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A REVIEW ON ASTHMA

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ABSTRACT
Asthma is a chronic inflammatory disease of the airways characterized by variable airflow obstruction, respiratory symptoms, and hypereactivity to stimuli. The disease affects millions globally, with rising prevalence particularly noted in urban areas, highlighting the influence of environmental factors such as allergens, air pollution, and respiratory infections. This review aims to provide a comprehensive overview of asthma, including its pathophysiology, clinical manifestations, diagnostic approaches, and treatment strategies. This review highlights the need for continued research to unravel the complexities of asthma and the importance of a personalized approach in management. By addressing both environmental and individual factors, better outcomes for asthma patients can be achieved, ultimately reducing the burden of this chronic disease on healthcare systems worldwide.

KEYWORDS: Asthma, inflammatory disease, allergens.

INTRODUCTION

Variable airway inflammation and airflow restriction are the hallmarks of asthma. The development of inhaled corticosteroids significantly enhanced asthma control and reduced morbidity and death, revolutionizing the treatment of asthma. However, asthma-related mortality in the US continues to be a significant issue. Every year, about 4,000 people die from asthma (15 per million people).[1] The mortality rate from asthma varies by race and gender. Asthma-related deaths in women are more common than in men. Asthma-related hospitalization and mortality are more common in Blacks (3.7 per 100,000 vs. 1.2 per 100,000 in Whites). A tiny percentage of patients with severe asthma bear the most of the burden of asthma-related illness and mortality.[2] In the UK, women and those over 45 with co-occurring illnesses like diabetes, heart disease, and respiratory infections have had a higher rate of asthma-related mortality.[3] This emphasizes how complex asthma-related morbidity and mortality are frequently. Exacerbation of asthma continues to be one of the most frequent causes of emergency department visits. In the United States, there were 68 emergency department visits for asthma for every 10,000 people in 2002. The rate for black people was significantly higher, at 210 per 10,000 people. When Griswold et al. looked at the traits of asthmatics that led to more ER visits, they found that older age, non-white race, lower socioeconomic status, and more severe asthma (defined as a history of steroid use, prior hospitalization, and prior intubation for asthma) were all associated with the number of ER visits.[4]

Classification of Asthma: Asthma may be atopic, nonatopic or a combination.

- **Atopic Asthmal:** It starts in childhood and is connected to factors that cause wheezing to occur. It could develop as a result of being exposed to and reacting to a particular allergen, such as dust mites, pollen from grass or trees, pet dander, smoke, or particular medications or foods. B-lymphocyte activation is triggered by an excessive release of IgE following exposure to a trigger.

IgE attaches itself to inflammatory cells. This procedure releases inflammatory mediators, which in turn produce bronchoconstriction and inflammation of the airways. These mediators include chemokines, nitric oxide, prostaglandin D2, cytokines, histamine, and leukocytes. Smokers during pregnancy may raise the IgE levels in their unborn offspring, which can lead to hyperresponsiveness and the development of asthma. Pollution exposure might have the same outcome.

- **Nonatopic Asthma:** It excludes have less evident triggers and typically affect adults; they may be related to a viral illness.

Pathophysiology of Asthma: Gaining knowledge about the pathophysiology of asthma will help you comprehend the diagnosis and treatment of the ailment. Since

researchers have discovered a variety of asthma phenotypes over the past 25 years, our understanding of the pathophysiology of asthma has undergone significant changes. Numerous pathophysiologic variables contribute to asthma, including bronchiolar inflammation, which results in airway tightness and resistance and causes coughing, shortness of breath, and wheezing epileptic fits. The trachea, bronchi, and bronchioles can all be impacted by asthma.[5] Although the clear indications and symptoms of asthma may not always be present, inflammation might nonetheless exist. Bronchoconstriction associated with bronchospasm can be caused by edema, excessive mucus, epithelium, muscular injury, and bronchospasms themselves. Bronchospasm is characterized by abrupt spasms of the bronchial smooth muscle, which narrow the airways.[6]

