LITERATURE REVIEW

Late-Onset Asthma: A Review

Yandi Noer Moelamsyah[1*], Faisal Yunus[1], Fariz Nurwidya[1], Bagus Radityo Amien[2]
[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia.
[2]Department of Respiratory Medicine, Juntendo University, Tokyo, Japan.

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ABSTRACT

Asthma is a chronic respiratory condition with a growing global prevalence, affecting millions of individuals annually. While asthma can develop at any age, late-onset asthma is a specific phenotype that begins in adulthood, as recognized by the Global Initiative for Asthma (GINA) in its 2024 guidelines. This form of asthma is often associated with several predisposing factors, including gender, obesity, occupational exposure, rhinitis, respiratory infections, smoking, stress, and diminished lung function. Unlike early-onset asthma, which frequently involves a history of allergies, late-onset asthma tends to lack allergic triggers, making it a distinct and challenging form of the disease. Managing late-onset asthma is often more complex, as it typically requires higher doses of corticosteroids and demonstrates a reduced responsiveness to standard steroid treatments. The exact mechanisms and pathophysiological processes contributing to the increased severity and poorer clinical outcomes in late-onset asthma remain largely unclear. This uncertainty often leads to underdiagnosis and inadequate management, further complicating patient care. Phenotypic analysis is recommended to improve treatment outcomes. This includes assessing clinical features and utilizing biomarkers, such as inflammatory markers and immunoglobulin E (IgE) levels, to guide targeted therapy when conventional steroid treatments are insufficient. However, there is a significant need for further research to elucidate the underlying mechanisms of late-onset asthma. This literature review is essential to develop more effective, personalized treatment strategies that can address the unique challenges posed by this asthma phenotype, ultimately leading to better management and improved patient outcomes.

INTRODUCTION

Asthma is a condition marked by persistent inflammation of the airways. Complaints and airway obstructions in asthma may vary, and various factors, such as physical activity level, exposure to allergens/irritants, inclement weather, and viral infection, trigger them. Asthma is a global health problem. In 2019, there were 262 million patients suffering from asthma and 455,000 deaths caused by asthma. The number of asthma cases may increase by 100 million cases by 2025. Asthma has a higher prevalence in high-income countries compared to low-income countries. However, deaths caused by asthma occur more often in low- and medium-income countries.[1,2]

The prevalence of asthma in Indonesia in 2018 stood at 4.5%.[3] This figure had increased by 2.1% compared to that of 2013.[3] The prevalence of asthma in Indonesia is highest at age 75 years old and above at 5.1%.[3] However, the increase in the prevalence of asthma in age >75 years old may not be caused by asthma because asthma has similar symptoms with airway stricture in chronic obstructive pulmonary disease (COPD).[4] The prevalence of asthma in women is 2.5%, which is higher compared to that of men at 2.3%.[3] The prevalence of asthma in urban areas is 2.6%, which is higher compared to rural areas at 2.1%.[3] Socioeconomic and technological improvements in large cities in Indonesia greatly alter the quality of the environment. This alteration happens due to cities becoming denser and more crowded, fumes from motorized vehicles and cigarette smoke, and pets, which can affect the lungs' health.[5]

Asthma often starts to develop in childhood. However, it can also begin to develop at any age. A number of factors can cause someone to have a risk of developing late-onset asthma.[6] The predisposing factors

*Corresponding author: mohamad.yandinoer@ui.ac.id

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of late-onset asthma are gender, obesity, work exposure, rhinitis, airway infection, smoking, stress, and low pulmonary function.[7] The aging process has an impact on methacholine response, which affects airway hyperreactivity. Decreased forced expiratory volume after 1 second (FEV_1) is more prevalent each year in late-onset asthma, especially in old people or smokers who smoke more than 10 packs of cigarettes per year.[7] Late-onset asthma is often seen in women and is associated with changes in pulmonary function and the immune system. It is also associated with a lack of atopy.[8]

DEFINITION OF LATE-ONSET ASTHMA

Late-onset asthma is asthma in which the symptoms onset during adulthood. The terminology of age varies across literature, but it is generally between 12 and 65 years old.[9] Patients complain about symptoms that occur without prior medical history, and they experience continuous breathing problems.[6] 2024 Global Initiatives for Asthma (GINA) defines late-onset asthma as one phenotype of asthma that begins in adulthood, often in women who experience asthmatic symptoms for the first time during adulthood.[1] Patients who suffer from this tend to have no history of allergy and require larger dosages of inhaled corticosteroids (ICS) or are particularly resistant to treatment with ICS. Work-related asthma must be differentiated in patients with late-onset asthma.[1]

