Advances in the Diagnosis and Management of Asthma in Older Adults

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ABSTRACT

Global estimates on aging predict an increased burden of asthma in the older population. Consequently, its recognition, diagnosis, and management in clinical practice require optimization. This review aims to provide an update for clinicians, highlighting advances in the understanding of the aging process and immunosenescence together with their applicability to asthma from a diagnostic and therapeutic perspective. Aging impacts airway responses and immune function, and influences efficacy of emerging phenotype-specific therapies when applied to the elderly patient. Differentiating eosinophilic and neutrophilic disease accounts for atopic illness and distinguishes long-standing from late-onset asthma. Therapeutic challenges in drug delivery, treatment adherence, and side-effect profiles persist in the older patient, while novel recording devices developed to aid detection of an adequate inhalation evaluate treatment effectiveness and compliance more accurately than previously attainable. Anticytokine therapies improve control of brittle asthma, while bronchial thermoplasty is an option in refractory cases. Multidimensional intervention strategies prove best in the management of asthma in the older adult, which remains a condition that is not rare but rarely diagnosed in this patient population.

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A World Health Organization report on active aging estimates that the proportion of individuals over the age of 65 years is expected to more than double by 2050.[1] The burden of respiratory disease is concurrently set to increase in the same period, with an estimated 300 million people worldwide suffering from asthma, with 250,000 annual deaths attributed to the disease.[2] Age-specific mortality associated with asthma in the older patient contrasts with the falling figures in younger age groups, highlighting a basic need to improve asthma care and its management in the older population. Despite this, evidence from The Epidemiology and Natural history of asthma: Outcomes and treatment Regimens (TENOR) study reports that hospitalization among older asthmatics remained lower than that of a younger population.[3] This is in contrast to prospective data demonstrating that older patients with asthma were twice more likely to be hospitalized over a year-long follow-up period.[4]

The National Institute on Aging convened a workshop on asthma in the elderly that highlights differences in the pathophysiological mechanisms underpinning the disease in older patients that influence clinical course and outcomes.[5] The aim of this current review is to provide an update for clinicians on the advances in understanding the biology and impact of the aging process in regard to the diagnosis and treatment of asthma in the older adult. With major progress in the available and phenotype-specific therapies for asthma, its applicability to the older patient is described in the context of specific clinical challenges in this unique age group.

LONG-STANDING VERSUS LATE-ONSET ASTHMA

Asthma in the older adult is broadly divided into patients with long-standing disease present from childhood, and late-onset

disease describing those developing symptoms following the sixth decade of life. The diagnosis of the latter is particularly challenging as its symptoms mimic alternative pathologies present in an older age-group such as chronic obstructive pulmonary disease or congestive cardiac failure (**Tables 1**, **2**). Airway inflammatory cell types determine the physiological responses observed, and in the older asthmatic, eosinophilic inflammation is associated with airway hyperresponsiveness, while neutrophils are an important determinant of airflow limitation at rest and during bronchoconstriction.[6] Interestingly, chronic residential traffic pollution exposure is associated with eosinophilic but not neutrophilic inflammation in the older asthmatic.[7] These findings strengthen the relationship between airway pathophysiology and clinical phenotypic differences observed in the older patient with asthma.

THE BIOLOGY OF AGING AND ITS EFFECT ON THE DIAGNOSIS OF ASTHMA

Aging is the natural process of physiological change occurring within organ systems, decreasing their functional capacity. This in turn increases risk of disease. Whereas all individuals undergo this process, vast heterogeneity exists, giving the impact of a particular disease the potential to manifest differently depending on molecular, epigenetic, and individual factors. Environmental insult, when combined with reduced capacity for DNA repair with aging, increases the fragility of the lung to regenerate. Like other organs, the lung continually loses capacity over time, resulting in compromised pulmonary function. We have previously highlighted the inherent difficulties in performing and interpreting pulmonary function testing in older patients because of the effects of age-related changes in lung function on respiratory physiology.[8] Aging leads to an obstructive defect on pulmonary function testing that may be challenging in distinguishing from a superimposed active disease process such as asthma. Therefore, a combination of clinical history, physical examination, and diagnostic testing are critical to achieve an appropriate diagnosis that in turn directs treatment.