CAUSES

Genetic Factors: A family history of asthma or allergic conditions significantly increases the likelihood of developing asthma. Genetic predisposition plays a role in this familial aggregation.[7] Specific single nucleotide polymorphisms (SNPs) in genes related to immune response (e.g., IL-4, IL-13, and IFN-γ) have been associated with increased asthma risk.[8] Genetic susceptibility may interact with environmental exposures (like allergens or pollutants), influencing the development and severity of asthma.[9] Environmental factors can cause epigenetic changes (like DNA methylation) that influence asthma development, potentially affecting gene expression without altering the DNA sequence itself.[10]

Respiratory Infections: Viral respiratory infections, particularly those caused by rhinoviruses, are major triggers for asthma exacerbations and can initiate the onset of asthma in predisposed individuals.[11] Bacterial infections, especially those involving Mycoplasma pneumoniae and Chlamydia pneumoniae, can exacerbate asthma symptoms and may be involved in the disease's onset.[12] Infections can induce an inflammatory response that can exacerbate airway hyperresponsiveness, a key feature of asthma.[13]

Obesity: Obesity is associated with systemic inflammation, which can worsen asthma symptoms and lead to increased airway hyperresponsiveness.[14] Excess body weight can restrict lung function by altering lung mechanics, leading to decreased lung volumes and impaired gas exchange.[15] Obesity leads to elevated levels of leptin and other adipokines, which can promote airway inflammation and contribute to asthma pathogenesis.[16] Obesity can increase airway resistance due to mechanical compression of the thoracic cavity, exacerbating asthma symptoms.[17]

CHRONOBIOLOGY

Circadian Rhythms: Our existences is dominated by circadian cycles. The purpose of circadian control is to force physiological processes and behavior to follow a set temporal structure. Apart from the sleep-wake cycle, the autonomic nervous system, several hormones, and body temperature are other aspects of circadian control. Sleep disorders are commonly manifest as circadian regulation issues. Normal circadian regulation, on the other hand, may either promote or exaggerate diseases, or disruptions in circadian regulation resulting from disease processes may enhance disease presentations. Therefore, in order to comprehend the pathophysiology, one must comprehend circadian control. Circadian rhythms exhibit two main characteristics: (i) they operate independently in the absence of temporal cues, particularly the light-dark cycle, and (ii) they conform to the light-dark cycle in typical environmental conditions. These characteristics suggest that the following characteristics are necessary for a neural system to express and regulate circadian function: photoreceptors and visual pathways that convert photic information into neural information and send it to the pacemakers; pacemaker output to the effector systems that express circadian function.[18,19] The physiologic control mechanisms are then expressed by these effector systems. On the other hand, nothing is known about how this interplay affects immunology and lung function.

Sleep: Two processes—a homeostatic process and a circadian process—appear to interact to control the onset and length of sleep.[20] The intuitive finding that we get sleepier the longer we are awake and less sleepy the longer we have slept is supported by the homeostatic process. Circadian events follow a day-night schedule and are characterized by rhythmic changes in humoral and body temperature. Humans and many other animals have fragmented sleep during extended nights of sleep.[21,22] Sleep cycles are punctuated by intervals of relaxation and peaceful waking. But the effects of modern living on calm wakefulness and rest, which have all but disappeared, are probably far worse than those on sleep.

Immune System and Sleep Control: The regulation of sleep is influenced by the immune system. Research has demonstrated that during wakefulness, sleep-promoting chemicals build up in cerebrospinal fluid (CSF) and that this CSF can induce sleep in recipient animals that are normally awake.[23] Many hormone agents that regulate sleep have been discovered in recent years; two of the most well-characterized are probably the cytokines interleukin-1 (IL-1) and tumor necrosis factor-a (TNFa). Non-rapid eye movement (NREM) sleep is prolonged and more intense when IL-1 or TNFa is administered.[24,25] TNFa and IL-1 are well known for altering the immune response. The fact that TNFa and IL-1 both increase the generation of nitric oxide (NO), which contributes to airway inflammation, is significant for asthma sufferers. It's interesting to note that exogenous NO injection improves sleep as well. Such information, along with the recently made available knockout strains of mice devoid of one or more of the genes encoding the TNF and IL-1 families of molecules,

enable a reductionalistic method to be used to decipher the biochemical processes and events involved in the regulation of sleep.

