Acute exacerbation of asthma

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SUMMARY

Title: Acute Exacerbation of Asthma

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Asthma is a chronic respiratory condition that causes inflammation and obstruction of the airways. An acute asthma exacerbation presents as an acute or subacute episode of progressive worsening of asthma symptoms, such as shortness of breath, wheezing, cough, and chest tightness. Triggers for an asthma exacerbation can vary between individuals but commonly include exposure to allergens (such as dust mites, pollen, or pet dander), respiratory infections (like the common cold or flu), irritants (such as tobacco smoke or air pollution), exercise, stress, certain medications. Besides, incorrect, and irregular medication intake is a significant risk factor. The symptoms of an acute asthma exacerbation can range from mild to life-threatening. In assessing the severity of the exacerbation, it is crucial to evaluate pulse rate, respiratory rate, subjective assessment of respiratory distress, and accessory muscle use. Prompt and appropriate management is crucial to prevent further deterioration and complications. Administration of bronchodilators and corticosteroids relieves airflow obstruction and helps to prevent future relapses. Severe exacerbations often require additional therapy including oxygen, magnesium, and, in some circumstances, mechanical ventilation. Individuals with asthma need to have an asthma action plan, which outlines the steps to take during an exacerbation and when to seek emergency medical care. Prevention of acute asthma exacerbations involves identifying and avoiding triggers whenever possible. This may include maintaining good indoor air quality, using allergen-proof bedding covers, practicing proper hand hygiene, getting vaccinated against respiratory infections, and managing stress effectively. Regular follow-up appointments with a healthcare provider are necessary to monitor asthma control, ensure that medications are taken regularly and correctly, and to identify potential triggers.

SAŽETAK

Naslov: Akutna egzacerbacija astme

Ključne riječi: akutna egzacerbacija astme, biološki čimbenici astme, prilagođeno liječenje astme

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Astma je kronična respiratorna bolest karakterizirana upalom i opstrukcijom dišnih putova. Akutna egzacerbacija astme je akutna ili subakutna epizoda progresivnog pogoršanja simptoma astme, kao što su otežano disanje, piskanje, kašalj i stezanje u prsima. Okidači za pogoršanje astme mogu varirati među pojedincima, ali obično uključuju izloženost alergenima (poput grinja, peludi ili dlake kućnih ljubimaca), respiratornim infekcijama (poput obične prehlade ili gripe), nadražujućim tvarima (poput duhanskog dima ili onečišćenja zraka) tjelovježbi, stresu, određenim lijekovima. Osim toga, nepravilno i neredovito uzimanje lijekova značajan je faktor rizika za nastup akutnog pogoršanja. Simptomi akutne egzacerbacije astme mogu varirati od blagih do opasnih po život. U procjeni težine egzacerbacije ključna je procjena pulsa, brzine disanja, korištenja pomoćne musculature, subjektivna procjena respiratornog distresa. Brzo i odgovarajuće liječenje je neophodno kako bi se spriječilo daljnje pogoršanje i komplikacije. Korištenje bronhodilatatora i kortikosteroida ublažava opstrukciju protoka zraka i pomaže u sprječavanju budućih recidiva. Teške egzacerbacije često zahtijevaju dodatnu terapiju uključujući kisik, magnezij i, u nekim okolnostima, mehaničku ventilaciju. Osobe s astmom moraju biti opskrbljene osobnim planom liječenja stme, koji opisuje korake koje treba poduzeti tijekom egzacerbacije i kada potražiti hitnu medicinsku pomoć. Prevencija akutnih egzacerbacija astme uključuje prepoznavanje i izbjegavanje okidača kad god je to moguće. To može uključivati održavanje dobre kvalitete zraka u zatvorenom prostoru, korištenje hipoalergijske posteljine, prakticiranje pravilne higijene ruku, cijepljenje protiv respiratornih infekcija i učinkovito upravljanje stresom. Potrebno je redovito liječničko praćenje kako bi se procijenila kontrola astme, osiguralo redovito i pravilno uzimanje lijekova te identificirali potencijalni okidači.

ABBREVIATIONS

GINA – Global Initiative for Asthma

AHR - airway hyperresponsiveness

Th2 - T helper cell type-2

IL - Interleukin

Ig – Immunoglobulin

ICS – inhaled corticosteroid

FEV 1 – Forced expiratory volume in 1 second

SABA – Short-acting beta2 agonist

LABA – Long-acting beta2 agonist

FeNO - fractional concentration of exhaled nitric oxide

NSAID – non-steroid anti-inflammatory drug

PEF – Peak expiratory flow

OCS – oral corticosteroids

pMDI - pressurized metered-dose inhalers

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1. INTRODUCTION

Asthma is a very common chronic respiratory disease characterized by airway hyperresponsiveness (AHR), reversible airflow obstruction and airway inflammation, which results in symptoms including wheezing, coughing, and chest tightness. Although there is no universal definition of an asthma exacerbation, the Global Initiative for Asthma (GINA) defines an exacerbation as episodes characterized by a progressive increase in symptoms of shortness of breath, cough, wheezing, or chest tightness, and progressive decrease in lung function, so they represent a change from the patient's usual status that is sufficient to require a change in treatment (1). Exacerbations may occur in patients with a pre-existing diagnosis of asthma or, occasionally, as the first presentation of asthma. Several factors can trigger this event. The most common asthma triggers include allergies, air pollution, and other airborne irritants, other health conditions include respiratory infections, exercise or physical activity, weather and air temperature, strong emotions, and some medicines. The severity assessment of exacerbation is crucial to better suit the treatment and avoid further deterioration and death.

This review aims to disclose and discuss the characteristics of an acute asthma exacerbation and look at the best course of treatment. The following will be elucidated:

- Overview of asthma and its treatment
- Acute exacerbation of asthma's pathophysiology, and triggers
- Diagnosis and severity assessment of exacerbation
- Treatment of exacerbation
- Self-management regime with a follow-up plan

2. Asthma

2.1 OVERVIEW

Asthma is a common, chronic respiratory disease affecting 1-18% of the population. There is a large geographical variation in asthma prevalence, severity, and mortality. While asthma prevalence is higher in high-income countries most asthma-related mortality occurs in low-middle income countries. It is characterized by variable symptoms of wheezing, shortness of breath, chest tightness, and/or cough, and by variable expiratory airflow limitation. Both symptoms and airflow limitation characteristically vary over time and in intensity. These

variations are often triggered by factors such as exercise, allergen, or irritant exposure, change in weather, or viral respiratory infections.

