each appointment.

Respiratory function, symptom recurrence, and frequency of exacerbations can all be used to determine the severity of asthma before starting medical treatment. Severity is defined as frequent, mild - to - moderate persistent or severe persistent, and can guide first therapy decisions. Mild intermittent symptomatology is no longer advised since it suggests that other severities cannot be symptomatic. Importantly, asthma severity is not a static attribute and should be reclassified at each visit based on the quantity of medication required to manage or relieve asthma symptoms. Changes in asthma severity might signal new environmental exposures, comorbidities, or disease progression. [52]

Non-pharmacological Managements:

Asthma care relies heavily on avoiding triggers. Common triggers and techniques for dealing with them are listed below: [56]

- Ambient air pollution :Remain indoors during poor air quality days. [56]
- Certain foods :Test for food-specific allergies, avoidance . [51]

- Cigarette smoke :Smoking cessation assistance, home smoking ban. [51]
- Cockroaches: Sweep and vacuum regularly, use roach traps. [52]

During periods of high pollen counts or poor outdoor air quality, patients with sensitivity to air pollution are advised to stay home. Pollen avoidance should be timed according to each patient's sensitivity profile, which should be established if the patient has a strong history of seasonal allergies and necessitates a referral to an allergist. The importance of avoiding secondhand smoke and quitting smoking is underlined. Indoor allergen avoidance, focusing on specific allergens to which the patient is allergic, is recommended but difficult to put into practice due to the difficulty of attaining total allergy remediation and the high cost of therapies.[48-50]. Overweight or obese patients should be counseled on weight loss as part of general health maintenance, and all patients should be urged to eat a balanced diet. Weight loss of 10 to 15 kgs has been shown to enhance asthma severity.[51]

Picrorrhiza kurroa (P kurroa)

P kurroa is a small herb with tuberous roots that is used in Ayurvedic medicine for the treatment of various conditions including lung diseases such as asthma and bronchitis. [65].

Solanum xanthocarpum/trilobatum

S xanthocarpum and*S trilobatum* as a powder of the whole dried plant or decoction are widely used to treat respiratory disorders by practitioners of the Sidda system of medicine in Southern India. [66].

Boswellia serrata (B serrata)

The gum resin of *B serrata* is known in the Indian Ayurvedic system of medicine as Salai guggal and contains boswellic acids which have been shown to inhibit leukotriene biosynthesis. [67].

Tylophora indica (T indica)

T indica *is a plant indigenous to India and reputed to be able to provide relief to patients with bronchial asthma. [68].*

Tsumura saiboku-to (TJ-96)

TJ-96 is the one of the most popular and best studied anti-asthmatic Kampo herbal medicines and is used both in Japan and China.[65]. It is a combination of two herbal preparations containing 10 herbs[69]. and has been used in China for steroid dependent asthma resulting in a steroid sparing effect. Despite its intensive use. [70].

MARIHUANA

Marihuana was used for the treatment of asthma in the last century. [71].

DRIED IVY LEAF EXTRACT

Pharmacological Managements:

Medication for controlling asthma:

The main goal of such medications is to block the inflammatory process that causes asthma and thus preventing any non-reversible airway remodeling. The backbone of controller therapy is inhaled corticosteroids. Oral thrush, which can be alleviated by using a spacer device and cleaning the mouth after ICS use, and dysphonia, which can be managed by switching to a different delivery system, are two common side effects. If control is inadequate, long-acting beta agonists (LABA) or leukotriene modifiers can be added to ICS, with the former being more successful than the latter. Long-acting muscarinic antagonists, which are routinely used to treat COPD, do not appear to be superior to LABA and are normally reserved for patients with severe disease. LABA mono-therapy is unsuitable and should never be given for a patient with asthma, as it was associated with an elevated asthma -related mortalities.[52-56]

Beta-2 agonists

Beta-2 agonists relax bronchial smooth muscle, decrease mast cell degranulation and histamine release, inhibit microvascular leakage into the airways, and increase mucociliary clearance. Beta-2 agonist preparations may be short-acting, long-acting, or ultra–long-acting (see tables Drug Treatment of Chronic Asthma and Drug Treatment of Asthma Exacerbations).

Short-acting beta-2 agonists (eg, albuterol) 2 puffs every 4 hours inhaled as needed are the drug of choice for relieving acute bronchoconstriction and preventing exercise-induced asthma. They should not be used alone for long-term maintenance of chronic asthma. They take effect within minutes and are active for up to 6 to 8 hours, depending on the drug. Tachycardia and tremor are the most common acute adverse effects of inhaled beta-2 agonists and are dose-related. Mild hypokalemia occurs uncommonly. Use of levalbuterol (a solution containing the *R*-isomer of albuterol) theoretically minimizes adverse effects, but its long-term efficacy and safety are unproved. Oral beta-2 agonists have more systemic effects and generally should be avoided.

Long-acting beta-2 agonists (eg, salmeterol) are active for up to 12 hours. They are used for moderate and severe asthma but should never be used as monotherapy. They interact synergistically with inhaled corticosteroids and permit lower dosing of corticosteroids.

Ultra-long-acting beta-2 agonists (eg, indacaterol) are active for up to 24 hours and as with long-acting beta agonists are used for moderate to severe asthma, and should never be used as a monotherapy. They interact synergistically with inhaled corticosteroids and permit lower dosing of corticosteroids.

The safety of regular long-term use of beta-2 agonists remains unclear. Long-acting beta-2 agonists may increase the risk of asthma-related death when used as monotherapy. Therefore, when treating patients with asthma, these drugs (salmeterol, formoterol, vilanterol) should be used only in combination with an inhaled corticosteroid for patients whose condition is not adequately controlled with other asthma controllers (eg, low- to medium-dose inhaled corticosteroids) or whose

disease severity clearly warrants additional maintenance therapies. Daily use or diminishing effects of short-acting beta-2 agonists or use of ≥ 1 canister per month suggests inadequate control and the need to begin or intensify other therapies.