The GINA 2024 guidelines continue to emphasize personalized asthma management, aiming for better control and reduction of exacerbations. Critical updates include refined treatment strategies, a greater focus on biologics for severe asthma, and updated recommendations for inhaler techniques and adherence. There is also an increased emphasis on environmental and social factors affecting asthma control, with new insights into asthma management across different populations. Late-onset asthma, typically defined as asthma that begins in adulthood, is highlighted in the GINA 2024 guidelines as an important phenotype requiring specific attention. Late-onset asthma may present differently from childhood-onset asthma and is often associated with a higher risk of severe exacerbations and comorbidities such as obesity and chronic sinusitis. The guidelines recommend thorough assessment and tailored treatment approaches, including the potential use of biologics, to manage the specific needs of these patients. The management of late-onset asthma is complex, often requiring a multidisciplinary approach to address both asthma and any associated conditions.[1]

EPIDEMIOLOGY

A study conducted in Europe examined six ethnic groups in the Netherlands and found that the prevalence of late-onset asthma varies from 2.4% to 6% among their population.[7] Older individuals, women, and those with an elevated body mass index (BMI) were more likely to develop asthma in the future.[7] The study found that ethnic background was a separate factor linked to the chance of developing asthma later in life.[7] Individuals of Turkish, Moroccan, and Surinamese ancestry faced a greater risk than those who were native to the Netherlands.[7]

A study in Taiwan showed that the prevalence of late-onset asthma stood at 2.1% of the study population.[9] It also showed similar results to a study in Europe, where women and people with high BMI were more prone to this disease.[10]

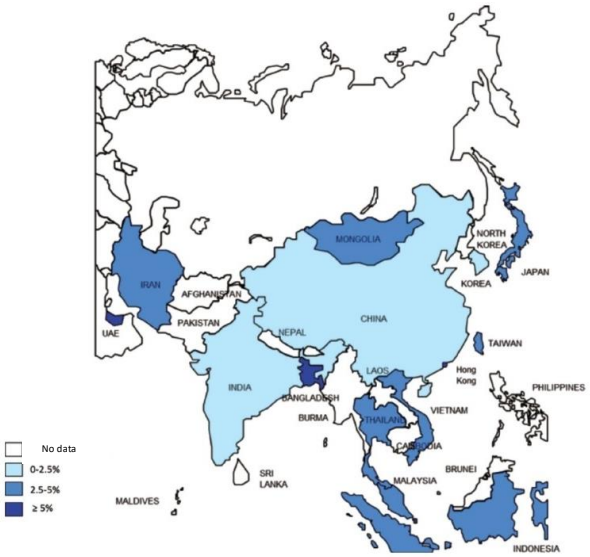

Figure 1. Demographic data of late-onset asthma in Asia[10]

LATE-ONSET ASTHMA PHENOTYPE

Hirano, *et al*. (2018) divided the phenotypes of late-onset asthma into late-onset asthma associated with T-helper 2 (Th2) and late-onset asthma not associated with Th2.[6] Th2-associated late-onset asthma is characterized by sinusitis, nasal polyps, and aspirin-exacerbated respiratory disease (AERD). This condition has the same prevalence in both men and women, with the highest severity during the early phase of the disease. Late-onset asthma not associated with Th2 is associated with gender, obesity, smoking, and aging. This phenotype often happens to women.[11,12]

Amelink, *et al.* (2013) divided late-onset asthma onset into three groups.[13] The first group consists of asthma characterized by significant eosinophilic inflammation and prolonged airflow limitation that

remains despite intensive anti-inflammatory therapy. The second group consists of obese women with asthma who experience frequent asthmatic symptoms, leading to frequent visits to healthcare facilities and low levels of eosinophils in their sputum. The third group consists of persons who suffer asthma attacks that range from mild to serious and have normal lung function and modest levels of inflammation markers, which are under control. The study also showed that late-onset asthma was not a single entity but comprised of different phenotypes.[13]

