Revisiting Late-Onset Asthma: Clinical Characteristics and Association with Allergy

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REVIEW

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Abstract: The Global Initiative for Asthma (GINA) 2020 defines late-onset asthma (LOA) as one of the clinical phenotypes of asthma wherein patients, particularly women, present with asthma for the first time in adult life, tend to be non-allergic and often require higher doses of inhaled corticosteroids (ICS) or are relatively refractory to corticosteroid treatment. In this review, we examine the published literature improve the understanding of the following aspects of LOA: 1) the age cut-off for its diagnosis; 2) its distinct clinical phenotypes, characteristics and risk factors; and 3) its association with allergic comorbidities and conditions. Overall, our review reveals that clinicians and researchers have used multiple age cut-offs to define LOA, with cut-off ages ranging from >12 years to ≥65 years. LOA has also been classified into several distinct phenotypes, some of which drastically differ in their clinical characteristics, course and prognosis. Although LOA has traditionally been considered non-allergic in nature, our review indicates that it is commonly associated with allergic features and comorbidities. Our findings suggest that there is an urgent need for the development of more clear clinical practice guidelines that can provide more clarity on the definition and other aspects of LOA. In addition, the association of LOA and allergy needs to be re-examined to frame a more optimal treatment strategy for patients with LOA.

Keywords: asthma, diagnosis, age of onset, allergy, allergic asthma, asthma phenotypes

Introduction

Asthma is a chronic inflammatory respiratory disease affecting approximately 339 million people worldwide.[1] It is characterized by symptoms of wheezing, shortness of breath, chest tightness and cough that vary over time and in intensity.[2] Age of onset of asthma plays an important role in predicting the clinical course and management of this disease.[3] Although asthma often begins in childhood, asthma symptoms can occur at any time during life and some patients experience symptoms for the first time at a later stage in life.[4,5]

For more than half a century, clinicians and researchers have been trying to devise an appropriate classification to differentiate adult-onset and childhood-onset asthma. In 1947, Rackeman classified asthma based on its age of onset into "extrinsic" asthma (onset before the age of 30 years) and "intrinsic" asthma (onset after the age of 40 years).[6] The official European Academy of Allergy and Clinical Immunology (EAACI) position statement in 2001 modified this terminology further. The terms "extrinsic" and "intrinsic" asthma were replaced by "allergic" and "non-allergic" asthma, respectively.[7] In 2004, Miranda et al introduced the terms "early-onset asthma" and "late-onset asthma" (LOA) to differentiate asthma based on age of onset.[8]

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The 2020 version of the GINA strategy defines LOA as one of the clinical phenotypes of asthma wherein patients, particularly women, present with asthma for the first time in adult life, tend to be non-allergic and often require higher doses of inhaled corticosteroids (ICS) or are relatively refractory to corticosteroid treatment.[2] A closer look at this definition reveals that many questions about this condition remain unanswered. A better understanding of all the aspects of LOA can help clinicians make more precise guided treatment decisions using existing or new treatment approaches and to devise optimal personalized management of the disease.

In this review, we examine published literature in an attempt to answer the questions on a) the age cut-off for the diagnosis of LOA; b) its distinct clinical phenotypes, characteristics and risk factors; c) its association with allergy and allergic comorbidities.

Methods

We conducted a literature search using EMBASE for literature between 1996 and May 2020 using the search terms "allergic asthma", "atopic asthma" "late onset", "adult onset", "asthma". Potentially relevant publications and registries were manually screened and reviewed and non-relevant publications were excluded on the basis of pre-determined criteria such as excluding editorials, opinion pieces, articles without the full text available, and articles without authors.

Defining the Age Cut-off for LOA

While the latest GINA strategy clarifies that asthma occurs for the first time in adult life in patients with LOA, it fails to define the exact age that can be considered as a cut-off to confirm the diagnosis of LOA.[2] We examined the published literature to understand how researchers and clinicians are defining the age cut-offs for LOA. Table 1 summarizes the different age cut-offs used in the publications we examined (n=18), which we shortlisted from our literature search.