Anticholinergics

Anticholinergics relax bronchial smooth muscle through competitive inhibition of muscarinic (M3) cholinergic receptors. Ipratropium may have an additive effect when combined with short-acting beta-2 agonists. Adverse effects include pupillary dilation, blurred vision, and dry mouth. Tiotropium soft mist inhaler (1.25 mcg/puff) is a 24-hour inhaled anticholinergic that can be used for patients with asthma. In patients with asthma, clinical trials of tiotropium added to either inhaled corticosteroids or to a combination of an inhaled long-acting beta-2 agonist plus a corticosteroid have shown improved pulmonary function and decreased asthma exacerbations.

Corticosteroids

Corticosteroids inhibit airway inflammation, reverse beta-receptor down-regulation, and inhibit cytokine production and adhesion protein activation. They block the late response (but not the early response) to inhaled allergens. Routes of administration include oral, IV, and inhaled. In acute asthma exacerbations, early use of systemic corticosteroids often aborts the exacerbation, decreases the need for hospitalization, prevents relapse, and speeds recovery. Oral and IV routes are equally effective.

Inhaled corticosteroids have no role in acute exacerbations but are indicated for long-term suppression, control, and reversal of inflammation and symptoms. They substantially reduce the need for maintenance oral corticosteroid therapy. Adverse local effects of inhaled corticosteroids include dysphonia and oral candidiasis, which can be prevented or minimized by having the patient use a spacer, gargle with water after corticosteroid inhalation, or both. Systemic effects are all dose related, can occur with oral or inhaled forms, and occur mainly with inhaled doses > 800 mcg/day. They include suppression of the adrenal-pituitary axis, osteoporosis, cataracts, skin atrophy, hyperphagia, and easy bruisability. Whether inhaled corticosteroids suppress growth in children is unclear. Most children treated with inhaled corticosteroids eventually reach their predicted adult height. Latent tuberculosis may be reactivated by systemic corticosteroid use.

Mast cell stabilizers

Mast cell stabilizers inhibit histamine release from mast cells, reduce airway hyperresponsiveness, and block the early and late responses to allergens. They are given by inhalation prophylactically to patients with exercise-induced or allergen-induced asthma. They are ineffective once symptoms have occurred. They are the safest of all antiasthmatic drugs but the least effective.

Leukotriene modifiers

Leukotriene modifiers are taken orally and can be used for long-term control and prevention of symptoms in patients with mild persistent to severe persistent asthma. The main adverse effect is liver enzyme elevation (which occurs with zileuton). Although rare, patients have developed a clinical syndrome resembling eosinophilic granulomatosis with polyangiitis.

Methylxanthines

Methylxanthines relax bronchial smooth muscle (probably by inhibiting phosphodiesterase) and may improve myocardial and diaphragmatic contractility through unknown mechanisms. Methylxanthines appear to inhibit intracellular release of calcium, decrease microvascular leakage into the airway mucosa, and inhibit the late response to allergens. They decrease the infiltration of eosinophils into bronchial mucosa and of T cells into epithelium.

The methylxanthine theophylline is used for long-term control as an adjunct to beta-2 agonists. Extended-release theophylline helps manage nocturnal asthma. Theophylline has fallen into disuse because of its many adverse effects and interactions compared with other drugs. Adverse effects include headache, vomiting, cardiac arrhythmias, seizures, and aggravation of gastroesophageal reflux (by reducing lower esophageal sphincter pressure).

Methylxanthines have a narrow therapeutic index; multiple drugs (any metabolized by the cytochrome P-450 pathway, eg, macrolide antibiotics) and conditions (eg, fever, liver disease, heart failure) alter methylxanthine metabolism and elimination.

Serum theophylline levels should be monitored periodically and maintained between 5 and 15 mcg/mL (28 and 83 micromole/L).

Immunomodulators

Immunomodulators include omalizumab, an anti-IgE antibody, 3 antibodies to IL-5 (benralizumab, mepolizumab, reslizumab), and a monoclonal antibody that inhibits IL-4 and IL-13 signaling (dupilumab), which are used for the management of severe allergic asthma.

Omalizumab is indicated for patients with severe, allergic asthma who have elevated IgE levels. Omalizumab may decrease asthma exacerbations, corticosteroid requirements, and symptoms. Dosing is determined by a dosing chart based on the patient's weight and IgE levels. The drug is administered subcutaneously every 2 to 4 weeks.

Mepolizumab, reslizumab, and benralizumab were developed for use in patients with eosinophilic asthma and are monoclonal antibodies that block IL-5. IL-5 is a cytokine that promotes eosinophilic inflammation in the airways.

Mepolizumab reduces exacerbation frequency, decreases asthma symptoms, and reduces the need for systemic corticosteroid therapy in patients with asthma who are dependent on chronic systemic corticosteroid therapy. Based on data from clinical trials, efficacy occurs with blood absolute eosinophil counts > 150/microL (0.15×10^9/L); however, for patients on chronic systemic corticosteroid therapy, the threshold for efficacy is unclear. Mepolizumab is administered subcutaneously 100 mg every 4 weeks.

Reslizumab also appears to reduce frequency of exacerbations and decrease asthma symptoms. In clinical trials, patients had blood absolute eosinophil counts of about 400/microL (0.4×10^9/L). In patients treated with chronic systemic corticosteroids, the eosinophil count threshold for efficacy is unclear. Reslizumab is administered 3 mg/kg IV over 20 to 50 minutes every 4 weeks.

Benralizumab is a monoclonal antibody that binds to IL-5 receptors. It is indicated for the add-on maintenance treatment of severe asthma in patients aged 12 years or

older with an eosinophilic phenotype. It has been shown to decrease exacerbation frequency and reduce and/or eliminate oral corticosteroid use. The recommended dose is 30 mg subcutaneously once every 4 weeks for 3 doses, followed by 30 mg once every 8 weeks. The treatment regimens of participants in clinical trials (1, 2references) included high-dose inhaled corticosteroids plus long-acting beta-2 agonists with or without other controllers. Blood eosinophil counts were typically > 300/microL (>0.3 × 10^9/L).