PATHOPHYSIOLOGY

Immune mechanism

Numerous studies indicate that Th2 inflammatory responses arise as a result of the stimulation of molecular pathways in innate and adaptive immune responses.[14] CD4 T cells are involved in adaptive immune responses, whereas natural killer cells (NK) and type 2 innate lymphoid cells (ILC2s) are involved in innate immunological responses. Epithelial alarmins, including IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), trigger signaling pathways in T cells and ILC2s. Interleukin 33 (IL-33) functions by binding to a transmembrane receptor called ST2, which triggers cell death or damage. This leads to the release of inflammatory cytokines and the activation of Th2-mediated immune responses. IL-25 and IL-33 induce the differentiation of CD4 cells into Th2 cells, while TSLP stimulates dendritic cells to establish a conducive environment for Th2 cells. Th2 cells secrete many cytokines, such as IL-4, IL-5, IL-9, and IL-13.[14]

Memory T cells activated by alarmins can also generate T2 cytokines. IL-4 activates B cells and enhances the synthesis of Immunoglobulin E (IgE). The binding of IgE to mast cells and basophils is responsible for the production of inflammatory chemicals such as histamine, serotonin, and tryptase. This causes the airway muscles to constrict and an excessive production of mucus. Mast cells further secrete prostaglandin D2 and function as a chemoattractant receptor-homologous expression on the Th2 lymphocytes (CRTH2) receptor to enhance the inflammatory cascade. CRTH2 is present on the plasma membrane of Th2 cells, mast cells, ILC2s, and eosinophils. CRTH2 activation leads to an augmentation in the production and release of Th2 cytokines, as well as an enhancement in eosinophil movement and degranulation. IL-5 and IL-13 induce eosinophilia, stimulate mucus secretion, and promote airway remodeling.[14]

ILC2s are specifically designed to secrete Th2 cytokines upon exposure to alarmins produced by epithelial cells without the requirement of antigen presentation. Thus, both the adaptive and innate immune responses play a role in the total Th2 inflammatory response and may exhibit variations among different asthma subtypes. The eosinophilic subtype of late-onset asthma is a recently identified subtype that requires specific attention due to its association with the biological development of the IL-5 pathway. The intrinsic and acquired immune systems have the potential to intensify eosinophilic inflammation. However, the specific contribution of each immunological response in individual patients remains uncertain. Eosinophil elevation can be observed in individuals with early-onset allergic asthma as well as in those with non-allergic asthma, suggesting that eosinophilia does not exclusively result from an adaptive immune system reaction. Patients with late-onset asthma in the eosinophilic group frequently exhibit Th2 inflammation, even in the absence of any signs of allergic sensitization.[14,15]

A rise in the fractional exhaled nitric oxide (FeNO) concentration is associated with the aging process. This increase is caused by changes in the distribution or activity of inflammatory cells in the respiratory tract, which differentiate asthma in young and old individuals. Late-onset asthma with sinusitis influenced by Th2 is associated with ILC2s. This relationship occurs because ILC2s constitute an essential component of the innate mucoid immune response, which has the potential to heighten allergic inflammation.[16–18]

The immune function declines as one ages, and this process is known as immunosenescence. The process of immunosenescence plays a key role in the development of late-onset asthma. It is amplified due to oxidative stress, which leads to an accelerated rate of telomere shortening caused by deoxyribonucleic acid (DNA) damage. The simultaneous presence of immunosenescence and viral infections leads to chronic inflammation. This mechanism occurs due to reduced B cell function. In this condition, antigen persistence is increased through cytokines or toll-like receptors (TLR) without the presence of infection. In addition, autoimmunity can increase the affinity of T cells to recognize themselves as antigen or latent viruses, which can lead to autoimmune processes. Generally, naive T lymphocytes in the thymus compartment or the periphery will decrease due to atrophy or loss of bone marrow function.[19]

The aforementioned event diminishes the efficacy of T-cell activation. As individuals experience more tissue damage and cell death with age, the levels of autoantibodies in their systems will rise. In response, the number of thymic-regulatory T cells (Tregs) will also grow in order to control and manage autoimmune disorders. Consequently, there will be a decline in CD4

and CD8 T cell responses, leading to an increased vulnerability to infection. Recurrent infections induce the production of proinflammatory cytokines and trigger the activation of regulatory T cells. Therefore, there will be an increase in Th17 production, resulting in long-lasting chronic inflammation.[20]