Clinical Assessment

Asthma is a heterogeneous disease entity with increasing emergence of varying clinical phenotypes. One major differentiation of relevance to the older patient is that between long-standing and late-onset asthma.[8] The clinical history remains pivotal to aid diagnosis. For example, allergic nasal

> ## CLINICAL SIGNIFICANCE
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> - Asthma in older adults remains a condition not rare, but rarely diagnosed.
> - Recognition, diagnosis, and management in clinical practice require optimization.
> - Major challenges exist in performing and interpreting diagnostic testing and overcoming challenging therapeutic issues unique to this age group.
> - This review provides an update on the advances in the biology and impact of the aging process with regard to the diagnosis and treatment of asthma in the older adult.

symptoms diminish with age, making a history of allergy less useful in this age group. A definitive history on environmental exposures and irritants such as cigarette smoking, household aerosols, paints, perfumes, and inhaled metabisulfites found in beer and food preservatives, is invaluable. Another critical aspect includes medication history such as aspirin, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, beta-blockers, and hormonal administration that could potentially induce bronchoconstriction. Differentiating asthma from other comorbidities is by far the greatest clinical challenge, as cardiac failure, chronic aspiration, upper airway obstruction, reflux disease, and chronic obstructive pulmonary disease (COPD) all mimic asthma (**Tables 1**, **2**).

Asthma in the older adult displays many of the hallmarks of COPD, such as onset of symptoms later in life, partial reversibility on pulmonary function testing, and association with neutrophilic inflammation.[9] Coexisting COPD with an asthmatic phenotype is encountered and poses an additional diagnostic challenge. Other factors accounting for a delayed diagnosis include poorer perception of dyspnea in the elderly and the psychosocial impact of aging. This results in aberrant reporting of symptoms exacerbated by the coexistence of depression, cognitive impairment, social isolation, and denial.

Physiological Assessment

Demonstrating physiological impairment assists the diagnosis of asthma. However, significant variability exists in the ability to detect airway obstruction in the older asthmatic. Initial spirometry may be normal and follow-up testing necessary for detecting airway obstruction.[5] The clinical utility of pulmonary function tests is user dependent: the inability to follow instructions due to poor coordination or cognitive impairment renders performance, and subsequently interpretation of results, challenging in this cohort.[8] One alternative is the measurement of respiratory impedance. This simple technique requiring minimal patient cooperation has been used successfully in young children and older adults for both diagnosis and therapeutic monitoring of respiratory symptoms associated with airway obstruction.[10] Assessment of institutionalized patients with cognitive impairment highlighted the superiority of respiratory impedance over spirometry in this patient group.[11] Home peak flow monitoring has been suggested as both a diagnostic and monitoring tool for asthma; however,

Table 1 Summary of Physiological Comparisons between Asthma and Chronic Obstructive Pulmonary Disease (COPD)

	COPD	Long-standing Asthma (LSA)	Late-onset Asthma (LOA)
Spirometry	Obstructive	Obstructive	Normal or obstructive
Reversibility*	None or Minimal	Significant (12% change in FEV_1 or 200 mL)	Significant (12% change in FEV_1 or 200 mL)
Diffusing capacity	Decreased	Normal	Normal
Hyperinflation	Increased	Normal or increased during attacks	Normal or increased during attacks

*Reversibility is measured by change in forced expiratory volume in 1 second (FEV_1) to bronchodilator therapy (salbutamol).

compliance is often challenging in the older patient.[12] Although significant early morning dips aid diagnosis, high variability remains a poor predictor of asthma, hence its limited role in late-onset disease.[13]

Aging and the Airway Response

The aging process impacts upon airway responses utilized in the diagnosis of asthma. Aging, however, does not alter the degree of response to inhaled bronchodilator drugs. The use of combined albuterol in conjunction with ipratropium bromide for diagnostic testing in the older adult often produces a more effective degree of bronchodilation. It is important to note that the time to achieve peak effect in bronchodilation is 30 minutes, in contrast to 5-10 minutes when using albuterol as a single-agent bronchodilator.[14,15] The changes in caliber of small airways in response to bronchodilation should not be used in the elderly asthmatic, as it often increases in response to the reduction of air trapping within the lungs.[16]