Dupilumab is a monoclonal antibody that blocks the IL-4R-alpha subunit, thereby simultaneously inhibiting IL-4 and IL-13 signaling. It is indicated for add-on maintenance treatment of patients with moderate-to-severe asthma aged 12 years or older with an eosinophilic phenotype or with oral corticosteroid–dependent asthma. The recommended dose is an initial dose of 400 mg subcutaneously followed by 200 mg every other week, or an initial dose of 600 mg subcutaneously followed by 300 mg every other week. The higher dosage is recommended for patients requiring concomitant oral corticosteroids or with co-morbid moderate-to-severe atopic dermatitis.

Clinicians who give any of these immunomodulators should be prepared to identify and treat anaphylaxis or allergic hypersensitivity reactions. Anaphylaxis may occur after any dose of dupilumab, benralizumab, omalizumab, or reslizumab even if previous doses have been well tolerated. Allergic hypersensitivity reactions have been reported with mepolizumab. Mepolizumab use has been associated with herpes zoster infection; therefore, zoster vaccination is recommend prior to initiation of therapy u-nless contraindicated.[76-77].

Drug	Form	Dosage		Comments
		Children	Adults	
Short-acting beta-agonists				
Albuterol	HFA: 90 mcg/puff	Same as adults	2 puffs every 4–6 hours as needed and 2 puffs 15–30 minutes before exercise	Albuterol is used mainly as a rescue drug. It is not recommended for maintenance treatment. Regular use indicates diminishing asthma control and need for additional
	DPI: 90 mcg/puff	≥ 4 years: Same as adults	2 puffs every 4–6 hours as	

Drug	Form	Dosage		Comments
		Children	Adults	
		< 4 years: Not used	needed and 2 puffs 15–30 minutes before exercise	drug. MDI-DPI is as effective as nebulized therapy if patients can coordinate the inhalation maneuver using the spacer and holding chamber. Nebulized albuterol can be mixed with other nebulizer solutions.
	Nebulized solution: 5 mg/mL and 0.63, 1.25, and 2.5 mg/3 mL	< 5 years: 0.63–2.5 mg in 3 mL of saline every 4–6 hours as needed ≥ 5 years: 0.05 mg/kg in 3 mL saline every 4–6 hours as needed (minimum 1.25 mg, maximum 2.5 mg)	1.25–5 mg in 3 mL saline every 4–6 hours as needed	
Levalbuterol	HFA: 45 mcg/puff	< 5 years: Not established ≥ 5 years: Same as adults	2 puffs every 4–6 hours as needed	Levalbuterol is the *R*-isomer of albuterol. 0.63 mg is equivalent to 1.25 mg racemic albuterol. Levalbuterol may have fewer adverse
	Nebulized solution: 0.31, 0.63, and 1.25	< 5 years: 0.31–1.25 mg in 3	0.63–1.25 mg every 6–8 hours	

Drug	Form	Dosage		Comments
		Children	Adults	
	mg/3 mL and 1.25 mg/0.5 mL	mL every 4–6 hours as needed 5–11 years: 0.31–0.63 mg every 8 hours as needed (maximum 0.63 mg every 8 hours) ≥ 12 years: Same as adults	as needed	effects.
Long-acting beta-2 agonists (not to be used as monotherapy)				
Arformoterol	Nebulized solution: 15 mcg/2 mL	Not established	15–25 mcg every 12 hours	Arformoterol is the *R*-isomer of formoterol.
Formoterol	Nebulized solution: 20 mcg/2 mL	Not established	20 mcg every 12 hours	DPI form is no longer available.
Salmeterol	HFA: 21 mcg/puff	≥ 12 years: Same as adults	2 puffs every 12 hours; when taken before exercise, should be taken 30–	Duration of action is 12 hours. One dose nightly is helpful for nocturnal asthma. Salmeterol is

Drug	Form	Dosage		Comments
		Children	Adults	
			60 minutes before exercise	not to be used for acute symptom relief in an exacerbation.
	DPI: 50 mcg/puff	< 4 years: Not established ≥ 4 years: Same as adults	1 puff every 12 hours and 30 minutes before exercise	
Ultra–long-acting beta-2 agonists (not to be used as monotherapy)				
Indacaterol	DPI: 75 mcg/puff	Not established	1 puff once a day	—
Olodaterol	SMI: 2.5 mcg/puff	Not established	2 puffs once a day	—
Vilanterol	DPI: 25 mcg/puff	Not established	1 puff once a day	Vilanterol is available only in combination with fluticasone 100 mcg or 200 mcg.
Anticholinergics				
Ipratropium	HFA: 17 mcg/puff	< 12 years: Not established ≥ 12 years: Same as	2 puffs every 6 hours as needed (maximum 12 puffs/day)	Ipratropium may be mixed in the same nebulizer as albuterol. It should not be used as first-line

Drug	Form	Dosage		Comments
		Children	Adults	
		adults		therapy. Regular use provides no clear benefit for long-term maintenance therapy but should be added for treatment of acute symptoms.
	Nebulized solution: 500 mcg (0.02%, 2 mL)	< 12 years: Not established ≥ 12 years: Same as adults	500 mcg every 6–8 hours as needed	
Tiotropium	SMI: 1.25 mcg/puff	< 6 years: Not established ≥ 6 years: Same as adults	2 puffs once a day (max 2 puffs/day)	Tiotropium is longer acting than ipratropium. The lower dose SMI tiotropium is the only dose recommended for use in asthma.
	DPI: 18 mcg/capsule	Not established	18 mcg (1 capsule) once a day	
Corticosteroids (inhaled)				
Beclomethasone	HFA: 40–80 mcg/puff	< 5 years: Not established 5–11 years: 1 puff every 12 hours (usual maximum 80 mcg twice a	1–2 puffs every 12 hours (usual maximum 320 mcg twice a day)	Doses depend on severity and range from 1–2 puffs to whatever dose is needed to control asthma. All may have systemic effects when used long