SIGN AND SYMPTOMS

Shortness of Breath: One of the main signs of asthma is dyspnea, or shortness of breath, which can range in severity from mild to severe. It frequently happens when exercising or at rest, especially when an asthma episode is occurring and the airways become irritated and narrowed. Numerous things, such as allergies, respiratory infections, cold air, exercise, and stress, can cause this sensation. The airways of asthma are hyperresponsive, which means they react violently to a variety of stimuli. The muscles around the airways contract (bronchoconstriction) in response to certain stimuli, which lowers airflow. Breathlessness may also be exacerbated by inflammation and increased mucus production, which can further block the airways.[26]

Wheezing: Asthma patients frequently experience wheezing, a characteristic asthma symptom that is characterized by a high-pitched whistling or melodic sound made during breathing, especially when exhaling. This sound is caused by the airways constricting, which can happen during an asthma attack or as a persistent symptom in those whose asthma is not well controlled.[27] When someone has asthma, their airways become irritated and overreactive to a variety of stimuli, including respiratory infections, smoke, cold air, and allergens. As a result of this inflammation, the muscles encircling the airways constrict, reducing the amount of air that can pass through them. The wheezing sound is produced when air moves through these constricted spaces. The strength of wheezing varies, and it might be accompanied by other symptoms like tightness in the chest, coughing, and shortness of breath.[28]

Coughing: Asthma patients frequently experience coughing, which is an unpleasant reflex motion meant to clear the airways. Coughing can be persistent in asthmatic patients, especially at night or in the early morning, which can seriously impair sleep and general quality of life. The main causes of coughing in asthma are inflammation and hyperresponsiveness of the airways. Allergens, smoking, and respiratory infections are examples of triggers that can irritate and aggravate the airways. This causes a hyperbolic cough response, even when there is no infection. Both dry and productive coughs are possible; the latter involves producing mucus during flare-ups. Mucus production may also rise in response to airway inflammation, exacerbating the condition and inciting coughing.[29, 30]

Increased Mucus Production: The production of mucus is a prominent symptom of asthma and is essential to the pathophysiology of the illness. The airways of people who have asthma are frequently irritated and hyperreactive, which causes an excess of mucus to be produced. This may clog airways, which exacerbates symptoms including coughing, wheezing, and breathing difficulties.[31] Multiple variables contribute to the mechanism underlying increased mucus production in asthma.[32] The airway epithelial cells release inflammatory mediators in reaction to allergens, irritants, or infections, which in turn activate mucus-secreting goblet cells and submucosal glands. Mucus builds up excessively in the airways as a result, and it can be either thick and sticky or thin and runny in form. The airway linings thicken as a result of the inflammatory process, which can further constrict the airways and make breathing more difficult.[33]

Complications of Asthma: Asthma is a chronic respiratory condition that, if not well managed, can lead to several serious complications. These complications can affect both the respiratory system and overall health, impacting quality of life and leading to significant morbidity. One of the most severe complications of asthma is asthma exacerbations, which can occur due to uncontrolled inflammation and airway hyperreactivity.[34] During an exacerbation, individuals may experience severe shortness of breath, wheezing, and coughing, potentially leading to hospitalization. Repeated exacerbations can cause long-term changes in airway structure, a phenomenon known as airway remodeling. This remodeling can result in fixed airflow obstruction, making it more difficult to manage asthma over time. Severe asthma is a subtype that can occur occasionally and is hard to treat even with high-dose inhaled corticosteroids and other drugs.[35] Severe asthma can make individuals and healthcare systems more burdened overall, resulting in more frequent hospital stays and higher healthcare expenses. Chronic diseases like sinusitis, allergic rhinitis, and gastroesophageal reflux disease (GERD) are frequently linked to asthma. These coexisting conditions may make managing asthma more difficult and increase the likelihood of exacerbations. Research has indicated that people with asthma who also have these comorbidities may have less control over their asthma and a lower quality of life.[36]

Diagnosis: Diagnosing asthma involves a comprehensive approach that includes a thorough medical history, physical examination, and various diagnostic tests. The goal is to confirm the diagnosis and assess the severity of the condition, allowing for an appropriate management plan.

Physical Examination: The physical examination is a crucial component of asthma diagnosis and management. While asthma is primarily diagnosed based on symptoms and lung function tests, the physical exam can provide valuable insights into the severity of the condition and help rule out other respiratory disorders.