Gronke et al (2002)[17] identified that airway hyperresponsiveness was evident in individuals with a short (≤ 16 years), but not with a long (≥ 16 years) duration of asthma. This suggests that methacholine challenge testing, an accurate diagnostic tool for asthma in symptomatic patients with normal pulmonary function tests, may be of greater use in late-onset versus long-standing asthma. Furthermore, the prevalence of hyperresponsiveness is greater in older adults despite correcting for atopy, degree of airway obstruction, and smoking history, suggesting that a lower provocative challenge dose (<4 mg/mL) may be more appropriate to define airway hyperresponsiveness in the older patient than the conventional <8 mg/mL.[18]

THERAPEUTICS AND ITS ASSOCIATED CHALLENGES IN THE OLDER ADULT

Effective asthma management in the older patient relies on similar principles applicable to all ages. Key features include education, monitoring, and effective control of environmental factors in addition to pharmacological therapy. The National Asthma Education and Prevention Program recommends a stepwise approach to therapy. A number of therapies are not recommended generally for use in the elderly asthmatic. Zileuton, an inhibitor of 5-lipooxygenase, necessitates a regular monitoring of liver function, while theophylline's wide range of drug interactions affect serum concentration, and subsequent toxicity precludes its routine use in the elderly patient.

Asthma in the older adult assumes a unique phenotype, and accordingly, we propose an algorithm adapted from the stepwise Global Initiative for Asthma (GINA) guidelines to aid clinical decision-making when managing asthma in an older individual[19] (**Figure**).

In addition, there is emerging evidence for the role of long-acting anticholinergic inhalers in the management of asthma. Bateman et al[20] report that tiotropium was not inferior to salmeterol in maintaining an improved lung function in asthmatics. Peters et al[21] explored the role of clinical parameters predicting a response to tiotropium therapy. They identified that an acute response to short-acting bronchodilators predicted a positive clinical response to tiotropium. Despite this, a meta-analysis carried out by Tian et al[22] highlighted that the duration of most trials was too short to allow for evaluation of long-term efficacy and safety of tiotropium. It also is important to recognize that current trials investigating the use of

Table 2 Summary of the Key Features to Distinguish Younger and Older Asthmatics

	Younger Asthmatic	Older Asthmatic
Allergic symptoms	Present	Likely absent
Airway responsiveness	Significant	Significant
Reversibility	Short acting β2-agonist	Short-acting β2-agonist ± anticholinergic
Time to achieve peak bronchodilation	5-10 minutes	Up to 30 minutes
IgE	Normal or elevated	Total IgE (likely normal) and allergen-specific IgE (may be elevated)
Eosinophil Counts	Normal or elevated	Likely normal
Airway inflammation	Eosinophilic	Neutrophilic
Comorbidities	Absent	COPD or CCF (most common)

CCF = congestive cardiac failure; COPD = chronic obstructive pulmonary disease; IgE = immunoglobulin E.
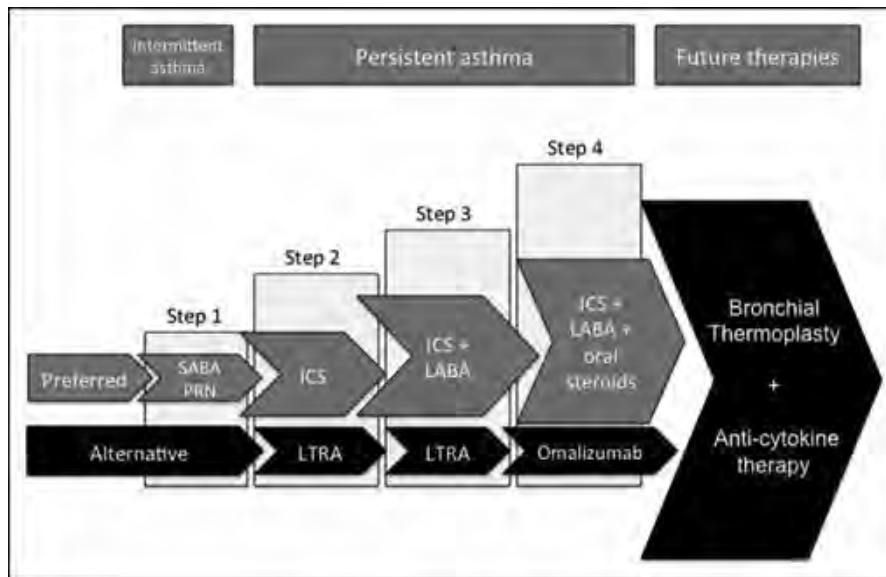
Figure Proposed stepwise approach to management of asthma in the older adult (adapted from Global Initiative for Asthma guidelines). ICS = inhaled corticosteroid; LABA = long acting β-agonist; LTRA = leukotriene receptor antagonist; PRN = as required; SABA = short-acting β-agonist.