The chance of developing asthma at a later age or an early age varies and is affected by the way exposure to pollutants throughout development and genetic differences interact. Genetic variations, such as those found on chromosome 17q21 or the C-C chemokine regulated and activated by normal T-cell expressed and secreted (RANTES), play a role in the development of late-onset asthma. Variances in leukotriene (LT) and wingless/integrase (Wnt) pathways at each stage of life contribute to disparities in the progression of airway remodeling. Moreover, the presence of murine mesenchymal stromal cells (MSCs) in the bone marrow can influence lung inflammation, potentially leading to the development of late-onset asthma.[21,22]

The precise mechanisms underlying non-Th2 asthma remain poorly known. Non-Th2 asthma is characterized by the absence of Th2 inflammation and the presence of neutrophilic or paucigranulocytic infiltrate in the airways. Airway remodeling is influenced by various pathways, including neutrophilic inflammation resulting from impaired innate immune response and inflammation mediated by IL-17. Animal research has demonstrated that IL-17 induces the growth of fibroblasts, resulting in airway remodeling. Asthma that is not of the Th2 subtype is frequently linked to unfavorable clinical outcomes and a lack of response to steroids. Neutrophilic patients often exhibit pulmonary air entrapment, reduced pulmonary function, and increased thickness of airway walls.[14]

IL-17, IL-8, and IL-6 are cytokines that play a role in non-Th2 asthma. IL-17 stimulates the movement of neutrophils by causing bronchial epithelial cells to produce IL-6 and IL-8. IL-23, secreted by macrophages in the tissue and dendritic cells, regulates the rise in IL-17 levels. Elevated IL-17 levels are a distinct contributing factor to the development of severe asthma. IL-8 is released by respiratory epithelial cells, T cells, and macrophages and acts as a strong chemoattractant. IL-6 is a pro-inflammatory cytokine that is released by several cells, including the innate immune system, B cells, CD4 effector Th cells, endothelial cells, septal cells, and fibroblasts. Elevated IL-6 levels are negatively correlated with FEV1 and contribute to an increase in asthma exacerbations.[14]

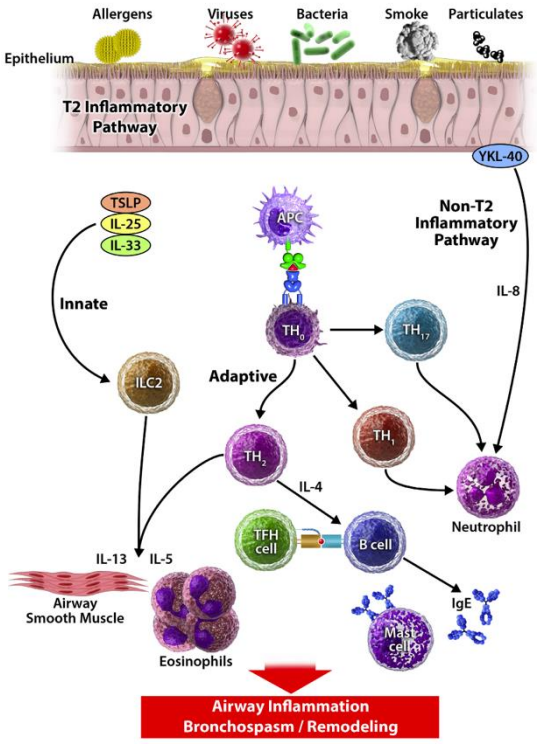

Figure 2. Inflammatory pathways in asthma[14]

Sexual hormones and gender

Following the onset of puberty, girls are more susceptible to developing asthma and tend to suffer more intense asthma symptoms. The smaller diameter of the airways in females may contribute to this phenomenon, but hormonal factors also play a significant role in the development of asthma. According to a prospective cohort study, the likelihood of developing asthma decreased in postmenopausal women, with the exception of those who engage in hormone replacement therapy.[8] Estrogen preparations elevate the likelihood of developing late-onset asthma, whereas the converse impact is evident when estrogen and progestin are used.[8]

Th2 cells enhance estrogen capacity in airway inflammation, as demonstrated in studies using mice.[8] The anti-inflammatory effects of progesterone are yet to be explained clearly. Testosterone can inhibit the synthesis of Th2 cytokines and enhance the production of IL-10 by acting on the androgen receptor found in T cells. Neutrophils and whole blood obtained from healthy guys have reduced production of 5-lipoxygenase (5-LO) products, namely leukotriene B4 and 5-hydroperoxyeicosatetraenoic acid (5-HPETE), in comparison to females. This is because males have a suppressive influence on the formation of these products. This process confers boys with a reduced vulnerability to the development of asthma later in life.[8]