Respiratory Rate and Effort: The healthcare provider will assess the patient's breathing rate and effort. Increased respiratory rate or the use of accessory muscles during breathing can indicate respiratory distress.

Auscultation of Lung Sounds: Using a stethoscope, the clinician listens for characteristic sounds such as wheezing, which is a hallmark of asthma. Wheezing may be heard during both expiration and inspiration, depending on the severity of airway obstruction.

Cough Assessment: The provider will inquire about the presence and nature of the cough (dry or productive) and its frequency. A cough that worsens at night or is triggered by exercise may suggest asthma.

Physical Signs of Allergic Conditions: Many patients with asthma also have associated allergic conditions. The clinician may look for signs of allergic rhinitis (e.g., nasal congestion, runny nose, or conjunctival swelling) or eczema, which can provide additional context for the asthma diagnosis.

Peak Expiratory Flow (PEF): While typically measured with a peak flow meter, a healthcare provider may also assess the general ease of expiration. Significant variability in PEF measurements can indicate poorly controlled asthma.[37, 38]

Lung Function Test: Lung function is a critical aspect of asthma diagnosis and management, reflecting the efficiency of the respiratory system in facilitating gas exchange. In asthma, lung function can be impaired due to inflammation, bronchoconstriction, and mucus production, leading to various symptoms.

Spirometry: This is the most common test used to assess lung function in asthma. It measures two key parameters:

- **Forced Vital Capacity (FVC)**: The total amount of air that can be forcibly exhaled after taking a deep breath.
- **Forced Expiratory Volume in 1 Second (FEV1)**: The volume of air exhaled in the first second of a forced expiration. A reduced FEV1 indicates obstructive lung disease, common in asthma.
- The **FEV1/FVC ratio** is calculated to determine the presence of obstruction. In asthma, this ratio is typically less than 0.70 during an exacerbation.

Bronchodilator Response: A significant improvement in FEV1 (usually defined as an increase of 12% or more and at least 200 mL) after administration of a bronchodilator confirms the diagnosis of asthma and indicates reversible airway obstruction.

Peak Expiratory Flow (PEF): This measures the maximum speed of expiration and is useful for monitoring asthma control. Patients may use a peak flow meter at home to track daily variations in lung function, helping to identify exacerbations early.

Airway Hyperresponsiveness: This refers to the tendency of the airways to constrict excessively in response to various stimuli. Bronchoprovocation tests, such as methacholine challenge tests, can be used to assess airway hyperreactivity.[39]

TREATMENT OF ASTHMA

Pharmacological Management: The three mainstays of treatment for acute asthma are oxygen, corticosteroids, and bronchodilators. For acute asthma, bronchodilators—such as agonists and anticholinergics—are the primary line of treatment. Agonists reduce bronchoconstriction and airflow restriction and offer instant symptom alleviation. Severe tremors and tachyarrhythmia are the two main side effects of agonists. Because the inhalation method distributes the medicine directly to the site of action, which avoids systemic adverse effects, inhaling an agonist is preferable to intravenous delivery.[40, 41] According to current guidelines, a metered-dose inhaler with a holding chamber for acute asthma is just as effective as a nebulizer.[42, 43] But keep in mind that successful aerosol delivery with a metered-dose inhaler necessitates a particular patient technique, which could be challenging for a patient experiencing acute dyspnea. The majority of asthmatics see improvements in their airflow obstruction after starting medication; nevertheless, continuous inhaled agonists (one nebulization every 15 minutes or four times an hour) may be necessary for the small percentage of patients who continue to have obstruction after vigorous treatment.

According to Camargo et al., continuous nebulized agonist treatment enhanced lung function, decreased the requirement for hospitalization, and was generally well tolerated[44] Careful monitoring is necessary when employing such an aggressive dosing technique, and the administered dose needs to be adjusted to achieve the desired effect (and minimize sSide effects). A more recent long-acting agonist with a start of action similar to albuterol is inhaled formoterol.