Symptoms and airflow limitation may resolve spontaneously or in response to medication and may sometimes be absent for weeks or months at a time. On the other hand, patients can experience episodic exacerbations of asthma that may be life-threatening and carry a significant burden to patients (1).

2.2 Pathophysiology of Asthma

The pathophysiology shows that interleukin (IL)-12 is the determining factor for which the cascade pathway takes predominance. When IL-12 is present, type 1 T helper (Th1) cells are formed which leads to CD-8 cell-mediated immunity and neutrophilic-mediated cytotoxic inflammatory responses that include the release of tissue necrosis factor and interferon-gamma. When IL-12 is not present, a Th2 response occurs which leads to more cascades of interleukin and cytokine release from CD-4 cells; IL-4 and IL-13 trigger immunoglobulin E (IgE) production, IL-4 and IL-9 which trigger mast cell activity, IL-3 which triggers basophil activity and IL-5 which is the primary trigger for eosinophil activation, proliferation and recruitment from bone marrow which then aggregates in the lung tissue. All those components are involved in the inflammatory response, leading to degranulation of histamine, prostaglandins, and leukotrienes. Further leads to bronchial hyper-responsiveness, increased mucous secretion, smooth muscle contraction, vascular leakage, shedding of epithelial cells, and ultimately airway obstruction and remodeling. Antigen-specific IgE binding to mast cells and basophil receptors sensitizes them to further allergen exposure. Re-exposure to allergens triggers receptor-bound IgE cross-linking, the rapid release of histamine and other granular-associated preformed mediators, as well as the production and release of prostaglandins and leukotrienes.

2.3 Asthma phenotypes

Asthma can be divided into two major phenotypes: non-atopic or intrinsic asthma and atopic or extrinsic asthma, where early-onset atopic asthma is most common in childhood and early adulthood, followed by non-atopic asthma in older age groups. On the other hand, a newer approach has been recognized, a biology methodology that systems reduce the impact of

assumed biases (2-4). Despite discrepancies in the paper, a consensus on specific subgroups has formed. They are divided into two categories: Th2-high and Th2-low phenotype.

2.3.1 Th2-high phenotype

Th2-high phenotypes are associated with certain types of asthma. The three identified groups of Th2-high phenotypes are early-onset allergic asthma, late-onset eosinophilic asthma, and aspirin-exacerbated respiratory disease (AERD):

- Early-onset allergic or "extrinsic" asthma is characterized by positive allergic skin tests and elevated serum-specific IgE that differentiates it from nonatopic asthma with high Th2. It can range from mild to severe.
- Late-onset eosinophilic asthma is characterized by relatively steroid-resistant eosinophilic inflammation in the airways and is often accompanied by chronic rhinosinusitis with nasal polyps (5). Clinically shows prominent blood and sputum eosinophilia refractory to inhaled/oral corticosteroid treatment. It is associated with intense production of IL-5 and IL-13 and may involve Th2/Th17 interactions. (6,7) Recognition of this type may be an indication to escalate therapy earlier.
- Aspirin-exacerbated respiratory disease (AERD) is a subtype of late-onset eosinophilic asthma characterized by asthma, chronic rhinosinusitis with nasal polyps, and respiratory reactions triggered by cyclooxygenase-1(COX-1) inhibitors like aspirin. AERD is thought to be related to dysregulated arachidonic acid metabolism and cysteinyl leukotrienes (cyLT) (potent bronchoconstrictors that are responsible for most of the symptoms in AERD) production. (8,9)

2.3.2 Th2-low/non-high Th2 phenotype

Th2-low phenotypes have been classified according to clinical phenotypes that include:

- Obesity-associated asthma is characterized by severe symptoms despite moderately preserved lung function in non-atopic, middle-aged women. The molecular mechanisms involve no eosinophilic inflammation, Th1 differentiation of CD4 cells, and innate immune responses involving Th17 pathways and innate lymphoid cells (ILCs) (13,14).

- Very late-onset asthma is diagnosed in individuals above 50 or 65 years of age. Mechanism involve aging lung, immunosenescence, and increased sputum neutrophilia secondary to Th1/Th17 inflammation. (15-18)

Several indicators can help classify individuals into Th2-high or non-Th2-high groups. Biomarkers of Th2-high phenotype include sputum eosinophils, peripheral blood eosinophils, serum total IgE, allergen sensitization panel (specific IgE), and fractional excretion of nitric oxide (FeNO) (12). These biomarkers can assist in identifying asthma phenotypes and guiding therapy selection. It is still a challenge is to identify biomarkers of Th2-low asthma. A good candidate seems to be IL-6, a pleiotropic cytokine, that is associated with metabolic dysfunction and asthma severity, particularly in obese asthmatic patients, its increase can also be seen in viral infections that trigger asthma exacerbations (19).

2.4 FeNO as a clinical measure

Fraction of exhaled nitric oxide (FeNO) is a product of airway inflammation (a biomarker of type 2 inflammation) which is increased in asthma patients' breath, so it can be acquired in a non-invasive method. Basal production is induced in the bronchial epithelium. However, when there is an increase in the expression of type 2 inflammatory cytokines such as IL-4 and IL-13, it leads to overexpression of inducible nitric oxide synthase (iNOS) and consequently to an overproduction of airway NO. Increased NO levels contribute to bronchial hyperreactivity and mucus hypersecretion, increases vascular permeability, reduce ciliary heartbeat, and promote free radical production, airway inflammation, and tissue damage. FeNO levels shows to be higher in atopic individuals and lower in smokers. Assessment of FeNO values helps to define asthma phenotype and to monitor the effectiveness of corticosteroid treatment and adherence to treatment. FeNO is useful in identifying those difficult-to-treat asthma patients that might benefit from personalized therapies with monoclonal antibodies (20,21).