Drug	Form	Dosage		Comments
		Children	Adults	
		day) ≥ 12 years: Same as adults		term. Maximum threshold is that above which hypothalamic-pituitary-adrenal suppression is produced. If higher doses are necessary for asthma control, specialist consultation is recommended.
Budesonide	DPI: 90 or 180 mcg/puff	< 6 years: Not recommended ≥ 6 years: Initial dose of 180 mcg twice a day (maximum 360 mcg twice a day)	Initial dose of 360 mcg twice a day (maximum 720 mcg twice a day)	
	Nebulized solution: 0.25, 0.5, or 1.0 mg (each in 2 mL solution)	1–8 years only: If previously taking bronchodilators alone, initial dose of 0.5 mg once a day or 0.25 mg twice a day (maximum 0.5 mg/day) If	Not indicated for adults	

Drug	Form	Dosage		Comments
		Children	Adults	
		previously taking inhaled corticosteroids, initial dose of 0.5 mg once a day or 0.25 mg twice a day If previously taking oral corticosteroids, initial dose of 0.5 mg twice a day or 1 mg once a day (maximum 1 mg/day)		
Ciclesonide	HFA: 80 or 160 mcg/puff	≤ 5 years: 160 mcg daily 6–11 years: Low dose = 80 mcg once a day, medium	If previously taking bronchodilators alone, initial dose of 80 mcg twice a	

Drug	Form	Dosage		Comments
		Children	Adults	
		dose > 80 to 160 mcg once a day, high dose > 160 mcg once a day ≥ 12 years: Same as adult	day (maximum 320 mcg twice a day) If previously taking inhaled corticosteroids, initial dose of 80 mcg twice a day (maximum 640 mcg twice a day) If previously taking oral corticosteroids, initial dose of 320 mcg twice a day (maximum 640 mcg twice a day)	
Flunisolide	HFA: 80 mcg/puff	< 5 years: Not established	2 puffs twice a day (maximu	

Drug	Form	Dosage		Comments
		Children	Adults	
		5–11 years: 1 puff twice a day (maximum 2 puffs twice a day [320 mcg/day]) ≥ 12 years: Same as adults	m 4 puffs twice a day [640 mcg/day])	
Fluticasone propionate	HFA: 44, 110, or 220 mcg/puffs	4–11 years: 88 mcg twice a day ≥ 12 years: Same as adults	If previously taking bronchodilators alone, initial dose of 88 mcg twice a day (maximum 440 mcg twice a day) If previously taking inhaled corticosteroids, initial dose of 88–220 mcg twice a day	

Drug	Form	Dosage		Comments
		Children	Adults	
			(maximum 440 mcg twice a day) If previously taking oral corticosteroids, initial dose of 440–880 mcg twice a day (maximum 880 mcg twice a day)	
	DPI: 50, 100, or 250 mcg/puff	0–4 years: not established 5–11 years: Initial dose of 50 mcg twice a day (maximum 100 mcg twice a day) ≥ 12 years: Same as adults	If previously taking bronchodilators alone, initial dose of 100 mcg twice a day (maximum 500 mcg twice a day) If previously taking inhaled corticoste	

Drug	Form	Dosage		Comments
		Children	Adults	
			roids, initial dose of 100–250 mcg twice a day (maximum 500 mcg twice a day) If previously taking oral corticosteroids, initial dose of 500–1000 mcg twice a day (maximum 1000 mcg twice a day)	
Fluticasone furoate	DPI: 50, 100, or 200 mcg/puff	0–4 years: Not established 5–11 years: 1 puff (50 mcg) once a day ≥ 12 years: Same as	If previously taking bronchodilators alone, initial dose of 100 mcg once a day (maximum 200 mcg/day)	

Drug	Form	Dosage		Comments
		Children	Adults	
		adults	If previously taking inhaled corticosteroids, initial dose of 100-200 mcg once a day (maximum 200 mcg/day)	
Mometasone	DPI: 110 or 220 mcg/puff	< 4 years: Not established 4–11 years: 110 mcg once a day in the evening ≥ 12 years: Same as adults	If previously taking bronchodilators alone or inhaled corticosteroids, initial dose of 220 mcg once a day in the evening (maximum 220 mcg twice a day or 440 mcg once a day in the evening) If previously	

Drug	Form	Dosage		Comments
		Children	Adults	
			taking oral corticosteroids, initial dose of 440 mcg twice a day (maximum 880 mcg twice a day)	
	HFA: 100 or 200 mcg/puff	< 12 years: Not established ≥ 12 years: Same as adults	If previously taking bronchodilators alone, initial dose of 220 mcg (delivering 200 mcg) once or twice a day (maximum 440 mcg/day) If previously taking inhaled corticosteroids, initial dose of	

Drug	Form	Dosage		Comments
		Children	Adults	
			110–220 mcg (delivering 100 or 200 mcg) twice a day , (maximum 800 mcg/day) If previously taking oral corticosteroids, initial dose of 440 mcg (delivering 400 mcg) twice a day (maximum 800 mcg/day)	
Systemic corticosteroids (oral)				
Methylprednisolone	Tablets: 2, 4, 8, 16, or 32 mg	0–11 years: Short-course burst: 1–2 mg/kg once a day (maximum 60 mg)	7.5–60 mg once a day in the morning or every other day in the morning Short-	Maintenance doses should be given in a single dose in the morning every day or every other day as needed for control. Some
Prednisolone	Tablets: 5 mg Solution: 5 mg/5 mL or 15 mg/5 mL			
Prednisone	Tablets: 1, 2.5, 5, 10, 20, or 50			

Drug	Form	Dosage		Comments
		Children	Adults	
	mg Solution: 5 mg/mL or 5 mg/5 mL	for 3–10 days ≥ 12 years: Same as adults	course burst: 40–60 mg once a day (or 20–30 mg twice a day) for 3–10 days	evidence suggests clinical effectiveness increases with no increase in adrenal suppression when dose is given at 3 PM. Short-course burst doses are effective for establishing control when initiating therapy or during a period of gradual deterioration. The burst should be continued until PEF = 80% of personal best or symptoms resolve, possibly requiring > 3–10 days of therapy.
Combination drugs				
Ipratroprium and albuterol	SMI: 20 mcg/puff ipratropium and 100 mcg/puff albuterol	Not established	1 puff qid (maximum 6 puffs/day)	Ipratroprium prolongs bronchodilator effect of albuterol.