Several parallel schools of thought seem to exist about the age cut-off for LOA. Genetic variants have been distinctly associated with asthma that sets at 12–16 years of age.[9,10] While some researchers have considered retirement age (≥65 years) as an appropriate cut-off for LOA, other researchers have defined LOA as asthma with onset after the end of childhood (12/16/18 years). Yet, other researchers have reported middle age (30 or 40 years) to be appropriate as the cut-off age for the diagnosis of LOA.

Table 1 Summary of Different Cut-Offs for Late-Onset Asthma

Cut-Off Age	Study (Year)
12 years	Wu et al (2016)[12] Miranda (2004)[8] Holguin et al (2011)[13] Bhaskar et al (2013)[14]
16 years	Toren et al (1999)[15] Jarvis et al (2012)[16]
18 years	Sood et al (2013)[17] Chaudhuri et al (2016)[18] Schwindt et al (2010)[19]
20 years	Bedolla-Barajas et al (2015)[20]
30 years	Nenasheva et al (2019)[30]
40 years	Maio et al (2018)[21] Heffler et al (2019)[22]
13–50 years	Wu et al (2015)[23]
64/65 years	Bauer et al (1997)[24] Gillman et al (2012)[25] Ariano et al (2012)[26] Gibson et al (2010)[27]

From these articles, it is quite evident that there is a lack of consensus amongst researchers and clinicians about the exact cut-off age for LOA.

It is important to note that clinical characteristics of LOA can manifest differently at different age cut-offs of LOA. For example, there has been epidemiological evidence to distinguish very late-onset asthma (defined as age-of onset at 60 years or older) from "classical" late-onset asthma (defined as age-of-onset at 12 years or older), eg, female predominance disappeared with increasing age, which was also modified by allergic status.[11]

Epidemiology of LOA

The inconsistency in defining LOA is one reason why the exact disease burden of LOA has not been adequately defined. The epidemiology of LOA has been assessed in several population-based studies in Europe. The HELIUS study examining six ethnic groups in the Netherlands (Dutch, South-Asian Surinamese, African Surinamese, Moroccan, and Turkish and Ghanaian origin) and evaluating 23,356 participants, demonstrated a prevalence of LOA (age cut-off ≥18 years) ranging from 2.4% to 6.0% in these populations.[28] A Swedish population-based study in 15,813 adults revealed that the incidence rate of LOA

(age cut-off ≥16 years) amongst males and females was 1.0/1000 person-years and 1.3 cases/1000 person-years, respectively. Furthermore, the incidence rate was reported to be high (3.0 cases/1000 person-years) in females aged 16–20 years.[15] The Global Allergy and Asthma Network of Excellence (GA(2)LEN) survey in Europe conducted in 52,000 adults found an overall asthma prevalence rate of 8.5%, of which 49.5% reported an age of onset after the age of 16 years.[16] A 2-year population-based study showed an annual incidence of LOA (no clear age cut-off given) rate of 160/100,000 per year.[29] Of the 439 patients with asthma analyzed in an Italian web-based registry, 30% reported LOA (age cut-off >40 years) symptoms and adult diagnosis.[21]

Similar epidemiological data for LOA are also available for other geographies. A population-based study from Taiwan demonstrated the prevalence of physician-diagnosed LOA (age cut-off ≥12 years) to be 2.1% (449/21,057) in the study population.[23] The age- and sex-adjusted incidence of LOA (age cut-off >65 years) in population-based study from Rochester, Minnesota in the US was reported to be 95/100,000 people.[24] Age-specific incidence of asthma in patients aged 65 to 74 years was 103 cases/100,000 people.[24] A prospective study in a Tasmanian population demonstrated that 10.8% of patients who reported asthma, exhibited first symptoms of asthma in adulthood (no clear age cut-off for adulthood provided).[5] The Russian registry for severe bronchial asthma (RSAR) contains data on the onset of the disease in 1791 patients (as of September 2019). If an age cut-off of ≥30 years is considered in this study, 66% of patients can be diagnosed with LOA.[30]

It is evident from these reports that, irrespective of the geography evaluated or age cut-off used, LOA affects a considerable proportion of patients with asthma.