2.5 Sputum eosinophilia as a clinical measure

Persistent sputum eosinophilia is a cellular component hallmark of airway inflammation in asthma as it is responsive to intervention with inhaled corticosteroids (ICS). This measure leads

to a reduced risk of exacerbations. It is especially useful for titrating treatment in frequent and severe asthmatics, resulting in lower steroid use.
Although this measure is shown to be an effective tool, only specialized centers for severe asthma use it, as this approach is time-consuming, demands trained personnel, and can delay results (22).

3. Asthma medication

3.1 Short and Long-Acting Inhaled Beta-2 Agonists

All patients who have been diagnosed should be prescribed a short-acting beta-2 agonist (SABA) "rescue" inhaler. This is usually a salbutamol/albuterol-metered-dose inhaler (MDI). Beta-agonists work by binding to beta-adrenergic receptors in the bronchioles. These receptors are linked to G proteins that stimulate adenylyl cyclase. Adenylyl cyclase activation causes an increase in intracellular cyclic adenosine monophosphate (cAMP). cAMP reduces total intracellular calcium levels in lung smooth muscle tissue, activating protein kinase A. As a result, myosin light chain kinase is inactivated, and myosin light chain phosphatase is activated, causing smooth muscle relaxation. A side effect of this reduced total intracellular calcium levels of calcium is the activation of calcium-activated potassium channels in the cell membranes, which leads to hyperpolarization of the smooth muscle cells, inhibiting further activation and muscle contraction. All those actions lead to decreased contractility and decreased smooth muscle responsiveness to stimulus.
Inhaled, long-acting, beta-agonists most used is salmeterol. These medications work in a similar way as short-acting beta 2 agonists, but their half-life is significantly longer, resulting in a slower onset of action and a longer duration of impact. These should not be taken as monotherapy, due to the Food and Drug Administration (FDA) black-box warning about the incidence of severe asthma exacerbations, which are connected with death in certain asthma patients. They should always be combined with inhaled corticosteroids (23,24).
Formoterol is a bronchodilator that can be used to relieve symptoms and for long-term control of symptoms, given that its onset of action is as fast as salbutamol, but its duration of action is up to 12 hours. It belongs to the group of fast-acting beta-2 agonists (FABA) (1).

Some side effects of beta-agonist medications have been noted to include tremor, increased nervousness and insomnia in children, low serum potassium level, nausea, fever, bronchospasm, vomiting, headache, pain, dizziness, cough, allergic reaction, dry mouth, sweating, chills, and dyspepsia.

3.2 Short and Long-Acting Inhaled Muscarinic Antagonists

Anticholinergic medicinesare classified into two groups: short-acting or long-acting. Short-acting muscarinic antagonist (SAMA) typically used include ipratropium bromide, and long-acting muscarinic antagonists (LAMA) include tiotropium, aclidinium, glycopyrronium, and umeclidinium. These medications function by binding to and blocking neural signals from parasympathetic muscarinic receptors. There are three types of muscarinic receptors: M1, M2, and M3. M1 receptors are found on the cholinergic ganglia and function to modulate the neural transmission of a parasympathetic signal. M2 receptors are found on postganglionic nerve bulbs of parasympathetic nerve fibers. Blockage of this receptor functions to decrease acetylcholine release from the postganglionic nerve endings with a net decrease in signal transmission. M3 receptors are found on smooth muscle cells, mucosal glands, and vascular endothelium along the airways. Blockage of these receptors leads to a decrease in bronchoconstriction, mucus secretion from glandular tissues, and edema of the mucosal linings. The primary effect on asthma is found from inhibiting M3 receptors. Blocking of the M3 receptor leads to a decrease in cyclic guanosine monophosphate (cGMP) levels within the smooth muscle cells. In turn, there is a decrease in calcium levels that activates protein kinase A inactivating myosin light-chain kinase and activating myosin light-chain phosphatase leading to smooth muscle relaxation. Decreases in intracellular calcium also function to decrease mucous secretion from glandular cells.(25,26) Common side effects from these medications are related to their systemic anticholinergic activity including urinary retention and lower urinary tract symptoms, particularly in elderly males, excessive dry mouth, headache, and dizziness. Others may, sinusitis, dyspnea, urinary tract infection, flu-like symptoms, back pain, cough, dyspepsia, and nausea (27).

3.3 Inhaled Corticosteroids

Inhaled corticosteroids (ICS) are typically taken as once or twice daily inhaled medicines which include beclomethasone, budesonide, ciclesonide, and fluticasone. These medications function to

decrease the inflammatory response of an overactive immune system and effectively decrease the airway's hyperresponsiveness by inhibiting the production and release of chemotactic mediators and epithelial adhesion molecules necessary for the extravasation of immune cells into the airways. They also function to decrease the survivability of inflammatory cells such as eosinophils, T lymphocytes, mast cells, and dendritic cells within the airways. Corticosteroids induce these effects on responsive cells by activating glucocorticoid receptors either directly or indirectly to regulate the transcription of specific target gene sequences in the nucleus of a cell. These modulations of transcription of DNA lead to the suppression of inflammation by increasing the synthesis of anti-inflammatory proteins annexin-1, secretory leukoprotease inhibitor, and interleukin-10.

Common combination therapy medicines include fluticasone and salmeterol, budesonide and formoterol, mometasone and formoterol, and fluticasone and vilanterol. ICS offers control of the underlying inflammatory pathology, thus reducing the recurrence of exacerbations, giving better long-term outcomes, has fewer potential side effects, and reducing the cost of medication long-term.

- Side effects that may be local and systemic. The most common local side effects of inhaled steroids are oropharyngeal candidiasis, cough, or hoarseness. Systemic side effects include adrenal suppression, bone loss, skin thinning, increased cataract formation, decreased linear growth in children, metabolic changes, and behavioral abnormalities (28).

3.4 Cromolyn and Zileuton

Cromolyn is a mast cell stabilizing medication that functions to decrease the degranulation of proinflammatory cytokines such as histamine. Furthermore, it is thought to decrease the neural response to irritation of sensory nerve fibers in the airways and decrease the release of cytokines from pre-formed eosinophils.

Zileuton is a 5-lipoxygenase inhibitor medication that decreases leukotriene production, effectively decreasing the immune system's inflammatory response.