Drug	Form	Dosage		Comments
		Children	Adults	
	Nebulized solution: 0.5 mg ipratropium and 2.5 mg albuterol in a 3-mL vial		3-mL vial via nebulization 4 times a day for ambulatory rescue therapy (maximum 6 doses/24 hours)	—
Fluticasone and salmeterol	DPI: 100, 250, or 500 mcg fluticasone and 50 mcg salmeterol	< 4 years: Not established 4–11 years: 1 puff (100/50) twice a day ≥ 12 years: Same as adults	1 puff twice a day	The 250/50 dose is indicated for asthma not controlled by low-to-medium doses of inhaled corticosteroids. The 500/50 dose is indicated for asthma not controlled by medium-to-high doses of inhaled corticosteroids.
	HFA: 45, 115, or 230 mcg fluticasone and 21 mcg salmeterol	< 12 years: Not established ≥ 12 years:	2 puffs twice a day	—

Drug	Form	Dosage		Comments
		Children	Adults	
		Same as adults		
Budesonide and formoterol	HFA: 80 or 160 mcg budesonide and 4.5 mcg formoterol	< 12 years: Not established ≥ 12 years: Same as adults	2 puffs twice a day (maximum 2 puffs of 160/4.5 mcg twice a day)	The 80/4.5 dose is indicated for asthma not controlled by low-to-medium doses of inhaled corticosteroids. The 160/4.5 dose is indicated for asthma not controlled by medium-to-high doses of inhaled corticosteroids.
Mometasone and formoterol	HFA: 100 mcg or 200 mcg mometasone and 5 mcg formoterol	< 5 years: Not established ≥ 5 years: Same as adults	2 puffs twice a day	The 100/5 dose is recommended for asthma not controlled by low-to-medium–dose inhaled corticosteroids. The 200/5 dose is recommended for asthma not controlled by high-dose inhaled corticosteroids.

Drug	Form	Dosage		Comments
		Children	Adults	
Fluticasone and vilanterol	DPI: 100 or 200 mcg fluticasone and 25 mcg vilanterol	Not established	1 puff once/day	Recommended starting dose is based on asthma severity.
Mast cell stabilizers				
Cromolyn	Nebulized solution: 20 mg/ampule	< 2 years: Not established ≥ 2 years: Same as adults	1 ampule 3 or 4 times a day	Cromolyn should be taken before exercise or allergen exposure. One dose provides effective prophylaxis for 1–2 hours.
Leukotriene modifiers				
Montelukast	Tablets, chewable tablets, and granules: 4, 5, or 10 mg	12 mo–5 years: 4 mg orally once a day in the evening 6–14 years: 5 mg orally once a day in the evening ≥ 15 years: Same as adults	10 mg orally once a day in the evening Exercise-induced asthma: 10 mg orally 2 hours before exercise	Montelukast is a leukotriene receptor antagonist that is a competitive inhibitor of leukotrienes D4 and E4.
Zafirlukast	Tablet: 10 or 20	< 5 years:	20 mg	Zafirlukast is a

Drug	Form	Dosage		Comments
		Children	Adults	
	mg	Not established 5–11 years: 10 mg orally twice a day ≥ 12 years: Same as adults	orally in the evening	leukotriene receptor antagonist that is a competitive inhibitor of leukotrienes D4 and E4. It must be taken 1 hour before or 2 hours after meals.
Zileuton	Tablet, immediate-release: 600 mg	< 12 years: Not established ≥ 12 years: Same as adults	600 mg orally 4 times a day	Zileuton inhibits 5-lipoxygenase. Dosing may limit adherence. Zileuton may cause liver enzyme elevations and inhibit metabolism of drugs processed by CYP3A4, including theophylline.
	Extended-release: 1200 mg	< 12 years: Not established ≥ 12 years: Same as adults	1200 mg orally twice a day within 1 hour after morning and evening meals	
Methylxanthines				
Theophylline	Capsule, extended-release: 100,	Initial dose of 10	Initial dose of 10	The wide variability in metabolic

Drug	Form	Dosage		Comments
		Children	Adults	
	200, 300, and 400 mg Elixir: 80 mg/15 mL Tablet, extended-release: 100, 200, 400, 450, or 600 mg	mg/kg/day up to 600 mg/day, then adjusted to achieve a serum concentration of 5–15 mcg/mL at steady state	mg/kg/day up to 600 mg/day, then adjusted to achieve a serum concentration of 5–15 mcg/mL at steady state	clearance, drug interactions, and potential for adverse effects mandate routine serum level monitoring. Availability of safer alternatives has led to declining use of this drug. Safety may be better with a target level < 10 mcg/mL.
Immunomodulators				
Benralizumab	Subcutaneous injection: 30 mg/mL	< 12 years: Not established >12 years: Same as adults	30 mg subcutaneously every 4 weeks for 3 doses then every 8 weeks thereafter	Benralizumab is used as an add-on treatment for patients with the eosinophilic phenotype.
Dupilumab	Subcutaneous injection: 300 mg/2mL or 200 mg/1.14 mL	< 12 years: Not established ≥ 12	400 mg subcutaneously once then 200 mg every 2	The initial dose should be given as two injections. Dupilumab is used as an

Drug	Form	Dosage		Comments
		Children	Adults	
		years: Same as adults	weeks or 600 mg subcutaneously once then 300 mg every 2 weeks	add-on treatment for patients with the eosinophilic phenotype.
Mepolizumab	Subcutaneous injection: 100 mg	< 12 years: Not established ≥ 12 years: Same as adults	100 mg subcutaneously once every 4 weeks	—
Omalizumab	Subcutaneous injection: 150 mg/1.2 mL	< 12 years: 75–375 mg subcutaneously every 2–4 weeks, depending on body weight and pretreatment serum IgE level ≥ 12 years: Same as adults	150–375 mg subcutaneously every 2–4 weeks, depending on body weight and pretreatment serum IgE level	Maximum dose per injection site is 150 mg.
Reslizumab	Intravenous:	Not	3 mg/kg	—

Drug	Form	Dosage		Comments
		Children	Adults	
	100 mg/10 mL	established	IV once every 4 weeks	

* All ages unless specified differently.