Clinical Phenotypes of LOA

Several clinical phenotypes of LOA have been described based on clinical presentation (allergic, non-allergic and occupational), underlying airway inflammation (eosinophilic and non-eosinophilic), severity and physiological parameters (Figure 1).

The Seinäjoki Adult Asthma Study, a 12-year follow-up study in patients with new-onset adult asthma identified five sub-phenotypes: nonrhinitic asthma, smoking asthma, female asthma, obesity-related asthma and early-onset atopic adult asthma.[31] In a review by Hirano et al, LOA was classified into two phenotypes — Type 2-LOA or non–type 2 LOA. Type 2-LOA is associated with sinusitis, nasal polyps, and, sometimes, aspirin-exacerbated respiratory disease (AERD) appears to be equally common in males and females and is often severe from the onset. Non–Type 2-LOA is associated with female gender, obesity, smoking, and aging.[32]

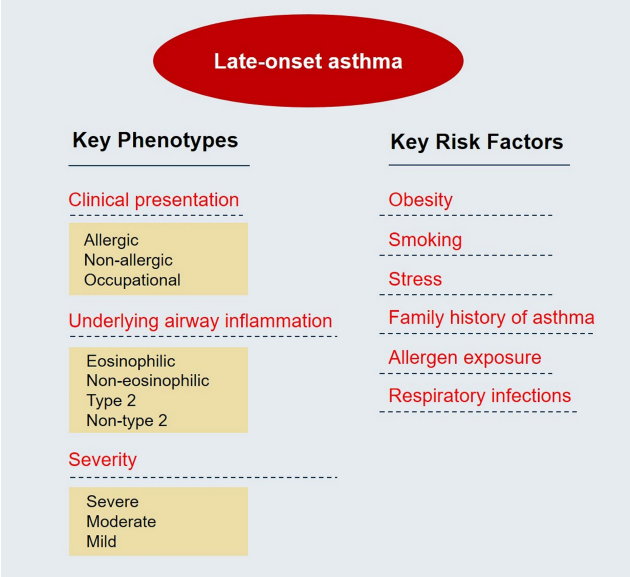

Figure 1 Key phenotypes and risk factors of late-onset asthma.

In a study in 2013 by Amelink et al, patients with LOA were classified into three clusters. The first cluster consisted of patients with severe eosinophilic inflammation-predominant asthma and persistent airflow limitation despite high-intensity anti-inflammatory treatment, with relatively low symptom scores. The second cluster consisted of obese women with frequent symptoms, high healthcare utilization and low sputum eosinophils. The third cluster consisted of patients with mild-to-moderate, well-controlled asthma with normal lung function and low inflammatory markers.[33]

In a review article by Nijs et al, the following 4 phenotypes of LOA have been proposed: adult-onset obese female preponderant asthma; adult-onset nonatopic, inflammation-predominant phenotype with fixed airflow limitation; adult-onset mild asthma and smoking-related asthma.[3]

Another important observation is the role of innate lymphoid cells group 2 (ILC2) in both early-onset and late-onset asthma phenotypes. It has been speculated that the activation of ILC2s in the absence of T cells and B cells is enough to induce asthma-like symptoms, and that ILC2s may play a role in early onset allergic asthma.[34]

Moreover, role of ILC2 has also been indicated in the LOA with nasal polyposis phenotype.[8] ILC2s in both early-onset asthma and LOA with polyposis are regulated by epithelial-cell-derived thymic stromal lymphopoietin (TSLP), interleukin 25 (IL-25) and IL-33.[34]

It is worth to note that phenotypes of asthma may not always provide deep insights into the underlying disease process; therefore, endotypes have been proposed to indicate a subtype of a condition defined by a specific biologic mechanism. For example, LOA can be distinguished from early-onset asthma in the case of severe LOA hypereosinophilic asthma that is not thought to be Th2-driven in spite of marked peripheral and tissue eosinophilia and response to IL-5 antibody.[35]

The aforementioned publications suggest that LOA is not a single entity, but consists of distinct phenotypes some of which drastically differ in their clinical characteristics and prognosis. This implies that treatment strategies of LOA cannot be the same for all, and physicians should be mindful of the different presentations of the same condition.