- side effects for cromolyn include cough, flushing, palpitation, chest pain, nasal congestion, nausea, fatigue, migraine, sneezing, wheezing, psychosis, pruritus, dysphagia, esophagus spasm, pancytopenia, polycythemia, tinnitus, and pharyngitis.

3.5 Monoclonal Antibody Immune-Modulating Drugs

Newer class monoclonal antibody immune-modulating drugs can be used in patients with severe asthma. These medications aim to decouple the Th2 inflammatory pathway to decrease the immune response to a triggering event, decreasing eosinophilia.

Omalizumab may be an option for adults and adolescents 12 years of age and older who have moderate to severe asthma, a positive skin or in vitro test result in response to a perennial aeroallergen, and symptoms not adequately controlled by inhaled corticosteroids. It functions to directly bind free IgE, thus reducing its ability to signal further Th2 response including eosinophilia and mast cell activation. Baseline IgE levels are not predictive of response but are needed for patient selection and dose determination.

- Possible side effects of omalizumab include injection site reactions, viral infections, upper respiratory infection, sinusitis, headache, pharyngitis, pain, arthralgia, fracture, fatigue, dermatitis, arm pain, leg pain, dizziness, earache, pruritus, nasopharyngitis, pyrexia, upper abdominal pain, streptococcal pharyngitis, otitis media, viral gastroenteritis, epistaxis, alopecia, edema, anaphylaxis, bronchitis, and urticaria.

Mepolizumab is an add-on treatment indicated for patients 12 years of age and older with severe asthma and high eosinophil levels at 150 cells/mcL or greater despite optimal asthma treatment. It binds to IL-5, thus inhibiting its signal to proliferate eosinophils in the bone marrow. (30)

- Some possible side effects of mepolizumab include headache, injection site reactions, systemic allergic/nonallergic reactions, back pain, fatigue, systemic allergic/hypersensitivity reactions, influenza, urinary tract infection, upper abdominal pain, pruritus, eczema, and muscle spasms.

Reslizumab is an add-on therapy for adults ages 18 years and older with severe asthma and eosinophilia. As discussed above, this medicine binds to IL-5, thus inhibiting its signal to proliferate eosinophils in the bone marrow.

- Possible side effects of reslizumab include elevated creatine phosphokinase (CPK), oropharyngeal pain, myalgias, and anaphylaxis.

3.6 Bronchial Thermoplasty

In patients with severe persistent asthma that is poorly or non-responsive to medical therapy, non-medical approach called bronchial thermoplasty, is possible. This is the delivery of controlled, therapeutic radiofrequency energy to the airway wall. The energy disrupts normal airway smooth muscle resulting in destruction, atrophy, and finally in decreased bronchoconstriction. Patient selection and appropriate time of delivery is the key as it can cause a post-procedure exacerbation of bronchospasm and should be avoided in individuals with ongoing exacerbation or with chronic changes of interstitial disease and bronchiectasis. Clinical trials excluded patients with 3 or more exacerbations per year, FEV1 below 60%, and chronic rhinosinusitis (31).

3.7 Medication classification

The pharmacological options for the long-term treatment of asthma can be separated into the following three main categories:

- Controller medications: These medications are used to minimize airway inflammation, control symptoms, and lower future risks such as exacerbations and accompanying lung function decline (32). Low-dose ICS is the treatment of choice for most patients even if symptoms are infrequent in patients with mild asthma. Another controller treatment may consist of ICS-formoterol (ICS-FABA) administered in a single (33). The dose and regimen of controller drugs should be modified to reduce the risk of medication adverse effects, as well as the necessity for oral corticosteroids (0CS).

- Reliever medications: These are given to all patients for treatment of breakthrough symptoms, particularly during asthma attacks or exacerbations. They are also helpful in preventing exercise-induced bronchoconstriction in the short term. As-needed low-dose ICS-formoterol (the preferred reliever, but not if the maintenance controller contains a different ICS-LABA) or as-needed SABA are used. It has been shown that patients who excessively use SABA (e.g., dispensing three or more 200-dose canisters in a year, equating to daily use) have an increased risk of asthma exacerbations (34,35). Reducing and, essentially, eliminating the requirement for SABA relievers is a key goal in asthma management as well as a measure of asthma therapy success.

- Add-on therapies for patients with severe asthma may be considered when patients have persistent symptoms and/or exacerbations despite optimized treatment with high-dose controller medications (usually a high dose of ICS plus a LABA) and treatment of modifiable risk factors (36).

3.8 Stable asthma management

When considering the long-term goals for asthma the main points are to achieve good control of symptoms, maintain normal activity levels, and minimize the risk of asthma-related death, exacerbation, persistent airflow limitation, and side effects. Confirming the patient's own goal is an important consideration in management as it builds on the physician-patient relationship which leads to improved outcomes (37). ICS-containing controller treatment is the preferred initial treatment after the diagnosis of asthma was made, as it has been shown that early initiation of low-dose ICS in asthma leads to a greater improvement in lung function than if symptoms have been present for more than 2-4 years (38). Patients not taking ICS, who experience a severe exacerbation, have a greater long-term decline in lung function than those who are taking ICS, and starting treatment with SABA alone can encourage patients to regard it as their main asthma treatment and increases the risk of poor adherence when daily ICS is eventually prescribed (39). The initial treatment of asthma depends on the severity of the patient's symptoms. Depending on the choice of drug to relieve symptoms, ICS-formoterol or SABA, GINA suggests two approaches. The preferred approach is the use of an ICS-formoterol combination as it has been shown to reduce the risk of severe exacerbations compared to a SABA-containing regimen. If a regimen in which SABA will be the drug to relieve symptoms is chosen, it is necessary to ensure that the patient is ready to take an additional drug containing ICS regularly. Four steps of treatment are suggested:

1. If the patient presents with symptoms less than twice a month and without risk factors for exacerbations, it is preferred to start with a low dose of ICS-formoterol as needed. Another option is low doses of ICS, whenever the patient needs SABA.
2. If the patient has symptoms of asthma or needs to take a drug that relieves symptoms twice a month or more often, it is recommended to start treatment with a low dose of ICS-formoterol as needed. Another option is the regular use of low doses of ICS with SABA as needed.