DPI = dry-powder inhaler; HFA = hydrofluoroalkane; MDI = metered-dose inhaler; SMI = soft mist inhaler; PEF = peak expiratory flow.

Adapted from the National Heart, Lung, and Blood Institute: Expert Panel Report 3, Guidelines for the diagnosis and management of asthma—full report 2007. August 28, 2007. Available at www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf.

Rescue Medications:

All patients should be provided with an albuterol rescue inhaler. In individuals with acute symptoms, this short-acting drug delivers rapid bronchodilator and can be used up to four times per day. Albuterol administered by metered-dose inhaler (MDI) without spacer, MDI with spacer, or nebulizer is equally effective in an adult patient with appropriate guidance. In practice, though, spacers and nebulizers are more reliable at delivering medication. Patients with episodic asthma may be able to manage their symptoms with just a short-acting beta-agonist; however, those with chronic asthma (those who use their albuterol inhaler more than twice weekly to relieve symptoms) will require the addition of an inhaled corticosteroid (ICS).[57,58]

Other Treatment Options in Severe Asthma:

A typical target is the allergic inflammatory pathway. Omalizumab is an anti-IgE antibody that interacts with mast cells, eosinophils, and basophils in the allergic pathway. It's approved for people with mild to severe asthma who don't respond to ICS and have confirmed allergen sensitivity. It's given every 2 to 4 weeks. Antibodies such as mepolizumab, reslizumab, and benralizumab target the interleukin-5 pathway, which is implicated in eosinophil recruitment and activation.[59-62] Bronchial thermoplasty (BT) is an endoscopic technique that uses radiofrequency heat radiation to ablate airway smooth muscle, diminishing its ability to cause bronchoconstriction. In people with severe asthma, data shows that BT lowers exacerbations, minimizes asthma-related health-care utilization, and enhances the quality of life. [63,64]

- Asthma affected an estimated 262 million people in 2019 and caused 461000 deaths (1).

WHO strategy for prevention and control of asthma

Asthma is included in the WHO Global Action Plan for the Prevention and Control of NCDs and the United Nations 2030 Agenda for Sustainable Development.

WHO is taking action to extend diagnosis of and treatment for asthma in a number of ways. The WHO Package of Essential Noncommunicable Disease Interventions (PEN) was developed to help improve NCD management in primary health care in low-resource settings. PEN includes protocols for the assessment, diagnosis, and management of chronic respiratory diseases (asthma and chronic obstructive pulmonary disease), and modules on healthy lifestyle counselling, including tobacco cessation, and self-care.

Reducing tobacco smoke exposure is important for both primary prevention of asthma and disease management. The Framework Convention on Tobacco Control is enabling progress in this area as are WHO initiatives such as MPOWER and mTobacco Cessation. [78].

Conclusion:

Asthma is one of the most known respiratory disorders that require long-term managements. Diagnosis of asthma is complicated by the common features between asthma and other respiratory diseases. Severe asthma is considered when the patient is not responding to the normal medication, where inhaled corticosteroids are the main management technique beside avoidance of the trigger that causes case exacerbation. Patient awareness about the disease and adequate methods for its management is an important step in the management of this disorder.

References:

1. Villarroel MA, Blackwell DL. Percentage of adults aged 18–64 years with current asthma,* by State-National Health Interview Survey,(Dagger) 2014–2016. Atlanta (GA): Centers Disease Control 1600 Clifton Rd; 2018. 30333 USA.
2. Pavord ID, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G, et al. After asthma: redefining airways diseases. Lancet. (London, England). (2018) 391:350−400. doi: 10.1016/S0140-6736(17)30879-6
3. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. Am J Respirat Critic Care Med. (2008) 178:218−24. doi: 10.1164/rccm.200711-1754OC.
4. Winer RA, Qin X, Harrington T, et al. Asthma incidence among children and adults: findings from the behavioral risk factor surveillance system asthma call-back survey—United States, 2006–2008. J Asthma 2012;49(1):16–22. [PubMed: 22236442]
5. Huovinen E, Kaprio J, Koskenvuo M. Factors associated to lifestyle and risk of adult onset asthma. Respir Med 2003;97(3):273–80. [PubMed: 12645835]
6. Guerra S, Sherrill DL, Martinez FD, et al. Rhinitis as an independent risk factor for adult-onset asthma. J Allergy Clin Immunol 2002;109(3):419–25. [PubMed: 11897985]
7. Jamrozik E, Knuiman MW, James A, et al. Risk factors for adult-onset asthma: a 14-year longitudinal study. Respirology 2009;14(6):814–21. [PubMed: 19703063].
8. Centers for Disease Control and Prevention. 2012 National Health Interview Survey (NHIS) data. Available at: https://www.cdc.gov/asthma/ nhis/2012/data.htm. Accessed May 24, 2017.
9. Centers for Disease Control and Prevention. Asthma Facts—CDC's National Asthma Control Program Grantees. Atlanta, Ga: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2013.
10. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43:343-373.
11. Nunes C, Pereira AM, Morais-Almeida M. Asthma costs and social impact. Asthma Res Pract. 2017;3:1.
12. Bahadori K, Doyle-Waters MM, Marra C, et al. Economic burden of asthma: a systematic review. BMC Pulm Med. 2009;9:24.
13. Mazurek JM. Prevalence of asthma, asthma attacks, and Emergency Department visits for asthma among working adults — national health interview survey, 2011 — 2016. MMWR Morb Mortal Wkly Rep 2018;67 10.15585/mmwr.mm6713a1.
14. 7 Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014; 43: 343-373.
15. 8 Bel EH, ten Brinke A. New anti-eosinophil drugs for asthma and COPD. Chest 2017; 152: 1276-1282.