Clinical Characteristics and Risk Factors of LOA

While genetic factors, early respiratory infections and environmental exposures are well-recognized risk factors for childhood asthma, risk factors associated with LOA asthma are not well documented (Figure 1).

The risk of asthma in adults is reported to be higher in obese patients (BMI ≥30) when compared to non-obese patients.[36] Some studies have suggested that obesity may lead to changes in the structure of the lung in patients with LOA.[37,38] Women are more likely than men to develop asthma after the age of 20.[39,40] LOA mainly affects females with high body mass index (BMI).[28,39,41] Furthermore, Ilmarinen et al reported that obese LOA patients experienced more exacerbations and respiratory-related hospital admissions compared to normal-weight patients during 12-year follow-up.[42] In the Severe Asthma Research Program, obese patients with LOA showed increased respiratory symptoms, reduced lung function, lower IgE levels, and reduced fractional exhaled nitric oxide.[43] Smoking has also been indicated to be correlated to LOA. A clear dose-response association for exposure to tobacco and risk of new-onset asthma was observed in a multivariate analysis. In this study, smokers had an odds ratio (OR) of 2.05 with 1–10 pack-years (95% CI 0.99–4.27), an OR of 3.71 (95% CI 1.77–7.78) in those with 11–20 pack-years, and an OR of 5.05 (95% CI 1.93–13.20) in those with >21 pack-years compared with never-smokers.[44] In smokers with late-onset asthma, the risk of airway obstruction compared with never-smokers was higher.[45] Coogan et al reported in a longitudinal study with >14 years of follow-up that both active and passive smokers exhibited an increased incidence of new adult-onset asthma (approximately 40% and 20%, respectively) versus non-smoking asthmatics.[46] Stress has been shown to modulate and activate a number of biological pathways that may be involved in asthma pathophysiology.[47] High versus low stress was found to be associated with a two- to three-fold higher risk of self-reported asthma incidence in several longitudinal population studies.[48–50]

Family history of asthma has been reported to be a stronger determinant of early-onset asthma when compared to LOA.[51,52] However, Toren et al reported that a family history of asthma was also strongly associated [odds ratio (OR) (95% CI), 2.1 (1.7–2.6)] with LOA.[15] Furthermore, parental allergy and exposure to pets in childhood have been associated with increased risk of asthma development in adulthood.[53]

Respiratory infections may also play a role in LOA. A large population-based study that included a follow-up of 581,000 person-years showed that both upper and lower respiratory tract infections 12 months prior to the asthma-onset are strong determinants of LOA in the working population.[54] LOA and severe asthma have also been associated with occupational exposures.[55] Furthermore, it has been reported that occupational asthma-chronic obstructive pulmonary disease overlap is more common in patients with LOA.[56]

In addition to having distinct risk factors, the clinical characteristics of LOA also are quite different from childhood-onset asthma. LOA commonly runs a much more severe course and is associated with poor prognosis,[57] rapid decline in lung function[58,59] and severe persistent airflow limitation.[60,61] A cross-sectional analysis of 80 patients with severe asthma reported lower mean forced vital capacity (percent predicted) [66 ± 4 vs 76 ± 3] and mean forced expiratory volume in one second (FEV_1) (percent predicted) [48 ± 4 vs 56 ± 3] in patients with severe LOA versus patients with early-onset asthma.[8] Compromised lung function in patients with LOA, despite shorter duration of illness, suggests that significant loss of lung function occurs at/or soon after the initial diagnosis.[3]

