

Late-onset asthma: current perspectives

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Abstract: Because the pathophysiology of asthma has diverse characteristics, to manage the disease effectively, it is important for clinicians to distinguish among the clinical phenotypes. Among them, adult-onset asthma, that is, late-onset asthma (LOA), is increasing because of the aging of the population. The phenotype of LOA is largely divided into two types according to the presence or absence of eosinophilic inflammation, T-helper (Th)2- and non-Th2-associated LOA. Especially in Th2 LOA related to rhinosinusitis, as pulmonary function at onset is poor and asthma exacerbations occur frequently, it is important to detect this phenotype in the early phase by using a biomarker of Th2-type inflammation such as fractional exhaled nitric oxide (FE_{NO}). As non-Th2-LOA is often resistant to corticosteroids, this phenotype often requires another treatment strategy such as macrolide, diet, or smoking cessation. We often struggle with the management of LOA patients due to a lack of evidence; therefore, the elucidation of the mechanism of LOA contributes to increased efficiency of diagnosis and treatment of LOA. Age-related immune system and structural changes are thought to be associated with the pathophysiology of LOA. In the former case, changes in inflammatory cell function such as variations in the innate immune response and acquisition of autoimmunity or upregulation of oxidative stress are thought to be involved in the mechanism. Meanwhile, the latter can also become triggers or exacerbating factors of LOA via enhancement of airway hyperresponsiveness, decline in lung function, increased air trapping, and reduction in chest wall compliance. Therefore, appropriate individualized management in LOA may be possible through precisely assessing the pathophysiology based on age-related functional changes, including the immune and structural system.

Keywords: aging, immunosenescence, rhinosinusitis, obesity, phenotype, endotype

Introduction

Many patients develop asthma during childhood; however, asthma symptoms can occur at any time in life. Several factors may make a person more likely to develop late-onset asthma (LOA).¹⁻³ For example, women are more likely to develop asthma after the age of 20, and obesity also appears to increase the risk of developing asthma as an adult.⁴ Moreover, individuals who had asthma as a child may see asthma recur later in life.⁵ In any case, because of the worldwide population trend toward enhanced longevity, clinical concerns about LOA are developing and have been increasingly recognized by clinicians. However, the mechanisms that underlie the relationship between aging and asthma are still unclear and the condition is frequently underdiagnosed in older age groups.⁶ In this review, we discuss these issues with a focus on the pathophysiology and treatment of LOA.

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Clinical feature

Usually, asthma symptoms appear early in life. However, some people develop asthma symptoms for the first time in adulthood; their clinical status is called LOA, defined as: “asthma with onset of symptoms in adult life in a patient with no pre-existing, persistent respiratory symptoms,” but the definition of age has not been clarified.⁷ It is reported that the age- and sex-adjusted incidence of newly diagnosed asthma in people older than 65 years was estimated by 0.1% per year.⁸

Aging itself, however, has a significant effect on the methacholine response and has an impact on airway hyper-reactivity.⁹ Therefore, higher annual declines in FEV₁ are observed in LOA,^{10–12} especially among elderly people¹³ or smokers of over 10 pack-years.^{14,15} Obesity-associated LOA is characterized by lack of atopy, female predominance, and it is suggested that obesity may cause LOA through changes in the structure of the lung or in the function of the immune system.^{16–26} The above risk factors are characterized by chronic inflammation and oxidative stress, with an increase in the mediators of innate immunity. Women are more likely to be affected by LOA than men.²⁷ Possible explanations for gender differences in the rate of incidence of LOA may include endogenous and exogenous hormonal factors.²⁸ In addition, LOA is associated with worse lung function and lower atopic status.¹⁰ Furthermore, among some patients with LOA, being elderly, having multi-comorbidities, polypharmacy, and poor inhaler technique, being inactive and home alone, as well as psychological status (depression, dementia, etc.)^{29,30} are beginning to be recognized as major issues. Actually, LOA is an independent risk factor for cardiovascular disease events.³¹

At least 9%–15% of LOA can be attributed to occupational exposures, and one of the mechanisms may be related to work-related stress.³² Mood disorders such as comorbid anxiety and depression are also associated with LOA.³³