tiotropium have evaluated its role as additional therapy to current management guidelines rather than a first-choice stand-alone therapeutic option. Future longer-term studies are expected to address this. It is likely, however, that tiotropium therapy will provide clinicians with a future option in controlling symptoms in the elderly asthmatic by concomitant treatment of age-related COPD in a convenient once-daily dosing regimen.

The role of long-term macrolide therapy to improve asthma control has been explored in a number of trials. A meta-analysis of 4 randomized controlled trials identified improvement in symptoms, quality of life, and airway hyperreactivity, but highlighted the limited statistical power to detect significant differences in lung function.[23]

If considered for use in the elderly asthmatic, it is critical to highlight a number of complex drug interactions occurring between macrolide therapy and a number of pharmacological agents used for symptom maintenance, including antihistamines and theophyllines (Table 3). Future longer-term trials focusing on both the safety and efficacy of macrolides on exacerbation rates may highlight these agents as a useful adjunct in the management of late-onset asthma.

Beta-blockade therapy may exacerbate symptoms of asthma when administered topically for glaucoma or orally for acute coronary syndromes. Initiating beta-blocker therapy in the older asthmatic must be performed under close supervision, as severe life-threatening symptoms may be triggered by the initial dose.[24,25] There is, however, evidence suggesting that escalating beta-blocker therapy in asthmatics is well tolerated.[26] The risk–benefit ratio of beta-blocker maintenance therapy in asthmatics has a limited evidence base. This is further complicated by

potential beneficial effects on airway inflammation and hyperresponsiveness in some patients with asthma.[27-29] Clinical benefits of selective beta-blocker therapy in patients with coronary disease necessitates a careful assessment by the prescribing clinician with regard to the presence of concomitant poorly controlled asthma or the potential risks of poor symptom control following initiation. Holding beta-blockade may be appropriate in the setting of hospital admission for decompensated asthmatic symptoms in the older adult, but the relative risk–benefit ratio must be considered in terms of other comorbid illness.

Drug Delivery and Adherence

Despite the fundamental role of inhaled bronchodilators and corticosteroids, many elderly patients remain undertreated.[30] Early work estimates that half of all patients are unable to use the inhalers prescribed, and despite increased awareness, only marginal improvements have occurred.[31,32] Availability of preconstituted combination therapies and spacer devices has increased clinical efficacy and treatment adherence. Limitations to the latter do remain, owing to cumbersome sizes and difficulty with maintenance of a sterile spacer device key to eliminate unfavorable electrostatic charges.[33] In an older patient, maintaining a clean spacer is particularly challenging as contamination due to colonization with *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus*, *Burkholderia*, and *Stenotrophomonas maltophilia* has been reported.[34]

Major technological advances have occurred in the field of assessing inhaler compliance and adherence to prescribed treatment. Such methods have the capacity to revolutionize

Table 3 Macrolide Therapy Drug Interactions with Antihistamines and Theophyllines

Class	Drug	Mechanism	Effect
Antihistamines	Terfenadine	CYP 3A4	QT prolongation
	Loratadine	CYP 3A4	QT prolongation
		CYP 2D6	
Theophyllines	Aminophylline	CYP 1A2	Decreased
		CYP 3A4	theophylline
			excretion by 25%