3. If the symptoms are present most days (e.g. 4-5 days a week) or the patient wakes up at night due to asthma symptoms more than once a week, especially if risk factors are present, it is recommended to regularly take a low dose of the ICS-formoterol combination as the basic drug, and additional inhalations of ICS-formoterol for relief of symptoms. Another option is to use an ICS-long-acting β2-agonist (LABA) with SABA as the main drug, or medium doses of ICS with SABA as needed.
4. In patients who initially present with severe, uncontrolled asthma or an acute exacerbation, it is recommended to start treatment with medium doses of ICS-formoterol as the main drug, and to use additional inhalations of ICS-formoterol to relieve symptoms. In this phase, it may be necessary to apply low doses of oral corticosteroids. Alternatively, medium or high doses of ICS-LABA can be administered, with SABA as needed. Another option is the use of high doses of ICS with SABA as needed, but adherence to this therapy has been shown to be poor (1).

To determine the best management approach, asthma severity should be assessed where a retrospective assessment of the level of treatment required to control the patient's symptoms and exacerbation after several months of continuous treatment (40,41).
Severe asthma is defined as asthma that remains uncontrolled despite adherence to maximally optimized treatment with high dose ICS-LABA, or that requires high dose ICS-LABA to prevent it from becoming uncontrolled. Severe asthma must be distinguished from asthma that is difficult-to-treat due to inappropriate treatment, persistent problems with adherence, or comorbidities such as chronic rhinosinusitis or obesity, as different treatments are applied (42).

- Difficult-to-treat asthma - uncontrolled despite prescribing of medium/high dose ICS with LABA and second controller/ OCS maintenance/ high dose is required to have good symptom control. In many cases, modifiable factors such as incorrect inhaler use, poor adherence, or comorbidities cause such as asthma.

Before initiating any treatment there are several points to take and consider:

- Evidence of asthma diagnosis.
- Patient's level of symptom control and risk factors, including lung function.
- Patient's competence in using the inhaler correctly.
- Schedule a follow-up appointment

- Taking into account different factors for available treatments (i.e. adherence with daily controllers)

By this retrospective definition, asthma severity can only be assessed after good asthma control has been achieved and treatment stepped down to find the patient's minimum effective dose or if asthma remains uncontrolled despite at least several months of optimized maximal therapy.

4. <u>Acute asthma exacerbation and triggers</u>

Exacerbations of asthma are described as periods marked by a sudden worsening of symptoms like shortness of breath, coughing, wheezing, or chest tightness as well as a sudden decline in lung function; therefore, mark a departure from the usual asthmatic condition where it's sufficient to call for a change in therapy. Exacerbations can happen in patients who have already been diagnosed with asthma or, occasionally, they can be the first sign of asthma (1). Severe exacerbations can occur even in patients with mild or well-controlled asthma symptoms. Common exacerbation triggers include:

- **Viral respiratory infections**

  Respiratory tract viruses enter and replicate within airway epithelial cells and damages both ciliated and nonciliated respiratory epithelial cells, leading to necrosis of the airway epithelium, ciliostasis, loss of cilia, and impairment of mucociliary clearance (43-45). The clinical manifestations might be secondary to the release of proinflammatory mediators by damaged bronchial epithelial cells (BECs), as well as a direct cytotoxic effect of the virus. Rhinoviruses (the most common pathogen) attachs to epithelial cells through intercellular adhesion molecule 1 (ICAM-1) for major human rhinovirus (HRV) serotypes or low-density lipoprotein receptors for minor HRV serotypes. Rhinovirus infection itself upregulates the expression of ICAM-1 to further the availability of receptors to bind to and infect epithelial cells (46,47). Infection of BECs with rhinovirus induces the secretion of a wide range of cytokines and chemokines (48). BEC-derived cytokines and chemokines are able to induce neutrophilic, lymphocytic, and eosinophilic inflammation, as well as airway hyperresponsiveness and airway remodeling (48).
- **Allergen exposure e.g., grass pollen, soybean dust, fungal spores**

The upper airways passing air into the lungs carrying high pollen triggering swelling of the airways and constricting breathing by cross-linking with preformed IgE bound to mast cell receptor causing it to degranulate, causing inflammation. (49).

- **Food allergy**

  By cross-linking performed food specific IgE situated on tissue mast cells with food protein, re-exposure causes the release of histamines and leukotrienes causing allergic reaction that further exacerbate the chronic condition (50).

- **Outdoor air pollution**

  Pollutants like ozone, nitrogen oxides, acidic aerosols, and particulate matter show significant association with exacerbation with proximity to main roads at home and school that show an increase in morbidity (51).

- **Poor adherence to ICS**

  It is due to inappropriate use of the medication or due to SABA therapy where patient can be reluctant to use ICS every time. The correlation between poor control and exacerbation is evident as it shows that every 25% increase of ICS adherence results in 11% decreased risk of exacerbation (52).

- Epidemics of severe asthma exacerbations may occur suddenly, putting high pressure on local health system responses. Such epidemics have been reported in association with springtime thunderstorms and either rye grass pollen or fungal spores, and with environmental exposure to soybean dust.

5. Prevention of exacerbations

Prevention of acute asthma exacerbation is a critical part of the management of the disease, focusing on the control of type 2 airway inflammation. Most commonly today it is achieved with ICS treatment which is also effective at reducing the risk for exacerbation and death-related risk. (53) The use of biological therapy (i.e., omalizumab, a monoclonal antibody to IgE) also reduces the risk of exacerbation and makes it possible to reduce the dose of OCs (53). Also, monoclonal antibody therapy against IL-5 and IL-5 receptors have been shown to reduce exacerbation frequency by almost half (53).

In certain cases, non-pharmacological methods can be also implemented to prevent asthma exacerbations, for example:

- Avoidance of medications like Aspirin and other NSAIDs which can cause severe exacerbation and need to be stopped if exacerbation continues, but it is not contraindicated in asthma.
- Smoking cessation and avoidance of tobacco smoke can improve lung function and reduce airway inflammation as well as increases ICS and OCS effectiveness. Encouragement to quit should be provided with counseling and smoking cessation programs.
- Weight reduction for obese patients as asthma can be difficult to control, even 5-10% weight loss with diet can lead to improved asthma control, lung function, and reduced medication needs (1).