Phenotype and endotype

Some studies proposed clinical sub-phenotypes of LOA based on cluster analyses.^{34,35} At first, LOA was split down the middle and phenotypes were classified into Th2-LOA or non-Th2-LOA.^{36,37} Th2-LOA is associated with sinusitis, nasal polyps, and, sometimes, aspirin-exacerbated respiratory disease (AERD), but appears to be equally common in males and females.³⁸ This type is often severe from the onset and has been recently defined as uncontrolled asthma.³⁹ Non-Th2-LOA is associated with gender, obesity, smoking, and aging. However, because these analyses have been done using a cross-sectional study, the asthma variability has still not been fully examined. Therefore, a longitudinal-study is needed to clarify these complex phenotypes. Then, such analyses will

become useful to predict the prognosis of LOA patients and to develop appropriate treatment strategies.⁴⁰ Ilmarinen et al identified five sub-phenotypes of LOA by using long-term follow-up (12-year) data.⁴⁰ This study suggested that identifying clusters with different disease prognoses is important for clinicians to determine the most effective treatment. In addition, fluctuations in lung function are a characteristic of asthma and represent a marker of brittle asthma.^{41,42} In this regard, detrended fluctuation analysis (DFA) has shown that intrinsic fluctuations in pulmonary function over time show a complex fractal-type behavior.⁴³ Kaminsky et al reported that identifying patients with similar fluctuation patterns and disease stability by using DFA could be helpful for personalized treatment.⁴⁴ Some patients with Th2-LOA have been reported to exhibit a distinct profile such as chronic rhinosinusitis (CRS), air trapping, and male sex.⁴⁵ Air trapping is associated with high computed tomography sinus scores, and this phenotype is frequently associated with severe exacerbations, as mentioned earlier.⁴⁶ It is suggested that inflammation of the distal airways and that of paranasal sinuses are important predisposing factors for the development of exacerbations.⁴⁶ In such cases, systemic inflammation-targeted management, such as with monoclonal antibodies against anti-IL-5, might be an ideal treatment to prevent future exacerbations and lung function decline.⁴⁷ In this manner, by using biological markers in cluster analyses, we are able to explore disease pathogenesis by analyzing endotypes based on molecular characteristics and obtain novel guidelines for treatment of severe asthma. Furthermore, as we discuss later, it is assumed that age-related changes in immune function have an impact on the airway inflammation of LOA. This change exists in both innate and adaptive immunity cells. Especially, type 2 innate lymphoid cells (ILC2) are intimately related to LOA nasal polyps of patients with chronic nasal sinusitis.⁴⁸ Moreover, this endotype is related to interleukin (IL)-4,⁴⁹ IL-5, and IL-13.⁵⁰

Pathophysiology

Immune system

An increase in fractional exhaled nitric oxide (FE_{NO}), which can provide noninvasive assessment of airway inflammation, was found to be associated with advancing age.⁵¹ The increase of the values may reflect the altered distribution of inflammatory cells or altered activity of inflammatory cells in the airway. Such altered activity may account for differences in clinical phenotypes between younger and older asthma subjects.⁵² Th2-LOA with sinusitis is reported to be associated with ILC2.^{48,53,54} One of the reasons could be that these cells represent a key factor in the mucoid innate immune

response that boosts allergic inflammation.⁵⁵ Furthermore, these cells can be activated in an allergen-independent manner by IL-25, IL-33, and thymic stromal lymphopoietin, all of which are released from bronchial epithelial cells upon stimulation with air pollutants.⁵⁶ Actually, it is reported that they have a greater effect on LOA than on early-onset asthma (EOA).⁵⁷ *Staphylococcus aureus* enterotoxin (SE) sensitization is known to be an independent risk factor in asthma,⁵⁸ and it is reported that SE-immunoglobulin (Ig) E sensitization with LOA in the elderly is associated with particularly severe eosinophilic asthma with CRS.^{58–63} Thus, it is suggested that SE–IgE sensitization could represent a clue to the pathogenesis of severe late-onset eosinophilic asthma in the elderly.^{58,64,65} Matsumoto et al reported that, in women with asthma, the cysteinyl leukotriene receptor 1 gene (CysLTR1) variant might be associated with sensitization to SE and age at asthma onset.⁶⁶