Patients with LOA are almost five times more likely to have persistent rather than intermittent asthma than patients with early-onset asthma.[18] Although the incidence of asthma is highest in childhood, asthma deaths occur more commonly in older age groups.[62]

LOA is often associated with increased use of corticosteroids and short-acting β_2-agonists (SABA).[23,63] A population-based study from Taiwan reported higher OR of SABA use and healthcare use in LOA (onset age of 26–50 years) versus early-onset asthma.[23] Similarly, the results of a cluster analysis from the Severe Asthma Research Program reported higher use of healthcare resources in late-onset asthmatics with mean onset age of 42 years compared to other clusters.[60]

The Role of Allergy in LOA

In addition to all the risk factors and comorbidities described in the previous section, we also reviewed the current literature to explore the role of allergy in the development of LOA. Although LOA has been conventionally thought to be non-allergic in nature, the published literature reveals that LOA is commonly associated with allergic comorbidities.

Allergic rhinitis is more prevalent in LOA compared to childhood-onset asthma.[23] A strong association of nasal allergies with both early-onset asthma and LOA has been reported.[16] A population-based study in Swedish population reporting high incidence rate of LOA showed a strong association between incidence of asthma and allergic comorbidities such as allergic rhinitis [OR (95% CI), 4.1 (3.4–5.2)] and atopic dermatitis [OR (95% CI), 1.4 (1.04–1.9)]. Among the patients reporting hay fever, the incidence of LOA was 2.7/1000 person-years.[15] In an epidemiological study in 4173 subjects in Finland, in the age groups 0–9, 10–19, 20–29, 30–39, 40–49, 50–59 and 60–69 years, 70.4%, 62.0%, 58.3%, 52.5%, 37.7%, 19.2% and 33.3% of the new asthma cases, respectively, were classified as allergic.[64]

In addition to being associated with allergic comorbidities, patients with LOA also have elevated signs of immunoglobulin E (IgE) and show signs of atopy.[65–67] In a study by Burrows et al, high levels of serum IgE were reported to be a strong predictor of LOA. Some of the common antigens and allergens that might induce increases in IgE include dust mite, mold exposure and superantigens such as *Staphylococcus aureus*.[19,65–67] A population-based study in adults aged 21–63 years living in South Finland showed that the risk of asthma was related to the presence of visible mold and/or mold odor in the workplace (OR, 1.54; 95% CI, 1.01–2.32). About 35.1% of asthma incidence amongst the exposed population was attributed to workplace mold exposure. Fungal (aspergillus, penicillium, alternaria) sensitization is associated with moderate asthma; however, this can progress to severe asthma if exposed to abnormally high fungal concentrations.[68,69] In a study by Ariano et al, the most commonly found allergen was the dust mite species *Dermatophagoides pteronyssinus* (75%).[67] Another population-based study from St. Vincent and the Grenadines also reported that dust mite was the most common allergen in positive skin test with 66% reactivity.[19]

We examined different registries and population-based studies to evaluate the prevalence of allergic conditions with early- and late-onset asthma. The information obtained from these publications is summarized in Table 2. On examination of these data, it is evident that allergy is frequently associated with the LOA phenotype and plays a significant role in it.

Conclusions

Patients with LOA constitute a significant subset of the population suffering with asthma. LOA presents with clinical characteristics and risk factors, which are distinct from childhood-onset asthma. Despite this, our review reveals that there are some noticeable gaps in the understanding and management of this condition. Unfortunately, there seems to exist no consensus among the medical community about the exact age cut-off that defines LOA. Our review also reveals that, contrary to conventional thinking, patients with LOA are frequently allergic and have allergic comorbidities. These findings should help update existing management strategies with more treatment options and reduce systemic corticosteroid usage; nevertheless, there is a need to first clearly differentiate between different LOA phenotypes before applying the findings to treatment strategies.