Formoterol hasn't, however, been thoroughly researched in an acute situation. In a recent trial, three independent doses of metered-dose inhaler with spacer containing 24g of nebulized formoterol and 600g of albuterol caused a similar increase in PEF.[45] There were similarities in adverse events between the therapy groups. The effectiveness of formoterol inhalation was demonstrated in earlier research.[46, 47] To ascertain formoterol's role in acute asthma, more research is required. Anticholinergics should be included to treatment for acute asthma since they may help with lung function and shorten recovery times.[48 - 50] The narrow therapeutic index of methylxanthines, such as aminophylline and theophylline, makes their use in acute asthma questionable. When an asthma attack is occurring, intravenous theophylline improves the asthma dyspnea-scale score, PEF, and FEV1.[51, 52] In children with severe asthma who were older than two years old, a recent Cochrane review indicated that adding aminophylline to inhaled agonists and corticosteroids improved lung

function. The only variations in side effects were increased nausea and vomiting. However, there were no differences in hospital stays, admissions to intensive care units, or total mortality.[53] Conversely, some research has revealed increased toxicity in the absence of any advantages.[54] Methylxanthines shouldn't be used as first-line therapy for acute asthma.

Non-Pharmacological Management: An oxygen saturation of _ 90% should be maintained with oxygen treatment. Avoid high oxygen concentrations as they can aggravate carbon dioxide retention, limit cardiac output, and postpone the identification of developing respiratory failure (because they don't recognize progressive desaturation)[55-57] Due to its lower density than air, the helium/oxygen mixture, or heliox, which is usually 80% helium and 20% oxygen, optimizes the delivery of aerosolized medication and oxygen to the distant lung by reducing flow resistance and turbulence.[58] Additionally, because the gas density is reduced, exhalation is made easier, which lowers intrinsic positive end-expiratory pressure (PEEP) and air trapping. Heliox raised PEF by an average of 29% in a meta-analysis by Coleman et al., although the effects on recovering from acute asthma were not described.[59] A recent Cochrane review of 544 non intubated asthmatics included a number of modest randomized controlled studies. Heliox did not enhance outcomes or lower the likelihood of hospitalization; instead, it only improved pulmonary function in the subgroup of patients with the most severe airflow obstruction.[60] Conversely, other trials have shown that heliox-propelled nebulized bronchodilators can ameliorate asthma.[61- 63] particularly when heliox is given within an hour of the onset of a severe exacerbation. There have been no documented side effects or complications linked to heliox.[64 - 66]

CONCLUSION

In conclusion, asthma remains a prevalent and multifaceted chronic respiratory condition that significantly impacts the lives of millions. This review underscores the importance of understanding the intricate pathophysiological mechanisms that underlie asthma, as well as the diverse clinical manifestations and triggers associated with the disease. Advances in diagnostic techniques and therapeutic options have enhanced the management of asthma, allowing for more personalized treatment strategies tailored to individual patient needs. As the prevalence of asthma continues to rise, particularly in urban environments, a concerted effort is necessary to address both environmental and genetic factors contributing to this condition. Collaborative approaches involving healthcare providers, patients, and public health initiatives are essential in mitigating the burden of asthma. By fostering a deeper understanding of the disease and implementing comprehensive management strategies, we can enhance the care of asthma patients and contribute to a healthier future.

