TREATMENT

Asthma Management: An Update

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Introduction

Independent clinicians such as physicians and nurse practitioners are expected to draw on evidence-based information to guide their treatment of various disorders in a safe and effective manner.[1] In disorders such as asthma, clinicians are expected to diagnose the patient based on a cluster of symptoms they present, categorize the severity of their condition, and decide on a treatment plan.[2]

The authors of this article will present an overview of asthma, and provide an outline for treatment based on different levels of asthma severity. This will assist NPs in the process of prescribing asthmatic treatment.

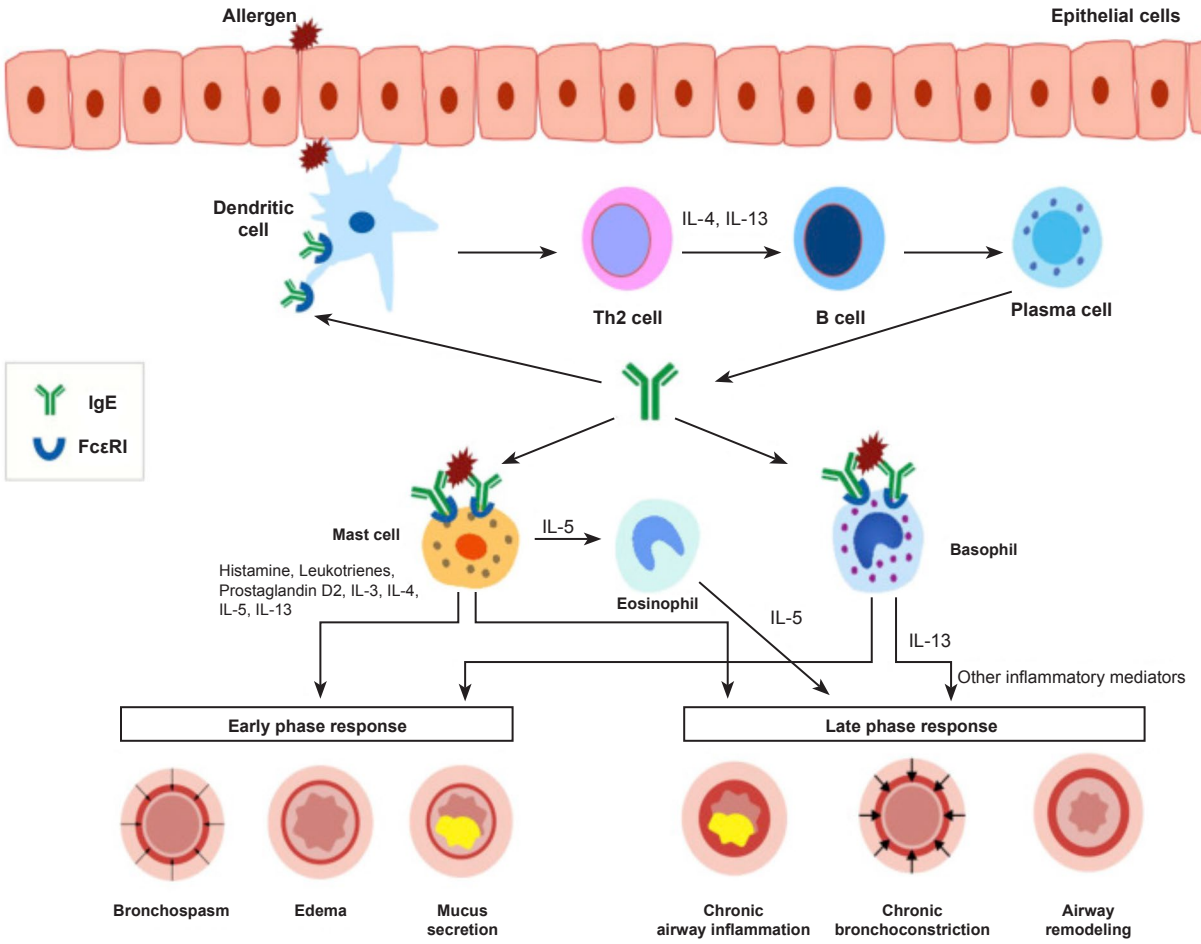
Pathophysiology

Asthma is a chronic respiratory condition that affects more than 300 million people across the globe.[3] It is a challenging syndrome due to its vague and complex pathogenesis and while there are several approaches to controlling asthma, there is no cure.[4] Asthma continues to be a burden not only for the patients, but also the healthcare system, and there is a continued need for better management of this syndrome.[4]