Age-related declines in immune function, known as immunosenescence, also play a key role in the development of LOA. The immunosenescence process is boosted by oxidative stress through the increased rate of telomere shortening as a consequence of DNA damage. The coexistence of immunosenescence and viral infection promotes persistent inflammation.⁶⁷ The mechanism is suggested to represent diminished B-cell function.⁶⁸ In this condition, antigen persistence is enhanced, especially in the elderly, and pulmonary age-related inflammation is increased via cytokine or toll-like receptor without infection.⁶⁹ In addition, autoimmunity may increase the affinity of T cells to self-antigens or latent viruses, thereby promoting an autoimmune process.⁷⁰ In general, with age, naïve T lymphocytes in the thymic compartment as well as in the periphery are thought to decrease through thymic atrophy or loss of bone marrow function, including telomere shortening and impaired enzymes.⁷¹ By contrast, with age, the numbers of memory T lymphocyte are reported to increase.^{72,73} These phenomena diminish the efficiency of T-cell activation.⁷² However, when autoantibodies are increased in elderly individuals because of increased tissue damage and apoptosis, thymic T-regulatory cells (Tregs) become enhanced to regulate this autoimmunity.⁷⁴ As a result, CD4+ and CD8+ T-cell responses are reduced, and susceptibility to infection increases. Recurrent infection stimulates proinflammatory cytokines, and this leads to activation of Tregs. Consequently, the production of Th17 is enhanced, leading to persistent chronic inflammation. With increased age, total serum IgE is known to decrease because of impaired B-cell-mediated antibody production and specificity.⁷⁵ However, it is reported that the rate of allergen sensitization in older asthmatics is higher than that of age-matched controls.⁷⁶ The difference in

B-cell activation which has caused such a status may play a potential role in autoimmunity. The risk of EOA and LOA is differently influenced by the interaction between childhood farming exposure and genetic variations.⁷⁷ A genetic variation, such as on chromosome 17q21, or the C–C chemokine regulated on activation, and normal T-cell expressed and secreted (RANTES) could play a part in the LOA.^{78,79} Age differences in the leukotriene (LT) and wingless/integrase (Wnt) pathways during airway inflammation underlie the differential development of airway remodeling.⁸⁰ Thirty-eight percent of asthmatics are reported to have paucigranulocytic type disease.⁸¹ The mechanism is speculated to be derived from abnormalities or dysfunction of structural cells, such as airway smooth muscles and nerve. Therefore, increased bronchomotor tone from muscarinic and adrenergic pathways can cause symptoms, and a long-acting muscarinic antagonist might be effective therapy.⁸² Bronchial thermoplasty (BT) is an endoscopic procedure that targets primarily airway remodeling and improves quality of life or exacerbation with asthmatics although pulmonary function is not improved.^{83–85} One of the mechanisms underlying the clinical improvement is related to alterations in different bronchial structures, such as airway smooth muscles and neuroendocrine cells, without any impact on eosinophilic inflammation.⁸⁶ Therefore, BT may be an option for paucigranulocytic type of severe LOA. Furthermore, murine mesenchymal stromal cells from the bone marrow are reported to have an impact on pulmonary inflammation; bronchiolitis obliterans syndrome (BOS) following organ transplantation, stem/progenitor hematopoietic stem cell transplantation (s/p HSCT), and immune dysregulation can contribute to the pathogenesis of LOA.^{87,88}

Pulmonary structure and function

Additional data suggest that advanced age, irrespective of any concomitant pulmonary disease, is associated with increased bronchial hyperresponsiveness.^{9,89} In a study of 148 subjects, ranging from age 5 to 76 years, age had an independent association with bronchial hyperresponsiveness as measured by a methacholine challenge.⁹ In another study, bronchial hyperresponsiveness to histamine challenge was associated with increased eosinophil count and allergic sensitization; however, older age maintained an independent association with bronchial hyperresponsiveness, which was more prominent in subjects with respiratory symptoms.⁴² In addition to age, it is recognized that smoking and the baseline forced expiratory volume in 1 second (FEV₁) have strong effects on bronchial hyperresponsiveness.^{90,91} Furthermore, aging is associated with a progressive decline in lung function.⁹² Coupled with these findings, breathing is exaggerated

through increased air trapping and a reduction in chest wall compliance with increased age.⁹³ Actually, it is reported that bronchodilators, such as long-acting beta2 agonist (LABA), have an add-on effect to inhaled corticosteroid (ICS).⁹⁴