6. <u>Diagnosis of acute exacerbation</u>

Acute exacerbations represent a change in symptoms, signs, and lung function from the patient's usual status. In the diagnosis, a brief history should be taken informing on:

- Timing of onset and cause (if known) of the present exacerbation.
- Severity of asthma symptoms, including any limiting exercise or disturbing sleep.
- Any symptoms of anaphylaxis.
- Any risk factors for asthma-related death.
- All current reliever and controller medications, including doses and devices prescribed, adherence pattern, any recent dose changes, and response to current therapy.

As well as a physical examination including:

- Symptoms such as chest tightness, cough (productive or not), a sensation of “air hunger”, inability to lie flat, insomnia, and severe fatigue.
- Signs include the use of accessory muscles of respiration, hyperinflation of the chest, tachypnea, tachycardia, diaphoresis, obtundation, apprehensive appearance, wheezing, and inability to complete sentences.
- Complicating factors such as anaphylaxis, pneumonia, or pneumothorax.
- Different conditions that can explain acute breathlessness such as cardiac failure, inhaled foreign body, or pulmonary embolism (54).

The decrease in lung function can be quantified by measurements of peak expiratory flow (PEF) and forced-exhaled volume in 1 second (FEV1). These data should be compared with the patient's previous lung function. PEF rate is a simple, quick, and cost-effective assessment of the severity of airflow obstruction. Patients can be supplied with an inexpensive PEF meter and can be taught to perform measurements at home to detect exacerbation at home. FEV1 is measured by means of spirometry to assess the volume of air exhaled over 1 second and is the most sensitive test for airflow obstruction. FEV1 is also less independent of expiratory effort once a moderate effort has been made by the patient, unlike PEF (54).

Proper interpretation of the pH, arterial oxygen pressure, and partial pressure of arterial carbon dioxide (PaCO2) might help further assess the severity of an acute asthma exacerbation.

Even though most patients do not require a laboratory, and should not delay the acute asthma attack treatment, testing for the diagnosis of acute asthma might assist in detecting other comorbid conditions that complicate asthma treatment, such as infection, cardiovascular disease, and diabetes. Besides frequent SABA administration can cause transient decreases in serum potassium, magnesium, and phosphate levels.

6.1 Severity assessment

Through the presentation of symptoms, signs, and measurements a pattern of severity score can help in distinguishing different clinical entities and managing the exacerbation event more accurately. Such score divides into mild or moderate, severe, and fatal/life-threatening (1):

- Mild or moderate exacerbation- experiencing breathlessness while walking, prefer sitting than lying, talking in phrases, not necessarily agitated, increased respiratory rate, no accessory muscle use, pulse rate of 100-120 bpm, O2 saturation of 90-95%, PEF >50%
- Severe exacerbation – experiencing breathlessness while at rest, prefers sitting hunched forward, agitated, respiratory rate >30/min, accessory muscle use, pulse rate of >120 bpm, O2 saturation <90%, and PEF 50% or less

- Fatal/life-threatening – Drowsy or confused, paradoxical thoracoabdominal movement, absence of lung sounds, bradycardia, PEF <25 (although maybe not needed) (54).

Certain accommodations based on the severity can be made to reduce future decline and exacerbation like regular PEF monitoring for severe asthma that has the potential to be life-threatening as well as urgent visits to the nearest medical facility to initiate treatment.

7. Treatment of exacerbation

In the case of exacerbation primary treatment (i.e., administration of oxygen, inhaled beta2-agonists, and systemic corticosteroids) is the same for all asthma exacerbations, but the dose and frequency of administration, along with the frequency of patient monitoring, differ depending on the severity of the exacerbation as seen above. In addition to these three primary treatments, therapy with inhaled ipratropium bromide or other agents might also be necessary for severe exacerbations.

7.1 Prehospital Management

Emergency medical services (EMS) providers carry and administer supplemental oxygen and inhaled short-acting bronchodilators for all patients who have signs or symptoms of an asthma exacerbation. EMS providers have a standing order allowing them to provide SABA to patients with an asthma exacerbation. They should also have available a nebulizer, an inhaler plus a spacer/holding chamber, or both for beta2-agonist administration. If beta2-agonist treatment is not possible, subcutaneous epinephrine or terbutaline can also be administered for severe exacerbations (55).

When administering bronchodilator treatment, EMS personnel should not delay patient transport to the hospital. Treatment can be repeated while transporting the patient to a maximum of three bronchodilator treatments during the first hour and then one per hour thereafter. (55)

7.2 Oxygen

Oxygen is administrated through a nasal cannula or a mask to maintain oxygen saturation at 93-95%. This is monitored with pulse oximetry as after stabilization, oxygen should be weaned off. (56,57).

7.3 Inhaled short-acting beta2-agonists

Inhaled SABA is given as the initial treatment of any acute exacerbation. In the emergency department, three doses are administered every 20 to 30 minutes, thereafter the treatment changes according to the improvement of obstruction and related symptoms. Most patients respond sufficiently to the three doses and off them must respond to the first dose significantly (55). Due to the potentially cardiotoxic effect, only selective SABA (salbutamol, albuterol) could be administered in high doses. In milder exacerbation treatment of high dose (4-10 puffs), beta2 agonist can be administered by metered-dose inhaler (MDI) with a valve holding chamber or by nebulizer therapy. Using of nebulizer or MDI is preferred in acute exacerbation because patients cannot properly use MDI due to dyspnea or agitation. Nebulizers should be used consciously as they can disseminate aerosols and potentially contribute to speared of respiratory viral infection.

7.4 Systemic corticosteroids/OCS

It is recommended to administer this treatment to all patients, except those with the mildest exacerbation, as it helps to quickly resolve airway obstruction and lowers the risk of relapse after leaving the emergency department (58). Ideally, the administration should be completed within the first hour of the patient's presentation (59,60). This therapy is particularly important for patients with moderate-to-severe exacerbations who do not respond to initial SABA therapy, patients who experience exacerbation while on OCS, and those who have had a previous exacerbation requiring OCS.