16. 9 Grainge CL, Maltby S, Gibson PG, et al. Targeted therapeutics for severe refractory asthma: monoclonal antibodies. Expert Rev Clin Pharmacol 2016; 9: 927-941.
17. 10 Upham JW, Chung LP. Optimising treatment for severe asthma. Med J Aust 209 (2 Suppl): S22-S27.
18. 11 Bel EH, Sousa A, Fleming L, et al; Unbiased Biomarkers for the Prediction of Respiratory Disease Outcome (U-BIOPRED) Consortium. Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). Thorax 2011; 66: 910-917.
19. 12 Agustí A, Bafadhel M, Beasley R, et al. Precision medicine in airway diseases: moving to clinical practice. Eur Respir J 2017; 50: 1701655.
20. Price D, Bjermer L, Bergin DA, Martinez R. Asthma referrals: a key component of asthma management that needs to be addressed. J Asthma Allergy. 2017;10:209-223.
21. Rance KS. Helping patients attain and maintain asthma control: reviewing the role of the nurse practitioner. J Multidiscip Healthc. 2011;4:299-309.
22. Murphy KR, Meltzer EO, Blaiss MS, Nathan RA, Stoloff SW, Doherty DE. Asthma management and control in the United States: results of the 2009 Asthma Insight and Management survey. Allergy Asthma Proc. 2012;33:54-64.
23. Schierhorn C. Avoiding pitfalls in caring for patients with asthma. Available at: https://thedo.osteopathic.org/2014/03/avoiding-pitfalls-in-caring -for-patients-with-asthma. Accessed September 26, 2017. 2014.
24. Reddel HK, Sawyer SM, Everett PW, et al. Asthma control in Australia: a cross-sectional web-based survey in a nationally representative population. Med J Aust 2015; 202: 492-496. https://www.mja.com.au/ journal/2015/202/9/asthma-control-australia-cross-sectional-web-based-survey-nationally .
25. Gibson PG, McDonald VM. Management of severe asthma: targeting the airways, comorbidities and risk factors. Intern Med J 2017; 47: 623-631.
26. Centre of Excellence in Severe Asthma [website]. 2017 www.severeasthma.org.au (viewed May 2018).
27. Tay TR, Lee J, Radhakrishna N, et al. A structured approach to specialist-referred difficult asthma patients improves control of comorbidities and enhances asthma outcomes. J Allergy Clin Immunol Pract 2017; 5: 956-964.
28. van der Meer A-N, Pasma H, Kempenaar-Okkema W, et al. A 1-day visit in a severe asthma centre: effect on asthma control, quality of life and healthcare use. Eur Respir J 2016; 48: 726-733.
29. Gibeon D, Heaney LG, Brightling CE, et al. Dedicated Severe asthma services improve health-care use and quality of life. Chest 2015; 148: 870-876.
30. Global Initiative for Asthma. Global strategy for asthma management and prevention. Available at: http://www.ginasthma.org. Accessed May 24, 2017.
31. National Heart, Lung and Blood Institute. National asthma education and prevention program. In: Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Full Report 2007. Bethesda, Md:NHLBI Health Information Center; 2007.
32. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43:343-373.

33. Cordier T, Slabaugh SL, Havens E, et al. A health plan's investigation of Healthy Days and chronic conditions. Am J Manag Care. 2017;23:e323-e330.
34. O'Byrne PM, Pedersen S, Schatz M, et al. The poorly explored impact of uncontrolled asthma. Chest. 2013;143:511-523.
35. Shen H, Hua W, Wang P, et al. A new phenotype of asthma: chest tightness as the sole presenting manifestation. Ann Allergy Asthma Immunol 2013;111(3):226–7. [PubMed: 23987204]
36. Dixon AE. Rhinosinusitis and asthma: the missing link. Curr Opin Pulm Med 2009; 15(1):19–24. [PubMed: 19077701]
37. Vernon MK, Wiklund I, Bell JA, et al. What do we know about asthma triggers? a review of the literature. J Asthma 2012;49(10):991–8. [PubMed: 23574397]
38. Henneberger PK, Redlich CA, Callahan DB, et al. An official American Thoracic Society statement: work-exacerbated asthma. Am J Respir Crit Care Med 2011;184(3):368–78. [PubMed: 21804122]
39. Tarlo SM, Lemiere C. Occupational asthma. N Engl J Med 2014;370(7):640–9. [PubMed: 24521110]
40. Work-related asthma: number of cases by classification and state, 2009–2012 Available at: https://wwwn.cdc.gov/eworld/Data/Work-related_asthma_Number_of_cases_by_classification_and_state_20092012/924. Accessed September 14, 2018.
41. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J 2005;26(5):948–68. [PubMed: 16264058]
42. Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary (vol 31, pg 143, 2008). Eur Respir J 2018;51(2):143–78.
43. Busse WW, Boushey HA, Camargo CA, et al. Expert panel report 3: guidelines for the diagnosis and management of asthma. Washington (DC): US Department of Health and Human Services, National Heart Lung and Blood Institute; 2007 p. 1–417.
44. Borak J, Lefkowitz RY. Bronchial hyperresponsiveness. Occup Med (Lond) 2016; 66(2):95–105. [PubMed: 26590957]
45. Cockcroft DW. Direct challenge tests: airway hyperresponsiveness in asthma: its measurement and clinical significance. Chest 2010;138(2, Supplement): 18S–24S. [PubMed: 20668014]
46. Cockcroft DW, Murdock KY, Berscheid BA, et al. Sensitivity and specificity of histamine PC20 determination in a random selection of young college students. J Allergy Clin Immunol 1992;89(1, Part 1):23–30. [PubMed: 1730837]
47. Kitch BT, Paltiel AD, Kuntz KM, et al. A single measure of FEV1 is associated with risk of asthma attacks in long-term follow-up. Chest 2004;126(6):1875–82. [PubMed: 15596687]
48. Gautier C, Charpin D. Environmental triggers and avoidance in the management of asthma. J Asthma Allergy 2017;10:47–56. [PubMed: 28331347]
49. GØtzsche PC, Johansen HK. House dust mite control measures for asthma. Cochrane Database Syst Rev 2008;(2). 10.1002/14651858.CD001187.pub3.