CYP = cytochrome families and relevant isoforms.

treatment compliance and effectiveness in the older population. Many older patients are unable to achieve a peak inspiratory flow rate necessary to fully extract medication from a dry-powdered inhaler. Novel recording devices have been developed to aid identification and detection of an adequate inhalation utilizing acoustic signals.[35]

Treatment Effectiveness

Effectiveness of therapy in the elderly population has only been investigated on a trial basis by 2 current therapies. The Accolate Clinical Experience and Pharmacoepidemiology Trial (ACCEPT) explored the effect of age on the response to zafirlukast. It failed to demonstrate a significant change in rescue inhaler use; however, it highlighted clinically significant differences in asthma symptoms.[36] Omalizumab therapy in an elderly veteran population demonstrated significant positive clinical responses where moderate numbers of patients on long-term corticosteroids were able to discontinue treatment.[37]

A limited pool of available evidence highlights a growing need to evaluate therapies and treatment algorithms for older asthmatics in specific trials fit for this purpose. A major factor contributing to the lack of available evidence in the elderly asthmatic population remains the screening techniques employed by large multicenter work. Older patients are frequently excluded from such investigational work due to burden of comorbidity and the need to simplify the measured outcomes of clinical trials.[38] The screening criteria employed in clinical trials for asthma inherently exclude the elderly asthmatic as phenotypic changes in the degree of airway hyperresponsiveness, reductions in eosinophil counts and function, and change in fractional exhaled nitric oxide (FeNO) responses render the elderly individual ineligible for inclusion. Dupilumab, an interleukin (IL)-4 monoclonal antibody, has been recently trialed for persistent asthma with elevated eosinophil counts, and within the study, a number of Th2 biomarkers were analyzed at various time points.[39] Any patient over 65 years of age was excluded from the trial, as surrogate markers used to monitor response to treatment are influenced by aging. Serum biomarkers including thymus activation and regulated chemokine, immunoglobulin E (IgE), FeNO, and blood/sputum eosinophils are impacted upon by immunosenescence. Future research initiatives should address such inherent problems in patient selection and outcome measures during asthmatic trials. Differences between older and younger asthmatics need to be sought in the appropriate clinical context, limited at present because of a lack of enrollment within asthma trials.

PATHOPHYSIOLOGICAL IMPACT OF AGING AND EFFECTS ON EMERGING ASTHMA THERAPIES

Atopic Asthma

Aging is associated with a decrease in the prevalence of atopic symptoms, IgE levels, and positive skin allergen tests. Healthy older adults have at least a single positive allergen skin test, in contrast to the older patient with asthma that develops multiple sensitizations to common indoor allergens such as cats, dogs, mites, and cockroaches.[40,41] Older patients that may have become sensitized to cockroaches tend to develop more severe asthma and experience a steeper decrease in lung function.[42,43] Places of residence are known to influence the frequency of acute respiratory infections from 1%-2% per year to 6%-11% per year at daycare and long-term centers.[44] Clinical utility of controlling triggers in the elderly with measures to control aeroallergen exposure to known agents should be initiated. Some of the common provocative agents include cigarette smoke, paints, varnish, and cleaning aerosols.

The eosinophil remains the cellular conductor of allergic asthma, and eosinophil counts remain comparable between older and younger asthmatics. Degree of degranulation is, however, reduced significantly in the elderly patient. A critical limitation of published work to date remains the use of peripheral blood rather than airway eosinophils. The 2 populations exhibit crucial differences in cell surface markers and activation states that remain unaddressed by use of sole peripheral sampling.[45]

Furthermore, an inverse relationship between aging and IgE production exists, suggestive of a natural desensitization process. Current evidence suggests that development of asthma in the older patient is not linked to total IgE, but rather, to sensitization and the development of allergen-specific IgEs following a prolonged environmental exposure to allergens. This remains an important consideration when evaluating the use of anti-IgE strategies in elderly asthmatics. A potential false elevation in total serum IgE must be recognized and may be confounded by factors including sex, smoking status, concurrent infections, and environmental sensitization.[6,46] During both the diagnosis and, more importantly, escalation of therapy to include the anti-IgE agent omalizumab, such features must be taken into account. Omalizumab therapy should, however, always be considered in the elderly asthmatic as a safe escalation option, but confounding total IgE levels may complicate its initiation and possibly effectiveness. Importantly however, omalizumab has been reported to reduce exacerbations, improve symptoms, and limit the

need for rescue medication in asthmatics. Its global effectiveness reported by both clinicians and patients extends to elderly patients with moderate-severe allergic asthma and remains, in the right circumstances, a viable therapeutic option.[37]