Healthy human pulmonary tissue expresses sex hormone receptors, enabling direct actions on respiratory cells. Sex hormones primarily regulate gene expression, but they can exert non-genomic effects. These effects encompass the activation of G-protein coupled estrogen receptor (GPER), the regulation of ion channel activity, and the modification of kinase function. A relationship exists between female sex hormones and eosinophils. A study by Ilmarinen, *et al*. (2015) indicated that eosinophils were specifically allocated to female reproductive tissue.[8] Eosinophils in the peripheral circulation can produce GPER, a receptor. When this receptor is activated, it increases the movement of eosinophils toward eotaxin, a substance that attracts them. This process helps regulate eosinophil survival.[8]

Obesity

Obesity significantly raises the likelihood of developing late-onset asthma by approximately 50% in both males and females. It is characterized by systemic inflammation, which is shown by elevated levels of inflammatory markers such as C-reactive protein (CRP), IL-6, tumor necrosis factor α (TNF α), and leptin. Systemic inflammation is typically regarded as a result of the enlargement of fat cells and heightened metabolic function, together with the infiltration of immune cells called macrophages into fatty tissue in individuals who are obese. Adipose tissue macrophages can be categorized into two categories: proinflammatory M1 and anti-inflammatory M2. These types have distinct functions, with M1 being involved in promoting inflammation and M2 playing a role in tissue healing.[6]

In obese patients with asthma, there is an increase in the number of macrophages but a reduction in macrophage function (efferocytosis) toward macrophages in the airways, accompanied by a lack of M2 macrophage expression in blood monocytes. Oxidative stress is a possible mechanism for macrophage alterations. Increased systemic IL-6 and CRP levels are also markers of systemic macrophage activation (CD163) and are associated with poorer pulmonary function. Obese patients breathe more shallowly than normal patients with normal functional residual capacity, resulting in a risk of limited expiratory airflow, airway closure, and excessive respiratory responsiveness.[6]

A study by Holguin, *et al*. (2011) investigated the pathobiology of the association between obesity and slow-onset asthma.[23] A negative correlation between BMI and FeNO has been documented in cases with late-onset asthma. Elevated concentrations of asymmetric dimethyl arginine (ADMA), a substance that inhibits the activity of different types of nitric oxide synthase (iNOS), and a reduction in the ratio of L-arginine to ADMA have been seen in obese individuals suffering from asthma that develops later in life, but not in those with asthma that starts at an earlier age. Elevated levels of ADMA can cause iNOS to produce superoxide instead of nitric oxide (NO). Given that NO functions as a bronchodilator, the decreased production of NO by iNOS could potentially play a significant role in the development of late-onset asthma in individuals with obesity. Reduced levels of L-arginine and NO will enhance the activation of the arginase-polyamine pathway. This pathway may contribute to the development of asthma by promoting an increase in eosinophilia (a high number of eosinophils in the blood) and airway responsiveness.[23]

Rhinitis, sinusitis, and airway infection

Asthma is frequently linked to rhinitis and sinusitis. Both allergic and non-allergic rhinitis are separate factors that increase the risk of developing asthma later in life. Respiratory tract infections are a primary cause of rhinitis and sinusitis. This infection, in addition to repeated respiratory tract infections, is a contributing factor to the development of asthma later in life. The risk increases if there is allergic rhinitis, previous atopic dermatitis, or a history of atopy from parents. The underlying mechanisms of the relationship between rhinitis, sinusitis, and respiratory tract infections are not yet fully understood. A study by Song, *et al*. (2014) revealed that the presence of IgE against *Staphylococcus aureus* enterotoxin is associated with a more severe airway inflammation.[16]

S. aureus is a bacterium commonly found in infections but can also be a commensal bacterium. Serum-specific IgE against *S. aureus* enterotoxin (SA-IgE) is associated with late-onset asthma and worse outcomes. *S. aureus* enterotoxin can act as an antigen that raises specific IgE responses (SA-IgE) or can act as a superantigen that triggers massive lymphocyte activation, polyclonal IgE production that is reflected as high total IgE, and Th2 response. SA-IgE is also detected in nasal polyps, which causes massive IgE production and Th2 inflammation. This is one of the mechanisms that explains the relationship between asthma, rhinitis, and nasal polyps.[24,25]