Asthma has been described as a heterogenous disorder as it involves a collection of various symptoms such as wheezing, coughing, chest tightness, and shortness of breath.[4] The complexity of asthma is due to its various clinical phenotypes whose expression is influenced by environmental factors and gene susceptibility.[3] Asthma phenotypes are defined as recognizable combinations of clinical and/or pathophysiological characteristics.[2] Some phenotypes identified by the Global Initiative for Asthma (GINA)[2] include allergic asthma, non-allergic asthma, adult-onset, asthma with persistent airflow limitation, and asthma with obesity.

Asthma is initiated when a certain trigger, such as a pollutant or other risk factor, enters the body and triggers the immunoglobulin E (IgE) antibodies which are sensitized and released

Figure 1. Shows the pathophysiology as an allergen which triggers dendritic cells, which then triggers plasma cells to release immunoglobulin E antibody (IgE). The IgE attaches to mast cells to result in bronchospasm, edema, and mucus secretion, along with the help of interleukins. In severe cases, The IgE will attach to basophils which will result in chronic inflammation and bronchoconstriction, along with airway remodeling.



Adapted from Humbert et al., 2019, p. 1420

by plasma cells.[5] The IgE antibodies bind to mast cells in the body which causes the mast cells to release cytokines and degranulate.[5] The degranulation of mast cells releases histamine, prostaglandins, and leukotrienes which cause reversible inflammation and bronchoconstriction.[5]

In severe cases, airway remodeling also takes place which results in the thickening of the mucosal cells in the airway.[6] Airway remodeling paired with bronchoconstriction can result in excessive airway narrowing which can be fatal in some patients.[6]

Diagnosis

Asthma is a general term that encompasses a variety of pulmonary disorders who all share the characteristic of having reversible airway obstruction.[7] Patients with asthma display clinical symptoms such as chest tightness, wheezing, cough, and dyspnea.[7] According to GINA patients diagnosed with asthma have confirmed variable expiratory airflow limitations, altering their forced expiratory volume in one second (FEV_1) and peak expiratory flow (PEF) scores. The

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definition of airway obstruction is a spirometry measurement of FEV_1 less than 0.8. As the FEV_1 score decreases asthma patients tend to deteriorate and their management becomes challenging.[5] Asthma can be classified into four different groups depending on spirometry and/or clinical indications: intermittent, mild, moderate, and severe.[5] Intermittent asthma is when the patient experiences symptoms less than two days a week, and nighttime awakenings less than two times a month.[5] Mild asthma is classified as experiencing symptoms more than two times a week, with nighttime awakenings averaging three to four times per month.[5] Those with moderate asthma experience symptoms daily, and have nighttime awakenings greater than once a week. Lastly, severe asthma is where the patient is symptomatic throughout the day and can have more than seven nighttime awakenings per week.[5]

Chronic obstructive pulmonary disease (COPD) adds to the difficulty of diagnosing asthma as the two conditions have similar symptoms such as wheezing, coughing, and dyspnea.[7] However, the distinguishing feature between the two is the irreversible damage of the lung parenchyma and limited response to therapy in patients with COPD.[7] COPD is also highly associated with the inhalation of cigarette smoke whereas asthma has many different triggers and, in most cases, begins at a young age.[7]

Pharmacological management

Corticosteroids are known as the controller medication for asthma as they are used to reduce airway inflammation, prevent exacerbations, and generally control symptoms.[2] Overall, their effect is to suppress activated inflammatory genes, and increase transcription of anti-inflammatory genes in order to reduce airway hyperresponsiveness.[8] The following outline provides an overview of the common drugs used to manage asthma and will guide NPs when deciding the proper treatment plan for different severity levels of asthma. It also includes information on the use of desensitization therapy, which is used for allergen specific asthma.