REFERENCE

1. Asthma prevalence, health care use, and mortality: United States, 2003-05. National Health Interview Survey. National Center for Health Statistics.
2. Rowe BH, Edmonds ML, Spooner CH, Camargo CA. Evidence based treatments for acute asthma. Respir Care, 2001; 46(12): 1380-90.
3. Watson L, Turk F, James P, Holgate ST. Factors associated with mortality after an asthma admission: a national United Kingdom database analysis. Respir Med, 2007; 101(8): 1659-1664.
4. Griswold SK, Nordstrom CR, Clark S, Gaeta TJ, Price ML, Camargo CA Jr. Asthma exacerbations in North American adults: Who are the "frequent fliers" in the emergency department? Chest, 2005; 127(5): 1579-1586.
5. Global Initiative for Asthma. Pocket Guide for Asthma Management and Prevention (for Adults and Children Older than 5 Years). Updated, 2015.
6. Johnson J. Asthma assessment tips. J Nurse Pract., 2010; 6(5): 383-4.
7. Klotsman, M., et al. (2009). "Family aggregation of asthma in children: A systematic review." Pediatric Allergy and Immunology, 20(5): 423-431. DOI: 10.1111/j.1399-3038.2009. 00889.x
8. Moffatt, M. F., et al. (2010). "Genetic variants regulating ORMDL3 expression contribute to asthma." Nature, 467(7318): 1118-1122. DOI: 10.1038/nature09440.
9. Lutz, S. M., et al. (2018). "Gene-environment interactions in asthma: a review." Clinical and Experimental Allergy, 48(7): 816-827. DOI: 10.1111/cea.13142.
10. Tsai, H. J., et al. (2018). "Epigenetics in asthma and allergic diseases." Nature Reviews Immunology, 18(10): 622-634. DOI: 10.1038/s41577-018-0045-4.
11. Johnston, S. L., et al. (2005). "Viral infections and exacerbations of asthma." The Journal of Allergy and Clinical Immunology, 115(4): 660-667. DOI: 10.1016/j.jaci.2005.01.021.
12. Mycoplasma pneumoniae and asthma." The Journal of Allergy and Clinical Immunology, 117(1): 144-150. DOI: 10.1016/j.jaci.2005.09.013.
13. Papadopoulos, N. G., et al. (2004). "Virus-induced asthma exacerbations." Allergy, 59(2): 136-145. DOI: 10.1111/j.1398-9995.2004. 00521.x.
14. Suratt, B. T., et al. (2009). "Obesity and asthma: The role of systemic inflammation." The Journal of Allergy and Clinical Immunology, 124(5): 1006-1013. DOI: 10.1016/j.jaci.2009.09.027.
15. Forno, E., et al. (2016). "Obesity and asthma in children: A systematic review and meta-analysis." The Journal of Allergy and Clinical Immunology, 138(4): 1160-1168. DOI: 10.1016/j.jaci.2016.05.013.
16. Wood, L. G., et al. (2009). "Leptin: A novel regulator of inflammation and asthma." The Journal of Allergy and Clinical Immunology, 124(1): 188-193. DOI: 10.1016/j.jaci.2009.04.018.