Nonatopic Asthma

One of the key advances in the recent era of asthma care has been novel approaches to testing for airway inflammation. This allows differentiation between eosinophilic, neutrophilic, or lymphocytic-based disease, differentiating atopic from nonatopic asthma, as well as from COPD.

Nitric oxide is generated by a variety of inflammatory cells that include polymorphonuclear leukocytes, mononuclear cells, and eosinophils. Identification of nitric oxide in exhaled breath may predict asthma exacerbations.[47] Hardaker et al (2011)[48] highlighted that although exhaled nitric oxide is a strong predictor of asthma severity in the younger patient, this correlation disappears rapidly with age. Clinical utility of exhaled nitric oxide is currently limited by absence of evidence to determine if it is causative of airway dysfunction or a marker of a normal homeostatic mechanism.[49-52] The development of noninvasive bedside testing for airway inflammation, such as analysis of breath condensate cytokines and induced sputum, will allow differentiation between eosinophilic, neutrophilic, and lymphocytic bronchial inflammation.[53] These may be of greater clinical value than exhaled nitric oxide in the older adult, allowing a directed and more personalized therapeutic approach.

Most reflective of late-onset disease, nonatopic asthma is often triggered by viral upper respiratory tract infections, which leads to exacerbations. Detecting exacerbations early requires clinical acumen in this population because of relatively poor distinguishing features from COPD and a lack of sensitive viral diagnostic testing.[5] What remains intriguing in the older adult is whether viral exacerbations occur secondary to persistent airway inflammation or age-related immune-inflammatory changes, termed *immunosenescence*. This active and highly regulated process involves bidirectional crosstalk between hematopoietic cells and thymic epithelia.[54] While established evidence points toward a Th2-cytokine bias in early life, studies in older adults indicate a key role for Th1 responses, providing further evidence for age-associated changes in the airway inflammatory response.[55] Furthermore, murine models of asthma in the context of aging have demonstrated diminished B-cell populations and a transition from naïve to antigen-expressing B cells.[56] Parallel reductions in antibody production may be responsible for the enhanced antigen persistence and specificity observed in the elderly. Thymic involution evokes shifts in the T-cell population, alterations in antigen B-cell processing, eosinophil function, and reduction in phagocytic capabilities, all of which contribute to a unique immunological milieu in the older adult with asthma.

Anticytokine Therapies

In the context of immunosenescence, promising avenues of therapeutics targeting inflammatory cascades continue to emerge. Asthmatic airways contain CD4+ T cells that produce IL-4 and -13, which are both therapeutic targets that have been investigated. The range of antigenic activators associated with the CD4 pathway is being expanded continually, and this group of therapeutics may yet provide novel avenue streams to treat the elderly asthmatic. Serum obtained from older asthmatics demonstrates increased concentration and persistence of certain T-cell subsets highlighting the key role of prolonged activation and survival of these cell types in the pathophysiology of late-onset asthma. This expanding arsenal of anticytokine therapies utilized in poorly controlled asthma is summarized ([Table 4](#)), and despite a lack of data in older patients, provides the most promising newer therapeutic options. It must, however, be noted that the emergence of anticytokine therapy does not come without risk, as IL-4, -5, and eosinophils have important innate immunological roles. Development of serious infections and neoplasia both at higher risk in an elderly population halted the development of golimumab (antitumor necrosis factor-α antibody) and highlighted the key protective effects of IL-17A and -17F in immunologic surveillance.[57] The true risk–benefit effects of these emerging agents applicable to the older asthmatic are yet to be fully elucidated.