Psychosocial factors

Depressive symptoms increase two-fold in patients with asthma. Psychosocial factors such as stress, depression, and harassment in women have been reported as risk factors in adult asthma. IL-1, TNF-α, IL-6, and IL-4 levels increase in individuals with depression. These cytokines increase asthma and can enhance excessive reactivity in the hypothalamic-

pituitary-adrenal (HPA) axis, thereby increasing cortisol levels, which can cause depressive symptoms. Oxidative stress markers such as reactive oxygen species (ROS) increase depression and also in asthma. Similarly, cholinergic activation that can cause bronchoconstriction is associated with depression. It is concluded that dysregulation of the autonomic nervous system can cause two disorders, namely asthma and depression.[24]

Smoking and oxidative stress

The latest scientific evidence suggests that both active and passive smoking are the risk factors for late-onset asthma and are most pronounced in patients who also have concomitant allergic rhinitis.[8] Smoking exacerbates the intensity of asthma, induces oxidative stress, and elicits an inflammatory response in the lungs. It also increases inflammatory cells in the airways, such as neutrophils and macrophages, and increases the production of inflammatory cytokines. The respiratory epithelium that comes into direct contact with cigarette smoke produces IL-1β and IL-8, thereby expanding the invasion of neutrophils, leading to disruption of the tight junctions of the epithelium and increasing permeability, reducing the barrier function of epithelial cells. Changes in mitochondrial structure, gene expression patterns, and aging processes also affect the respiratory epithelial cells.[8]

The pathogenesis of smoking-related asthma involves an increase in free radical oxygen and NO, causing damage and shedding of the respiratory epithelium. Oxidants damage the lipid membrane of respiratory epithelial cells, form inactive oxidized/nitrosylated transcription factor receptors or enzymes, and form the bronchoconstrictor molecule 8-isoprostane. In general, the cause of smoking-related late-onset asthma is an increase in oxidative stress and a decrease in antioxidant levels. The TSLP mediator increases in the sputum of late-onset asthma patients who smoke.[8]

CLINICAL MANIFESTATIONS OF LATE-ONSET ASTHMA

The diagnosis of asthma relies on the current symptoms and an objective evaluation of airflow restriction, independent of the individual's age. However, late-onset asthma is often underdiagnosed and becomes a severe problem, especially in elderly patients. In elderly patients, symptoms are often nonspecific. To strengthen the diagnosis, objective examinations such as spirometry can be used more widely. Although spirometry can effectively identify patients with severe late-onset asthma, it is difficult to reach a diagnostic conclusion in cases of mild to moderate asthma.[19]

Structural changes in older age are associated with persistent airflow limitations, and interpreting spirometry curves in older age can be challenging, especially in cases with borderline values. Changes in pulmonary structure also consider the loss of the lungs' reversibility, which results in the inability to use bronchodilator reversible tests in late-onset asthma. FeNO measurements can help diagnose late-onset asthma, but routine use is not recommended because some patients may experience neutrophilic inflammation in the airways due to non-eosinophilic phenotypes.[26]

Differentiating between late-onset asthma and COPD can be challenging, particularly in older individuals, due to the shared characteristics of chronic airway inflammation and blockage, which impact spirometry results. The reversibility of airway obstruction in older adults with asthma is frequently diminished as a result of structural alterations in the airways that have undergone remodeling. Additional pulmonary function tests, such as total lung capacity or carbon monoxide diffusing capacity of the lung (DLCO), can distinguish between these disorders. Imaging can also help diagnose late-onset asthma. A study by Choi, *et al.* (2017) revealed that late-onset asthma involves narrowing of the airways, reduced pulmonary shape changes, and increased trapped air in the lungs.[18]

The risk of exacerbation in late-onset asthma is generally higher compared to early-onset asthma due to several factors, among them reduced steroid responsiveness, non-allergic triggers, underlying inflammation, and delayed diagnosis. Patients with late-onset asthma are also more likely to have comorbid conditions such as obesity, chronic rhinosinusitis, gastroesophageal reflux disease (GERD), and cardiovascular diseases. These comorbidities can worsen asthma symptoms and contribute to more frequent and severe exacerbations. Individuals with late-onset asthma often have lower baseline lung function, which can make them more susceptible to exacerbations when faced with triggers.[27]