Mild asthma

GINA recommended that patients with mild asthma be prescribed a controller medication such as an ICS, especially if the main concern is symptom control.

In addition to ICS, GINA recommended that NPs also prescribe patients with mild asthma, a short-acting beta agonist inhaler for as needed symptom relief. Beta agonist medications work on beta-adrenergic receptors within the bronchioles which are coupled with G protein receptors. The medication will activate the neurotransmitter cyclic adenosine monophosphate (cAMP) which will activate smooth muscle relaxation resulting in bronchodilation.[9] Before 2019, GINA supported the use of Short-Acting Beta-Agonists (SABA) alone for the as needed treatment of asthma. However, with the evidence emerging from current literature, GINA updated its recommendation to include regular daily dose of ICS with as needed SABA to avoid over-reliance on SABA medications.[2]

Recently, researchers started exploring the efficacy of taking an inhaled combination of ICS/fast-onset long-acting beta-agonists (LABAs) as reliever therapy for patients with mild asthma, as an alternative to regular maintenance dose ICS with as needed SABA. In Canada, O'Byrne et al.[10] conducted a randomized controlled trial (RCT) (n=3836) to explore the efficacy of combined ICS/fast-onset LABA where budesonide-formoterol, a common ICS/fast-onset LABA was administered to patients with mild asthma. Participants were split into three different groups: maintenance dose placebo with as needed terbutaline (SABA) (n=1280), maintenance dose placebo with as needed budesonide-formoterol (n=1279), and maintenance dose budesonide with as needed terbutaline (n=1290).[10] O'Byrne et al.[10] established that the duration of asthma symptoms control with the as needed budesonide-formoterol was longer in comparison to the as needed terbutaline alone (34.4% vs. 31.1% of weeks; odds ratio, 1.14; 95% CI, 1.00 to 1.30; P=0.046). However, as needed budesonide-formoterol was shown to be inferior to maintenance budesonide and as needed terbutaline with regards to recorded weeks with well-controlled asthma (34.4% of 1279 participants vs. 44.4% of 1290 participants; odds ratio, 0.64; 95% CI, 0.57 to 0.73).[10] O'Byrne et al.[10] also demonstrated that budesonide-formoterol used as needed resulted in a 64% decrease in severe exacerbations (annualized exacerbation rate, 0.07 vs. 0.20; rate ratio, 0.36; 95% CI, 0.27 to 0.49), but that the rates of severe exacerbations between the budesonide-formoterol as needed, and the budesonide maintenance/terbutaline as needed group did not differ significantly (annualized exacerbation rate, 0.07 and 0.09, respectively; rate ratio, 0.83; 95% CI, 0.59 to 1.16).[10] The researchers concluded that patients who adhere to the twice daily budesonide and use terbutaline as needed, would achieve effective daily asthma control and decrease the odds of severe exacerbations.[10]

In South Africa, Bateman et al.[11] conducted an RCT (n=4176) where they separated their participants into two groups; budesonide-formoterol as needed or budesonide as a maintenance medication with as needed terbutaline. Bateman et al.[11] demonstrated that as needed budesonide-formoterol was equal to maintenance budesonide with terbutaline with regards to limiting or decreasing the rate of severe exacerbation (0.11 vs. 0.12, 95% CI, 0.10-0.135). However, the results also showed that the budesonide maintenance with terbutaline as needed therapy resulted in better control of asthma symptoms (asthma control questionnaire-5 [ACQ-5]; 40.3% vs 44.3%; odds ratio, 0.86; 95% CI, 0.75 to 0.99) and quality of life (asthma quality of life questionnaire [AQLQ]; mean difference, -0.10; 95% CI, -0.14 to -0.05).[11]

Given the evidence provided by Bateman et al.[12] and O'Byrne et al.,[10] NPs should prescribe patients with mild asthma, an ICS maintenance drug along with a separate, as needed, SABA.