In conclusion, there is an urgent need for the development of clinical practice guidelines that can provide more clarity on the definition and aspects of LOA, particularly its diagnosis and management. Furthermore, the association of allergy in LOA needs to be re-examined, so that clinicians can tailor their treatment strategies to ensure optimal outcome for these patients.

Table 2 Prevalence of Allergy in Early- and Late-Onset Asthma (LOA) in Different Registries and Population-Based Studies

Study	Population (N)	Definition of LOA	Presence of Allergy			Positive Skin Prick Tests		Presence of Allergic Comorbidities	
			Definition of Allergy	Early-Onset	Late-Onset	Early-Onset	Late-Onset	Early-Onset	Late-Onset
Miranda et al 2004[8]	Severe asthma patients (80)	≥12 years	Responded positively to wheezing "most or all of the time" to dust and pollens	75%	<40%	98%	76%	-	-
Heffler et al 2019[22]	Severe asthma patients; Severe Asthma Network in Italy (437)	>40 years	Sensitization to at least 1 airborne allergen	75.5%	62.9%	67.8% (sensitization to perennial allergens)	53.3% (sensitization to perennial allergens)	• Allergic rhinitis 50.0% • Food allergy 13.0% • Atopic eczema 11.8% • Bronchiectasis 17.0%	• Allergic rhinitis 35.9% • Food allergy 1.8% • Atopic eczema 6.0% • Bronchiectasis 14.4%
Busse et al 2013[70]	NHANES 2005–2006 database (2573)	≥55 years	Sensitization to at least 1 allergen	75.4%	65.2%	-	-	-	-
Huss et al 2001[71]	Asthma patients (80)	>65 years	Sensitization to at least 1 allergen	-	-	-	74.7%	-	-
Sözener et al[72]	Adult-onset patients (200)	≤40 years	Sensitization to at least 1 inhaled allergen	-	50.5%	-	49.5%	-	-
Chaudhuri et al 2016[18]	Patients with severe asthma (1042)	≥18 years	Positive to any allergen measured by skin prick test or by enzyme-immunoassay	84.7%	64.4%	-	-	• Perennial rhinitis: 39.9%	• Perennial rhinitis: 31.2%
Leynaert et al[73]	Population-based cohort in general population (9091)	≥20 years	Specific IgE ≥0.35 kU/L to any of the four common allergens tested	-	Women: 35% Men: 63%	-	Women: 78.1% Men: 67.7%	-	-
Aarab et al[28]	Community-based cohort study, patients from HELIUS study (23,356)	≥18 years	-	-	-	-	-	-	• Allergy/hay fever: 16.7–29%

Yáñez et al 2018[74]	Population-based study from Argentina (152)	>60 years		-	-	-	• Perennial rhinitis: 23%	• Perennial rhinitis: 20%
Nenasheva et al 2019[30]	RSAR (2534)	≥30 years	Specific IgE	64.8%	43.2%	91.3%	74.0%	• Allergic rhinitis: 46.3%	• Allergic rhinitis: 27.4%
Sood et al 2013[17]	CARDIA	≥18 years	Self-report of hay fever at first visit	41.1%	-	-	-	-	

Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults; IgE, immunoglobulin E; NHANES, National Health and Nutrition Examination Survey; RSAR, Russian Severe Asthma Registry.

Abbreviations

AERD, aspirin-exacerbated respiratory disease; EAACI, European Academy of Allergy and Clinical Immunology; FEV_1, forced expiratory volume in one second; GINA, Global Initiative for Asthma; GA^{2}LEN, Global Allergy and Asthma Network of Excellence; HELIUS study, the Healthy Life in an Urban Setting study; ICS, inhaled corticosteroids; IgE, immunoglobulin E; LOA, late onset manuscript; RSAR, Russian registry for severe bronchial asthma; SABA, short-acting β_2-agonists.

Consent for Publication

Not applicable.

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Author Contributions

All authors made substantial contributions to conception and design of this article; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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