MANAGEMENT

The management of late-onset asthma includes both pharmacological and non-pharmacological interventions. Non-pharmacological management is similar to other types of asthma, such as smoking cessation and weight reduction education. Pharmacological management is identical to other types of asthma, but in slow-onset asthma, particularly in cases influenced by Th2, inhaled corticosteroids are crucial. Th2-type markers such as blood eosinophils, FeNO, and periostin can be used to differentiate between

slow-onset asthma influenced by Th2 or not. The most effective and safe pharmacological therapy is through inhalation. Nevertheless, problems can arise, such as incorrect usage techniques and low compliance levels, especially in older patients, which makes caregiver education important for the success of therapy. The response and evaluation of inhaled steroids for slow-onset asthma are similar to early-onset asthma.[19]

If inhaled corticosteroid therapy is ineffective, then targeted endotype therapy can be considered. Some biological agents, such as anti-IL-5, can be given if the asthma endotype is eosinophil-dominant. New biological agents that target alarmins, such as TSLP, can work on both Th2 and non-Th2 endotypes. Drug targets include cytokines that act on the Th2 pathway, such as IL-4, IL-5, IL-13, and IgE. Providing appropriate therapy is crucial in conducting endotype classification examinations for asthma. Brusselle, *et al*. (2017) stated that reslizumab reduces exacerbations in asthma and improves pulmonary function in both early-onset and late-onset asthma patients compared to placebo.[21]

Omalizumab is a biological agent that was first available on the market and is known to play an important role in allergic asthma as an additional therapy for uncontrolled asthma. It works on the free fragment crystallizable (FC) portion of IgE. It inhibits the binding between IgE and the receptor, preventing the release of inflammatory mediators and reducing the number of eosinophils in the airways. It reduces exacerbations, asthma symptoms, and the required dosage of inhaled corticosteroids. The side effects of omalizumab include headaches, nausea, paresthesia, and anaphylaxis. Omalizumab is administered subcutaneously every 2-4 weeks, can be used in patients over 6 years old, and the dose is adjusted according to body weight and serum IgE levels.[8,19]

Currently, there are three anti-IL-5 medicines available for purchase: mepolizumab, reslizumab, and benralizumab. Each of these medications possesses distinct methods of action, pharmacokinetics, and pharmacodynamics. All of these drugs are also effective in eosinophilic asthma based on the cutoff point for eosinophil values. Omalizumab can be used in patients with blood eosinophil levels ≥260/µl. Mepolizumab, reslizumab, or benralizumab are given subcutaneously to patients over 12 years old and can be used in patients with blood eosinophil levels ≥150 or ≥300/µl. The side effects of these drugs range from injection site reactions to anaphylaxis, but these events are rare.[28]

In non-Th2 asthma, there is a poor response to steroids. Therefore, inhaled corticosteroids should be discontinued or have their dosage reduced if sputum eosinophils are <3% and blood eosinophils are <400/µl. Long-acting bronchodilators (LABA) and long-acting muscarinic antagonists (LAMA) may be effective in reducing neutrophilic sputum in asthma. The use of macrolides as an anti-inflammatory, at a dose of 500 mg three times a week for 48 weeks, can reduce the incidence of asthma exacerbations. The use of anti-TSLP, namely tezepelumab, provides promising results in randomized phase 2 clinical trials as it reduces asthma exacerbations by 60% to 70% and improves pulmonary function. Further research is needed to assess the effectiveness of new agents such as anti-TNF-α, IL-1, IL-6, and IL-17. Bronchial thermoplasty may be considered as an additional therapy if maximum medical therapy has been used in severe asthma cases.[29]

SUMMARY

Asthma can occur at any time. Late-onset asthma can occur in older age caused by risk factors that can trigger it. Several factors can contribute to the development of late-onset asthma, such as gender, obesity, occupational exposure, rhinitis, respiratory infections, smoking, and stress. The mechanisms and pathophysiology underlying the severity and poor clinical outcomes of late-onset asthma are still unclear. Therefore, it is often underdiagnosed and poorly managed. Identifying phenotypes using inflammatory markers and IgE is recommended if steroid therapy is ineffective. Hence, the appropriate medicine with targeted therapy can be used effectively. Evidence-based treatment standards are needed for late-onset asthma.

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Conflict of Interest
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Authors' Contributions
Conceptualization: YNM, FY, FN, BRA. Methodology: YNM, BRA. Investigation: YNM, BRA. Writing - original draft preparation: YNM. Writing - review and editing: YNM. Approval of final manuscript: YNM, FY, FN, BRA. All authors contributed and approved the final version of the manuscript.

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