Obesity

Obesity is characterized by chronic inflammation and oxidative stress, with an increase in the mediators of innate immunity.^{95,96} Obesity with and without type 2 diabetes mellitus (DM) is associated with an increase in the expression of IL-4 – homologous to lymphotoxins, exhibits inducible expression, competes with HSV glycoprotein D for herpesvirus entry mediator (HVEM), which is a receptor expressed by T lymphocytes (LIGHT; homologous to lymphotoxins, exhibits inducible expression, competes with HSV glycoprotein D for HVEM, a receptor expressed by T lymphocytes), matrix metalloproteinase (MMP)-9, and CC chemokine receptor (CCR)-2. Following gastric bypass surgery and weight loss, the expression of these factors falls significantly.⁹⁷ In addition, obesity may lead to abnormal nitric oxide (NO) metabolism, with the imbalance of l-arginine and one of its methylated products known as asymmetric dimethyl arginine (ADMA) in obese subjects who acquire asthma after childhood. Therefore, in LOA, the plasma ratios of l-arginine to ADMA may explain the inverse relationship between body mass index (BMI) and FE_{NO} (reduced FE_{NO} bioavailability in obesity). This is thought to occur because ADMA can be an endogenous inhibitor of NO synthase (NOS) isoforms.⁹⁸ Actually, these lower l-arginine/ADMA ratios are associated with reduced lung function and increased respiratory symptoms, and may have a role in the pathobiology of LOA.¹⁹ As another mechanism in the reduced value of FE_{NO} in obesity and asthma, it is thought that since excessive airway oxidative stress in obesity reacts with FE_{NO}, the value of FE_{NO} is apparently low in such status.⁹⁹ It has been reported that, although similar cases have occurred among patients with chronic obstructive pulmonary disease (COPD), excessive nitrosative stress, such as NO, is generated in the peripheral airways.¹⁰⁰ The same can be said of the pathophysiology of LOA, and it has been suggested that the persistent elevation of exhaled NO in the distal airway of the asthma patient can be a therapeutic target.¹⁰¹ However, in the actual clinical setting, ICS therapy cannot perfectly suppress the residual nitrosative stress elevation in the distal airways of asthmatics.¹⁰¹ In short, it is speculated that nitrosative stress in the airways may be associated with actual steroid-resistance mechanisms in some asthmatic phenotypes, such as LOA. Therefore, it can be an option to select some drugs other than ICS, such as low-dose theophylline, which might be useful to

reduce nitrosative stress.¹⁰² Dietary change, such as a highly saturated meal poor in vitamin D, may contribute to the pathogenesis of asthma in obesity.^{103,104} High consumption of fish was reported to be protective, especially in the elderly.¹⁰⁵ A possible mechanism for the effect of fish consumption may be derived from long-chain ω-3 polyunsaturated fatty acids (PUFAs), which inhibit arachidonic acid (AA) metabolism competitively via enzymatic pathways and suppress the production of active inflammatory eicosanoid mediators from AA.^{106,107} A schematic view of the pathophysiology in LOA is shown in Figure 1.

Diagnosis and treatment

It is often difficult to distinguish between LOA and COPD, especially in the elderly, because both diseases have similar underlying mechanisms characterized by chronic airway inflammation and obstruction, which show analogous patterns of simple spirometric parameters. It should be taken into account that the reversibility of airway obstruction in elderly asthmatics is often reduced because of irreversible structural changes resulting from airway remodeling.¹⁰⁸ Therefore, precise pulmonary function tests such as total lung capacity or the carbon monoxide diffusing capacity of the lungs (DL_{CO}) can help distinguish between these diseases.¹⁰⁹ Alternatively, it may be better to use chest imaging. Choi et al reported that, by using chest imaging biomarkers, LOA