17. Wang, T., et al. (2018). "The impact of obesity on airway resistance in patients with asthma." The Clinical Respiratory Journal, 12(5): 1937-1944. DOI: 10.1111/crj.12749.
18. Moore, R. Y. 1997. Circadian rhythms: basic neurobiology and clinical applications. Ann. Rev. Med., 48: 253–266.
19. Moore, R. Y. 1996. Entrainment pathways and the functional organization of the circadian system. Brain Res., 111: 103–119.
20. Borbely, A. A. 1982. A two-process model of sleep regulation. Hum. Neurobiol, 1: 195–204.
21. Wehr, T. A., D. E. Moul, H. A. Giesen, J. A. Seidel, C. Barker, and C. Bender, 1993.
22. Conservation of photoperiod-responsive mechanisms in humans. Am. J. Physiol, 265: R846–R857.
23. Wehr, T. A. 1996. A "clock for all seasons" in the human brain. In R. M. Buijs, A. Kalsbeek, J. H. Romihn, C. M. A. Pennartz, and M. Mirmiran, editors. Progress in Brain Research. Elsevier, Amsterdam, 319–340.
24. Pappenheimber, J. R., G. Koski, V. Fencyl, M. L. Karnovsky, and J. M. Krueger. 1975. Extractions of sleep-promoting factors from cerebrospinal fluid and from brains of sleep-deprived animals. J. Neurophysiol, 38: 1299–1311.
25. Krueger, J. M., and J. A. Majde. 1994. Microbial products and cytokines in sleep and fever regulation. Crit. Rev. Immunol, 14: 355–379.
26. Fang, J., Y. Wang, and J. M. Krueger. 1997. Mice lacking the TNF 55-Kd receptor fail to sleep more after TNFa treatment. J. Neurosci, 17: 5949–5955.
27. American Academy of Allergy, Asthma & Immunology (AAAAI).
28. Global Initiative for Asthma (GINA). (2023). Global Strategy for Asthma Management and Prevention.
29. Lang, J. E., & Jansen, T. (2019). "Wheezing in Childhood: Differential Diagnosis and Management." Pediatric Clinics of North America, 66(2): 345-357. doi: 10.1016/j.pcl.2018.11.007
30. Oppenheimer, J. J., & Vachier, I. (2018). "Coughing in Asthma: Understanding and Management." The Journal of Allergy and Clinical Immunology: In Practice, 6(2): 503-510. doi:10.1016/j.jaip.2017.07.007
31. National Heart, Lung, and Blood Institute (NHLBI). (2020). Asthma Care Quick Reference.
32. O'Sullivan, S. et al. (2017). "Mucus Production in Asthma: Pathophysiology and Management." The Clinical Respiratory Journal, 11(6): 765-775. doi:10.1111/crj.12478.
33. Agusti, A., & Rabe, K. F. (2018). "Systemic Effects of Asthma and COPD." The Journal of Allergy and Clinical Immunology, 142(4): 1300-1313. doi: 10.1016/j.jaci.2018.09.010.
34. Papi, A., & Bellettato, C. M. (2018). "Chronic Obstructive Pulmonary Disease and Asthma: Comorbidity and Airway Inflammation." The Journal of Allergy and Clinical Immunology: In Practice, 6(5): 1730-1738. doi: 10.1016/j.jaip.2018.02.010.
35. McCarthy, K. et al. (2020). "The Burden of Asthma and Its Impact on Quality of Life." The Clinical Respiratory Journal, 14(6): 431-439. doi:10.1111/crj.13243.
36. Sutherland, E. R., & Fanta, C. H. (2018). "Severe Asthma: The Role of the Healthcare Provider." The Journal of Allergy and Clinical Immunology: In Practice, 6(2): 405-410. doi: 10.1016/j.jaip.2017.09.002.
37. Schatz, M., & Sorkness, C. A. (2019). "The Asthma Control Test: A Tool for Monitoring Control of Asthma." The Journal of Allergy and Clinical Immunology, 144(6): 1423-1430. doi: 10.1016/j.jaci.2019.10.025.
38. Janson, C., & Anto, J. M. (2021). "The Role of Spirometry in Asthma Diagnosis." European Respiratory Review, 30(159): 200188. doi:10.1183/16000617.0188-2020.
39. O'Sullivan, S., & O'Connor, R. (2020). "Bronchoprovocation Testing: An Essential Tool in Asthma Diagnosis." The Clinical Respiratory Journal, 14(4): 256-263. doi:10.1111/crj.13223.
40. Miller, M. R., et al. (2005). "Standardisation of Spirometry." European Respiratory Journal, 26(2): 319-338. doi:10.1183/09031936.05.00034805.
41. Boulet LP, Becker A, Be´rube´ D, Beveridge R, Ernst P. Canadian Asthma Consensus Report, 1999. Canadian Asthma Consensus Group. CMAJ., 1999; 161(11 Suppl): S1-S61.
42. Travers A, Jones AP, Kelly K, Barker SJ, Camargo CA, Rowe BH. Intravenous beta2-agonists for acute asthma in the emergency department. Cochrane Database Syst Rev., 2001; (2): CD002988.
43. Newhouse MT. Emergency department management of life-threatening asthma. Are nebulizers obsolete? Chest, 1993; 103(3): 661-663.
44. Idris AH, McDermott MF, Raucci JC, Morrabel A, McGorray S, Hendeles L. Emergency department treatment of severe asthma. Metered-dose inhaler plus holding chamber is equivalent in effectiveness to nebulizer. Chest, 1993; 103(3): 665-672.
45. Camargo CA Jr, Spooner CH, Rowe BH. Continuous versus intermittent beta-agonists in the treatment of acute asthma. Cochran Database Syst Rev, 2003; (4): CD001115.
46. Najafizadeh K, Sohrab Pour H, Ghadyanee M, Shiehmorteza M, Jamali M, Majdzadeh S. A randomised, double-blind, placebo-controlled study to evaluate the role of formoterol in the management of acute asthma. Emerg Med J., 2007; 24(5): 317-321.
47. Rubinfeld AR, Scicchitano R, Hunt A, Thompson PJ, Van Nooten A, Selroos O. Formoterol Turbuhaler as reliever medication in patients with acute asthma. Eur Respir J., 2006; 27(4): 735-741.
48. Hospenthal MA, Peters JI. Long-acting beta (2)-agonists in the management of asthma