BRONCHIAL THERMOPLASTY

Bronchial thermoplasty is a treatment option for the poorly controlled asthmatic refractory to other therapies. The technique involves endoscopic application of thermal radiofrequency energy to ablate underlying smooth muscle altering airway structure. It has been shown that structural changes in the older fatal asthmatic share overlapping features with those of younger fatalities.[58] This suggests that bronchial thermoplasty may be of benefit in a selected subset of older patients with asthma. However, the safety and feasibility of the procedure remains to be determined in an elderly population, despite bronchoscopy being reported as a relatively safe and well-tolerated procedure in octogenarians.[59]

MULTIDIMENSIONAL INTERVENTIONAL STRATEGIES AND PULMONARY REHABILITATION

Use of a multidimensional assessment and intervention strategy has been highlighted for effective management of asthma in the older adult.[60] This approach, validated by systemic reviews and randomized controlled trials, identifies several dimensions of care, including pharmacotherapy, individual rehabilitation, and social interventions. By addressing specific age-related issues such as comorbidities and acute care complications, the strategy contributes to an improved quality of life and cost-effectiveness if domains are targeted appropriately. Owing to its success in managing

Table 4 Emerging Anticytokine Therapies in the Management of Asthma

Target Cytokine	Function	Therapeutic Agent(s)
IL-2	Activating factor: Th1 & Th2 cells	Daclizumab
IL-5	Eosinophil growth, maturation and activation	Mepolizumab
		Reslizumab
		Benralizumab
IL-9	Mast cell proliferation and mucus hyperplasia	MEDI-528
IL-4	Th2 differentiation, expansion, and isotype switching, eosinophil recruitment, mast cell development	Pitrakinra
		Dupilumab
IL-13	Bronchial fibroblast and airway smooth muscle proliferation, eosinophil and basophil recruitment	Lebrikizumab
		Anrukinzumab
		Tralokinumab
IL-17	Airway recruitment of neutrophils, lymphocytes, and eosinophils	Secukinumab
Anti-GM-CSF	Eosinophil differentiation and survival	MT203

GM-CSF = granulocyte macrophage colony-stimulating factor; IL = interleukin.

asthma, it has been adapted into the management of COPD affecting the older adult.[61] Additionally, the role of pulmonary rehabilitation programs in the management of asthma remains to be fully appreciated. Cox et al[62] initially highlighted a role for rehabilitation in a small population of patients with asthma illustrating improvements in symptom control and quality of life. Laurino et al[63] highlighted that breathing retraining improved symptoms of asthma related to anxiety, and subsequently, improved quality of life. Despite these small studies, the longer-term beneficial effects of a pulmonary rehabilitation program, particularly on an elderly asthmatic population, remain to be determined.

CONCLUSION

Despite advances in both diagnostics and therapeutics, asthma remains an underrecognized health issue in the elderly population. This diagnosis is not rare, but it is rarely diagnosed, as almost 10% of the adult population over 65 years of age are afflicted. Emerging evidence suggests that asthma in the older adult is phenotypically distinct from that seen in younger patients, particularly when physiological changes associated with the aging process are taken into account. In addition to an increased number of elderly patients being enrolled into asthma trials, dedicated and well-funded clinical studies of this population are required to evaluate future diagnostic and treatment approaches. Research in the field needs to focus on both human and animal model systems to investigate the impact of the aging process on the immunologic pathways underpinning asthma in the aging lung. Epigenetic, environmental, and microbiological triggers need to be considered in the clinical setting, while translational investigation of novel therapeutic targets must be pursued. Our current knowledge base is largely from specimens obtained from young adults; however, the role of allergic asthma diminishes with age, hence, a different phenotype presents in the elderly, with normal eosinophils and elevated sputum neutrophils. Neutrophilic asthma is associated with innate immune pathways in contrast to Th2-mediated allergic asthma; hence, research on

alternative signaling cascades involving Natural Killer T/Th17 lymphocyte subtypes must be pursued. Future work should not be limited to therapeutic targets, but also should identify noninvasive biomarkers of disease severity and progression. Clinical trials in this challenging population need to account for the unique phenotypic makeup of the elderly asthmatic and for the immunological and physiological changes associated with the natural process of aging that affect its diagnosis and management.

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