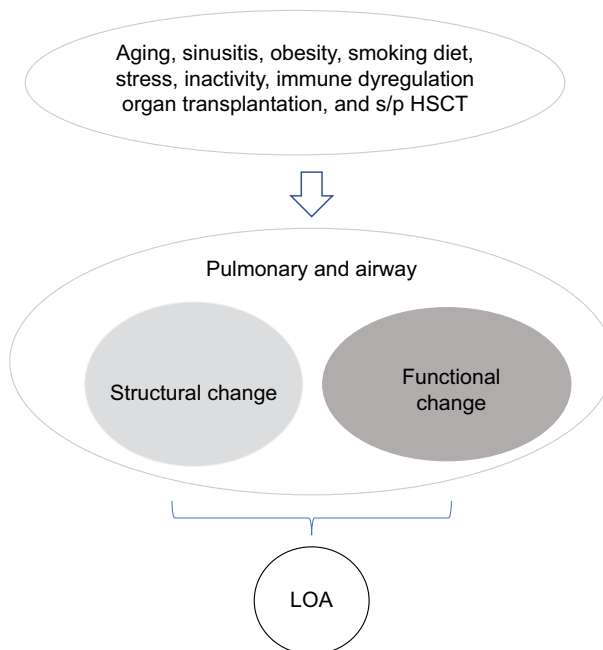


Figure 1 Pathophysiology of LOA. Structural or functional changes in the airway result from many factors including aging.
Abbreviations: s/p HSCT, stem/progenitor hematopoietic stem cell transplantation; LOA, late-onset asthma.

can be identified as an imaging-based phenotype.¹¹⁰ It has been suggested that the imaging characteristics of LOA show airway luminal narrowing, reduced lung deformation, and increased air-trapping.

Usually, pharmacological and non-pharmacological interventions (e.g., education) are prescribed based on the phenotype. Non-pharmacological interventions, such as encouraging smoking cessation and reducing body weight, should always be pursued whenever necessary.^{111–114} As for pharmacological treatments, ICS is absolutely essential for Th2-LOA.^{115–117} Th2-type biomarkers such as blood eosinophils, FE_{NO}, and periostin are used extensively to differentiate between Th2-LOA and non-Th2-LOA.^{118,119} Especially, for asthma and COPD overlapping, these biomarkers are useful for predicting the responsiveness to corticosteroids.^{120–124} However, when corticosteroid treatment is ineffective, the clinician should consider the possibility of poor inhaler technique because elderly patients with Th2-LOA often have functional disorders.^{112,125–128} In such cases, assisted inhalation therapy by a caregiver might be a more useful strategy than self-administered ICS therapy.¹²⁸ This strategy dovetails with

the result that, even when patients with LOA are elderly, their response to treatment is similar to that in patients with EOA.¹¹⁸ Therefore, an upgrading strategy for poor adherence should be encouraged.^{129,130} If ICS treatment is truly ineffective, endotype target therapy should be taken into consideration.¹³¹ Compared with placebo, reslizumab which is a monoclonal antibody against IL-5 produces greater reductions in asthma exacerbations and larger improvements in lung function in patients with LOA versus EOA.¹³² Omalizumab improves all asthma outcomes independently of age, although the magnitude of the effects observed in the elderly seems to be lower than in other age groups.¹³³ Post hoc analyses of the anti-IgE agent omalizumab indicate similar efficacy in both younger and older adults. Anti-IL-5 and anti-IL-13 therapy appear to show even more pronounced effects as targeted treatments in late-onset disease and in asthmatic patients 65 years or older, but evidence is lacking.^{45,47,134–138} As yet, for non-eosinophilic asthma in the elderly, there is a lack of high-level evidence for targeted therapy, but macrolides may offer a viable option.¹³⁹

In Figure 2, we show the time courses of LOA with or without intervention.