Moderate asthma

Similar to patients with mild asthma, GINA recommended that patients with moderate-severe asthma should be initiated on an ICS for symptom control.[2] However, for patients with moderate to severe asthma, who are not achieving the desired symptom control with the base ICS dose, GINA recommended increasing the dose of ICS.[12]

Zhang et al.[13] performed a systematic review of 8 RCTs (n=3866) at University in Sichuan, China to evaluate the efficacy and safety of increasing the dose of ICS. Zhang et al.[13] focused on the efficacy and safety of increasing ICS doses concluding that, increasing that dose of ICS was associated with lower risk of treatment failure (OR 0.82, 95% CI 0.70-0.97, P = 0.02). However, there was an association between increasing the dose of ICS and non-serious adverse events

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(OR 3.50, 95% CI 1.93-6.35). Zhang et al.[13] added that increasing the dose of ICS will reduce the odds of requiring systemic corticosteroids.

Chipps et al.[14] in an RCT studied the effect of different dosages of ICS on nighttime symptom score, nighttime rescue medication usage, FEV_1, and adverse events that led to withdrawals from the study. Based on these results, Chipps et al.[14] concluded that there was no significant difference between starting with low, moderate, and high doses of various ICS, and that all doses were seen equivalent with regards to the aforementioned outcomes. While administering moderate-to-high dose of ICS did show significant improvement in morning peak expiratory flow (PEF), it failed to establish improvement in other lung functions. Starting high-initial doses of ICS, were also linked to side effects associated with long-term use of high-dose corticosteroids.[13] Chipps et al.[13] also compared ICS alone with ICS/LABA. Chipps et al.[13] revealed that there was no significant difference between low or moderate doses of ICS/LABA (raw mean difference, 25; 95% credible intervals [CrI], 6.1-45.0; raw mean difference, 23; 95% CrI, 9.0-39.0; respectively) compared to the high doses of ICS with regards to improvement of morning PEF values.

GINA recommends that NPs start their patients on a maintenance dose of ICS. However, if the symptoms are not well controlled with the maintenance dose of ICS doubling or quadrupling the dose is recommended for further symptom control. The risks and potential adverse events such as stomatitis, pharyngitis, bitter taste in mouth, and sore throat must be taken into consideration. Therefore, replacing the ICS with an ICS/LABA such as fluticasone propionate with salmeterol combination, could also be beneficial as it would provide better symptom control without the need to increase the dose of corticosteroids, thus limiting the adverse effects from high-dose corticosteroids.

After four weeks of no progress from the ICS/LABA inhaler, it is suggested that NPs prescribe their patients an additional short-acting muscarinic antagonist (SAMA) or short-acting beta agonist (SABA) inhaler and/or switch the ICS/LABA medication to an ICS/LAMA (long-acting muscarinic antagonist medication).

Anticholinergic drugs such as SAMA and LAMA, act on muscarinic receptors on bronchial smooth muscle to inhibit bronchoconstriction and mucus secretion from hyperplasic goblet cells, which is usually caused by acetylcholine release; their main goal is to induce bronchodilation.[14] SAMA medications are an example of a reliever medication for asthma as they will have a fast onset of action providing quick relief of breakthrough symptoms.[2] This is why they are beneficial for additive treatment, when SABA alone is not enough.

Allergen-specific asthma

Another treatment that can be used for adjunct therapy for those who experience allergen-specific asthma is desensitization therapy also called immunotherapy. Desensitization therapy is used for patients with allergic asthma, and while there are many different phenotypes for asthma, allergic asthma is one of the best described phenotypes.[14] There are two different types of allergen immunotherapy (AIT) for asthma: subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT).[2]

NPs should refer patients to an allergist for AIT assessment if they suspect an allergic component. Examples of allergen extracts that could be used are grass, cat, dog, trees, moulds, latex, and weeds.[15]

Conclusion

This article presented an overview of the management of asthma, using an outline that uses severity levels of asthma as a framework. We have used data from rigorous and well-designed studies to support our recommendations. We were also intentional about including guideline driven intervention such as those highlighted by the Global Initiative for Asthma.[2] We believe that this manuscript has potential to be used as a knowledge translation vehicle to improve adherence to best practices.

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