50. Platts-Mills TAE. Allergen avoidance in the treatment of asthma and rhinitis. N Engl J Med 2003;349(3):207–8. [PubMed: 12867602].
51. Juel CT-B, Ali Z, Nilas L, et al. Asthma and obesity: does weight loss improve asthma control? a systematic review. J Asthma Allergy 2012;5:21–6. [PubMed: 22791994].
52. Halm EA, Mora P, Leventhal H. No symptoms, no asthma: the acute episodic disease belief is associated with poor self-management among inner-city adults with persistent asthma. Chest 2006;129(3):573–80. [PubMed: 16537854]
53. Chauhan BF, Ducharme FM. Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma. Cochrane Database Syst Rev 2014;(1). 10.1002/14651858.CD003137.pub5.
54. Ducharme F, Ni Chroinin M, Greenstone I, et al. The addition of long-acting beta2-agonists to inhaled steroids compared to higher doses of inhaled steroids alone as maintenance treatment for chronic asthma. Cochrane Database Syst Rev 2010;(4). 10.1002/14651858.CD005533.pub2.
55. Kew K, Dahri K. Long-acting muscarinic antagonists (LAMA) added to combination long-acting beta2-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma. Cochrane Database Syst Rev 2016;(1). 10.1002/14651858.CD011721.pub2.
56. Sobieraj DM, Baker WL, Nguyen E, et al. Association of inhaled corticosteroids and long-acting muscarinic antagonists with asthma control in patients with uncontrolled, persistent asthma: a systematic review and meta-analysis. JAMA 2018;319(14):1473–84. [PubMed: 29554174]
57. Newman KB, Milne S, Hamilton C, et al. A comparison of albuterol administered by metered-dose inhaler and spacer with albuterol by nebulizer in adults presenting to an urban emergency department with acute asthma. Chest 2002;121(4): 1036–41. [PubMed: 11948030]
58. Newman SP. Spacer devices for metered dose inhalers. Clin Pharmacokinet 2004;43(6):349–60. [PubMed: 15086274]
59. Thomson NC, Chaudhuri R. Omalizumab: clinical use for the management of asthma. Clin Med Insights Circ Respir Pulm Med 2012;6:27–40. [PubMed: 22745565]
60. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med 2014;371(13):1198–207. [PubMed: 25199059]
61. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet Respir Med 2015;3(5):355–66. [PubMed: 25736990]
62. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor a monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2016;388(10056):2128–41. [PubMed: 27609406]
63. Dombret M-C, Alagha K, Boulet LP, et al. Bronchial thermoplasty: a new therapeutic option for the treatment of severe, uncontrolled asthma in adults. Eur Respir Rev 2014;23(134):510–8. [PubMed: 25445950]

64. Chupp G, Laviolette M, Cohn L, et al. Long-term outcomes of bronchial thermoplasty in subjects with severe asthma: a comparison of 3-year follow-up results from two prospective multicentre studies. Eur Respir J 2017;50(2). 10.1183/13993003.00017-2017.
65. Bielory L, Lupoli K (1999) Review article: herbal interventions in asthma and allergy. J Asthma 36:1–65, . CrossRef PubMed Web of Science Google Scholar
66. Govindan S, Viswanathan S, Vijayasekaran V, et al. (1999) A pilot study on the clinical efficacy of Solanum xanthocarpum and Solanum trilobatum in bronchial asthma. J Ethnopharmacology 66:205–210, . CrossRef PubMed Google Scholar
67. Ammon HPT, Mack T, Singh GB, et al. (1999) Inhibition of LTB4-formation in rat peritoneal neutrophils by an ethanolic extract of the gum resin extract of Boswellia serrata. Planta Med 57:203–207, . Google Scholar
68. Shivpuri DN, Menon MPS, Parkash D (1968) Preliminary studies in Tylophora indica in the treatment of asthma and allergic rhinitis. J Assoc Physicians 16:9–15, . Google Scholar
69. Toda S, Kimura M, Ohnishi M, et al. (1988) Effects of the Chinese herbal medicine “saiboku-to” on histamine release from and the degranulation of mouse peritoneal mast cells induced by compound 48/80. J Ethnopharmacol 24:303–309, . CrossRef PubMed Google Scholar
70. Egashira Y, Nagano H (1993) A muticenter clinical trial of TJ-96 in patients with steroid-dependent bronchial asthma. Ann NY Acad Sci 685:580–583, . PubMed Web of Science Google Scholar
71. Vachon L, Fitzgerald MX, Solliday NH, et al. (1973) Single-dose effect of marijuana smoke. Bronchial dynamics and respiratory-center sensitivity in normal subjects. N Engl J Med 288:985, . Google Scholar
72. Sakula A. Henry hyde salter (1823-71): A biographical sketch. *Thorax.* 1985;40:887–888. [PMC free article] [PubMed] [Google Scholar]
73. 2. Vyas H, Krishnaswamy G. Paul ehrlich's "Mastzellen"--from aniline dyes to DNA chip arrays: A historical review of developments in mast cell research. *Methods Mol Biol.* 2006;315:3–11. [PubMed] [Google Scholar]
74. 3. McEwen BJ. Eosinophils: A review. *Vet Res Commun.* 1992;16:11–44. [PubMed] [Google Scholar]
75. 4. Osler W. *The Principles and Practice of Medicine.* 1st ed. NY: D. Appleton and Company; 1892. pp. 497–501. [Google Scholar]
76. . Bleecker ER, FitzGerald AM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet388(10056):2115–2127, 2016. doi: 10.1016/S0140-6736(16)31324-1
77. 2. FitzGerald AM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 388(10056):2128–2141, 2016. doi: 10.1016/S0140-6736(16)31322-8
78. World Health Organization 3 May 2021