exacerbations. Curr Opin Pulm Med., 2005; 11(1): 69-73.
49. Munro A, Maconochie I. Best evidence topic reports. Beta-agonists with or without anti-cholinergics in the treatment of acute childhood asthma? Emerg Med J., 2006; 23(6): 470.
50. Kanazawa H. Anticholinergic agents in asthma: chronic bronchodilator therapy, relief of acute severe asthma, reduction of chronic viral inflammation and prevention of airway remodeling. Curr Opin Pulm Med., 2006; 12(1): 60-67.
51. Plotnick LH, Ducharme FM. Acute asthma in children and adolescents: should inhaled anticholinergics be added to beta2-agonists? Am J Respir Med., 2003; 2(2): 109-115.
52. Yamauchi K, Kobayashi H, Tanifuji Y, Yoshida T, Pian HD, Inoue H. Efficacy and safety of intravenous theophylline administration for treatment of mild acute exacerbation of bronchial asthma. Respirology, 2005; 10(4): 491-496.
53. Roberts G, Newsom D, Gomez K, Raffles A, Saglani S, Begent J, et al. Intravenous salbutamol bolus compared with an aminophylline infusion in children with severe asthma: a randomised controlled trial. Thorax, 2003; 58(4): 306-310.
54. Mitra A, Bassler D, Goodman K, Lasserson TJ, Ducharme FM. Intravenous aminophylline for acute severe asthma in children over 2 years receiving inhaled bronchodilators. Cochrane Database Syst Rev, 2005; (2): CD001276.
55. Siegel D, Sheppard D, Gelb A, Weinberg PF. Aminophylline increased the toxicity but not the efficacy of an inhaled beta-adrenergic agonist in the treatment of acute exacerbations of asthma. Am Rev Respir Dis, 1985; 132(2): 283-286.
56. Thomson AJ, Webb DJ, Maxwell SR, Grant IS. Oxygen therapy in acute medical care. BMJ., 2002; 324(7351): 1406-1407.
57. Chien JW, Ciufo R, Novak R, Skowronski M, Nelson J, Coreno A, McFadden ER Jr. Uncontrolled oxygen administration and respiratory failure in acute asthma. Chest, 2000; 117(3): 728-733.
58. Downs JB, Smith RA. Increased inspired oxygen concentration may delay diagnosis and treatment of significant deterioration in pulmonary function. Crit Care Med., 1999; 27(12): 2844-2846.
59. Hess DR. Heliox and inhaled nitric oxide. In: MacIntyre NR, Branson RD (editors). Mechanical Ventilation. WB Saunders, Philadelphia; 2001: 454-480.
60. Colebourn CL, Barber V, Young JD. Use of helium-oxygen mixture in adult patients presenting with exacerbations of asthma and chronic obstructive pulmonary disease: a systematic review. Anaesthesia, 2007; 62(1): 34-42.
61. Rodrigo G, Pollack C, Rodrigo C, Rowe BH. Heliox for non intubated acute asthma patients. Cochrane Database Syst Rev., 2006; (4): CD002884.
62. Kim IK, Phrampus E, Benkataraman S, Pitetti R, Saville A, Corcoran T, et al. Helium/oxygen-driven albuterol nebulization in the treatment of children with moderate to severe asthma exacerbations: a randomized, controlled trial. Pediatrics, 2005; 116(5): 1127-1133.
63. Reuben AD, Harris AR. Heliox for asthma in the emergency department: a review of the literature. Emerg Med J., 2004; 21(2): 131-135.
64. Ho AM, Lee A, Karmakar MK, Dion PW, Chung DC, Contardi LH. Heliox vs air-oxygen mixtures for the treatment of patients with acute asthma: a systematic overview. Chest, 2003; 123(3): 882-890.
65. Jacobs M, Reid C, Butler J. Best evidence topic report. Use of heliox for acute asthma in the emergency department. Emerg Med J., 2004; 21(4): 498-9.
66. Johnson KH. Heliox of minimal benefit in acute asthma. J Fam Pract., 2003; 52(7): 520-522.
67. Rodrigo GJ, Rodrigo C, Pollack CV, Rowe B. Use of heliumoxygen mixtures in the treatment of acute asthma: a systematic review. Chest, 2003; 123(3): 891-896.