7.5 Controller medication

Patients that already use controller therapy should increase the dose of the medication for the next 2-4 weeks and those that do not should start with the treatment.

7.6 Inhaled ipratropium bromide

A short-acting anticholinergic is used in moderate-severe exacerbation in emergency department settings in combination with SABA (to increase bronchodilation), which improves PEF and FEV1 and also reduces hospitalizations. (61)

7.7 Impending Respiratory Failure/Life-threatening

Although most patients respond well to therapy, a small percentage will show signs of respiratory failure. Because respiratory failure can progress rapidly and is difficult to reverse, early recognition and treatment are necessary. Signs of impending respiratory failure include an inability to speak, altered mental status, intercostal retraction, and worsening fatigue. In that case, different additional treatments can be used:

7.7.1 Magnesium

Intravenous magnesium sulfate is not routinely used in acute exacerbation but can be used for patients that have fatal/severe exacerbations or patients that show no improvement from severe exacerbation after 1 hour of therapy. The usual dosage is 2g over 20 minutes (55).

7.7.2 Intubation

In the event of the need for intubation of a severely ill asthmatic patient which is difficult and can result in complications, there are certain recommendations to better understand when to use it:

- Patients presenting with apnea or coma should be intubated immediately. Persistent or increasing hypercapnia, exhaustion, and depressed mental status represent indications for urgent intubation as well.
- Consultation with or co-management by a physician expert in ventilator management is necessary due to the difficulty of intubating asthmatics.
- Once intubation is deemed necessary, it should not be delayed and done semi-electively and before a respiratory arrest occurs.
- Intravascular volume should be maintained or replaced because hypotension commonly accompanies the initiation of positive pressure ventilation. As well as, high ventilator pressures, with their associated risks of barotrauma, should be avoided (55).

8. Criteria for Hospitalization versus Discharge in the emergency department

After the first hour of the initial treatment, a reassessment of the clinical status and lung function is done to indicate discharge of the patient or to continue treatment, stopping further deterioration and asthma-related death (62). Titration of treatment will follow on the response of

the treatment as the aim is to reach a PEF/FEV1 plateau level or to return to pre-treatment condition.

The lung function criteria used for consideration for admission or discharge from the emergency department include:

- If pre-treatment FEV or PEF is <25% personal best, or post-treatment FEV/PEF is 40% personal best, hospitalization is necessary.
- If post-treatment lung function is 40-60% personal best, discharge can be considered after considering the patient's risk factors and availability of follow-up care.
- If post-treatment lung function is >60% personal best, discharge is considered after considering risk factors and availability of follow-up care (63).

Other factors to consider that can lead to further deterioration and asthma-related death to form a decision for admission include:

- Currently using or recently stopped using OCS.
- Not using ICS.
- Poor adherence to ICS-containing medications and or poor adherence to a written asthma action plan.
- History of psychiatric disease or psychosocial problems.
- Food allergy.
- Over-use of more than eight SABA puffs in the previous 24 hours/ more than one canister monthly.
- Severity of the exacerbation (e.g. need for resuscitation or rapid medical intervention on arrival, respiratory rate >22 breaths/minute, oxygen saturation <95%, final PEF <50% predicted).
- Past history of severe exacerbations (e.g. Intubations, asthma admissions).
- Previous hospitalization or emergency department visits requiring the use of OCS in the past year.
- Several comorbidities including pneumonia, diabetes, and arrhythmia (63,64).

Prior to discharge from the emergency department or hospital to home, arrangements should be made for a follow-up appointment within 2–7 days, discharging plan including reliever as

needed, controller either start or increase, short course of OCS following by assessment of inhaler technique and a written asthma action plan, should be addressed (63).

9. <u>Self-management of exacerbations</u>

Asthmatic patients must learn to live with their condition on a daily basis. Requiring them to take medication regularly, keep a supply of inhalers, avoid any triggers of exacerbation, and cope with the variability of the disease. Most importantly they need to recognize deterioration in their condition to make appropriate treatment adjustments, when to use the emergency services, and seek further professional help. Therefore, self-management education is crucial for the maintenance and achievement of the best outcome of treatment. As it ensures the best tailored treatment for specific status which therefore increases adherence to the treatment. This includes symptom monitoring and/or lung function monitoring, a written asthma action plan, and a regular review by a healthcare professional.

At first, the initial conversation of the self-management regime should be educational and tailored to the individual. Explaining the different factors and speaking on the patient level it will allow for better engagement and eventually better adherence, as in subsequent consultations to ensure everything is up to date. This can be achieved through the health professional or different community educators that are proficient with this treatment management. By explaining/demonstrating the proper use of the inhaler or how to utilize the PEF monitor, the patient can do better in the management and reduce the risk of adverse effects related to misuse of medications (i.e. difficult-to-treat asthma).

Monitoring of lung functions is done using a PEF monitor which is easily used at home. By setting personal best PEF value, the patient can be alert to the degree of the severity and initiate appropriate therapy, consult a healthcare professional, or even both. So, well that if PEF falls to 60% of personal best it can predict exacerbation 1 day prior or fall to 80% with an increase in symptoms it can predict 5 days prior to onset (65).

The most crucial component of effective self-management is an agreed (between the physician and patient) written action plan. This plan can be printed, digital, or visual. It includes explicit directions for the patient on how to adjust reliever and controller drugs, when and how to utilize OCS, and when and how to get medical treatment. The criterion for adjusting controller medication will be tailored to the patient's status. Once there is a change in the usual status like

asthma symptoms that interfere with normal activities or PEF has dropped by more than 20% for more than 2 days, patients that take maintenance-only ICS-containing treatment should increase the dose.

The personalized asthma plan is not a static document but needs constant review, revisiting, and refinement according to the current disease and lifestyle. With regular professional review, it leads to greater reductions in hospitalizations and emergency department visits (65).

9.1 Self-management treatment options

For patients with mild exacerbation asthma, an as-needed combination low dose ICS-formoterol is prescribed. Increasing the dosage when exacerbation ensues leads to reducing the need for OCS treatment and the risk of severe exacerbation for the following 3 weeks (66).