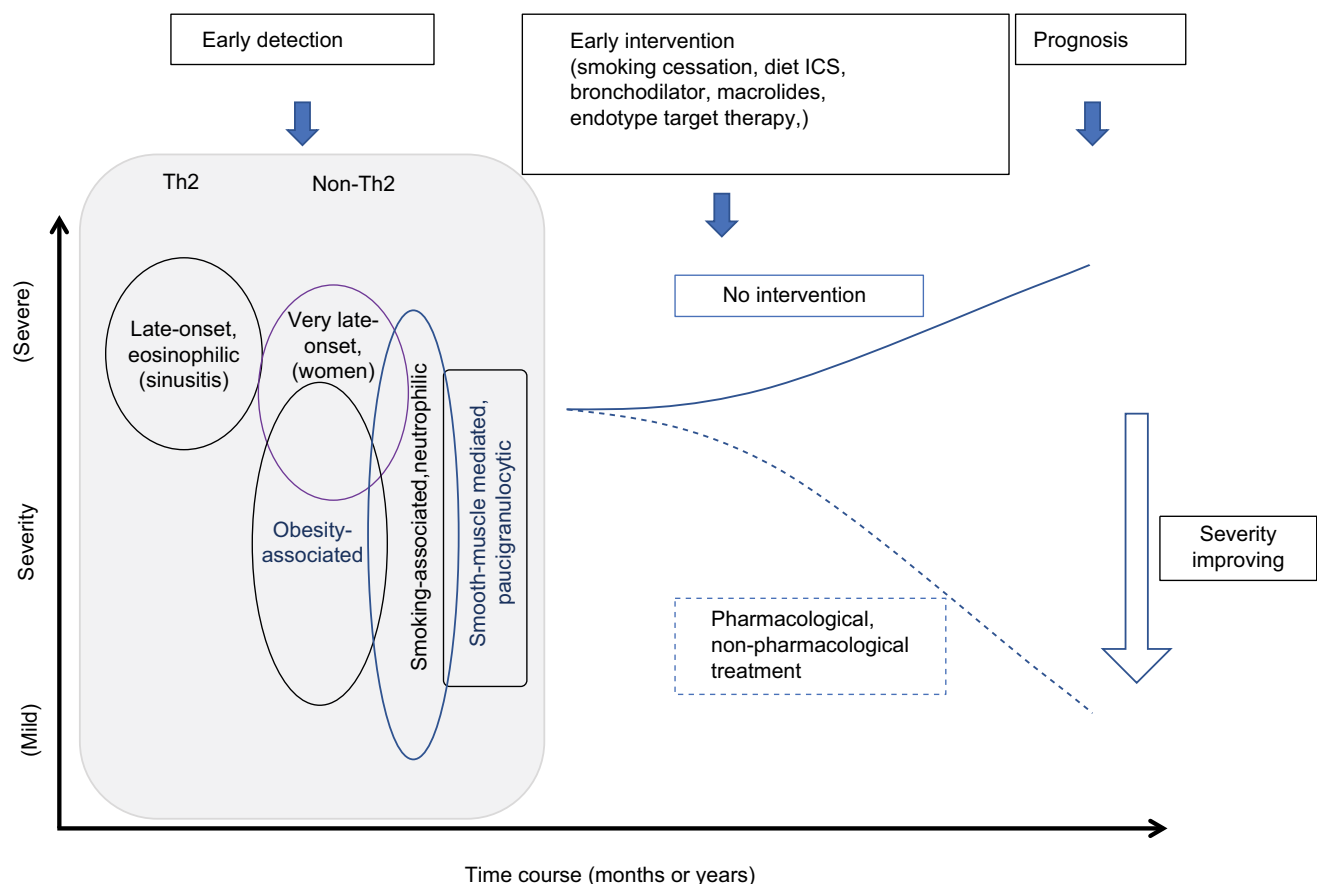


Figure 2 Time-course of LOA. The prognosis of LOA can be improved by early detection and precise intervention. Dotted and solid lines mean the time course of asthma severity by each intervention. Early intervention, such as pharmacological or non-pharmacological treatment, improve severity of asthma.

Abbreviations: Th2, T helper 2; ICS, inhaled corticosteroid; LOA, late-onset asthma.

Conclusion

Today, advances in the understanding of the phenotypes and endotypes of asthma syndrome have helped us in managing these diverse subtypes of the disease. Because the community continues to age, LOA is beginning to play a larger role in asthma. As LOA shows different phenotypes with heterogeneous backgrounds, appropriate individual management through estimating precisely the pathophysiology is required.

Disclosure

The authors report no conflicts of interest in this work.

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