For patients prescribed an inhaled SABA bronchodilator as their reliever, dosing can provide temporary relief until the cause of the worsening symptoms passes or increased controller treatment has had time to take effect. However, the use of SABA reliever is less effective in preventing progression to severe exacerbation requiring OCS than the use of low-dose ICS-formoterol reliever, with no connection to daily controller therapy (67-69). The need for repeated doses over more than 1-2 days shows a need for a review of therapy and even increase controller treatment especially if increased use of SABA wasn't responding.

9.1.1 Combination of low-dose ICS with LABA (formoterol) maintenance and reliever regimen in a single inhaler improves asthma symptom control and reduces exacerbation requiring OCS and hospitalization due to the effect of very early intervention of exacerbation. Different combinations of formoterol should not be used as it increases the risk of asthma-related death (65). With the ICS controller regime, when PEF falls significantly, quadrupling the dose (200mcg/day) to reduces OCS intake (70,71).

9.1.2 Oral corticosteroids

Prednisone or prednisolone is initiated once the patient is in severe exacerbation (PEF <60% personal best), does not respond to increased reliever and controller therapy for 2-3 days, or has a history of sudden severe exacerbations. It speeds the resolution of exacerbation and prevents

relapse and should, if possible, be used within one hour of presentation. It takes at least 4 hours for clinical improvement.

9.2. Follow-up

Following discharge, the patient should be regularly reviewed by their healthcare professional/ specialist over subsequent weeks until good symptom control is achieved, and the best lung function is reached or surpassed. Telephone reminders to make an appointment or telephone coaching and transportation vouchers can be used to improve primary care follow-up for the short term. (72) Once the patient arrives at the follow-up appointment it should be made clear that the exacerbation is resolved, if OCS can be discontinued, possible causes removed, and the patient's understanding of the medication and its use. As Patients who have more than 1-2 exacerbations per year despite increased medication dosage, should be referred to a specialist clinic for evaluation.

The written asthma action plan should be reviewed to ensure that it meets the needs of the patient. Unless the history indicates that the exacerbation occurred on a background of long-term poorly controlled asthma, maintenance controller treatment can normally be lowered to previous levels 2-4 weeks following the exacerbation (1). In this case, once the provided inhaler technique and adherence have been checked, a step-up in treatment can be initiated.

10. DISCCUSION AND CONCLUSSION

The aim of this paper was to describe and investigate acute exacerbation of asthma, its management both in health care and at home with self-management.

Asthma is a heterogeneous disease that can manifest in different forms and with different phenotypes. It can be shown that through different biomarkers two phenotypic asthma can be described: Th2 high and Th2 low. This allows clinicians to better monitor and treat each type and target the specific mechanisms. The initial treatment of asthma depends on the severity of the patient's symptoms. GINA suggests two approaches, depending on the choice of drug to relieve symptoms, ICS-formoterol, or SABA. The preferred approach is the use a ICS-formoterol fixed combination as it has been shown to reduce the risk of severe exacerbations compared to a SABA-containing regimen. If a regimen in which SABA will be the drug to relieve symptoms is

chosen, it is necessary to check whether the patient is ready to take an additional drug containing ICS regularly.

Assessing the severity of the disease based on a retrospective level of treatment is required to control the patient's symptoms and exacerbation. Exacerbations can be triggered by multiple factors through an allergic reaction, viral infection, or even poor adherence to ICS therapy.

The prevention of exacerbation as in any disease is very helpful as it keeps the deterioration to a minimum that is best achieved with low-dose ICS-formoterol combination pharmacologically. As well as Some non-pharmacological methods such as avoiding tobacco smoke or weight loss for obese patients.

Diagnosis of acute exacerbation is defined by the combination of symptoms and signs such as cough, wheezing, expressed accessory respiratory muscles, or even the inability to lie flat. Although it is not necessary for diagnosis clinical measures such as PEF, FEV1, and oxygen saturation can assist in defining the severity and the treatment response. The severity of exacerbation derived from symptoms signs and measurements guides the treatment in acute events. There are three treatments that should be used when an exacerbation is diagnosed: oxygen (preferably low flow and monitored), inhaled beta2 agonists, and systemic corticosteroids.

The challenge of managing acute exacerbation of asthma stems from its heterogeneity, so an immediate culprit cannot be always defined at first and the risk of exacerbation decline can be fast and aggressive. Therefore quick response with constant reassessment is a key part in achieving the best result possible in acute events.

In modern approach the therapy of acute asthma has shifted to a more combined effort between the physician and the patient with self-management. With this method, the patient is educated on the monitoring such as PEF monitor, signs of incoming exacerbation, and the medication prescribed.

In conclusion, as our understanding of asthma and its different mechanisms is expanding so will the improvement of the therapy given. Especially in acute exacerbation where treatment of stable asthma contributes to the preserved condition from reaching exacerbation as well as moving into a personalized approach of self-management that gives more authority to the patient and the tools

to deal with acute exacerbation, reducing the need for hospitalization and deterioration of the lung.

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Biography

My name is David Gershkovich, I was born in the city of Netanya, Israel on 02.06.1995.

2011-2013 As a high school student I was volunteering in the Star of David services which is equivalent to the Red Cross in Israel. There I learned for the first time how to give basic life support and handle injured people with basic care. I got exposed to the world of medicine and got to participate in emergency care.

2013-2015 After High school I served as a volunteer where I went through a medical course and got positioned on the basis of special forces. There I got to work in a small clinic, where soldiers could come for any medical problem day or night, with certain specialists that come on specific days. There I learned how day-to-day medicine is delivered, and handling trauma cases.

2020 As the SARS-Covid-19 pandemic was happening, I got the chance to work at sampling stations for the detection of infections. Working in a sterile and organized environment, thought me how to work in lab conditions.

2021 In the summer of that year I got to work at an assisted-living facility providing first care and emergency care in certain cases. Working with the elderly showed great benefits as their variety of diagnoses and different treatment courses were a challenge in managing symptoms. As well as working alongside great team of a nurse and a doctor taught me how to work as a multidisciplinary team and the right course of action in emergencies.

2016-2023 I started medical school and got to learn and experience medicine at full time.